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American Society of Clinical Oncology
54th Annual Meeting

2018 Abstracts

Descriptions of Scientific Sessions

*Plenary Session*
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

*Highlights of the Day Sessions*
Highlights of the Day Sessions invite expert discussants to provide an overview of the previous day’s Oral Abstract presentations, focusing on key findings and putting abstracts into clinical context.

*Oral Abstract Sessions*
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as discussants and provide comprehensive themed discussions of the findings from the abstracts.

*Clinical Science Symposia*
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with abstract presentations. Experts in the field serve as discussants, placing studies in the appropriate context and critically discussing the applicability of the conclusions in clinical practice. Three special Clinical Science Symposia will be designated around specific topics that cut across cancer types.

*Poster Discussion Sessions*
Select posters from the Poster Sessions will be discussed by expert discussants, with the abstract authors participating in a question and answer period as panel members. These sessions will be followed by networking with the discussants and authors.

*Poster Sessions*
Poster Sessions include selected abstracts of clinical research in poster format. Trials in Progress (TPS) abstracts are presented within a track’s Poster Session.

*Publication-Only Abstracts*
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but will not be presented at the Meeting.

_All presented and publication-only abstracts are citable to this Journal of Clinical Oncology supplement. For citation examples, please see the Letter from the Editor._

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2018 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.

Dates and times are subject to change.
All modifications will be posted on am.asco.org.
The 2018 ASCO Annual Meeting Proceedings (a supplement to Journal of Clinical Oncology) is an enduring record of the more than 2,400 abstracts selected by the ASCO Scientific Program Committee for presentation at the 54th ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of Journal of Clinical Oncology at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. Abstracts can be also accessed online through ASCO abstracts website (abstracts.asco.org) or Meeting Library (meetinglibrary.asco.org). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and first author only. The full-text versions of these abstracts will be publicly released during the Annual Meeting. Print versions of these abstracts will be available onsite at the Annual Meeting in the ASCO Daily News.

All abstracts carry Journal of Clinical Oncology citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 36:5s, 2018 (suppl; abstr LBA1)
J Clin Oncol 36, 2018 (suppl; abstr e12000)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD
Editor, 2018 ASCO Annual Meeting Proceedings
ASCO Abstracts Policy

Public Release of Abstracts

The abstracts published in the 2018 ASCO Annual Meeting Proceedings, including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 16, 2018. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Friday, June 1, will be publicly released Friday, June 1, through ASCO.org at 2:00 PM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Saturday, June 2, will be publicly released Saturday, June 2, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Sunday, June 3, will be publicly released Sunday, June 3, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Monday, June 4, or Tuesday, June 5, will be publicly released Monday, June 4, through ASCO.org at 7:30 AM (EDT).

Late-Breaking Abstracts will be available in Section D of ASCO Daily News on the day of their scientific presentation, with the exception of abstracts presented on Friday (these will appear in the Saturday issue) and those presented on Tuesday (these will appear in the Monday issue).

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.

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Conflict of Interest Disclosure

As the CE provider for the Symposium, ASCO is committed to balance, objectivity, and scientific rigor in the management of financial interactions with for-profit health care companies that could create real or perceived conflicts of interest. Participants in the Symposium have disclosed their financial relationships in accordance with ASCO’s Policy for Relationships with Companies; review the policy at asco.org/rwc.

ASCO offers a comprehensive disclosure management system, using one disclosure for all ASCO activities. Members and participants in activities use coi.asco.org to disclose all interactions with companies. Their disclosure is kept on file and can be confirmed or updated with each new activity.

Please email coi@asco.org with specific questions or concerns.
ABSTRACTS
American Society of Clinical Oncology
54th Annual Meeting
June 1-5, 2018
McCormick Place
Chicago, IL

SPECIAL AWARD LECTURE ABSTRACTS

David A. Karnofsky Memorial Award and Lecture
Saturday, June 2, 9:30 AM
Oligometastasis from conception to treatment.
Ralph R. Weichselbaum, MD; The University of Chicago Medical Center, Chicago, IL

Metastases account for 80-90% of cancer deaths. Despite recent advances in systemic therapies, almost all patients who develop metastases from adult solid tumors are not cured. We proposed that a subset of patients develop few metastatic lesions within limited destination organs, termed oligometastasis. These patients may be amenable to cure by ablative therapies including radiotherapy and surgery. We also proposed that patients who respond well to systemic therapies, but later re-present with a limited number of persistent or oligo-progressive tumors, may be cured when ablative therapies are combined with systemic therapies. I will review laboratory data that provides clues regarding the biological basis of oligometastases, and discuss retrospective data and early level 1 evidence to demonstrate improved PFS and OS in patients with oligometastatic disease. Looking forward, I will discuss a rationale for designing clinical trials that integrate ablative therapies combined with systemic approaches including hormonal manipulation, targeted cytotoxic drugs, and immunotherapy in order to optimize cure in various stages of metastatic disease.

Science of Oncology Award and Lecture
Sunday, June 3, 1:00 PM
Preventing HPV-associated cancers by vaccination.
Douglas R. Lowy, MD; Deputy Director, National Cancer Institute, Bethesda, MD

The laboratory developed the virus-like particle technology that underlies the three FDA-approved HPV vaccines, which have the potential to prevent the majority of the HPV infections that lead to ~30,000 anogenital and oropharyngeal cancers annually in U.S. men and women, and to ~8% of all female cancers worldwide. They are the first vaccines that successfully target an infectious agent that mainly induces local sexually transmitted disease. The vaccines, which are given systemically, confer more than 90% protection against new mucosal and cutaneous infections.

We have studied the mechanisms that underlie the efficacy of the vaccine, using an HPV mouse genital tract challenge model after validating that it recapitulates vaccine responses that are similar to those observed in women. Passive transfer studies indicate that neutralizing antibodies induced by the vaccine account for its high protective efficacy, although the vaccine also induces cell-mediated responses. Factors that contribute to vaccine efficacy include: intrinsically high immunogenicity of the virus-like particle (VLP) structure of the vaccine immunogen, high in vivo sensitivity of HPV to neutralizing antibodies, and high antibody levels at potential sites of infection.

The HPV vaccines are already having an impact on HPV-induced early disease markers in vaccinated populations, including evidence of herd immunity. The high immunogenicity of the vaccines has led us to hypothesize that, in contrast to most other protein-based subunit vaccines, it may be possible to safely reduce the number of recommended vaccine doses from the current two or three to a single dose in young adolescents, who represent the main target group for the vaccine. A randomized clinical trial has been started to test this hypothesis.

Disclosure: I am an inventor of the virus-like particle technology that underlies the technology for the HPV vaccines. The technology has been licensed by the NIH to Merck and GlaxoSmithKline, the manufacturers of the FDA-approved vaccines.
ASCO–American Cancer Society Award and Lecture
Monday, June 4, 9:45 AM
Hereditary cancer genetic testing and risk reduction: Evolving strategies.
Karen H. Lu, MD; The University of Texas MD Anderson Cancer Center, Houston, TX
As a gynecologic oncologist, I have had an ongoing interest in the intersection of cancer treatment and cancer prevention. With the approval of parp inhibitors for BRCA-associated ovarian cancer and immune checkpoint blockade for MSI-H endometrial cancers, there has been increasing emphasis on universal genetic screening for women who have these cancers. However, the real impact on decreasing mortality will be in the “cascade testing” of family members, who can then undergo risk reduction strategies. Traditional models of delivering cancer genetics services and cascading the information to family members need to be re-examined. Strategies for genetic testing must focus on increasing access and using technology to provide genetic counseling. We are currently studying this paradigm in a national study called Making Genetic Testing More Accessible (MAGENTA). Described as “Genetic Testing from your Living room,” the study aims to examine novel delivery models of genetic counseling and testing. Two other strategies need to be employed if we are to realize the full potential of cancer risk reduction through genetic risk assessment and testing. First, partnership with advocates at the time of research planning is essential, as the development of prevention strategies must consider patient preferences beyond efficacy. A national study of immediate salpingectomy and delayed oophorectomy in women at increased risk of ovarian cancer was based on scientific evidence that BRCA-associated ovarian cancer begins in the fimbriae of the fallopian tube, and was strongly driven by the advocacy community as an option to delay the effects of surgical menopause. Second, those of us in the cancer prevention community need to embrace a more patient-centered, multidisciplinary approach for care of these genetically high risk patients who are at risk for multiple cancers. As the number of “previvors” increases, we will need to continually innovate to develop novel approaches for multi-organ chemoprevention or coordinated screening.

B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology
Monday, June 4, 3:00 PM
Honoring the preferences of older patients with cancer and caregivers through improved communication.
Supriya Gupta Mohile, MD, MS; University of Rochester Medical Center, Rochester, NY
Geriatric oncology has undergone a transformation over the last 15 years. Following advocacy from key leaders in research such as BJ Kennedy, Lodovico Balducci, and John Bennett, ASCO partnered with the John Hartford Foundation to invest in geriatric oncology fellowship training programs that spawned 28 fellows. These fellows, working with senior mentors in the field such as Harvey Cohen, Hyman Muss, Stuart Lichtman, and Martine Extermann, developed a cohesive voice dedicated to improving care delivery for older patients with cancer. To translate this voice and passion into action, geriatric oncology investigators, spearheaded by Arti Hurria, formed the Cancer and Aging Research Group. Three investigators (Hurria, Dale, and Mohile) organized 3 conferences through a U13 partnership with the NIH to develop the research priorities in aging and cancer. By partnering with ASCO, the Society of International Geriatric Oncology, the Alliance, and the NCI Community Oncology Research Program, geriatric oncology investigators are now taking action to improve policy, foster educational efforts in geriatric oncology, and conduct high quality, high impact research. Better care for older adults with cancer requires geriatric assessment and management; a new ASCO guideline highlights the high quality evidence developed by geriatric oncology investigators from around the world, which demonstrates that geriatric assessment measures can identify older patients at highest risk for adverse outcomes. Geriatric oncology research will now need to undergo another transformational shift and should focus on how best to improve communication around decisions for treatment for “real world” older patients. Geriatric assessment can enhance communication about risks and benefits and thus allow us as clinicians to elicit, respect, and honor what older patients with cancer and caregivers want and need. The transformational shift in geriatric oncology research will require strong partnerships with stakeholders, including older patients and caregivers, and will be enhanced by innovative research methods such as mixed methods, social network analyses, and machine learning.

Pediatric Oncology Award and Lecture
Monday, June 4, 1:15 PM
Facilitating precision oncology for children: Implementing new legislative provisions for the therapeutic orphans.
Gregory H. Reaman, MD, FASCO; U.S. Food and Drug Administration, Silver Spring, MD
Although the cure rates for childhood cancer have improved dramatically over the past several decades resulting in extended disease-free survival for >80% of those afflicted, cancer remains the leading cause of death from disease in children. This is a direct result of suboptimal treatment results for some specific cancers particularly when metastatic at diagnosis and when recurrent due to resistance to therapy. The dismal outcomes for some rare
pediatric cancers have not improved. In addition, the short and long term toxicities related to current therapies negatively impact quality of life and survivorship. The unmet clinical need for new drugs for children with cancer and cannot be overstated.

Molecularly targeted drugs developed for cancers which occur predominantly in adults have advanced the concept of precision medicine in oncology, which is transforming cancer care for adults. Similar treatment advances are yet to be realized in children. Although large scale efforts at genomic interrogation of various pediatric cancers have provided evidence that the genetic and epigenetic repertoire of driver gene aberrations differ between the cancers of adults compared to those which predominate in children, recent evidence reveals that many of the same genetic and other molecular biological vulnerabilities evident in many adult cancers may present opportunities for the use of certain targeted agents in up to 50% of children with tumors which are histologically and biologically different. Pediatric cancer drug development has historically leveraged adult drug discovery and development. Laws envisioned to assure equitable access to new therapies for both children and adults by requiring or incentivizing sponsors to conduct studies to evaluate efficacy and safety in children have greatly improved therapeutic options in many clinical areas except cancer. Recent amendments to Section 505B of the Food, Drug, and Cosmetic Act promise to change the landscape of pediatric cancer drug development. Responsible implementation of these new provisions to expedite evaluation of novel agents promises a change for children as therapeutic orphans.

Gianni Bonadonna Breast Cancer Award and Lecture
Monday, June 4, 4:45 PM

Mentoring, empowering, opening doors.
Gabriel N. Hortobagyi, MD, MACP, FASCO; The University of Texas MD Anderson Cancer Center, Houston, TX

Gianni Bonadonna was an outstanding oncologist, clinical investigator, academic leader, educator, role model, writer, philosopher and most importantly, a dear friend. Our 40-year friendship started in 1975 and continued through collaborations in clinical research, publishing, international speaking, mentoring and sharing the finer aspects of life. At the top of his career, a sudden illness transformed his life; he then became an example to all of us about how to overcome adversity with dignity, persistence and grace. His continued productivity during the last decade of life is a testimony to his willpower, creativity, intelligence and dedication to oncology and medicine.

My own career focused on clinical and translational research in breast cancer and the training and mentoring of a number of young oncologists from around the world. My initial focus was the development and implementation of neoadjuvant chemotherapy, first, in the management of locally advanced and inflammatory breast cancer, later, in the curative therapy of earlier stages of operable breast cancer. I was fortunate to work with outstanding colleagues in surgical, radiation and medical oncology, as well as imagers and pathologists at one of the premier cancer centers in the world. Our multidisciplinary approach to the management of malignant disease was the cornerstone of our practice since the early 1970s. Since then, it has been adopted by many other institutions around the world as a superior method to manage all solid tumors. Other major research interests resulted in the development and implementation of clinical trials that demonstrated the role of multiple new drugs (anthracyclines, taxanes, bisphosphonates, everolimus and ribociclib) in the management of advanced and early breast cancer, the development of gene expression profiling for prognostication, classification and prediction of benefit from treatment, and the initial steps in gene therapy for solid tumors. However, the most satisfying aspect of my career has been the opportunity to interact with, mentor and empower my younger colleagues (residents, fellows, junior faculty) and open doors for successful career development. Many of them occupy today leadership positions in oncology all around the world. They will carry the torch and will train the next generation of oncologists to move the field forward.

Allen S. Lichter Visionary Leader Award and Lecture
Saturday, June 2, 3:00 PM

Serendipity and purpose.
Nancy E. Davidson, MD, FASCO; Fred Hutchinson Cancer Research Center, Seattle, WA

Reducing the burden of cancer is a daunting task and requires vision, collaboration, and hard work from all. During my career as a physician-scientist working in the biology and treatment of breast cancer and inspired by our patients, I worked in the nascent fields of apoptosis and epigenetics of breast cancer, moving lab discoveries from bench to bedside. Our teams at Johns Hopkins, University of Pittsburgh, and Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance enabled this work. The imperative to work nationally and internationally led us to found the Translational Breast Cancer Research Consortium and initiate the AURORA project in metastatic breast cancer to accelerate our goals to bring scientific discovery to patient care. My service as director of an NCI Cancer Center and advisor to many others crystallized the need for and importance of collaborative and visionary
leadership. The unusual honor of serving as president of both the American Society of Clinical Oncology and the American Association for Cancer Research provided an extraordinary platform to champion the vital roles of the entire community of cancer practitioners, researchers, and advocates to catalyze progress and change.
LBA1 Plenary Session, Sun, 1:00 PM-4:00 PM
TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score. First Author: Joseph A. Sparano, Montefiore Medical Center, Bronx, NY

LBA2 Plenary Session, Sun, 1:00 PM-4:00 PM
Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). First Author: Gianni Bisogno, Department of Women and Children Health, University Hospital of Padova, Padova, Italy

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 3, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

LBA3 Plenary Session, Sun, 1:00 PM-4:00 PM
CARMENA: Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma—Results of a phase III noninferiority trial. First Author: Arnaud Mejean, Department of Urology, Hôpital Européen Georges-Pompidou - Paris Descartes University, Paris, France

LBA4 Plenary Session, Sun, 1:00 PM-4:00 PM
Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. First Author: Gilberto Lopes, Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 3, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**100**

Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Ado-trastuzumab emtansine (T-DM1) in patients (pts) with HER2 amplified (amp) tumors excluding breast and gastric/gastro-esophageal junction (GEJ) adenocarcinomas: Results from the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) trial. First Author: Komal L. Jhaveri, New York University Cancer Institute, New York, NY

**Background:** The NCI-MATCH is the largest national signal-finding trial incorporating centralized genomics testing to direct pts to molecularly targeted phase 2 treatment arms. HER2 gene amp is observed in many different tumor types.

**Methods:** HER2 amp was defined as copy number (CN) ≥7 based on tumor sequencing on an adapted Oncomine Ampliseq panel under FDA investigational device exemption. Pts with prior trastuzumab, pertuzumab or T-DM1 treatment were excluded. Pts received T-DM1 at 3.6 mg/kg IV Q3 weeks until toxicity or disease progression. Tumor assessments occurred Q3 cycles for 33 cycles and Q4 cycles thereafter. Primary endpoint was objective response. Correlative studies included correlating HER2 CN, HER2 protein levels by IHC, HER2:CEP17 ratio (by FISH), PTEN loss, MYC amplification and PIK3CA mutation status with response. **Results:** 37 eligible pts were treated between 11/15-3/17. Median age was 65 (range 39-80). 33% had received > 3 lines of prior therapy. Median HER2 CN was 17 (7-59). Various histologies were treated: colon carcinoma (n = 7), ovarian (n = 6), rare tumors such as cholangioca (n = 1), carcinosarcoma of the uterus (n = 1), salivary gland (n = 3), among others. 3/37 (8.1%, 90% CI 2.2%-19.6%) had a confirmed partial response including 1 patient each with salivary duct ca of parotid gland, squamous cell ca of parotid gland and extramammary Paget disease of the vulva. Malignant ascites (SD) including 3/3 evaluable ovarian and uterine ca respectively. Median duration of SD was 4.6 months. The 6-month PFS rate was 24.8% (90% CI 15.0%-41.1%). Common toxicities included fatigue, anemia, fever and thrombocytopenia with no new safety signals. Median treatment duration was 4 cycles (range 1-23) and included 2 PRs, 1 in a patient with a hereditary parathyroid tumor syndrome. The MTD was not reached. AEs (16%) and dyspnea (12%); most were grade 1-2. No AEs associated with PFS < 6 mo was observed for pancreatic-biliary tumors/cholangiocarcinoma (3/6) and adenoid cystic carcinoma (3/4). Only 1 of 9 pts with BRAF, NRAS, HRAS, MAP2K1, MAPK1, or NF1 mutations achieved PFS ≥ 6 mo. **Conclusions:** In a mixed histology cohort selected at activating LOXO-2 fusion+, treatment with 3-5 lines of prior therapy, although 27% of pts had PFS > 6 mo, PIK3CA mutation independent of histology is an insufficient predictor of taselisib activity. Associations of individual histologies and PIK3CA mutation subtypes with PFS may be worthy of further study. Clinical trial information: NCT02465060.

**101**

Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Results from molecular analysis for therapy choice (MATCH) arm I: Taselisib for PIK3CA-mutated tumors. First Author: Ian E. Krop, Dana-Farber Cancer Institute, Boston, MA

**Background:** MATCH is a trial that assigns patients (pts) with solid tumors, lymphomas, or multiple myeloma to specific targeted therapies based on genetic alterations identified in fresh tumor biopsies. Arm I evaluated the PI3-kinase inhibitor taselisib in pts with activating mutations in PIK3CA, the catalytic subunit of PI3-kinase. Methods: Pts with KRAS mutations or PTEN mutation or loss were excluded, as were pts with breast or squamous lung cancer who had received taselisib 4 mg po daily on 28 d cycles until progression or intolerable toxicity. Staging was every 2 cycles. The primary endpoint was objective response (OR); secondary endpoints were PFS, 6-month PFS, and predictive biomarkers. **Results:** 65 pts (enrolled 3/2016-6/2017) received 1 dose of study therapy. 45 tumor types were represented; 38% of pts had > 3 prior lines of therapy. There were no ORs, but prolonged stable disease was observed (estimated PFS6 rate 27%, 90% CI 19%-39%), and 2 pts remain on study > 1 yr. The most common toxicities were fatigue (38%), diarrhea (38%) and nausea (34%); all predominantly grade 1-2, with 2% of pts requiring dose reductions, and 11% discontinuing taselisib because of toxicity. No hyperglycemia was observed. Clinical data will be presented at the meeting.

**Conclusions:** Taselisib was well tolerated. Clinical activity was observed in HER2 amp non breast and gastric/GEJ adenoca pts warranting further study either alone or in combinations particularly in some histologies such as salivary gland tumors. Clinical trial information: NCT01351728.

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**102**

Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-activated cancers. First Author: Alexandra E. Dhion, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Multikinase inhibitors (MKIs) have limited activity in RET fusion-positive (+) and RET-mutant cancers, questioning the therapeutic potential of these targets. LOXO-292 selectively targets RET and has preclinical activity against activating RET fusions/mutations, potential resistance mutations, and brain metastases.

**Methods:** This global phase 1 study of patients for pts w/ advanced solid tumors included RET fusion+ NSCLC and papillary thyroid cancer (PTC), RET-mutant medullary thyroid cancer (MTC), and any other cancer w/ these alterations. Pts were dosed orally in 28-day cycles. Dose escalation followed a 3+3 design. The primary endpoint was MTD determination. Secondary endpoints included safety, overall response rate (ORR, REGIST 1.1) and duration of response (DoR). **Results:** As of 05-Jan-18, 57 pts were treated at 7 doses (20 mg QD–160 mg BID), including 35 RET fusion+ tumors (27 NSCLC, 7 PTC, 1 pancreatic) and 20 RET-mutant MTCs. 67% were MKI pre-treated (median 1, range 1-4; included pts w/ acquired MKI resistance). No DLTs were observed. The MTD was not reached, AE (+10% of pts were fatigue (16%), diarrhea (16%) and dyspnea (12%); most were grade 1-2. No AE > grade 3 were attributed to LOXO-292. The ORR in evaluable RET fusion+ pts was 69% (95% CI 50%-84%, n = 22/32, 11 pending confirmation, 9/13 MKI-naive, 13/20 MKI pretreated): 65% (n = 17/26) in NSCLC and 83% (n = 3/3) in PTC. 84% (27/32) had radiographic tumor reduction (range -19% to -67%). NSCLC responses occurred independent of upstream partner when known (9/13 KIF5B vs 7/9 non-KIF5B) and included 3 pts w/ baseline brain metastases. Tumor reduction was achieved in 79% of MTC pts (n = 11/14 evaluable, range -9% to -45%), including 2 PRs, 1 in a patient w/ a hereditary RET V804Q garynoma mutation treated w/ 3 prior MKIs. 78% (n = 11/14) of pts had a ≥50% decrease in serum calcitonin (for ≥4 weeks). Most pts (n = 52/ 57) remained on treatment. The median DoR was not reached (all responses ongoing, longest > 6 months). **Conclusions:** LOXO-292 was well-tolerated and had marked antitumor activity in pts w/ RET-activated cancers, including those w/ resistance to prior MKIs and brain metastases. Rapid development w/ registrations is planned. Clinical trial information: NCT03151728.

**103**

Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Impact of next-generation sequencing (NGS) on treatment selection in acute myeloid leukemia (AML). First Author: Rita Elias Assi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Until recently, therapy options for AML patients (pts) were limited. The advent of NGS and novel targeted agents raise the question of how broader use of testing will impact treatment and outcomes. **Methods:** From October 2012 to June 2016, we included 1470 AML pts with available NGS-based detection of somatic mutations. 17 genes (ALK, CSF1R, FOPRI, FLT3, IDH1/2, JAK2, KDR, KRAS/NRAS, NPM1, PDGFRA, PTPN11, RET and TP53) were considered potentially actionable due to the possibility to be directly or indirectly targeted with standard or investigational agents. **Results:** Of the 1271 treated pts, 982 (77%) had a median of 2 actionable mutations (AMs) (1-5); TP53 (n = 241; 16%), IDH2 (n = 240; 16%), IDH1 (n = 238; 16%), FLT3 (200; 14%), NPM1 (n = 195; 13%), KRAS (n = 175; 12%), JAK2 (103; 7%), 69% (n = 316; 25%) of pts had PFS > 6 mo. PIK3CA mutation independent of histology is an insufficient predictor of taselisib activity. Associations of individual histologies and PIK3CA mutation subtypes with PFS may be worthy of further study. Clinical trial information: NCT02465060.
Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC).

**Background:** Combining immune-checkpoint inhibitors with chemotherapy has shown high response rates in patients (pts) with metastatic TNBC. Therefore, we evaluated the addition of durvalumab, an anti-PD-L1 checkpoint inhibitor, to standard neoadjuvant chemotherapy in pts with primary TNBC.

**Methods:** GeparNuevo randomized pts to durvalumab (D) 1.5 g i.v. or placebo (P) every 4 weeks (wks) + D/placebo plus nab-paclitaxel (nP) 125 mg/m² weekly for 12 wks, followed by D/placebo plus epirubicin/cyclophosphamide (EC) q2 wks for 4 cycles. Randomization was stratified by stromal tumor infiltrating lymphocyte (sTILs) (low (=10%), intermediate (11-59%), high (=60%), Pts with primary cT1b-cT4a-d disease, centrally confirmed TNBC and sTILs status were included. Primary objective compares pCR (ypT0 ypN0) rates. Secondary objectives are pCR rates in stratified subpopulations and according to other pCR definitions; response rates; breast conservation rate; toxicity; compliance and survival. Sample size was planned assuming a pCR rate of 48% for placebo based on historical historic and our results and 66% for D (as clinically meaningful benefit), requiring 158 pts to show superiority of D (2-sided α=0.02, 80% power). Assuming a 10% drop-out rate, randomization of 174 pts was planned. Results: A total of 174 pts were enrolled between June 2016 and September 2017 and all pts had completed treatment. Median age was 55 years (range: 36-71) and 68% were female, 44% cT1, 49.7% cT2, 3.5% cT3, 2.3% cT4; 83.3% G3 and 31.4% cN-positive tumors assessed by sonography; sTILs categories were 37.9% low, 47.7% intermediate, and 14.4% high; median Ki67 was 49.0% (range 3.0%-96.0%). A total of 86 SAEs and 65 immune related AEs of special interest (irAESIs) were reported. 44% of pts had at least one irAE. OS was not significantly different between D and P arms. 84 of 174 pts (48.3% 95%CI [40.7-56.0]) had a pCR. Conclusions: Combination of chemotherapy with durvalumab/placebo yielded high pCR rate in TNBC. Treatment was feasible. Unblinded results will be presented at the meeting. Funding and drug was provided by AstraZeneca and Celgene. Clinical trial information: NCT02685059.

**Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC).**

First Author: Sibylle Loibl, German Breast Group (GBG), Neu-Isenburg, Germany

**Background:** Breast Group (GBG), Neu-Isenburg, Germany

**Methods:** GeparNuevo randomized pts to durvalumab (D) 1.5 g i.v. or placebo (P) every 4 weeks (wks) + D/placebo plus nab-paclitaxel (nP) 125 mg/m² weekly for 12 wks, followed by a biopsy and D/placebo plus nab-paclitaxel (nP) 125 mg/m² weekly for 12 wks, followed by D/placebo plus epirubicin/cyclophosphamide (EC) q2 wks for 4 cycles. Randomization was stratified by stromal tumor infiltrating lymphocyte (sTILs) (low (=10%), intermediate (11-59%), high (=60%), Pts with primary cT1b-cT4a-d disease, centrally confirmed TNBC and sTILs status were included. Primary objective compares pCR (ypT0 ypN0) rates. Secondary objectives are pCR rates in stratified subpopulations and according to other pCR definitions; response rates; breast conservation rate; toxicity; compliance and survival. Sample size was planned assuming a pCR rate of 48% for placebo based on historical historic and our results and 66% for D (as clinically meaningful benefit), requiring 158 pts to show superiority of D (2-sided α=0.02, 80% power). Assuming a 10% drop-out rate, randomization of 174 pts was planned. Results: A total of 174 pts were enrolled between June 2016 and September 2017 and all pts had completed treatment. Median age was 55 years (range: 36-71) and 68% were female, 44% cT1, 49.7% cT2, 3.5% cT3, 2.3% cT4; 83.3% G3 and 31.4% cN-positive tumors assessed by sonography; sTILs categories were 37.9% low, 47.7% intermediate, and 14.4% high; median Ki67 was 49.0% (range 3.0%-96.0%). A total of 86 SAEs and 65 immune related AEs of special interest (irAESIs) were reported. 44% of pts had at least one irAE. OS was not significantly different between D and P arms. 84 of 174 pts (48.3% 95%CI [40.7-56.0]) had a pCR. Conclusions: Combination of chemotherapy with durvalumab/placebo yielded high pCR rate in TNBC. Treatment was feasible. Unblinded results will be presented at the meeting. Funding and drug was provided by AstraZeneca and Celgene. Clinical trial information: NCT02685059.

**Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC).**

First Author: Luis G. Paz-Ares, University Hospital 12 de October, Madrid, Spain

**Background:** Pembro plus pembrolizumab and carboplatin resulted in superior objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) for untreated pts with non-sq NSCLC. Pembro is active in sq NSCLC, so combining with chemo is a rational next step. Methods: KEYNOTE-407 (NCT022775435) is a randomized, placebo-controlled, global study of 560 untreated pts with metastatic sq NSCLC with ECOG 0-1. Pts were stratified by type of taxane, PD-L1 (TPS <1% vs ≥1%), and site (East Asia vs other). Investigators chose taxane. Pts were randomized 1:1 to receive carboplatin 6 mg/m²/min and paclitaxel 200 mg/m² every 3 weeks or nab-paclitaxel 100 mg/m² weekly plus pembrol or saline placebo for 4 cycles followed by pembrol/ placebo for a total of 35 treatments. Imaging is sent for blinded independent central review (BICR) per RECIST 1.1. The primary endpoints are PFS by BICR and OS in the intent-to-treat population. Alpha is strictly controlled at 0.025 one-sided; PFS and OS each have 0.01. A key secondary endpoint is ORR by BICR in about the first 200 pts randomized with 0.005 alpha. A second interim analysis will be performed on PFS and OS when approximately 332 PFS events will have occurred. The hazard ratio (target 0.7) will be estimated using a strafied Cox regression model. The arms will be compared with a stratified log-rank test. Enrollment completed at the end of 2017. Results: In the first interim analysis, the initial 204 pts were randomized 101 to pembrol + chemo and 103 to placebo + chemo with median OS 7.7 vs 4.2 months (HR=0.67; 95% CI 0.44-1.01). Response rates were 71.2% vs 49.5% (HR=0.57; 95% CI 0.34-0.94). No new safety concerns were observed. Conclusions: Adding pembrol almost doubled the ORR of chemo for pts with untreated metastatic sq NSCLC. Pembro + chemo has a tolerable safety profile. Results from a second interim analysis may be available prior to the meeting. Clinical trial information: NCT02775435.

**Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC).**

First Author: Georgina V. Long, Department of Medical Oncology and Translational Research, Melanoma Institute Australia, The University of Sydney, Mater Hospital and Royal North Shore Hospital, Sydney, Australia

**Background:** In a phase 1/2 study, the combination of E, a selective oral inhibitor of the IDO1 enzyme, plus P, a PD-1 inhibitor, suggested promising antitumor activity with minimal additive toxicity. ECHO-301/KEYNOTE-252 (NCT02752074) is a phase 3, randomized, double-blind study evaluating the efficacy and safety of E + P vs placebo + P in pts with untreated unresectable or metastatic melanoma. Methods: Pts had histologically confirmed unresectable stage III or IV melanoma and were treatment naive for advanced or metastatic disease, except for pts with the BRAF V600 mutation who could have received prior BRAF/MEK therapy. Pts were stratified by PD-L1 expression and BRAF mutation status (BRAF mutant with prior BRAF-directed therapy, BRAF mutant without prior BRAF-directed therapy, and BRAF wild type) and randomized 1:1 to E 100 mg Bid + P 200 mg Q3W or matched E placebo + P 200 mg Q3W. Response was assessed per RECIST v1.1 and in irRECIST (both by central review). The primary endpoints were PFS per RECIST v1.1 and OS. Secondary endpoints were ORR per RECIST v1.1, duration of response, and safety. This is the final analysis for PFS and interim analysis for OS. Results: A total of 706 pts were randomized (354 to E + P and 352 to placebo + P); 72.5% of pts were PD-L1 positive, 33% BRAF mutant (12.2% received prior BRAF/MEK therapy). Median follow-up was 14 mos. E + P did not result in a significantly longer FFS vs placebo + P (median 4.7 vs 4.9 mos; HR=1.00; CI 0.83-1.21; P=0.517). PFS rate at 12 mos was 37% in both groups. Findings were consistent across PD-L1 and BRAF subgroups. OS was not expected to reach statistical significance based on the results of this interim analysis (HR=1.13; CI 0.86-1.49; P=0.807). The OS rate at 12 mos was 74% in both groups. ORR was 34.2% and 31.5% in the E + P and placebo + P groups, respectively. Grade ≥3 treatment-related AEs occurred in 21.8% of patients receiving E + P and 17.0% receiving placebo + P. Conclusions: The addition of E to P did not result in a statistically significant OS benefit for patients with unresectable or metastatic melanoma. The safety profile was consistent with that observed in previously reported studies of this combination. Clinical trial information: NCT02752074.
A comparative clinical study of PF-06439535, a candidate bevacizumab biosimilar, and reference bevacizumab, in patients with advanced non-squamous non-small cell lung cancer. First Author: Mark A. Sosnicki, Florida Hospital Cancer Institute, Orlando, FL

**Background:** This ongoing, double-blind, randomized, global clinical trial evaluated the efficacy, safety, and immunogenicity of PF-06439535 vs. reference bevacizumab sourced from the EU (bevacizumab-EU), in combination with paclitaxel (P) and carboplatin (C), as a first-line therapy in patients with advanced non-squamous non-small cell lung cancer (NSCLC). Methods: Eligible pts were randomized 1:1 to PF-06439535 bevacizumab-EU plus P or C on Day 1 of every 3-week (wk) cycle followed by PF-06439535 or bevacizumab-EU blinded monotherapy until disease progression or unacceptable toxicity. The primary objective was to compare objective response rate (ORR) by wk 19 between treatment arms. Secondary objectives included safety, 1 year (yr) PFS, 1 yr survival rate and immunogenicity. Results: 719 pts were randomized: PF-06439535 (n = 358) and bevacizumab-EU (n = 361). The majority of patients were male (65%) with a median age of 61y and newly diagnosed Stage IV NSCLC (76%). For the primary endpoint, relative risk of ORR was 1.015. The 90% confidence interval (CI), 0.866-1.17, was contained within the pre-specified therapeutic equivalence margin of 0.73-1.37. Secondary endpoints further support similarity between the 2 treatment arms (Table). Incidence of treatment-emergent adverse events (AEs) (all-causality) was similar (PF-06439535: 96.6%) and (bevacizumab-EU: 96.1%). AE results indicate no clinically meaningful differences between the 2 arms for arterial thromboembolic event (TE)/venous TE events, bleeding events, hypertension, GI perforation, and proteinuria. Conclusions: In patients with advanced non-squamous NSCLC, PF-06439535 and bevacizumab-EU showed similar ORR (primary endpoint) PFS, OS, safety and immunogenicity. Clinical trial information: NCT02364999.

**Efficacy endpoints.**

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<th>PF-06439535</th>
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<tr>
<td>ORR</td>
<td>45.3% (95%: 40.01%, 50.57%)</td>
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<tr>
<td>1 yr PFS rate</td>
<td>29.4% (95% CI: 23.2%, 35.9%)</td>
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<tr>
<td>1 yr survival rate</td>
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**Clinical Science Symposium, Mon, 9:45 AM-11:15 AM**

**Comparison of efficacy and safety of biosimilar filgrastim in a RCT (PIONEER) and real-world practice (MONITOR-GCSF).** First Author: Nadia Sabarbe, Brustzentrum der Universität München (LMU), Munich, Germany

**Background:** Sandoz biosimilar filgrastim has been approved in the US since 2015 for several indications including prevention of chemotherapy-induced neutropenia. US approval was based on results from PIioneer, a phase III confirmatory trial in breast cancer (BC) patients receiving chemotherapy randomized to either Sandoz biosimilar or reference filgrastim (Blackwell et al, JAMA 2015;294:1648-53). BC is considered a resistant tumor type to demonstrate filgrastim biosimilarity. Post-approval, safety of Sandoz biosimilar filgrastim has been monitored in MONITOR-GCSF, an observational study in patients with solid or hematological malignancies undergoing chemotherapy (Gascón et al. Support Care Cancer 2016;24:911-25). The results from PIioneer were compared to the MONITOR-GCSF BC cohort to evaluate Sandoz biosimilar filgrastim in a RCT and a real-world practice setting in BC. Methods: Results were compared for corresponding endpoints. Patient- and cycle-level comparisons were made between patients in PIioneer, and all BC patients receiving biosimilar filgrastim in MONITOR-GCSF. Results: There were 217 evaluable patients in PIioneer and 466 in MONITOR-GCSF. Patients were generally younger in PIioneer (mean age, years ± SD: 48.9 ± 11.3 vs 56.2 ± 11.7). Patient level results are reported. Febrile neutropenia (FN) was reported in 5.1% (PIioneer) vs 6.2% (MONITOR-GCSF). All grade adverse events (AEs) were generally reported at a higher level in PIioneer than MONITOR-GCSF, including musculoskeletal/connective tissue disorders (PIioneer: 261, MONITOR-GCSF: 20) (absolute numbers)); infections/infestations (PIioneer: 31, MONITOR-GCSF: 3); skin/subcutaneous tissue disorders (PIioneer: 258, MONITOR-GCSF: 5) and general disorders/administration site conditions (PIioneer: 673, MONITOR-GCSF: 7). Cycle level results were generally similar between studies. Conclusions: Sandoz biosimilar filgrastim prevented FN in a RCT and in real-world practice in BC patients receiving (neo-)adjuvant chemotherapy. In real-world practice, experiencing AEs may be perceived as unavoidable in order to achieve clinical efficacy. Thus Phase III RCTs remain an effective tool to assess and monitor AEs.

**Clinical Science Symposium, Mon, 9:45 AM-11:15 AM**

Biosimilar trastuzumab-dkst monotherapy versus trastuzumab monotherapy after combination therapy: Toxicity, efficacy, and immunogenicity from the phase 3 Heritage trial. First Author: Alessia Manikhas, City Clinical Oncology Dispensary, St. Petersburg, Russian Federation

**Background:** The Heritage trial is a multicenter, double-blind, randomized, parallel-group, phase 3 study (NCT02472964) evaluating efficacy and safety of trastuzumab-dkst (Ogivri), a trastuzumab biosimilar, vs trastuzumab, in combination with taxane as first-line therapy for patients with HER2+-metastatic breast cancer. The primary endpoint, overall response rate on combination therapy at week 24, was previously reported (Rugo et al, JAMA 2017). Methods: Eligible patients were randomized 1:1:1 to trastuzumab-dkst or trastuzumab, combined with taxane. After 24 weeks, patients with responding or stable disease received monotherapy as per randomization. Here, we describe secondary endpoints of safety and immunogenicity during monotherapy and cumulative through 48 weeks; progression-free survival (PFS) and event-based overall survival (OS) will be presented in the future. Results: 500 patients were randomized, 342 continued treatment after 24 weeks, and 214 continued through 48 weeks. Treatment-emergent adverse event (TEAE) rates during monotherapy were similar (trastuzumab-dkst, 54.7%; trastuzumab, 60.1%); most were low severity. Grade ≥3 TEAEs were more frequent with trastuzumab (11.7%) vs trastuzumab-dkst (6.7%); serious TEAEs were similar (trastuzumab-dkst, 2.8%; trastuzumab, 2.5%). When assessed over 48 weeks of combination and monotherapy, cumulative rates of TEAEs of special interest were similar for pulmonary events, significant cardiac disorders, and infusion-related events (trastuzumab-dkst, 13.0% vs. 13.0%); trastuzumab, 12.2%, 4.1%, and 8.1%, respectively). Immunogenicity and incidence of left ventricular ejection fraction <50% ±10 time baseline and ≥10% reduction at week 48 were similar between groups (trastuzumab-dkst, 3.9% and 3.6%; trastuzumab, 4.4% and 2.8%, respectively). No new safety signals were detected in both week 48, mean PFS was 11.1 months and 95% for trastuzumab-dkst and trastuzumab, respectively. 11.3 vs 56.2

**Clinical Science Symposium, Mon, 9:45 AM-11:15 AM**

Treatment approach for non-Hodgkin lymphoma patients since first biosimilars of rituximab were approved in EU. First Author: Alessandra Franceschetti, Ipsos Healthcare, London, United Kingdom

**Background:** Non-Hodgkin Lymphoma (NHL) is the tenth most common cancer in Europe. In 2017, the first biosimilars of rituximab were approved in Europe to treat NHL. Using real world data from Ipsos’ Global Oncology Monitor, this study explores prescription patterns of rituximab biosimilars in EUS to determine if biosimilars are favoured over branded versions for certain patient types. Methods: An online multi-country, multi-centre medical chart review study of NHL patients; 97 physicians provided de-identified data on 640 patients treated with anti-cancer drugs in France (117), Germany (73), Italy (117), Spain (136) and UK (197) between July and September 2017. Physicians were geographically representative and screened for treatment involvement level and number of patients managed per month. Reporting on patients seen in consultation, they provided date of diagnosis, current and historic treatment, and reasons for prescribing/discontinuing anti-cancer drug treatment. Data on patients treated with and without a rituximab biosimilar were compared using descriptive statistics. Results: Of the 640 NHL patients studied, 77% were treated with a regimen that included branded rituximab. Prescribing of rituximab biosimilars was highest in Germany and UK (14% and 13%, respectively). For recently-initiated patients in Germany and UK, prescription of biosimilars increased towards 2nd and 3rd lines of treatment (11L: 11%; 2L:18%; 3L:30%). A profile comparison of German and UK patients treated with a rituximab biosimilar (27 vs. branded rituximab (179) shows that the former is more likely to have: ECOG 0-1 (93% vs. 82%); no comorbidities affecting cancer drug treatment (52% vs. 31%); indolent vs. aggressive status (70% vs. 52%); and Follicular Lymphoma as sub-type of cancer (56% vs. 35%). Conclusions: Physicians responsible for the drug treatment of NHL patients in EUS have begun prescribing rituximab biosimilars. This seems to be more frequent after first line treatment, in fitter patients and for patients with indolent disease and Follicular Lymphoma.

**Total EUS France Germany Italy Spain UK**

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Adjuvant denosumab in early breast cancer: Disease-free survival analysis of 3,425 postmenopausal patients in the ABCSG-18 trial. First Author: Michael Grünert, Breast Care Center, Medical University of Vienna, and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria

Background: Adjuvant aromatase inhibitors (AI) are standard of care for postmenopausal women with hormone receptor-positive (HR+) early stage breast cancer but cause osteoporosis and fractures. ABCSG-18 showed previously that adjuvant denosumab significantly reduces clinical fractures (primary endpoint, HR = 0.5, p < 0.001, Lancet 2015). Here, we present the impact of adjuvant denosumab on disease-free survival. Patients and Methods: 3,425 postmenopausal patients with early HR+ BC receiving adjuvant AI were recruited in 58 trial centers into this prospective, double-blind, placebo-controlled, phase-III trial. Patients were randomized 1:1 to receive either denosumab 60mg s.c. (N = 1712) or placebo (N = 1713) q6 months during AI therapy. We here present results of ABCSG-18’s secondary endpoint disease-free survival (DFS), including relevant subgroup and sensitivity analyses (accounting for cross-over either by censoring or by using a rank preserving structural failure time model). Results: After a median follow-up (FU) of 72 months, 287 events occurred in the placebo group, and 240 in the denosumab group. DFS was significantly improved in the denosumab arm (HR = 0.823, 95% CI 0.69-0.98, Cox p = 0.026*). In the denosumab group, DFS was 89.2% (95% CI 87.6-90.7) at 5 years and 80.6% (78.1-83.1) at 8 years of FU, compared to 87.3%, (85.7-89.0) at 5 years and 77.5% (74.8-80.2) at 8 years for patients who received placebo. Similar results were obtained from sensitivity analyses where DFS was 89.8% (87.8-91.8) at 5 years and 81.2% (78.5-83.7) at 8 years for patients who received placebo. These results were obtained from sensitivity analyses where DFS was 89.8% (87.8-91.8) at 5 years and 81.2% (78.5-83.7) at 8 years for patients who received placebo. Based on these results and the previously reported dramatic reduction of fractures, adjuvant denosumab 60mg s.c. q6 months should be offered to postmenopausal HR+ breast cancer patients receiving AI. * descriptive, without controlling for multiplicity. Clinical trial information: EudraCT #: 2005-005275-15.

Role of adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain menstruating after chemotherapy: The ASTRA study. First Author: Woo Chul Noh, KRAMS, Seoul, Republic of Korea

Background: The role of adding ovarian function suppression (OFS) to tamoxifen (T) for premenopausal patients with breast cancer after completing chemotherapy is uncertain. The prospective randomized phase III trial was conducted to evaluate the efficacy of adding OFS to T in patients with hormone receptor-positive breast cancer who remain menstruating after chemotherapy. Patients and Methods: Enrolled 1483 premenopausal women (aged 44-55 years) with estrogen receptor-positive breast cancer who were treated with definitive chemotherapy and had residual disease after chemotherapy. Ovarian function was assessed every 6 months for 2 years since enrollment based on follicular-stimulating hormone levels and menstruation history. If ovarian function was confirmed to be premenopausal at each visit, the patient was randomized to receive 5 years of T (T-only group) or 5 years of T plus 2 years of OFS by monthly goserelin (T + OFS group). A total of 1282 patients was randomly assigned. Disease-free survival was defined as the time from enrollment to the detection of recurrence of breast cancer, contralateral breast cancer, secondary malignancy, or death by any cause. Results: After a median follow-up of 63 months, the estimated disease-free survival rate at 5 years was 91.1% in the T-only group and 87.5% in the T+OFS group (hazard ratio 0.310, 95% CI 0.102 to 0.941; P = 0.029). Conclusions: Ovarian function needs to be monitored for at least 24 months after completing chemotherapy to establish eligibility for OFS. Adding 2 years of OFS to T significantly improved disease-free survival as compared to T alone in those who remained premenopausal or resumed ovarian function after chemotherapy. Clinical trial information: NCT00912548.

Adjuvant denosumab in early breast cancer: First results from the international multicenter randomized phase III placebo controlled-D-CARE study. First Author: Robert E. Coleman, University of Sheffield, Weston Park Hospital, Sheffield, United Kingdom

Background: Denosumab (Dmb) is a potent RANK ligand inhibitor approved for the management of treatment induced bone loss in early breast (EBC) and prevention of skeletal morbidity associated with metastatic bone disease. Preclinical data suggested that Dmb could prevent development of bone metastases. This trial evaluated the addition of Dmb to standard (neo) adjuvant therapy for high-risk EBC patients (pts). Methods: 4500 pts with EBC (93.5% node+) from 407 centers were randomized to standard loco-regional and (neo)adjuvant therapy plus either Dmb 120mg sc or matching placebo (P) monthly x 6 then 3 monthly for up to 5 years. In addition to routine clinical follow-up, pts underwent annual CT and bone scan imaging to screen for recurrence. Primary endpoint was bone metastasis free survival (BMFS) defined as first bone metastatic event confirmed by central imaging review or death from any cause. Secondary endpoints included disease free survival (DFS), DFS in the postmenopausal (PM) subgroup, overall survival (OS) and safety. Results: Patient groups were balanced for baseline characteristics with median age 51, 77% ER+, 20% HER2+ and use of anthracycline and/or taxane chemotherapy in 95.9%. No benefits for the addition of Dmb were seen at a time-driven analysis performed after a median follow-up of 67 months that allowed for the full 5 years of treatment in all pts. Hazard ratio (HR) for BMFS (597 events) was 0.97, 95% CI 0.82-1.14, p = 0.70 and 1.04, 95% CI 0.91-1.19, p = 0.36 for OS (412 events) similar in both groups (HR = 1.03, 95%CI 0.85-1.25). Denomab did not improve BMFS, DFS or OS in the PM subset (n = 2149). Exploratory analysis of time to bone metastases as first recurrence suggested benefit for Dmb (HR = 0.76, 95%CI 0.59-0.97) for this endpoint. Time to second bone fracture was reduced with Dmb compared to P (HR = 0.79, 95%CI 0.63-0.99). No OS benefit was seen in the tamoxifen group (HR = 0.91, 95%CI 0.71-1.18). DFS in the Dmb group was 89.6% (95% CI 87.3-91.1) vs 87.5% (95% CI 85.6-89.3) in the P group. Conclusions: Dmb does not reduce breast cancer recurrences or deaths in EBC pts receiving optimal loco-regional and standard of care systemic adjuvant therapy. Clinical trial information: NCT01077154.
PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3

PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3

Background: EORTC trial 22922-10925 investigates whether internal mammary and medial supraclavicular (IM-MS) lymph nodes (LN) irradiation improves outcome for stage I-III breast cancer patients (Clinicaltrials.gov NCT00002851). The 10 years analysis showed an improvement of 3.0% in metastases-free survival (p = 0.02) and of 1.6% in overall survival (p = 0.056). Toxicity was limited and no increased lethal side effects were seen. This is the second of 3 scheduled analyses, at 15-year follow-up. Methods: Eligible patients had involved axillary nodes and/or a medially located primary tumour. Randomisation was to irradiate or not the IM-MS. The final trial design aimed at detecting a 4% increase in 10-year overall survival (OS) (from 75 to 79%, HR = 0.82) with 2-sided unadjusted Log-rank test at the 5% significance level. Secondary endpoints are disease-free survival (DFS), metastases-free survival (MFS) and cause of death. Two long-term analyses were planned, at respectively 15 and 20 years of follow-up.

Results: Between 1996 and 2004, 4004 patients were randomized in 43 centres. Median age was 54 years; 59.0% were postmenopausal; 55.6% had involved axillary LN; 32.0% and 14.2% had stage I, II and III, respectively. Nearly all LN-positive (99.0%) and 66.3% of LN-negative patients received adjuvant systemic treatment. At a median follow-up of 15.7 years, 1117 patients died. At 15 years, overall survival was 73.2% in the nodal-irradiation group and 70.8% in the control group (HR = 0.95; 95%CI, 0.87-1.06; p = 0.25). In the nodal-irradiation group, IM-MS LN occurred in 1.8% vs. 3.1% of patients. Distant disease-free survival rate was 70.1% vs. 68.1% (HR = 0.92; 95%CI, 0.83-1.04; p = 0.178), breast-cancer mortality was 15.8% vs. 19.7% (HR = 0.81; 95%CI, 0.69-0.94; p = 0.005). Probability of breast cancer recurrence was 24.5% vs. 27.1% (HR = 0.89; 95%CI, 0.79-1.01; p = 0.07). The IM-MS analysis for the incidence of second malignancies, contralateral breast cancer or cardiovascular deaths. Conclusions: The 15-years results show a significant reduction of breast cancer mortality and breast cancer recurrence by internal mammary and supraclavicular lymph node irradiation in stage I-III breast cancer. However, this is not converted in improved overall survival without a clear explanation for this. Subgroup analyses and continued follow-up will be performed to better define patients that may benefit from this treatment and define the causes of death. Clinical trial information: NCT00002851.

PERSEPHONE is a phase II, multicentric, non-profit study for postmenopausal, operable HER2+/HR+ BC pts. Eligible pts received 2 wks window therapy with L, then underwent re-biopsy for Ki67 evaluation. Pts classified as Ki67 responders (relative Ki67 reduction ≥20% from baseline) continued L and started trastuzumab (T) and pertuzumab (P) q21 days for 5 cycles. Pts without Ki67 response discontinued L and started wks paclitaxel for 13 wks combined with P and T. Primary aim was breast and axillary pCR. At least 8 pCR in 43 Ki67 responders were required to satisfy the study hypothesis in a two-step Simon’s design. Correlative analyses included: PAM50, TILs, PIK3CA. Results: 64 pts from 8 centers were enrolled: median age 63 yrs (49-83 yrs); stage IIA 67%, IIB 33%; IIA 9%. Median (range) ER, PgR and ki67 expression: 90% (10-100), 14% (0-100); 30% (7-90). Median TILs level 10% (Q1-20% 15%). PIK3CA mutation was reported in 25% of the cases. 44 pts (69%) achieved a Ki67 response after 2 wks L and underwent surgery after L+T+P (breast conserving 66%; mastectomy 34%). A pCR was observed in 9 cases (20.5%), pCR rate was significantly higher in HER2-E vs other subtypes (45.5% vs 13.8%, p = 0.042). Intrinsic subtype was significantly associated with ki-67 response (p < 0.001).

The PerELISA study, aimed to evaluate the efficacy of a de-escalated, chemotherapy-free adjuvant regimen in HER2+ and/or HR+ patients (pts) selected on the basis of Ki67 response after a short course letrozole (L). Methods: PerELISA is a phase II, multicentric, non-profit study for postmenopausal, operable HER2+HR+ BC pts. Eligible pts received 2 wks window therapy with L, then underwent re-biopsy for Ki67 evaluation. Pts classified as Ki67 responders (relative Ki67 reduction ≥20% from baseline) continued L and started trastuzumab (T) and pertuzumab (P) q21 days for 5 cycles. Pts without Ki67 response discontinued L and started wks paclitaxel for 13 wks combined with P and T. Primary aim was breast and axillary pCR. At least 8 pCR in 43 Ki67 responders were required to satisfy the study hypothesis in a two-step Simon’s design. Correlative analyses included: PAM50, TILs, PIK3CA. Results: 64 pts from 8 centers were enrolled: median age 63 yrs (49-83 yrs); stage IIA 67%, IIB 33%; IIA 9%. Median (range) ER, PgR and ki67 expression: 90% (10-100), 14% (0-100); 30% (7-90). Median TILs level 10% (Q1-20% 15%). PIK3CA mutation was reported in 25% of the cases. 44 pts (69%) achieved a Ki67 response after 2 wks L and underwent surgery after L+T+P (breast conserving 66%; mastectomy 34%). A pCR was observed in 9 cases (20.5%), pCR rate was significantly higher in HER2-E vs other subtypes (45.5% vs 13.8%, p = 0.042). Intrinsic subtype was significantly associated with ki-67 response (p < 0.001).

The PerELISA study, aimed to evaluate the efficacy of a de-escalated, chemotherapy-free adjuvant regimen in HER2+ and/or HR+ patients (pts) selected on the basis of Ki67 response after a short course letrozole (L).
Her2-enriched subtype and ERBB2 mRNA as predictors of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer: A combined analysis of TBCRC006/023 and PAMELA trials. First Author: Aleix Prat, Department of Medical Oncology, Hospital Clinic, Barcelona, Spain.

Background: HER2-Enriched (HER2-E) intrinsic subtype within HER2-positive breast cancer is characterized by high expression of ERBB2 and low expression of ERBB1. Here we retrospectively evaluated the value of the HER2-E subtype and ERBB2 mRNA expression alone to predict pathological complete response (pCR) in tumor samples from PAMELA and TBCRC006/023 trials.

Methods: All patients who had HER2-positive early breast cancer and were treated with neoadjuvant lapatinib and trastuzumab. Patients with hormone receptor-positive tumors were also treated with letrozole or tamoxifen. In PAMELA (NCT01973660), 151 patients were treated for 18 weeks. TBCRC006 (NCT00548184) treated 66 patients for 12 weeks and TBCRC 023 (NCT00999804) randomized 97 patients to 12 vs. 24 weeks of treatment. pCR was defined as no residual invasive carcinoma in the breast. Baseline intrinsic subtypes and ERBB2 mRNA expression were determined using the nCounter-based PAM50 predictor. ERBB2 expression was dichotomized as low (lowest 1/3) vs high (highest 1/3) as used in PAMELA. Results: Two-hundred and sixty-five tumors (84.4%) were profiled; 65.7% were classified as HER2-E. pCR was more likely to occur if HER2-E (35.1% vs. 9.3%; odds ratio [OR] = 4.92; 95% CI 2.45-9.90; P = 0.0001) or ERBB2-low (36.1% vs. 8.2%; OR = 6.51; 95% CI 2.96-14.31; P < 0.001). HER2-E subtype represented 84.0% and 46.0% of ERBB2-high and ERBB2-low groups, respectively. Rates of pCR in HER2-E/ERBB2-high, nonHER2-E/ERBB2-high, HER2-E/ERBB2-low, and nonHER2-E/ERBB2-low groups were 45.0%, 15.8%, 11.1%, and 10.5%, respectively. Finally, the HER2-E/ERBB2-high group independently predicted pCR (adjusted OR = 6.0; 95% CI[3.13-11.8]; P < 0.001).

Conclusions: Combining HER2-E subtype and ERBB2 mRNA levels better identifies anti-HER2 sensitivity than each variable alone in HER2-positive breast cancer. The combined biomarker identified nearly 50% of patients with pCR to an all-biologic regimen, and if validated could provide a means for rational therapeutic de-escalation.
Factors associated with lymphedema in patients/women with node positive breast cancer treated with neoadjuvant chemotherapy and axillary dissection on a prospective clinical trial. First Author: Judy Caroline Boughey, Mayo Clinic, Rochester, MN

Background: Lymphedema (LE) is a known complication of breast cancer treatment. Herein we report the factors associated with LE after neoadjuvant chemotherapy (NAC) and axillary dissection (ALND) in the ACOGOG Z1071 (Alliance for Clinical Trials in Oncology) trial of patients with node-positive breast cancer. Methods: Patients who consented to the LE substudy underwent prospectively arm measurements and symptom assessment after completion of NAC and at 6, 12, 18, 24, and 36 months after surgery. All patients had node-positive disease and underwent ALND after NAC. LE was defined based on symptoms of arm heaviness or swelling (LE-symptoms) or by arm volume increase of >10% (LE-V10); severe LE was defined as volume increase >20%. Kaplan-Meier methods were used to determine cumulative incidence. Results: 488 of 701 eligible patients consented to the LE substudy. Cumulative incidence of LE at 3 years was 37.8% (33.0-43.1%) by LE-symptoms; 58.6% (53.4-64.4%) by LE-V10; 37.2% (32.2-42.9%) for severe LE. In a univariable analysis, patient age, type of chemotherapy regimen used, breast surgical procedure, number of positive lymph nodes, and use of adjuvant radiation were not associated with risk of LE. Incidence of LE-symptoms was higher in obese patients (BMI >30, p = 0.02) and patients with NAC duration >144 days (p = 0.02). An additional analysis showed that LE-V10 incidence was also higher with longer duration of NAC (p = 0.01). LE-V10 incidence was highest in patients with 30+ lymph nodes removed and lower when fewer lymph nodes were removed (p = 0.009). On multivariable analysis, obesity and length of NAC remained significant for LE-symptoms. Conclusions: Patient age, obesity, and NAC duration independently contribute to LE incidence after neoadjuvant chemotherapy for breast cancer. Further studies are needed to understand the underlying mechanisms of LE development and potential prevention strategies.
Molecular alterations and late recurrence in postmenopausal women with hormone receptor-positive node-negative breast cancer (BC): Results from the “SOLE” trial. First Author: Elena Guerini Rocco, Department of Pathology, European Institute of Oncology, Milan, Italy

Background: Women with hormone receptor-positive BC have an ongoing risk of relapse. We performed molecular analyses of primary BC from postmenopausal patients (pts) enrolled in the extended adjuvant intermittent letrozole (SOLE) trial to identify prognostic factors and potential targets. Methods: From 4884 pts enrolled, 3162 had FFPE tumor samples and were eligible. A case-cohort design selected 599 pts, and 499 DNA samples underwent next-generation sequencing of 35 and 19 actionable genes for mutation (SNV) and copy number gain (CNG) analyses. Correlations of SNV/CNG with clinicopathologic factors were analyzed. HRD/CNG association was assessed as per the cancer-free interval (BCFI) and distant recurrence free-interval (DRFI) were assessed using weighted proportional hazards models to obtain unbiased and consistent estimates representing the overall trial population. With 403 pts there was 90% power to detect a hazard ratio (HR) = 2.0 (SNV/CNG) vs. –; assuming a 40% median survival, with 0.05 two-sided significance level and adjusted standard error estimate from the weighed Cox model. Results: SNV and CNG data were available for 403 (81%) and 350 (70%) of 499 samples, respectively. 294 samples had ≥1 SNV or CNG; 132 had concurrent alterations. PIK3CA was the most frequently mutated gene (42%), followed by TP53 (32%), and alterations of FGFR1 (13%), MYC (8%), AKT1 (7%), TP53N (6%), FGFR1 (6%), CNG (4%), and BRCA1 (2%). HRD status was available for 438 pts. Mutations in PIK3CA, TP53, AKT1, and FGFR1 showed a gene set enrichment (GSE) score >24. Among HRD+ pts, 44% had concurrent alterations in PIK3CA, TP53, AKT1, and FGFR1 relative to HRD-. HRD status was associated with worse outcomes (BCFI: HR = 3.2; 95% CI, 1.5-6.9, p = 0.003; and DRFI: HR = 3.5; 95% CI, 1.6-7.7, p = 0.002). The results were consistent in multivariable models adjusting for clinicopathologic factors. Conclusions: We showed that pts with hormone receptor-positive node-negative BC with FGFR1 CNG had an increased risk of late recurrence despite extended therapy. FGFR1 analysis may improve the risk stratification in this population and represent a potential therapeutic target. Clinical trial information: NCT020553410.

519 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Evaluation of homologous recombination deficiency (HRD) status with pathological response to carboplatin +/- veliparib in BrighTNess, a randomized phase 3 study in early stage TNBC. First Author: Melissa L. Teili, Stanford University School of Medicine, Stanford, CA

Background: HRD status is significantly associated with a higher rate of response to neoadjuvant platinum-based therapy and improved PFS following adjuvant doxorubicin and cyclophosphamide (AC) chemotherapy. In BrighTNess, a randomized, phase 3 study in early stage TNBC, the addition of veliparib to carboplatin was associated with a higher pathological complete response (pCR) rate, with 95% CI = (0.6-45.7); Fisher’s exact test 1-sided p-value = 0.11. Conclusions: GES failed to improve rates of RCB 0-I in TNBC; however, in pts with resistant disease identified by US after AC, RCB 0-I rates were higher in pts treated with targeted therapy compared to chemo alone. Clinical trial information: NCT02276443.

520 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Residual cancer burden (RCB) as prognostic in the I-SPY 2 TRIAL. First Author: William Fraser Symmans, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: I-SPY 2 is a multicenter phase 2 trial in high risk stage I/II breast cancer (BC) using adaptive randomization within biomarker subtypes to evaluate novel treatment agents added to standard neoadjuvant chemotherapy (NAC) in different pathologic response (pathR) randomization arms. Residual cancer burden (RCB) quantifies the extent of residual disease (RD) for patients who did not achieve pathologic complete response (pCR = RCB>0). Methods: Local site pathologists reported RCB in the I-SPY 2 trial. We performed a pooled analysis of 678 patients in I-SPY 2 with RCB data and known follow-up (median 2.5 years). Cox models for event-free survival (EFS) were evaluated for RCB index (continuous) and RCB classes (hazard ratio; 95% CI) in all patients and in subtypes defined by hormone receptor (HR) and HER2 status. We separately compared experimental and control arms (Wilcoxon rank sum test) in a pooled analysis of RCB index (498 patients in total) from the first six treatment arms at time of randomization and “graduated” therapy based on ≥85% predicted probability of increasing pCR rate over control therapy in a future 300-patient phase 3 trial. Results: RCB index was prognostic overall (hazard ratio; 95% CI; 1.86; 1.62-2.14) and in each subtype: TNBC (2.09; 1.70-2.57, N = 224), HR-/HER2+ (2.91; 1.79-4.73, N = 134), and HR+/HER2- (2.08; 1.54-2.81, N = 251). Overall, estimates of 3-year EFS for RCB classes were: pCR 94%, RCB-I 87%, RCB-II 80%, RCB-III 62%. The distribution of RCB index decreased with graduating treatments, relative to control therapy, in TNBC (p < 0.001) and HER2+ (p = 0.03), but not in HR +/HER2- (p = 0.21). Conclusions: Atezolizumab + nab-paclitaxel, with or without bevacizumab, significantly improved EFS in patients who did not achieve pCR. Clinical trial information: NCT01042379.
521 Poster Session (Board #13), Sat, 8:00 AM-11:30 AM
Patient-reported function and symptoms in APHINITY: A randomized comparison of chemotherapy (C) + trastuzumab (H) + placebo (Pla) versus C + pertuzumab (P) as adjuvant therapy in T1N0M0 breast cancer (EBC). First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In APHINITY (NCT01358877), adding P to H + C significantly improved invasive disease-free survival in pts with HER2-positive EBC (von Minckwitz, NEJM 2017). Pt-reported health-related quality of life (HRQoL; symptoms of therapy, patient functioning, and global health status) was a secondary outcome, assessed by EORTC QLQ-C30, EORTC BR23, and EQ-5D 3L questionnaires. Methods: Pts received 1 year (18 cycles) of P or Pla and H + standard adjuvant C (3–4 cycles of anthracycline-based C followed by 3–4 cycles of taxane, or 6 cycles of docetaxel + carboplatin). Pts completed measures until recurrence or 36 months post-randomization (whichever was first). Assessments were performed at screening, end of anthracycline, taxane, and HER2-targeted therapy, at Week 25, and at 6, 12, and 24 months following the end of HER2-targeted therapy. Mean and median change from baseline (BL) scores were assessed in each arm and time point; results were defined as clinically meaningful if they differed by ≥ 10 points (Osoba, JCO 1998). Results: Questionnaire completion rates were > 85% throughout. Mean physical function scores (SD; 95% CI) decreased from BL to Week 13 (end of taxane): –10.7 (17.2; –11.4, –10.0) with P and –10.6 (17.7; –11.4, –9.9) with Pla during C. Scores returned to BL during HER2-targeted treatment. There was no clinically meaningful decline in role function from BL to Week 13 for either arm (C: –0.2 (9.6; –0.8, 9.2) with P and –1.7 (9.3; –2.3, 0.2) with Pla during C. Diarrhea symptom score differences from BL were clinically meaningful with P (at Week 13), and scores returned to BL at the end of targeted therapy (P + H). Diarrhea symptom scores were worst at Week 13 in both arms (P +22.3 (29.8, 21.0, 23.6); Pla +9.2 (23.9, 8.2, 10.2)). Conclusions: In one of the largest HRQoL data sets reported to date in HER2-positive EBC, there was no clinically meaningful worsening of role function, indicating that patients’ abilities to conduct daily activities did not differ by treatment arm. Patient-reported diarrhea symptoms worsened to a greater extent in the P arm during both C and HER2-targeted treatment. Clinical trial information: NCT01358877.

522 Poster Session (Board #14), Sat, 8:00 AM-11:30 AM
Pooled analysis of two randomized phase III trials (PlanB/SuccesC) comparing six cycles of docetaxel and cyclophosphamide to sequential anthracycline taxane chemotherapy in patients intermediate/high risk HER2-negative early breast cancer (n=5,923). First Author: Wolfgang Janni, University of Ulm, Ulm, Germany

Background: Recent studies draw different conclusions concerning whether omission of anthracyclines (A) in adjuvant chemotherapy for HER2-negative early breast cancer (EBC) may reduce toxicity without compromising efficacy. Methods: The prospectively randomized PlanB and Success C trials compared 6 cycles of docetaxel (D) and cyclophosphamide (C) with either 4 cycles of epirubicin (E) and C, followed by 4 cycles of D (EC-D, PlanB) or 3 cycles of 5-FU, E and C, followed by 3 cycles of D (FEC-D, SuccessC). Disease-free survival (DFS) was analyzed using univariable and multivariable Cox models adjusted for hormone receptor status (HRS) and histologic grade (G), age, menopausal status, type of surgery, pt, pN, and histologic type. Results: Overall, 5923 patients with follow-up data were available for this pooled analysis, with 2979 and 2944 patients randomized to A-free and A-containing chemotherapy, respectively. After 62 months median follow-up, DFS of patients receiving A-free vs A-containing chemotherapy was quite similar in univariable analysis (hazard ratio, HR = 1.04; 95% confidence interval, CI: 0.88 – 1.22, p = 0.64) and in multivariable analysis (HR = 1.00, 95% CI: 0.85 – 1.19, p = 0.96). Defining biological subtypes “luminal A-like” as HRS positive, G1/2, “luminal B-like” as HRS positive, G3, and TN (triple negative), no significant differences were seen in DFS between A-free and A-containing chemotherapy. In univariable analysis (HR = 0.95, 95% CI: 0.80 – 1.13, p = 0.33) and in multivariable analysis (HR = 0.94, 95% CI: 0.78 – 1.13, p = 0.35) no significant differences were seen in DFS between A-free and A-containing chemotherapy. Conclusion: Our data suggest that 6 cycles of DC provide sufficient efficacy compared to an anthracycline-containing regimen in most patients with HER2-negative EBC. However, subgroup analyses indicate that high-risk patients might benefit from anthracycline-containing chemotherapy.

523 Poster Session (Board #15), Sat, 8:00 AM-11:30 AM
A prospective study on the effect of endoxifen concentration and CYP2D6 phenotypes on clinical outcome in early stage breast cancer patients receiving adjuvant tamoxifen. First Author: Anabel Beatriz Sanchez-Spitman, Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, Netherlands

Background: It has been postulated that endoxifen levels are better predictors of tamoxifen efficacy than CYP2D6 phenotype. Although in a retrospective study an endoxifen threshold of 5.9 ng/ml for efficacy was described, confirmation based on prospective studies is lacking. The objective of the prospective CYPTAM study (NTR1509) is to associate endoxifen levels and CYP2D6 phenotypes with clinical outcome in early stage breast cancer patients receiving tamoxifen. Methods: Breast cancer patients who were receiving adjuvant tamoxifen were included. Blood samples were used for CYP2D6 genotyping and endoxifen levels by HPLC (high-performance liquid chromatography) and tandem mass spectrometry assay, respectively. Endoxifen levels and CYP2D6 phenotypes were associated with relapse-free survival (RFS) by using Cox-regression analysis. Patients who changed to another aromatase inhibitor, were censored at the time of switch. Results: A total of 667 pre- and post-menopausal patients were enrolled. No association was found between endoxifen serum levels used as a continuous variable and RFS (Adjusted Hazard Ratio (HR): 0.991, 95% CI: 0.94-1.038, p-value: 0.691). Categorizing endoxifen levels in quartiles, or using 5.9 ng/ml as threshold did not alter these results. In addition, no association was found between endoxifen serum levels and CYP2D6 phenotype (Q1: 0.929, 95% CI 0.525-1.642, p-value 0.799). Conclusions: This prospective clinical study shows no association between endoxifen levels and CYP2D6 phenotypes with RFS in early breast cancer patients using adjuvant tamoxifen. These results do not support the use of these drug monitoring methods on endoxifen levels or CYP2D6 genotyping. Associations between Endoxifen levels and CYP2D6 phenotypes with RFS, clinical trial information: NTR1509.

524 Poster Session (Board #16), Sat, 8:00 AM-11:30 AM
Duration of extended adjuvant therapy with neratinib in early-stage HER2+ breast cancer after trastuzumab-based treatment: Exploratory analyses from the phase III ExteNET trial. First Author: Michael Grant, Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria

Background: The optimal duration of adjuvant therapy with targeted agents remains a question of ongoing relevance in oncology. ExteNET, an international, randomized, placebo-controlled phase III trial, showed that neratinib given for 12 months after trastuzumab-based therapy significantly improved 2- (HR 0.67, p = 0.009) and 5-year (HR 0.73, p = 0.008) invasive disease-free survival (IDFS) in early-stage HER2+ breast cancer (Chan et al. Lancet Oncol 2016; Martin et al. Lancet Oncol 2017). We examined the influence of duration of neratinib therapy on efficacy in the ExteNET study. Methods: Patients with early-stage HER2+ breast cancer were randomly assigned to oral neratinib 240 mg/day or placebo for 12 months (or until disease recurrence) after standard primary therapy and trastuzumab-based (neo)adjuvant therapy. Patients who received neratinib for > 3 or ≥11 months (the median duration of neratinib treatment) were each compared with the ITT placebo group. IDFS (primary endpoint) was analyzed using Kaplan-Meier methods and Cox proportional-hazards models adjusted for prognostic factors. Data cut-off: March 1, 2017. Clinicaltrials.gov: NCT00878709. Results: IDFS population comprised 2840 patients (neratinib, n = 1420; placebo, n = 1420). Median treatment duration (ITT population) was 11.6 and 11.8 months in the neratinib and placebo groups, respectively. 391 patients received neratinib for <3 months, 872 patients received neratinib for ≥11 months or stopped treatment prior to 11 months due to recurrence. Results after a median of 5.2 years follow-up are shown below. Conclusions: These exploratory data suggest that patients who remained on neratinib for ≤11 months derived clear benefits from therapy, whereas neratinib efficacy was considerably reduced in patients who stopped treatment early (<3 months). Clinical trial information: NCT00878709.
525 Poster Session (Board #17), Sat, 8:00 AM-11:30 AM
Predicting expected absolute chemotherapy treatment benefit in women with early-stage breast cancer using a 12-gene expression assay. First Author: William John Gradishar, Feinberg School of Medicine, Northwestern University, Chicago, IL

Background: Previous studies have validated the ability of a 12-gene expression assay to predict risk of distant recurrence (DR) in women with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) early stage breast cancer. Here, we employed a mathematical approach to estimate an expected absolute chemotherapy benefit based on the 12-gene expression test results. Data was included for patients who had clinical testing with the 12-gene expression assay in the US (Myriad Genetic Laboratories Inc., Salt Lake City, Utah) or Germany (Myriad GmbH, Munich, Germany). FFPE breast resections of treatment-naive ER+, HER2- breast tissue were tested to generate a combined molecular and clinical score (EPclin score). For the entire group, the relative chemotherapy benefit was assumed to be 30% based on meta-analyses from the Early Breast Cancer Trialists' Collaborative Group. This was used to calculate the expected absolute chemotherapy benefit across the EPclin score continuum. This was first done in a conservative scenario where chemotherapy benefit was assumed to be independent of interaction. The degree of interaction between expected chemotherapy benefit and the EPclin score was then systematically increased until the maximum possible EPclin score was associated with the maximum chemotherapy benefit. The mean absolute benefit was calculated for patients at high risk (EPclin >3.3) and low risk (EPclin <1.4) for patients with low risk EPclin scores compared to high risk EPclin scores.

Results: Overall, 2,205 ER+, HER2- breast resections (303 tested in USA, 1,902 tested in Germany) were included here (1,286 samples [58%] with low EPclin scores; 919 [42%] with high EPclin scores). The mean absolute benefit ranged from 1.5% to 1.8% (mean 10-year risk of DR 4.6% to 4.3%) for patients with low risk EPclin scores compared to high risk EPclin scores. For patients with a 10-year risk of DR 14.7% to 12.8% for patients with high risk EPclin scores.

Conclusions: In this analysis, the 12-gene expression assay was able to predict absolute benefit from adjuvant chemotherapy in women with ER+, HER2- early stage breast cancer, regardless of which EPclin score cohorts accrued maximal relative treatment benefit.

527 Poster Session (Board #19), Sat, 8:00 AM-11:30 AM
Tumor infiltrating lymphocytes to predict DFS from intense dose-dense (idd) EPC regimen: Results from the German Adjuvant Intergroup Node-positive study (GAIN-1). First Author: Aurelia Noske, Institut für Pathologie, Universitätsklinikum Münster, Münster, Germany

Background: Immune infiltrate in breast cancer (BC) may influence the prognosis and response to systemic therapies. The association and prognostic role of tumor infiltrating lymphocytes (TILs), PD-1 and PD-L1 expression were investigated in high-risk, node positive breast carcinomas.

Methods: The prospective adjuvant phase III GAIN trial compared two dose-dense chemotherapies, idddEPC (epirubicin (E), paclitaxel (P), cyclophosphamide (C)) vs. EC-PX (capecitabine (X)) and Ibandronate vs. observation in patients with node-positive primary breast cancer. A total of 1318 FFPE tumor samples were available for analysis of TILs by HE morphology, and PD-1, and PD-L1 by immunohistochemistry. The association of immune parameters and their prognostic and potential predictive role were analyzed by Cox regression models. The median FU was 74.3 months (range: 0.11-13.7).

Results: Increased TILs, PD-1 and PD-L1 positive TILs were significantly associated with higher grade, higher Ki67, ER/PR negative and triple negative BC (each p < 0.0001). TILs and PD-L1 positive TILs were slightly more frequent in HER2 positive BC (p = 0.005). Spearman analysis revealed positive, moderate to low correlations between TILs, PD1 and PD-L1. At multivariate Cox regression analysis with clinical covariables, TILs had a significant positive impact on DFS in the idddEPC-arm (HR = 0.57 [0.39-0.84], p = 0.0043) but not in the EC-PX-arm (HR = 1.26 [0.86-1.87], p = 0.35) (interaction p = 0.0334). Especially, HR=HER2+BC with the above regimen had an increased DFS compared to TILs and treated with idddEPC had a better DFS compared to no TILs (HR = 0.59 [0.38-0.93], p = 0.0227). PD-1 positive TILs in TNBC were associated with a significant better DFS (HR = 0.50 [0.25-0.99], p = 0.0457). PD-L1 expression had no impact on patient outcome.

Conclusions: TILs and expression of immune markers were important in breast cancer. TILs, PD1 and PD-L1 were significantly associated with higher grade, higher Ki67, ER/PR negative and triple negative and in part in HER2 positive BC. Tumor infiltrating lymphocytes predict the benefit from intense dose-dense EPC whereas the prevalence and prognostic impact of PD-1/PD-L1 seem to play an important role in this node-positive breast cancer cohort with adjuvant chemotherapy.

529 Poster Session (Board #21), Sat, 8:00 AM-11:30 AM
Residual risk assessment with the Breast Cancer Index (BCI) for prediction of late distant recurrence (DR). First Author: Iwona Sestak, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom

Background: The Breast Cancer Index (BCI) is a gene-expression based signature comprised of two complementary functional domains: the molecular grade index (MGI) for tumor proliferation, and the HOXB13/117BR ratio (H/I) for estrogen signaling. BCI provides a quantitative assessment of the likelihood of overall (0-10yr), late (5-10yr) DR and reported to show endocrine benefit in patients with estrogen receptor positive (ER+) breast cancer. The aim of the current study was to further characterize BCI performance to predict late DR for postmenopausal women with N- and N+ disease treated with either anastrozole or tamoxifen.

Methods: 883 women with ER+, N- or N+ (1 to 3 nodes) breast cancer from TransATAC study who were recurrence free at 5 years were included in this analysis. Time to late DR (5 years after diagnosis) was the primary endpoint. Cox regression models were utilized to determine the prognostic value of the BCI and KM-estimates were used to determine 5-10 year DR.

Results: 75 late DRs were recorded in all 883 patients who were recurrence free at 5 years. Patients with a high BCI score were associated with a significantly worse outcome compared to those with a low BCI score (HR = 1.88 [1.49-2.39]). This relationship was observed for both N- (HR = 1.96 [1.41-2.72]) and N+ (HR = 1.51 [1.08-2.12]) patients. BCI added significant prognostic information beyond that from CTS in all patients ($LR^2$ = 11.51, P = 0.0007). For women with N- disease, significant differential risk stratification was observed between low and intermediate groups and between low and high groups. For N+ patients a significant difference was observed between low and high risk groups (HR = 3.10 [1.29-7.49]), but not low intermediate or intermediate and high. For N+ patients, a BCI model integrating tumor size and grade provided significantly more prognostic value than BCI alone ($LR^2$ = 21.34 vs. LR-$^2$ = 5.86, respectively).

Conclusions: In this post-hoc analysis with an expanded group of patients from the TransATAC cohort, BCI was a significant prognostic factor for late DR in both N- and N+ patients, with a combined BCI model providing more prognostic value in N+ patients.

530 Poster Session (Board #22), Sat, 8:00 AM-11:30 AM
Overall survival in female Medicare beneficiaries with early stage breast cancer receiving bisphosphonates or denosumab. First Author: Raul A Herrera Pena, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Adjuvant bisphosphonates in early breast cancer (BC) have resulted in reduction in bone metastasis and improved overall survival (OS), particularly in post-menopausal women. We aim to evaluate the effect of bone-modifying agents (BMA) on survival in a population based cohort of older BC patients.

Methods: Patients aged ≥ 66 yo diagnosed with stage I-III BC between 2007 and 2013 were identified in SEER-Medicare and TCR-Medicare database. Patients were required to have Medicare Parts A, B and D coverage. Patients receiving at least 6 months of an oral bisphosphate, two doses of ibandronate or one dose of zoledronic or denosumab at doses equivalent or higher to those approved for osteoporosis, during the first two years of BC diagnosis were identified as having received a BMA. Five-year OS was estimated with Kaplan-Meier with groups compared with the log rank test. Cox proportional hazards models were fitted to determine the association of BMA and OS after propensity score adjustment. Subgroup analysis were stratified by stage.

Results: The final cohort included 37,604 patients. Median age was 75 years. 32,045 (85.2%) of the patients had hormone receptor-positive tumors. Overall, 8,591 (22.8%) of the patients were treated with BMA. Of these, 7,349 (85.5%) received bisphosphonates only. The unadjusted 5 year OS was 81% and 77 % for those who did and did not receive BMA, respectively (P < 0.0001). After multivariate analysis including propensity scores adjustment, treatment with BMA was associated with a statistically significant increased survival (Hazard ratio [HR] 0.91, 95% CI = 0.85-0.96). When stratified by stage, BMA vs no BMA showed an improvement in unadjusted 5 year OS in patients with Stage II (by OS 79% vs 72%, P < 0.0001) and Stage III (64% vs 57%, P < 0.002) but not for Stage I (86% vs 85%, P = 0.88). After multivariate adjustment, survival remained significantly more favorable for Stage II (HR 0.81, 95% CI = 0.73-0.90) but not for Stage III (HR 0.91, 95% CI = 0.78-1.07).

Conclusions: Use of BMA in post-menopausal woman with early stage BC patients was associated with improved 5 year OS. Stratified subgroup analysis showed that the difference in survival was significant only for patients with stage II.
alkaline phosphatase (5.3%). The only ENZA-related grade (gr) AE possibly attributed to ENZA: fatigue (31.5%), hot flashes (21%). A subset of triple negative breast cancer (TNBC) is characterized by androgen receptor (AR) expression and dependence on AR signaling (Doane Oncogene 2006; Gucalp CCR 2013). Enzalutamide (ENZA), an AR-antagonist, has a clinical benefit rate of 33% in evaluable patients (NCT00772070). We now report safety data observed in our phase II trial. Methods: Eligible pts have centrally confirmed, Stage I-III, ER/PR −, HER2 − (AR ≥1% BC and AR >1% 67% T1, 67% N0, and 86% low/intermediate grade. Despite initiation was 114 days. 29.2% of patients used tamoxifen, 28.2% used anastrozole. 8% used letrozole, 4% used exemestane, and 32.3% used more than one type of HT drugs. Each year, about 60 to 70% patients were adherent to HT. The five year adherence rate decreased from 81.4% in the first year to 21.1% in the 5th year. Patients who were ≥ 50 years old, lived not in the South, with insurance other than HMO, received lumpectomy or mastectomy combined with chemotherapy and radiation therapy, with no comorbidity, used AI, and received surgery in 2003 were more likely to be adherent to HT. Conclusions: The five year HT adherence rates were low among breast cancer patients. Health care providers need to identify ways to improve HT adherence to prevent breast cancer recurrence. [1996 characters]

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Comprehensive transcriptomic profiling to identify breast cancer patients that may be spared adjuvant systemic therapy. **First Author:** Martin Sjostrum, Lund University, Department of Oncology and Pathology, Lund, Sweden

**Background:** Some women with early stage breast cancer (BC) may not require additional systemic therapy after breast-conserving surgery (BCS). While this subgroup of ultra-low-risk women has been difficult to identify with conventional clinical metrics, transcriptomic profiling may offer improved risk stratification. Previously described genomic signatures perform well on the group level, but reports indicate that there may be substantial disagreement between signatures for an individual patient. **Methods:** We analyzed tumors from 765 patients in the SweBCG91-RT trial, which randomized node-negative BC patients to +/- radiation following BCS, with minimal use of adjuvant systemic treatment (9%). Median follow-up was 18.6 years for breast cancer-specific survival (BCSS). The original study demonstrated a benefit from radiation on locoregional events, but not BCSS. Tumors were profiled with the Affymetrix Human Exon 1.0 ST microarray and 14 genomic signatures from literature (including Mammaprint-like, OncotypeDX-like and PAM50-like signatures) were calculated. The average of all signatures was used as an average genomic risk (AGR), which was further used to derive a novel 141-gene signature, with independent features from signatures. **Results:** Most previously described signatures performed well in our data and were highly prognostic for BCSS. The performance of AGR was in line with the best individual genomic signatures, and among the systematically untreated, ER+, HER2- and postmenopausal patients (N = 454, 59% of the entire study population), the highest 3% of patients with lowest AGR was 93% (95%CI 90-97%). The 141-gene signature had a similar performance with 92% (95%CI 88-96) BCSS for the 50% of patients with lowest risk at 15 years. **Conclusions:** AGR, based on 14 previously published signatures, is highly prognostic for BCSS and identifies large groups of patients with optimal risk: benefit from adjuvant systemic therapy. An associated novel 141-gene signature performs similarly and identifies patients that may be spared adjuvant systemic treatment. Based on several individual signatures, AGR and the novel 141-gene signature may be more robust on an individual patient level.

**Dose tailoring of breast cancer adjuvant chemotherapy aiming at avoiding both overtreatment and undertreatment: Results from the prognostic outcome.** **Study. First Author:** Alexios Matikas, Department of Oncology, Karolinska Institutet and University Hospital, Stockholm, Sweden

**Background:** Adjuvant breast cancer chemotherapy (ACT) improves relapse free (BCRFS) and overall survival (OS). Differences in terms of efficacy and toxicity could partly be explained by the significant interpatient variability in pharmacokinetics which cannot be captured by dosing according to body surface area. Consequently, tailored dosing was prospectively evaluated in the phase III PANTHER trial with 2017 patients. **Methods:** PANTHER is a multicenter, open-label, randomized phase III trial which compared tailored, dose dense epirubicin/cyclophosphamide (EC) and docetaxel (D) (group A) with standard interval 5-fluorouracil/E/C and D (group B), with identical pharmacokinetics which cannot be captured by dosing according to body surface area. Consequently, tailored dosing was prospectively evaluated in the phase III PANTHER trial with 2017 patients. Methods: PANTHER is a multicenter, open-label, randomized phase III trial which compared tailored, dose dense epirubicin/cyclophosphamide (EC) and docetaxel (D) (group A) with standard interval 5-fluorouracil/E/C and D (group B), with identical duration of therapy in both arms. The primary endpoint was BCRFS. The primary efficacy analysis revealed an improved event free survival and favorable trends for BCRFS, OS and distant disease free survival compared with standard ACT. In this secondary analysis, we aimed to explore the concept of dose tailoring. Our two hypotheses regarding patients treated at the higher dose were that BCRFS would not differ according to the cumulative administered dose; and that dose tailoring would lead to appropriate dosing and improved outcomes for obese patients. **Results:** Patients randomized in group A had similar BCRFS regardless of the cumulative epirubicin (p = 0.495) or docetaxel dose (p = 0.575). There were consistent, non-statistically significant trends in favor of patients receiving < 360 mg/m² epirubicin compared to 360-420 and ≥ 420 mg/m². In addition, there were no differences in outcomes between patients receiving tailored ACT with a body mass index (BMI) of < 24 (n = 307), 24-28 (n = 296) and 28-40 (n = 312) (p = 0.384). Patients with a BMI of 28-40 had a non-significant trend for improved BCRFS, using BMI < 24 as reference (HR = 0.73, 95% CI 0.45-1.18). **Conclusions:** Dose tailoring could spare patients from unnecessary overdosing without compromising outcomes and may overcome the negative impact on prognosis conferred by obesity. Although exploratory, these results highlight the feasibility of tailored ACT, and underscore the need for further studies. An in-depth discussion will be presented at the ASCO meeting.

**Clinical trial information:** NCT00798070.
Breast Cancer—Local/Regional/Adjuvant

540 Poster Session (Board #32), Sat, 8:00 AM-11:30 AM
Long-term benefit from tamoxifen therapy for patients with Luminal A and Luminal B breast cancer: Retrospective analysis of the STO-3 trial. First Author: Linda Lindström, Karolinska Institutet, Stockholm, Sweden
Background: Breast cancer patients with estrogen receptor (ER)-positive disease have a continuous long-term risk for fatal breast cancer spanning more than 20 years, but the biological factors influencing this risk are unknown. Here we aimed to investigate the long-term survival and benefit from tamoxifen therapy for patients with Luminal A and Luminal B subtype tumors. Methods: The Stockholm Tamoxifen (STO-3) trial enrolled 1780 postmenopausal women from 1976 until 1990 with lymph node-negative breast cancers and tumors less than or equal to 30 mm in diameter, randomly assigned to at least two years of adjuvant tamoxifen (40 mg daily) vs no adjuvant treatment. All patients had a complete long-term follow-up until December 31, 2012, and detailed patient and clinical information. Gene expression data was generated using custom designed Agilent arrays from FFPE breast cancer tumor tissue and was used to define Luminal A and Luminal B subtype tumors. ER, PR, HER2 and Ki-67 were also reassessed in 2014. Long-term breast cancer-specific survival was performed using Kaplan-Meier analysis and flexible parametric survival models were used to estimate the time-varying hazard ratios (HRs) adjusting for patient and tumour characteristics. Results: A statistically significant difference in long-term survival (25 years) by Luminal subtype and trial arm was seen (Log Rank, P < 0.0001). For Luminal A and Luminal B patients, the 25-year survival was 88% versus 69% for treated patients and 73% versus 58% for untreated patients. Luminal A patients treated with tamoxifen had a significantly reduced long-term risk of fatal breast cancer up to 20 years after breast cancer diagnosis (HR at 15-years: 0.59, 95% CI, 0.35-0.98; and HR at 20-years: 0.65; 95% CI, 0.32-1.30) as compared to the untreated arm. However for patients with Luminal B tumors, a significantly reduced long-term risk was only seen for 10 years after diagnosis (HR at 5-years: 0.37; 95% CI, 0.18-0.73; and HR at 10-years: 0.68; 95% CI, 0.31-1.47). Conclusions: Patients with Luminal A subtype tumors have a long-term benefit from tamoxifen therapy, whereas the benefit for patients with Luminal B tumors is up to ten years after diagnosis. Clinical trial information: STO-3 trial from 1976 no registration at the time.

542 Poster Session (Board #34), Sat, 8:00 AM-11:30 AM
Next-generation targeted sequencing (NGTS) investigating CDK4 as a prognostic driver in pure invasive lobular breast carcinoma (ILC): Preliminary results from early-stage patients (pts) stratified according to a validated clinicopathological model. First Author: Luisa Carbognin, University of Verona, Verona, Italy
Background: The aim of this analysis was to investigate the distribution of molecular abnormalities and their potential role as therapeutic targets (with particular regard to CDK4/6 alterations) in resected ILC pts, grouped according to prognosis. Methods: Clinicopathological multi-center data of early-stage pure ILC pts were correlated to disease-free survival (DFS). A continuous score was derived according to multivariate Hazard Ratios, to develop a 3-class model. The model was validated in an external pts’ cohort. Mutational and Copy Number Variation (CNV) analyses by NGTS, including an additional stratifications of ILC, ODx, and the combined assay. Conclusions: ILC is a significant predictor of breast cancer recurrence and contributes prognostic information independent of ODx. The combined genomic and morphometric assay outperforms either individual assay. Also, while ODx was reported to lose predictive power when restricted to HER2- patients in E2197, ILCB remains a predictor of recurrence.

Performance of assays (N = 116).

<table>
<thead>
<tr>
<th>% of patients without recurrence classified as low-risk</th>
<th>10-year recurrence rate in low-risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILCB</td>
<td>37.5%</td>
</tr>
<tr>
<td>ODx</td>
<td>35.3%</td>
</tr>
<tr>
<td>ILCB + ODx</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

543 Poster Session (Board #35), Sat, 8:00 AM-11:30 AM
Association of a low-expression SLC01B1 polymorphism with estrogen concentrations before and during aromatase inhibiting treatment for breast cancer. First Author: Jacqueline M Dempsey, University of Michigan College of Pharmacy, Ann Arbor, MI
Background: Three aromatase inhibitors (AI), the steroid exemestane, and the azoles anastrozole and letrozole, are effective in the treatment of estrogen receptor positive (ER+) breast cancer by preventing biosynthesis of estrogens including estradiol (E2), estrone (E1), and estrone-sulfate (E1S) in postmenopausal women. OATP1B1, encoded by SLC01B1, transports E1S into the liver for desulfation to active E1. Women carrying the low-expression SLC01B1 rs4149056 single nucleotide polymorphism (SNP) have higher E1-conjugate levels (Dudenkov Breast Cancer Res Treat 2017). We hypothesized that patients carrying this SNP would have increased E1 at baseline, and this E1 reserve could resupply E1 and E2 resulting in detectable estrogen levels during AI treatment. Methods: Five hundred postmenopausal women with ER+ breast cancer were randomized 1:1 to either exemestane 25 mg/day or letrozole 2.5 mg/day. Plasma estrogen concentrations were measured prior to and after 3 months of AI treatment using LC/MS/MS (LLOQ for E2 = 0.626 pg/mL, E1 = 1.56 pg/mL, E1S = 3.13 pg/mL). The additive genetic associations between rs4149056 and 1) log-transformed concentrations before and during aromatase inhibiting treatment for breast cancer.

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Fatigue

50 (37%) 27 (20%) 12 (67%) 32 (65%) 9 (41%) 25 (52%) .20

Anxiety

30 (22%) 9 (7%) 7 (39%) 16 (33%) 6 (27%) 10 (22%) .47

Peripheral neuropathy

34 (25%) 15 (11%) 3 (17%) 14 (27%) 15 (68%) 17 (37%)

Diarrhea

21/142 (15%) 7/16 (44%)

Dyspnea

19/112 (17%) 9/46 (20%) .70

Depression

17/107 (16%) 11/51 (22%) .38

Nausea

14/99 (14%) 14/59 (24%) .13

Diarrhea

15/88 (17%) 13/70 (19%) .80

Insomnia

21/142 (15%) 7/16 (44%)

Muscle pain

5/54 (9%) 23/104 (22%) .05

Insomnia

12/69 (17%) 16/89 (18%) .92

Anxiety

15/88 (17%) 13/70 (19%) .80

Arthralgia

16/98 (17%) 12/60 (20%) .56

Constipation

14/99 (14%) 15/24 (29%) .13

Myalgia

16/98 (16%) 12/60 (20%) .56

Diarhrea

17/94 (18%) 16/74 (22%) .89

Nausea

14/102 (14%) 14/56 (25%) .09

Peripheral neuropathy

17/107 (16%) 11/51 (22%) .38

Depression

19/112 (17%) 9/46 (20%) .70

Dyspnea

17/127 (13%) 11/31 (35%) .004

Vomiting

21/142 (15%) 7/16 (44%) .004

* No HT x HT

Breast Cancer—Local/Regional/Adjuvant

544 Poster Session (Board #36), Sat, 8:00 AM-11:30 AM

Patient-reported toxicities by chemotherapy regimen.

Toxicities

Fatigue

50 (37%) 27 (20%) 12 (67%) 32 (65%) 9 (41%) 25 (52%) .20

Anxiety

30 (22%) 9 (7%) 7 (39%) 16 (33%) 6 (27%) 10 (22%) .47

Peripheral neuropathy

34 (25%) 15 (11%) 3 (17%) 14 (27%) 15 (68%) 17 (37%)

Diarrhea

21/142 (15%) 7/16 (44%)

Dyspnea

19/112 (17%) 9/46 (20%) .70

Depression

17/127 (13%) 11/31 (35%) .004

Vomiting

21/142 (15%) 7/16 (44%) .004

545 Poster Session (Board #37), Sat, 8:00 AM-11:30 AM

Impact of high deductible insurance on out-of-pocket cost burden in breast cancer.

First Author: Christine Lu, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

Background: High-deductible health plans (HDHP) requiring out-of-pocket (OOP) costs for most services may place heavy economic burden on patients. This study examined the impact of modern HDHPs on OOP costs among women with early-stage breast cancer.

Methods: We included 886 women with incident early-stage breast cancer, age 25 to 64 years, who were insured by employers that mandated a transition from low-deductible (< $500/year) to high deductible (> $1000/year) coverage, and 3099 exact matched contemporaneous patients whose employers offered only low-deductible plans. Measures were pharmacy and medical OOP costs per person-year. Medical services were categorized as inpatient, emergency room (ER), primary care visits, and outpatient care which included specialist visits, radiology, lab tests, and chemotherapy. We calculated OOP costs as the sum of deductibles, copays, and coinsurance. Effect estimates of changes between study groups were established using difference-in-differences analyses. Results: HDHP members faced an absolute baseline-to-follow-up increase in total OOP costs of $1067 per person-year compared to controls (p = 0.001). The absolute change in medical OOP costs per person-year among HDHP members compared to controls from baseline to follow-up was significant ($1004, 95% CI: [$580, $1429]) and the relative change was also significant (41.2%, 95% CI: [17.8%, 64.5%]). The increase in medical OOP costs was driven by increases in outpatient care OOP costs. The absolute change in pharmacy costs per person-year among HDHP members compared to controls from baseline to follow-up was $919 (95% CI: [$506, $1332]; relative change: 43.7%, 95% CI: [17.0%, 70.5%]). Changes in OOP costs for pharmacy, inpatient, ER, and primary care visits were not significant. Conclusions: In this rigorous, natural experimental study, women with early-stage breast cancer who experienced increases in total OOP costs after employer-mandated HDHP switches, a change driven by a 44% increase in outpatient care OOP costs. Further research should examine which outpatient services contributed to this substantial economic burden, when the differences occur and the proportion of women reaching their annual deductible.

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**548**  
**Poster Session (Board #40), Sat, 8:00 AM-11:30 AM**  
**Urgent hypertension as a biomarker for bevacizumab in the curative setting.**  
*First Author: Nawal Kassem, Indiana University School of Medicine, Indianapolis, IN*

**Background:** Bevacizumab is FDA approved across many tumors including lung, colon, and glioblastoma. It is unclear which patients are destined to respond and/or experience the most toxicity. We previously demonstrated that bevacizumab-induced hypertension (HTN) in the metastatic breast cancer setting (E2100) was correlated with an improved overall survival (OS). In this study we evaluated the impact of bevacizumab-induced urgent HTN on outcome in the curative setting in E5103 and BEATRICE. We further evaluated for germline biomarkers to predict patients destined to experience HTN using whole exome sequencing (WES).

**Methods:** Cases were defined as those who experienced urgent HTN (systolic blood pressure (SBP) > 180 mmHg) and controls those with SBP < 160 mmHg. Log rank test was used to compare DFS and OS between cases and controls. WES was performed using germline DNA from patients in E5103 and BEATRICE. Exomes were enriched via Ion AmpliSeq Exome RDK kits. Templates were prepared on Ion Chef Systems and sequenced on Ion Proton Sequencers. Rare variants with a minor allele frequency < 1% and those which were predicted to be deleterious by standard protein prediction programs were retained. A gene-based, case-control analysis using SKAT was performed to generate level of significance.

**Results:** There were 93 cases of urgent HTN and 3000 matched controls. Patients with urgent HTN had a markedly superior DFS (p-value = 0.01) and superior OS (p-value = 0.02). There was no effect seen in the control arm. We also identified rare variants in SLCO7A1 as predictors of urgent hypertension.

**Conclusions:** Urgent HTN is associated with improved outcomes in the curative setting. We have also identified rare variants associated with severe HTN through WES. Exploring the biology of those who experience bevacizumab-induced HTN may help explain the heterogeneity of outcomes and elucidate secondary drug targets.

**549**  
**Poster Session (Board #41), Sat, 8:00 AM-11:30 AM**  
**Timing of initiation of neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ hormone receptor (HR)-negative breast cancer: Exploratory analyses from the phase III ExteNET trial.**  
*First Author: Bent Ejlertsen, Department of Oncology, Rigshospitalet, Copenhagen, Denmark*

**Background:** ExteNET, an international, randomized, placebo-controlled phase III trial, showed that neratinib given for 1 year after trastuzumab-based adjuvant therapy significantly improved 2- (HR 0.67, p = 0.009) and 5-year (HR 0.73, p = 0.008) invasive disease-free survival (iDFS) in early-stage HER2+ breast cancer (Chan et al. 2016; Martin et al. 2017). Pre-specified subgroup analyses showed greater benefit with neratinib in HR+ than HR tumors, and in patients who initiated neratinib ≤12 months of completing trastuzumab. To better understand the effects of neratinib in patients with HR disease, we examined the impact on efficacy of the interval from prior trastuzumab to start of neratinib in the HR subgroup.

**Methods:** Patients with early-stage HER2+ breast cancer received oral neratinib 240 mg/day or placebo for 1 year after standard trastuzumab-based (neoadjuvant) therapy. iDFS, the primary study endpoint, was examined in subgroups categorized according to the interval between completing trastuzumab and randomization (i.e. 0, 612 and >12 months). Data cut-off: March 1, 2017. ClinicalTrials.gov: NCT00878709. Results: The ITT population comprised 2840 patients; 1209 (43%) had HR disease (neratinib, n = 604; placebo, n = 605). Results after a median of 5.2 years in the HR subgroup are shown below. Conclusions: Patients with HER2+ HR tumors tend to recur early. The risk of recurrence is higher in patients who have recently completed trastuzumab-based therapy (reflected in the iDFS rates of the placebo group). Consistent with these observations, our analyses suggest that the benefits of neratinib in HR disease are greater when treatment is started closer to completion of trastuzumab (i.e. ≤6 months).

**550**  
**Poster Session (Board #42), Sat, 8:00 AM-11:30 AM**  
**Adjuvant tamoxifen adherence in men with early stage breast cancer.**  
*First Author: Oluchi Oke, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Most male breast cancers (MBC) are hormone-receptor positive, part of the standard treatment of these patients includes adjuvant tamoxifen. Prior small, single-institution studies have suggested that men may have high rates of discontinuing adjuvant endocrine treatment. We examined rates of tamoxifen discontinuation and medication adherence in a large population-based cohort of MBC patients.

**Methods:** In the SEER-Medicare database male patients with non-metastatic MBC, diagnosed between 2007-2013, age 65 and older, with Part D coverage, and with tamoxifen prescriptions within one year of diagnosis were identified. The cumulative incidence of drug discontinuation was calculated for each year after diagnosis. Adherence was defined as a medication possession ratio (MPR) of > -80% among those patients who were filling tamoxifen prescriptions. A logistic regression model was used to assess predictors of tamoxifen adherence.

**Results:** We identified 451 patients who met eligibility criteria. Median age at diagnosis was 75 years. Median follow-up was 32.5 months. 34% of patients had Stage I breast cancer, 48% Stage II, and 18% Stage III. Among those with known hormone receptor status, 99% had hormone receptor positive cancer. Rates of tamoxifen discontinuation were 19.8%, 30.7%, 39.6%, 46.8% and 61.4% at 1, 2, 3, 4, and 5 years after diagnosis, respectively. Among the men who were still taking tamoxifen, the corresponding adherence rates were 77.4%, 75.2%, 71.4%, 67.9%, and 63.5%. In the adjusted model, significant predictors of lower adherence included residing in a high poverty area (OR 0.26, 95% CI 0.08-0.86) and Charlson comorbidity score of ≥2 (OR 0.46, CI 0.21-1.00). Conclusions: Older men with breast cancer have high rates of tamoxifen discontinuation, with 61% of patients discontinuing tamoxifen before the end of year 5. In addition, even among those patients continuing tamoxifen, a substantial number of patients are non-adherent. Further research should evaluate potentially modifiable reasons for treatment discontinuation and lack of adherence to tamoxifen.

**551**  
**Poster Session (Board #43), Sat, 8:00 AM-11:30 AM**  
**Predicting Oncotype DX scores using clinicopathologic features: A report from microarray-based gene expression data.**  
*First Author: Catherine Pasce, Department of Surgery, NorthShore University Health System, Evanston, IL*

**Background:** The Oncotype DX recurrence score is used to predict the benefits of chemotherapy added to adjuvant hormone therapy in ER positive early-stage breast cancer. While its use has been validated and cost effectiveness has been established, its expense remains a concern in some health care systems and communities. Using clinical and pathologic features as predictors of Oncotype DX scores from the National Cancer Database (NCDB) for patients with low or high Oncotype DX scores, we aim to identify factors that predict high and low Oncotype DX scores using logistic regression.

**Methods:** From 2010-2014, 78,663 breast cancer patients with Oncotype DX scores were selected from the NCDB. Seven clinical and pathologic variables including age, ER, PR, histologic subtype, lymphovascular invasion (LVI), grade, and tumor size were used to predict high-risk (> 30) or low-risk (< 18) Oncotype DX scores using logistic regression. Data were split into training (70%) and testing (30%) sets for external validation. The predictive accuracy of the regression model was assessed using a Receiver Operator Characteristic (ROC) analysis. Model fit was analyzed by plotting the predicted probabilities against the actual probabilities. Nomograms were created for visualization of the high-risk and low-risk models using bootstrap estimation method of the model coefficients.

**Results:** Estrogen receptor status, progesterone receptor status, and grade were the strongest predictors of both low-risk and high-risk Oncotype DX scores. Followed by age, histology, tumor size, and LVI, yielding AUC of 0.70 for the low-risk model and 0.86 for the high-risk model.

**Conclusions:** We have developed a model that can predict high-risk Oncotype DX scores with very good reliability. Such a tool may be useful in health care systems with limited resources. Model Coefficients of Strongest Predictors of High-Risk Oncotype DX Score

**Factors**  
ER negative 2.977  
PR negative 2.095  
Graded differentiated well 0.000  
moderately differentiated 1.356  
poorly differentiated 3.374  
Tumor size < 10mm 0.370  
10-20mm 0.264  
20-30mm 0.584  
30mm+ 0.78

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Background: A randomized, controlled trial is the optimal method to evaluate the effect of an experimental therapy. However, a single arm trial can be used when randomization is feasible or unethical. POSITIVE is a prospective, single arm, international study aimed at young (age 18-42) women with endocrine responsive (ER+/) breast cancer (BC) who desire pregnancy. It will assess whether temporary interruption of adjuvant endocrine therapy (for up to 2 yrs) after 18-30 months of use is safe in terms of risk of recurrence. We describe methods to estimate a historical control rate for POSITIVE using data from the SOFT/TEXT Phase 3 trials. Methods: The primary endpoint of POSITIVE is breast cancer recurrence (BCR) at 3 yrs. In this analysis, we first identified a cohort of SOFT/TEXT pts meeting POSITIVE eligibility criteria. Method I uses the SOFT/TEXT cohort to calculate 3 yr annualized hazard rates by a piecewise exponential model and 3 yr BCR rate by Kaplan-Meier (KM) estimate. Method II uses the SOFT/TEXT cohort to group-match SOFT/TEXT pts to POSITIVE pts; sample sets of SOFT/TEXT pts were randomly drawn with replacement 5000 times to obtain sets having baseline characteristics well-balanced. ROSITIVE eligibility criteria. Method I uses the SOFT/TEXT cohort to calculate 3 yr annualized hazard rates by a piecewise exponential model and 3 yr BCR rate by Kaplan-Meier (KM) estimate. Method II uses the SOFT/TEXT cohort to group-match SOFT/TEXT pts to POSITIVE pts; sample sets of SOFT/TEXT pts were randomly drawn with replacement 5000 times to obtain sets having baseline characteristics well-balanced. Results: Method I included 149 POSITIVE pts; included 1499 SOFT/TEXT pts met the eligibility criteria. POSITIVE pts were younger, had fewer positive nodes, and fewer received chemotherapy. Method II is refining these estimates to adjust for imbalanced characteristics and provides more precise estimates of the annualized BCR hazard rates and 3 yr BCR rates (Table). Clinical trial information: NCT02308085. Conclusion: Methods I and II are being applied using data from other sources (e.g., ABCSG-12, ASCO CancerLinQ) to assure a robust estimate of an historical control rate across different cohorts.

Balancing the risks versus benefits of trastuzumab: A call to action for oncologists, cardiologists, and cardiovascular patients. First Author: Zhuoxin Sun, IBCSG Statistical Center, Br, Linkin, PA. 554 Poster Session (Board #46), Sat, 8:00 AM-11:30 AM Background: One year of adjuvant trastuzumab (T) is standard for early stage (I-II) HER2 + breast cancer (BC) patients (pts). Cardiac imaging is recommended every 3 months during treatment to monitor for cardiotoxicity (CTx) without evidence this practice improves pt care. Up to 30% of pts will experience transient, asymptomatic, cardiac toxicity (CTx). Cardiotoxicity fraction (LVEF) on T, which may lead to early termination of T. Our objective was to evaluate the impact of routine CI on disease free survival (DFS) and overall survival (OS) in early stage HER2+ BC. Methods: Retrospective population-based cohort study of early stage BC pts treated with adjuvant T in Ontario, Canada, 2007-2016. Patient-level data was sourced through the Institute for Clinical Evaluative Sciences, which captures all patients in Ontario. The cohort was divided into three arms; A: 17-18 cycles T, no CTx; B: no CTx; C: ≥16 cycles T, stopped within 30 days of last cardiac imaging; C: developed CTx. CTx was defined as new diagnosis heart failure (HF), cardiomyopathy (CM) or pulmonary edema within 90 days of last cycle of T. Primary outcome: DFS; secondary outcomes: OS, cancer-specific, and cardiovascular mortality. Survival analysis was performed using Cox and subdistribution hazard models. Results: 4820 pts met inclusion criteria; 4018, 442 and 356 in arms A, B, and C, respectively. Median cycles of T were 18, 13 and 14 in arm A, B and C. 5-year DFS was significantly worse in arms B (70.3%, 95% CI 63.5-74.7) and C (74% 69-57.9) vs. 93.2% (92-94.0) arm A; HR for DFS were 2.96 (2.35-3.72) and 2.41 (1.87-3.12) respectively. 5-year OS was significantly worse in arms B (75.4%) and C (80.1%) vs. arm A (95.2%); HR for OS 3.99 (3.10-5.14) and 2.98 (2.24-3.95) respectively. All p-values were < 0.001. Conclusion: For pts in Ontario who did not complete adjuvant T had significantly worse DFS and OS. A significant population stopped T shortly after cardiac imaging, without developing CTx, likely due to detection of asymptomatic drops in LVEF. These findings support the need to consider strategies to continue cancer therapy in pts with asymptomatic cardiac imaging, including concurrent optimization of cardiac function and cardiac risk factors.

Comparison of outcomes for AJCC 8th Anatomic and Prognostic staging in contemporary triple negative breast cancer (TNBC) multisite registry. First Author: Rajvi H. Shah, University of Kansas Medical Center, Westwood, KS. 555 Poster Session (Board #47), Sat, 8:00 AM-11:30 AM Background: Eighth edition of the AJCC TNM staging system incorporates biological prognostic factors along with the traditional anatomical factors and currently Prognostic (P) stage must be used for reporting of all cancer patients in the US. Comparison of patient distribution between P and Anatomic staging and outcomes associated with the P stages in a contemporary TNBC population are not known. Methods: 674 patients with stage I-III TNBC were enrolled in an IRB approved multisite prospective registry between 2011 and 2017. Patients were followed for recurrence and survival. AJCC 8th edition Anatomic (A) Stage and clinical Prognostic (P) stage groups were applied to all patients. Recurrence free survival (RFS) (STEEP criterion) was estimated according to the Kaplan-Meier method and compared among groups by log-rank test. Results: Median age was 53 years (23-85); 96% of patients received neo/adjuvant chemotherapy. 82% (468/574) of patients were upstaged on P compared to A staging. Significantly lower numbers of patients were categorized within P stage II (36%) compared to A stage II (51%) (p = 0.001). Conversely, higher number of patients were categorized within P stage III (29%) compared to A stage III (14%) (p = 0.0001), with largest relative increase in stage IIIC (3% to 13%). Table 1 provides 5 years RFS for all A and P stages. Compared to A stage IIIB, P stage IIIB was associated with better RFS (HR = 0.42 [0.21-0.86], p = 0.013), whereas P and A stages IIIC had similar RFS. This suggests appropriate upstaging of TNBC patients to IIIC on P staging. Conclusions: 82% of TNBC patients are upstaged on P staging compared to A staging. Knowledge of outcomes associated with various P stages can guide prognostic counselling for TNBC patients who plan to undergo standard local and systemic treatment.
556 Poster Session (Board #48), Sat, 8:00 AM-11:30 AM
Role of cardiac reserve as a tool to unmask cardiotoxicity following anthracycline therapy and whether exercise training can attenuate cardiotoxicity. First Author: Steven Fraser, Deakin University, Burwood, Australia
Background: Anthracycline-based chemotherapy (AC) is associated with an increased risk of cardiac damage and long-term heart failure. However, diagnosis of cardiac damage is infrequent, while long-term heart failure risk is substantial. Thus, we sought to evaluate whether exercise cardiac reserve may be a more sensitive marker of cardiac toxicity than standard measures of cardiac function and if exercise training maintained cardiac function and exercise capacity during AC. Methods: 268 BC patients enrolled in AC were recruited into a non-randomised trial and allocated to exercise training (ET) (46.7±9.0 yrs, n = 14) or usual care (UC; 53.2±8.9 years, n = 14), respectively. Tests including echocardiography (left ventricular ejection fraction [LVEF] and global longitudinal strain [GLS]), cardiopulmonary exercise test (peak oxygen uptake, VO2peak), and exercise cardiac magnetic resonance imaging (eCMR, cardiac reserve) were performed prior to and after completion of AC. The ET group completed a twice weekly supervised aerobic and resistance exercise program at a moderate-vigorous intensity. Results: There was a small statistically significant reduction resting in LVEF in both UC and ET, whereas GLS was unchanged (Table 1). VO2peak fell by 15% in the UC, while ET significantly attenuated the decline in fitness (-4%). Cardiac reserve was reduced following AC (Visit×Exercise P= 0.05), which was not attenuated by exercise training (Visit×Exercise×Group P= 0.006). Exercise training had no effect on resting measures of LV function (Table 1). Clinical trial information: ACTRN12616001602415. Conclusions: Exercise treatment caused profound reductions in peak oxygen uptake and impaired cardiac reserve. Resting measures of cardiac function did not account for the large reduction in VO2peak which was attenuated by exercise training. 

557 Poster Session (Board #49), Sat, 8:00 AM-11:30 AM
CA15-3/MUC1 in CCTG MA-32 (NCT01101438): A Phase III RCT of the effect of metformin vs. placebo on invasive disease free and overall survival in early stage breast cancer (BC). First Author: Ryan J0 Dowling, Princess Margaret Cancer Centre, Toronto, ON, Canada
Background: The diabetes drug metformin may improve BC outcomes through enhanced obesity-related physiology or direct anti-tumor effects. We studied the effect of metformin on CA15-3 (the soluble moiety of the MUC1 protein), a marker associated with BC prognosis that also has mitogenic and metabolic effects that favor tumorigenesis. Methods: 3,256 women with T1-3, N0-3, MO BC who had completed standard therapy (ongoing hormone therapy permitted) provided fasting blood (stored at -80°C) at baseline and 6 months. CA15-3 and insulin were measured by Roche ECLIA; leptin, and hs-CRP by Luminex Milliplex MAP and Roche ITA. Spearman coefficients were calculated and comparisons analyzed using Wilcoxon signed rank test and multivariable linear regression models. Tests were two-sided. Results: Mean age was 52.3 and BMI 28.6 kg/m². Tumor and treatment characteristics were balanced between arms (overall: T2/3 in 59.8%, N +ve in 52.9%, grade 1/2/3 in 9.1/35.3/54.4%, ER + in 69.6%, HER2+ in 17.1%; 50.4% underwent mastectomy, 74.0% received radiation, 89.2% chemotherapy, 17% trastuzumab, and 64.4% hormone therapy). Baseline values and 6 month changes are shown below. In multi-variable analyses (including age, BMI, tumor characteristics, treatment, metformin vs placebo) led to a greater relative reduction in CA15-3 (-5.1%; 95% CI: -3.9% to -7.64%, p < 0.0001). CA15-3 change at 6 months significantly correlated with change in BMI (r=0.10, p<0.0001), glucose (r=0.05, p=0.011) and hs-CRP (r=0.05, p=0.022). Conclusions: Metformin significantly lowered CA15-3; change in CA15-3 was associated with improved obesity-associated physiology and BMI, consistent with hypothesized beneficial actions of metformin. Clinical trial information: NCT01101438.

559 Poster Session (Board #51), Sat, 8:00 AM-11:30 AM
Association of clinical/pathological parameters with axillary involvement in early breast cancer in patients with limited sentinel node involvement (SLN). First Author: Hans-Christian Kolberg, Marienhospital Bottrop, Klinik für Gynäkologie und Geburtshilfe, Bottrop, Germany
Background: The association between pathological complete remission (pCR) in the breast and clinical/pathological parameters is well established, whereas the association of clinical/pathological parameters and residual axillary involvement after NACT is still not sufficiently defined. We used data from the SENTINA trial to analyze this association in a patient population with limited sentinel lymph node (SLN) involvement. Methods: Patients were included if before NACT they presented with a clinically negative axilla with limited sentinel lymph node (SLN) involvement. All patients involved SLNB and axillary dissection after NACT. Univariate and multivariate analyses were carried out to evaluate the association between clinical/pathological parameters and axillary involvement after NACT. Results: Of the SENTINA study contained 360 patients, 265 of which were evaluable (Table 2). T2/3, N +ve in 52.9%, grade 1/2/3 in 9.1/35.3/54.4%, ER + in 69.6%, HER2+ in 17.1%; 50.4% underwent mastectomy, 74.0% received radiation, 89.2% chemotherapy, 17% trastuzumab, and 64.4% hormone therapy. Baseline values and 6 month changes are shown below. In multi-variable analyses (including age, BMI, tumor characteristics, treatment, metformin vs placebo) led to a greater relative reduction in CA15-3 (-5.1%; 95% CI: -3.9% to -7.64%, p < 0.0001). CA15-3 change at 6 months significantly correlated with change in BMI (r=0.10, p<0.0001), glucose (r=0.05, p=0.011) and hs-CRP (r=0.05, p=0.022). Conclusions: Metformin significantly lowered CA15-3; change in CA15-3 was associated with improved obesity-associated physiology and BMI, consistent with hypothesized beneficial actions of metformin. Clinical trial information: NCT01101438.

560 Poster Session (Board #52), Sat, 8:00 AM-11:30 AM
Hypofractionated whole breast IMRT and brachytherapy boost after conservative surgery: Early results of a prospective non-randomised trial. First Author: Ines Quix, IMOR Foundation, Medical Institute for Radiotherapy and Oncology, Barcelona, Spain
Background: To report the early results obtained in a prospective group of patients (pts) treated with whole breast IMRT radiotherapy plus brachy. boost to tumor bed after conservative surgery (CS), given either with hypofractionated or normofractionated radiotherapy. Methods: Between 10/ 2008 and 06/2016, 1,277 pts with T1-3N0-3M0 BC who had completed standard therapy (ongoing hormone therapy permitted) provided fasting blood (stored at -80°C) at baseline and 6 months. CA15-3 and insulin were measured by Roche ECLIA; leptin, and hs-CRP by Luminex Milliplex MAP and Roche ITA. Spearman coefficients were calculated and comparisons analyzed using Wilcoxon signed rank test and multivariable linear regression models. Tests were two-sided. Results: Mean age was 52.3 and BMI 28.6 kg/m². Tumor and treatment characteristics were balanced between arms (overall: T2/3 in 59.8%, N +ve in 52.9%, grade 1/2/3 in 9.1/35.3/54.4%, ER + in 69.6%, HER2+ in 17.1%; 50.4% underwent mastectomy, 74.0% received radiation, 89.2% chemotherapy, 17% trastuzumab, and 64.4% hormone therapy. Baseline values and 6 month changes are shown below. In multi-variable analyses (including age, BMI, tumor characteristics, treatment, metformin vs placebo) led to a greater relative reduction in CA15-3 (-5.1%; 95% CI: -3.9% to -7.64%, p < 0.0001). CA15-3 change at 6 months significantly correlated with change in BMI (r=0.10, p<0.0001), glucose (r=0.05, p=0.011) and hs-CRP (r=0.05, p=0.022). Conclusions: Metformin significantly lowered CA15-3; change in CA15-3 was associated with improved obesity-associated physiology and BMI, consistent with hypothesized beneficial actions of metformin. Clinical trial information: NCT01101438.
561 Poster Session (Board #53), Sat, 8:00 AM-11:30 AM

Results from a pilot of an innovative 4R Cancer Care Delivery Model in early breast cancer: Impact on timing and sequencing of guideline recommended care. First Author: Christine E. Weldon, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Under the "NCI ASCO Teams" Project, we proposed a 4R Model of teamwork and patient self-management (Trosman JOP '16). 4R = Right Info / Care / Patient / Time. It enables patient and care team to manage timing / sequencing of interdependent care with an innovative multimodality personalized 4R Care Project Plan. We piloted 4R at 3 centers (academic, community safety net) and assessed impact on timing / sequencing of guideline based care.

Methods: 4R Plans were administered to breast cancer patients stage 0-III Sept '17 – Aug '17. Clinical data for 185 patients who received 4R (4R cohort) were compared with a historical control cohort of comparable patients who received care pre-4R, Jun '16 – May '17. We used simple frequencies and Fisher's exact test in analyses.

Results: We improved timing / sequencing of 7 guideline recommended metrics (Table). Significant improvements were shown for care lacking standard BCS (eRFA) may not only reduce the need for re-excision for close or focally positive margins but may obviate the need for whole breast irradiation in favorable breast cancer patients. Methods: In an IRB-approved risk-adjusted protocol, 267 T0-2, No breast cancer patients from 7 different sites were screened for a Phase II multicenter protocol of BCS followed by cavity RFA (eRFA) without adjuvant radiation and followed for margins, recurrence, breast pain, cosmesis and QOL. Results: 242 patients were accrued to the study with a median follow-up of 36 months. Re-excision for positive margins was < 5%. The in breast recurrence rate was 2.5%. In this risk adjusted model XRT was added when SLNB was positive. 20% of cohort received XRT. Breast pain ≤ 6 months was 19% with RFA/XRT Versus 1.7% with RFA alone (p < .05). Cosmesis was good or excellent in > 90% of patients. QOL did not change after eRFA. Conclusions: eRFA may be a new paradigm for treating favorable patients that desire lumpectomy who either cannot or do not want radiation. A majority of the patients avoided re-excision, WBI and/or mastectomy. Treatment in lieu of XRT is safe and effective and may increase definitive treatment compliance for patients as it is complete at the time of surgery. Clinical trial information: NCT0153035.

562 Poster Session (Board #54), Sat, 8:00 AM-11:30 AM

Prospective phase II multicenter trial of ablation after breast lpectomy added to treatment (ABLATE) breast cancer without radiation. First Author: V. Suzanne Klimberg, University of Arkansas for Medical Sciences, Little Rock, AR

Background: Background:A plethora of studies have failed to define a group of patients that can forgo radiation to complete BCS without a significant increase in recurrence rate. This has resulted in overtreatment with radiation of an estimated 85% of patients with favorable breast cancers. RFA added to standard BCS (eRFA) may not only reduce the need for re-excision for close or focally positive margins but may obviate the need for whole breast irradiation in favorable breast cancer patients. Methods: In an IRB-approved risk-adjusted protocol, 267 T0-2, No breast cancer patients from 7 different sites were screened for a Phase II multicenter protocol of BCS followed by cavity RFA (eRFA) without adjuvant radiation and followed for margins, recurrence, breast pain, cosmesis and QOL. Results: 242 patients were accrued to the study with a median follow-up of 36 months. Re-excision for positive margins was < 5%. The in breast recurrence rate was 2.5%. In this risk adjusted model XRT was added when SLNB was positive. 20% of cohort received XRT. Breast pain ≤ 6 months was 19% with RFA/XRT Versus 1.7% with RFA alone (p < .05). Cosmesis was good or excellent in > 90% of patients. QOL did not change after eRFA. Conclusions: eRFA may be a new paradigm for treating favorable patients that desire lumpectomy who either cannot or do not want radiation. A majority of the patients avoided re-excision, WBI and/or mastectomy. Treatment in lieu of XRT is safe and effective and may increase definitive treatment compliance for patients as it is complete at the time of surgery. Clinical trial information: NCT0153035.

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566 Poster Session (Board #58), Sat, 8:00 AM-11:30 AM
Prediction of pathologic complete response by image-guided biopsy before surgery in breast cancer with complete clinical response to neoadjuvant chemotherapy: A prospective feasibility trial. First Author: Hong Sung Lee, Department of Surgery, Seoul National University College of Medicine, Seoul, Korea, Republic of (South)

Background: Patients who attain a pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) have a favorable long-term outcome. In patients with pCR, it is suggested that the role of surgical excision may be limited to pathological confirmation, and thus may be omitted when pCR can be correctly predicted. The purpose of this study was to evaluate how accurately pCR can be predicted using MRI and image-guided biopsy.

Methods: We prospectively enrolled 40 patients (mean age 47.1) between September 2016 and January 2018 who were suggested to have pCR on preoperative MRI. Lesion size ≤0.5cm or lesion-to-background parenchymal signal enhancement (SER) ratio ≤1.6 on MRI was defined as complete clinical response. Multiple core needle biopsies (CNB) (14G) or vacuum-assisted biopsies (VAB) (10G) was alternatively performed for the tumor bed around a clip marker placed during the course of NAC. Standard surgical excision was performed after biopsy. Matched biopsy and surgical specimens were compared for pCR assessment. Results: Pathologic pCR was confirmed in 27 (67.5%) surgical specimens, including 14/19 (73.7%) of HR-/HER2- and 6/8 (75%) of HR-/HER2+ patients. Preoperative biopsy had an accuracy of 90% (95% CI: 76-97%), negative predictive value of 87.1% (95% CI: 75-94%), and a false-negative rate of 30.8% (95% CI: 14-70%). Among four patients whose biopsies were not accurate, pCR was not predicted to be >0.5cm on MRI and two had less than five cores biopsied. Obtaining at least five cores in patients with ≤0.5cm lesion on MRI resulted in an accuracy of 97.1% (33/34), negative predictive value of 96.2% (25/26), and a false negative rate of 10%. There was no difference in accuracy between multiple biopsy techniques, and the results did not correlate with nodal status in 11.3% (3/27).

Conclusions: Image-guided CNB or VAB can accurately identify patients with breast pCR in selected patients using preoperative MRI findings. This information will be used in a prospective clinical trial evaluating clinical safety of omitting breast surgery in patients with a breast pCR as determined by image-guided biopsy. Clinical trial information: NCT03273742.

569 Poster Session (Board #60), Sat, 8:00 AM-11:30 AM
Investigating denosumab as an add-on neoadjuvant treatment for RANKL-positive and HER2-negative breast cancer and two different nab-paclitaxel schedules: 2x2 factorial design (GeparX)—An interim safety analysis. First Author: Sherko Kummel, Klinikum Essen Mitte, Essen, Germany

Background: The GeparX study aims to investigate whether denosumab, a monoclonal antibody targeting RANKL, increases the pCR rate when added to an anthracycline/taxane containing neoadjuvant chemotherapy (NACT) in patients (pts) with primary breast cancer (BC). Methods: GeparX enrolls pts with primary BC ct1c-t4d, after central assessment of HER2, HR, TILS, Ki67. 778 pts will be randomized to NACT+/denosumab (120mg q3w, q4w for 6 cycles), stratified by lymphocyte predominant BC (LPBC, ≤50% vs >50%), subtype (HER2+/HR- vs triple negative (TNBC) vs HER2+), and epirubicin/cyclcophasamide schedule (EC, q2w vs q3w). Secondarily, pts are randomized to different nab-paclitaxel schedules (nP): nPT: 125mg/m² weekly or nPT:125mg/m² daily 1,8, q22 followed by EC. Pts with TNBC receive capecitabatin (AUC 2) and with HER2+ BC ACP 980 (trastuzumab biosimilar)+ pertuzumab. Co-primary objectives compare the pCR (ypT0 pypN0) rates of NACT+/denosumab and the pCR rates between nPT 125 weekly and nPT 125 d1,8 q22. Secondary objectives are toxicity, compliance amongst others. An interim safety analysis is planned after the first 200 pts have completed nP treatment.

Results: A total of 202 pts randomized to denosumab and the nP treatment (101 pts with weekly and 101 pts with nP d1,8 q22) were included in the interim analysis. Overall, median age was 50 years (range 23-76). 38.6% of pts were cT1c and 5% had LBBC, 102 pts (50.5%) had HER2+/HR- BC, 82 (40.6%) had TNBC and 18 pts (8.9%) HER2+ BC. Overall, 13.5% with and 13.1% w/o denosumab discontinued nP. 21.0 % of pts with nP weekly vs 5.3% with nP d1,8 q22 discontinued nP mainly due to AEs (17.0% vs 3.2%). During nP treatment 24 SAEs with nP weekly vs 25 SAEs with nP d1,8 q22 were reported. 17 (16.7%) SAEs were reported in the HER2-HR+ cohort, 29 (35.4%) for the TNBC (with capecitabatin) and 3 (16.7%) in the HER2+ cohort (dual-blockade, no capecitabatin).

Conclusions: The addition of denosumab to NACT does not increase toxicity. Weekly nP resulted in a higher rate of treatment discontinuations mainly due to non-serious AEs. The addition of capecitabatin resulted in a higher rate of SAEs. Clinical trial information: NCT02682693.
570 Poster Session (Board #64), Sat, 8:00 AM-11:30 AM
Impact of PIK3CA mutation status on immune marker response and pCR in the WSG-ADAPT HER2+ phase II trial. First Author: Natascha Marbeck, Brustzentrum der Universität München (LMU), Munich, Germany
Background: The ADAPT HER2+/HR phase II trial (NCT01745965) compared for the first time 12 wks. neoadjuvant T-D1M1 (± endocrine therapy (ET)) with trastuzumab (T)+ET; pCR (ypT0/is ypN0) was > 40% in T-D1M1 arms and 15% in T+ET. High CD8 at baseline or cycle 2, as well as increased CD8 expression on treatment, were associated with favorable pCR. In HER2+ mBC, T-D1M1 was reported effective in both mutant and wildtype (WT) PIK3CA tumors. Methods: This pre-planned translational analysis aimed to identify potential early predictors for response to neoadjuvant therapy (containing T-D1M1 or T) in HER2+/HR+ EBC. PIK3CA mutations were assessed by high-throughput microfluidics qPCR (MUT-MAP 1.3-gen panel). Immune markers, focusing here on CD8 in tumor center, were assessed by IHC in core biopsies at baseline and cycle 2. CD8 positivity was coded as percentage of positively stained cells; CD8 change was defined as cycle 2 minus baseline value. Associations between pCR and PIK3CA mutation status (mutated vs. WT) or with other variables were characterized by Fisher’s exact test and T-statistics. Results: In 190 patients, PIK3CA mutation status was assessed in baseline biopsies (177/190) or surgical samples (or both). Results were identical in all 8 repeated assays (baseline & surgery). Prevalence of PIK3CA mutations was 31/190 (16.3%). pCR was 37.4% in WT vs 16.7% in PIK3CA mutated tumors (p = 0.035). Distributions of nodal status, grade, and Ki67 were independent of PIK3CA mutation status, but T1 tumors were less prevalent (25.8% vs. 47.2%) for PIK3CA mutations (p = 0.03); the unfavorable impact of PIK3CA mutations on pCR was strong within the T2+ patient subgroup (9.1% vs 33.8%; p = 0.017). While CD8 protein expression generally increased following 3 weeks of therapy, and larger positive CD8 responses were themselves associated with pCR (particularly in the T-D1M1 containing arms (p = 0.009), CD8 changes in PIK3CA mutated tumors were small and lower than in WT (p = 0.020). Conclusions: PIK3CA mutations were associated both directly (lower pCR) and indirectly (stagnation of CD8 change) with poorer response to neoadjuvant therapy in HER2+/HR+ EBC. Poor response in PIK3CA mutated cases occurs despite excellent overall pCR with T-D1M1. Clinical trial information: NCT01817452.

571 Poster Session (Board #63), Sat, 8:00 AM-11:30 AM
Prognostic implications of residual disease (RD) tumor-infiltrating lymphocytes (TIL) in triple negative breast cancer (TNBC) after neo-adjuvant chemotherapy (NAC). First Author: Stephen James Luen, Peter MacCallum Cancer Centre, Melbourne, Australia
Background: For primary TNBCs treated with NAC, higher pre-treatment TILs correlate with increased pathological complete response (pCR) rates, better recurrence-free survival (RFS) and overall survival (OS). We evaluated the prognostic value of RD TILs to pathological stage and Residual Cancer Burden (RCB) in predicting survival post NAC. Methods: We combined individual patient data from 4 TNBC patient series treated with NAC who did not achieve pCR. TILs were evaluated on the RD using our previously published method on H&E stained slides. TILs were investigated for associations with yp stage, RCB, RFS and OS using Cox models with stromal TILs as a continuous variable, stratified by series. The likelihood ratio (LR) test was used to evaluate added prognostic value of TILs to standard yp stage and RCB class. Results: In total 376 RD samples were evaluable for TILs. For 6 years median follow-up we observed 193 RFS events and 165 deaths. The median age was 50 years (range 24-83). 62% received combination anthracycline/taxane chemotherapy, and 27% anthracyline alone. For RD stage, 32% were yp0 vs yp3 positive; RCB class was yp1/yp2 11%/50%/39% respectively. The median RD TIL level was 20% (IQR 10-40). TIL levels were significantly lower with increasing yp stage (p < 0.01), but did not differ significantly by RCB class (p = 0.84). Higher RD TILs were significantly associated with improved RFS (HR per 10% increment 0.86, 95%CI 0.79-0.92; P < 0.01) and OS (HR 0.87; 95%CI 0.80-0.94; P < 0.01), but were only significant for RFS in multivariate analysis after adjusting for yp stage (p = 0.03). RCB class was significant for RFS and OS (both P < 0.01). RD TILs added significant prognostic value to RCB class for both RFS and OS (both LR P < 0.01). The positive prognostic effect of RD TILs was of greater magnitude in yp3 vs yp1+2, and RCB class 2 vs both RFS and OS (interaction P < 0.01). Conclusions: TIL levels in TNBC RD are significantly associated with improved RFS and OS and add further prognostic information to RCB class. The positive prognostic influence of TILs is significantly greater in patients with less RD burden. This data may help refine NAC clinical trial endpoints.

572 Poster Session (Board #64), Sat, 8:00 AM-11:30 AM
Impact of PIK3CA mutation status on immune marker response and pCR in the WSG-ADAPT HER2+ phase II trial. First Author: Natascha Marbeck, Brustzentrum der Universität München (LMU), Munich, Germany
Background: The ADAPT HER2+/HR phase II trial (NCT01745965) compared for the first time 12 wks. neoadjuvant T-D1M1 (± endocrine therapy (ET)) with trastuzumab (T)+ET; pCR (ypT0/is ypN0) was > 40% in T-D1M1 arms and 15% in T+ET. High CD8 at baseline or cycle 2, as well as increased CD8 expression on treatment, were associated with favorable pCR. In HER2+ mBC, T-D1M1 was reported effective in both mutant and wildtype (WT) PIK3CA tumors. Methods: This pre-planned translational analysis aimed to identify potential early predictors for response to neoadjuvant therapy (containing T-D1M1 or T) in HER2+/HR+ EBC. PIK3CA mutations were assessed by high-throughput microfluidics qPCR (MUT-MAP 1.3-gen panel). Immune markers, focusing here on CD8 in tumor center, were assessed by IHC in core biopsies at baseline and cycle 2. CD8 positivity was coded as percentage of positively stained cells; CD8 change was defined as cycle 2 minus baseline value. Associations between pCR and PIK3CA mutation status (mutated vs. WT) or with other variables were characterized by Fisher’s exact test and T-statistics. Results: In 190 patients, PIK3CA mutation status was assessed in baseline biopsies (177/190) or surgical samples (or both). Results were identical in all 8 repeated assays (baseline & surgery). Prevalence of PIK3CA mutations was 31/190 (16.3%). pCR was 37.4% in WT vs 16.7% in PIK3CA mutated tumors (p = 0.035). Distributions of nodal status, grade, and Ki67 were independent of PIK3CA mutation status, but T1 tumors were less prevalent (25.8% vs. 47.2%) for PIK3CA mutations (p = 0.03); the unfavorable impact of PIK3CA mutations on pCR was strong within the T2+ patient subgroup (9.1% vs 33.8%; p = 0.017). While CD8 protein expression generally increased following 3 weeks of therapy, and larger positive CD8 responses were themselves associated with pCR (particularly in the T-D1M1 containing arms (p = 0.009), CD8 changes in PIK3CA mutated tumors were small and lower than in WT (p = 0.020). Conclusions: PIK3CA mutations were associated both directly (lower pCR) and indirectly (stagnation of CD8 change) with poorer response to neoadjuvant therapy in HER2+/HR+ EBC. Poor response in PIK3CA mutated cases occurs despite excellent overall pCR with T-D1M1. Clinical trial information: NCT01817452.

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Signatures of mutational processes and response to neoadjuvant chemotherapy in breast cancer: A genome-based investigation in the neoadjuvant GeparSepto trial.

First Author: Carsten Denkert, Institute of Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany

Background: Different mutational processes act over the evolutionary history of a malignant tumor, driven by e.g. abnormal DNA editing, mutagens or age-related DNA alterations. Many of these processes generate defined combinations of mutation types, which have been described as mutational signatures. The clinical relevance of mutational signatures has not been studied to a great extent. We investigate the hypothesis that the individual patterns of mutational signatures determine the clinical behavior of breast cancer (BC), in particular response to neoadjuvant chemotherapy. Methods: In the GeparSepto study (NCT01583426) women with primary invasive BC were randomized to either nab-paclitaxel or solvent-based paclitaxel followed by EC. Pretherapeutic FFPE core biopsies of HER2-negative BC were used for whole genome/exome sequencing (n = 405). Mutational signatures were identified as described by Alexandrov et al. (Cell Rep. 3, 2013). Results: 24 of the 30 mutational signatures were present in at least 10% of the 405 tumors, the most predominant were Sig1 (age-related, 94.8%), Sig13 (APOBEC-related, 97.7%), Sig6 (MMR-def-related, 69.9%), Sig3 (BRCAness-related, 61.5%), Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC

Conclusions: Whole-exome sequencing in breast cancer FFPE core biopsies from clinical cohorts can be used to identify mutational signatures. The pattern of these signatures, in particular the presence of BRCA-related (Sig3) and APOBEC-related (Sig13) reflect the clinical behavior of breast cancer and might be used to identify tumors with an increased response rate to neoadjuvant chemotherapy.
Immune profiling of pre- and post-treatment breast cancer tissues from the S0800 randomized neoadjuvant trial of weekly nab-paclitaxel with or without bevacizumab and dose-dense cyclophosphamide. First Author: Xiaotong Li, Yale University, New Haven, CT

**Background:** We examined changes in the tumor immune microenvironment during neoadjuvant chemotherapy by comparing immune gene mRNA expression, tumor infiltrating lymphocyte (TIL) count and PD-L1 protein expression in pre- and post-treatment tissues. **Methods:** Paired pre- and post- treatment tumor samples from 60 patients were profiled using the Nanostring Immune Oncology 360 platform to measure the expression of 770 immune-related genes that also allowed us to test 14 immune cell type and 27 previously published prognostic and immunity therapy response predictive gene signatures. All samples were also assessed for TIL counts and PD-L1 protein expression by immunohistochemistry. Gene expression levels were compared by paired t-test with Bonferroni correction. TIL count, PD-L1 protein expression and immune gene signatures were compared using Wilcoxon signed-rank test. Baseline immune markers were correlated with pathologic complete response (pCR) using estrogen receptor (ER) and treatment adjusted logistic regression. **Results:** TIL counts were significantly lower in post- compared to pre-treatment samples and stromal PD-L1 protein expression was not significantly different. At baseline, higher TIL count and PD-L1 expression were associated with pCR. High expression of a mast cell metagene was associated with residual disease (RD). No individual genes or VEGF gene signature were associated with benefit from bevacizumab. In patients with HER2-positive tumors, genes associated with tissue repair and inflammation (DUSP1, EGR1, IL6, ATF3, CD36, CXCL2, CD69, NGFR, KLF2, THBD, DAB2) showed significantly higher expression after therapy while most other immune markers decreased. The T effector, T-reg, MHC-I, MHC-II, IFNgamma, STAT-1 and M1 macrophage gene signatures were significantly lower in post-treatment samples and only the IL8/VEGFR and T-helper gene signatures showed higher expression after therapy. **Conclusions:** High mast cell gene expression is associated with lower pCR rate. TIL counts and most immune parameters decrease after neoadjuvant chemotherapy.

Integrative cluster classification to predict pathological complete response to neoadjuvant chemotherapy in early breast cancer. First Author: Emilio Alija, Hospital Clinico Universitario Virgen de la Victoria. GEICAM Spanish Breast Cancer Group., Malaga, Spain

**Background:** Integrative Clustering (IntClust) is a breast cancer (BC) classification of 10 different subgroups with distinctive molecular profiles and clinical outcomes (Curtis et al., Nature 2012). We implemented an IntClust classifier based on Copy Number Alterations (CNAs) and explored its prognostic role in a cohort of pre- and post-treatment (ttm) tumors from the neoadjuvant trials GEICAM/2006-03 (NCT00432172) and GEICAM/2006-14 (NCT00841828). **Methods:** GEICAM/2006-03 HER2-negative pts were selectively treated according to clinical subtypes: triple negative (TN) pts with standard taxane/anthracycline-based chemotherapy (TA-CT) +/- carboplatin, and luminal A patients were randomised to TA-CT vs. hormone therapy. GEICAM/2006-14 HER2+ pts received TA-CT + anti-HER2 therapy. Shallow-whole genome Illumina sequencing DNA data from 204 paraffin-BCC (100 pre- and 104 post-ttm tumors) were used to identify CNAs and grouped samples in the 10-IntClust classification. A functional clustering by grouping IntClust 1-2-6-9 as Luminal good prognosis (LGP), IntClust 10 (Basal-like) and IntClust 5 (HER2+) were defined. Fisher test was used to analyze IntClust distribution. Logistic regression analyses were performed to explore the association of IntClust groups with outcome (pCR in breast and axilla).

**Results:** The comparative analysis for IntClust groups in pre- vs post-ttm samples showed significantly different distribution (p = 0.01), with an enrichment of the LGP group (32% vs 55%) in the residual samples after neoadjuvant ttm, due to an increase in IntClusters 3 and 4 (both of them characterized by a low-genomic instability), and a decrease in the rest of the groups. Logistic regression analysis showed that IntClust classification in post-ttm tumors were significant associated with pCR independently to historical grade, Ki67 and clinical subtype (p = 0.0015). **Conclusions:** Our data suggest an association between IntClust classification and clinical outcome in terms of pCR after neoadjuvant therapy in early BC. In our study, residual tumors after ttm were predominantly Luminal-like phenotypes with low genomic instability. Clinical trial information: GEICAM2006-03 NCT00432172. GEICAM/2006-14 NCT00841828.
582 Poster Session (Board #74), Sat, 8:00 AM-11:30 AM
Predicting neo-adjuvant chemotherapy response from pre-treatment breast MRI using machine learning and HER2 status. First Author: Nathaniel Braman, Carestream Research Laboratories, Cleveland, OH

Background: Many breast cancer patients receiving neo-adjuvant chemotherapy (NAC) will ultimately fail to achieve pathological complete response (pCR). A pre-treatment clinical marker of pCR could guide NAC without requiring potentially ineffective initial treatment periods. Advances in medical image analysis, such as deep learning (pattern recognition using neural networks) and radiomics (computer-extracted quantitative image features), demonstrate significant potential for non-invasive assessment of NAC outcome. We present a machine learning (ML) approach for pre-NAC response prediction fusing deep learning, radiomics, and clinical variables.

Methods: 166 patients with pre-treatment contrast-enhanced MRI from the ISPY1-TRIAL and surgically-confirmed NAC response outcome (ypT0N0, 49 NAC outcome. We present a machine learning (ML) approach for pre-NAC response prediction fusing deep learning, radiomics, and clinical variables.

Methods: 166 patients with pre-treatment contrast-enhanced MRI from the ISPY1-TRIAL and surgically-confirmed NAC response outcome (ypT0N0, 49 NAC outcome. We present a machine learning (ML) approach for pre-NAC response prediction fusing deep learning, radiomics, and clinical variables.

583 Poster Session (Board #75), Sat, 8:00 AM-11:30 AM
Efficacy analyses of central laboratory pCR results from the LILAC study comparing the biosimilar ABP 980 and trastuzumab. First Author: Hans-Christian Kolberg, Marienhospital Bottrop, Klinik für Gynäkologie und Geburtshilfe, Bottrop, Germany

Background: The phase 3 LILAC Study compared ABP 980 with trastuzumab (TRAS) on pathologic complete response (pCR) in women with HER2+ early breast cancer. The primary efficacy results, based on local laboratory evaluation of tumor samples, have been reported previously. Here we report the results of pCR analysis based on central laboratory evaluation of tumor samples.

Methods: After run-in anthracycline-based chemotherapy, patients were randomized 1:1 to ABP 980 or TRAS plus paclitaxel Q3W x 4 or Q1W x 12. The co-primary endpoints were risk difference (RD) and risk ratio (RR) of pCR adjusted for baseline covariates in breast tissue and auxiliary lymph nodes. Clinical similarity was supported by the central pathology evaluation as the 2-sided 90% CIs were within the equivalence margin for RD (-13% to 13%) and RR (0.759 to 1.318). Representative samples of tumor material were sent to the central laboratory for evaluation. Samples were determined to be adequate for evaluation based on the presence of tumor bed and integrity of nuclear detail. Each sample was evaluated by 2 independent central pathologists, who were blinded to patients’ treatment and to each other’s assessment. If discordance between the 2 pathologists was found, the case was sent to a third blinded pathologist to determine the outcome.

Results: 725 patients were randomized: 696 (ABP 980: n = 358; TRAS: n = 338) were included in the pCR evaluable population. pCR was achieved in 46.5% for ABP 980 and 40.4% for TRAS, based on local review, and was 7.3% (90% CI: 1.2%, 13.4%). RR was 1.19 (90% CI: 1.033, 1.366). The upper limit of the CIs slightly exceeded the equivalence margin. Based on central review, pCR was achieved in 47.8% for ABP 980 and 41.8% for TRAS. RD was 5.8% (90% CI: 0.5, 12.0%); RR was 1.14 (90% CI: 0.993, 1.318). Compared with NAC chemotherapy, the potential clinical benefit of switching to ABP 980 was demonstrated.

Conclusions: Results based on central evaluations support clinical equivalence of ABP 980 and TRAS. All sensitivity analyses based on central pathology evaluation were within the prespecified equivalence margins. This study demonstrates the feasibility of including central laboratory review of pCR rates in a large multicenter, multinational study. Clinical trial information: NCT01901146.

584 Poster Session (Board #76), Sat, 8:00 AM-11:30 AM
Impact of residual nodal disease burden on sentinel node mapping and accuracy of intraoperative frozen section in node positive (cN1) breast cancer patients treated with neoadjuvant chemotherapy (NAC). First Author: Alison Laws, University of Calgary, Calgary, AB, Canada

Background: Recent trials have demonstrated the feasibility of SLN biopsy in cN1 patients who become cN0 after NAC. We sought to evaluate success of SLN mapping and accuracy of intraoperative frozen section (FS) by residual nodal disease burden. Methods: CT-3 cN1 patients receiving NAC and surgery (1/2016 to 5/2017) were identified from a prospective database. Pts who converted to cN0 and had SLN biopsy with dual-tracer were included. Adequate mapping (defined as ≥3 SLN) and false negative rate (FNR) of intraop FS were assessed by residual nodal disease burden (ypN0, ypN1-3T1c-3N1, ypN1-3). Results: Among 137 CT-3 cN1 pts, 76 met inclusion criteria. Median age 45 yrs (27-82); median tumor size 4.3 cm (0.8-15.0). 32 (42%) pts were ER+HER2-, 24 (32%) HER2+ and 20 (26%) ER-HER2-. Adequate mapping was achieved in 50 (66%) pts; 14 (18%) failed to map and 12 (16%) had < 3 SLN identified. Adequate mapping was not associated with residual node burden (table, p = 0.21). Among 48 pts with adequate mapping and FS, 16 were ypN+ on FS and 28 were ypN+ on final pathology; FNR of 12/28 (43%). Smaller residual nodal disease burden was associated with false negative FS (table, p = 0.005). 28/76 (37%) pts achieved axillary pCR, of whom 20 (71%) had ≥3 negative SLN and were spared ALND. Of 36 pts with successful mapping and positive SLN, 22 (61%) underwent ALND, of whom 8 (36%) had additional nodal disease; the remaining 14 (39%) had axillary radiation. Among pre-NAC cN1 pts, SLN biopsy was technically adequate in 66%. Of these, 40% achieved axillary pCR and avoided ALND. The FNR of intraop FS was 43%. Residual nodal disease burden was not associated with adequate mapping; micrometastases and ITCs were associated with higher likelihood of false negative FS. Preoperative counseling for SLN biopsy should include realistic assessment of the likelihood of SLN mapping and the potential need for ALND.

585 Poster Session (Board #77), Sat, 8:00 AM-11:30 AM
Immune profiling of BRCA-mutated breast cancers. First Author: Jeremy Meyer Force, Duke University Medical Center, Durham, NC

Background: Increased tumor infiltrating lymphocytes (TILs) are predictive and prognostic for improved outcomes in breast cancers. Increased tumor mutational burden can be immune activating. BRCA-mutated (BRCA+) breast cancers may have increased tumoral mutational burden compared to BRCA wildtype (BRCA-). Immune system responses to BRCA- breast cancers have not been well described. The primary aim of our study was to assess tumor infiltrating immune cells in early stage breast cancers with and without germline BRCA mutations. Methods: Here we report TILs and genomic profiling from our full study cohort. Assuming the %TILs in the BRCA- group was 20% we determined 124 early stage breast cancers with and without BRCA mutations was needed to detect a 20% difference in TILs between cohorts to attain 80% power with a one-side alpha of 0.05. We identified 124 early stage untreated breast cancers with BRCA mutations (n = 62) and without (n = 62). Our BRCA control group was matched by hormone receptor (HR) status followed by age then stage. TILs were measured on pretreatment H&E slides. A NanoString BC360 panel was applied to RNA isolated from 80 breast cancers (BRCA+ = 39; BRCA- = 41). Results: Compared to BRCA- early stage breast cancers, median TILs were increased in the BRCA+ cohort (median 5 vs 10, p = 0.007). BRCA+HR- samples did not have more TILs compared to BRCA-HR (median 10 vs 15, p = 0.10). BRCA+HR+ had increased TILs compared to BRCA-HR+ (median 1 vs 5, p = 0.005). An 18 gene RNA tumor immune score (TIS) moderately correlated with TILs (R²=0.339, p < 0.001), was increased in BRCA+ cancers (p = 0.29), but was primarily elevated in those with a basal-like phenotype (p = 0.001). Conclusions: Early stage BRCA breast cancers have increased TILs compared to BRCA- TILs are significantly more abundant in BRCA+HR+ breast cancers, which might be explained by an increased basal-like phenotype. TIS moderately correlates with TILs. TIS is increased in BRCA+ breast cancers, but reaches significance in the basal-like phenotype. Many BRCA+HR+ cancers with luminal phenotypes had increased TILs and elevated TIS. To guide development of immunomodulating therapies in BRCA+ cancers, further immune analyses should be investigated in hereditary breast cancers and compared to sporadic cancers.
586 Poster Session (Board #78), Sat, 8:00 AM-11:30 AM

Duvalrumbal (MED4736) concurrent with nab-paclitaxel and dose dense doxorubicin cyclophosphamide (ddAC) as neoadjuvant therapy for triple-negative breast cancer (TNBC). First Author: Lajos Pusztai, Yale Cancer Center, New Haven, CT

Background: The goal of this Phase III trial is to assess the safety and efficacy of concurrent administration of duvalrumbal with weekly nab-paclitaxel (100 mg/m²) x 12 followed by dd AC x 4 as neoadjuvant therapy for stage III TNBC. The primary efficacy endpoint is pathologic complete response (pT0 pN0, pCR).

Methods: The Phase I portion of the trial assessed two dose levels of duvalrumbal; 3 mg/kg and 10 mg/kg iv every 2 weeks in combination with chemotherapy, dose limiting toxicities (DLT) were evaluated over the entire 20 weeks of therapy. The Phase II portion follows Simon’s two step design, with early stopping for futility if < 7 patients achieve pCR among the first 22.

Results: No DLT were encountered during the Phase I portion of the trial; the 10 mg/kg was recommended as the phase II dose. Thirty-two patients were enrolled in the trial 14 are still receiving therapy, 16 have completed treatment and underwent surgery and 1 patient withdrew consent. Nine patients (56%, 95% CI: 32%-78%) achieved pCR, 2 of the 4 patients at the 3 mg/kg dose level and 7 of the 12 at the 10 mg/kg dose. Eight patients (25%) experienced grade 3 adverse events including 3 patients with neutropenia (1 neutropenic fever), and one patient each with fatigue, dyspnea, line trans-site, trans-aminitis, hypertension/skin rash. No perioperative adverse events were seen.

Conclusions: Concomitant administration of duvalrumbal with weekly nab-paclitaxel and sequential ddAC neoadjuvant chemotherapy is safe and the pCR rates appear to be higher than what is expected with chemotherapy alone. Clinical trial information: NCT02489448.

587 Poster Session (Board #79), Sat, 8:00 AM-11:30 AM

The impact of chemotherapy sequence on survival in node-positive invasive lobular carcinoma. First Author: Nina Prabha Tamirisa, Duke University Medical Center, Durham, NC

Background: Breast cancer patients with invasive lobular carcinoma (ILC) have lower rates of downstaging after neoadjuvant chemotherapy (NACT) than those with invasive ductal carcinoma; however, similar criteria – including lymph node involvement – are used to determine administration of NACT in both subtypes. We sought to determine the impact of chemotherapy sequence on survival among node-positive (cN+) ILC patients receiving systemic therapy. Methods: We identified cN+1-3 ILC patients in the National Cancer Data Base (2004-2014) who received chemotherapy and divided them into neoadjuvant and adjuvant cohorts. Unadjusted overall survival (OS) was estimated using the Kaplan-Meier method, and differences between groups were tested using the log-rank test. Cox proportional hazards modeling was used to estimate the effect of chemotherapy timing on OS after adjustment for known covariates. Results: 75.7% (n = 17,957) of patients with cN+ ILC (n = 23,736) received chemotherapy; 7,609 (42.3%, median age 54, IQR 47-63) received NACT and 10,348 (57.6%, median age 58, IQR 49-66) received adjuvant chemotherapy. In both cohorts, most patients had stage III (NACT 25.1% vs adjuvant 24.2%), ER+ (NACT 86.6% vs adjuvant 92.3%), HER2- (NACT 80.6% vs adjuvant 87.6%) disease. NACT patients had higher rates of cT4 disease vs adjuvant patients (17.4% vs 2.3%, p < 0.001). Unadjusted 5-year OS was worse for NACT patients vs those receiving adjuvant chemotherapy (73.6% vs 83.1%, log-rank p < 0.001). In multivariable adjusted analyses, NACT continued to be associated with worse OS (HR 1.33, 95% CI 1.21-1.46). Improved OS was associated with age < 50 (HR 0.82, 95% CI 0.75-0.91), receipt of endocrine therapy (HR 0.60, 95% CI 0.53-0.68), and receipt of radiation therapy (HR 0.81, 95% CI 0.73-0.90). Worse OS was associated with ER- status (HR 1.22, 95% CI 1.03-1.42), PR-status (HR 1.55, 95% CI 1.34-1.79), cT4 stage (HR 1.99, 95% CI 1.76-2.47), and receipt of mastectomyectomy (HR 1.30, 95% CI 1.15-1.45). Conclusions: Among node-positive ILC patients, receipt of NACT is associated with worse survival compared with receipt of adjuvant chemotherapy. These findings suggest that use of NACT in node-positive ILC may be of limited benefit and should be used judiciously.

588 Poster Session (Board #80), Sat, 8:00 AM-11:30 AM

Incidence of PI3K pathway aberrations and their impact on response to neo- adjuvant chemotherapy (NACT) in triple-negative breast cancer (TNBC) subtypes. First Author: Reva K Basho, Cedars-Sinai Medical Center, Los Angeles, CA

Background: TNBC cell lines characterized as mesenchymal (M) and luminal androgen receptor (LAR) commonly have aberrations in the PI3K pathway. However, the incidence in human tumors and impact on response to therapy is less clear. Methods: Pre-treatment biopsies were collected from TNBC patients (pts) prior to NACT. Tumors were categorized into 5 groups using the Pietenpol criteria (Lehmann JCI 2011): basal-like (BL) comprised of BL-1 patients (pts) prior to NACT. Tumors were categorized into 5 groups using the Pietenpol criteria (Lehmann JCI 2011): basal-like (BL) comprised of BL-1, BL-2, M comprised of M and mesenchymal stem-like, immunomodu- latory genes evaluated. There was no significant difference in incidence of mutated tumors did not have a significantly worse response to NACT overall (46% vs 54%; P = 0.61) or within the M subset (25% vs 50%; P = 0.58).

Conclusions: In this cohort of TNBC pts, the incidence of PI3K pathway aberrations was higher than previously reported, likely due to the comprehensive genes evaluated. There was no significant difference in incidence of aberrations across subtypes, and PI3K pathway aberration was not associated with altered response to NACT. Larger cohorts are needed to clarify the impact of PI3K pathway aberrations in TNBC subtypes.

Subtype N PI3K Mutated Tumors (N%) RCB 0/I if PI3K Wild Type (N%) RCB 0/I if PI3K Mutated (N%)
All 63 39 (62) 13 (54) 18 (46)
BL 13 9 (77) 4 (53) 2 (27)
M 14 8 (57) 3 (50) 2 (25)
IM 12 9 (75) 2 (16) 6 (50)
LAR 7 7 (100) 2 (29)
UNS 10 4 (41) 3 (50) 2 (20)

589 Poster Session (Board #81), Sat, 8:00 AM-11:30 AM

Ki67 to predict RCB0I after neoadjuvant chemotherapy and endocrine therapy. HER2- breast cancer patients from ABCSG 34. First Author: Christian F. Singer, Department of Gynecology and Obstetrics, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

Background: Achievement of complete or near complete pCR (RCBOI) after neoadjuvant systemic therapy is associated with improved DFS. We have evaluated the utility of Ki67 measurements in predicting RCB0I in women with early breast cancer who were treated with neoadjuvant endocrine (NET) therapy or chemotherapy (NACT). Methods: This translational study was carried out within a prospectively randomized phase-II trial in 400 patients with HER2- eBC (ABCSG 34): 89 postmenopausal women with ER++, or ER+ and Ki67 < 14%, and G1/2/X tumors received 24 weeks of letrozole (NET). 311 postmenopausal patients with ER-, or ER+ and Ki67 > 14%, or with G3 tumors, or premenopausal patients, received 8 cycles of anthracycline/ taxane-based NACT. Ki67 was measured in the whole specimen area at baseline, after 12 weeks of therapy, and at surgery after weeks, and was correlated with Residual Cancer Burden (RCB) and pCR. Results: Median Ki67 profoundly decreased after 12 weeks of NET and NACT, and there was no significant further decrease at 24 weeks. NACT-treated patients with a ≥30% decrease at week 12 were more likely to achieve RCB0I (OR 2.778 [95% CI 1.25-6.19], p = 0.0124), while no such effect was found in NET-treated patients. NACT-treated patients with baseline Ki67≥50% were markedly more likely (OR 3.568 [95% CI 2.08-6.11], p < 0.0001) to achieve RCB0I and pCR (OR 5.797 [2.88-11.66], p < 0.0001) when compared to patients with Ki67 < 50%. Conversely, NET-treated patients with baseline Ki67≥20% were less likely (OR of 0.268 [95% CI 0.08-0.85], p < 0.0247) to achieve RCB0I. 76/153 patients with Ki67≥50% vs 26/120 with Ki67 < 50% experienced RCB0I in response to NACT (NET: 78.3%; PPV: 49.7%), 5/47 patients with Ki67<20% vs 12/39 with Ki67≥20% experienced RCB0I in response to NET (PPV: 89.4%; PPV: 30.8%). Conclusions: Maximal Ki67 suppression was achieved after 12 weeks of neoadjuvant therapy, and a decrease of ≥30% under NACT predicted excellent response (RCB0/I). Baseline Ki67 values were per se already highly predictive in a clinically meaningful manner. NACT-treated patients with a Ki67≥50% had a ≥30% decrease at 12 weeks to achieve RCB0I, while NET-treated patients with a Ki67≥70% achieved RCB0I in only 1 out of 9 cases. Clinical trial information: 2011-004822-B5.
Pathological complete response in basal subtype tumors to predict improved distant metastasis free survival in the NBRST trial. First Author: Pat W. Whitworth, Nashville Breast Center, Nashville, TN, USA

Background: In the multi-institutional NBRST study (NCT01479101), conducted from June 2011 to December 2014, 20% of ER+/HER2- patients were classified as Basal subtype by the 80-gene functional subtype signature (80-GS). 3-year event-driven follow-up (FU) is now available. Methods: The 70-gene risk of recurrence signature (70-GS) and 80-GS results were combined to classify patients (Pts) into four molecular subtypes: Basal, HER2, Luminal-B (high risk Luminal), and Luminal-A (low risk Luminal). Rate of pathological complete response (pCR) was previously assessed following neoadjuvant therapy. Here we evaluated FU for these Pts to determine if pCR was predictive of positive outcome using distant metastasis free interval (DMFI) as an endpoint. Results: Of 706 NBRST Pts currently reporting FU, 35% were Basal, 16% HER2, 34% Luminal-B, and 15% Luminal-A. Overall 26% of Pts had a pCR, with notable differences by subtype: 34% in Basal, 67% in HER2, 9% in Luminal-B, and 5% pCR in Luminal-A patients. FU from diagnosis ranged from 0.3-70.8 months (median 34 months). Sixty-nine percent of Pts received some adjuvant therapy: 51% endocrine therapy (AET), 10% chemotherapy (ACT), and 16% received adjuvant targeted therapy (53% with AET/ACT). There were 94 DMFI events at last FU: 81 in Pts who did not have a pCR, 13 in Pts who did have a pCR. 80-GS basal subtype Pts who achieved a pCR exhibited better 3-year probability of DMFI, compared to those who did not. Conclusions: NBRST’s event-driven FU supports the I-SPY2 TRIAL’s findings that pCR predicts better distant metastasis free outcomes. The results of this prospective population further show that 80-GS basal subtype Pts with pCR have substantially better outcome at 3 years, compared to those who do not have a pCR. 70-GS low risk Luminal Pts showed minimal impact with neoadjuvant chemotherapy. Clinical trial information: NCT01479101.

Pharmacokinetics of CT-P6 and reference trastuzumab by clinical factors in early breast cancer (EBC). CT-P6 or H in HER2+ EBC patients. Methods: CT-P6 is a proposed biosimilar to reference trastuzumab, Herceptin (H) (Genentech, S San Francisco, CA, USA). A randomized phase III trial showed efficacy equivalence and comparable pharmacokinetics (PK) and safety between CT-P6 and H (NCT02640671). Clinical factors have been shown to affect trastuzumab parameters. We compared known factors that may affect the PK of CT-P6 and H in HER2 positive early breast cancer (EBC). First Author: Justin Staubing, NIH Research Professor, Imperial College, London, United Kingdom

Background: CT-P6 is a proposed biosimilar to reference trastuzumab, Herceptin (H) (Genentech, S San Francisco, CA, USA). A randomized phase III trial showed efficacy equivalence and comparable pharmacokinetics (PK) and safety between CT-P6 and H (NCT02640671). Clinical factors have been shown to affect trastuzumab parameters. We compared known factors that may affect the PK of CT-P6 and H in HER2 positive early breast cancer (EBC). Methods: A total of 549 patients were randomized to receive CT-P6 (n = 271) or H (n = 278) with combination chemotherapy in the neoadjuvant setting. CT-P6 was administered at 8 mg/kg (cycle 1 only) by 60min IV every 3 weeks. The primary endpoint was pathological complete response (pCR). Key PK parameters for CT-P6 and H were assessed during the neoadjuvant period in terms of CtroughSS and CmaxSS at steady state (predose of cycle 8, CtroughSS and CmaxSS was analyzed by age, race, weight, and pathological response. Results: The serum concentration gradually increased and steady state was reached at cycle 7 (predose of cycle 8). There was no statistically significant difference between CT-P6 and H in any of the subgroups analyzed. Clinical trial information: NCT02162667. Conclusions: The serum CtroughSS, level of trastuzumab was comparable between CT-P6 and H groups in all subanalyzed. These data support the PK similarity between CT-P6 and H independently of age, race, weight or pCR assessment method.

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Background: Inflammation plays an important role in cancer development and proliferation. Host systemic markers of inflammation including the neutrophil-to-lymphocyte ratio (NLR) have been associated with a poor prognosis in solid tumours. The objectives of our study were to evaluate NLR and platelet-to-lymphocytes ratio (PLR) in patients (pts) with operable HER2pos breast cancer (BrCa) treated with neo-adjuvant trastuzumab (T)-containing chemotherapy (NACT) and to correlate NLR and PLR with Disease Free Survival (DFS) and Overall Survival (OS). Methods: This was a retrospective, single-center analysis of a prospectively accrued Institutional database (The One-Thousand HER2pos Patients project) of non-metastatic operable HER2pos BrCa pts who received NACT. Pts with confirmed supraclavicular/ internal mammary nodes were excluded. NLR and PLR were calculated at baseline prior to HER2 therapy (Tx) initiation. All patients underwent curative surgery (Sx) following T-containing NACT. Results: 156 female patients were included. Pts characteristics: median age 55.6(27-78) yrs, median time from diagnosis to initiation of HER2 Tx 4(1-18) weeks, ER positive 93(60%), cytology- proven positive lymph nodes at diagnosis 41 (26%), NACT was: TCH 116(74%), Docetaxel/Cyclophosphamide/T or single-agent taxane/T 20 (13%), AC-TH/FEC-TH 7 (4%), other regimens 13 (8%). Median follow-up is 4.3(1.11)-yrs. Pts with NLR > 2.5 at baseline had significantly better PFS (HR 0.29 p = 0.03) and OS (HR 0.14 p = 0.07) compared to pts with NLR > 2.5. Baseline PLR < 150 was associated with superior OS (HR 0.15 p = 0.08) compared to PLR > 150. No statistically significant association was observed between NLR and PLR vs placebo upon invasive disease-free survival (iDFS) in high risk HER2 patients. Conclusions: Baseline NLR > 2.5 and PLR > 150 are inexpensive and readily available prognostic markers of adverse outcome and may play a clinically significant role in refinement of risk estimates within disease stages and subgroups and treatment de-escalation.

POSITIVE (IIBCSG 48-14/ BIG 8-13/ A212405): Evaluating outcomes after interrupting endocrine therapy (ET) for women with endocrine-responsive (ER+) early breast cancer (BC) who desire pregnancy, First Author: Ann H. Partridge, Dana-Farber Cancer Institute, Boston, MA

Background: Retrospective evidence suggests that pregnancy after BC does not negatively impact disease outcomes in pts with ER + BC and is safe for the offspring. Young BC pts are often diagnosed before completing family planning, and cannot wait 5-10 yrs to complete ET before attempting pregnancy. Thus, prospectively evaluating the safety of temporary interruption of ET to allow conception is an unmet, patient-oriented, medical need. Methods: Young pts with ER+ early BC who desire pregnancy interrupt ET for approximately 2 yrs to attempt pregnancy (treatment wash-out (3 mos), and, ideally, conception (>3-6 mos), delivery (>9 mos), breast feeding if feasible (>6 mos)). Pts are advised to resume ET as soon as child-bearing is completed to finish 5-10 yrs ET. Major eligibility requirements: pt wishes to become pregnant; histologically-proven stage II-III ER+ BC; age ≥ 18 yrs and ≤42 yrs; prior adjuvant ET for ≥18 mos but ≤30 mos; premenopausal status at BC diagnosis. With 500 pts enrolled and followed for a median of 3 yrs, the statistical design is based on the 95% CI for the 3 yr BC recurrence rate; interim monitoring assumes a 2% BC recurrence risk/y with continuous ET and high chance to stop early if the BC risk exceeds 4%/y with ET interruption. Translational research will evaluate aspects related to fertility, pregnancy and BC biology. The Psycho-oncological Companion Study (POCS) explores psychological distress, fertility concerns and decisional conflicts (mandatory in the US and open to interested centers elsewhere), with a target accrual of 200. More than 170 participating centers in 20 countries: USA/Alliance, Canada/CCGT, Switzerland/SAKK, Italy, Belgium, Spain/SOLT/GIECAM, Slovenia, Japan/JBCRG, Norway/NBCG, Netherlands/BOOG, Ireland/CTI, Portugal/SOLTI, Australia, Israel, Greece/HORG, Hungary, South Korea, Serbia, Austria/ABCBSG and France. Eligible sites can open POSITIVE through NCTN (Alliance) or IBCSG, and referral to participating centers of eligible pts on ET who are interested in having a pregnancy after BC is strongly encouraged. Current Accrual (13 Feb 2018): 205 main study; 114 POCS, Clinical trial information: NCT02308085.
TPS598  Poster Session (Board #89a), Sat, 8:00 AM-11:30 AM
The Breast Cancer Weight Loss (BWELO) trial: Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early-stage breast cancer (Alliance A111101). First Author: Jennifer A. Ligibel, Dana-Farber Cancer Institute, Boston, MA
Background: Obesity is a growing health problem in the Unites States and around the world. Excess body weight has been linked to both an increased risk of developing breast cancer and poor prognosis in women diagnosed with early stage disease. A recent meta-analysis of 82 studies demonstrated that risk of breast cancer mortality was increased by 35% in women who were obese at the time of breast cancer diagnosis compared to women who were of normal weight. The Breast Cancer Weight Loss (BWELO) study will evaluate the effect of weight loss after breast cancer diagnosis on risk of cancer recurrence.
Methods: BWELO is a Phase III randomized trial evaluating the impact of a telephone-based weight loss intervention vs control on invasive disease-free survival (iDFS) in 3136 overweight and obese women with Stage II-III breast cancer. Eligibility criteria include diagnosis of hormone receptor positive or triple negative breast cancer within the preceding 12 months, body mass index of ≥27kg/m², and completion of surgery, chemotherapy, and radiation (if administered). Participants are randomized to a 2-year telephone- and mail-based weight loss intervention, adapted from the Diabetes Prevention Program, plus a health education program or to a health education alone control group. The study has 85% power, using a one-sided Type I error rate of 0.025, to detect a hazard ratio of 0.80 between groups. This equates to a 4.1% absolute reduction in iDFS events in the intervention group vs controls. Secondary aims will evaluate the impact of the weight loss intervention upon overall survival, weight and body composition, and patient-reported outcomes. Fasting blood is collected serially over time, and tissue samples of malignant and benign breast tissue are collected at baseline to provide insight into the biologic mechanisms linking obesity and breast cancer. BWELO opened in September 2016. To date, 1015 patients have been randomized and more than 1100 sites in the US and Canada have activated the trial. Support: U10CA180821, U10CA180882, U10CA180820, U10CA180868, U10CA077202. Clinical trial information: NCT02750826.

TPS600  Poster Session (Board #90a), Sat, 8:00 AM-11:30 AM
POSNOC: Positive Sentinel Node—Adjuvant therapy alone versus adjuvant therapy plus clearance or axillary radiotherapy. First Author: Amit Goyal, Royal Derby Hospital, Derby, United Kingdom
Background: Role of additional axillary treatment (AxT) (axillary lymph node dissection (ALND) or axillary radiotherapy (ART)) in women with macrometastases and undergoing systemic therapy remains unclear. Z11 included both micro and macrometastases (around 40% micrometastases) and showed that ALND may be omitted in women with ≤2 positive nodes undergoing breast conserving surgery (BCS) and receiving whole breast RT. Paradoxically, MA20, demonstrated improved DFS following the addition of regional RT. 51.8% (949/1832) had 1 or 2 positive nodes. 98.9% (1812/ 1832) had T1/T2 tumors. A post Z11 survey shows that most US oncologists treat the undissected axilla in women with macrometastases with ART rather than omitting AxT. Therefore, a confirmatory study is needed to clarify the role of additional AxT in women with ≤2 macrometastases undergoing BCS and other subgroups that were not included in Z11 e.g. mastectomy, extranodal invasion and sentinel node biopsy (SNB) before NACT. Methods: Primary objective is to assess whether for women with ≤2 macrometastases at SNB, systemic therapy alone is non inferior to systemic therapy plus AxT in terms of axillary recurrence at 5 years. Secondary objectives are arm morbidity assessed by LBCQ and QuickDASH questionnaires; QoL assessed by FACT B+4 questionnaire; anxiety assessed by STA; locoregional recurrence; distant metastasis; time to axillary recurrence; axillary recurrence free survival; DFS; OS; contralateral breast cancer; non breast malignancy; economic evaluation. Eligibility criteria are: ≥ 18 yrs, unir or multifocal invasive cancer, T1/T2, 1 or 2 macrometastases, with or without extranodal invasion. Target sample size is 1900 with a projected drop out and non compliance with treatment allocation rate of 10%. Primary analysis will be per protocol. Following pre specified subgroup analyses shall be performed: number of macrometastases, age (50, ≥50), type of breast surgery, ER status, tumour grade (1 or 2, 3), SN assessment technique (OSNA, non OSNA), extranodal invasion. POSNOC opened to recruitment in July 2014. To date 960 women have been recruited at 82 sites in the UK and 18 sites in Australia and New Zealand. Clinical trial information: NCT02401685.

TPS601  Poster Session (Board #90b), Sat, 8:00 AM-11:30 AM
NRG Oncology/NSABP B-51/TROG 1304. Phase III trial to determine if concurrent whole breast radiotherapy (CWRNRt) in patients (pts) with positive axillary (PAx) nodes who are ypNO after neoadjuvant chemotherapy (NC). First Author: Eleftherios P. Mamounas, NSABP/NRG Oncology, and Orlando Health UF Cancer Center, Orlando, FL
Background: This phase III post-NC trial evaluates if CWRNRt post-Mx or whole breast irradiation (WBI) with RNRT after BCS significantly reduces the IBCT-FI rate in pts with PAx nodes that are negative after NC. Secondary aims are OS, LRR-FI, DF-FI, DFS-DCIS, second primary cancer, and comparison of RT effect on cosmesis in reconstituted Mx pts. Correlative science examines RT effect by tumor subtype, molecular outcome predictors for residual disease pts, and predictors for the degree of reduction in locoregional recurrence. Methods: Clinical T1-3, N1 IBC PAX nodes (FNCA or core needle biopsy) pts complete ≥8 weeks of NC (anthracycline and/or taxane). HER2+ pts receive anti-HER2 therapy. Following NC, BCS or Mx, sentinel node biopsy (≥2 nodes) and/or Ax dissection with histologically negative nodes is performed. ER/PR and HER-2neu status before NC is required. Pts receive appropriate adjuvant systemic therapy. Radiation credentialing with a facility as a whole breast irradiation. Random assignment for Mx pts is to no CWRNRt or CWRNRt and for BCS pts to WBI or WBI+RNRT. Statistics: 1636 pts to be enrolled over 5 yrs (definitive analysis at 7.5 yrs). Study is powered at 80% to test that RT reduces the annual hazard rate of events for IBCT-FI by 35% for an absolute risk reduction of 4.6% (5-year cumulative rate). Intent-to-treat analysis with 3 interim analyses (43, 86, and 129 events) and a 4th/final analysis at 172 events. Pt-reported outcomes focusing on RT effect will be provided by 736 pts before random assignment and at 3, 6, 12, and 24 mos. Accrual as of 1-23-18 is 848 (51.83%). Contacts: Protocol: CTSG member website: https://www.ctsg.org; Questions: NRG Oncology Pgh Clinic Coord: Dpt: 1-800-477-7227 or ccd@nsabp.org. Pt entry: Open at: https://open.ctsg.org or the OPEN tab on CTSU member website. Support: U10 CA-21166; -180868, -180822; 189867; Elekta Clinical trial information: NCT01827976. 
TPS602  Poster Session (Board #91a), Sat, 8:00 AM-11:30 AM
KEYNOTE-522: Phase III study of pembrolizumab (pembrol) + chemotherapy (chemo) vs placebo + chemo as neoadjuvant therapy followed by pembrol vs placebo as adjuvant therapy for triple-negative breast cancer (TNBC). First Author: Peter Schmid, Barts Cancer Institute, Centre for Experimental Cancer Medicine, London, United Kingdom

Background: Recently presented data from the I-SPY 2 trial showed that pembrolizumab, a humanized, anti–PD-1 monoclonal antibody, significantly increased the pathologic complete response (pCR) rate in early-stage TNBC, when combined with neoadjuvant chemotherapy (Nanda et al. ASCO 2017. Abs 506). KEYNOTE-522 (NCT03036488) is a phase III study of pembrol+chemo vs placebo+chemo as neoadjuvant treatment, followed by pembrol vs placebo as adjuvant treatment in pts with TNBC. Methods: Approximately 855 pts with TNBC, defined as combined primary tumor (T) and regional lymph node (N) stage per AJCC (investigator-assessed: T1c N1-2, T2-4 N0-2), will be randomly assigned to 1 of 2 arms. Stratification will be by tumor nodal status (positive vs negative), size (T1/T2 vs T3/T4), and castration-resistant regimen choice (Q3W vs QW). In arm 1, pts will receive 4 cycles of pembrol 200 mg Q3W+paclitaxel (80 mg/m² QW on d 1, 8, 15)+carboplatin (AUC 5 Q3W on d 1 or AUC 1.5 QW on d 1, 8, 15) and then 4 cycles of pembrol+doxorubicin (60 mg/m² Q3W on d 1 or every 3 wks) concurrently with trimodality imaging. In arm 2, pts will receive pembrol. Definitive surgery will be 3-6 wk after the last cycle, then pts will receive 9 cycles of pembrol (200 mg Q3W) or placebo as adjuvant therapy. All cycles = 21d; treatment is up to 17 cycles or until disease progression or unacceptable toxicity. Primary end points are pCR rate using ypT0/Tis ypN0 and EFS. Secondary end points include safety, OS, and pCR rate by ypT1-3N0, ypT4N0, and ypT4N1 in all pts; and OS, EFS, and pCR rate by ypT0/Tis ypN0, ypT3N0, and ypT4N0 and ypT4N1 in pts with PD-L1+ tumors (combined positive score, CPS ≥ 1). Eligible pts are aged ≥ 18 y with previously untreated, locally advanced, nonmetastatic, ECOG PS 0-1, TRM ≤ 2%, and inflammatory breast cancer or bilateral or multifocal primary tumors are allowed. Adequate organ function and ECOG PS 0-1 are required. Pts with a history of invasive malignancy that was diagnosed and/or treated within the last 5 y are excluded. Clinical trial information: NCT03036488.

TPS603  Poster Session (Board #91b), Sat, 8:00 AM-11:30 AM
NSABP B-59/GBG 96-GepaDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo+standard therapy (ST) for patients (pts) with triple-negative breast cancer (TNBC) randomized by adjuvant atezolizumab or placebo. First Author: Charles E. Geyer, NSABP/NRG Oncology and Virginia Commonwealth University Massey Cancer Center, Richmond, VA

Background: TNBC is associated with higher percentages of pathological complete response (pCR) to neoadjuvant chemotherapy (NAC), and women with a pCR have a favorable prognosis. However, Liedtke (2008) and Loibl (2011) found that women with residual disease have a substantially higher risk of recurrence than women with other subtypes of breast cancer. Additionally, Adams (2017) and Schmid (2017) found that therapeutic blockade of PD-L1 binding by atezolizumab has resulted in relevant anti-tumor efficacy. Methods: Design: This is a phase III, double-blind, placebo-control trial evaluating neoadjuvant atezolizumab with NAC followed by adjuvant atezolizumab in TNBC. Pts are stratified by region (North America; Europe), tumor size (1.1-3.0 cm; > 3.0 cm), AC/EC schedule (q2w; q3w), and nodule status (positive; negative), then randomized 1:1 to receive atezolizumab/placebo 1200 mg IV for 4 doses with AC/EC every 2-3 wks (per investigator discretion) for 4 cycles. Following surgery, pts receive atezolizumab/placebo 1200 mg IV every 3 wks as adjuvant therapy for 6 months. Radiotherapy based on local standards is co-administered with atezolizumab/placebo. NAC is neoadjuvant chemotherapy (NAC) of either arm 1: docetaxel 75 mg/m² x 1 + carboplatin AUC 5 q3w on d 1+cyclophosphamide (600 mg/m² q3w on d 1)+doxorubicin (90 mg/m² q3w on d 1)+vinorelbine (60 mg/m² q3w on d 1)+cyclophosphamide (600 mg/m² q3w on d 1) as neoadjuvant therapy. In arm 2, placebo will replace pembrol. Definitive surgery will be 3-6 wk after the last cycle, then pts will receive 9 cycles of pembrol (200 mg Q3W) or placebo as adjuvant therapy. All cycles = 21d; treatment is up to 17 cycles or until disease progression or unacceptable toxicity. Primary end points are pCR rate using ypT0/Tis ypN0 and EFS. Secondary end points include safety, OS, and pCR rate by ypT1-3N0, ypT4N0, and ypT4N1 in all pts; and OS, EFS, and pCR rate by ypT0/Tis ypN0, ypT3N0, and ypT4N0 and ypT4N1 in pts with PD-L1+ tumors (combined positive score, CPS ≥ 1). Eligible pts are aged ≥ 18 y with previously untreated, locally advanced, nonmetastatic, ECOG PS 0-1, TRM ≤ 2%, and inflammatory breast cancer or bilateral or multifocal primary tumors are allowed. Adequate organ function and ECOG PS 0-1 are required. Pts with a history of invasive malignancy that was diagnosed and/or treated within the last 5 y are excluded. Clinical trial information: NCT03281954.

TPS604  Poster Session (Board #92a), Sat, 8:00 AM-11:30 AM
NRG Oncology BR005: Phase II trial assessing accuracy of tumor bed biopsies (bx) in predicting pathological response in patients (Pts) with early-stage TNBC with complete response (CR) after neoadjuvant chemotherapy (NCT) in order to explore the feasibility of breast-conserving treatment (BCT) without surgery. First Author: Mark Basik, NRG Oncology, and The Jewish General Hospital, Montreal, QC, Canada

Background: The increased use of neoadjuvant chemotherapy (NCT) has enabled higher rates of breast-conserving surgery (BCS) as well as provided prognostic information for women with breast cancer. High pathological complete response (pCR) rates question the requirement for surgery, with its attendant morbidity. In order to avoid surgery, the ability to predict pCR prior to it must be very high. Trimodality imaging alone is inadequate to predict pCR prior to surgery. We hypothesize that performing core needle biopsy (bx) of the tumor bed in addition to trimodality imaging in pts having had a clinical complete response (cCR) will increase the ability to predict pCR. Utilizing predetermined imaging response criteria of complete or near-complete response coupled with a stereotactic core needle bx of the tumor bed, BR-005 aims to determine the predictive value of imaging followed by tumor bx for pCR and demonstrate its reproducibility across a multi-institutional setting. Methods: 175 pts with operable focal or multifocal (T1-T3), stage II/IIIa invasive ductal carcinoma [all receptor subtypes] will be entered. Pts must have completed a minimum of 8 wks of standard neoadjuvant chemotherapy and achieved a complete or near-complete radiologic tumor response on breast imaging with mammogram, ultrasound, and MRI, and undergone BCS. Following cCR and prior to surgery, pts will undergo a stereotactic-vacuum-assisted breast bx with clip placement. The primary end point is the proportion of pts with post-NCT neg image-directed bx who have a pCR. Residual cancer burden (RCB) scores and core bx pathology will be collected along with trimodality imaging data. Evaluation after 135 pts will allow for the possibility of early termination of the study. Results will provide the first step towards a paradigm change in the treatment of breast cancer, enabling a study to assess the criteria for successful avoidance of surgery in pts with high response rates to NCT. Accrual as of 1/19/ 2018: 135, Support from Genentech/Roche. NCT0188393.

TPS605  Poster Session (Board #92b), Sat, 8:00 AM-11:30 AM
PARTNER: Randomised, phase II/III trial to evaluate the safety and efficacy of triplenegative basal-like breast cancer patients. First Author: Jean Abraham, University of Cambridge, Department of Oncology & NIHR Cambridge Biomedical Research Centre & Cambridge University Hospitals NHS Foundation Trust, Cambridge Breast Cancer Research Unit, Cambridge, United Kingdom

Background: No specific targeted therapies are available for triple-negative breast cancer (TNBC), an aggressive and diverse subgroup. The basal TNBC subgroup show some phenotypic and molecular similarities with germline BRCA mutated BC (gBRCA). In gBRCA patients, and potentially other hormone recombination deficiencies, these already compromised pathways may allow PARP inhibitors to work more effectively. PARTNER was designed to establish if the addition of olaparib to neoadjuvant platinum-based chemotherapy for basal TNBC and/or gBRCA BC is safe and improves efficacy (pathological complete response (pCR)). Methods: Trial design: 3-Stage open label randomised Phase II/III trial of neoadjuvant CP: Carboplatin AUC5 with weekly Paclitaxel 80mg/m2 +/- olaparib 150mgBD for 12 days x 4 cycles, followed by clinicians’ choice of anthracycline regimen x 3 cycles. Basal-TNBC and/or gBRCA patients are eligible for inclusion. Tumour infiltrating lymphocytes and basal profile are assessed at baseline. Stage 1 and 2: Patients are randomised (1:1:1:1) to: CP; CP + olaparib from day (D) 0; or CP + olaparib from D 3. Stage 3: Patients are randomised (1:1:1) to either control arm or to the research arm selected in stage 2. Primary end-points: Stage 1 – Safety; Stage 2 - Schedule selection criteria by pCR rate and completion rate of olaparib protocol treatment. 53 patients in each research arm will be evaluated within a “pick the winner” design. Null hypothesis of pCR ≤ 35% versus alternative hypothesis of pCR > 55% will be tested with 90% power and with one sided significance level of 0.05 for the research arms. Stage 3 - Efficacy: anticipated pCR = 45-55% for all trial patients and ~50-60% for gBRCA patients. The trial is powered to detect an absolute improvement of 15% (all patients) and 20% (gBRCA patients) by adding olaparib to chemotherapy (enriched design). Enrichment design is applied with overall significance level 0.05(3). Stage 1 accrual is complete. Stage 2 began in August 2017. 19 sites open and 12 more in active set-up. Clinical trial information: NCT03150576.

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Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2−) advanced breast cancer (ABC). Results from MONALEESA-3. First Author: Dennis J. Slamon, UCLA Medical Center, Santa Monica, CA

Background: First-line RIB + letrozole significantly prolonged progression-free survival (PFS) in postmenopausal women with HR+, HER2−ABC. Here we report results from MONALEESA-3 (NCT02422615), a Phase 3 randomized, double-blind, placebo-controlled study of RIB + FUL in pts with HR+, HER2−ABC who received no or up to 1 line of prior endocrine therapy (ET). ABC: Methods: Postmenopausal women with HR+, HER2− ABC were randomized 2:1 (stratified by presence of liver and/or lung metastases and prior ET) to RIB (600 mg/day; 3-weeks-on/1-week-off) + FUL (500 mg) or placebo (PBO) + FUL. Primary objective: investigator-assessed PFS. Secondary objectives included overall survival, overall response rate (ORR), clinical benefit rate (CBR), and safety. Results: 726 pts were enrolled. Baseline pt characteristics were balanced between arms. Median duration from randomization to data cut-off: 20.4 months. The primary objective was met: PFS was significantly improved in the RIB arm vs the PBO arm (hazard ratio: 0.933; 95% confidence interval [CI]: 0.840–0.732; p = 0.00–10<sup>3</sup>); median PFS: 20 months; 95% CI: 18.5–23.5 vs 12.8 months; 95% CI: 10.9–16.3. Blinded independent review committee data supported primary efficacy results. Consistent PFS benefit was observed in pts with no (hazard ratio: 0.577; 95% CI: 0.415–0.802) and up to 1 line of prior ET for ABC (hazard ratio: 0.565; 95% CI: 0.428–0.744). In pts with measurable disease at baseline, ORR was 33% vs 29% (RIB vs PBO; p = 0.0033); CBR was 69% vs 60% (p = 0.015). Common all-grade (G) adverse events (AEs; ≥30% of pts; RIB vs PBO arm) were neutropenia (70% vs 2%), nausea (45% vs 28%), and fatigue (31% vs 33%). In the RIB vs PBO arms, G3/4 neutropenia occurred in 47%/7% vs 0%/0% of pts, G3/4 increased ALT in 7%/2% vs 1%/0% of pts, and G3/4 infections occurred in 5%/1% vs 2%/0% of pts. Conclusions: RIB + FUL vs PBO + FUL significantly prolonged PFS and demonstrated a manageable safety profile in postmenopausal pts with HR+, HER2−ABC who received no or up to 1 line of prior ET for advanced disease. RIB + FUL may, therefore, be a treatment option for this pt population. Clinical trial information: NCT02422615.

Abemaciclib for pre/perimenopausal women with HR+, HER2− advanced breast cancer. First Author: Patrick Neven, University Hospitals Leuven, Leuven, Belgium

Background: Abemaciclib is a selective inhibitor of CDK4 & 6 that is dosed to placebo (P) + F (16.4 vs 9.3 months; hazard ratio [HR] .553; 95% CI: .449–.681; p < .0000001; ORR in measurable disease 48.1% vs 21.3%; p = .006). Here, we compare the efficacy and safety of abemaciclib + F vs P + F in the pre/perimenopausal subgroup. Methods: MONARCH 2 was a Phase 3 randomized, double-blind, placebo-controlled study of abemaciclib + F vs placebo (PBO) + F in pts with HR+, HER2−ABC that progressed on (neo) endocrine therapy. Key eligibility criteria were: pre/perimenopausal women with HR+, HER2−ABC (pre/perimenopausal pts received a GnRH agonist); ECOG PS ≤ 1; progression on (neo) adjuvant ET, ≤12 months from end of adjuvant ET, or on first line ET for metastatic disease; ≤1 line of ET; no prior chemotherapy for metastatic disease; ≤1 line of ET; no prior chemotherapy for metastatic disease; ≤1 line of ET; no prior chemotherapy for metastatic disease. Pts received orally administered abemaciclib 150 mg twice daily + 500 mg F (per label) or P + F. Primary objective was investigator-assessed PFS. Secondary objectives included ORR, clinical benefit rate, disease control rate, duration of response, safety and tolerability. Results: 114 pre/perimenopausal pts were randomized 2:1 to abemaciclib + F (N = 72) and P + F (N = 42) arms, 57 PFS events were observed. Median PFS was not reached for the abemaciclib + F arm and was 10.5 months for the P + F arm (HR, 0.446; 95% CI: 0.264, 0.754; p = 0.002). In pts with measurable disease (n = 79, 69.3%), ORR was significantly higher in the abemaciclib + F arm; 60.8% (95% CI: 63.5–58.1%) vs 45.1% (95% CI: 41.6–48.6%) (p = 0.001). The most frequent adverse events (any grade) for abemaciclib + F vs P + F were diarrhea (87.3% vs 23.8%), neutropenia (59.2% vs 7.1%) and leucopenia (43.7% vs 4.8%). Conclusions: Abemaciclib + F in combination with a GnRH agonist significantly improved PFS and ORR, and had a generally tolerable safety profile in pre/perimenopausal women with HR+, HER2−ABC. Clinical trial information: NCT02107703.

Genetic landscape of resistance to CDK4/6 inhibition in circulating tumor DNA (ctDNA) analysis of the PALOMA3 trial of palbociclib and fulvestrant versus placebo and fulvestrant. First Author: Nicholas C. Turner, Royal Marsden NHS Foundation Trust, London, United Kingdom

Background: CDK4/6 inhibition combined with endocrine therapy is now a standard of care for advanced estrogen receptor (ER) positive breast cancer. Mechanisms of resistance to CDK4/6 inhibitors have been described in pre-clinical models, although there is limited evidence from clinical samples. We investigated the mechanisms of resistance to CDK4/6 inhibitor in the PALOMA3 trial using ctDNA analysis. The PALOMA3 phase III trial randomized 521 patients with endocrine pre-treated disease to palbociclib and fulvestrant (P+F) versus placebo and fulvestrant (F). Using driver mutation targeted sequencing we conducted a longitudinal ctDNA analysis in 193 pairs of baseline and end of treatment (EOT) plasma samples, supplemented with exome ctDNA sequencing in 16 paired samples of high tumor purity from patients treated with P + F. Results: Paired ctDNA analysis was performed on P+F (n = 125) and F alone (n = 68), with the ctDNA cohort representative of the overall study. R1I mutations emerged at EOT on P+F in a small minority of patients (6/125, 4.8%; p = 0.041), with no R1I mutations emerging at EOT on F alone. New driver mutations emerged in both PIK3CA (p = 0.00018) and ESR1 at EOT, in particular the ESR1 Y5135S mutation (p = 0.006), with no difference in frequency between P+F and F groups. Evolution of driver gene mutations was uncommon in patients progressing early on P+F, but common in patients progressing late on treatment. Paired exome analysis (n = 16) showed clonal evolution was frequent during P+F therapy, with copy number profiles remaining consistent before and after treatment. Conclusions: Breast cancer driver mutation landscapes are largely similar after treatment with P+F and with F alone, with acquired PIK3CA and ESR1 Y5135S mutations that likely contribute to fulvestrant resistance. Acquired R1I mutations are selected infrequently by P+F. These findings may inform future treatment strategies to address resistance to palbociclib and fulvestrant.

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Efficacy of sacituzumab govitacan (anti-Trop-2-SN-38 antibody-drug conjugate) for treatment-refractory hormone-receptor-positive (HR+)/HER2- metastatic breast cancer (mBC). First Author: Aditya Bardia, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Sacituzumab govitacan is a novel antibody-drug conjugate consisting of SN-38, the active metabolite of irinotecan, conjugated to a humanized mAb targeting Trop-2 (trophoblastic antigen-2), which is highly expressed in many epithelial cancers. A phase III basket trial (NCT01631552) investigated its activity in patients (pts) with advanced cancers, and we previously reported on pts with triple-negative mBC. Results in HR+/HER2 negative (as per ASCO/CAP guidelines) mBC pts who had ≥ 1 prior hormonal therapy are presented here. Methods: Pts received sacituzumab govitacan at a dose of 10 mg/kg on days 1 & 8 of a 21-day cycle until progression or unacceptable toxicity. Eligibility included ≥ 1 prior line of standard therapy for metastatic disease, measurable disease by CT or MRI. Efficacy was assessed locally by RECIST 1.1. Adverse events (AE) were evaluated according to CTCAE v4.0.

Results: Fifty-four pts with HR+/HER2- mBC (all female; median age 54 yrs, range 33-79) were accrued between 2/2015 and 6/2017. For metastatic disease, all pts received at least 2 prior treatments, with a median of 3 prior hormonal agents and 2 prior chemotherapy regimens. Prior treatments in any setting included taxane (93%), anthracycline (69%) and CDK 4/6 inhibitors (69%). 16 pts have died, 27 are in long-term follow-up and 11 still on treatment. The median number of doses was 11 (range 1-74). Treatment was generally well tolerated, with no treatment-related deaths. Based on current available AE data, grade ≥ 3 toxicity (≥10%) included neutropenia and febrile neutropenia. As of 12/31/2017 data cutoff, the overall response rate (ORR) was 24% (9 PRs/37). Maturing durability of response and progression-free survival was estimated using the hazard ratio (HR) of progression-free survival (PFS) for EVE + EXE vs EVE. The secondary objective was to estimate the HR of PFS for EVE + EXE vs CAP. Other secondary objectives were overall survival (OS) and safety. This was not a confirmatory study and no statistical comparisons were planned.

Conclusions: Sacituzumab govitacan as a single agent induced objective responses in heavily pre-treated HR+/HER2neg mBC, and was well tolerated with a safety profile consistent with previous reports. Clinical trial information: NCT01631552.

LBA1006

Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) vs FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER. First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

Everolimus (EVE) + exemestane (EXE) vs EVE alone or capcitabine (CAP) for estrogen receptor-positive (ER+), human epidermal growth factor receptor-2 (HER2-) metastatic breast cancer (ABC): BOLERO-6, an open-label phase 2 study. First Author: Guy Heinrich Maria Johannesburg, CHU Sart Tilman Liège and Liège University, Liège, Belgium

Background: BOLERO-6 (NCT01783444) was designed to evaluate the clinical benefit of EVE + EXE vs EVE alone or CAP for ER+ HER2- ABC that progressed on nonsteroidal aromatase inhibitors. Methods: Patients were randomized 1:1:1 to EVE 10 mg/day + EXE 25 mg/day, EVE alone or CAP 1000 mg/m² twice-daily. The primary objective was to compare the estimated HR of PFS for EVE + EXE vs EVE. The key secondary objective was to estimate the HR of PFS for EVE + EXE vs CAP. Other secondary objectives were overall survival (OS) and safety. This was not a confirmatory study and no statistical comparisons were planned.

Results: 309 patients received EVE + EXE (n=104), EVE (n=103) or CAP (n=102). Baseline characteristics were generally consistent; however the EVE + EXE arm, patients in the CAP arm were younger (68% vs 63%) were aged <65 years, more had bone-only lesions (24% vs 13%), were Caucasian (89% vs 75%) or fully active (56% vs 52%) and fewer had visceral disease (62% vs 66%) or ≥3 metastatic sites (44% vs 50%). Median follow-up from randomization to data cut-off (June 1, 2017) was 37.6 months. The estimated HR of PFS for EVE + EXE vs EVE was 0.74 (90% CI 0.57-0.97). The estimated HR of PFS for EVE + EXE vs CAP was 1.26 (90% CI 0.96-1.66) but a stratified multivariate Cox regression model adjusted on prognostic factors and baseline covariates with imbalances between arms gave a HR closer to 1 (HR 1.15; 90% CI 0.86-1.52). More patients in the CAP arm were censored for initiating new antineoplastic therapies (20% vs 9% with EVE + EXE). Median OS was 23.1 months with EVE + EXE vs 29.3 months with EVE (HR 1.27; 90% CI 0.95–1.70) and 25.6 months with CAP (HR 1.33; 90% CI 0.99–1.79). Grade 3/4 adverse events (AEs) were most common with CAP. Serious AEs were most common with EVE + EXE. Conclusions: The estimated HR of PFS for EVE + EXE vs EVE (0.74) is indicative of a treatment benefit. While the estimated HR of PFS for EVE + EXE vs CAP was 1.26, the CAP arm may have been favored by baseline imbalances and potential informative censoring. The safety profile of EVE + EXE was consistent with the known profile of this combination. Clinical trial information: NCT01783444.

1004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

1005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (MBC): A randomised, double-blind, placebo-controlled, phase II trial. First Author: Peter Schmid, Queen Mary University of London, London, United Kingdom

Background: The PI3K/AKT signalling pathway is frequently activated in triple-negative breast cancer (TNBC). AZD5363 is a highly-selective, oral, small molecule AKT inhibitor. The PAKT trial investigated the addition of AZD5363 to paclitaxel as 1st-line therapy for TNBC. Methods: This investigator-led, double-blind, placebo-controlled, randomised phase II trial, recruited women with previously untreated, metastatic TNBC at 42 sites in 6 countries. Patients were randomly assigned (1:1) to paclitaxel 90mg/m² (days 1, 8, & 15) with either AZD5363 (400mg BD) or placebo (days 2-5, 9-12, 16-19) every 28 days until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), PFS in the subgroup with PIK3CA/ AKTI1/PTEN alterations, response, and safety.

Results: Between 05/2014 and 06/2017, 140 patients were randomised to paclitaxel + AZD5363 (n = 70) or paclitaxel + placebo (n = 70). Median duration of follow-up was 18.2 months (95% CI, 13.6 to 24.0). In the ITT analysis, median PFS was 5.9 months (m) for AZD5363 compared to 4.2m for placebo [hazard ratio (HR), 0.75; 95% CI, 0.52 to 1.08; one-sided p = 0.06; two-sided p = 0.11 [predefined significance level of 0.10, one-sided]]. Median OS was 19.1m for AZD5363 compared to 12.6m for placebo (HR, 0.64; 95% CI, 0.40 to 1.01; one-sided p = 0.02; two-sided p = 0.04). Results for the subgroup with PIK3CA/ AKTI1/PTEN-altered tumours will be presented. Most common grade 3 or worse adverse events were diarrhoea (12% [8/68] of AZD5363-treated patients vs 1% [1/70] of placebo-treated patients), infection (4% vs 1%), neutropenia (3% vs 3%), rash (4% vs 0) and fatigue (4% vs 0). Conclusions: The trial met its primary endpoint. Addition of AZD5363 to 1st-line paclitaxel therapy for TNBC resulted in significantly longer PFS and OS. AZD5363 warrants further investigation for the treatment of MBC. First Author: Francois de Vries, Boston Medical Center, Boston, MA

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatients (IPAT) + pachetaxel (PTX) for locally advanced/metastatic breast cancer (mTNBC). 

**Background:** In LOTUS (NCT02162719), adding the oral AKT inhibitor IPAT to first-line PAC for mTNBC improved progression-free survival (PFS; primary endpoint) (Kim, Lancet Oncol 2017). The stratified PFS hazard ratio (HR) in the intent-to-treat (ITT) population (n = 124) was 0.60 (95% CI 0.30–0.99; p = 0.037; median PFS 6.2 vs 4.9 months with IPAT vs PBO, respectively). In prespecified analyses of patients (pts) with PIK3CA/ATK1/PTEN–mutated tumors, the unstratified PFS HR was 0.44 (95% CI 0.20–0.99; median 9.0 vs 4.9 months). We now report updated OS results in the ITT population after OS events in 50% of pts. OS results in the PIK3CA/ATK1/PTEN–mutated subgroup are immature. 

**Methods:** Pts had measurable inoperable mTNBC previously untreated with systemic therapy. Pts were stratified by prior (neo) adjuvant therapy, chemotherapy-free interval (6–12 months vs >12 months not applicable) and tumor IHC PTEN status, and randomized 1:1 to PAC 80 mg/m² (d1, 8, & 15) with either IPAT 400 mg or PBO (d1–21) q28d until progression or unacceptable toxicity. OS was a prespecified secondary endpoint. The table shows results after 23 months’ follow-up (data cutoff 26 July, 2017). No new safety signals were seen. 

**Results:** The previously observed PFS improvement with IPAT was followed by a trend toward improved OS (~5-month difference in the medians) at the updated OS analysis. Post-progression therapy was similar. These findings further support evaluation of first-line IPAT + PAC for mTNBC with ongoing phase 3 trial. Final OS results from LOTUS are expected in 2019. 

**Clinical trial information:** NCT02162719

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**1010 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM**

**Determinants of high tumor mutational burden (TMB) and mutational signatures in breast cancer.**

**First Author:** Romaindu Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA

**Background:** High TMB correlates with high neoantigen burden, and this is thought to be predictive of response to immunotherapy. The aim of this work is to evaluate frequency, mutational patterns, and genomic profile of hypermutated breast cancer. 

**Methods:** We used sequencing data from publicly available on cbiortal.org, including TCGA, France 2016, MSK-IMPACT, MBCProject, AACR-GENIE, and ongoing studies at our institute (The Center for Cancer Precision Medicine Metastatic Breast Cancer Study; The Young Women’s Breast Cancer Study) to evaluate mutational load across breast cancers. Samples were classified as having high TMB if they had > 10 mutations (mut) per megabase (MB). 

**Results:** We included 3689 samples for the analysis. The median TMB was 1.55 mut/MB. TMB significantly varied according to histology (ductal > lobular, p = 4.6x10^-13), tumor subtype (HR-/HER2+ > TNBC > HR+/HER2+ > HR+/HER2+, p < 0.05), staging (metastatic > primary, p = 2.2x10^-14) and site of metastasis (higher soft tissue, and lowest lung, p < 0.05). We found a total of 70 (~2%) hypermutated tumors (62.8% metastatic & 37.2% primary samples).

Mutational signature analysis of the hypermutated samples showed the presence of dominant APOBEC (77.1%), homologous recombination (HR; 2.9%), defective DNA mismatch repair (MMR; 18.6%), and PHEE mutation (1.4%) signatures. Median TMB was higher for samples with POLE and HR signature, followed by those with MMR and APOBEC (93.1, 38.7, 14.6 and 12.4 mut/MB, respectively). Among hypermutated tumors, 8 samples had somatic mutation in the POLE gene, but only the case with POLE signature high had a characterized POLE driver mutation. In addition, 80% of hypermutated tumors with APOBEC signature had PIK3CA mutations versus 31% of hypermutated tumors with other signatures (p = 0.0005).

**Conclusions:** TMB is correlated with clinical parameters including histology, receptor subtype and site of metastasis. Different mutational signatures are present in this population, including POLE, defective DNA MMR, HR and APOBEC. The potential role of these different signatures in predicting benefit to immunotherapy in hypermutated breast cancers is unclear, and warrants further investigation.

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**1011 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM**

**TOPACIOX/keynote-162: Niraparib + pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC), a phase 2 trial.**

**First Author:** Shveta Vinayak, Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH

**Background:** Chemotherapy is a standard of care for TNBC despite its sub-optimal efficacy. ~15–20% of TNBC have BRCA1/2 mutations (mut); ~75% of BRCA1 mut BCs are TN. Single agent poly(ADP-ribose) polymerase (PARP) inhibitors have clinical activity in pts with BRCA1/2 mutations (BRCAmut) BC and provide median PFS of 6 mos in pts with BRCAmut TNBC vs 3.5 mos for chemotherapy. Single-agent pembrolizumab (pembro), a programmed death 1 (PD-1) inhibitor, has shown objective response rates (ORR) of 5–18% in previously treated TNBC. TOPACIO (NCT02657889) is a fully enrolled study evaluating the safety and efficacy of combination treatment with selective PARP1/2 inhibitor niraparib + pembro in pts with met TNBC. 

**Methods:** Pts received niraparib 200 mg orally once daily + pembro 200 mg IV on day 1 of each 21-day cycle. Primary efficacy endpoint was ORR and secondary endpoints included disease control rate (DCR = CR + PR + SD) (stable disease). 

**Results:** As of Jan 2018, 12 of 54 enrolled TNBC pts (22%) had deleterious BRCAmut, 9 (17%) not tested/indeterminate results. Median age was 54 yrs, with median of 1 prior line of therapy in the met setting (range 0–3); 22 (41%) had received prior platinum in the met setting; 39 (72%) had received prior (neo)adjuvant therapy. Forty-five pts were evaluable, with ≥1 on-study scan. To date, ORR is 29% and DCR is 49%, including 3 CR (7%), 10 PR (22%), 9 SD (20%), and 23 progressive disease (PD) (51%). Ten of 13 responders have ongoing responses; 13 pts have received > 6 mos of treatment (6 BRCAmut, 5 BRCAwt, 2 BRCAunk); 11 pts remain on treatment. The 12 BRCAmut pts were 1 CR, 7 PR, 1 SD and 3 PD. Median PFS in BRCAmut group is 8.1 mos (95% CI 0.2–NE). ORR (any BRCA status) was 33% in PD-L1–pos (combined proportion score ≥1%) vs 15% in PD-L1–neg pts. Treatment-related grade ≥3 AEs occurred in 27 pts (30%); the most common were thrombocytopenia (13%) & anemia (11%). Follow-up is ongoing. 

**Conclusions:** Preliminary activity is encouraging with durable responses observed irrespective of BRCA1/2 or PD-L1 status or prior platinum exposure with the highest ORR in BRCAmut pts. No new safety signals were identified with the combination. Clinical trial information: NCT02657889.
1012 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM Adaptive phase II randomized trial of nivolumab after induction treatment in triple negative breast cancer (TONIC trial). Final response data stage I and first translation data. First author: Marleen Kok, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Anti-PD-L1 can result in durable responses in patients with metastatic triple negative breast cancer (TNBC). However, only a subgroup of TNBC patients benefits from anti-PD(L)1 with response rates of 5-10% in unselected cohorts. Strategies to render the tumor micro-environment (TME) more susceptible to anti-PD(L)1 might include stimulation of anti-cancer immune responses by induction treatment with irradiation or low dose chemotherapy. Methods: In stage I (non-comparative Simon’s two stage design) patients with metastatic TNBC who received ≤ 3 lines of palliative chemotherapy were randomly allocated to one of five 2-week induction treatments consisting of 1) 3x8 Gy irradiation of one metastatic lesion 2) 2x doxorubicin 15mg weekly flat dose 3) cyclophosphamide 50mg daily orally 4) 2x cisplatin 40mg/m2 weekly 5) no induction treatment. After this induction period, all patients received nivolumab until uRECIST progression. For the total group the ORR is 20% with 2 CRs and 11 PRs. In the nivolumab-only cohort the benefit rate of 23%. ORR on nivolumab after induction with irradiation, before nivolumab is feasible. Final clinical and translational results of stage I will be presented at ASCO 2018. Clinical trial information: NCT02499367.

1013 Poster Discussion Session; Displayed in Poster Session (Board #94), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM Final overall survival (OS) analysis of PHEREXA: A randomized phase III trial of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) in patients with HER2-positive metastatic breast cancer (MBC) who experienced disease progression during or after H-based therapy. First Author: Andor Urmio, Onkologikoa Foundation, San Sebastian and Catalain Institute of Oncology-IDIBELL, Oncology Hospital, Donostia, Spain

Background: In PHEREXA (NCT01026142), adding P to H + X did not significantly improve independent review facility-assessed progression-free survival (IRF-PFS; primary endpoint) in patients with HER2-positive MBC who received a prior taxane and progressed during or after H-based therapy (hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.65–1.02; p = 0.1731). An 8-month increase in median OS of 36.1 months was observed with P, but due to hierarchical testing of IRF-PFS, and subsequently of OS, statistical significance could not be claimed. No new safety signals were identified. We now report the final prespecified analysis. Methods: Randomized arms were: A: intravenous H 8 mg/kg – 6 mg/kg every 3 weeks (q3w) + oral X 1250 mg/m2 twice daily (2 weeks on, 1 week off q3w) and B: intravenous P 840 mg—420 mg q3w + intravenous H per Arm A + oral X 1000 mg/m2 (same schedule as Arm A). Treatment was given until disease progression, unmanageable toxicity, or patient request for discontinuation. OS and investigator-assessed PFS (INV-PFS) were assessed in the intent-to-treat population (all assigned patients); adverse events (AEs), in the safety population (patients who received ≥ 1 dose of study drug). Results are descriptive. Results: At clinical cutoff (20-Sep-17), median time on study, including follow-up, was 23 months in Arm A and 33 months in Arm B. Efficacy is shown in the table. There was a small increase in AE incidence with longer follow-up, but no new symptomatic left ventricular systolic dysfunction (0 patients in Arm A and 5 [2.2%] in Arm B). Conclusions: While final OS results of PHEREXA are descriptive, median OS of 37.3 months in Arm B, with a 9.1-month increase versus Arm A, shows that clinical efficacy of H + P is maintained with longer follow-up. There were no new safety signals and no evidence of late cardiac toxicity. Clinical trial information: NCT01026142.

1014 Poster Discussion Session; Displayed in Poster Session (Board #95), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer. First Author: Cristina Saura, Medical Oncology Department, Breast Cancer Group, Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: SYD985, (vic-)trastuzumab duocarmazine, is a HER2-targeting antibody-drug conjugate with a cleavable linker-duocarmycin payload that causes irreversible alkylation of the DNA in tumor cells. The dose-escalation part of a Phase I study was completed previously; we herein present preliminary efficacy data of the breast cancer expansion cohorts and safety data of all expansion cohorts (breast, gastric, urothelial and endometrial cancer). Methods: HER2 tumor expression was determined by a central lab and had to be immunohistochemistry (IHC) 1+ or higher; HER2-positive was defined as IHC 2+/3+ or IHC 1+ with IHC 2+/3+ by ISH. SYD985 was treated with 1.2mg/kg SYD985 IV every 3 weeks until disease progression or unacceptable toxicity. Tumor evaluation scans were done every 6 weeks. Results: Ninety-nine (99) breast cancer patients were enrolled. Of the 50 patients with HER2-positive breast cancer, the majority received 3 or more prior HER2-targeting regimens in the locally advanced or metastatic setting, including (ado-)trastuzumab emtansine in 80% of the patients. Preliminary results showed that SYD985 demonstrated an overall response rate (ORR) of 33% and a median PFS of 9.4 months. At the time of data cut-off, 8 patients (16%) received SYD985 for over one year and 5 patients (10%) continued to receive treatment. Efficacy has also been demonstrated in heavily pretreated patients with HER2-low metastatic breast cancer, including hormone-receptor positive (N = 32) and triple-negative breast cancer (N = 17). The ORRs were 27% and 40%, respectively, with several patients ongoing on SYD985. The safety profile is manageable and mainly characterized by grade 1 and 2 events. The most common adverse drug reactions were fatigue, dry eyes, conjunctivitis and increased lacrimation. Grade 3/4 adverse drug reactions most commonly reported included neutropenia (6%) and conjunctivitis (4%). Conclusions: SYD985 showed promising clinical activity in heavily pretreated breast cancer patients, both HER2-positive and HER2-low tumors with or without hormone receptor expression. A Phase III study (TULIP) is currently ongoing in HER2-positive breast cancer patients. Clinical trial information: NCT02277717.

1015 Poster Discussion Session; Displayed in Poster Session (Board #96), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM Clinical benefit of tucatinib after isolated brain progression: A retrospective pooled analysis of tucatinib phase 1b studies in HER2+ breast cancer. First Author: Rashmi Krishna Murthy, University of Texas MD Anderson Cancer Center, Houston, Texas

Background: For MBC patients with isolated brain progression, current guidelines recommend treatment with CNS-directed therapy and continued systemic therapy, although systemic therapy alone may be considered during relapse. Two Phase 1b trials of tucatinib permitted patients with HER2+ MBC to continue study treatment following CNS-directed therapy in instances of isolated brain metastases (BM) progression. Methods: 2 Phase 1b studies of tucatinib were pooled to identify patients with isolated brain progression (defined as new or progressive BM with stable or responding systemic disease) while on study. In patients treated for isolated brain progression, the median time to any subsequent progression or death was determined. Results: 117 patients were analyzed; 57 in the 004 (tucatinib + T-DM1) and 60 in the 005 (tucatinib +/- trastuzumab +/- capcitabine) trial. 28 patients (21%) with isolated BM were identified and comprised 2 groups: 14 who discontinued study and 11 who continued study treatment following CNS-directed therapy. Median time to isolated brain progression differed between these groups (12.3 months in post-progression treated vs. 6.3 months). The median time to any second event was 8.3 months in the post-progression CNS-treated patients. Patients selected for post-progression treatment had less exposure to pertuzumab, were more frequently treated with the triplet combination, had a longer time from pre-study CNS-directed therapy, had better preserved performance status, and were less likely to have new neurologic adverse events compared to patients not treated post-progression. Conclusions: Patients with isolated BM progression treated with post-progression with CNS-directed therapy and continuation of study therapy had a median of 8.3 months to any second event, suggesting a substantial benefit for this treatment strategy. The selection of patients with post-progression treatment appears to be a composite of both factors and at time of progression. These results support the further evaluation of this approach to patients with isolated brain progression in the ongoing randomized HER2CLIMB trial. Clinical trial information: NCT01983501 and NCT02025192.
Background: Overall response rates of 5-7% have been reported with checkpoint inhibitor monotherapy in PD-L1-unselected mTNBC as second line or subsequent therapy. RT is frequently used to enhance local control in mTNBC and has been reported to induce distant (abscopal) tumor responses when combined with immunotherapy. In this study, we evaluate the safety and efficacy of RT combined with pembrolizum, a programmed death 1 (PD-1) inhibitor, in a phase II, single-arm, Simon two-stage, study in mTNBC.

Methods: Eligible women had biopsy-proven mTNBC and ≥2 measurable sites of metastatic disease with at least one site requiring RT. PD-L1 expression was not required for study entry. A total RT dose of 3000 cGy was delivered in 5 daily fractions. Pembrol was given intravenously at 200 mg within 3 days of the first RT fraction, then every 3 weeks +/-3 days until disease progression. The primary endpoint was overall response rate at week 13 in the non-irradiated lesions by RECIST v1.1. Secondary endpoints included safety and overall survival. Tumor biopsies were obtained at baseline and at week 7. Results: Of the 17 women enrolled, the median age was 52 y (range 37-73y), and the median number of prior cytotoxic therapies for metastatic disease was 3 (range 0 to 8). Of the 8 women not evaluable at 13 weeks: 5 died secondary to disease-related complications (weeks 2, 4, 6, 7, 8, and 9) and 3 progressed prior to week 13. Of the 9 women evaluable at week 13, 3 (33%) had a partial response, 1 (11%) had stable disease and 5 (56%) had disease progression. The stable disease response was durable for 22 weeks. The 3 partial responses represented 60%, 54%, and 34% decreases in tumor burden by RECIST v1.1 and were durable for 31, 21, and 40 weeks, respectively. Common toxicities were mild and included fatigue, myalgia and nausea. Conclusions: The combination of pembrol and RT was well-tolerated with durable responses outside the RT field in 3/9 (33%) evaluable patients unselected for PD-L1 expression. Thus, the addition of RT to PD-1 blockade represents a promising strategy for improving the response rates in pre-treated mTNBC. Clinical trial information: NCT02730130.

ABSTRACT WITHDRAWN
Genes implicated preclinically in mechanisms of resistance to CDK4/6 inhibitors require subgroups; H vs L NCT01958021.

Results:
• Among 232 patients with ctDNA testing, 232 (92%) had detectable mutations. Of those 232 cases, 196 (84%) had actionable mutations and 86 patients with actionable mutations received matched therapy with agents including CDK 4/6, mTOR, PI3K, AKT, PARP, androgen receptor, and FGFR inhibitors, SERDs, HER2 directed therapy, and DNA damaging chemotherapy.

Conclusions:
- Benefit of ctDNA testing was consistent across gene expression subgroups. This study highlights the potential clinical utility in development of genotype driven trials for patients with MBC.

Background:
- While molecular alterations in PI3K pathway, including PIK3CA mutations, are common in HR+ breast cancer, molecular alterations in MAPK pathway, including KRAS and BRAF mutations, are considered rare in HR+ breast cancer. However, tumors can acquire new molecular alterations over time, and blood-based genotyping via circulating tumor DNA (ctDNA) could provide a more accurate molecular snapshot.

Methods:
- This study analyzed data collected from metastatic breast cancer (MBC) patients who had genotyping (2016-2017) via a next generation sequencing-based (NGS) assay that detects ctDNA mutations (Guardian 360 panel), including alterations in MAPK pathway. Mutation profiles were also analyzed in tissue biopsies via SNApShot-NGS, an institutional genotyping assay.

Multivariant analysis was performed to evaluate the hazard ratio (HR) for the association between these mutations and time to progression (TTP), adjusting for key prognostic variables. Results:
- Among the HR+ MBC patients (N = 174), 25% (N = 44) were found to have molecular alterations in MAPK pathway in ctDNA, including mutations in BRAF (7.5%), KRAS (5.7%), NRAS (0.5%), MAP2K1 (1.1%) and NF1 (14.4%).
- 16.5% had a concurrent PIK3CA mutation, 2.9% had a concurrent TP53 mutation, and 14% alterations were detected in PI3KCA. There was no significant difference in baseline characteristics, including age at metastatic diagnosis (57 vs 55; p = 0.78) and visceral metastases (74% vs 81%; p = 0.87).
- In multivariate analysis, patients with MBC harboring MAPK molecular alterations had worse TTP (HR: 2.08; p = 0.02) compared to controls. However, there was no significant difference among those with PI3KCA mutant tumors versus not (HR: 1.09; p = 0.74).

Conclusions:
- Molecular alterations in MAPK pathway, hitherto considered rare in primary HR+ breast cancer, are not uncommon in metastatic HR+ breast cancer and are associated with worse outcomes. The study highlights the value of blood-based assays for identification of novel targets and their potential clinical utility in development of genotype driven trials for patients with MBC.
Benefit of CDK 4/6 inhibition in less common breast cancer subsets: A U.S. Food and Drug Administration pooled analysis. First Author: Jennifer J Gao, U.S. Food and Drug Administration, Silver Spring, MD

Background: Cyclin dependent kinase 4/6 inhibitors (CDKIs) are approved for 1st and 2nd line endocrine-based therapy in hormone-receptor positive, HER2-negative advanced breast cancer. There is limited clinical data on the benefit and value of adding CDKIs to endocrine therapy in less common subtypes, such as progesterone receptor negative (PR-), de novo metastatic, and lobular breast cancer, which may have differing degrees of endocrine sensitivity. Methods: We pooled data from 5 phase 3 randomized registration trials of CDK1 with an aromatase inhibitor (AI) in the 1st or fulvestrant in the 2nd-line setting. Exploratory subset analyses focused on patients with de novo metastatic, PR-, and lobular cancer. Progression free survival (PFS) was examined in the ITT populations using Kaplan Meier plots and hazard ratios (HR) with 95% confidence intervals (CI). Results: We estimated median PFS differences between the CDKI and control arms (Table 1). In patients with PR- tumors (n = 490), the estimated median PFS difference with the addition of CDKI to endocrine therapy was 9.1 mo (HR 0.50, 95% CI 0.40-0.64). In patients with de novo metastatic disease (n = 877), the estimated median PFS difference was 9.6 mo (HR 0.59, 0.48-0.71). In patients with lobular cancer(n = 264), the estimated median PFS difference was 6.9 mo (HR 0.58, 0.42-0.80). Analyses of studies limited to the 1st line setting with an AI and studies in the 1st- and 2nd-line setting were consistent with these results. These results are considered hypothesis generating. Conclusions: Addition of CDKIs to endocrine-based therapy appears to confer a similar benefit in the relative risk of disease progression or death for the studied subsets of patients compared to the broad population in the labeled indication. Further research is needed to develop robust clinical criteria which identify patients benefit most from addition of CDKI to endocrine therapy and which should receive CDKI in the 1st-line, 2nd-line, or both settings. Results:

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1026 Poster Session (Board #107), Sat, 8:00 AM-11:30 AM

A phase II study of cabozantinib ( cabo) alone or in combination with trastuzumab ( T) in patients (pts) with breast cancer brain metastases (BCBM). First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Boston, MA

Background: BCBM rely on VEGF pathway activation for angiogenesis and dissemination. Activation of MET leads to tumor invasion and resistance to anti-VEGF therapy. The aim of this study was to analyze the efficacy and tolerability of cabo — a small molecule inhibitor of MET and VEGFR2— alone or with T in BCBM pts. Methods: This is a single-arm, two-stage phase II study. Eligible pts had measurable progressive measureable BCBM. The study was an open-label, single-arm, randomized 2:1 (Cabo 1:1: T) trial. Cohort 2 (HR+ HER2-) and Cohort 3 (triple negative). Pts received cabo 60 mg daily on a 21-day cycle. Cohort 1 also received standard T every 1 (HER2+), Cohort 2 (HR+ HER2-) and Cohort 3 (triple negative). Pts received cabo 60 mg daily on a 21-day cycle. Cohort 1 also received standard T every 3 weeks. Pts had restaging scans every 6 weeks for 6 cycles, then every 9 weeks; in Cohort 2, adequate hematologic, renal, and liver function. Pts with stable brain metastases (CNS) were eligible. Treatment was T-DM1 at 3.6 mg/kg iv q 3 wk and N at escalating doses of 120, 160, and 200 mg/d using 3+3 design. HER2 + was required on primary tissue but was not reassessed at entry. Blood samples were required upon entry. Pharmacokinetic (PK) studies were performed on a limited number of pts. Primary endpoint was CNS objective response rate (ORR) by RECIST 1.1 in Cohort 1. Target sample size for Cohort 1 was 21 pts; if ≤ 3 pts had CNS ORR the null rate (5%) would be rejected in favor of a 30% rate of activity. Secondary objectives were CNS ORR in Cohorts 2 and 3, progression-free survival (PFS), overall survival (OS), toxicity, and changes in MRI vascular parameters and plasma biomarkers. Results: 35 pts (Cohort 1 n = 21, Cohort 2 n = 6, Cohort 3 n = 8) were enrolled and this analysis was done with a median follow up of 7.3 months (range 0.8-30.6). Median age was 50 years (range 28-69). Pts had a median of 3 prior lines for metastatic disease (range 1-9). Prior to enrollment, 4 pts underwent craniotomy, 24 pts whole brain radiation and 11 pts stereotactic radiosurgery. Efficacy is shown in the Table. Most common grade 3/4 AE included elevations in lipase (12%), AST (9%), ALT (6%), hypernatremia (9%), thromboembolism (9%), hypertension (6%), fatigue (6%) and vomiting (6%). Ongoing studies are exploring MRI perfusion changes with cabo, and biomarkers of response. Conclusions: Cabo was well tolerated but had insufficient activity in heavily pretreated patients. MRI changes were observed and will be presented at the meeting. Clinical trial information: NCT02260531.

1027 Poster Session (Board #108), Sat, 8:00 AM-11:30 AM

NSABP FB-10: Phase Ib dose-escalation trial evaluating trastuzumab emtansine (T-DM1) with neratinib (N) in women with metastatic HER2+ breast cancer (MBC). First Author: Jamie Abraham, NSABP Foundation and Cleveland Clinic, Cleveland, OH

Background: T-DM1 is an antibody-drug conjugate composed of trastuzumab and the maytansinoid antimebolitube, DM1. T-DM1 was granted FDA approval in 2nd-line MBC after prior trastuzumab (T) and taxane. Current practice in USA is for pts to receive T and pertuzumab (P) as neoadjuvant or as 1st-line therapy. The primary endpoint of the study was the safety and efficacy of T-DM1+n in women with HER2+ metastatic breast cancer (MBC). Methods: Eligible pts had prior T and/ or P neoadjuvant or as 1st-line, measurable disease, ECOG PS ≤ 2, adequate hematologic, renal, and liver function, Pts with stable brain metastases (CNS) were eligible. Treatment was T-DM1 at 3.6 mg/kg q 3 wk and N at escalating doses of 120, 160, 200, and 240 mg/d using 3+3 design. HER2 + was required on primary tissue but was not reassessed at entry. Blood samples were required upon entry. Pharmacokinetic (PK) studies were performed on a limited number of pts. Primary endpoint was CNS objective response rate (ORR) by RECIST 1.1 in Cohort 1. Target sample size for Cohort 1 was 21 pts; if ≤ 3 pts had CNS ORR the null rate (5%) would be rejected in favor of a 30% rate of activity. Secondary objectives were CNS ORR in Cohorts 2 and 3, progression-free survival (PFS), overall survival (OS), toxicity, and changes in MRI vascular parameters and plasma biomarkers. Results: 20 pts from Cohort 1 were evaluable for efficacy. A dose-limiting toxicity occurred in 6 during cycle 1. The RP2D was N 160 mg/d. Treatment-related grade 3 toxicities included diarrhea (5 pts), thrombocytopenia (4), nausea (3), and ALT elevation (1). Of 20 pts evaluable after 2 cycles, 3 had CRs and 9 had PRs (ORR 64%). The duration of response ranged from 42 d to 650+ d. New CNS disease occurred in 1 (8/27 at entry). Nine pts had PK determinations during the first 24h, and 13 had steady-state neratinib level on cycle 2 d. There was no correlation between N dose and peak or steady-state levels; responses were seen at all doses. Data from blood samples collected on d 1 for HER2 amplification by cDNA will be presented. Conclusions: Full-dose T-DM1 + N at 160 mg/d was well tolerated with notable activity. Responses were seen at all dose levels of N. Limited PK analysis did not show that peak or steady-state concentration of N was related to response. Baseline peripheral blood samples will be assessed for HER2 amplification. Support: Puma Biotechnology Clinical trial information: NCT02236000.
An open-label, multicenter, phase Ib study to evaluate RC48-ADC in patients with HER2-positive metastatic breast cancer. First Author: Bingjie Xu, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: RC48-ADC is a novel HER2-targeting antibody-drug conjugate (ADC) that selectively delivers antitumor agent MMAE into HER2-overexpressing tumor cells. A Phase I study (NCT02881138) has preliminarily demonstrated that RC48-ADC is well tolerated and has clear clinical activity in patients (pts) with metastatic breast cancer (MBC). Methods: This was a phase Ib, open-label, multicenter study with 3 dose cohorts (0.5, 1.0, 1.5 mg/kg and 2.5 mg/kg, Q2W). Eligible pts (18-70 years; assessed HER2-positive (IHC 2+ or IHC 3+). MBC, with relapsed/refractory to prior standard treatment. Results: From Dec 2016, 131 pts were enrolled in 14 pts (46.7%). ORR was 26.7% and 46.7% in the 1.5 mg/kg and 2.0 mg/kg cohorts, respectively; it was 51.7% in trastuzumab-naive pts and 33.3% in trastuzumab-pretreated pts (12 pts treated with<3 prior chemotherapy). The combination of RC48-ADC with pertuzumab therapy was evaluated in a 3:2:1 ratio. The most common treatment-related AEs were leucopenia (33.3%), lymphopenia (33.3%), neutropenia (33.3%), numbness (23.3%); most were Grade 1-2 in severity. Only 3 pts (10%) reported Grade ≥2 thrombocytopenia. Grade 3 TRAEs occurred in 4 pts (13.3%), including neutropenia (10%), lymphopenia (6.7%), AST elevation (6.7%), ALT elevation (6.7%), leucopenia (6.7%), and CD8 cell depletion (3.3%). Pharmacokinetic analyses showed dose-dependent exposure with 1.15 d half-life. Conclusions: RC48-ADC has shown manageable safety and encouraging efficacy profiles in pts with HER2-positive MBC. Investigation of 2.5 mg/kg expansion cohort has not yet been started. Results obtained from ongoing dose-escalation phase I study will determine whether 2.5 mg/kg cohort expansion is performed. Clinical trial information: NCT03052634. Clinical trial information: NCT03052634.

An open-label, dose-escalation phase I study to evaluate RC48-ADC, a novel antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer. First Author: Jiayu Wang, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: There is still urgent medical need for new therapeutics in the patients with metastatic breast cancer (MBC) and other solid tumors with HER2 overexpression. RC48-ADC is an antibody-drug conjugate drug with a novel humanized anti-HER2 antibody conjugated to monomethyl auristatin E (MMAE) through a cleavable linker. Preclinical data in various animal models, including breast cancer, gastric cancer and ovarian cancer, suggested excellent antitumor efficacy. Methods: It was an open-label, single-center, phase I study. Eligible pts (18-65 years) were confirmed by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) as HER2-positive (IHC 2+ or IHC 3+). MBC. A 3+3 dose-escalation was conducted with a 28-day window to evaluate dose limiting toxicity (DLT). DLT was mainly defined as Grade 4 neutropenia effectively managed with cytotoxic antibiotics. Tumor response was assessed per RECIST 1.1 every 6 weeks. Results: As of 29 Jan, 2018, 23 female pts with MBC were treated in 5 dose escalation cohorts (dose levels 0.5, 1.0, 1.5, 2.0, 2.5 mg/kg) on average every 4 weeks (Q2W). Median age was 57 (32-65), and the course of disease was more than 3 years in 15 pts (65.2%). 16 pts (69.5%) were previously treated with trastuzumab, and the course of disease was more than 3 years in 15 pts (65.2%). 16 pts (65.2%) were previously treated with trastuzumab and the course of disease was more than 3 years in 15 pts (65.2%). The most common treatment-related AEs were leucopenia (33.3%), lymphopenia (33.3%), neutropenia (33.3%), numbness (23.3%); most were Grade 1-2 in severity. Only 3 pts (10%) reported Grade ≥2 thrombocytopenia. Grade 3 TRAEs occurred in 4 pts (13.3%), including neutropenia (10%), lymphopenia (6.7%), AST elevation (6.7%), ALT elevation (6.7%), leucopenia (6.7%), and CD8 cell depletion (3.3%). Pharmacokinetic analyses showed dose-dependent exposure with 1.15 d half-life. Conclusions: RC48-ADC has shown manageable safety and encouraging efficacy profiles in pts with HER2-positive MBC. Investigation of 2.5 mg/kg expansion cohort has not yet been started. Results obtained from ongoing dose-escalation phase I study will determine whether 2.5 mg/kg cohort expansion is performed. Clinical trial information: NCT03052634. Clinical trial information: NCT03052634.
1032 Poster Session (Board #113), Sat, 8:00 AM-11:30 AM

Results from a phase I study of andecaliximab in combination with paclitaxel in patients with previously untreated metastatic breast cancer. First Author: Erika Paige Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

Background: Matrix metalloproteinase-9 (MMP-9) is highly expressed in several advanced cancers, including metastatic breast cancer, and confers an adverse prognosis. In a preclinical breast cancer model, inhibition of MMP-9 was demonstrated with tumor growth inhibition. Andecaliximab (ADX) is a chimeric antibody directed against MMP-9, engineered to remove T cell epitopes and reduce risk of immunogenicity. In this phase I multi-cohort study, we hypothesized that the combination of ADX with standard of care chemotherapy (paclitaxel) should be safe and tolerable, and demonstrate clinical activity in patients with previously untreated metastatic breast cancer. (Clinicaltrials.gov NCT# 01803282)

Methods: We enrolled 15 eligible (13 female) patients with radiographically measurable disease and previously untreated metastatic breast cancer. The median age was 59 years (range 23-81). Patients were treated with 800 mg ADX IV every 2 weeks + paclitaxel (80mg/m² on days 1, 8, and 15 of a 28-day cycle). The primary endpoints of this study were safety and tolerability. Exploratory endpoints were investigator assessed objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: As of September 22, 2017, the median ADX treatment duration for this study was 5.3 months. The most common adverse events were alopecia (60%), fatigue (60%), constipation (47%), neutropenia (40%), diarrhea (33%), and nausea (33%). Serious adverse events (SAEs) were reported in 33% of patients. Two patients experienced grade 3 non-hematologic SAEs; one was acute kidney injury and atrial fibrillation (7% each). The median PFS was 7.4 months (90% CI 5.3-8.6 months) and the overall response rate was 53% (95% CI 30-76%) with 7% complete response rate. The median OS was not reached at the time of the study. Study treatment continues in 27% of patients.

Conclusions: Combination ADX with paclitaxel was safe and acceptable in first-line treatment of patients with metastatic breast cancer. Updated data will be presented at the time of the meeting. Clinical trial information: NCT01803282.

1033 Poster Session (Board #114), Sat, 8:00 AM-11:30 AM

Safety and efficacy of pembrolizumab (pembro) plus capecitabine (cape) in metastatic triple negative breast cancer (mTNBC). First Author: David B. Page, Early A. Chiles Research Institute, Portland, OR

Background: In mTNBC, anti-PD-1/L1 monotherapy was associated with objective response rates (ORR) of 23-26% in the first-line setting, but ORR of 5-6% in later lines. We hypothesize that concurrent pembro plus standard-of-care chemotherapy is safe, and may increase clinical benefit by allowing for earlier treatment with anti-PD-1, when tumor burden and iatrogenic immunosuppression are minimized. This is the first study to explore the combination cape with PD-1/L1 blockade in breast cancer. Methods: In a pilot/phase II study, we evaluate the tolerability and preliminary efficacy of concurrent pembro (200mg IV q21 day) plus investigator-selected 1st/2nd line paclitaxel (80mg/m² IV weekly) or oral cape (2,000mg BID, weekly 1/0 1/off). The primary endpoint of the pilot phase is tolerability, defined as the proportion of subjects receiving > 6 weeks concurrent therapy without dose discontinuation. Toxicities are reported per CTCAE v4.0. The secondary endpoint is 12-week ORR by RECIST1.1, with potential phase II expansion according to a Simon 2-stage design if ≥4/14 ORR.

Exploratory objectives include intratumoral/peripheral immunologic assessments by T-cell receptor sequencing, multiplexed immunofluorescence, and real-time multi-parametric flow cytometry. Here, we report the results of the pilot phase of the cape cohort (NCT02734290). Results: As of 1/1/2018, 100% (9/9) of safety-evaluable subjects tolerated concurrent cape+pembro for at least 6 weeks. Toxicities were generally consistent with monotherapy experience (diarrhea: grade I-II 56%; hand-foot: grade I-II 67%), and improved with dose-reduction. Partial responses have been observed in three subjects, two having metaplastic pathology. A fourth subject experienced durable stable disease, with ongoing response at 48 weeks. Conclusions: This study met the primary endpoint of safety for cape plus pembro in mTNBC and the combination will be explored for efficacy in the next stage of this study. These data may also inform the evaluation of concurrent anti-PD-1/L1 plus cape in the adjuvant setting. Clinical trial information: NCT02734290.

1034 Poster Session (Board #115), Sat, 8:00 AM-11:30 AM

Effect of breast tumor subtype and site of distant metastatic disease on prognostic outcome among patients with breast metastases at stage IV denovo breast cancer. First Author: Shaheenah S. Dawood, Medecinic City Hospital, Dubai, United Arab Emirates

Background: The objective of this study was to examine the impact of breast tumor subtype and site of distant metastatic disease on prognostic outcome among patients with stage IV denovo breast cancer who have brain metastases at diagnosis. Methods: We searched the SEER registry to identify 1025 patients(pts) with stage IV denovo breast cancer and upfront brain metastases diagnosed between 2010 and 2014. Pts were divided into four groups depending on the breast tumor subtype: a) triple negative (TNBC), b) HER2-ve/HR+ve, c) HER2+ve/HR-ve, and d) HER2+ve/HR+ve. The presence of distant metastatic disease (DM) other than the brain was defined as disease in the lung, liver or bone. Overall survival (OS) was computed using the Kaplan Meier product limit method. Multivariable cox models were then fit to look at the association of breast tumor subtype and OS adjusted for various pt and tumor characteristics. Results: Median age at diagnosis was 60 years and median OS was 9m. 225 (21.5%), 480 (46.8%), 138(13.4%) and 186 (18.1%) pts had TNBC, HER2-ve/HR+ve, HER2+ve/HR-ve and HER2+ve/HR+ve disease respectively. Median OS was 5m(TNBC), 13m(HER2-ve/HR+ve), 9m (HER2+ve/HR+ve), and 21m(HER2+ve/HR+ve) across the subtypes(p < 0.0001) respectively. Median OS among those who did and did not have surgery of their primary tumor was 14m and 7m respectively (p < 0.0001). Median OS among those with lung, liver, bone only or no distant metastases was 8m, 6m, 1.5m and 10m respectively (p < 0.0001). In the multivariable cox model compared to pts who had TNBC pts who had HER2+ve/HR+ve (HR 0.59, CI 0.48-0.73, p < 0.0001), HER2+ve/HR-ve (HR 0.79, CI 0.60-1.04, p = 0.09) and HER2+ve/HR+ve (HR 0.35, CI 0.27-0.47, p < 0.001) had a lower risk of death. 250 (24%)pts did not have DM at presentation. Median OS in this cohort was 5m(TNBC), 10m (HER2-ve/HR+ve), 14m(HER2+ve/HR-ve) and 34m (HER2+ve/HR+ve) across the subtypes respectively(p = 0.0003). Conclusions: Among pts with stage IV denovo breast cancer and brain metastases at diagnosis factors such as bone only or no distant metastatic disease and HER2+ve/HR+ve subtype was associated with the best prognostic.

1035 Poster Session (Board #116), Sat, 8:00 AM-11:30 AM

Phase ib study of trastuzumab emtansine (TDM1) in combination with lapatinib and nab-paclitaxel in metastatic HER2-negative or overexpressed breast cancer patients: Stela results. First Author: Tejal Amar Patel, Methodist Cancer Center, Houston, TX

Background: Based on our preclinical data, we conducted a phase I study oftrastuzumab-emtansine (TDM1) in combination with Lapatinib and Nab-paclitaxel in patients with HER2 over-expressed stage IV breast cancer. Methods: Phase Ib study was conducted using 3+3 dose de-escalation design, with TDM1 with Lapatinib and Nab-paclitaxel administered for a total of 4 cycles. Primary purpose was to evaluate the maximum tolerated dose (MTD) of TDM-1 with Lapatinib and Nab-paclitaxel. Safety, tumor response and pharmacokinetics (PK) were also assessed. Dose limiting toxicities (DLTs) were defined as ≥ grade 3 non hematological toxicity attributed to the study drugs. Key inclusion criteria were stage IV HER2 positive breast cancer, LVEF ≥ 45%, and peripheral neuropathy < grade 2. Results: The MTD was TDM-1 3.0 mg/kg every 3 weeks along with Lapatinib 750mg oral daily and Nab-paclitaxel 80mg/m² weekly. Twenty four patients, median age 50 (47.9-55.9) years were enrolled. The dose limiting toxicities were diarrhea and elevated liver function tests. At MTD, 42.9% (6/14) experienced grade 3 or higher toxicity. Fortyteen patients with median of 1 (range 0-5) prior metastatic treatments were evaluable for response. 12 patients (85.7%) had an objective response including 6 CR and 2 PR. TDM-1 pharmacokinetics was unaffected by Lapatinib. Conclusions: TDM-1 with Lapatinib and Nab-paclitaxel therapy was relatively well tolerated with significant anti-tumor activity observed. Clinical trial information: NCT02073916.
A phase Ib trial of copanlisib and trastuzumab in pretreated recurrent or metastatic HER2-positive breast cancer “PanHER2”. First Author: Niamh M. Keegan, Beaumont Hospital, RCSI, Dublin, Ireland.

Background: PI3K pathway activation is implicated in resistance to trastuzumab (T) therapy in breast cancer (BC), Copanlisib (C) is a pan-class I PI3K inhibitor with particular activity against PI3Kα, the isoform encoded by PIK3CA gene. PIK3CA mutation may predict response to PI3K inhibition. Methods: The maximum tolerated dose (MTD) and safety of C + T were evaluated in an open label, single arm, adaptive multicenter phase Ib dose escalation clinical trial in patients (pts) with HER2-positive BC with ≥2 previous therapies for BC and ≥1 metastasis that had disease progression following at least one line of (T) or TDM-1 based therapy in the metastatic setting. Pts were treated with T (4mg/kg loading dose then 2mg/kg weekly) given with C intravenously on Day 1, 8 + 15 of 28 day cycle at one of two dose levels (DL) according to a modified 3+3 design. Cycle 1 safety data were used to determine dose limiting toxicities (DLTs). Disease assessments were made every 8 weeks. PIK3CA mutation status was determined in formalin-fixed paraffin-embedded (FFPE) primary tumor blocks by standard sequencing and in serial samples of plasma circulating tumor DNA (ctDNA) during treatment by droplet digital PCR. Results: Twelve pts were treated with C + T, 6 on DL1 (45mg), and 6 on DL2 (60mg). Median age was 53yrs. Pts had 15 to 85 months of prior therapy in the metastatic setting with a median of 4 prior lines. There were no DLTs. The MTD and recommended dose for phase II is 60mg. Eleven SAEs were reported. Of these, 36% (n = 4) were infections requiring hospitalization and all were manageable with no change in C/treatment. C3 liver ablation, and G3 abdominal pain SAEs were reported being related to C. All others were considered unlikely or not related to C. G3 liver enzyme rise was reported in 1 pt with a single episode of G4 rise in GGT. G3 hypertension was reported in 33% (n = 4) pts. Best response was stable disease in 9/12 pts and 6 pts continued treatment >16 weeks. PIK3CA mutation was detected in 6/12 (50%) of tumors. Concordance between PIK3CA mutation in tissue and plasma pre-treatment was 80% with evidence of dynamic change in quantity of mutation during treatment. Conclusions: C+T is a safe, well tolerated combination. Efficacy of C+T will be assessed in a phase 2 study at the MTD of 60mg. Clinical trial information: NCT02705959.

SAFE-HEaRt: A pilot study assessing the cardiac safety of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function. First Author: Filipa Lynce, Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC

Background: HER2 targeted therapies have substantially improved the prognosis of patients with BC however they can be associated with cardiac toxicity. SAFE-HEaRt is the first investigator-initiated trial that prospectively tests whether HER2 therapies may be safely administered in patients with reduced LV function in the setting of ongoing cardiac treatment and monitoring. Methods: Eligibility criteria: stage I-IV HER2 positive BC candidates for non-lapatinib therapy; LV ejection fraction (LVEF) ≤40% and < 50% and no symptoms of heart failure (HF). All patients had cardioiology visits and echocardiograms at baseline, during treatment and 6 months after treatment, and received beta blockers (BB) and ACE inhibitors (ACEI) unless contraindicated. Primary endpoint was completion of planned oncologic HER2 therapy without development of a cardiac event (CE), defined as HF symptoms or asymptomatic decline in LVEF ≤10% points from baseline and/or to LVEF < 35%. Results: Of 31 enrolled patients, 30 were evaluable. Mean age was 54 years, 18 had early stage and 13 metastatic disease. Seventeen patients had prior exposure to anthracyclines and 13 had hypertension. On study 15 patients were treated with trastuzumab, 14 trastuzumab/peruzumab and 2 ado-trastuzumab emtansine. Mean LVEF was 45% at baseline and 46% at the end of treatment. Twenty-two patients completed HER2 therapy as defined per protocol without development of a CE and 5 are still on study. Three patients met CE criteria: 2 developed symptomatic HF (at 24 and 36 wks) and 1 had protocol defined LVEF decline to 35% at 12 wks, all were taken off study. Two of these 3 patients are alive and in continuous and 1 died of disease progression. Demographic, previous anthracyclines and baseline LVEF did not predict development of CEs. Elevation of highly sensitive troponin preceded 2 of 3 CEs which was significant (p = 0.003). Conclusions: Patients with BC and mildly reduced LVEF can safely receive HER2 therapies in the setting of regular cardiac monitoring and treatment with BB and ACEI. Our results provide new safety data in this unique population and have potential to contribute to clinical practice changes. Clinical trial information: NCT01904903.
**1040 Poster Session (Board #121), Sat, 8:00 AM-11:30 AM**

Neoadjuvant chemotherapy (NACT) trials have demonstrated improved response and survival in patients (Pts) with hormone receptor (HR)+ locally advanced breast cancer (MBC) and HR+ metastatic breast cancer (MBC) (B2151009).

**Methods:** Pts eligible for TOB203 had HER2- MBC, ECOG PS 0-1, measurable disease and adequate organ function. Adjuvant chemotherapy (including taxanes) was allowed. T was included genomics of PI3K/mTOR pathway.

**Results:** Any Grade NTP (Multivariate Cox)

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**Conclusions:** The NTP was associated with disease response to single agent palbociclib (PAL) as a predictive biomarker of efficacy. Blood count and response data were analyzed from two phase II clinical trials at different institutions using single-agent palbociclib (PAL) at standard of care doses for patients with the full study population of MONALEESA-2, HRQoL was maintained in patients aged ≥65 y with ribociclib + letrozole treatment at the end of treatment. First-line ribociclib + letrozole significantly prolong progression-free survival vs letrozole alone in patients aged ≥65 y with hormone receptor-positive (HR+), HER2- advanced breast cancer (ABC). The efficacy benefits observed with combination therapy, elderly patients may be receiving single-agent therapy because of toxicity and health-related quality of life (HRQoL) concerns. This study aims to determine whether NTP is associated with disease response to single agent palbociclib (PAL) and an analysis of the EORTC QLQ-C30 symptom scales, a clinically relevant improvement (> 5 points) was observed for mean pain score in the ribociclib group through the first year of treatment, while mild improvement was observed with the placebo group. Results of the QLQ-BR23 questionnaire showed similar breast symptom scores between treatment groups through the end of treatment. Conclusion: Consistent with the full study population of MONALEESA-2, HRQoL was maintained in patients aged ≥65 y treated with ribociclib + letrozole. Preclinical analysis indicated a clinically meaningful improvement in pain score for patients aged ≥65 y treated with ribociclib + letrozole. Clinical trial information: NCT01938021.

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Exhausted CD8+ cells (Tex) to predict response to PD-1 therapy in estrogen receptor (+) hormone therapy resistant breast cancer predictive of response to immune checkpoint inhibitors after epigenetic priming.

**Background:** Immune checkpoint inhibitors have revolutionized cancer treatment, yet have limited efficacy in estrogen receptor (ER)+ breast cancer. Implicated factors include scarcity of tumor infiltrating lymphocytes (TILs), low PD-L1 expression, female gender and liver involvement. *In vitro* and *in vivo* studies suggest that epigenetic modulation with HDAC inhibitors modulate regulatory T cells (Treg) and change TIL composition which is further associated with the presence of a specific immune signature.

**Methods:** Patients (pts) with ER+ metastatic breast cancer, who progressed on multiple prior therapies, were treated with tamoxifen in combination with vorinostat or pemetrexid either immediately or after 3 weeks of epigenetic priming in a phase II trial. Comprehensive flow-cytometric immuno phenotyping, PD-L1 staining and histone acetylation were evaluated on tumor and blood cells. Results: 34 patients (median age 56 years [32-81], heavily pretreated with a median of 5 (2-13) prior regimens received at least one dose of vorinostat and evaluable for response. Grade 3/4 toxicities: anemia (26%) included immune hepatitis, fatigue and thrombocytopenia. Grade 2 toxicities were pneumonitis and colitis in 3%, fatigue in 27% and thrombocytopenia in 12% pts. Six patients did not receive pemetrexid due to rapid progression or toxicity. Clinical benefits rate defined as CR, PR and stable disease > 6m was seen in 5/28 (18%) pts. Vorinostat infiltration and PD-L1 expression were low. High expression of PD-1/CTLA-4 dual staining in CD8 cells of > 20% in tumor or blood was seen in 5 pts overall, 4/5 (80%) patients with benefit and in one other patient, who was withdrawn due to immune hepatitis in week 3. Both tumor and peripheral blood CD8 PD-1/CTLA-4 dual expression was correlated with time to progression and reduction in FoxP3+CTLA-4+Tregs Pregulation in tumors by vorinostat. **Conclusions:** Our data highlight the potential for patient selection on exhausted CD8+ cells in tumor or blood to predict response to immune checkpoint inhibitors in a small subset of (ER)+ breast cancer patients. Clinical trial information: NCT02395627.

A randomized phase II trial evaluating CYP2D6 genotype-guided tamoxifen dosing in hormone receptor-positive metastatic breast cancer: TARGET-1.

**Background:** Tamoxifen (TAM) is a prodrug that requires metabolic activation by CYP2D6. Genetic polymorphism of CYP2D6 has been speculated to cause suboptimal efficacy of TAM. **Methods:** In a phase II multicenter open-label randomized controlled study, we enrolled candidates for first-line TAM therapy who had hormone receptor-positive (HR+) metastatic breast cancer. CYP2D6 genotyping was performed using DNA extracted from whole blood at baseline. Patients with heterozygous (wt/V) or homozgyous (VV) variant alleles of decreased or no function were randomly assigned to TAM at regular dose (20 mg/day, RD arm) or increased dose (40 mg/day, ID arm), and patients with homozgyous wild-type alleles (wt/wt) received TAM at 20 mg/ day. The primary endpoint was 6-month (6M) progression-free survival (PFS) rate. Secondary endpoints included PFS and plasma levels of TAM and its metabolites. **Results:** From December 2012 to July 2016, 186 Japanese patients were enrolled. Of 184 evaluable patients, 136 carried wt/V or V/V (ID arm) were neutropenia (prior CT: 77% vs 4%; no prior CT: 76% vs 8%), constipation (36% vs 10%) and those in patients in the RD arm were significantly lower (P = .0026). Adverse events did not differ significantly between arms. **Conclusions:** In patients with CYP2D6 variant alleles, increasing TAM dosing resulted in higher plasma END levels. There was no PFS rate difference at 6M, but there was a trend for longer PFS for TAM at 40 mg/day than 20 mg/day (HR, 3.6). Long-term follow-up is needed. Clinical trial information: UMIN000009155.
Methods: Enrollment criteria and study designs of MONARCH 2 and 3 were previously reported (Sledge et al., 2017; Goetz et al., 2017). Exploratory analyses were performed to assess TCT and PFS2 using the Kaplan-Meier (KM) method. Hazard ratios (HR) were estimated using a Cox model. TCT was defined as time from randomization (R) to the discontinuation date of next-line (first line of post-discontinuation treatment), or starting date of the second line of post-discontinuation treatment if treatment was earlier. Results: Among randomized patients, 51% and 49% of patients in the MONARCH 2 and 3 trials, respectively, received a post-discontinuation systemic therapy (CT) (35%, 26%), endocrine (28%, 38%), targeted agent (18%, 15%), or other (6%, 7%). Initiation of CT was deferred by adding abemaciclib to F (median: abemaciclib arm, not reached; placebo [P] arm, 32.52 m; HR 0.54, 95% CI 0.38-0.76; p < .01) or NSAI (median: abemaciclib arm, not reached; P, 32.52 m; HR 0.54, 95% CI 0.38-0.76; p < .001). KM analyses of PFS2 showed an improvement in the abemaciclib + F vs P + F arms (HR 0.78, 95% CI 0.61-1.00; p < .05) and in the abemaciclib + NSAI vs P + NSAI arms (HR 0.94, 95% CI 0.74-1.20; p = .57). Conclusions: Adding abemaciclib to F or NSAI delayed the start of subsequent chemotherapy, which is a patient-relevant outcome. Overall, the treatment benefit of abemaciclib + F or + NSAI was extended to the next line of the therapy after the initial disease progression. Clinical trial information: NCT02107703, NCT02246621.

1050
Poster Session (Board #131), Sat, 8:00 AM-11:30 AM
Combination of paclitaxel and a LAG-3 fusion protein (efitlagimod alpha), as a first-line chemotherapy in metastatic breast cancer (MBC): Final results from the run-in phase of a placebo-controlled randomized phase II. First Author: Francois P. Duhoux, Department of Medical Oncology, King Albert II Cancer Institute, Cliniques universitaires Saint-Luc and Institut de Recherche Expérimentale et Clinique (Pôle MIRO), Université Catholique de Louvain, Brussels, Belgium
Background: Efitlagimod alpha (efti, previously called IMP321) is a recombinant LAG-3/Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CDB T-cell activation. The activation of the dendritic cell network with efti the day after chemotherapy may lead to stronger anti-tumor CDB T-cell responses. We report final results of the safety run-in of a phase I/IIb trial (NCT02614833) in patients (pts) with hormone receptor positive MBC receiving weekly paclitaxel as first line chemotherapy. Methods: In the safety run-in phase 15 pts with MBC received paclitaxel (80 mg/m²; D1, D8, D15; IV) in a 4-week cycle in conjunction with either 6 mg (n = 6; cohort 1) or 30 mg (n = 9; cohort 2) efti injections (D2 and D16; SC) for 6 cycles. Pts without progressive disease could continue for a maximum of 12 additional efti injections every 4 weeks. Blood samples for pharmacokinetics and immuno-monitoring were taken in cycle 1, 4 and 6. The primary endpoint was determination of the recommended phase 2 dose of this combination. Results: Between Jan and Oct 2016 15 pts (median age 53 years) were enrolled. A majority (67%) of pts were pre-treated with hormonal therapy. Nine (67%) pts had a serious adverse event, out of which 1 was related to paclitaxel (dizziness grade 3) and 1 to efti (cytokine release syndrome grade 1). No grade 4 or grade 3 adverse events (AEs) in 4 pts were related to efti. Grade 1 and 2 injection site reactions were the most common efti related AEs and occurred in 14 pts (93%). Increased number of circulating monocytes, dendritic cells and CD2 T cells as well as increased cellular activation were observed. This sustained (≥ 6 months) activation of the cellular response was associated with increased Th1 markers (IFN-γ, CXCl10) levels in the plasma. Seven pts (47%) had a partial response according to RECIST 1.1 (mean duration of 9 months). The disease control rate at the final imaging mg efti SC is thus in the extended phase 2 dose and is currently investigated in the ongoing phase II part of the study. Efti leads to a steady and sustainable APC and T cell activation. Clinical trial information: NCT02614833.
1052 Poster Session (Board #133), Sat, 8:00-AM-11:30 AM

Olaparib versus chemotherapy treatment of physician’s choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer (OlympiAD): Efficacy in patients with brain metastases. First Author: Nadine M. Tung, Beth Israel Deaconess Medical Center and Dana-Farber Harvard Cancer Center, Boston, MA

Background: The OlympiAD study showed a significant progression-free survival (PFS) benefit for olaparib over chemotherapy treatment of physician’s choice (TPC) in patients with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm; HR 0.58, 95% CI 0.43–0.80). Objective response rate (ORR) was 59% in the olaparib and 28.8% in the TPC arm. Progression may vary by location of metastases, so we investigated the overall efficacy of olaparib vs TPC in mBC patients with specific sites of visceral metastases. Methods: OlympiAD was a randomized Phase III study in patients with HER2-negative mBC and a gBRCAm who had ≤2 chemotherapy lines for mBC (NCT000260622). Patients were randomized 2:1 to olaparib tablet monotherapy (300 mg bd) or single-agent TPC (capecitabine, eribulin or vinorelbine). Cox proportional hazard models were used for these post-hoc analyses. Results: The study was not powered to detect differences in treatment effect between subgroups, and results should be interpreted with caution due to modest patient numbers and baseline imbalances. Key baseline characteristics and PFS by site of metastases are shown in the table. Within these subgroups, overall ORR in evaluable patients was: lung/pleura, 61.2% vs 22.2%; liver, 59.5% vs 25.8%; and brain/CNS metastases, 64.7% vs 20.0%, for olaparib vs TPC, respectively. Conclusions: Among patients with metastatic mBC and a gBRCAm who had metastases in the lung/pleura, liver or brain/CNS, the benefit for olaparib vs TPC appeared consistent with that seen overall, for both PFS and ORR. Clinical trial information: NCT000260622.

Lung/pleura Liver Brain/CNS

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<td>PFS at 5 months</td>
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HR, hazard ratio.

1054 Poster Session (Board #135), Sat, 8:00-AM-11:30 AM

The tumor-immune microenvironment (TME) in HR+/HER2- metastatic breast cancer (mBC): Relationship to non-metastatic (mT) tumors and prior treatment (tx) received. First Author: Adrienne Gropper Waks, Dana-Farber Cancer Institute, Boston, MA

Background: HR+/HER2- primary breast tumors demonstrate less anti-tumor immune activity than HER2+ or triple-negative BC. However, minimal data exist about the TME of HR+/HER2- met tumors, particularly in the tx-refractory metastatic setting; Prior analyses also have not looked at macrophages (macs), which may be important in HR+ BC. We obtained met tumor biopsies (bx) from HR+/HER2- mBC patients (pts) on a prospective tissue collection protocol. Tumor-infiltrating lymphocytes (TILs) were scored histologically, and cytokeratin, CD68, CD163, and PD-L1 on tumor cells (tpD-L1) were assessed by multiplex immunohistochemistry (IF). Correlation between biomarkers and prior lines of tx was assessed by Spearman coefficient. A previously presented cohort of HR+/HER2- non-mets is used for comparison. Biomarker differences between non-mBC and mBC samples were assessed by Wilcoxon rank sum (TILs) and chi² (tpD-L1) tests.

Results: 33 HR+/HER2- mBC bx were analyzed from 30 pts (17 pts assessed for TILs, 21 by IF). Bx sites were 17 (52%) liver, 8 (24%) breast, and 8 (24%) other. Bx were obtained after a mean of 3.9 (range 0-10) lines of tx. Median TILs were 1% (range 0-20%). Ratio of M2 (CD68+CD163+) to M1 (CD68+CD163+) macs was ≥1 in 19/21 samples, suggesting dominance of M2 (immunomodulatory) macrophages (IF). A positive correlation between biomarkers and prior lines of tx assessed by Spearman coefficient is illustrated. A previously presented cohort of HR+/HER2- non-mets is used for comparison. Biomarker differences between non-mBC and mBC samples were assessed by Wilcoxon rank sum (TILs) and chi² (tpD-L1) tests.

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Conclusion: Among patients with metastatic HR+/HER2- mBC, the tumor microenvironment (TME) is similar to that of non-metastatic HR+/HER2- tumors, with higher TILs and lower TP53 and MAP3K1. Consideration of TME in HR+/HER2- met tumors, particularly in the tx-refractory metastatic setting, may be important in HR+ BC.

1055 Poster Session (Board #134), Sat, 8:00-AM-11:30 AM

The association of early toxicity and outcomes for patients treated with abemaciclib. First Author: Hope S. Rugo, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Abemaciclib is a CDK4 & 6 inhibitor dosed on a continuous schedule and has demonstrated efficacy with an acceptable safety profile in patients (pts) with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer as monotherapy and in combination with endocrine therapy in the MONARCH 1, 2, and 3 trials. Early onset, low grade diarrhea and grade 3/4 neutropenia were most common toxicities and was typically manageable and reversible with antiemetic medication and/or dose reduction. Neutropenia was the most frequent grade 3/4 toxicity in the abemaciclib arms typically occurring in the first 2 cycles. Here we provide an assessment of the association between these early toxicities, dose adjustment, and progression-free survival (PFS). Methods: Enrollment criteria, study designs, and endpoints were previously reported (Dickler et al. 2017; Sl GC et al. 2017; Goetz et al. 2017). To examine the impact of dose reductions on efficacy, a time-dependent covariate analysis of dose level versus PFS was performed. A landmark analysis was performed for pts with/no toxicity occurring early in treatment (diarrhea: 7 days; neutropenia: 56 days) by comparing PFS for pts of these arms to the placebo arm using a Cox model. Results: Discontinuation of abemaciclib due to diarrhea or neutropenia were each <3% in the abemaciclib arms. Management of toxicity included dose adjustment as necessary. An exploratory time-dependent covariate analysis showed no difference in PFS for pts who dose-reduced compared to those who did not. Compared to placebo, pts in the abemaciclib arms received benefit whether or not diarrhea or neutropenia was observed early in treatment. Conclusions: The dose adjustment strategy used in the MONARCH trials appeared to be an effective way to manage toxicity without compromising efficacy. Clinical trial information: NCT02102490, NCT02107703, NCT02466261.

HR+/HER2- breast cancer (mBC) and mBC samples were assessed by Wilcoxon rank sum (TILs) and chi² (tpD-L1) tests.

Plasma and tumor genomic correlates of response to BYL719 in PI3KCA-mutated metastatic ER-positive breast cancer (ER+/HER2- BC). First Author: Sarah-Jane Dawson, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Mutations of genes involved in the PI3K signalling pathway occur frequently in BC. We performed a phase II study of BYL719, a selective PI3Kα inhibitor, in BC to evaluate its efficacy and identify biomarkers that correlate with tumor response. Methods: Eligible patients had advanced ER+/HER2- BC and documented genetic alteration of the PI3K pathway detected in either tumor or plasma. Patients received BYL719 350 mg orally daily. The primary end point was RECIST objective response rate (ORR). Secondary endpoints were clinical benefit rate (CBR) including stable disease for ≥24 weeks, progression-free survival (PFS) and efficacy according to baseline and week 8 change in cTNA values. cDNA analysis was performed through droplet digital PCR. Results: Of the total 17 patients treated, 16 (94%) had a PIK3CA mutation (mt) and 1 had a PTEN deletion. Of the PI3KCA mutant patients, 8 (47%) had a kinase domain mt, 7 (41%) had a helical domain mt and 6 (35%) had a PIK3CA mts (92%). 15 (94%) patients had their alteration detected in plasma at baseline; concordance between plasma and tumor was 94% (15/16). Median age was 60 years (45–77). Patients had received a median of 3 prior treatment lines (1-7) in the metastatic setting; 16 (94%) had received prior endocrine therapy and 14 (82%) prior chemotherapy. 15 (88%) had visceral disease. The ORR (centrally reviewed) was 41% (71/17) and CBR was 59% (101/17). Median PFS was 9.4 months (95% CI 7.0-13.5). Most common grade ≥3 adverse event was hyperglycaemia (51/17, 29%). Co-existent MAP3K1 or ESR1 mt (N = 7, 41%) had a longer clinical benefit (mPFS 12.02 (95%CI, 5.44-11.2) with 3 (18%) ±1 yr compared with co-existent TP53 mt, CCND2 or FGFR1 amplification (N = 10, 59%) (mPFS 3.11 (95%CI, 1.38-4.8) and 2 patients who mBC and a clinical benefit with a significantly greater decrease in cTNA levels at week 8 from baseline (median 97.3% ±9.1% decrease, p = 0.04). Conclusions: BYL719 in previously treated advanced ER+/HER2- BC with PIK3CA mt detectable in plasma at baseline demonstrated robust clinical benefit. This biomarker should be considered in the Phase III setting. Clinical trial information: NCT02506556.
1056 Poster Session (Board #137), Sat, 8:00 AM-11:30 AM
Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidural growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the phase 3b CompLEEment-1 trial. First Author: Michelle DeLaurenitis, National Cancer Institute “Fondazione G. Pascale”, Napoli, Italy

Background: CDK4/6 inhibitor RIBO has been approved for use in combination with LET for the treatment of HR+, HER2- ABC in postmenopausal women with no prior therapy for advanced disease, based on the significantly prolonged PFS versus placebo + LET observed in the phase 3 MONALEESA-2 trial (Horowitz et al, NEJM 2016). Here we present baseline characteristics and early safety results for the first 1,007 pts enrolled in CompLEEment-1, an open-label, phase 3b trial evaluating RIBO+LET as first-line therapy in an expanded pt population.

Methods: Pts (N=3,000) with HR+ ABC, ≤1 line of prior chemotherapy, and no prior ET for ABC received RIBO (600 mg/day; 3 wk on/1 wk off) + LET (2.5 mg/day); men and premenopausal women continued LET until 12 cycles. Study followed a continual reassessment method (TITE-CRM), starting at 120 mg daily, and 15 until progression of disease or unacceptable toxicity. The primary endpoint was PFS and secondary endpoints included ORR, duration of response, disease control rate, overall survival, pharmacokinetics, and safety.

Results: Of the 1,007 pts enrolled, 62% were postmenopausal, 89% were HR+, 92% were HER2-, 57% were ≥65 yrs, 46% were ≥70 yrs, 47% had received ≥1 ET, 49% had bone or visceral metastases, and 58% had visceral involvement. Thirty-nine percent of pts received ≥2 prior ETs. The median number of evaluable cycles was 9 (range: 1-9). Median PFS was 10.8 mos (95% CI: 9.4-12.7 mos) in the 964 evaluable pts. ORR was 14% and 11% of pts had PD-L1 ≥25%.

Conclusions: Based on the preliminary results, the combination of RIBO + LET is generally tolerated with manageable toxicity and clinically meaningful results were seen in PFS and ORR. This is the first exploratory analysis of pts enrolled in this study and more data will be presented in the future.

1057 Poster Session (Board #138), Sat, 8:00 AM-11:30 AM
Mutation signature of patients with ER+ metastatic breast cancer patients who received endocrine therapy. First Author: Fei Ma, National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Approximately eighty percent of breast cancer patients are estrogen receptor alpha (ER-α) positive. Although women initially respond well to endocrine therapies, resistance often emerges. In this study we try to analyze the mutations in ER+ metastatic breast cancer patients (MBC) who have received endocrine therapies. Methods: Using next-generation sequencing (NGS)-based gene panel test (NGS), we analyzed the mutation profiling in 194 patients (pts) with MBC who were treated by endocrine therapies. Results: Somatic genomic alterations in cDNA including copy number variants and point mutations were identified in 179 of 194 patients (92.3%). ESR1 activating point mutations or amplifications were identified in 28.9% (56/194) patients, which has been described to be associated with resistance to tamoxifen and AI therapies in patients with ER+ MBC. The most described hot-spot activating mutations Y537C/S and D538G were detected in 26 and 21 patients, and other described mutations E380Q (13 pts), S463P (2 pts), L536H (2 pts), ESRI amplifications (2 pts) were also detected. Additionally, nine novel point mutations were identified in ESR1 (including A58T, T311M, P406A, T435L, R436H, H488N, Q580L, V560E, Y526C). Polyclonal ESR1 mutations were identified in 13 patients.

Another mechanism of resistance to endocrine therapy FGFRI amplification was identified in 10 patients and one co-occurring with ESR1 mutation. For other genes associated with targetable therapies, PKN2 mutations or PTEN deficiency were more commonly detected in patients with ESR1 mutation than ESR1 WT (50.0% vs 35.5%, p = 0.01). CDKN2A deficiency/CCND1 amplification were detected in 4 (7.1%) and 15 (10.9%) patients with or without ESR1 mutation. In addition, HER2 amplifications were less common detected in patients with ESR1 mutation versus without ESR1 mutation (5 vs 14.5%, p = 0.03). Conclusions: In ER+ MBC patients with endocrine therapies, ESR1 and FGFRI activating variants were common resistance to endocrine therapies and other targetable variants were also detected. Thus, these patients may benefit from combined treatment, such as endocrine therapies combined with mTOR inhibitors, CDK4/6 inhibitors when other pathways activating together.

See abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Hematologic adverse events following palbociclib (PAL) dose reduction in patients (pts) with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC). Aims: To perform a pooled analysis from randomized phase 2 and 3 studies. First Author: Sunil Verma, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

Background: A previous pooled analysis showed that 36.9% of pts receiving PAL required dose reduction, most occurring during the first 6 mo of treatment and with decreasing frequency during subsequent 28-day treatment cycles (C). Previous data have also shown that PAL dose reductions do not affect efficacy (Im S-A, et al. ESMO Asia 2017). This analysis evaluated the incidence of hematologic adverse events (AEs) 30 d before and after dose reduction (during each treatment C1–C6) among pts who required PAL dose reduction. Data were pooled from 3 randomized studies: PALOMA-1, a phase 2, open-label study of postmenopausal pts untreated for ABC receiving PAL+letrozole (L) or L alone; PALOMA-2, a phase 3, double-blind study of postmenopausal pts untreated for ABC receiving PAL+L or placebo (PBO)+L; PALOMA-3, a phase 3, double-blind study of pre- or postmenopausal pts who progressed on prior endocrine therapy receiving PAL+fulvestrant (F) or PBO+F. Results: A total of 311 pts with HR+/HER2– ABC required a PAL dose reduction (93.6% due to AEs) from 125 to 100 mg. Mean age was 59.9 y, and 46.9% of pts had visceral disease. Median time to dose reduction was 70 d. Incidences of grades 3/4 hematologic AEs were lower after dose reduction (Table), with decreased severity after dose reduction. Conclusions: A decrease in frequency and severity of hematologic adverse effects, including febrile neutropenia, following PAL dose reduction was observed, supporting timely PAL dose reduction in AE management. Funding: Pfizer (NCT00721409, NCT01744247, NCT01942135). Clinical trial information: NCT00721409, NCT01744247, NCT01942135.

1062 Poster Session (Board #143), Sat, 8:00 AM-11:30 AM
Evoleriosis exposure and early metabolic response as predictors for treatment outcomes in breast cancer patients treated with everolimus and exemestane. First Author: Anneleke Willemsen, Radboud university medical center, Nijmegen, Netherlands

Background: Treating breast cancer patients (BC) pts with everolimus and exemestane can be challenging due to toxicity and suboptimal treatment responses. We investigated whether everolimus exposure, elderly age, and early metabolic response are predictive of toxicity and effectiveness in these pts. Methods: We collected blood samples from 35 pts and 55 days after starting everolimus and exemestane, to measure everolimus trough level (Cmin). Toxicity, defined as dose interventions (reduction or discontinuation) < 3 months, and progression free survival (PFS) according to RECIST 1.1 were recorded. 18F-FDG-PET was performed at baseline, and 14 and 35 days after start of therapy. SUVmax of normal lean body mass was calculated for the maximum voxel and highest peak (SULmax and SULpeak), for up to 5 target lesions. Results: In 44 evaluable pts, the geometric mean (GM) Cmin was higher in pts with dose interventions < 3 months compared to pts without: 17.4 vs 12.3 μg/L (p = 0.02). The optimal cut-off value to predict toxicity was Cmin > 19.2 μg/L (AUC 0.71, sensitivity 0.55, specificity 0.92). Elderly pts (> 70 years) compared to pts < 70 years had a shorter median time to dose intervention: 42 vs 141 days (p = 0.01), but no significant difference in everolimus GM at 17.6 vs 13.5 μg/L (p = 0.12). GM Cmin of pts with and without progressive disease (PD) < 3 months was not significantly different: 12.0 μg/L vs 15.2 μg/L, respectively (p = 0.12). FDG-PET scans of 30 pts were analyzed. The percentage decrease in SULpeak of the lesion with highest avidity at day 14 (SULpeak high d14) was the best predictor of PD < 3 months. Pts with > 11% vs < 11% decrease in SULpeak high d14 had a median PFS of 411 days vs 90 days respectively (p = 0.001), and 11 vs 70% of these pts had PD < 3 months. Conclusions: Our results show that everolimus toxicity is related to everolimus Cmin and by monitoring everolimus Cmin, toxicity might be prevented. We recommend diligent monitoring of elderly pts, as they have toxicity more frequently. No relation was observed between everolimus exposure and effectiveness. FDG-PET is able to early identify pts at high risk of early progression. Further validation of these results is required. Clinical trial information: NCT01948960.

1063 Poster Session (Board #144), Sat, 8:00 AM-11:30 AM
18F-Fluoroestradiol (FES) and 18F-Fluorodeoxyglucose (FDG) PET imaging in lobular breast cancer. First Author: Poorni Manohar, University of Washington/ Fred Hutchinson Cancer Research Center, Seattle, WA

Background: The histology and pattern of spread in lobular breast cancer has presented challenges in estimating extent of disease by traditional imaging methods. 18F-FES is an estrogen analogue PET imaging tracer which measures tumor ER expression at multiple tumor sites simultaneously. We compared quantitative FES-PET and clinical FDG-PET SUV uptake between predominantly lobular breast cancer (LABC) and ductal breast cancer (DBC). The primary objective was to compare the difference in SUVmax and FDG SUVmax. Overall survival (OS), from time of FES-PET scan to death, was evaluated between histologies using Kaplan-Meier curves and the Log-Rank test. Results: Among metastatic breast cancer patients with positive FES scans, approximately 10% of patients with ductal histology and 9% with lobular histology had absent FES uptake in at least one lesion. Mean (range) SUVmax in FES and FDG respectively for ductal was 3.48 (0.32, 20.9) and 5.2 (1.1, 26.7) and for lobular was 3.34 (0.61, 9.62) and 4.42 (1.09, 20.0). Difference in FES and FDG SUVmax between histologies was marginal and non-significant. On the natural log scale, lobular carcinomas demonstrated a higher SUVmax (Difference = 0.05, 95%CI = [-0.16, 0.26], p = 0.63) and a lower FES SUVmax (Difference = -0.53, 95%CI = [-1.61, 0.56], p = 0.34. Following FES-PET imaging, patients with ductal carcinomas had a lower, non-significant median survival time (2.97 vs. 3.03 years, p = 0.81). Conclusions: In the metastatic setting, FES and FDG uptake in multiple lesions in ER+ lobular breast cancer patients did not statistically differ from ductal breast cancer. Metastatic lobular breast cancers have similar FES and FDG avidity to metastatic ductal tumors, suggesting these patients may benefit from similar diagnostic and treatment algorithms.
### 1064 Poster Session (Board #145), Sat, 8:00 AM-11:30 AM

**Outcome of everolimus based therapy in hormone receptor positive metastatic breast cancer patients after progression on palbociclib combination.**

**First Author:** AJW Fisher, Memorial Sloan Kettering, NY

**Background:** BOLERO 2 trial showed improved progression free survival (PFS) with everolimus (EV) + exemestane combination over exemestane alone in hormone receptor positive, HER2 non-amplified metastatic breast cancer patients (HR+ HER2- MBC) who progressed on a aromatase inhibitor (AI). Recent studies have established CDK 4/6 inhibitors (CDKI) as front line therapy in HR+ HER2- MBC. There are no clinical outcome data of HR+ HER2- MBC on EV after they progress on CDKI. Objective of retrospective study to analyze clinical outcomes of HR+ HER2- MBC on EV after progression on palbociclib (PA) & compare them with BOLERO 2 results. **Methods:** This is a retrospective, two-institute review of HR+ HER2- MBC from Jan 2015–July 2017 treated with EV after progression on PA. Women who received EV or PA < 4 weeks were excluded. PFS was defined as the time from the initiation of EV to the date of progression as determined by treating physician based on radiological, biochemical and/or clinical criteria. Response rates were determined based on available radiological data. **Results:** 26 women with median age 61 (33-70) were identified. 76% had prior sensitivity to endocrine therapy, 69% had adjuvant chemo/hormonal therapy, 54% had visceral disease, 23% had 3 or more metastatic sites, 100% had ECOG performance status 0 or 1, 92% had prior AI, 65% had received chemotherapy, 35% had received chemotherapy for metastatic disease, 81% had 3 or more lines of prior therapy. Kaplan Meier estimate showed median PFS (95% CI) of 4.4 mo (2.2-6.5), median OS (95% CI) was 11.6 and 18.7 months (9.0- not reached). Median PFS and OS of EV cohort of BO-LERO 2 (EV BOL) were 6.9 months (6.4-8.1) and 31.0 months (28.0-34.6). Fisher’s exact test comparing current study cohort vs. EV BOL showed significant difference in objective response (complete + partial responses) of 62.6% (23%) vs. 46/48 (9.5%), p = 0.014. OS was overall survival 100% vs 93.2% (95% CI, 86-84.8 months). This small study, for the first time, suggests that EV has evidence of clinical benefit after progression on PA in HR+ HER2- MBC. Larger studies are needed to confirm the results.

### 1066 Poster Session (Board #147), Sat, 8:00 AM-11:30 AM

**Sperm associated antigen 5 (SPAG5) as a predictor and monitor for response and distant relapse risk (DRR) to endocrine (ET) and chemotherapeutic (CT) treatments in breast cancer (BC).**

**First Author:** Tarek Mohamed Ahmed Abdel-Fatah, Nottingham University City Hospital NHS Trust, Nottingham, United Kingdom

**Background:** SPAG5 is an ultimate proliferation marker and important driver that is commonly amplified in “luminal B” BC. **Methods:** SPAG5 copy number aberrations (CNAs), mRNA and protein expression and their association with BC specific survival (BCSS) were determined in 4998 cases of ER+ BC. The association between the pathological complete response (pCR) to neoadjuvant anthracycline based CT (NACT) and SPAG5 expression was evaluated in 1073 (mRNA) and 332 (protein) patients with ER+ BC. The association between the dynamic response to the neoadjuvant ET (NAET) and SPAG5 mRNA expression was evaluated in 101 cases of ER+ BC. The association between distant relapse risk (DRR) and SPAG5 expression were tested in ER+/HER2- patients who received (if eligible) NACT or adjuvant CT in addition to 5-year tamoxifen (mRNA: n = 2819; protein: n = 2501). Results: **SPAG5 amplification (CNA) and overexpression (SPAG5+, mRNA, protein) were all associated with shorter BCSS (HR: 1.55, 1.31, and 1.90, p < 0.01, respectively).** After receiving NACT, multivariable logistic regression analyses confirmed that SPAG5+ mRNA and protein expression were independently associated with higher pCR (OR: 1.90; p = 0.041 and 23.03; p < 0.001, respectively). Downregulation of SPAG5 has been observed after 2-weeks on NECT and this was predictive the dynamic clinical response (p < 0.01). In contrast, in patients received CT+Tamoxifen with LN+ or LN- disease, SPAG5+ (mRNA, protein) exhibited a similar DRR to that with SPAG5- disease. ER+ patients with SPAG5+ mRNA tumours receiving CT+Tamoxifen has improved 5-year-DRFS by 28% for those with LN- disease (89% vs., 67%; p < 0.001) and 22% for those with LN+ disease (76% vs., 54%; p < 0.001), as compared to receiving Tamoxifen alone. **Conclusions:** SPAG5 could be used as a prognostic and predictive tool for selecting systemic therapies and monitoring response to the selected therapy in patients with ER+ BC.

### 1067 Poster Session (Board #148), Sat, 8:00 AM-11:30 AM

**Healthcare medical costs among post-menopausal women with hormone receptor positive human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (mBC) managed with systemic therapy following CDK 4/6 inhibitor (CDKI) in the real-world setting.**

**First Author:** Nicole Prinicic, Truven Health Analytics, an IBM Company, Cambridge, MA

**Background:** To examine US healthcare costs among HR+/HER2- women with mBC having systemic therapy with chemotherapy, endocrine therapy, or everolimus following CDKI. **Methods:** This population-based analysis used MarketScan Commercial and Medicare administrative claims data to select post-menopausal women diagnosed with HR+/HER2–mBC between 1/1/2012-10/31/2017 (index = first evidence of metastatic disease). Eligible patients had ≥ 1 line of systemic therapy on a chemotherapy, endocrine only, or everolimus-based regimen following a CDKI. **Results:** Patients with HR+/HER2– mBC on everolimus-based therapies relative to chemotherapy following treatment with a CDKI incurred lower medical costs, after accounting for observable confounders.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Endocrine</th>
<th>Everolimus</th>
<th>Everolimus vs. Chemotherapy</th>
<th>Everolimus vs. Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total medical</td>
<td>$11,505</td>
<td>$6,767</td>
<td>$5,448</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total medical without BC-related office administered treatment</td>
<td>$9,075</td>
<td>$5,254</td>
<td>$4,821</td>
<td>0.005</td>
</tr>
<tr>
<td>Total BC-related medical without office administered treatment</td>
<td>$8,506</td>
<td>$4,899</td>
<td>$3,607</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total BC-related medical</td>
<td>$6,076</td>
<td>$3,387</td>
<td>$2,689</td>
<td>&lt; 0.001</td>
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</tbody>
</table>
Conclusions: The RP2D was the maximal tolerated dose (MTD) of PALBO 100mg/d and ET. The majority of patients experienced grade 3+ hematologic toxicity and non-hematologic toxicity, with the most frequent grade 3+ adverse events being neutropenia. The phase II portion of this trial demonstrated that the triplet combination of PALBO 100mg/d (21 of 28 days) + EVE 5mg/d + EXE 25mg/d is safe in patients with HR+/HER2- MBC. The phase II trial involved 431 patients, and the data was ongoing at the time of publication.

Methods: The primary objective of the phase Ib was to evaluate the safety, tolerability, and pharmacokinetic (PK) properties of the combination of PALBO 100mg/d (21 of 28 days) + EVE 5mg/d + EXE 25mg/d in hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC) patients. Patients received the combination for up to 12 months or until unacceptable toxicity or disease progression. Analysis was conducted at the time of database lock (November 1, 2019).

Results: Of 431 patients randomized, 287 were assigned to receive TALA and 144 to PCT. PFS and ORR were shown (Table). Conclusions: The combination of PALBO 100mg/d (21 of 28 days) + EVE 5mg/d + EXE 25mg/d was well tolerated and demonstrated activity in HR+/HER2- MBC.
1072 Poster Session (Board #153), Sat, 8:00 AM-11:30 AM
Antitumor activity of PM1183 (lupinotecidin) in combination with capecitabine in metastatic breast cancer patients: Results from a phase I trial. First Author: Ahmad-Abed, Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Background: PM1183 (lupinotecidin, Zeperyx) is a new anticancer drug that blocks transcription, induces DNA double-strand breaks, and modulates the tumor microenvironment. Single-agent PM1183 has antitumor activity in various solid tumors, including metastatic breast cancer (MBC), and pre-clinical synergies/additivities with fluoropyrimidines. A phase I trial determined the recommended dose (RD) for the oral fluoropyrimidine capecitabine (XEL) as 1650mg/m^2 BID Day (D) 1 to D14 plus PM1183 2.2 mg/m^2 D1, every 3 weeks. Here we present results of *12/20 pts; **5/9 pts.

Progression free survival (95% CI; mo)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>95% CI</th>
<th>mo</th>
</tr>
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</table>
| PM1183+XEL until disease progression, or unacceptable toxicity | Stable asymptomatic brain metastases were allowed. Results: A total of 28 female MBC pts were treated between April 2013 and September 2016; 15 at RD. At cut-off, 5 pts (3 at RD) were still on treatment. Baseline characteristics and efficacy data are shown in Table 1. Baseline characteristics and efficacy data are shown in Table 1. At RD, hematological toxicities consisted of neutropenia (40% grade (G) 3; 7% G4) and anemia (13% G3). No febrile neutropenia was observed. Non-hematological toxicities were generally mild to moderate, including nausea, fatigue, palmar-plantar erythrodysesthesia syndrome, diarrhea, and decreased appetite. All AEs were reversible and manageable with dose reductions, omissions and/or delays. Main dose-limiting toxicities (DLTs) at maximum tolerated dose were hematological. Conclusions: The PM1183+XEL combination showed encouraging clinical activity in MBC. Further development is warranted in this indicated clinical trial. Clinical trial information: NCT02210364.

Baseline characteristics and efficacy of PM1183+XEL.

<table>
<thead>
<tr>
<th>All dose levels (n=28)</th>
<th>RD (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>51 (29-71)</td>
</tr>
<tr>
<td>ECOG 0/1 (%)</td>
<td>64/36</td>
</tr>
<tr>
<td>Visceral disease (%)</td>
<td>96</td>
</tr>
<tr>
<td>HR+triple negative (%)</td>
<td>71/29</td>
</tr>
<tr>
<td>Efficacy of PM1183+XEL</td>
<td>57 (39-79)</td>
</tr>
<tr>
<td>ORR (95% CI; %)</td>
<td>60* (36-81)</td>
</tr>
<tr>
<td>ORR of HR+ (95% CI; %)</td>
<td>68</td>
</tr>
<tr>
<td>Clinical benefit rate (%)</td>
<td>68</td>
</tr>
<tr>
<td>Duration of response (95% CI; mo)</td>
<td>6.8 (3.9-10.2)</td>
</tr>
<tr>
<td>Progression free survival (95% CI; mo)</td>
<td>7.3 (3.9-10.2)</td>
</tr>
</tbody>
</table>

*12/20 pts; **5/9 pts.

1074 Poster Session (Board #155), Sat, 8:00 AM-11:30 AM
Efficacy of olaparib monotherapy in patients (pts) with HER2-negative metastatic breast cancer (MBC) with germline BRCA mutation (gBRCAm) or leisional BRCA mutation (lBRCAm). First Author: Eleanor Meissner, University of Illinois at Rockford, Rockford, IL

Background: A recent Phase III study in MBC with gBRCAm, olaparib monotherapy provided a statistical significant and clinically meaningful PFS benefit compared to standard physician of choice treatment. (Robson M, NEJM 2017) Recently, olaparib was FDA approved for MBC with gBRCAm. Methods: Baseline characteristics and efficacy data are shown in Table 1. The objective of this analysis was to determine the PFS2/PFS1 ratio. von Hoff DD, 2014. IBCRam were detected in 12 out 19 pts (8 Foundation One, 3 Foundation Act and 1 Guardant 360) where somatic versus germline nature was not determined and gBRCAm 7 out 19 pts. Results: From 03/2014 to 08/2017, 319 pts with advanced cancer were treated with targeted therapy based on molecular abnormality. Overall 19 out 319 (6%) was defined as mut detected in tBx but not in ctDNA. Median age 45.1 years (range, 31-67), 18 out 19 pts were female, 14/19 were Caucasians, median number of previous lines of treatment for MBC was 4 (range, 2-8). Olaparib was dosed at 300 mg po bid until disease progression. A total of 12 out 19 pts (63%) the PFS ratio was ≥ 1.3, with a Wilson score 95% CI of (0.7, 3.3). Nine out 12 pts (75%) with lBRCAm had increased PFS ratio. The 6-month PFS was 69.4% (95% CI: (40%, 86.4%)), and the 6-month OS was 88.8% (95% CI: (62.1%, 97.1%)). There was no Grade 3-4 toxicity. Conclusions: Olaparib monotherapy provided a statistically significant increment of PFS in almost 2/3 (63%) of heavily pretreated MBC pts harboring gBRCAm and lBRCAm. Interestingly, 75% of patients with lBRCAm resulted in improvement the PFS with minimal toxicity. Further research is necessary to extend the olaparib approval for IBCRam in MBC pts.

1075 Poster Session (Board #156), Sat, 8:00 AM-11:30 AM
Differences of TILs, hormone receptor, and HER2 status between primary and recurrent tumors. First Author: Makiko Oka, Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Tumor-infiltrating lymphocytes (TILs) are reported to be as-}
Background. We performed a quantitative meta-analysis of randomized clinical trials of PARPi in pts with BC. Methods. 2 registries (ClinicalTrials.gov, WHO ICTRP) and 4 electronic databases (CBGC SR, CENTRAL, Medline, EMBASE) were searched from 2008 to 1/2018 for randomized clinical trials (RCTs) of PARPi therapy vs. control in BC. RCTs that reported overall survival (OS) or progression-free survival (PFS) were included. Pooled hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using a fixed effects model. Results. We identified 418 citations, of which 2 RCTs with a pooled sample size of n = 733 were included. There was a low/moderate risk of bias in both RCTs (Table). Both RCTs compared a PARPi to physician’s choice of chemotherapy in pts with germline BRCA mutated HER2-negative BC in first or later line setting, with PFS as the primary outcome. The pooled analysis of PFS showed a statistically significant improvement with PARPi therapy, with an HR of 0.56 (95% CI 0.45-0.68). The pooled analysis of OS did not show a statistically significant improvement, with an HR of 0.82 (95% CI 0.64-1.05). There was an acceptable safety profile with PARPi therapy in both RCTs, with a grade 3 adverse event rate of 25.5% and 36.6% in the 2 RCTs respectively. Conclusions. The use of PARPi in pts with germline BRCA mutated HER2-negative BC offers a PFS benefit compared to physician’s choice of chemotherapy in the first or later line setting, with an acceptable adverse events rate. Lack of OS benefit may be explained by availability of further lines of therapy, relative immaturity of the trials and not being powered to assess OS. This systematic review is part of a planned Cochrane Breast Cancer Group protocol.

Efficacy of mirtazapine in preventing delayed nausea and vomiting induced by highly emetogenic chemotherapy. An open-label, randomized, multicenter phase III trial. First Author: Jun Cao, Fudan University Shanghai Cancer Center, Shanghai, China

Background. We examined the efficacy of mirtazapine for the prevention of delayed nausea and vomiting in patients who received highly emetogenic chemotherapy (HEC). Methods. Patients with breast cancer who experienced delayed emesis after receiving AC or cisplatin containing regimens, and who subsequently accept at least 3 cycles of the same chemotherapy were randomly assigned to a mirtazapine group (15 mg daily on days 2 to 4) or control group, both with aprepitant, a 5-HT3 receptor antagonist and dexamethasone (7.5 mg on day 2 to 4). Primary end point was complete response (CR) to vomiting (no emesis and no rescue treatments) in the delayed phase (25 to 120 h). Secondary end points included CR during acute (0 to 24 h) and overall (0 to 120 h) periods, complete control (CC) (no emesis, no rescue medication use, and no more than grade 1 nausea) during the 3 periods above. Results. The study was closed early in January, 2018 due to the slow enrollment. Of 95 patients, 46 in the mirtazapine group and 49 in the control group. Compared with control group in the 1st cycle, delayed and overall CR rates were significantly higher with mirtazapine: 78.3% versus 49.0% (P = 0.003) and 58.7% versus 34.7% (P = 0.019), respectively. Similar result was observed in the 3rd cycle, which showed that delayed CR rates was significantly higher with mirtazapine: 88.2% versus 55.0%, respectively (P = 0.010). Delayed and overall CC rates were significantly higher with mirtazapine both in the 1st and 2nd cycles: 76.1% versus 49.0% (P = 0.006) and 56.5% versus 32.7% (P = 0.019), respectively in the 1st cycle and 70.0% versus 45.7% (P = 0.049) and 50.0% versus 25.7% (P = 0.043), respectively in the 2nd cycle. In the 3rd cycle, delayed CC rates was significantly higher with mirtazapine: 88.2% versus 50.0% (P = 0.001). Conclusions: Mirtazapine with aprepitant, a 5-HT3 receptor antagonist and dexamethasone significantly improved HEC-induced delayed nausea and vomiting prevention in patients with breast cancer. Efficacy of mirtazapine was maintained in the same chemotherapy pretreated patients. Clinical trial information: NCT02336750.
the no surgery group, and there was no significant difference in OS (Hazard with locoregional surgery with similar patients who received no surgery. The and 164 (46.4%) underwent no surgery. We matched 202 patients treated locoregional surgery and no surgery. Overall survival (OS) was estimated of the primary tumor in de novo stage IV breast cancer. We used patient-level data to investigate the effect of locoregional surgery versus no surgery. In contrast, we analyzed the meta-analysis from five prospective specifically comparing hazard ratios. A total of 67,978 patients met the inclusion criteria (median age 61 y). The patients in LRT subset (21,120) had 2 subsets based on the therapy received: no LRT and LRT (surgery and radiation). The 3 groups in training cohort yielded mixed results indicating that patient/tumor characteristics might influence the survival. We analyzed the predictors of survival after LRT in stage 4 BC by using National Cancer Data Base (NCDB). The Cox proportional method was used to calculate HRs based on which a 17 point survival prediction scoring system was developed (Table). Both the cohorts were stratified into 3 groups based on the scores—group (G)1 (0-3), G2 (4-7) and G3 (8-17). Kaplan Meier (KM) method and log-rank test were used to compare survival among the 3 groups. We validated the prognostic score by comparing the OS between the respective groups in each cohort. Results: A total of 67,978 patients met the inclusion criteria (median age 61 y). The patients in LRT subset (21,120) had significantly better survival (median: 45 vs 24 m (p < .0001). The 3 groups in training cohort showed significant difference in the OS (p < 0.0001) – G1 having better prognosis. The 3-year OS rates of the groups were 84% (G1), 66% (G2), and 38% (G3). On validation, comparable OS was seen between the respective groups in each cohort (p = 0.77). Conclusions: LRT was associated with improved OS in de novo stage 4 BC. Based on the patient/tumor characteristics, we developed a prediction model to characterize the prognostication in patients undergoing LRT for stage 4 BC.
**Poster Session (Board #165), Sat, 8:00 AM-11:30 AM**

**Analysis of circulating tumor cells (CTC) in patients across multiple metastatic breast cancer (mBCa) cohorts identifies correlated intra- and inter-patient heterogeneity in CTC size, shape, and overall morphology.**

First Author: Gordon Vansant, Epic Sciences, Inc., San Diego, CA

**Background:** The choice between hormonal therapies and chemotherapy is a frequent decision in the care of mBCa pts. We previously developed quantitative measures of phenotypic CTC heterogeneity in mCRC, and found higher heterogeneity was associated with better survival on chemotherapy vs. targeted hormonal therapies, and the reverse was true in low heterogeneity patients (Scher et al. 2017 Cancer Research). We sought to apply our previous heterogeneity quantitation methodologies to a cohort of mBCa patient CTCs to ascertain feasibility in mBCa.

**Methods:** 295 blood samples from mBCa patients were processed for CTC analysis utilizing digital pathology features. Features from each CTC (3994 CTCs from 165 pts, 84 HR+, 19 Her2+, 8 HR+/Her2+, 54 TNBC) were compared by unsupervised clustering, Shannon Index and intra-patient variance analyses to assess the intra-patient heterogeneity among mBCa CTC phenotypes.

**Results:** CTCs were detected in 76.9% (227/295) of mBCa patients. ROC analysis showed that miR-21 (AUC = 0.772; p = 0.012), miR-200b (p = 0.034) and miR-200c (p = 0.001) between the two disease states.

**Conclusions:** Distinct CTC phenotypes were identified and associated with mBCa subtypes. Subset of CTCs from TNBC pts had larger nuclear area and higher CK expression vs. other subtypes. In addition, we observed marked differences in heterogeneity in CTCs across patients, with some patients having highly uniform CTC phenotypes, and others with high phenotypic diversity. mBCa subtypes had similar intra-patient heterogeneity level.

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**Poster Session (Board #167), Sat, 8:00 AM-11:30 AM**

**Role of circulating miRNAs in detecting metastasis and having prognostic significance in metastatic breast cancer.**

First Author: Ingeborg Elisabeth de Kruijff, Department of Medical Oncology, University General Hospital of Heraklion, Heraklion, Greece

**Background:** Metastasis is the leading cause of breast cancer associated death. In the current study we evaluated the expression of (a) micro-RNA (miR)-23b and miR-190 which are involved in tumor dormancy (b) miR-21 which is involved in metastasis and (c) miR-200b and miR-200c which are involved in EMT and metastasis, in the plasma of patients with early and metastatic breast cancer (BC) in order to investigate whether they could distinguish the two disease states. Furthermore the prognostic significance of the above miRNAs was investigated in patients with metastatic disease.

**Methods:** Plasma samples were obtained from patients with early (n = 84) or metastatic (n = 57) BC before adjuvant or 1-st line treatment, respectively. Plasma miR-21, miR-23b, miR-190, miR-200b and miR-200c expression levels were assessed by RT-qPCR and expression was classified as high or low according to the median values. Results: miR-21 (p = 0.001), miR-23b (p = 0.012), miR-200b (p < 0.001) and miR-200c (p = 0.001) were higher and miR-190 (p = 0.013) was lower in metastatic compared to early BC patients. ROC analysis showed that miR-21 (AUC = 0.772; p < 0.001), miR-23b (AUC = 0.625; p = 0.012), miR-190 (AUC = 0.629; p = 0.013), miR-200b (AUC = 0.744; p < 0.001) and miR-200c (AUC = 0.668; p = 0.001) could distinguish between patients with metastatic and early BC. However, logistic regression and combined ROC analysis revealed that a panel of four miRs (miR-21, miR-190, miR-200b and miR-200c) discriminated with higher accuracy (AUC = 0.857; p < 0.001) between the two disease states. In patients with metastatic disease, miR-21 high was correlated with pre-menopausal (p = 0.013) and HER2 status (p = 0.017). The combined expression of miR-23b high and miR-190 high was correlated with progressive disease at the end of treatment (p = 0.034). Patients with miR-23b high had shorter PFS and OS (p = 0.024 and p = 0.031, respectively).

**Conclusions:** Circulating micro-RNAs discriminate between patients with metastatic and early breast cancer. In addition, their expression holds predictive information in patients undergoing first-line chemotherapy.

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**Poster Session (Board #166), Sat, 8:00 AM-11:30 AM**

**Polymorphisms of MTHFR and TYMS to predict capecitabine-induced hand-foot syndrome in patients with metastatic breast cancer.**

First Author: Shaoyan Lin, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, P.R.CHINA, Beijing, China

**Background:** Breast cancer is a global problem, and 1.7 million new cases are diagnosed per year. Capecitabine, an oral prodrug of fluorouracil, has been reported to be effective in patients with metastatic breast cancer (MBC) and approved by the United States Food and Drug Administration for treatment of MBC. Hand-foot syndrome (HFS) is one of the most relevant dose-limiting adverse effects of capecitabine. If HFS is not handled well, it can deteriorate rapidly and lead to the treatment interruptions which may influence on the treatment efficacy.

**Methods:** In our study, we investigated the association between single nucleotide polymorphism (SNP) and capecitabine-based HFS in patients with MBC in Chinese Han population, in an attempt to identify some predictive genetic biomarkers. We selected 3 genes involved in capecitabine metabolism and screened genetic variants in the target genes. We genotyped a total of 22 SNPs in the thymidylate synthase gene (TYMS), the methylene tetrahydrofolate reductase gene (MTHFR) and the ribonucleotide reductase M1 gene (RRM1) in 342 patients treated with capecitabine-based chemotherapy.

**Results:** Logistic regression analyses showed that genotype of AR rs7377964 (odds ratio (OR) = 0.54, 95% confidence interval (CI) = 0.31-0.97, P = 0.038) and genotype of rs4846048 (OR = 0.54, 95% CI = 0.30-0.98, P = 0.042) in MTHFR were protective factors that was to say low AR genotypes and high MTHFR genotypes will lower the risk of developing HFS. Genotype of rs2606241 (OR = 1.27, 95% CI = 0.73-2.32, P = 0.012) and genotype of rs2853741 (OR = 2.25, 95% CI = 1.31-3.87, P = 0.012) in TYMS increased the incidence of HFS. Patients with the high risk genotype of rs2606241 and genotype of rs2853741 were found to have 1.27-fold and 2.25-fold higher risk of suffering from HFS.

**Conclusions:** In summary, we have identified a panel of clinically useful pharmacogenetic markers predicting capecitabine-induced HFS in MBC patients.

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**Poster Session (Board #168), Sat, 8:00 AM-11:30 AM**

**Androgen receptor expression in circulating tumor cells of metastatic breast cancer patients.**

First Author: Ilse Pieters, Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands

**Background:** The androgen receptor (AR) is of clinical relevance in metastatic breast cancer (mBC). AR has been associated with resistance to endocrine therapy and could be a potential target for therapy, especially in the triple negative (TN) subtype. A minimal-invasive way to determine AR expression is by characterization of circulating tumor cells (CTCs). We therefore assessed AR mRNA expression in CTCs (CTC-AR) from mBC patients representing different breast cancer subtypes in relation to outcome on endocrine therapy and 25 genes related to the ER and AR pathways. Furthermore, we assessed AR in matched primary tumors and CTC samples taken at advanced disease. Methods: AR and AR- and ER-related gene expression levels were measured in CellSearch-enriched CTCs from 133 mBC patients with ≥5 CTCs and in 48 matched formalin-fixed paraffin embedded primary tissues using quantitative reverse-transcriptase PCR. AR was considered positive if the expression was 1 standard deviation higher than the expression measured in 12 healthy blood donors. mBC subtypes were established based on ER, PR and HER2-status of the primary tumor (9 unknowns). Results: 31% of the CTC samples were AR-positive (AR+). The HER2+ subtype had most frequently AR+ CTCs (4/8, 50%), which was significantly higher than observed in the TN subtype (2/16, 12%) (p = 0.046). The ER+/HER2- subtype had 35% (27/78) AR+ samples and the ER-/HER2+ 23% (5/22). There was no significant difference between PFS in ER-targeting treated patients and CTC-AR-status (17 AR+ / 41 AR-negative (AR-) cases, p = 0.991). 65% of the matched CTC samples and primary tissues were discordant with respect to AR, observing both switches from AR+ to AR- and vice versa. Conclusions: AR can be determined in RNA isolated from CTCs from different mBC subtypes, with in our set 31% AR-positive samples. Because there was a 65% discordancy between AR in CTC samples and the primary tumor, it seems that AR should be determined in CTCs, but more research should be conducted in a larger set. In our current analysis patients had similar outcome in ER-targeting regardless of their CTC-AR-status. Thus, determination of AR expression in CTCs might be a promising tool to select mBC patients for AR inhibiting agents.
Benefits and risks from maintenance therapy after first-line chemotherapy in patients with metastatic breast cancer. First Author: Yunfang Yu, Guangdong Provincial Key Laboratory of Malignant Tumor Immunology and Gene Therapeutics, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: Current guidelines lack definitive evidence regarding the clinical outcomes associated with different maintenance strategies for metastatic breast cancer (MBC). We aimed to investigate the benefits and risks of different maintenance therapy after first-line treatment of MBC.

Methods: We searched for randomized clinical trials (RCTs) investigating maintenance chemotherapy, endocrine therapy or immunotherapy after first-line chemotherapy in MBC. The primary endpoint was progression-free survival (PFS); overall survival (OS) and adverse events (AEs) were secondary endpoints. Direct and indirect evidence for data were combined using random-effects meta-analysis. The GRADE system was used to assess the quality of evidence.

Results: A total of 3,290 patients from 16 RCTs were included. Maintenance chemotherapy resulted into a significantly prolonged PFS (hazard ratio [HR] 0.63, 95% confidence interval 0.54 to 0.73, P = 0.000; high certainty) and OS (HR 0.87, 95% CI 0.78 to 0.97, P = 0.016; high certainty) compared with observation, although higher odds of G1-G2 AEs (moderate certainty). Among patients who developed an immune response, maintenance immunotherapy combined with chemotherapy extended PFS (HR 0.57, 95% CI 0.33 to 0.97, P = 0.04; low certainty) and OS (HR 0.71, 95% CI 0.52 to 0.97, P = 0.029; low certainty) than chemotherapy alone. Hormone-receptor-positive patients who received maintenance endocrine therapy might provide similar PFS (HR 1.0, 95% CI 0.70 to 1.50, P = 0.998; very low certainty) and OS (HR 1.15, 95% CI 0.59 to 2.22, P = 0.679; very low certainty) versus chemotherapy, but with lower odds of G1-G2 AEs (moderate certainty).

Conclusions: Our study provided strong evidence for OS and PFS benefits of maintenance chemotherapy over observation after first-line chemotherapy in MBC patients. Limited prospective trial indicated that maintenance endocrine therapy was noninferior to chemotherapy with less treatment-related toxicity, which was worthy of a clinical recommendation.

Support: ChiCTR-IIR-17014036, SYS-C-201801.

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What are the drivers of healthcare cost among patients with metastatic breast cancer (mBC)? Total cost of care analysis to inform value-based reimbursement. 

First Author: Chakkarin Burudpakdee, IQVIA, Fairfax, VA

Background: Given the move toward value-based payment in oncology, total cost of care data are needed to evaluate value. The objective of this study was to quantify cost of care and identify key drivers of healthcare cost in patients (pts) with mBC. Methods: Adults with systemic treatment for mBC from 1/1/2014 – 12/1/2016 were identified from IQVIA’s claims database. Pts were indexed on the first mBC treatment, had ≥2 diagnoses, and had breast and non-breast cancer, ≥12 months of continuous medical and drug coverage before and ≥30 days after index. Healthcare resource use and costs were measured during follow up, standardized as per patient per month (PPPM), and compared between overall and high cost (defined as top 10%) pts. Results: 7,032 pts with mBC were included; mean (±SD) age was 55.5 ± 9.6; mean follow up was 14.0 ± 9.1 months. Total cost of care is shown in Table 1. The mean total PPPM cost of high cost pts (n = 703) was 3.7-fold higher than that of the overall population. The largest difference in cost between overall and high cost pts was for outpatient drugs ($7,348 PPPM); 76% was related to breast cancer medications. Other cost drivers in high cost pts included hospitalization ($6,152 PPPM higher), radiology procedures ($2,238 PPPM higher), and pharmacy services ($1,755 PPPM higher). The proportion of total costs due to outpatient surgery, office visits, lab services, and ED visits was lower in high cost pts compared to the overall population (10.5% vs. 7.1%). Conclusions: Our findings suggest that medications, hospitalizations, and radiology services are the main drivers of high costs in mBC pts. Further research is needed to identify if there are services and costs that are unintended and avoidable. Findings from this study can help inform evidence-based decisions when evaluating alternative payment models for cancer care. 

<table>
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<th>Total cost of care</th>
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Lapatinib plus veliparib in the metastatic, triple-negative breast cancer. First Author: Zachary William Neil Veitch, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Pembro is a PD-1 immune checkpoint inhibitor with a low toxicity profile and durable objective responses among patients (pts) with metastatic melanoma (MM) and metastatic breast cancer (BC), often resistant to standard of care therapies. We previously showed an induced synthetic lethal interaction with combined EGFR (epidermal growth factor receptor) and PARP (Poly (ADP-ribose)-polymerase) inhibition in TNBC cells. Therefore, we tested a pilot clinical trial using lapatinib and veliparib in patients with locally advanced unresectable or metastatic TNBC. Here we report safety results and clinical activity of the combination of veliparib and lapatinib. Methods: Key eligibility criteria include histologically confirmed TNBC (ER negative, PR negative, HER-2 Neu negative), measurable disease, failed anthracyclines and taxanes in the neoadjuvant, adjuvant, or metastatic setting, left ventricular ejection fraction ≥ 50, and ECOG PS of 0-2. Patients with known germline BRCA 1 or 2 mutations were excluded. Eligible patients received continuous doses of lapatinib 1250 mg PO daily and veliparib 200 mg PO twice daily. Dose limiting toxicity (DLT) evaluation period was 28 days (cycle 1). Adverse events (AEs) were assessed by CTCAE v4.03 and best objective response per RECIST v1.1. Results: Twenty patients were enrolled and 17 were evaluable for response. The median number of prior therapies for advanced BC was 1 (range 0-2). Fifty percent of the patients enrolled were Caucasian, 45% African-American, and 5% Hispanic. Of the evaluable patients, 4 had a partial response and 2 had stable disease. There were no dose-limiting toxicities. The majority of toxicities occurred during cycles 2 and 3. Toxicities were manageable. Most adverse events (AEs) were limited to grade 1 or 2 (no grade 5). Common treatment-related AEs were fatigue (64%), diarrhea (51.5%), constipation (5.5%), and nausea (2.3%). Other common AEs included vomiting (2.9%), anemia (2.6%), headache (2.6%), dizziness (2.3%), dyspnea (2.3%), and rash (2.3%). Conclusions: Lapatinib plus veliparib in the treatment of advanced TNBC resistant to SoC has a manageable safety profile and promising antitumor activity. Further investigation of EGFR inhibition in combination with a PARP inhibitor is needed. Clinical trial information: NCT02158507.
Mechanisms of immune evasion in triple-negative breast cancer patients. First Author: Javier Ignacio Orozco, John Wayne Cancer Institute at Providence Saint John Health Center, Santa Monica, CA

Background: Immunotherapy has shown promising results in enhancing response rates for patients with triple-negative breast cancer (TNBC). The success of immunotherapy is affected by poor tumor antigen presentation. This immune evasion is facilitated by genetic and epigenetic alterations, including aberrant RNA splicing (AS). Here we examined the role of PTBP1, a key RNA splicing factor related to immune evasion in TNBC.

Methods: Clinical and gene expression data from 3,614 breast cancer patients were used for this study. Patients with PTBP1 and tumor samples were compared to databases of normal breast tissue and TNBC. RNA-seq and immunohistochemical (IHC) were employed to validate our findings in TNBC cell lines, including Breast Cancer Cell Line Panel (MDA-MB-231). A portrait of infiltrating immune cells was compiled with relapse-free survival (RFS), disease-free survival (DFS), and overall survival (OS) data. Statistical modeling was performed to test the association of PTBP1 expression with clinical outcomes.

Results: PTBP1 was significantly upregulated in TNBC patients (P<0.001). TNBC patients with high PTBP1 presented significantly shorter RFS (P=0.018; HR=1.66, 95% CI 1.1-2.5; n=255), DFS (P=0.017; HR=3.2, 95% CI 1.1-8.3; n=151), and OS (P=0.037; HR=1.48, 95% CI 1.02-2.1; n=162). To explore potential mechanisms linking PTBP1 overexpression and poor survival, we performed a similar analysis using the available data. The results showed a significant enhancement on antigen presentation pathways, as identified by increased expression of MHC class I and II molecules.

Conclusions: This study highlights the importance of PTBP1 in immune evasion, identifying new prognostic and potentially therapeutic targets for patients with aggressive TNBC.
A phase II study of atezolizumab (Atezo) combined with pertuzumab (P) and high-dose trastuzumab (H) for the treatment of central nervous system (CNS) metastases in patients with HER2-positive metastatic breast cancer (MBC), First Author: Romualdo Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA

Background: There is no clear standard of care to address the management of refractory CNS metastases in HER2+ MBC. The ongoing study (NCT03417544) is evaluating the efficacy of the combination of Atezo with P and high-dose H for the treatment of CNS metastases in patients (pts) with HER2-positive MBC. Methods: This is a phase II, single-arm, open-label, non-randomized trial assessing the efficacy of Atezo with Pertuzumab plus high-dose H for the treatment of CNS metastases in HER2+ MBC. Participants will receive Atezo (1200mg every 3 weeks (q3w)), P (840-mg loading dose, then 420mg q3w), and high-dose H (6 mg/kg weekly for 24 weeks, and then q3w). Eligibility Criteria include pts with HER2+ MBC, at least one measurable CNS metastasis (>10 mm), unequivocal evidence of new and/or progressive CNS metastases, and left ventricular ejection fraction (LVEF) ≥ 50%. Exclusion criteria include CNS complications for whom urgent neurosurgical intervention is needed; known leptomeningeal / brainstem metastases; and treatment dexamethasone > 2mg/day or bioequivalent within 7 days of initiating therapy. The primary endpoint is objective response rate (ORR) in the CNS per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. Secondary endpoints include the duration of CNS response, bi-compartmental progression-free survival according to RANO-BM, and the extracranial ORR according to RECIST 1.1. Tumors, tissues, peripheral blood, and cerebrospinal fluid will be obtained at baseline, on treatment, and at progression. In the first stage, 19 pts will be enrolled. If there are at least 4 CNS responses, accrual will continue to the second stage where up to 14 additional pts will be enrolled. If at least 8 of these 33 pts have assessed responses, the regimen will be considered worthy of further study. With this design, if the true response rate is 15%, the chance the regimen is declared worthy of further study is less than 10% (exact alpha = 0.096). If the true response rate is 35%, the chance that the regimen is declared worthy of further study is 90.4%. The trial opened in February 2018, with a target accrual of 33 pts. Clinical trial information: 03417544.

A phase II, multicenter, open-label study of trastuzumab denuxemab (DS-8201a) in subjects with HER2-positive, unmetastatic and/or metastatic breast cancer, First Author: Daniel A. Zhu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: There is no standard of care for HER2-positive breast cancer refractory to T-DM1. DS-8201a is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a cleavable peptide-based linker (deruxtecan), and with a high drug-to-antibody ratio of 7 to 8. In the ongoing phase 1 DS8201-A-J101 trial, DS-8201a showed a manageable safety profile and promising antitumor activity in HER2-positive breast cancer subjects previously receiving T-DM1 (confirmed objective response rate (ORR) of 61.4%; Oct 2017 data cutoff) (Modi et al, SABCS 2017). In August 2017, the FDA granted breakthrough therapy and fast track designations.

Methods: The phase 2, open-label, multicenter, 2-part, DESTINY-Breast01 study will assess the efficacy and safety of DS-8201a in subjects with HER2-positive (confirmed by centralized testing) unmetastatic or and/or metastatic breast cancer previously treated with T-DM1. Part 1 will enroll 120 subjects and includes pharmacokinetic (PK) and dose finding stages to identify the recommended phase 2 dose (RP2D). The PK stage will randomize 60 subjects (1:1:1) to 1 of 3 DS-8201a doses (7.4, 6.4, and 5.4 mg/kg; once every 3 weeks). In the dose finding stage, an additional 60 subjects will be randomized (1:1:1) to 1 of 2 doses selected in the PK stage. Part 2b will enroll an open-ended number of subjects who discontinued T-DM1 for reasons other than progressive disease. Overall, enrollment of ≥ 100 subjects with a history of prior pertuzumab treatment for metastatic breast cancer is planned at the RP2D. The primary endpoint, ORR, will be assessed in all subjects enrolled in parts 1 and 2a who received the RP2D and who had baseline measurable tumors assessed by an independent central imaging facility. Secondary endpoints include duration of response, disease control rate, progression-free survival, and overall survival. Enrollment began in August 2017. As of Feb. 12, 2018, 35 of approximately 230 subjects have been enrolled. Clinical trial information: NCT03248492.

A phase II trial of palbociclib and trastuzumab (H+) with or without letrozole in trastuzumab-pretreated, postmenopausal patients with HER2-positive metastatic breast cancer, First Author: Patricia Villagrasa, SOLTI Breast Cancer Research Group, Barcelona, Spain

Background: Despite the high efficacy of anti HER2-agents, HER2-positive (HER2+) metastatic breast cancer (BC) remains incurable and in need of additional options. In this context, CDK4/6 inhibition combined with anti-HER2 therapy is currently being explored in phase II/III trials. Preclinical evidence from different HER2+ BC models have shown that CDK4/6 inhibition leads to deep cytoplastic arrest and inhibition of its invasive properties, underlining the role of CDK4/6 in HER2 signaling. Moreover, Identification of the luminal subtype in HER2+HR+ disease might be important since the median IC50 of palbociclib (P) in HER2+ BC cell lines falling into the luminal subtype is lower than in non-luminal HER2+ cell lines (47.5 vs. 300 nM). We have recently reported that PAM50 luminal subtype predicts progression-free survival (PFS) in HER2+/HR+ advanced BC treated with P and trastuzumab (T) compared to non-luminal disease (10.37 vs. 3.53 months, p-value = 0.023). PATRICIA is a Simon 2-Stage study to evaluate the efficacy of combining T plus P, +/− letrozole (L), assessed by PFS in humanized treated HER2+ patients. Methods: Postmenopausal HER2+ patients who had received 2-4 prior lines of anti-HER2-based regimens are included in 3 cohorts: A: HR−negative; B1: HR+, receiving both T and P; B2: HR+, receiving T, and P. P is administered at 200 mg/day for 14 days of 21-day cycles. T and L are administered at usual doses. The primary objective is to test the clinical efficacy measured by PFS at 6 months (F6M). Assuming an increase of at least 20% in PFS6 by the addition of P +/− L to T, PFS6 should be ≥30% for a cohort to be successful and proceed to stage 2. Thus, it will be necessary to include 15 patients in each cohort in stage 1. In stage 2, each cohort may continue recruitment for up to 46 patients. Translational research for predictive biomarkers will be implemented. To date, 55 patients, 15 in A and 20 in each B cohort, have been included in 14 sites across Spain. The 1st stage efficacy analysis was performed for B cohorts, leading 2nd stage accrual began in September 2017. Cohort A stage 1 effectiveness analysis is intended for June 2018. Clinical trial information: NCT02448420.

A multicenter, phase I/II trial of anastrozole, palbociclib, trastuzumab and pertuzumab in HR-positive, HER2-positive metastatic breast cancer, First Author: Krystal Pauline Cascetta, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Overexpression or amplification of HER2 occurs in approximately 15 – 20% of patients and about half of these tumors are hormone receptor (HR) positive. Studies suggest that this 10% of all breast cancer cases may derive less benefit from endocrine therapy than those with HR− disease without HER2 overexpression. The use of aromatase inhibitors in the metastatic setting is well established while significant improvement in overall survival has been established with the use of trastuzumab or pertuzumab in HER2-overexpressing tumors. To date, no studies have examined the combination of endocrine therapy, palbociclib, and dual HER2 therapy with pertuzumab and trastuzumab in this patient population. Trial Design: Multicenter, Phase I/II Trial of Anastrozole, Palbociclib, Trastuzumab and Pertuzumab in HR-positive, HER2-positive Metastatic Breast Cancer. Eligibility Criteria: Stage IV HR+, HER2+ breast cancer patients. Specific Aims: Phase I: To determine the maximum dose tolerated of palbociclib. Phase II: To determine the clinical benefit rate (CBR) of treatment with anastrozole, palbociclib, trastuzumab, and pertuzumab in HR+, HER2+ metastatic breast cancer patients. Exploratory: Examine potential biomarkers of response to palbociclib including expression of cyclin D1, cyclin E1 and E2, retinoblastoma, phosphorylated retinoblastoma, and p16 levels. RNA sequencing will be used to assess for other predictors of response in an unbiased manner to assess for correlation with inhibition of Ki-67 and phosphorylated retinoblastoma expression as well as evaluate for potential mechanisms of resistance. Methods: This study will evaluate the maximum tolerated dose (MTD) of the Anastrozole, Palbociclib, Trastuzumab and Pertuzumab in HR-positive, HER2-positive metastatic breast cancer patients.
Palbociclib after CDK and endocrine therapy (PACE): A randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2- metastatic breast cancer. First Author: Erica L. Mayer, Dana-Farber Cancer Institute, Waban, MA

Background: CDK4/6 inhibition (CDK4/6i) has a well-established role in the management of hormone receptor positive/HER2 negative (HR+/HER2-) metastatic breast cancer (MBC). The addition of a CDK4/6i to endocrine therapy (ET) in HR+/HER2- MBC leads to prolongation of progression-free survival in the first-line and pre-treated settings. Mechanisms of resistance to CDK4/6i are not well described, and it is not known if continuation of CDK4/6i with subsequent lines of ET improves outcomes over ET alone. Further, preclinical data suggest combination therapy with ET, CDK4/6i, and anti-PD-L1 may provide synergistic efficacy. The PACE trial was designed to determine optimal subsequent line of therapy in patients (pts) with HR+ / HER2- MBC that has progressed despite prior CDK4/6 inhibition and endocrine therapy. Methods: PACE is a multicenter phase II trial randomizing pts 1:2:1 to Arm A: fulvestrant alone (with option for palbociclib mono-therapy crossover at time of progression); Arm B: fulvestrant and palbociclib; or Arm C: fulvestrant, palbociclib, and avelumab. The primary objective is to evaluate progression-free survival (PFS) with the combination of fulvestrant and palbociclib vs. fulvestrant alone; secondary objectives include overall response (OR) and PFS comparisons for other arms; assessment of outcomes in predefined molecular subgroups including ESR mutation, PI3K mutation, loss of RB; safety and tolerability; and comparing OR by RECIST vs irRECIST. Exploratory analysis of minimal residual disease (MRD) in ctDNA, and (CT) for mutations of resistance may or may not be present at the time of progression; and reversal of resistance to therapy is planned. Eligible pts have HR+/HER2- MBC, with prior response to and subsequent progression on CDK4/6i and ET, defined as at least 6 months of prior treatment, with confirmed subsequent progression, and no more than one prior P D dose reduction for toxicity. Pts may have had 1-2 prior ET, and 0-1 prior lines of chemotherapy. A sample size of 220 patients is planned. NCT03147287.

Contessa: A multinational, multicenter, phase 3 registration study of Texetaxel in post-treatment of PIK3CA mutant, hormone receptor-positive (HR+), locally advanced or metastatic breast cancer (MBC). First Author: Joyce O’Shaughnessy, Texas Oncology - Baylor Charles A. Sammons Cancer Center and The US Oncology Network, Dallas, TX

Background: Chemotherapy treatments that offer improved quality of life are needed. Texetaxel (T) is a novel, oral taxane that has potential advantages over currently available taxanes, including; oral administration with a low pill burden and Q3W dosing; no history of hypersensitivity reactions; and improved activity against chemotherapy-resistant tumors (Shionoya 2003; Chan 2006). 555 pts have been treated with T in clinical studies (492 monotherapy; 63 in combination with capecitabine (C)). In MBC, T had robust single-agent activity in 2 multicenter, Phase 2 studies. In TOB203, 38 pts with HER2- HR MBC received single-agent T Q3W for MBC; the confirmed ORR per RECIST 1.1 in all 38 pts was 45% (95% CI: 29% - 62%); the median PFS was 5.7 mo (95% CI: 4.1 – 9.8 mo). In a Phase 1 study, the combination of T plus a reduced dose of C was associated with a tolerable AE profile with minimal overlapping toxicity. C is a preferred agent for pts with MBC. Combining the approved dose of C with currently available taxanes results in robust efficacy but significant toxicity, while preclinical and clinical studies suggest that reducing the dose of C in combination with a taxane may result in reduced toxicity without a reduction in efficacy. CONTESSA investigates T plus a reduced dose of C as an all-or-nothing regimen in HER2-, HR+ MBC. Methods: CONTESSA is a 600-patient, multinational, multicenter, randomized (1:1:1), Phase 3 registration study comparing T (27 mg/m^2 on Day 1 of a 21-day cycle) plus a reduced dose of C (1,650 mg/m^2/day on Days 1-14 of a 21-day cycle) to the approved dose of C alone (2,500 mg/m^2/day on Days 1-14 of a 21-day cycle) in pts with HER2-, HR+ MBC previously treated with a taxane in the frontline or neoadjuvant setting. Where indicated, pts must have received endocrine therapy with or without a CDK 4/6 inhibitor. The primary endpoint is PFS assessed by an Independent Radiologic Review Committee (IRC). CONTESSA is 90% powered to detect a 42% improvement in PFS (HR = 0.57). Secondary endpoints are OS, ORR assessed by IRC, disease control rate in the overall and IRC assessed setting. Where indicated, pts must have received endocrine therapy with or without a CDK 4/6 inhibitor. The trial was initiated in Dec 2017. Clinical trial information: NCT03326674.

Breast Cancer—Metastatic

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: 75% of all breast cancers (BC) are hormone receptor-positive (HR+). Despite the efficacy of endocrine therapies, HR+ BC development, and cytotoxic chemotherapy is ultimately the only option to treat these patients. TTC-352 is a selective human estrogen receptor (ER) partial agonist (ShERPAP) that was developed for treatment of HR+ BC. ShERPAs mimic the effects of estradiol (E2) in hormone-independent, endocrine-resistant BC cells, but since it has only partial agonist activity in HR+ BC cells, it could have an improved side-effect profile. Specifically, TTC-352 does not support the growth of HR+, hormone-dependent BC xenografts that normally require E2 for growth nor result in uterine proliferation in mouse xenograft models as does E2. PKCa is a predictive biomarker for response to TTC-352 in endocrine-resistant BC xenografts. Thus, TTC-352 could be a promising treatment option for endocrine-resistant BC.

Methods: This is an open-label, accelerated dose escalation study that will evaluate up to five dose levels of TTC-352 in patients with HR+ endocrine-resistant metastatic BC. The maximum tolerated dose (MTD) of TTC-352 will be determined using initial single-patient cohorts until grade 2 toxicity, then an expanded-Fibonacci dose-escalation 3+3 design. Patients enrolled at each dose level can start. The MTD dose level cohort will be expanded to a total of (12 injections). The primary endpoint is progression-free survival. Secondary endpoints include: tumor PKCa expression, steady-state dose cohort can start. The MTD dose level cohort will be expanded to a total of 28-day cycle before enrollment to the next dose levels of TTC-352 in patients with HR+ endocrine-resistant metastatic BC. The maximum tolerated dose (MTD) of TTC-352 was determined using initial single-patient cohorts until grade 2 toxicity, then an expanded-Fibonacci dose-escalation 3+3 design. Patients enrolled at each cohort must complete the first 28-day cycle before enrollment to the next dose cohort can start. The MTD dose level cohort will be expanded to a total of 9 patients, to further evaluate safety. The secondary objectives are: to determine patient best response (BR) to treatment, progression-free survival (PFS), overall survival (OS), treatment tolerability of TTC-352, and to establish the pharmacokinetic profile of TTC-352 in patients with metastatic ER+ BC. Correlative objectives include: tumor PKCa expression, steady-state values for Cmax, and AUC0-12 correlation with BR, PFS and OS. Patient population: patients with metastatic HR+ BC that has progressed on at least two lines of endocrine therapy, with one that included a CDK4/CDK6 in-human xenografts as does E2. PKCa is a predictive biomarker for response to TTC-352 in endocrine-resistant BC xenografts. Thus, TTC-352 could be a promising treatment option for endocrine-resistant BC.

Methods: This is an open-label, accelerated dose escalation study that will evaluate up to five dose levels of TTC-352 in patients with HR+ endocrine-resistant metastatic BC. The maximum tolerated dose (MTD) of TTC-352 will be determined using initial single-patient cohorts until grade 2 toxicity, then an expanded-Fibonacci dose-escalation 3+3 design. Patients enrolled at each cohort must complete the first 28-day cycle before enrollment to the next dose cohort can start. The MTD dose level cohort will be expanded to a total of 9 patients, to further evaluate safety. The secondary objectives are: to determine patient best response (BR) to treatment, progression-free survival (PFS), overall survival (OS), treatment tolerability of TTC-352, and to establish the pharmacokinetic profile of TTC-352 in patients with metastatic ER+ BC. Correlative objectives include: tumor PKCa expression, steady-state values for Cmax, and AUC0-12 correlation with BR, PFS and OS. Patient population: patients with metastatic HR+ BC that has progressed on at least two lines of endocrine therapy, with one that included a CDK4/CDK6 in-
An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity. First Author: Amanda Papoutsis. Institute of West Cancerology Paul Papout, Angers, France.

Background: Rucaparib, a potent oral PARP-1, -2 and -3 inhibitor, has shown activity in a phase 3 study of patients (pts) with ovarian carcinoma (ARIEL 3) harbouring a BRCA4 mutation or an homologous recombination deficient (HRD) profile defined by high percentage of genome-wide loss of heterozygosity and in a phase 1 study that included breast cancer pts with germline BRCA mutation (Kristeleit et al, Clin Can Res, 2017). High genomic LOH score identified HRD tumors (also known as BRCAness tumors), including both known BRCA1 methylation and unknown genetic/epigenetic mechanisms and somatic BRCA1/2 mutations. This single arm, open-label, multicenter phase II RUBY study (NCT02505048) is evaluating the efficacy and safety of rucaparib in pts with HER2- metastatic breast cancer (MBC) associated with a high tumor genomic LOH score and/or a somatic BRCA1 mutation (excluding BRCA1 and BRCA2 germline mutations). Methods: Women with HER2- MBC with a HRD phenotype who received at least 1 prior chemotherapy regimens are eligible. ECOG PS 0-1 and adequate organ function is required. HRD phenotype is defined by a “high tumor genomic LOH” score, generated from the CytoScan HD SNP array, which is available from SAFIR-2 (NCT02299999) or SAFIR-TOR (NCT02444390) protocols. Pts received oral rucaparib 600 mg BID continuously in 21-day cycles until disease progression. The primary endpoint is clinical benefit rate (CBR), defined by complete and partial response and stable disease lasting for at least 16 weeks. If CBR is significant the objective response rate (ORR) will be computed. Secondary endpoints include progression-free survival, overall survival, safety, and the prognostic value of the HRD signature. This trial design is intended to establish proof-of-concept that rucaparib can improve ORR in HER2- MBC with HRD. Targeted enrollment is 41 pts using a Simon two-stage design, 19 pts in the first step and 22 pts in the second one. The prespecified goal of the first step was achieved; enrollment into the second step is ongoing. Clinical trial information: NCT02505048.

A phase II clinical trial to analyze olaparib response in patients with BRCA1 and/or BRCA2 promoter methylation with advanced breast cancer (GEICAM/2015-06 COMETA-Breast study). First Author: Juan De La Haba, Biomedical Research Institute Maimonides. Hospital UniversitarioReina Sofia, Universidad de Cordoba, Spain.Centro de Investigación Biomédica en Red de Oncología, CIBERONC-IDCI. GEICAM, Spanish Breast Cancer Group, Spain, Cordoba, Spain.

Background: Identification of targeted therapies for advanced triple negative breast cancer (TNBC) remains as an important clinical challenge. TNBC frequently shows BRCA dysfunction and 80% of germline BRCA1 mutation (gBRCA1m) carriers with BC diagnosis are TNBC patients (pts). In addition to germline mutations, epigenetic silencing by aberrant methylation of BRCA1/2 promoters can be responsible for a dysfunctional BRCA protein. Methylation of BRCA1 promoter occurs in 15-57% of TNBC. Interestingly, BRCA1-methylated sporadic breast cancers display pathologic features and gene expression profiles similar to those of gBRCA1m carriers, a phenotype called “BRCAless”. Olaparib (O) is an oral poly (ADP-ribose) polymerase (PARP) inhibitor approved by the FDA for treatment of gBRCA-mutated HER2-negative metastatic BC. Tutt et al. have shown antitumor activity in gBRCA4-mutated advanced TNBC (54% Objective Response Rate (ORR)). We report an ongoing phase II clinical trial to analyze the O efficacy in advanced TNBC pts with BRCA1/2 promoter methylation (NCT03205761). Methods: Eligible pts are advanced TNBC cases with ≥ 1 prior treatment for advanced disease, without germline BRCA1/2 mutations and centrally confirmed somatic BRCA1/2 promoter methylation in metastatic lesions. Pts receive O 300 mg b.i.d. orally. Primary objective is to analyze O efficacy in terms of ORR according to RECIST 1.1 by investigator assessment. Secondary objectives include safety, other efficacy endpoints, and biomarker analyses. Sequential tumor and blood samples are collected to explore changes in methylation status, b) correlate BRCA-methylation status both in blood vs. tumor and in primary vs. metastatic counterpart lesions, and c) correlate methylation status with BRCA1/2 expression and outcome. Thirty-four evaluable pts are required based on an optimal two-stage Simon model (α = 0.05, power = 0.80). Recruitment started in October 2017, with 17 pts screened for methylation status, 3 pts enrolled by 31st January 2018, and 14 active sites out of 16 participants. Primary endpoint analysis is planned for Q2 2020. Clinical trial information: NCT03205761.

A randomized phase II study of pembrolizumab, an anti-PD (programmed cell death) 1 antibody, in combination with carboplatin compared to carboplatin alone in breast cancer patients with chest wall disease. Background: Chest wall disease from breast cancer has limited treatments. Given the inflammatory nature of this disease and the increased expression of PD-1 seen with lymphocytic infiltration, we hypothesize that pembrolizumab may be effective. Combining immunotherapy with platinum chemotherapy may facilitate anti-tumor immunity, as demonstrated in lung cancer. This study is evaluating the combination of pembrolizumab and carboplatin in breast cancer patients with chest wall disease. Methods: This is a randomized phase II multicenter trial in the Translational Breast Cancer Research Consortium. Eighty-four patients with breast cancer (hormone resistant, triple negative, or refractory HER2+) with chest wall disease will be enrolled. Patients may have had prior surgery but prior radiation is not required, and patients may have distant metastases. Patients will be randomized 2:1 to treatment with pembrolizumab 200 mg IV and carboplatin AUC 5 every 3 weeks for at least 3 cycles followed by pembrolizumab 200 mg IV every 4 weeks (Arm A) or carboplatin AUC 5 every 3 weeks (n = 28, Arm B) until progression. Patients in Arm B may cross over to pembrolizumab 200 mg IV every 3 weeks (Arm Bx) on progression. After 18 patients are enrolled in Arm B, an interim analysis for futility will be performed, to allow for early closure if lack of efficacy. The primary objective is to determine the disease control rate (DCR) at 12 weeks. 95% confidence interval (CI) for this study is powered to detect a 20% difference between arms, with a hazard ratio of 0.52 (α = 0.10, β = 0.20). The secondary objectives are to determine toxicity, progression free survival, and response based on irRECIST and PD-L1 expression. Exploratory objectives, using tumor biopsy and peripheral blood sampling before and at the end of treatment, include correlations of response with biomarkers including tumor PD-L1 expression, tumor and peripheral blood immune composition, circulating tumor cells, circulating tumor DNA, soluble PD-L1 and tumor MYC expression. This study is open to accrual; the first patient was enrolled in 11/17. Clinical trial information: NCT03095352.

IMpassion132: A double-blind randomized phase 3 trial evaluating chemotherapy (CT) + pembrolizumab (atezo) for early progressing locally advanced/metastatic triple-negative breast cancer (mTNBC). First Author: Rebecca Dent, National Cancer Center, Singapore, Singapore.

Background: Atezolizumab (atezo) blocks the interaction of PD-L1 with receptors PD-1 and B7.1, restoring anti-tumor immunity. PD-L1 pathway inhibitors may be synergistic with CT. In a phase 1b study in mTNBC, atezo + nab-paclitaxel showed durable confirmed responses (Adams 2016). The IMpassion130 and 131 randomized phase 3 trials are evaluating atezo combined with nab-paclitaxel and paclitaxel, respectively, as 1st-line therapy for mTNBC. Both exclude patients (pts) with disease progression (PD) within 12 mo of CT for early breast cancer (eBC). IMpassion132 (NCT03371017) compares atezo + CT vs placebo + CT in pts with PD ≥ 12 months after completing CT for eBC, and combines atezo with 2 commonly used non-taxane CT regimens. Methods: In this multinational placebo-controlled randomized phase 3 trial, pts with recurrent (inoperable locally advanced/metastatic) TNBC treated with standard (neo)adjuvant anthracycline and taxane CT and relapsing ≥12 months after the last treatment with curative intent for eBC are eligible if they have received no prior CT for advanced/metastatic TNBC. PD-L1 status (for stratification) and TNBC status are centrally before randomization. Investigators select CT (gemcitabine 1000 mg/m2 + carboplatin AUC 2, d1 & 8 q21 d[X]) before randomization. All pts with prior platinum for eBC are eligible. Pts are randomized 2:1 to treatment with pembrolizumab 200 mg IV and carboplatin (Arm A) or carboplatin alone (Arm B) depending on PD-L1 expression. The primary endpoint is overall survival (OS). Secondary endpoints include 12- and 18-mo OS rates, progression-free survival, objective response rate (RECIST v1.1), duration of response, clinical benefit rate, pt-reported outcomes (PROs; EORTC QLQ-C30) and safety. Exploratory endpoints include further PROs, pharmacokinetics and translational research. Clinical trial information: NCT03371017.
TPS1116 Poster Session (Board #189a), Sat, 8:00 AM-11:30 AM

VIOLETTE: A randomized phase II study to assess DNA damage response inhibitors in combination with olaparib (Ola) vs Ola monotherapy in patients (pts) with metastatic, triple-negative breast cancer (TNBC) stratified by alterations in homologous recombination repair (HRR)-related genes. First Author: Andrew Tutt, Breast Cancer Now Toby Robins Research Centre The Institute of Cancer Research, and Breast Cancer Now Research Unit, King’s College London Division of Cancer Studies, King’s Health Partners Academic Health Sciences Centre, London, United Kingdom

Background: Invasive BC is diagnosed in > 255,000 pts in the US annually, and TNBC comprises ~15% of cases. Alterations in BRCA1/2 are detected with ~5% of all BCs. Ola (a poly ADP-ribose polymerase inhibitor [PARPi]) is approved in the US for treating pts with HER2-negative metastatic BC with germline BRCA mutation (gBRCAm). Pts treated with Ola had significant and clinically meaningful improvements in progression-free survival (PFS) vs pts treated with “physician’s choice” of chemotherapy. Similarly, alterations in other non-BRCA1/2 HRR genes (non-BRCA HRRm) may confer sensitivity to Ola therapy in pts with TNBC. Ola, AZD1775 (a WEE1 inhibitor) and AZD6738 (an ataxia telangiectasia and Rad3-related protein inhibitor) target DNA damage repair and cell cycle regulation. Both Ola + AZD1775 and AZD6738 had synergistic antitumor effects in preclinical studies, supporting the clinical evaluation of these combinations vs Ola monotherapy in pts with TNBC. Methods: In this global, multicenter, open-label, phase II study (NCT03330847), 450 pts with advanced TNBC will be randomized (1:1:1) to 3 treatment arms 1) Ola 200 mg bid + AZD1775 175 mg bid, 2) Ola 300 mg bid + AZD6738 160 mg bid, or 3) Ola 300 mg bid. All pts will undergo centralized tumor molecular testing to detect mutation(s) in 15 HRR genes and ~150 pts will be assigned to each of the 3 biomarker strata (A: BRCAm; B: non-BRCA HRRm; C: non-HRRm). All pts will be stratified by prior platinum exposure. Eligible pts will have received < 2 prior lines of chemotherapy for metastatic disease, including an anthracycline or taxane. Exclusion criteria include prior PARPi therapy. The primary endpoint is PFS (each combination vs Ola alone) analyzed by blinded, independent central review (RECIST v1.1). Secondary endpoints are objective response rate, duration of response, change in tumor size, and overall survival for comparisons between combinations and for each combination vs Ola alone; drug exposure; and safety and tolerability. Enrollment is ongoing. Clinical trial information: NCT03330847.

TPS1117 Poster Session (Board #189b), Sat, 8:00 AM-11:30 AM

IPATunity130: A pivotal randomized phase III trial evaluating ipatients (IPAT) + paclitaxel (PAC) for PIK3CA/AKT1/PTEN-altered advanced triple-negative (TN) or hormone receptor-positive HER2-negative (HR+/HER2-) breast cancer (BC). First Author: Rebecca Dent, National Cancer Center, Singapore, Singapore

Background: In the LOTUS trial in advanced TNBC, adding IPAT to first-line PAC improved progression-free survival (PFS; primary endpoint), particularly in patients (pts) with PIK3CA/AKT1/PTEN-altered tumors (Kim, Lancet Oncol 2017). The pivotal double-blind placebo (PBO)-controlled randomized phase III IPATunity130 trial (NCT03337724) aims to confirm and build on findings from LOTUS. Methods: Eligible pts have ECOG performance status 0/1 and RECIST-measurable locally advanced/metastatic BC not amenable to resection with curative intent. Pts are allocated to either cohort A (TNBC; n=249) or cohort B (HR+/HER2- not suitable for endocrine therapy; n=201) according to their most recently assessed receptor status (in recurrent/metastatic tumor if available). In cohort A, any prior systemic therapy for advanced TNBC is prohibited, whereas cohort B pts may have received prior systemic therapy except chemotherapy for advanced BC. Tumor PIK3CA/AKT1/PTEN eligibility is tested centrally by next-generation sequencing (Foundation Medicine). Stratification factors are prior (neo) adjuvant chemotherapy, geographic region, and either tumor PIK3CA/AKT1-activating mutation status (cohort A) or prior PI3K/mTOR inhibitor therapy (cohort B). Pts in both cohorts are randomized 2:1 to 28-day cycles of PAC 80 mg/m2 (d1, 8, & 15) combined with either oral IPAT 400 mg/day (d1–21) or PBO until disease progression, intolerable toxicity, or withdrawal. Cross-over to IPAT after progression on PAC + PBO is prohibited. The primary endpoint is investigator-assessed PFS by RECIST v1.1. Secondary endpoints include overall survival (key secondary), objective response rate (RECIST v1.1), duration of response, clinical benefit rate, EORTC QLQ-C30 global health status/health-related quality of life, and safety. Cohorts A and B will be analyzed separately. For each cohort, PFS will be compared between treatment arms using a stratified log-rank test. The trial is actively accruing pts. Clinical trial information: NCT03337724.

TPS1118 Poster Session (Board #190a), Sat, 8:00 AM-11:30 AM

A randomized phase II trial of carboplatin with or without nivolumab in first- or second-line metastatic TNBC. First Author: Ana Christina Garrido-Castro, Dana-Farber Cancer Institute, Boston, MA

Background: Triple negative breast cancer (TNBC) has an aggressive clinical course with higher relapse rates and shorter overall survival compared to patients with hormone receptor-positive or HER2-positive disease. Increasing data suggest that interaction with the immune system is critical for outcomes in TNBC. Tumor infiltrating lymphocytes (TIL) correlate with immune-related responses and are predictive of survival in metastatic breast cancer. However, response rates with single agent checkpoint inhibitors reach only ~25% in first-line TNBC. Platinum agents are DNA crosslinkers that cause accumulation of genotoxic stress, which stimulates immune activation via IFN-γ signaling. In preclinical models, platinum has been shown to generate CD8-driven anti-tumor immune responses, making the combination with nivolumab (PD-1 antibody) an attractive strategy to enhance the benefit of either agent alone. Methods: This Phase II open-label, multicenter trial will enroll 132 patients with metastatic TNBC randomized 1:1 to receive carboplatin (AUC 6) with or without nivolumab (360 mg) IV every 3 weeks. Eligible patients must have unresectable locally advanced or metastatic TNBC treated with 0 to 1 prior line of chemotherapy in the metastatic setting. Prior platinum exposure is allowed in the neo/adjuvant setting if ≥12 months elapsed since the end of adjuvant therapy to the development of metastatic disease. The primary objective is to compare the efficacy, defined as progression-free survival (PFS) per RECIST 1.1, of carboplatin in combination with nivolumab versus carboplatin alone. Key secondary objectives include objective response rate, overall survival, clinical benefit rate, and duration and time to objective response. Patients must be willing to undergo mandatory radiographic imaging every 2 cycles of therapy, if safely accessible, to assess the correlation between TIL and PD-1 and to explore pharmacodynamic changes in TIL and other biomarkers of response and resistance to treatment. Additional correlative studies, including analyses of circulating tumor DNA, peripheral blood mononuclear cells and intestinal microbiome, are planned. Clinical trial information: NCT03146848.

TPS1119 Poster Session (Board #190b), Sat, 8:00 AM-11:30 AM

A phase II study of nivolumab in combination with cabozantinib for metastatic triple-negative breast cancer (mTNBC). First Author: Romualdo Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA

Background: Patients with mTNBC have a poor prognosis, and new therapies are needed. Vascular endothelial growth factor (VEGF)-A and myeloid-derived suppressors cells (MDSCs) have been recognized as critical players of tumor immune suppression of T-cell mediated responses. We hypothesize that cabozantinib, a multikinase inhibitor that blocks the VEGF receptor 2, and reduced MDSCs will result in increased number of T cells, enhance the activity of the anti-PD-1 checkpoint blocker nivolumab in mTNBC. Methods: This is a phase II, single arm, single-center study assessing the efficacy of nivolumab (480 mg intravenously on day 1, every 28 days) plus cabozantinib (40 mg daily by mouth) in patients with mTNBC (NCT03316586). Eligibility Criteria include patients with mTNBC, or estrogen and progesterone receptor-driven breast cancer, with measurable disease, and who have received 0-3 prior lines of chemotherapy in the advanced setting. The primary aim is to evaluate the efficiency of the combination, as defined by ORR according to RECIST 1.1. Secondary objectives include to determine the ORR according to immune-related criteria, the progression-free survival, the clinical benefit rate, the safety and tolerability of the combination. Tumor biopsies and peripheral blood will be obtained at baseline, on treatment and at disease progression for immunoprofiling and to examine biomarkers of treatment response. Using the Simons “optimal” method, in the first stage, 18 patients will be enrolled. If there are less than 3 responses, accrual will continue to the second stage where up to 17 additional patients will be enrolled. If at least 7 of these 35 patients have an objective response the regimen will be considered worthy of further study. With this design, if the true response rate is 10%, the chance the regimen is declared worthy of further study is less than 5% (exact alpha = 0.047). If the true response rate is 30%, the chance that the regimen is declared worthy of further study is 90%. The trial opened in December 2017 and has accrued 5 patients with a target accrual of 35 patients. Accrual should be completed in 12 months. Clinical trial information: 03316586.
Cancer Prevention, Hereditary Genetics, and Epidemiology

1500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Low-fat dietary pattern and all cancer mortality in the Women's Health Initiative (WHI) randomized trial. First Author: Rowan T. Chlebowski, City of Hope National Medical Center, Duarte, CA

Background: In the Women's Health Initiative randomized (WHI) Dietary Modification (DM) primary prevention trial, after 16.1 years median follow-up, implementation of a low-fat dietary pattern significantly reduced deaths after breast cancer. Mortality from other cancer sites has not been reported.

Methods: To determine low-fat dietary pattern influence on deaths from and after breast cancer and other cancers during 8.5 years (median) dietary intervention and now with 17.1 years (median) cumulative follow-up, 48,835 postmenopausal women with no prior cancer, aged 50-79, were randomized to 40 US clinical centers from 1993-1998 to dietary intervention (DM-I) (40%, n = 19,541) to reduce fat intake to 20% of energy and increase fruits, vegetables and grains intake, or usual diet comparison (DM-C) (60%, n = 29,294). DM-I influence on breast, colorectal, endometrium and ovarian cancers alone and as a composite were prospectively determined primary analyses. Results: During dietary intervention, deaths after breast cancer was the only statistically significant cancer mortality finding. During cumulative follow-up with 3,867 deaths after all cancers, significant reduction in deaths after breast cancer occurred in the DM-I group (HR 0.85 95% CI 0.74-0.99, P = 0.03) especially in subgroup with waist circumference > 88 cm (HR 0.78 95% CI 0.64-0.95). Deaths after pancreatic cancer were somewhat lower in the DM-I group (HR 0.89 95% CI 0.70-1.13, not significant). In addition, in no other cancer or cancer composite group was a dietary intervention effect on death (HR 1.06 - 1.13). To identify any potential effect of DM-I on breast cancer seen (Table). Conclusions: Adoption of a low-fat dietary pattern led to a lower incidence of deaths after breast cancer. No reduction in mortality from other cancer sites was seen. Clinical trial information: NCT00000611.

Deaths from cause after cancer DM-I DM-C HR (95% CI) P-value
Primary analysis
Deaths after breast cancer 2800 (0.98) 5705 (1.12) 0.85 (0.74-0.99) 0.03
Deaths after colorectal cancer 164 (0.057) 228 (0.052) 1.10 (0.90,1.35) 0.34
Deaths after ovarian cancer 92 (0.032) 143 (0.033) 0.98 (0.75,1.27) 0.87
Deaths after endometrial cancer 69 (0.024) 98 (0.039) 1.07 (0.79,1.46) 0.66

1502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Cardiopulmonary fitness and incident lung and colon cancer: FIT-Cancer Cohort. First Author: Catherine Handy, Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: Cardiorespiratory fitness (CRF), an objective measure of exercise tolerance, is a strong predictor of cardiovascular disease and mortality yet its relationship with cancer incidence is unclear. The goal of this analysis was to assess the relationship between CRF and lung and colon cancer in a large, multi-ethnic clinical cohort. Methods: From The FIT Project, a retrospective cohort of 69,885 consecutive patients who underwent physician-referred treadmill testing using the Bruce protocol in the Henry Ford Health System (HFHS) between 1991 and 2009, we created the FIT-Cancer Cohort by linkage with the HFHS Tumor Registry. We included patients aged 40-70 years who were cancer free at baseline. Multivariable adjusted Cox proportional hazard models were used to evaluate the association between CRF (measured in peak metabolic equivalents (METs)) and incident lung and colon cancer. Results: 49,143 individuals (46% women, 64% White), with a mean age of 54 years, were included. During a median follow up of 8.3 years (IQR 7.1 years), there were 388 and 238 incident lung and colon cancers. Compared to those with the lowest level of CRF, individuals in the highest CRF category had a 77% (CI: 63-85%) decreased risk of developing lung cancer and a 60% (CI: 33-75%) decreased risk of colon cancer in multivariable adjusted models. There was a significant, inverse METS-incident cancer dose response relationship (Table 1, p trend for lung and colon < 0.01). Subgroup analyses in smokers, by sex and race showed similar results. Conclusions: In the largest study of its kind, CRF measured during exercise testing is a strong predictor of future lung and colon cancer risk. Our study provides another important reason for optimizing CRF.

Adjusted risk of incident lung and colon cancer, per category of CRF.

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*Adjusted for age, race, sex
**Adjusted for age, race, sex, smoking, BMI

1503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Inherited mutations in breast cancer patients with and without multiple primary cancers. First Author: Kochielle Maxwell, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background: Women with breast cancer have a 5-12% lifetime risk of a second primary cancer. Whether mutations in genes other than BRCA1/2 are enriched in patients with breast and another primary cancer (MP-BC) over those with a single breast cancer (S-BC) is unknown. Methods: We identified pathogenic germline mutations in cancer susceptibility genes in BRCA1/2 negative patients in two differently ascertained cohorts: Cohort #1, high risk breast cancer program (MP-BC, n = 551 vs S-BC, n = 464) and Cohort #2, familial breast cancer research study (MP-BC, n = 340 vs S-BC, n = 1464). Mutation rates in patients of European descent were compared to ExAC. Results: Overall pathogenic mutation rates for cancer panel testing genes were two-fold higher in patients with MP-BC versus S-BC in both cohorts (8.7% vs 4.1%, p = 0.003 and 8.2% vs 4.2%, p = 0.003, respectively). However, there were differences in individual gene mutation rates between cohorts (Table). In comparison to a race and ethnicity matched control group, mutations in TP53 and MSH6 were statistically significantly enriched in MP-BC but not S-BC patients. Mutations in ATM, CHEK2 and PALB2 were statistically significantly enriched in both MP-BC and S-BC patients relative to controls. Conclusions: These data demonstrate that mutations in high risk genes are typically found in patients with multiple primaries; whereas rates of moderate penetrance gene mutations are similar. Patients with multiple primary cancers should be offered multiplex panel testing.

Conclusions: In the largest study of its kind, CRF measured during exercise testing is a strong predictor of future lung and colon cancer risk. Our study provides another important reason for optimizing CRF.
1118 pts consented to tumor-normal sequencing and 42 to return of germline findings; the median age of the two groups was 68 and 59, respectively (p < 0.05). For the 42 pts receiving germline findings, 24% had early onset and 52% multiple cancer diagnosis, and 31% had P/LP mutations in 10 genes (3 BRCA2, 2 MENI, 1 APC, 1 ATM, 1 BAP1, 1 BLM, 1 CHEK2, 1 FH, 1 FLCN, 1 RAD51D). Among 1118 pts, 8% had P/LP mutations in 16 genes (20 APC, 15 CHEK2, 13 MUTHY, 7 BRCA2, 6 BRCA1, 5 FH, 4 ATM, 4 FANCA, 4 RECQL4, 3 FANCA, 3 TP53, 2 RAD50, 2 RAD51, 1 BRIP1, 1 XPC, 1 RAD51), 45% of the P/LP mutations of CHEK2, APC, MUTHY, BRCA1 were population “founder” mutations. There was no statistically significant increase in burden of these pathogenic variants in the lung cancer cases studied. The 31% prevalence of germline variants in pts enriched for family history of cancer was greater than the 8% prevalence in patients unselected for family history (p < 0.0002).

Conclusions: Our preliminary findings demonstrate an increased prevalence of clinically actionable germline mutations in patients with lung cancer with either a family history of other cancers, early age at onset, or multiple cancer diagnosis, compared to unselected lung cancer patients.

1506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
A breast cancer risk model as a predictor of interval cancer rate and tumor characteristics. First Author: Nicholas Dreher, University of California, San Francisco, San Francisco, CA

Background: The Breast Cancer Surveillance Consortium (BCSC) Risk Calculator is a validated and widely used risk model that predicts five- and ten-year risk of developing invasive breast cancer for women age 40-75. However, little research has been conducted to determine if women with high BCSC risk are also more likely to develop any particular type of cancer. These women may be at elevated risk to develop interval cancers, those that present symptomatically following a normal screening mammogram and are often faster-growing. If this were the case, women with high BCSC risk (defined here as the top 2.5% by age) may merit increased screening frequency.

Methods: We calculated BCSC 5-year risk scores for female breast cancer patients who completed an online intake survey distributed by the Athena Breast Health Network before being seen at the UCSF Breast Care Center, and whose BI-RADS density category was available. We reviewed charts of patients who were in the top 2.5% of risk for their age according to national averages estimated by the BCSC, and we compared them to an equal number of female breast cancer patients from the lower 97.5%. We then compared the proportion of interval, ER-negative, node-positive, and high-grade cancers between each group using a Chi-squared test (two-sided alpha = .05).

Results: Of 5253 female breast cancer patients who completed an intake survey, 1880 had BI-RADS data available. 131 of these patients fell in the top 2.5% of breast cancer risk for their age. Compared to 131 breast cancer patients from the lower 97.5% of risk, more high-risk patients developed an interval cancer within one year of a normal screening mammogram, with preliminary rates of 24.1% vs 4.1% respectively (p = 0.003). There was no significant difference between the rates of ER-negative, node-positive, or high-grade cancers between the two groups.

Conclusions: Breast cancer patients in the top 2.5% of breast cancer risk according to the BCSC model are more likely to develop interval cancers, which may warrant tailored screening strategies.
Polygenic risk score for breast cancer in high-risk women. First Author: Mary Helen Black, Ambry Genetics, Aliso Viejo, CA

Background: While assessment of genetic contribution to breast cancer (BC) risk was once limited to high-penetrance genes such as BRCA1/2, additional genes conferring two- to five-fold increased risks of BC, as well common SNPs with relative risks ranging 1.03-1.57, have recently been identified. Although several reports suggest that a score based on combined genotypes across a large number of SNPs may have substantial predictive value for risk stratification in the general population, few studies have examined the performance of such a score in high-risk women.

Methods: We genotyped 102 BC-associated SNPs using next-generation sequencing in order to examine whether a risk score based on these SNPs was predictive of BC in 2,910 women (1,758 cases with no other cancer primaries and 1,152 controls unaffected with any cancer) referred for genetic testing at a single diagnostic laboratory. All women were self-reported Caucasian, 18-85 years of age and provided family history information at the time of testing, and tested negative for pathogenic variants in BC-related genes (mean ± SD age at testing 52 ± 13 years). We constructed a polygenic risk score (PRS), with each SNP weighted by per-allele relative risks in Caucasians from large genome-wide association studies and population-specific allele frequencies, and tested PRS association with BC using logistic regression. Results: The PRS was significantly higher in cases than controls (mean ± SD 1.41 ± 0.86 vs. 1.06 ± 0.66, p < 0.0001). Compared to women in the 1st quartile of PRS, those in the 2nd, 3rd and 4th quartile were 1.65 (95% CI: 1.34-2.05), 2.12 (95% CI: 1.71-2.64) and 2.75 (95% CI: 2.20-3.44) times as likely to have BC (all p < 0.0001). PRS predictive performance was consistent with prior literature (AUROC = 0.61). Conclusions: These data suggest that a 102-SNP PRS assessed in high-risk patients performs similarly to risk scores reported in the broader population, and has direct implications for their clinical management. Our ongoing analysis of the ability of the PRS to discriminate among specific pathologic subtypes, as well as validity and utility of a PRS combined with clinical models to estimate residual lifetime risk, has the potential to further inform screening guidelines and improve patient care.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Implementing universal genetic counseling (GC) and multigene germline testing (MGT) for pancreatic cancer (PC) patients (pts). First Author: Matthew B. Yurgelun, Dana-Farber Cancer Institute, Boston, MA

Background: MGT will identify cancer susceptibility gene variants in 4-10% of unselected PC pts. Such data have prompted calls for universal GC and MGT of all PC pts, but the real-world benefits and barriers to implementing such systematic testing are unknown. This study’s aim was to study the implementation of universal hereditary cancer risk assessment for PC pts seen in an academic oncology practice. Methods: All gastrointestinal medical oncologists at the Dana-Farber Cancer Institute (DFCI) were recommended to refer all PC pts for GC and MGT beginning 12/2016. A special referral sheet was placed in new PC pt charts to remind providers and streamline GC-referral workflows. Clinical and germline data were collected on a consecutive cohort of PC pts undergoing GC and MGT from 3/1/2017-12/31/2018. Results: Over the 11-month study period, 443 (43.9/month) PC pts were seen for medical oncology new patient visits at DFCI, 114 (10.4/month) were referred for GC, and 92 (8.4/month) eligible PC pts underwent GC and consented to MGT and study enrollment. Among the 92 participants, median time from first DFCI appointment to GC was 44 days (IQR 23-142 days), 33 (35.9%) underwent MGT within 30 days of their first DFCI appointment, and 4 (4.3%) died within 30 days of receiving MGT results. 8/92 (8.7%; 95% CI 2.9-14.5%) were found to carry germline mutations (2 BRCA1, 2 BRCA2, 2 PALB2, 1 CHEK2, 1 MSH2). There were no significant differences in patient age, sex, race, personal cancer history, family history of PC, or family history of other cancers between mutation carriers and non-carriers. 4/8 (50%) carriers received targeted therapy (eg, PARP inhibitors) based on MGT results (2 remain on 1st line monotherapy, 1 on 2nd line monotherapy, and 1 on targeted therapy) and 5/8 (63%) have family members who are actively pursuing cascade testing for the identified mutation. Conclusions: Clinical implementation of universal GC/MGT in PC pts is potentially feasible and results in the detection of mutations that are actionable for PC pts and their at-risk family members. In spite of streamlined workflows, lack of oncologist referral is a critical barrier to the real-world efficacy of universal GC/MGT in PC.

Clinical trial information: NCT03060720.

Identification and referral of women at risk for BRCA1 mutations. First Author: Cecelia Bellocross, Emory University, Atlanta, GA

Background: It is estimated that less than 10% of BRCA1/2 mutation carriers have been identified, despite well-documented evidence of reduced cancer morbidity and mortality with targeted screening and prevention. The United States Preventive Services Task Force endorsed the Breast Cancer Genetics Referral Screening Tool (B-RST) as one of several validated screening tools to assist clinicians in identifying women appropriate for cancer genetics referral. The purpose of this study was to implement B-RST in mammography clinics to determine the most effective means of follow-up for screen positive women. Methods: Women undergoing routine screening mammography at one of four Emory clinics were approached to complete the B-RST. Participants were given written information about their results and appropriate resources. Those who screened positive, indicating increased risk for a BRCA1/2 mutation, were randomized to one of three follow-up groups: self-referral (Group 1), electronic health record (EHR) messaging (Group 2), or direct contact (Group 3). We compared genetic counseling (GC) appointment scheduling and completion rates by group. Those who did not schedule an appointment were invited to participate in an online survey. Results: Of 2,422 participants, 610 (25.2%) screened positive. Demographic factors did not differ between the three groups. GC appointments were scheduled by 9.2% of Group 1 participants, 19.7% of individuals in Group 2, and 12.5% of Group 3 participants (p = 0.001). Challenges to scheduling included lack of physician response to EHR messages and unsuccessful direct contact. Among those scheduled (n = 76) 69.7% completed the appointment, with no difference in completion rate between the three groups. The most common barriers to scheduling reported by survey respondents (n = 97) were lack of physician recommendation (71%), health insurance concerns (67%) and indecision about GC (66%). However, 52% reported interest in future GC contact. Conclusions: B-RST can be used effectively in mammography settings to identify high-risk women at increased risk for breast cancer. With improvements to scheduling, additional strategies are needed to facilitate completion of the GC process in routine clinical practice. Clinical trial information: NCT02786147.

Cancer Prevention, Hereditary Diseases, and Epidemiology

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DNA damage repair (DDR) germline mutations in patients (Pts) with urothelial carcinoma (UC). First Author: Maria Isabel Carlo, Memorial Sloan Kettering Cancer Center, New York, NY

Background: We previously reported on germline mutations in cancer predisposition genes in 113 pts with UC, with a 19% rate of pathogenic or likely pathogenic (P-LP) variants in DDR genes. Here we report on an expanded cohort of 176 pts and on a separate cohort of 327 anonymized patients identified through clinical annotation.

Methods: Pts with UCNs were prospectively enrolled to a matched tumor-germline DNA sequencing protocol from 3/2013 to 9/2017; starting in 2014, patients could opt in to receive germline results. Germline analysis was done with an institutional, CLIA-certified next generation sequencing (NGS) platform (IMPACT) and analyzed for germline mutations. This analysis includes pts seen in medical oncology clinicians who consented to receive germline results (Cohort 1), and additional pts seen in urology and medical oncology clinicians who had anonymized germline testing (Cohort 2) with an extended DDR panel.

Results: Cohort 1 consisted of 176 pts, 90% with muscle invasive or metastatic disease, median age 63 (31-87), 76% male. Primary sites were bladder (B) (70%), upper tract (UT) (28%), or unknown (2%). 8% had early onset (<45 yrs at diagnosis), 9% had a family history of UC, 19% had documented non-UC cancers. 30 P-LP DDR gene mutations were identified in 28 patients. The most frequent mutations are shown in the Table. P-LP mutations were present in 29% of pts with UT and 13% of pts with B primaries. Of pts with DDR germline mutations, 29% did not have additional somatic DDR mutations. Cohort 2 consisted of 327 anonymized pts. 32 P-LP DDR germline mutations, including in ERCC3, were identified in 30 pts. Including both cohorts, 77% of mutations were of high or moderate penetrance.

Conclusions: Germline predisposition genes are common in UC pts and may be greater in higher stage disease, further investigation into mutation frequency by stage is warranted. Most mutations are highly penetrant and have potential implications for both pts and family members. Clinical trial information: NCT01775072.

Table

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<th>Gene</th>
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<th>Total n = 176</th>
<th>Mutation Carriage (%)</th>
<th>Total n = 327</th>
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*Not analyzed

1516 Poster Discussion Session; Displayed in Poster Session (Board #87), Sat, 1:15 PM-4:45 PM, Discuss in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Clinical factors associated with urinary tract cancers (UTCs) among Lynch syndrome (LS) patients (Pts). First Author: Jonathan W. Wischhusen, Beth Israel Deaconess Medical Center, Boston, MA

Background: LS is one of the most common inherited causes of cancer and predisposes to a wide variety of cancers. UTCs (kidney, renal pelvis, ureter, and bladder cancer) are collectively the second- and fourth-most common LS-associated cancers in male and female LS pts, respectively. This study's aim was to identify clinical factors associated with UTC among LS pts.

Methods: The study population was a cohort of 52758 consecutively ascertained patients undergoing germline LS testing from 6/2006-7/2013 at a commercial laboratory. Clinical data, including age at genetic testing, personal history (PHx) of cancer, and family history of cancer in first- and second-degree relatives (FDRs and SDRs, respectively) were obtained from test request forms completed by the ordering provider. Multivariable logistic regression was performed to identify clinical factors associated with PHx of UTC among LS carriers. Results: Data from 51086 pts was analyzed after excluding 1072 pts without clinical data (N = 1664) or > 1 LS mutation (N = 8). Of these, 38282 carried pathogenic LS mutations (1346 MLH1, 1639 MSH2, 670 MSH6, 145 PMS2, and 28 EPCAM, 158/3822 (4.1%; 95% CI 3.5-4.8%) LS pts had a PHx of UT (49 kidney; 62 ureter/pelvis; 67 bladder; 21 multiple UTCs) and 369 (9.6%; 95% CI 8.7-10.6%) had any family history of UT. Compared to non-carriers, LS pts were significantly more likely to have a PHx of any UT (OR 1.24; 95% CI 1.19-1.29; P < 0.0001), bladder cancer (1.8% vs 0.4%; P = 0.0004), and any family history of UT (9.6% vs 6.5%; P = 0.0001). By multivariable logistic regression, PHx of UT among LS pts was significantly associated with male sex (OR 2.04; 95% CI 1.73-2.41; age at genetic testing (OR 1.97; 95% CI 1.67-2.34), MSH2 mutation carriage (OR 4.03; 95% CI 3.29-4.94; ref: non-MSH2 LS mutations), and family history of UT (OR 2.07 for each FDR/SDR with UT; 95% CI 1.80-2.40). Conclusions: Increasing number of FDR/SDR with UT, male sex, age, and MSH2 mutations are each independently associated with PHx of UT among LS pts. LS pts with these clinical features should be considered for UTC screening/prevention strategies.

1519 Poster Discussion Session; Displayed in Poster Session (Board #90), Sat, 1:15 PM-4:45 PM, Discuss in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Nutrition assessment among men undergoing genetic counseling for inherited prostate cancer: A teachable moment. First Author: Veda N. Giri, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Genetic counseling (GC) for men with or at-risk for prostate cancer (PCA) is growing with advancements in genetic testing (GT). GC provides a unique opportunity to promote a healthy lifestyle and is underutilized in these men. We conducted a retrospective diet assessment of men or at-risk for PCA who have undergone GC and GT in the Genetic Evaluation of Men (GEM) study at two academic centers. Methods: GEM participants completed a structured lifestyle questionnaire (QA) which included dietary behaviors. QA included frequency of consuming six different types of foods (rich in vitamins C, A and D, cruciferous vegetables, rich in lycopene, smoked meats, seafood, chicken, legumes/other protein sources, vegetables, fruit, grains, milk products, foods high in saturated fat) and alcohol. Diet intake was compared to USDA’s dietary recommendations for cancer survivorship. Distributions of dietary consumption were assessed by PCA status, PCA aggressiveness (Gleason > 7, T3, or metastatic disease), family history (FH), and body mass index (BMI) with Chi-Square contingency analyses and adjusted residuals (adj resid). Alpha levels were set a priori at <.05. Results: Self-reported dietary data among men with PCA (n = 239) and at-risk for PCA (n = 81) who underwent GC was included. Overall, 84% were overweight/obese per CDC guidelines. Consumption of Vitamin C (2-3 times per week was significantly lower among men with aggressive PCA (adj resid = -1.9) vs. less aggressive PCA (adj resid = 1.9). Men with aggressive PCA also reported eating more red meat vs less aggressive PCA (p = 0.01). A higher percentage of men with aggressive PCA and higher weight did not meet the recommended guideline for vegetables (p = 0.047) and red meat (p = 0.015) than expected per contingency analyses. Conclusions: In this sample, specific dietary patterns were associated with aggressive PCA. A high proportion of men receiving GC for inherited PCA were overweight and/or obese, affording a teachable moment for lifestyle intervention. Key focus areas to develop diet intervention include consumption of less red meat and more vegetables among men at-risk or in survivorship.
Risk of second primary HPV-associated cancers after index HPV-associated cancers. First Author: Ryan Suk, University of Florida, Gainesville, FL

Background: For the HPV-associated index cancer survivors, persistent HPV infection may remain a risk factor for preventable HPV-associated secondary primary cancer (HPV-SPC). However, the risk of HPV-SPCs among HPV-associated index cancer patients has not been well documented. Methods: Longitudinal data from 9 cancer registries and the Surveillance, Epidemiology, and End Results (SEER) database were used to identify cases of HPV-associated cancers diagnosed from 1973 to 2014. The HPV-SPC risk was quantified using standard incidence ratios (SIRs) and excess absolute risk (EAR) per 10,000 person-years at risk (PYR). Results: The SIR for second primary HPV-related cancers after index HPV-related cancers among women and men were 3.3 (95% CI 3.2 to 3.4) and 15.8 (95% CI, 15.0 to 16.7), respectively. When the same site second primary cancers were excluded, the risk remained significant both among women (SIR = 2.7) and men (SIR = 2.3). The risk of HPV-SPC was highest for oropharyngeal cancer both among women (SIR = 20.6; EAR = 83.8) and men (SIR = 18.8; EAR = 64.3), and lowest for cervical (SIR = 2.0; EAR = 2.4) and penile (SIR = 7.0; EAR = 20.7) cancer. Conclusions: The risk of developing HPV-SPCs for HPV-related cancer survivors is significant, implying that HPV might be a cause of developing HPV-SPC. Our findings have the potential to inform surveillance recommendations among HPV-related cancer survivors.

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Expanding BRCA1/2 testing criteria to include other confirmed breast and ovarian cancer susceptibility genes. First Author: Fergus Couch, Mayo Clinic, Department of Laboratory Medicine and Pathology, Minn.

Background: The National Comprehensive Cancer Network (NCCN) has expanded its breast and ovarian cancer (BC and OC) genetic testing and management recommendations to address the broader spectrum of cancer predisposition genes. However, management recommendations are pending for some candidate BC genes (e.g. BARD1, RAD51D) and OC genes (e.g. ATM, NBN) due to insufficient evidence of increased cancer risk, and indications for multi-gene panel testing (MGPT) remain vague overall. We aimed to further characterize BC and OC risks for 21 candidate susceptibility genes and explore the potential utility of BRCA1/2 testing criteria as an indication for MGPT. Methods: Gene-specific pathogenic variant (PV) frequencies among Caucasian BC and OC patients (unadjusted for other personal/family cancer history) ascertained from a cohort of ~175,000 patients referred for MGPT were compared to non-Finnish European control variants from the genome aggregate database (gnomAD). Clinical histories of BC and OC patients were also reviewed to assess whether NCCN BRCA1/2 testing criteria were met (version 2.2017). Results: We confirmed the inclusion of 15 genes with increased risk (e.g. > 2.0-fold) of BC (ATM, BARD1, BRCA1/2, CDH1, CDKN2A, CHEK2 (excluding p.1157T), MLH1, MSH2, MSH6, NF1, PALB2, PTEN, RAD51D, TP53). The pooled frequency of PVS in these genes was 9.2% among BC patients of all ethnicities (3.5% in BRCA1/2 and 5.7% in other genes) and 8.6% among BC patients meeting BRCA1/2 testing criteria. For OC, 5.0% in BRCA1/2 and 0.8% in other genes were associated with risk of OC (> 2.0-fold, ATM, BRCA1/2, BRIP1, MSH2, MSH6, NBN, PMS2, RAD51C, RAD51D, TP53). PVS in these genes were detected among 13.0% of OC patients of all ethnicities (8.0% for BRCA1/2 and 5.0% for other genes combined). Therefore, inclusion of additional risk genes increases detection rate for BC and OC patients meeting BRCA1/2 testing criteria by 152.9% and 62.5%, respectively. Conclusions: These results further characterize gene-specific BC and OC risks, which can be used to refine management recommendations for at-risk patients. Current testing criteria fail to capture a substantial proportion of women with increased risk of BC and OC.

Evaluation of whole body MRI for early detection of cancer in TP53 mutation carriers: Final results of the LIFSSCREEN study. First Author: Olivier Caron, Gustave Roussy Cancer Campus, Villejuif, France

Background: Li Fraumeni syndrome (LFS) is a rare cancer predisposition caused by TP53 germline mutation associated with a broad tumor spectrum making surveillance very complex. Whole body MRI (WBMR) is an attractive strategy. The LIFSSCREEN nation-wide trial was designed to evaluate the impact of adding WBMRI as a screening tool on the overall survival (OS) of LFS patients. Method: A total of 96 pts were randomized in one of the 19 French centers. In 318 screening rounds, 24 pts presented 31 new primary cancers (NPC): 20 in A arm and 11 in B arm. 12 NPC were diagnosed at the first round. Cancer-free survival (NPC and relapses) was similar at 3 years in both arm (p = 0.23). 27 Biopsies were carried out in A arm and 20 in B arm. 157 WBMRIs were performed, with a sensitivity and specificity of 0.8 and 0.89, respectively (10% false positive). Their review showed a 31% diskgradation rate (44/141). The 3-years OS was 90% (91–95), with no difference between the 2 arms (p = 0.58). The 3-years OS with NPC was 54.8% (32-75). 10 pts voluntarily left the study. Psychological impact was similar in both arms, with low screening-related distress. Conclusions: This first randomized study performed on one of the largest TP53 carrier series did not show WBMRIs efficiency on OS. Nevertheless, it displayed correct sensitivity and specificity, with few biopsy generation. Long-term follow-up was acceptable and feasible in each participating center. Despite its tricky interpretation, WBMRI was the only modality to detect lung cancer, whose incidence was surprisingly high. TP53 mutation carrier surveillance might be completed with WBMRIs in a multimodality setting. The very low long-term mortality in pts with new cancer makes prevention and treatments improvement mandatory.

Clinical trial information: NCT01464086.


Background: Lynch syndrome is a cancer predisposition caused by inherited mutations in mismatch repair genes MLH1, MSH2, MSH6 and PMS2, or EPCAM. Accurate cancer risk estimates are required for mutation carriers and their family members to develop appropriate genetic counselling guidelines and targeted screening and clinical management. Cancer risks for Lynch syndrome may differ not only by age, sex and the gene mutated but also by the genetic variant and geographic region of the carrier. Methods: We analysed pedigree data (age, sex, cancer histories and mutation status of family members) of Lynch syndrome families that were submitted by researchers and clinicians from 23 countries to the International Mismatch Repair Consortium (IMRC) (http://www.sphinx.org.au/imrc). For each cancer, we estimated age-specific cumulative risk (penetrance) and hazard ratios for carriers compared with the general population. We estimated penetrance by: cancer site, sex, the gene mutated, type of mutation, and geographic region. Results: IMRC has already received pedigree data from 6651 families with a mismatch repair gene mutation (2214 MLH1, 1118 MSH6, 958 PMS2, 44 EPCAM) throughout the world (2482 in North America, 101 in South America, 3307 in Europe, 431 in Asia, 330 in Australasia). Preliminary analyses suggest that the risk of colorectal cancer to age 70 is highest for both male and female carriers in Australasia and North America and lowest for carriers in South America and Australia. Preliminary results of the largest study on Lynch syndrome penetrance suggest that cancer risks for people with Lynch syndrome differ by geographic region, which is consistent with existence of environmental modifiers for the disease and might justify region-specific screening guidelines.

Differences between screen-detected and interval breast cancers among BRCA mutation carriers. First Author: Melissa Louise Pilewskie, Memorial Sloan Kettering Cancer Center, New York, NY

Background: BRCA mutation carriers have an elevated lifetime and interval breast cancer risk. We sought to compare BRCA mutation carriers with screen-detected versus clinically detected, interval breast cancers. Methods: Women with a known BRCA mutation prior to a breast cancer diagnosis were identified. Clinical and pathologic factors, and imaging within 18 months of diagnosis were compared among women with clinically detected and screen-detected breast cancers. Results: Of 115 breast cancers, 93 were screen and 22 clinically detected, of which 11 were interval cancers among regular screeners. Women with clinically detected/interval cancers were younger, had lower BMIs, and were more likely to be Black than those with screen-detected cancers (p < 0.05). Clinically detected/interval cancers were all invasive, were larger, more likely to be node positive and to have lymphovascular invasion, and were more likely to require axillary lymph node dissection and chemotherapy (p < 0.05). No significant differences were seen by BRCA mutation, mammographic density, MRI background parenchymal enhancement, tumor grade, or receptor status between cohorts. Women screened with both mammogram and MRI had significantly lower rates of clinically detected/interval cancer rates compared to women screened with only mammogram or MRI alone (p < 0.05). Conclusions: Clinically detected/interval breast cancers among BRCA mutation carriers have worse clinicopathologic features than screen-detected tumors, and require more aggressive medical and surgical therapy. Imaging with mammogram and MRI is associated with lower interval cancer detection and should be utilized among this high-risk population.

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1530 Poster Session (Board #101), Sat, 1:15 PM-4:45 PM

Effect of breastfeeding on the risk of breast cancer in Li-Fraumeni syndrome.

First Author: Payal Khincha, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Li-Fraumeni syndrome (LFS) is an autosomal dominant inherited cancer predisposition syndrome associated with germline pathogenic variants in TP53. It is characterized by early-onset cancer and a high lifetime risk for multiple cancers. Although women with LFS are at very high risk of pre-menopausal breast cancer some women will perhaps never develop the disease. This may be due to non-genetic factors that may modify the risk. Methods: The aim of this retrospective cohort study was to evaluate the impact of female reproductive factors such as age at menarche, parity, breastfeeding (BF) and use of oral hormonal contraceptives (OCP) on the risk of breast cancer (BC) in LFS patients. Results: We enrolled 154 TP53 mutation-positive women from the NCi’s LFS protocol, 86 of whom had at least one breast cancer. Median age at first breast cancer diagnosis was 32 years (range 20-54 years), 32 women had a second BC. Sixty percent of first breast cancers were ER/PR+, and 57% were HER2/neu+. Our data showed that breastfeeding (BF) reduced the risk of breast cancer in LFS, most notably in patients with over 6 months of BF (Odds Ratio (OR) 0.36, p = 0.04, OR at 12 months of BF 0.32, p = 0.02). The association was strongest in ER+ BC versus BC-free women, but was not significant when comparing odds of developing ER+ to ER- BC. Controlling for age and parity, women with BF > 12 months had a lower risk of BC versus BF < 12 months (p = 0.02). Neither parity nor OCP independently altered BC risk significantly, a finding limited by limited sample size of the comparator group of OCP-non-user LFS women. Conclusions: Our data show that while BF for any duration reduces risk of BC, the risk is significantly reduced with BF for at least 6 months, a protective effect similar to previous studies of BF and BC risk in the general population and BRCA1 cohorts. Neither parity nor OCP independently altered BC risk significantly. This is the first study to evaluate BC reproductive risk modifiers in LFS patients. Larger, prospective case-control studies are needed to validate these findings. If confirmed, women with LFS would warrant education regarding BF’s protective effect to inform management decisions.

1532 Poster Session (Board #103), Sat, 1:15 PM-4:45 PM

Development of HOPE-Genomics: An IT platform for patient-directed cancer genomic sequencing education and return of results. First Author: Ilana Solomon, City of Hope, Duarte, CA

Background: Profiling of somatic/germline tissue has the potential to improve outcomes for patients with cancer. However, the realization of precision medicine is hindered by patients’ inability to understand and their own tumor/germline results. Innovations to improve patient education and care engagement are urgently needed. Methods: We recruited patients at a comprehensive cancer center to help develop a web-based, patient-directed cancer genomic sequencing education and reporting tool: HOPE-Genomics. We obtained clinical data through patient surveys and chart reviews. We obtained feedback on the tool from patients, family members, and clinicians via focus groups. Results: 40 patients (mean age 40, 92% White, 8% Asian, 15% Hispanic, 15% high school) completed the survey; 93% had advanced disease and 30% had lung, 25% breast, 10% ovarian, 18% colon, and 17% other cancers. Although 98% had tumor and/or germline profiling on chart review, 33% of patients were unaware this test occurred. All breast and gastric cancer patients knew they had HER2 testing whereas only 20% of CRC patients knew they had KRAS testing. The majority of participants wanted to see, or their patients to see, “patient-friendly” reports. When presented with HOPE-Genomics, themes identified in patient/family focus groups included the opinion that the tool could help patients prepare questions, a desire for all types of information (e.g., prognostic, uncertain), and favorable attitudes about including genetic counseling information. Themes identified in clinician focus groups included the opinion that the tool could help patients share information with family and decrease patient confusion. Clinicians had mixed feelings about tool implementation (e.g., provider control vs. time-dependent release of report, concern over disclosure of some types of information). Conclusions: Many patients do not recall having molecular/genomic testing but are interested in learning their results. Early development of a web-based education and reporting tool appears to be acceptable to patients, family members and clinicians. We plan to refine the tool and develop processes for optimal clinical integration.

1531 Poster Session (Board #102), Sat, 1:15 PM-4:45 PM

Interest in and outcomes with web-based education for return of genetic research results for inherited susceptibility to breast cancer. First Author: Augusta R. Bradbury, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background: How frequently research participants are interested in receiving genetic individual research results (IRR) and the best method for returning IRR remains unknown. Methods: Women at three centers with a personal or family history of cancer, who provided a bio-sample for research, were offered the opportunity to receive IRR for 25 cancer susceptibility genes. Participants could complete pre-disclosure education by a self-directed web-education (WebEd) or by telephone with a genetic counselor (GC). All participants received IRR by phone with a GC. Participants completed surveys at baseline, after pre-disclosure education and disclosure. We used t-tests and multiple linear regressions of change scores. Results: 1277 participants were contacted. Mean age was 61.4 years, 68% were white, 68% had a history of cancer and 56% had a college education. 393 (31%) enrolled to receive IRR, 120 (9%) actively declined, and 764 (60%) have not responded to multiple contacts. Age, education and race/ethnicity were not significantly associated with interest in IRR. To date, 211 (81%) completed pre-disclosure education before IRR. Among participants who received IRR, there was high interest in a web-based pre-disclosure education. Web-education was not associated with negative outcomes after receipt of IRR with a genetic counselor, suggesting a potential alternative resource reducing model for return of IRR.

1533 Poster Session (Board #104), Sat, 1:15 PM-4:45 PM

Genomic profiling of tumors from patients with germline BRCA mutations. First Author: Anne-Vibeke Laenkholm, Department of Surgical Pathology, Zealand University Hospital, Slagelse, Denmark

Background: Gene expression profiling assays are not commonly used for therapy selection for breast cancer patients with germline BRCA mutations but a complete molecular characterization could lead to identification of novel subgroups where therapy modification may be considered. We hypothesized that the PAM50 intrinsic subtypes and ROR score in combination with characterization of the immune response could provide biological insights to guide the next generation of treatment strategies for BRCA-mutated tumors. Methods: The Danish Breast Cancer Group database was used to identify a cohort of 584 BRCA-mutated breast cancer patients diagnosed between 1977 and 2011. Tumor RNA from archived FFPE tissue samples was analyzed on the NanoString platform using a 770-genome Breast Cancer Panel and the PAM50 intrinsic subtypes were determined using the Prosigna gene signature algorithm. The immune response was evaluated with the Tumor Inflammation Signature (TIS) score. Results: Of the 532 samples assessable for PAM50 subtype, 54% were Basal-like, 7% Her2-Enriched, 23% Luminal B, and 16% Luminal A, with significant heterogeneity between BRCA1 and BRCA2 tumors. BRCA1 tumors were primarily Basal-like while BRCA2 tumors were enriched for Luminal subtypes. There was a wide range of Prosigna ROR scores with 15% of the Luminal tumors identified as low-risk (ROR<40). Similarly, there was a broad spectrum of immune response with BRCA1 tumors demonstrating a higher average TIS5 score (P < 0.001). However, the heterogeneity of TIS by BRCA4 mutant was explained by intrinsic subtype with basal-like tumors exhibiting higher inflammation. Conclusions: To our knowledge, this is the largest study of a prognostic signature on BRCA-mutated tumors presented to-date. We observed heterogeneity in the intrinsic subtypes and a wide range of inflammation response with differences between BRCA1 and BRCA2 tumors being explained by intrinsic subtype. Additional analyses are ongoing including evaluation of signatures associated with DNA Damage, immune profile, and HRD as well as association of expression signatures with outcomes.
Risk of pediatric malignancy in families known to carry BRCA1/2 mutations.

**Background:** Inherited mutations in cancer predisposition genes typically associated with adult-onset cancers, including BRCA1/2, have been found in children with cancer. However, it is unknown whether such mutations are causative. Our objective is to determine whether there is an increased risk of pediatric malignancy in families known to carry BRCA1/2 mutations.

**Methods:** We utilized the Cancer Risk Evaluation Program (CREP), a registry of non-risk breast and ovarian cancer families undergoing BRCA1/2 testing. We compared pediatric malignancy rates in BRCA1/2 mutation positive families from CREP to the general population from SEER (Surveillance, Epidemiology and End-Results) using an incidence rate ratio (IRR). **Results:** We compared 1,313 BRCA1/2 mutation negative and 1,402 BRCA1/2 mutation positive families. 3,168 siblings had 10 pediatric malignancies (0.3%) in BRCA1/2 mutation positive families. When examining at-risk family members there were 30 BRCA1/2 mutation negative families (2.3%) with a pediatric malignancy (31 malignancies) and 24 BRCA1/2 mutation positive families (1.7%) with a pediatric malignancy (25 malignancies). We found no evidence for an increase in pediatric malignancy risk in BRCA1/2 positive vs BRCA1/2 negative families in the sibling (OR = 0.69, 95% CI, 0.25-1.92; p = 0.482) or family based (OR = 0.76, 95% CI, 0.42-1.35; p = 0.342) multivariable adjusted analyses. We compared pediatric malignancy rates (per 100,000 person-years) among BRCA1/2 mutation positive and negative families in CREP and SEER. IRR (incidence rate [IR] = 16.1, 95% CI, 0.9-23.9) and SEER (IR = 70 F/wOC and FhX cancer; a MUTHY PV in a 52M wOC. On UR arm, only 40.7% (11/27) have completed GE—PVs in MSH6 (70 M/wCR) and BRCA1 (44F/wOC were found). Among these patients, 230 (32%) had at least one HR criteria. Of the HR women, 51% were given GCR and 13 (19%) were given i-MGPT. Among those given i-MGPT, 11% (3/27) had actionable genes. 89% consented to i-MGPT. We found no evidence for an increased risk of pediatric malignancy in BRCA1/2 mutation positive families. Our data supports delaying BRCA1/2 testing in BRCA1/2 mutation positive families until adulthood.

Conclusions: We find no evidence for an increased risk of pediatric malignancy in families known to carry BRCA1/2 mutations. The pediatric malignancy in families with BRCA1/2 mutations is low (IRR = 1.00; 95% CI, 0.65-1.48). Further studies are needed to confirm this finding.
Genetic testing and clinical management practices for variants in non-BRCA1/2 breast (and/or ovarian) cancer susceptibility genes: An international survey by the ENIGMA Clinical Working Group

**Methods:** Data were collected via in-person and paper/electronic surveys. ENIGMA members from around the world were invited to participate. Additional information was collected via country networks in the UK and in Italy. **Results:** Responses from 61 cancer genetics centers across 20 countries showed that 16 genes were tested by more than 50% of the centers, but only 6, from 61 cancer genetics centers across 20 countries showed that 16 genes collected via country networks in the UK and in Italy.

**Results:**

- The cumulative frequency of BRCA1: 77 (21%); BRCA2: 76 (20%); ATM: 45 (12%); CHEK2: 47 (12.5%); PALB2: 32 (8.5%); TP53: 16 (4.3%); MUTHY: 13 (3.5%); 58 (18.2%) patients tested for other genes (APC, BRIP1, BARD1, PTEN, STK11, CHD1, MLH, MSH, PMS, CDKN2A, NBN, NFI, RAD50, RAD51, SDHD, AXIN2, MIFT, GALNT12, XRCC2). As expected, BRCA1 mutation was associated with triple negative breast cancer (p < 0.0001). The tumor characteristics of all other carriers were similar to those seen in BRCA1 carriers with the exception of MUTHY carriers who were more likely to have invasive lobular cancers (p < 0.0001) and TP53 carriers were younger at diagnosis (p < 0.001) and more likely to have HER-2/neu positive cancers (p = 0.006).

**Conclusions:** Our collected series of patients with non-BRCA hereditary breast cancers demonstrates specific tumor characteristics associated with TP53 mutations. Further exploration is warranted to expand this data set and further characterize cancers that are associated with low frequency genetic mutations. The frequency of ER positive tumors in these patients suggests that chemoprevention may be an important strategy in this population.

**Methods:** Non-BRCA hereditary gene mutations and breast cancer phenotype: An ISC-RAM Consortia study. First Author: Banu Arun, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** The use of multi-gene panel testing (MGP) for hereditary breast cancer has been increasing. Currently, the indications for MGP depend on personal and/or family history of cancer, as tumor phenotype and patient characteristics for non-BRCA related cancers are not well described. The present study analyzed tumor characteristics of breast cancers associated with non-BRCA hereditary mutations. **Methods:** Institutional IRB-approved prospective databases from the International Society of Cancer Risk Assessment and Management (ISC-RAM) members were queried for patients with invasive breast cancer who underwent MGP between 2013-2017. Clinical and tumor characteristics for mutation carriers were analyzed using descriptive statistics and Pearson’s and Fisher’s Chi-Square analyses. **Results:** Of a total of 1,854 patients with invasive breast cancer who underwent MGP, 374 (20%) had a positive pathogenic gene mutation. Median age at diagnosis was 46 years (range: 22-85). Positive testing results were as follows: BRCA1: 77 (21%); BRCA2: 76 (20%); ATM: 45 (12%); CHEK2: 47 (12.5%); PALB2: 32 (8.5%); TP53: 16 (4.3%); MUTHY: 13 (3.5%); 58 (18.2%) patients tested for other genes (APC, BRIP1, BARD1, PTEN, STK11, CHD1, MLH, MSH, PMS, CDKN2A, NBN, NFI, RAD50, RAD51, SDHD, AXIN2, MIFT, GALNT12, XRCC2). As expected, BRCA1 mutation was associated with triple negative breast cancer (p < 0.0001). The tumor characteristics of all other carriers were similar to those seen in BRCA1 carriers with the exception of MUTHY carriers who were more likely to have invasive lobular cancers (p < 0.0001) and TP53 carriers were younger at diagnosis (p < 0.001) and more likely to have HER-2/neu positive cancers (p = 0.006).

**Conclusions:** Our collected series of patients with non-BRCA hereditary breast cancers demonstrates specific tumor characteristics associated with TP53 mutations. Further exploration is warranted to expand this data set and further characterize cancers that are associated with low frequency genetic mutations. The frequency of ER positive tumors in these patients suggests that chemoprevention may be an important strategy in this population.
Background: Prospective Registry of Multiplex Testing (PROMPT) is an online registry for individuals who completed multiplex panel testing for cancer susceptibility. The overall objective of this registry is to ascertain more complete family histories to allow penetrance calculations for mutations in less characterized genes.

Methods: Since September 2014, health care providers and commercial laboratories have provided PROMPT information to eligible participants and ordering providers with the test results. The PROMPT registry has self-enrolled those with pathogenic variants and variants of unknown significance (VUS) in cancer susceptibility genes. Registrants consent to full participation (FP), permitting study investigators to have contact information, or partial participation (PP), with de-identified information only. In 2016, we expanded to Phase II, targeting enrollment by genes of interest for family co-segregation, and collecting additional risk factor data and saliva samples. Results: Over 4500 individuals have enrolled into PROMPT. Using initial recruitment goals, to date we have reached 250% of our initial recruitment. 94% of enrollees are women, representing 33 countries (96% from the United States). 63% of participants reported at least one cancer (67% breast cancer) and 23% reported two or more cancers. 29% report likely pathogenic/pathogenic alteration, 25% VUS, and the remaining are in the process of being verified. The most frequently reported genes are ATM (13%), CHEK2 (12%), PALB2 (7%), BRIP1 (4%), and BARD1 (4%). 58% of participants have participated more than 1 year and of those, 46% completed the first annual follow-up survey. A gene-specific survey sent to participants with CDH1 genetic alterations had a 61% response from FP and a 32% response rate from PP. Conclusions: The continued linear enrollment since the inception of PROMPT and the willingness of participants to respond to survey studies, annual follow-up, and PROMPT II enrollment supports the feasibility and sustainability of a prospective registry for the collection of genetic epidemiology data. Strategies to increase follow up participation are underway, including gene-specific surveys and transitioning PP to FP, for those who are willing.

Identification and characterization of germline pathogenic variants using matched tumor-normal next-generation sequencing in Chinese pan-cancer patients in China. First Author: Yuting Yi, Geneplus-Beijing Institute, Beijing, China

Background: Comprehensive NGS panel based genetic testing is becoming more common to help clinicians provide personalized cancer care. Matched tumor-normal sequencing is recommended primarily to detect tumor-specific variants. Previously under-explored, it could also detect pathogenic germline alterations in cancer patients. Using targeted matched tumor-normal NGS, we identified and characterized germline variants in a large pan-cancer patient cohort in China. Methods: We surveyed the germline variants in 7363 Chinese patients across more than 18 diverse cancer types. Germline variants in 62 cancer-susceptibility genes were called from a 1021 gene NGS panel analyzing matched normal DNA. Following AMCG guidelines, variants were classified into pathogenic, likely pathogenic, variant of unknown significance, likely benign, or benign. Following AMCG guidelines, variants were classified into pathogenic, likely pathogenic, variant of unknown significance, likely benign, or benign. Results: 385 germline pathogenic and likely pathogenic variants (GPVs) were identified in 374/7363 (5.1%) patients. Ovarian cancer (24.7%, 37/134) represented the highest prevalence. Breast cancer (11.3%, 92/813), colorectal cancer (8.3%, 66/791), pancreatic cancer (6.2%, 8/130), renal cell cancer (5% 5/734), and gastric cancer (5.1%, 14/273) displayed relatively high rates of GPVs in line with expectations. Interestingly, NSCLC (2.5%, 88/3572) and hepatocellular cancer (2.3%, 5/214) also showed such events. In total, only 192/385 (49.9%) participants presented with GPVs in cancer-susceptibility genes in the expected cancer types. BRCA2 and BRCA1 were the top two common genes, which were found in 146 patients across 15 cancer types including 27/3572 (1%) NSCLC and 2/3572 (0.1%) hepatocellular cancer patients. 285/385 (74%) of the GPVs were actionable for targeted therapy. Conclusions: Germline variants can be identified on routine targeted matched tumor-normal NGS and commonly exist in patients with cancers of diverse tissue origin. Recognition of germline variants may be valuable in therapeutic interventions and genetic risk analysis. We are currently performing retrospective family history analysis and genetic counseling for those patients with unreported GPVs.
Influence of vitamin D (Vit D) on mammographic density (MD) and insulin like growth factor 1 (IGF1): Results of CALGB (Alliance) 70806. First Author: Marie Wood, University of Vermont, Burlington, VT

Methods: Premenopausal women were assigned to receive either 2000IU of Vit D or placebo for 12 months, stratified by baseline (BL) vit D level (sufficient vs insufficient). Eligible women were premenopausal, age < 55, with at least 25% dense breast tissue. Biomarker specimens were collected at baseline and 12 months. MD was determined using the Breast Imaging Reporting and Data System (BIRADS), semi-automated and automated methods. Serum IGF1 was determined by ELISA. Biomarkers were compared between arms using Wilcoxon and t-tests. Results: 300 women were recruited from 41 institutions across the US between 1/11-12/13. The mean age was 42.6 years with 14% Hispanic, 12% African American, 74% European. 62% of participants were vitamin D deficient at enrollment and 49% of women had MD between 25-50% with only 12% >50% dense. 216 (72%) of participants completed treatment, 8 withdrew due to side effects, and 76 for other reasons (28% withdrawal rate). A significant increase in Vit D was seen with treatment with 99% and 72% of experimental and control subjects having sufficient levels at 12 months (P < 0.0001). MD decreased 2.2% over 1 year for the entire cohort, with no significant difference between arms. Surprisingly, no significant change in MD was seen with Vit D. Conclusions: Vit D supplementation resulted in a significant increase in serum Vit D (from a mean of 35.5 to 49.7 ng/mL, p < 0.0001). However, no significant change in MD was observed with treatment; potentially due to small change in MD seen at 1 year, the low percentage of high MD or that Vit D works by another mechanism. Further study with longer Vit D exposure is warranted. Support: UG1CA189823, U24CA196171. Citation: NCT01224678.
Poster Session (Board #122), Sat, 1:15 PM-4:45 PM

Case-only analyses for identifying genotypes that modify the effect of finasteride in the Prostate Cancer Prevention Trial (PCPT): SWOG S9217. First Author: James Dai, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: The Prostate Cancer Prevention Trial (PCPT) reported decreased risk of all prostate cancers but increased risk of high-grade prostate cancer in the finasteride arm. The aim of the present analysis was to identify genotypes that modify the effect of finasteride using case-only methods for estimating gene-treatment interactions. Methods: Germline genetic data from 1157 prostate cancer cases in the Prostate Cancer Prevention Trial (PCPT, NCT00288106) were analyzed by case-only methods. Genotypes included 357 single nucleotide polymorphisms (SNPs) from 83 candidate genes in androgen metabolism, inflammation, circadian rhythm and other pathways. Univariate case-only analysis was conducted to evaluate whether individual SNPs modified the finasteride effect on the risk of high-grade and low-grade prostate cancer. Case-only classification trees and random forests, which are powerful machine learning methods with resampling-based controls for model complexity, were employed to identify a predictive signature for genotype-specific treatment effects. Results: Accounting for multiple testing, a single SNP in SRD5A1 gene (rs472402) significantly modified the finasteride effect on high-grade prostate cancer (Gleason score > 6) in PCPT (p-value = 8 × 10^{-9}, family-wise error rate < 0.05). Men carrying GG genotype at this locus had a 55% reduction in the risk of developing high-grade cancer (RR = 0.45, 95% CI [0.27, 0.75]). Additional effects modifying SNPs with moderate statistical significance were identified by case-only trees and random forests. A prediction model built by the case-only random forest method classified 36% of PCPT men to have reduced risk of high-grade prostate cancer when taking finasteride, while the others have increased risk. No SNP-finasteride interaction was found for low-grade prostate cancer. Conclusions: Case-only methods identified SNPs that modified the effect of finasteride on the risk of high-grade prostate cancer in PCPT and predicted a subgroup of men who had reduced cancer risk by finasteride. Clinical trial information: NCT00288106.

Poster Session (Board #124), Sat, 1:15 PM-4:45 PM

Long-term effectiveness and immunogenicity of quadrivalent HPV vaccine in young men: 10-year end of study analysis. First Author: Stephen Goldstone, Laser Care Surgery, New York, NY

Background: The quadrivalent human papillomavirus (qHPV) vaccine prevented HPV6/11/16/18-related persistent infection and external genital lesions in young men in an international, randomized, placebo-controlled pivotal efficacy study. We report the end-of-study analysis of a long-term follow up (LTFU) extension study that assessed the effectiveness and immunogenicity of the qHPV vaccine through 10 years after the first dose. Methods: In the 3-year base study, young men (16-26 years old) were randomized 1:1 to receive a 3-dose regimen of qHPV vaccine or placebo; we report results from those who received 3 doses of qHPV vaccine in the base study and participated in the LTFU. The entire study population was assessed annually in the 7-year LTFU for HPV6/11-related genital warts and HPV6/11/16/18-related external genital lesions (EGL), and a subpopulation was assessed for HPV6/11/16/18-related anal intraepithelial neoplasia (AIN) or anal cancer. Persistence of anti-HPV6/11/16/18 antibodies was evaluated from serum samples collected 48-72 months (first LTFU visit) and 10 years post-Dose 1. Results: A total of 917 participants were followed for effectiveness for up to 11.5 years (median: 9.5 years) post-Dose 3. There were no new cases of HPV6/11-related genital warts, HPV6/11/16/18-related EGL, or HPV6/11/16/18-related high-grade AIN during the LTFU (Years 3 to 10 of the study) in the per-protocol population. One case of low-grade AIN (AIN1) with positive PCR results for HPV16 and HPV58 was reported. Seropositivity rates compared to baseline were > 97% at Month 7 (1 month post-Dose 3); remained high over time for HPV6, 11, and 16; and decreased over time for HPV18 (40.2% at Month 120 by cLIA). Seropositivity rates at Month 120 assessed by competitive Luminex immunoassay (a more sensitive assay) were 90% for all 4 HPV types. Conclusions: The qHPV vaccine provides durable protection from vaccine-type-related anogenital disease and elicits persistent HPV antibody responses through 10 years post-vaccination onset in 16-26-year-old men. Clinical trial information: NCT00090285.

Poster Session (Board #125), Sat, 1:15 PM-4:45 PM

Breast cancer risk perception and adherence to u.s. cancer prevention guidelines. First Author: Jillian Eckrote, Yale University, New Haven, CT

Background: In the United States, nearly 300,000 cancer diagnoses each year are attributed to poor diet and physical inactivity. We sought to determine whether perceived personal breast cancer risk was associated with adherence to healthy lifestyle habits. Methods: The National Health Interview Survey (NHIS) is conducted annually by the CDC, designed to broadly represent the U.S. civilian population. We utilized data from the 2010 and 2015 NHIS adult and cancer supplements to evaluate fruit/vegetable intake, alcohol use, and exercise habits among women who perceived themselves to be at high risk of developing breast cancer, as compared to those women who perceived themselves to be at average or low risk. Results: In 2010 and 2015, 12,055 and 14,542 women without a history of cancer were surveyed, representing 94,990,140 and 98,404,285 people, respectively. In 2010, those who perceived themselves to be at higher risk of breast cancer were more likely to follow the fruit/vegetable and physical activity guidelines, but less likely to follow the alcohol intake guidelines than those at low to average risk, but these differences were not statistically significant (p = 0.57, 0.15, 0.31 respectively). In 2015, those who perceived themselves to be at high risk were significantly more likely to follow the fruit/vegetable guidelines (p = 0.02) as their low/average risk counterparts, but had similar rates of following alcohol and physical activity guidelines (p = 0.58 and 0.67 respectively). In general, guideline adherence did not improve from 2010 to 2015 (see table). Conclusions: Less than a third of women adhere to nutrition and physical activity guidelines regardless of self-perceived breast cancer risk, a trend that has remained stable over time and indicates a need to educate patients on healthy lifestyle habits.

2010 2015 p-value
High Risk—% meeting guidelines
Fruit/Veg Intake (3 servings/daily) 4.90% 6.25% 0.25
Alcohol Intake (> 7/week) 94.22% 95.80% 0.16
Physical Activity (75+150 min vig-mod activity/week) 30.11% 28.97% 0.64
Low/Avg Risk—% meeting guidelines
Fruit/Veg Intake (3 servings/daily) 4.42% 3.92% 0.11
Alcohol Intake (7/week) 95.3% 95.35% 0.53
Physical Activity (75-150 min vig-mod activity/week) 27.74% 29.79% 0.01
1555 Poster Session (Board #126), Sat, 1:15 PM-4:45 PM
Clinical characteristics and EGD surveillance in Lynch-syndrome patients with small bowel/duodenal carcinomas. First Author: Deepak B. Yangala, Department of Medicine, Knappschaftskrankenhaus, Ruhr-University Bochum, Bochum, Germany

Background: Small bowel carcinomas (SBC) account for less than 5% of all gastrointestinal malignancies in the general population. However in patients with Lynch Syndrome (LS) the lifetime-risk for SBC is reported as high as 10%. The aim of this study was to evaluate the effectiveness of esophagogastro-duodenoscopy (EGD) surveillance for early detection of proximal SBC. Methods: The German Consortium for Intestinal Cancer database was screened for patients with a diagnosis of SBC. General tumor characteristics such as mutational status and age specific incidence where analyzed. Tumor stage at diagnosis was used as a surrogate parameter for prognosis and correlated to patients being diagnosed by symptoms compared to patients diagnosed by EGD-surveillance. Furthermore, adherence to EGD-surveillance after SBC diagnosis was correlated to survival. Statistics were calculated using Fisher’s exact test. Results: A total of 125 SBC in 112 patients were included in the study (45.6% duodenal, 32% jejunal, 11.4% ileal, 9.6% unclassified). The median age at diagnosis was 51.7 years (15.1 – 80.7) with 62% of patients being male. MLH1 and MSH2 germine mutations were most prevalent with 37.7% each. Of all SBCs, 10.4% of patients were younger than 35 years at diagnosis (8.8 % of duodenal cancers). Duodenal cancer patients undergoing surveillance were diagnosed with early stage disease (UICC I-IIa) significantly more often than patients diagnosed because of symptoms (69.2 % vs 66.7%; p = 0.008). With regard to screening of SBC in LS, there was no stage difference between these groups. Adherence to EGD surveillance was better after SBC diagnosis with significantly less cancer deaths among patients undergoing surveillance after SBC. Conclusions: To our knowledge, this is the largest study regarding the role of EGD surveillance for detection of SBC in LS patients. Of note, the use of EGD as a surveillance instrument for duodenal cancer, which make up nearly half of SBC in LS patients. In contrast to current practice in Germany, the results of this study suggest an earlier beginning of EGD surveillance than at the age of 35.

1557 Poster Session (Board #128), Sat, 1:15 PM-4:45 PM
Profile of cancer-screening resistant individuals (EDIFICE 6). First Author: Thibault De La Motte Rouge, Groupe Hospitalier Pitie Salpetriere, Paris, Cedex 13, France

Background: The efficacy of cancer screening (cost effectiveness, reduced mortality) relies on a minimum threshold uptake rate. Target populations are asymptomatic with only average risk, and thus likely to avoid screening. We studied the characteristics of cancer-screening resistant individuals. Methods: The French nationwide observational survey, EDIFICE 6, was conducted online from 26 June-28 July 2017 on a core sample of 12,046 individuals (age 18-69 y). Representativeness was ensured by quota sampling on age, gender, profession, and stratification by geographical area and type of urban district. Multivariate stepwise logistic regression analyses were conducted with a common set of variables to identify factors likely to explain non-uptake of cancer screening. The analysis focused on individuals in the age range of target populations for organized programs: 50-69 y for breast (BC) and colorectal cancer (CRC) (N = 1954 and N = 4300, respectively) and 25-65 y for cervical cancer (CC) (N = 4499). Results: Of those who had never taken part in a screening program, 6% (N = 108) were in the target population for BC screening, 12% (N = 539) for CC, and 38% (N = 1625) for CRC screening. Items associated with not undergoing screening included: for BC, the statement “progress is accomplished through clinical research” rated as unimportant (OR = 2.14, 95% CI [1.16-3.82]); social vulnerability (OR = 2.09, [1.36-3.25]); rating BC prevention programs as ineffective (OR = 1.60, [1.01-2.51]); for CC: living alone (OR = 2.31, [1.89-2.82]); manual worker (OR = 1.95, [1.21-3.05]); social vulnerability (OR = 1.83, [1.49-2.26]). For CRC: self-employed (OR = 1.83, [1.24-2.71]); rating CRC prevention programs as ineffective (OR = 1.76, [1.48-2.08]); current smoker (OR = 1.45, [1.25-1.68]); manual worker (OR = 1.40, [1.05-1.87]). Conclusions: Mistrust in clinical research—possibly linked to medical skepticism—and social vulnerability play major roles in resistance to BC screening. A disadvantaged socioeconomic profile has a negative impact on CC screening uptake and yet is an acknowledged risk factor for the disease. Self-employed people who mistrust cancer prevention are resistant to CRC screening. Our findings highlight the need for tailored education campaigns.

1558 Poster Session (Board #129), Sat, 1:15 PM-4:45 PM
A health system experience with an electronic medical record based application to increase lung cancer screening. First Author: Brandon Weckbaugh, UMCK School of Medicine, Kansas City, MO

Background: Screening high risk patients for lung cancer with Low Dose Computed Tomography (LDCT) reduces lung cancer-specific mortality, however its adoption in routine clinical care has been limited. We designed an Electronic Medical Record (EMR) based application to identify patients for screening in the primary care setting. Methods: A two-step screening application was created to identify patients meeting CMS criteria for LDCT screening in a visit to a primary care provider (PCP). First, the application directs medical assistants to complete a patient’s smoking history. If the patient meets eligibility for LDCT screening, step-by-step direction for PCPs to complete the screening process, including reviewing smoking history, shared decision making and ordering the LDCT scan, is initiated. We compared the number of referrals for screening LDCT in the 12-month periods before and after implementation of the screening application. Results: During the 12-month period prior to implementation of the screening application in a 18-person PCP group, there were a total of 198 referrals for LDCT screening. Of these, 152 (81.8%) were negative (CAT 1 and 2), 20 (10.1%) required follow up CT (CAT 3), 16 (8.1%) were positive (CAT 4), 3 (1.5%) required an invasive diagnostic procedure (bronchoscopy with biopsy, endobronchial ultrasound, CT guided biopsy, thoracic surgery). Cancer was diagnosed in 2 patients (1.0%), both of whom received cancer treatment. In the 12 months after implementation, referrals increased by 40% to 278. Of these, 241 (86.7%) were negative, 19 (6.8%) required follow up CT, 18 (6.5%) were positive, 4 (1.4%) required an invasive diagnostic procedure, and 3 (1.1%) were di- agnosed with cancer and are receiving treatment. Major challenges include variable user compliance in completing accurate smoking history and providers ignoring alerts to initiate lung cancer screening. Conclusions: To our knowledge this is the first report on the use of an EMR based application to identify patients at risk for lung cancer. Implementation of the EMR based application correlated with an increase in referrals for LDCT screening and led to the identification of high risk lung lesions including lung cancer.
Poster Session (Board #130), Sat, 1:15 PM-4:45 PM

Attributable failure and costs associated with continued smoking by cancer patients.
First Author: Graham W. Warren, Medical University of South Carolina, Charleston, SC

Background: Smoking by cancer patients causes adverse outcomes including increased cancer specific mortality, but there are no estimates of the effects of continued smoking in cancer patients on costs of continued medical care for cancer. Methods: Attributable failure (AF) was modeled across expected first-line cancer treatment failure in non-smoking patients (ns-FLF), prevalence of current smoking, risk for escalated first-line cancer treatment failure caused by smoking, and cost of subsequent treatment after failure of first-line cancer treatment. Results: As smoking prevalence increases, AF increases with peak AF in cancer treatment conditions where ns-FLF ranged from 30-50%. In disease sites with 90% ns-FLF, the AF caused by smoking was lower than in patients with 10% ns-FLF, supporting a more significant effect of continued smoking in patients with higher expected cure rates. Using a conservative 60% increased risk of treatment failure caused by smoking across all cancer patients and cancer treatments published from median cancer related mortality estimates of risk from the 2014 Surgeon General’s Report, the conditions of 20% smoking prevalence and 30% ns-FLF resulted in 10.7 AF per 100 smoking patients. Cost per smoking patient per $100,000 incremental cost of ns-FLF cancer treatment was $10,675. Extending results to 1.6 million cancer patients, treatment of AF due to continued smoking by cancer patients costs $3.4 billion for every $100,000 increment of cost of cancer treatment per AF. Conclusions: Treatment of AF caused by continued smoking in cancer patients results in significant costs. Because estimates did not include costs associated with medical care not related to cancer progression, results are expected to underestimate the true costs of medical care caused by smoking in cancer patients.

Poster Session (Board #131), Sat, 1:15 PM-4:45 PM

Overweight and breast cancer risk in the International Breast Cancer Intervention Studies I and II. First Author: Samuel G Smith, University of Leeds, Leeds, UK

Background: Overweight increases breast cancer risk in population risk postmenopausal women. Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 and P2 chemoprevention trials indicate premenopausal overweight, but not postmenopausal overweight, increases breast cancer risk in high risk women. We estimated the relationship between overweight and breast cancer risk in the International Breast Cancer Intervention Studies I and II. Methods: The IBIS II prevention trials compared tamoxifen (IBIS-I) and anastrozole (IBIS-II) vs. placebo in women at increased risk of breast cancer. Baseline body mass index (BMI) was calculated for premenopausal (n = 3138) and postmenopausal (n = 3733) women in IBIS-I and postmenopausal women in IBIS-II (n = 3783). BMI change (< 5%, 5-9.9%, > 10%) was available for 2504 IBIS-I women. There were 542 (IBIS-I) and 168 (IBIS-II) invasive breast cancer events and median follow-up was 19.6 years (IQR 7.2–11.4). Results: Higher BMI was associated with increased invasive breast cancer risk in IBIS-I (HR = 1.02, 95% CI = 1.00-1.03, p = 0.044) and IBIS-II (HR = 1.06, 95% CI = 1.03-1.09, p < 0.001). In IBIS-I, the association between BMI and breast cancer risk was restricted to premenopausal women (HR = 1.03, 95% CI = 1.01-1.05, p = 0.004). Among IBIS-I postmenopausal women, compared with healthy weight, HRS were 1.20 (95% CI = 0.92-1.56) for overweight and 1.29 (95% CI = 0.97-1.72) for obese women. In IBIS-II HRS were 1.15 (95% CI = 0.75-1.75) for overweight and 1.90 (95% CI = 1.27-2.84) for obese women. Conclusions: contrary to NSABP P1 and P2 data, we found no evidence for increased breast cancer risk among overweight premenopausal women. IBIS-I and IBIS-II data suggest higher BMI increases breast cancer risk in postmenopausal women with elevated breast cancer risk. Clinical trial information: ISRCTN91879928 and ISRCTN31488319.

Poster Session (Board #132), Sat, 1:15 PM-4:45 PM

Smoking cessation after a cancer diagnosis and survival in cancer patients.
First Author: Graham W. Warren, Medical University of South Carolina, Charleston, SC

Background: Extensive literature confirms that continued smoking by cancer patients and survivors increases overall mortality, but the benefits of smoking cessation specifically after a cancer diagnosis has not been well described. Methods: Comprehensive evaluation of all Pubmed studies identified using "smoking" and "cancer" published since 2000 was performed to identify all studies with at least 100 patients reporting on the effects of smoking cessation after a cancer diagnosis on overall mortality. Studies that evaluated the exclusive or combined effects of smoking cessation before a cancer diagnosis were not included. Results: Ten (10) studies were identified that met all inclusion criteria including 7 prospective and 3 retrospective studies. The effects of smoking cessation were evaluated for lung cancer patients in 4 studies, head/neck cancer patients in 3 studies, breast cancer patients in 1 study, and multiple cancers in 2 studies. In 3 prospective studies, continued smoking increased risk of overall mortality as compared with never smoking and quitting smoking had an intermediate risk between continued smoking and never smoking. In 7 studies comparing smoking cessation with continued smoking, the median risk of overall mortality in patients who quit smoking was 0.55 (range 0.19-0.92) as compared with continued smoking including 6 of 7 studies with statistically significant reductions in overall mortality risk. Only 1 study reported on overall mortality in cancer patients who were actively enrolled in a smoking cessation program after a cancer diagnosis, and quitting smoking was observed to reduce overall mortality by 44% (HR 0.56, 95% CI 0.36-0.89). Conclusions: Of larger contemporary studies evaluating the effects of smoking cessation after a cancer diagnosis on overall mortality, most demonstrate a significant benefit of quitting smoking.

Poster Session (Board #133), Sat, 1:15 PM-4:45 PM

Community based lung cancer screening program: Evaluation of the initial lung cancer screening CT scan. First Author: Tripuran Mishra, Advocate Lutheran General Hospital, Park Ridge, IL

Background: Low-dose chest CT for lung cancer screening has shown to have a significant impact on the early diagnosis of lung cancer. In the initial trials, approximately a 20% decrease in lung cancer mortality was found. Patients enrolled in a community-based lung cancer screening program initiated in March 2013 at Lutheran General Hospital and Illinois Masonic Hospital were evaluated for initial outcomes. Methods: All patients who completed an initial consultation in oncology clinic from March 2013-June 2017 were included in the analysis. Eligibility criteria for the program included patients within the age range of 55-77, with a > 30 pack year history, and that were current smokers or quit tobacco less than 15 years ago. In addition, between 50-55 years old were also included if they had > 20 pack year smoking history and at least one additional risk factor. All patients with significant abnormalities were discussed at a multidisciplinary conference prior to embarking on any invasive procedures. Also, they underwent a low-dose chest CT for lung cancer screening and were subsequently seen in consultation by a thoracic surgeon. All patient data was entered into a REDCap database and subsequently evaluated. Results: 392 patients were enrolled during the study timeframe. Majority of the patients were Caucasian (88%) and male (60%). They were referred by their primary physician (95%). The average age of the sample was 64 years (±6.6). 211 (53.8%) patients were found to have pulmonary nodules. A total of 506 pulmonary nodules were found with an average size of 4.9 (± 4.3) mm. Of the 392 patients who underwent lung cancer screening, a total of 11 lung cancers were found (2.8%). Of the 11 patients, 6 (55%) patients were Stage I, 1 (9%) patient was Stage II, 2 (18%) patients were Stage III, and 1 (9%) patient was Stage IV. There was also 1 (9%) patient with limited stage small cell cancer. Conclusions: Of the 11 cancer patients identified, 64% presented with early stage lung cancer on initial lung cancer screening. In fact, 55% of the patients presented with Stage I lung cancer. These data suggest that lung cancer screening is a viable tool in discovering early stage lung cancer with the potential to improve lung cancer survival.
Herpes zoster vaccine and varicella zoster virus infection among cancer patients having chemotherapy. 

**First Author:** Lisa Y. Law, Kaiser Permanente, Daly City, CA

**Background:** Varicella zoster virus (VZV) infection is an opportunistic infection among immunocompromised patients. The herpes zoster (HZ) vaccine is a live vaccine not approved for administration to oncology patients receiving chemotherapy. We aimed to assess the association between HZ vaccine given prior to cancer diagnosis and VZV infection in this population.

**Methods:** In this retrospective cohort study conducted in Kaiser Permanente Northern California (KPNC) we assessed the association between prior HZ vaccination and VZV infection in cancer patients age 60-89 years having chemotherapy January 1, 2010-December 31, 2014. Subjects were followed until death, loss of membership, or end of study (December 31, 2016). Multivariable analyses were performed using adjusted relative risk models. Variables controlled for included age, sex, hematological vs. non-hematological cancers, high dose steroid therapy, prior immunomodulation therapy, and antiviral prophylaxis. Subanalyses were performed for subjects with and without hematological cancers.

**Results:** Our study consisted of 13,069 subjects having cancer and chemotherapy; of these 5090 (39.9%) had prior administration of the HZ vaccine. Median follow-up was 26.0 months (IQR: 10.6-42.9). Of vaccinated subjects 198 (3.9%) developed VZV infection compared to 410 (5.1%) of unvaccinated subjects (Adjusted Relative Risk [ARR] 0.73, 95% CI 0.62-0.86). Hematological cancers were associated with VZV infection (referent: other cancers, ARR 2.76, 95% CI 1.23-3.20). In subanalyses the HZ vaccine was more protective against VZV infection in subjects with hematological cancers (ARR 0.62, 95% CI 0.47 – 0.83) than in those with other cancers (ARR 0.81, 95% CI 0.66-0.99). There were 7965 deaths (60.9%) during follow-up. The HZ vaccine was protective against all-cause mortality in all subjects (ARR 0.76, 95% CI 0.74-0.78).

**Conclusions:** The live HZ vaccine is protective against VZV infection in oncology patients receiving chemotherapy; this effect is greater in subjects having hematological cancers. The vaccine is also associated with decreased all-cause mortality.

### Risk of secondary malignancies in breast cancer patients who received chemotherapy: A SEER analysis. 

**First Author:** Snigdha Nutalapati, Morehouse School of Medicine, Atlanta, GA

**Background:** Chemotherapy agents used in breast cancer have carcinogenic potential and can cause malignancies. Patients with breast cancer could also be at risk for a second malignancy as well. We aimed at determining the risk of after adjuvant chemotherapy for breast cancer. **Methods:** We did an observational study of women who received a diagnosis of breast cancer from 1990 to 2009 using Surveillance, Epidemiology, and End Results (SEER) registries database 9 registries. Secondary malignancy (SM) was defined as any malignancy diagnosed 6 months after initial diagnosis of breast cancer (includes both chemotherapy-related malignancies and second primary malignancies). Hormone receptor (HR) status into estrogen receptor (ER) and progesterone receptor (PR), positive (+) and negative (-). Standardized incidence ratios (SIR) was calculated based on United States population in 2000. p-value of < 0.05 is considered statistically significant. **Results:** Total of 245,235 cases (2,409,502 person-years) were identified, 36.3% received chemotherapy. 66.2% were ER-PR+, 11.9% were ER-PR+, 2.5% ER-PR+ and 19.5% were ER-PR-. Median follow up was 11.3 years (range 1-22.9 years), 36,005 (14.7%) cases eventually developed SM. In patients who received radiotherapy (RT), risk of developing SM was increased by 43% (SIR 1.43 [95% CI 1.39-1.46] in those who received chemotherapy (CT) compared to only 22% (SIR 1.22 [95% CI 1.20-1.24]) in those who did not receive chemotherapy (non-CT). In patients who were not treated with radiotherapy, those who got chemotherapy (CT) had an increased risk of developing SM: SIR 1.27 [95%CI 1.23-1.31]. Breast cancers represented 37% of all SM followed by digestive system (16.6%), uterine (14.3%), bronchopulmonary (12.7%), colorectal (9.4%), urinary system (4.6%), lymphoma (3.4%) and ovarian cancers (3.0%). Acute myeloid leukemia (AML) and salivary gland tumors represented only 1.3% and 0.3% of all SM.

**Conclusions:** Risk of secondary malignancies, which includes second primary cancers is significantly higher for cases that received chemotherapy and the risk is increased irrespective of radiation status. Radiation therapy increases the risk for secondary malignancies.

### Impact of prophylactic bilateral salpingo-oophorectomy on bone health in BRCA1 or BRCA2 mutation carriers: A prospective cohort study. 

**First Author:** Elizabeth Hall, Women’s College Research Institute, Toronto, ON, Canada

**Background:** Women who inherit a deleterious mutation in BRCA1 or BRCA2 face a high lifetime risk of ovarian cancer. Prophylactic bilateral-salpingo-oophorectomy (PBSO) is recommended prior to natural menopause; however, the impact of abrupt hormonal withdrawal on bone health in this high-risk population is not known. We conducted a longitudinal study to evaluate the impact of PBSO on bone mineral density (BMD) in BRCA mutation carriers. **Methods:** The study population included women who underwent PBSO at the University Health Network (Toronto, Canada) between January 2000 and May 2013. Eligibility criteria included having a BRCA mutation, at least one ovary prior to surgery, and no personal cancer history other than breast cancer. Information regarding medical history, medication use, and lifestyle factors was collected via questionnaire. BMD measurements using dual x-ray absorptiometry were collected at baseline (prior to surgery) and follow-up. The % change in BMD from baseline to follow-up was calculated for the lumbar spine, femoral neck, and total hip. **Results:** A total of 103 women had baseline and follow-up BMD measurements available. Mean age at PBSO was 49 years (range 37-52). Mean time to first follow-up was 2.04 years (range 0.98-4.74). Among women premenopausal at the time of surgery (n = 58), there was a significant change in BMD from baseline to first follow-up in the lumbar spine (-5.32%, 95% CI -7.17 to -3.48), femoral neck (2.94%, 95% CI -4.62 to -1.26), and total hip (-2.75%; 95% CI -4.86 to -0.60), but not for total hip (-0.78%; 95% CI -2.40 to 0.85).

**Conclusions:** These preliminary findings suggest a significant post-operative bone loss, particularly among women who were premenopausal prior to PBSO. Targeted interventions as well as routine BMD measurements may be needed to improve management of bone health in this population. Additional analyses evaluating the impact of supplement use, body mass index, as well as hormone replacement therapy are underway.
Compared the prevalence of non-AIDS defining cancers by HIV status in the Ohio Medicaid population. First Author: Siran M. Koroukian, Case Western Reserve Univ, Cleveland, OH

Background: Persons living with human immunodeficiency virus (PLWHV) are over-represented in low income and minority populations. This makes Medicaid data particularly relevant for evaluating cancer care needs and outcomes among PLWHV. As a first step, we compare the prevalence of non-AIDS defining cancers (NADCs) between PLWHV and their non-HIV counterparts, hypothesizing that, adjusting for age, race, and sex, PLWHV are more likely than others to have been diagnosed with NADCs. Methods: This is a cross-sectional of Medicaid beneficiaries 18-64 years of age, using the 2012 Ohio Medicaid Analytic eXtract (MAX) file. Demographics included age, race (White, Black, and Other), and sex (male, female). We identified HIV status, as well as cancer for the different anatomic sites based on ICD-9 diagnosis codes documented in inpatient and outpatient claims data. We conducted descriptive analysis, and multivariable logistic regression analysis to evaluate the association between HIV status and NADCs after adjusting for age, race and sex. Given that a large percentage of Medicaid beneficiaries are enrolled in Medicaid for only part of the year, we also adjusted for the length of enrollment in Medicaid in our multivariate logistic regression analysis. Results: Our study population included 1,061,471 individuals; 0.28% were PLWHV. Men and Blacks represented 55.2% and 58.9% of PLWHV, respectively, compared with 35.7% and 28.5% of their non-HIV counterparts. Adjusting for age, race, and sex, the two NADCs with which PLWHV were significantly more likely to have been diagnosed were rectal cancer (adjusted odds ratio: 4.03 (95% confidence interval: 2.31 - 7.03)), and anal cancer (34.19 (21.82-53.57)). Conclusions: For some cancers, the burden is significantly higher in PLWHV than among others. The higher prevalence of rectal and anal cancer highlights the importance of cancer prevention through screening and safe sex practice.

Milk intake and mammographic density in premenopausal women. First Author: Yunan Han, Division of Public Health Sciences. Department of Surgery, Washington University School of Medicine, St. Louis, MO

Background: Mammographic density (MD), which reflects the amount of epithelial and stromal tissues in relation to adipose tissue in the breast, is a strong risk factor for breast cancer. Although diet is associated with breast cancer risk, studies evaluating the associations of adult diet with MD have mainly reported null associations. Few studies have, however, investigated the associations of dairy intake with MD, with conflicting results. Therefore, we investigated the associations of milk intake with MD in premenopausal women. Methods: We recruited 375 premenopausal women, with no history of cancer, who had routine screening mammography at the Breast Health Center, Washington University in St. Louis in 2016. We used Volpara to measure MD: volumetric percent density (VPD), dense volume (DV) and non-dense volume (NDV). In addition to known breast cancer risk factors, all participants completed a detailed questionnaire on milk intake (skim milk and 1%/2% milk were categorized into 4 groups: < once/week, once/week, 2-6 times/week, ≥ once/day; whole and soy milk were categorized into 2 groups: < once/week, ≥once/week, because fewer women consumed them). We used multivariable linear regression models (adjusted for age, body mass index (BMI), parity, oral contraceptive use, family history of breast cancer, race) to evaluate the associations between milk intake and log transformed VPD, DV and NDV. Beta coefficients (b) were evaluated and back transformed for easier interpretation. Results: The mean age was 47.5 years (range: 32-58 years), mean VPD was 9.48%, mean DV was 80.69 cm³, and mean NDV was 1079 cm³. Compared with women who drank 1%/2% milk < once/week, VPD was 20% (p-value = 0.003) lower in the once/week group, 14% (p-value = 0.047) lower in the 2-6 times/week group, and 12% (p-value = 0.144) lower in the ≥once/day group. NDV was 19% (p-value = 0.039) lower among women who drank soy milk ≥once/week compared with women who drank < once/week. There were no associations of skim and whole milk with MD. Conclusions: We observed that 1%/2% milk intake was inversely associated with VPD, while soy milk intake was inversely associated with NDV. Further studies on how 1%/2% and soy milk intake impact MD are needed, as this could have implications in breast cancer prevention.

Association between pesticides use and incidence of diffuse large B cell lymphoma (DLBCL). First Author: Alaa Alatham, University of Tennessee Health Science Center, Memphis, TN

Background: Some studies have linked pesticide exposure to risk of developing cancers. However, these studies were limited to single or few pesticides. We analyze association between incidence of DLBCL and all chemicals reported by The United States Geological Survey (USGS). Methods: Using International Classification of Diseases for Oncology (ICD-3) code 9680, patients (pts) diagnosed with DLBCL in 2012 were extracted from Lymphoma leukemia dataset from The Surveillance, Epidemiology, and End Results (SEER) database. Pts were grouped by Federal Information Processing Standards (FIPS) code. United States Census data (www.census.gov) was used to obtain population estimates for each FIPS code in 2012. USGS data (www.usgs.gov) was used to extract quantitative pesticides use in the year of 1992 per FIPS code*. Incidence of DLBCL per FIPS code was calculated then matched to USGS data. SSPP software was used for statistical analysis. Association between level of pesticides use and incidence of DLBCL was analyzed using linear regression. Two tailed P value of < 0.05 on Pearson correlation was used for statistical significance. Results: A total of 2258 pts with DLBCL in 167 counties were identified. Of the 290 chemicals reported by USGS, 65 were excluded due to lack of data. Of the remaining 225, forty showed statistically significant correlation (30 positive and 10 negative) with incidence of DLBCL. Of these chemicals, 8 have moderate or strong correlation with R coefficient > 0.4 (table). Conclusions: Some agricultural chemicals have significant correlation with incidence of DLBCL. This warrants further evaluation of these chemicals as potential carcinogens or protective agents. Analysis of the underlying mechanisms may reveal some common mechanisms.

Cancer Prevention, Hereditary Genetics, and Epidemiology

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The role of adiposity in the association between type 2 diabetes and the risk of breast cancer. First Author: Maria Bota, University of Strathclyde Institute for Global Public Health at iPRI, Ecully, France

Background: Studies have shown an increased risk of breast cancer (BC) among women with type 2 diabetes (T2D). This association could be causal, related to hyperglycaemia or hyperinsulinaemia, or could be triggered by other factors such as obesity and physical inactivity which are known risk factors for T2D and for BC in post-menopausal women. Methods: A meta-analysis was performed to assess the risk of BC in T2D patients compared to non-diabetic women, with special attention to changes in the risk of BC according to BMI. Studies that compared BC incidence in T2D women to the incidence in the general population were selected if they had a prospective design. Studies that compared BC incidence in T2D women to the incidence in the general population were excluded. Summary relative risks (SRR) and 95% confidence intervals (CI) were computed using random-effects models. Results: Eighteen studies were included in the meta-analysis, based on 28,230,143 person-years of follow-up and 320,111 BC cases. Compared to non-diabetic women, the SRR of BC among T2D women was 1.13 (95% CI: 1.04, 1.24). There was a large amount of unexplained heterogeneity of results across studies (I² = 95%), but no indication of publication bias. The risk of BC by BMI category, with a consistently higher risk of BC associated with increasing BMI. In the 9 studies that adjusted for adiposity, the SRR decreased to 1.05 (95% CI: 0.97, 1.14) while the heterogeneity of results across studies reduced to I² = 21%. Only two studies reported data by menopausal status. In contrast, in the 9 studies that did not adjust for adiposity, the SRR increased to SRR = 1.19 (95% CI: 1.01, 1.39), while the heterogeneity remained high (I² = 98%). Five studies reported data for post-menopausal women only, with a SRR of 1.13 (95% CI: 0.89; 1.44) and high heterogeneity (I² = 94%) with one study representing 82% of the weight in the meta-analysis. Conclusions: This analysis indicates an increased risk of BC in T2D women. The effect of the adjustment for adiposity on the SRR was consistently higher for premenopausal women.

1574 Poster Session (Board #145), Sat, 1:15 PM-4:45 PM

Background: Cancer is a leading cause of death in Alaska Native (AN) people. Significant cancer health disparities exist in both incidence and mortality between AN people and the US Whites. Nasopharyngeal cancer (NPC) is the leading cancer disparity among AN people, with an incidence rate 17.3 times higher (2009-2013) and a mortality rate that is 21 times higher (1992-2011) than those in US whites. The etiologic basis for these disparities has not been identified. Methods: To better understand this health disparity, we created an Alaska Native NPC patient database derived from the Alaska Native Tumor Registry and Alaska Native Medical Center Tumor Registry to characterize all cases of NPC in AN people over the last forty years. We identified 186 cases of NPC in AN people from 1976 to 2016 by merging electronic data sets from the Alaska Native Medical Center Tumor Registry and the Alaska Native Tumor Registry, and analyzed, baseline demographics, clinical and pathologic features, patterns of care, and treatment outcomes for this disease for which data were available for analysis. Results: The median age of AN NPC patients was 60 years, and 68% of patients were male. The highest numbers of NPC were Anchorage/Mat-Su, followed by Yukon-Kuskokwim and Norton Sound regions of Alaska. The histologic subtype of NPC by World Health Organization category were 55% of tumors type 3, 25% type 1, and 15% type 2. Most AN patients with NPC presented at advanced AJCC TNM clinical stages at the time of diagnosis with 22% diagnosed at stage I, 10% at stage II, 9% at stage III, and 43% at stage IV. Patients were treated with chemotherapy (62%), radiation (69%), and combinations of chemotherapy and radiation (58%). Median survival for all patients was 2.5 years (95% Confidence Interval 1.9-3.0). Conclusions: This study represents the first characterization of NPC in AN patients. It includes treatment outcomes and survival data, and it may serve as a useful database to develop treatment guidelines and future translational studies to better understand this cancer health disparity.

1575 Poster Session (Board #146), Sat, 1:15 PM-4:45 PM
Prevalence of HIV infection among cancer patients in a Haitian hospital. First Author: Joseph Bernard, Université Notre Dame d’Haiti, Faculté de Médecine et des Sciences de la Santé, Port-Au-Prince, Haiti

Background: Malignancies are nowadays among the main conditions affecting HIV-infected patients. The state of immunosuppression puts these patients at high risk of developing cancer in their lifetime. The objectives of this study were to determine the prevalence of HIV infection among cancer patients and compare the overall mortality rate between the HIV-positive and HIV-negative subpopulations. Methods: A two-year retrospective study was conducted in the cancer program of Innovating Health International (IHI). Included all cancer patients with a known HIV status enrolled from January 1st, 2016 to December 31st, 2017. Date of admission, age, gender, cancer type, stage, antiretroviral therapy status for HIV-infected patients and outcome were the main variables selected for this chart review. HIV infection was tested as a factor associated with mortality. Results: Among the 785 cancer patients selected for this study, 398 (50.7%) had a known HIV status. Thirty (7.5%) of them were HIV-infected, among them 19 women and 11 men. The mean age was 45.9 years (25-69) versus 49.5 years (16-87) for the HIV-negative patients (p = 0.15). There were 11 patients with AIDS-defining cancers (ADC) such as invasive cervical cancer (n = 8) and Non-Hodgkin lymphoma (n = 3). 18 patients had Non-AIDS-defining cancers (NADC) such as head and neck cancers (n = 8), among them 3 oral cancers and 3 ocular cancers, breast cancer (n = 4), penile cancer (n = 2), and one case each of Hodgkin’s lymphoma, lung cancer, ovarian cancer and pancreatic cancer. 1 patient had a carcinoma of unknown primary (CUP). 22 of these 30 patients (73.3%) were already known HIV-infected before their admission and were on antiretroviral therapy, 75% of the staged patients were at stages III or IV of their cancer. The overall mortality rate was 33.3% (95% CI, 17.3% - 52.8%) versus 20.9% (95% CI, 16.9% - 25.4%) for the HIV-negative patients. HIV-infected cancer patients were more likely to die than HIV-negative ones. (Odds ratio = 1.9, p = 0.01). Conclusions: The prevalence of HIV infection among the cancer patients was 7.5% (95% CI, 5.1% - 10.6%), with a predominance of Non-AIDS-defining malignancies. HIV infection was not for this cancer cohort a significant factor associated with mortality.
Prevalence of germline genetic alterations in colorectal cancer patients. First Author: Andrea Cercek, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Although universal screening of all colorectal tumors for Lynch syndrome (LS) is recommended, the prevalence of other germline mutations, with potential clinical implications, in colorectal cancer (CRC) patients is less well-defined. We performed comprehensive germline testing (GT) in a prospective cohort of CRC patients in order to determine the proportion of clinically actionable germline mutations detected by universal tumor-normal sequencing.

Methods: Between 11/2015 to 1/2017, 427 unselected CRC patients were prospectively consented to GT in 76-genes associated with CRC-risk were identified in 14 cases, including 7 high- (4 BRCA2, 1 FLCN, 1 CHEK2) and 23 PGAs in moderate-low penetrance (CHEK2, mono-MUTYH, APC 11307K) CRC-associated risk genes. The prevalence of moderate/high PGAs was 12.5% (20/160) versus 6% (17/267) in patients with CRC age ≥50 versus age > 50, respectively (p-value = 0.045). LS accounted for 12 (60%) and 5 (30%) of high or moderate mutations in the age ≤50 versus age > 50 groups. All LS-associated tumors exhibited concordant tumor findings with high-frequency microsatellite instability, deficient mismatch repair protein expression, or high mutational load. Seventeen (31%) of patients with PGAs were present in 55 (13%) of CRC patients including 24 PGAs in high-penetrance (MLH1, MSH2, MSH6, EPCAM, PMS2) and 23 PGAs in moderate-low penetrance (CHEK2, mono-MUTYH, APC 11307K) CRC-associated risk genes. The prevalence of moderate/high PGAs was 12.5% (20/160) versus 6% (17/267) in patients with CRC age ≤50 versus age > 50, respectively (p-value = 0.045). LS accounted for 12 (60%) and 5 (30%) of high or moderate mutations in the age ≤50 versus age > 50 groups. All LS-associated tumors exhibited concordant tumor findings with high-frequency microsatellite instability, deficient mismatch repair protein expression, or high mutational load. Seventeen (31%) of patients with PGAs did not meet current guidelines for GT. PGAs not traditionally associated with CRC-risk were identified in 14 cases, including 7 high- (4 BRCA2, 1 FLCN, 1 NF1, 1SDHA) and 7 moderate-penetrance (3 BRIP1, 3 ATM, 1 HBO131) genes. Correlative tumor data, including assessment of somatic mutations and absence of heterozygosity at the genetic site corresponding to germline mutations will be presented. Conclusions: Although the prevalence of PGAs is higher in patients with young-onset CRC (<50), LS accounts for the vast majority of germline mutations in these patients. Analysis of PGAs not traditionally associated with CRC will be correlated with causality versus incidental findings will be performed.

Impact of pre-surgical germline multigene panel testing on choice of surgery for breast cancer. First Author: Elena Zarcaro, Massachusetts General Hospital Cancer Center, Boston, MA

Background: Knowledge of hereditary risk-associated mutations may impact primary surgical decision-making for breast cancer (BC) patients (pts). Since 2015, all new pts seen in the Massachusetts General Hospital (MGH) multidisciplinary BC clinic have been screened by genetic counselors (GCs) for rapid GC consultation and multigene panel testing. We sought to determine the impact of pre-surgical BC multigene panel testing on the timing and type of surgery.

Methods: All pts screened and tested by the MGH GCs from July, 2016 through December, 2017 were identified, and only those who had surgery at MGH were included. Pts may have had genetic testing prior to initial visit at our institution. Screening criteria for rapid GC consultation included personal or family history of BC with the following features: age < 45, triple negative age < 60, male, Ashkenazi Jewish descent, or ovarian ca. Surgical and genetic testing outcomes were collected by retrospective chart review and Fishers exact test was used for statistical analysis.

Results: During our study period, 1341 eligible pts were screened in the MGH multidisciplinary BC clinic. Of 628 pts who met genetic testing criteria, 588 (93.6%) were tested and 50 (8.5%) were positive for a germline mutation including 16 BRCA1, 10 BRCA2, 8 ATM, 8 CHEK2, 5 PALB2 and 1 each of TP53, BRIPI, and RAD51C. In 24 pts with BRCA1/2 mutations who had genetic results prior to surgery, 21 (87.5%) had upfront bilateral mastectomies (BM). In 21 pts who tested positive for other germline mutations before surgery, 14 (66%) had upfront BM. In a cohort of 120 pts with negative test results before surgery, only 37 (30.8%) had upfront BM (p < .05 compared to BRCA1/2 and other germline mutations). Conclusions: Screening newly diagnosed BC pts for rapid GC consultation and testing prior to surgery successfully identified pts with germline mutations in our population. Pts with BRCA1/2 mutations had a higher rate of BM than gene-negative pts and pts with other germline mutations also had a higher rate of BM. Further studies should explore factors influencing pre-operative decision-making in the context of non-BRCA1/2 germline mutations to assess concordance with guideline recommendations.

Poster Session (Board #148), Sat, 1:15 PM-4:45 PM

Genetic testing and results in population-based breast cancer patients and ovarian cancer patients. First Author: Allison W. Kurian, Stanford School of Medicine, Stanford, CA

Background: Genetic testing for cancer risk has expanded rapidly, with more genes tested. Little is known about test use or pathogenic variant (PV) prevalence among population-based cancer patients. Methods: Women aged ≥20 years, diagnosed with breast or ovarian cancer in 2013-14 and reported to SEER registries covering the entire populations of Georgia and California, were included. Registry data were linked to clinical genetic testing results, performed from 1/1/2012 through 4/30/2016, by 4 laboratories that did nearly all cancer genetic testing in these states. Results: There were 77,085 breast cancer and 6,001 ovarian cancer patients, with almost 30,000 patients of racial groups other than non-Hispanic (NH) White. One-quarter (24.1%) of breast and one-third (30.9%) of ovarian cancer patients had genetic test results. While test use was similar across racial groups for breast cancer, testing in ovarian cancer patients was lower in NH Blacks (21.6%, CI 18.2-25.4%), vs NH Whites: 33.8%, CI 32.3-35.4%). The most prevalent PVs in breast cancer patients were BRCA1 (3.2%), BRCA2 (3.1%), CHEK2 (1.6%), PALB2 (1.0%), ATM (0.7%), NBN (0.3%) and TP53 (0.3%) and in ovarian cancer patients, BRCA1 (8.7%), BRCA2 (9.8%), CHEK2 (1.4%), BRIPI (0.9%), MSH2 (0.8%), ATM (0.6%) and RAD51C (0.6%). Racial differences in PVs included BRCA1 (ovarian cancer: NH Whites, 7.2%, CI 5.9-8.8%; Hispanics, 16.1%, CI 11.8-21.2%) and CHEK2 (breast cancer: NH Whites, 2.3%, CI 1.8-2.8%; NH Blacks, 0.2%, CI 0.0-0.8%). Among those tested for all genes designated by the National Comprehensive Cancer Network as associated with their cancer type (breast: ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, TP53; ovarian: BRCA1, BRCA2, BRIPI, EPCAM, MLH1, MSH2, MSH6, PMS2, STK11, RAD51C, RAD51D), 7.7% of breast and 14.5% of ovarian cancer patients had genetic test results. Conclusions: Knowledge of hereditary risk-associated mutations may impact clinical and somatic findings. Correlative tumor data, including assessment of somatic mutations and absence of heterozygosity at the genetic site corresponding to germline mutations will be presented. Although the prevalence of PGAs is higher in patients with young-onset CRC (<50), LS accounts for the vast majority of germline mutations in these patients. Analysis of PGAs not traditionally associated with CRC will be correlated with causality versus incidental findings will be performed.

Poster Session (Board #150), Sat, 1:15 PM-4:45 PM

Mosaic TP53 pathogenic variants on multi-gene hereditary cancer panel testing: Clinical characteristics and follow-up testing. First Author: Sarah A. Jackson, GeneDx, Inc., Gaithersburg, MD

Background: Li-Fraumeni Syndrome (LFS) is an autosomal dominant cancer susceptibility syndrome due to germline pathogenic variants in TP53 and is associated with a significant risk for sarcomas, female breast, and other cancers. A subset of individuals undergoing germline TP53 analysis will have a variant with an allele fraction (AF) less than that in heterozygous individuals, consistent with mosaicism. TP53 mosaicism may be limited to hematopoietic cells, such as in age-related hematopoietic expansion, or may be constitutional, in which case the variant exists in additional tissues and may increase LFS-associated cancer risks. This study aims to characterize the clinical characteristics and follow-up results of cases with a TP53 mosaic pathogenic or likely pathogenic variant (PV). Methods: We performed a retrospective review of all individuals undergoing multi-germ hereditary cancer panel testing at our diagnostic laboratory. Cases included those with mosaicism for one or more TP53 PV, characterized as an AF of < 35.0% on next-generation sequencing (NGS) on a blood or oral rinse specimen. Data were analyzed utilizing descriptive statistics and hypothesis tests, including Fisher’s exact test. Results: We identified 117 TP53 mosaic PV cases. Among 37 cases that had one or more relatives undergo testing for the mosaic PV, no relatives were positive. Among 21 cases that underwent subsequent fibroblast (FB) testing, 19.0% (4/21) correlated with the initial mosaic result, suggesting constitutional mosaicism. Of those that confirmed on FB, the mean AF for the original sample was 28.3% (n = 4; SD = 3.2%), whereas the mean for those negative on FB was 18.5% (n = 17; SD = 6.3%). Confirmation of mosaicism on FB was associated with an initial NSG AF ≥ 25.0% (p = 0.0276; FB Pos: 3/4, FB Neg: 2/17) and with a personal history of a breast cancer or sarcoma diagnosed < 46 years (p = 0.0276; FB Pos: 3/4, FB Neg: 2/17). Conclusions: Although NGS is not purely quantitative, apparent constitutional mosaicism appears to correlate with higher AF on NGS. In addition, phenotypes of cases with TP53 mosaicism confirmed via FB are more suggestive of LFS. Further studies are required to establish clinical correlation.
**Background:** Cancer screening guidelines recommend that germline carriers with a pathogenic variant (PV) in a breast cancer susceptibility gene undergo more intensive breast screening including breast magnetic resonance imaging (MRI). We assessed the impact of genetic counseling and MGPT on adherence to recommended screening. **Methods:** In a prospective cohort study of 2000 patients undergoing MGPT, patients completed self-administered questionnaires to document breast cancer screening within one year of testing. Patients were surveyed at 3, 6, and 12 months after genetic results disclosure. Multivariable logistic regression was used to analyze an association between MGPT result and breast MRI after adjusting for study center, personal history of breast cancer and personal history of breast surgery. **Results:** 2000 patients completed MGPT and 1532 (77%) completed at least one follow-up survey. 242 (12%) tested positive for at least 1 PV in any one of 25 (or 28) genes. MGPT identified a PV in the following increased risk breast cancer genes: *BRCA1* (n = 41), *BRCA2* (n = 36), *CHEK2* (n = 17), *ATM* (n = 16), *APN* (n = 17), *PMS2* (n = 10), *PALB2* (n = 9), *TP53* (n = 6), and *CDH1* (n = 1). Within 1 year, patients with a PV (OR = 2.1, 95% CI [1.45-3.15], p < 0.001) were 2.1 times more likely to undergo MRI versus those testing negative. Patients with a PV in *BRCA1* (OR = 3.5, 95% CI [1.96-6.33], p < 0.001) or a moderate risk breast cancer gene (*CHEK2, ATM, NBN*) (OR = 3.3, 95% CI [1.30-8.15], p = 0.012) were three times more likely to have MRI versus those testing negative. Patients with a PV in other high risk breast cancer genes (*PALB2* or *CDH1*) were 9 times more likely to undergo MRI (OR = 9.5, 95% CI [0.76-15.97], p = 0.107) versus those testing negative, but the results did not reach statistical significance. There was no difference in Breast MRI (OR = 1.0, 95% CI [0.78-1.37], P = 0.814) use among those with a variant of uncertain significance (VUS) versus those with negative results. **Conclusions:** MGPT and genetic counseling prompted patients with a *BRCA1* to appropriate adoption and adherence to breast cancer screening. There was no difference in screening between those with VUS or negative results. Clinical trial information: NCT03240622.

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**Promoting colorectal cancer (CRC) screening after multiplex genetic testing and genetic counseling. First Author: Gregory Idos, USC Norris Comprehensive Cancer Center, Los Angeles, CA.**

**Background:** Cancer screening guidelines recommend that germline carriers with a pathogenic variant (PV) in a CRC susceptibility gene should undergo more frequent colonoscopy screening. We assessed the impact of genetic counseling and multiplex genetic panel testing (MGPT) on adherence to colonoscopy screening. **Methods:** In a prospective cohort study of 2000 patients undergoing MGPT, patients completed self-administered questionnaires to document colon cancer screening within one year of testing. Patients were surveyed at 3, 6, and 12 months after genetic results disclosure. Multivariable logistic regression was used to analyze an association between MGPT result and colonoscopy after adjusting for study center, personal history of colorectal cancer and personal history of colorectal surgery. **Results:** 2000 patients completed MGPT and 1622 (81%) completed at least one follow-up survey. 242 (12%) tested positive for at least 1 PV in any one of 25 (or 28) genes. High risk CRC gene mutations were in *PM2* (n = 11), *MLH1* (n = 10), *MSH2* (n = 8), *EPCAM* (n = 1), *TP53* (n = 6), *Biallelic MUTHY* (n = 2), *APC* (n = 3). Moderate risk CRC mutations were in *MO21* (n = 1), *CDH1* (n = 1), and *APC I1307K* (n = 16). Within 1 year of testing, patients with a PV were twice more likely (OR = 2.0, 95% CI [1.33, 2.92], p < 0.001) and patients with a VUS were as likely (OR = 1.2, 95% CI [0.86, 1.62], p = 0.312) to have a colonoscopy as compared to patients with a negative test result. Patients identified to carry a PV in a mismatch repair gene (*MLH1, MSH2, MSH6*) (OR = 3.3, 95% CI [1.66-7.91], p = 0.001) or a PV in *APC, Biallelic MUTHY, or TP53* were 3x (OR = 10.1, 95% CI [1.80-57.29], p = 0.009) more likely to undergo colonoscopy. **Conclusions:** With a moderate risk gene were 3x (OR = 3.3, 95% CI [1.79-5.95], p < 0.001) more likely to undergo colonoscopy.

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**Examining patients’ medical and psychosocial experiences following detection of a CDH1 variant with multiplex genetic testing. First Author: Jada Hamilton, Memorial Sloan Kettering Cancer Center, New York, NY.**

**Background:** Germline CDH1 mutations are associated with hereditary diffuse gastric cancer and lobular breast cancer. We conducted a cross-sectional, self-report survey to understand genetic testing experiences, medical management, and psychosocial adaptation among patients with a *CDH1* variant. **Methods:** We recruited participants from the Prospective Registry of Multiplex Testing (PROMPT), an online genetic registry. We invited individuals with a *CDH1* variant to complete a survey of validated and investigator-designed items. We computed descriptive statistics, and used t-tests and chi-square tests to compare responses of individuals with pathogenic variants (PV) or variants of uncertain significance (VUS) versus those with negative results. **Conclusions:** MGPT and genetic counseling prompted patients with a PV in a high risk CRC gene to appropriate adoption and adherence to colonoscopy screening. In contrast, there was no difference in colonoscopy screening among those with a VUS or negative results. These findings demonstrate genetic testing and counseling can encourage appropriate CRC screening. Clinical trial information: NCT03240622.

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**Impact of germline BRCA1 identification on subsequent breast cancer stage and therapy: Implications for routine screening. First Author: Tal Hador, Sharee Zedek Medical Center, Jerusalem, Israel.**

**Background:** Screening healthy Ashkenazi Jews (AJ) for germline *BRCA1/BRCA2* mutations (gBRCA) is not standard policy, despite high (2.5%) carrier rates. Most carriers are identified only after breast cancer diagnosis. We hypothesized that pre-symptomatic knowledge of carrier status would favorably affect breast cancer stage and management. **Methods:** We reviewed records of gBRCA carriers who did not undergo risk-reduction mastectomy and were diagnosed with breast cancer between 4/1996-4/2016. Patient age, parity, family history, genotype, screening compliance, breast cancer detection, disease characteristics and treatment (breast and axillary surgery, chemotherapy) were compared between carriers whose gBRCA was identified pre-breast cancer vs. post-breast cancer. **Results:** 165 females with gBRCA and breast cancer were identified, of whom carrier status was determined pre-breast cancer in 45 (27%) and post-breast cancer in 120 (73%); both groups had similar mean age at cancer diagnosis (50.6y vs. 50.5y, range 27-86) and *BRCA1*/*BRCA2* distribution (64%/36% and 65%: 35%). Pre-breast cancer carriers were significantly (p < 0.001) more likely to have a suggestive family history (30% vs. 62%), prior breast cancer screening (78% vs 60%), and breast cancer diagnosis by imaging (78% vs 25%) rather than clinical symptoms (19% vs 73%). Pre-breast cancer carriers had a higher DCIS: invasive breast cancer presentation (40%/60% vs. 2%/98% in post-breast cancer) and lower stage (p < 0.005). No differences in tumor grade, ER or HER2 status were identified. Pre-breast cancer carriers were more likely to undergo sentinel lymph node biopsy (91% vs 45%), less likely to receive chemotherapy, and more likely to elect bilateral mastectomies (62% vs 10%) than post-breast cancer carriers (p <.001 for all comparisons). Overall, pre-breast cancer gBRCA identification and routine screening predicted for early stage (0-I) breast cancer diagnosis (p < 0.001, OR 16.8).

**Conclusions:** Presymptomatic identification of gBRCA status is significantly associated with earlier stage breast cancer diagnosis, requiring less extensive treatment. This supports routine gBRCA testing in all healthy AJ women.
Implementing genetic risk assessment in a community free clinic. First Author: Leah Marsh, Cedars-Sinai Medical Center, Los Angeles, CA

**Background:** Assessment of hereditary cancer risk plays an integral role in reproductive healthcare, ACOG and NCCN recommend that OB/GYNs assess hereditary cancer risk annually. The Saban Community Clinic is an inner-city, not-for-profit, free clinic in Los Angeles, California, serving a predominantly non-white, uninsured patient population of low socioeconomic status (SES) with no access to genetic counseling. Prior to this study, no formal cancer family history was elicited. **Methods:** We adapted a bilingual screening tool developed at the UCSF Cancer Risk Program that is compliant with NCCN and ACOG guidelines. It relies on fact recall that patients can complete independently assuming low health literacy. Clinic providers were briefed on the project and distribution commenced in April of 2017. The questionnaires were scored and entered into a secured database. **Results:** Between April 2017-January 2018, a total of 98 questionnaires were collected. Ages ranged from 19-67. Thirty-two percent (32%) of the patients identified as Hispanic. Of those who identified as non-Hispanic, only 3 of these identified as White, the others identified as Asian or Black. Twenty-one percent (21%) of the forms were completed in Spanish. First degree relative with ovarian cancer and/or multigeneration presence of breast cancer accounted for 11% of the patients who screened “positive” for referral to further genetic counseling. **Conclusions:** This study sought to 1) determine the feasibility of implementing a brief genetic risk screening tool and 2) assess the unmet need for referral to genetic counseling/testing in a community clinic serving predominantly non-white, low SES patients without health insurance. The preliminary data is promising that a patient administered survey can aid clinicians in identifying patients for referral. It also demonstrates the unmet need in this population, with 32% of these patients meeting criteria for referral. This tool identified an important area of health inequity in cancer prevention in this population.

Value of germline multi-gene panel next generation sequencing (NGS) in identification of hereditary cancer syndromes (HCS) in colorectal cancer population (CRC). First Author: Jing Gu, University of Southern California, Los Angeles, CA

**Background:** Identification of HCS in probands (PB) provides a mechanism for cancer screening and prevention in 1st degree relatives (FDR). Lynch syndrome (LS) is the most common HCS in CRC. However, other HCS known to increase risk of breast and ovarian cancers (BC/OC) have been reported in CRC. We evaluated the value of NGS vs. tumor immunohistochemistry followed by MMR gene sequencing (T-MMR) in a CRC cohort with > 5% probability of HCS based on a predictive model. **Methods:** In a modeled cohort of CRC patients, those with over 5% probability of HCS by MMRpro are assessed using either T-MMR or NGS. FDR of PB with a HCS are offered target genetic testing for the known mutation. The output of this population is input in a Markov model, which simulates the life history of FDR to calculate their costs and quality adjusted life years (QALYs). This model incorporates the effects & costs of cancer screening strategies, preventive procedures, and treatments. The model has 3 states: cancer free, diagnosed with cancer, and deceased; subjects transition among these states based on their known cancer risk and US life tables. Our model takes a US societal perspective and a 3% annual discount rate for both costs and QALYs. **Results:** For a cohort of newly diagnosed CRC with US epidemiology, 27,775 individuals had a MMRpro score > 5%. T-MMR identified 2,584 (9.3%) PB with LS and subsequently 1,915 FDR with LS and 516 false negative relatives. With NGS, 8,076 (29.1%) PB with a HCS are identified, and 5,984 FDR tested positive for a HCS; including 3,814 with a mutation in a CRC associated gene and 2,170 with BC/OC associated gene mutation. The T-MMR arm failed to identify 2,929 PB and 4,393 FDR with a BC/OC associated gene mutation. Testing for T-MMR arm yields 649,874 QALYs while NGS arm yields 671,507 QALYs for CRC. Total costs are $1,215,670,597 for T-MMR tested group vs. $1,036,167,834 for NGS tested group, defining NGS as the dominant strategy for testing for HCS. One-way sensitivity analysis shows robust results. **Conclusions:** Compared to the T-MMR testing for LS, using a multi-gene NGS panel that included BC/OC cancer risk genes for HCS among CRC patients increases QALYs and saves costs.

The incidence of germline cancer susceptibility mutations in primary CNS neoplasm patients. First Author: Katharine Lord, Texas Oncology - Austin Brain Tumor Center, Austin, TX

**Background:** Genomic profiling is performed on primary brain (CNS) tumors to identify somatic mutations. Several syndromes, (e.g. Neurofibromatosis) are well known causes of CNS neoplasms but data is limited on other germline cancer susceptibility mutations in CNS tumor patients. After a somatic mutation was unexpectedly found to be germline, we interrogated our database of somatic CNS tumor mutations. **Methods:** This IRB approved study reviewed patients at our center from May 2013 - November 2017. Tumors from 319 patients underwent next generation sequencing. At least 1 somatic mutation on a gene of interest was found in 208 tumors; 108 patients were deceased prior to study start. Of the remaining 100 patients, 28 were offered germline testing. **Results:** 26 patients completed germline testing: 12 had germline mutations (12%), 6 had germline variants of uncertain significance (6%) and 8 had negative germline testing (8%). Germline mutations were identified in the following genes: BRCA2 (3 patients), CHEK2 (4 patients), APC (3 patients), ATM (3 patients), MUTHY (2 patients), PMS2 (2 mutations in 1 patient). Of the 12 patients with germline mutations, five (41.6%) did not meet guidelines for hereditary cancer genetic testing. As a result of the germline findings, medical management was altered and additional family members with pathogenic mutations were identified. **Conclusions:** Based on somatic and germline mutational data from 319 CNS tumor patients, we estimate 5.8% of all CNS tumor patients (without an obvious CNS tumor syndrome) carry a germline cancer susceptibility mutation. Twelve percent of patients whose tumor contains a possible “germline” interest carry a germline cancer susceptibility mutation. Pathogenic germline variants were identified in the following genes: BRCA2, CHEK2, APC, ATM, MUTHY and PMS2. Five percent (4.3%) did not meet recognized criteria for germline cancer genetic testing, thus without the somatic data, would have been overlooked. Nearly 50% of CNS tumor patients with germline cancer susceptibility mutations are overlooked when using routine testing criteria; tumor genomic profiling is the only means for identifying these undiscovered germline mutations.
Incidence of pathogenic variants in individuals with a personal or family history of pancreatic cancer. First Author: Pashtoon Murtaza Kasi, Mayo Clinic, Jacksonville, FL

Background: Genetic testing related to pancreatic cancer is expanding. Many companies offer a multi-gene panel with a focus on pancreatic cancer. The purpose of this study was to evaluate the incidence and types of pathogenic variants detected in individuals with a personal and/or family history of pancreatic cancer. Methods: The genetic test results of patients visiting a genetic counselor at Mayo Clinic Florida from January 2012 to February 2018 were examined. Clinical and laboratory data were obtained through chart review. Results: Of the 2038 patients that completed testing, 223 (10.9%) were diagnosed with a hereditary cancer syndrome. 59 were referred due to personal history of pancreatic cancer, of which 3 (5.1%) were found to carry a germline mutation in BRCA1/2. One additional patient was found to carry a mosaic pathogenic variant in ATM. Of the 285 that reported any family history of pancreatic cancer, 35 (12.3%) carried a pathogenic variant. These variants were present in APC (3), ATM (4), BRCA1 (5), BRCA2 (13), CHEK2 (5), MSH6 (1), NBN (1), PALB2 (3), and PRSS1 (1). The incidence of pathogenic variants nearly doubled (21.4%) if the individual had at least two relatives with a history of pancreatic cancer. Conclusions: It has been difficult to determine who may benefit from pancreatic cancer screening, but identifying a pathogenic variant in an individual with a family history of pancreatic cancer is sometimes enough evidence to suggest surveillance. Gathering family history is an important piece of evaluating value of pancreatic cancer screening.

Number of individuals diagnosed with a hereditary cancer syndrome who had a personal and/or family history of pancreatic cancer.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of positives/Total (%)</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of pancreatic cancer</td>
<td>3/459 (0.6%)</td>
<td>ATM1, BRCA1 (2), BRCA2</td>
</tr>
<tr>
<td>Family history of pancreatic cancer</td>
<td>36/285 (12.6%)</td>
<td>APC2 (3), ATM (4), BRCA1 (5), BRCA2 (13), CHEK2 (5), MSH6, NBN, PALB2 (3), PRSS1 (1)</td>
</tr>
<tr>
<td>Family history of 2+ relatives with pancreatic cancer</td>
<td>12/56 (21.4%)</td>
<td>APC2 (2), ATM (2), BRCA1 (2), BRCA2 (4), CHEK2 (2)</td>
</tr>
</tbody>
</table>

1Apparently mosaic pathogenic variant in ATM. 2The APC Ashkenazi Jewish Founder mutation, 11307X.

Referral patterns and attrition rate for germline testing in pancreatic cancer (PC) patients. First Author: Evan Justin Walker, University of California San Francisco, San Francisco, CA

Background: Hereditary predisposition is estimated to account for 10% of all PC cases. Identification of pathogenic germline mutations can inform not only screening recommendations for family members but also, increasingly, treatment selection for pts. However, referral patterns and clinical workflow for germline testing in this disease differ significantly by institution, and many pts may not undergo recommended testing for a variety of reasons. Methods: We performed a retrospective review of all pts diagnosed w/ PC referred to our University of California, San Francisco Clinical Genetics program over a 3-yr period (1/2015 – 10/2017). Medical records were reviewed for demographic, medical/family history, and disease-specific data as well as genetic testing results. If testing did not occur, the reason was documented. Results were categorized as negative, variants of unknown significance (VUS), or established pathogenic mutations. Descriptive statistics included means with standard deviations (SD); associations were documented. Results: Of the 4104 pts seen at UCSF w/PC dx were referred to Clinical Genetics during this time period. Of these, only 64% attended the appt and 60% ultimately underwent germline testing. Reasons for attrition inc. lack of pt f/u (n = 20), worsening disease severity (n = 11), insurance concerns (n = 7), and logistic/travel difficulties (n = 6). Pathogenic germline mutations were detected in 20% (n = 16) of pts tested [CFTR (n = 4), BRCA2 (n = 3), CHEK2 (n = 2), ATM (n = 2), MLH (n = 1), MUTHY (n = 1), other (n = 3)]; while 48% (n = 39) of pts had ≥1 VUS. Confirmed pathogenic mutations in our cohort were distributed across races/ethnicities, and assoc w/ younger age (mean age 53.3 vs 60.5 y, p = 0.02) and FxHs of breast cancer (p = 0.05). Conclusions: PC pts frequently do not undergo genetic counseling/germline testing despite appropriate referrals, highlighting the need to develop streamlined processes to engage more pts in testing, esp those w/ high-risk features such as young age and (+) FxH of cancer. Based on these data, our Center plans to pilot a genetic testing station for all new PC pt visits, incorporating both same-day testing and flu remote counseling.

Implementation of strategies to increase genetic counseling referral rates for ovarian cancer patients. First Author: Kara J. Milliron, University of Michigan, Ann Arbor, MI

Background: Genetic counseling is recommended for all women diagnosed with epithelial ovarian cancer, independent of family history. Despite the potential benefits to the patient and her family, referral rates remain low. We sought to assess referral rates at our institution and implement two strategies to improve both the rate of referral and the completion of counseling and testing – (1) discussion of referral for all patients reviewed at multidisciplinary treatment planning conference and (2) option of telephone counseling. Methods: Patients with a diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer since 10/1/14 were identified through pathology reports and chart review was performed to obtain demographic data and cancer details including histology, grade and stage. Personal and family history of cancer, date of genetic counseling referral, method of genetic counseling (in-person vs. telephone), date of genetic testing and the result of genetic testing were also abstracted. Results: The rate of genetic counseling referral was 63.5% (214/337 patients). Of those referred, 61% (131/214) underwent counseling, with 77% (165/214) in person and the 23% (49/214) via telephone counseling program in September 2017. Overall, 90% of patients who received genetic counseling underwent testing, including 92.7% of the in-person counseling cohort and 67.9% of the telephone counseling cohort to date. In total, 24.1% of patients harbored a pathogenic gene mutation, with 83.3% (p = 0.001) and 77.4% (p = 0.05) of patients detected. Variants of unknown significance were identified in 11.3% of patients. Conclusions: Telephone genetic counseling and mandatory discussion of referral at the time of treatment planning conference both appear to facilitate genetic counseling and ascertainment of actionable germline mutations. Overall, referral rates are high at our institution. The implementation of telephone-based genetic counseling programs has the potential to improve both counseling and testing rates, particularly when in-person counseling is not available or is delayed.

The impact of genetic counseling on patients' knowledge about tumor genomic profiling. First Author: Rebecca D. Pentz, Emory University School of Medicine, Atlanta, GA

Background: Molecular testing is increasingly being integrated into cancer management. However, despite rapid advancements in this area, little work has been done to explore strategies for communicating genomic information to patients undergoing tumor profiling. This study evaluated the impact of an educational tool combined with genetic counseling on patients’ understanding of key terms related to tumor genomic profiling. Methods: A genetic counseling intern designed a picture book to explain six words found in prior research to be difficult for patients to understand: mutation, germline mutation, somatic mutation, biomarker, molecular testing, and targeted therapy. The picture book was cognitively tested with oncology patients and revised. After consent, patients who had previously discussed molecular testing with their oncologist were asked to define the six words in their own terms. The same patients then received an explanation of each word from the intern using the picture book, and were asked to redefine each word directly afterwards. All definitions were scored for correctness by two independent coders. The proportion of patients who defined each term correctly and total knowledge scores were compared before and after genetic counseling. Results: Twenty-eight patients with melanoma, colon, lung, or breast cancer were recruited. Correct understanding rates improved for all six terms, with significant improvement for germline mutation (p < 0.001), somatic mutation (p < 0.001), biomarker (p < 0.001) and molecular testing (p < 0.001). Mean total knowledge score significantly improved from 30% to 83.3% (p < 0.001). Conclusions: Our data suggest that the use of a simple educational tool combined with genetic counseling in the setting of genomic tumor testing increases patient knowledge and may improve the process of informed consent. Future studies are warranted to determine the feasibility of providing in person genetic counseling in this setting and whether the picture book can be effectively used by other advanced practice providers with knowledge of genomics.
Incidence and risk of second primary malignancy after an index potentially-human papillomavirus-associated cancer.

**Background:** Approximately 39,000 HPV-associated cancers are diagnosed annually in the US. Oncogenic HPV-infections are associated with virtually all cases of cervical, 95% of anal, 73% of oropharyngeal, 65% of vaginal, 50% of vulvar, and 35% of penile cancers. Cancer survivors are at increased risk of a second primary malignancy (SPM). We assessed the risk of developing a SPM after an index potentially-HPV-associated cancer (P-HPV-AC) developing a SPM after an index potentially-HPV-associated cancer. This population-based cohort study of patients with P-HPV-AC in the Surveillance, Epidemiology, and End Results registry (2000-2014). Only patients with invasive P-HPV-AC (cervical, vaginal, vulva, penile, anal canal, and oropharynx) per International Classification of Diseases, 3rd edition, were included. SPM was defined as the first subsequent primary cancer occurring at least 2 months after first cancer diagnosis. Excess SPM risk was quantified using standardized incidence ratios (SIRs) stratify by gender. Results: A total of 100,960 patients with an index P-HPV-AC were identified, and 7.37% developed a SPM overall. In all P-HPV-AC patients, the overall SIR was 1.72 (95% CI: 1.68–1.76). All index P-HPV-AC sites presented with a statistically significant increase in the risk of SPM. Among males, the greatest increase in risk of SPM was observed among patients diagnosed with an index P-HPV-AC oropharynx (SIR = 1.83; 95% CI, 1.76–1.90). Among females, the greatest increase in risk of SPM was observed among patients diagnosed with an index P-HPV-AC oropharynx (SIR = 2.47; 95% CI, 2.29–2.65). Conclusions: HPV cancer survivors experience significantly excess risk of SPM; thereby calling for a more effective program for surveillance of patients with HPV-associated cancers.

<table>
<thead>
<tr>
<th>Cancers</th>
<th>SIR Observed</th>
<th>Rate 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All potentially-HPV-associated cancers</td>
<td>7.447</td>
<td>1.72</td>
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<tr>
<td>Male and female</td>
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<td></td>
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<tr>
<td>Oropharynx (head and neck)</td>
<td>3.240</td>
<td>1.91</td>
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<tr>
<td>Anal</td>
<td>1.131</td>
<td>1.52</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx (head and neck)</td>
<td>2.672</td>
<td>1.83</td>
</tr>
<tr>
<td>Anal</td>
<td>4.53</td>
<td>1.48</td>
</tr>
<tr>
<td>Female</td>
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<td></td>
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<tr>
<td>Oropharynx (head and neck)</td>
<td>5.68</td>
<td>2.42</td>
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<tr>
<td>Anal</td>
<td>6.78</td>
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<tr>
<td>Cervix</td>
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<tr>
<td>Vaginal</td>
<td>6.18</td>
<td>2.33</td>
</tr>
<tr>
<td>Vulvar</td>
<td>190</td>
<td>1.78</td>
</tr>
</tbody>
</table>

**Methods:** We assessed the risk of a second primary malignancy (SPM) among patients diagnosed with an index P-HPV-AC oropharynx (SIR = 2.47; 95% CI, 2.29–2.65). Conclusions: HPV cancer survivors experience significantly excess risk of SPM; thereby calling for a more effective program for surveillance of patients with HPV-associated cancers.

**TPS1594 Poster Session (Board #165a), Sat, 1:15 PM-4:45 PM**

Evaluating intermittent dosing of aspirin for colorectal cancer prevention.

First Author: Katrina M. Alber, Northwestern University, Chicago, IL

**Background:** Colorectal cancer (CRC) remains the 4th most common cancer in the United States. Thus the identification of effective and safe prevention methods remains important. While long-term use of COX-2 inhibitors, NSAIDs, and aspirin are associated with a reduced risk of CRC, the cardiovascular (CV) toxicity of COX-2 inhibitors and NSAIDs inhibits use in the prevention setting. Aspirin (ASA) does not confer risk of CV side effects and is a promising chemopreventive agent for CRC, but risks include gastrointestinal side effects and bleeding. Preclinical data suggest that intermittent dosing of aspirin would retain efficacy, with reduced toxicity [Mohammed, AACR 2018, NCI-N01-CN-250026].

**Methods:** This ongoing double-blind placebo-controlled randomized trial will enroll 90 subjects (men and women) to three arms: daily oral ASA 325 mg for 12 weeks (N = 40); intermittent aspirin 325 mg daily (4 cycles, alternating 3 weeks aspirin/placebo for a total of 12 weeks, N = 40); or daily placebo for 12 weeks (N = 10). The primary objective is to test for the equivalence of the two aspirin schedules, as demonstrated by similar changes in the ratio of cell proliferation to apoptosis in rectal biopsy samples (Ki67: Bax). Secondary endpoints include spectral markers of colon cancer risk and DNA methylation changes. Eligibility requirements include a history of colorectal adenoma (any grade), and no history of the following: invasive malignancy in the past 2 years; chronic renal or liver disease; unstable angina, hemorrhagic stroke or uncontrolled hypertension; anemia, peptic ulcer, gastrointestinal bleeding, active colitis, or inflammatory bowel disease. Participants must not have taken aspirin, other NSAIDs, or COX-2 inhibitors 3 weeks prior to the intervention; alcohol use < 2 drinks/day. They will undergo blood draws and rectal biopsies at entry, at 9 weeks, and at end of intervention. A 3-month follow-up visit is planned. Statistical analyses will be based on 32 evaluable subjects in each of the two aspirin arms (allowing for drop-outs); we will have 81% power to detect a change in the Ki67:Bax ratio of -3.0 to +3.0, based on the standard deviation of similar data from an ongoing trial. Enrollment began in January 2018. Funding: NCI #HHSN261201200035I. Clinical trial information: NCT02965703.

**TPS1595 Poster Session (Board #165b), Sat, 1:15 PM-4:45 PM**

A phase IIb pre-surgical trial of oral tamoxifen (TAM) versus transdermal 4-hydroxytamofoxen (4-OHT) in women with DCIS of the breast.

First Author: Kelly A. Benante, Northwestern University, Chicago, IL

**Background:** Ductal carcinoma in situ (DCIS) is diagnosed in 60,000 women annually in the US. TAM is proven to reduce risk of local recurrence and new primary breast cancer in women with estrogen receptor (ER) positive DCIS. However, acceptance of TAM has been low, primarily because of toxicity related to systemic exposure. Local delivery to the breast is an attractive alternative as low systemic levels could minimize toxicity. 4-OHT is an active metabolite of TAM. When formulated as a gel and applied to the breast, it is well tolerated, and results in 4-OHT breast tissue drug levels comparable to oral TAM. In small pilot studies, its anti-proliferative effects on invasive breast tumors and DCIS are also similar to oral TAM [Lee O, et al. PMID 25028506].

The goal of our study is to validate these results in preparation for a Phase III trial of 4-OHT gel compared to oral TAM. Methods: We are conducting a randomized, double-blind, placebo-controlled, Phase IIb pre-surgical trial to demonstrate that daily application of 4-OHT gel will result in a reduction in the Ki-67 labeling index of DCIS lesions that is not inferior to that seen in women receiving daily oral TAM. Ki-67 of the base-line diagnostic core needle biopsy will be compared to that of the therapeutic surgical excision sample after oral TAM or 4-OHT gel for 8 ± 2 weeks. Secondary endpoints include changes in Oncotype DCIS-Score, IHC markers, hormone levels, coagulation markers, drug concentration in the plasma and breast, and expression changes. Eligibility requirements include a history of colorectal adenoma (any grade), and no history of the following: invasive malignancy in the past 2 years; chronic renal or liver disease; unstable angina, hemorrhagic stroke or uncontrolled hypertension; anemia, peptic ulcer, gastrointestinal bleeding, active colitis, or inflammatory bowel disease. Participants must not have taken aspirin, other NSAIDs, or COX-2 inhibitors 3 weeks prior to the intervention; alcohol use < 2 drinks/day. They will undergo blood draws and rectal biopsies at entry, at 9 weeks, and at end of intervention. A 3-month follow-up visit is planned. Statistical analyses will be based on 32 evaluable subjects in each of the two aspirin arms (allowing for drop-outs); we will have 81% power to detect a change in the Ki67:Bax ratio of -3.0 to +3.0, based on the standard deviation of similar data from an ongoing trial. Enrollment began in January 2018. Funding: NCI #HHSN261201200035I. Clinical trial information: NCT02993159.
Background: The need for treatment personalization is obvious as every cancer is molecularly unique. In addition glioblastoma (GB) are immunologically regarded as resistant, “cold” tumor with few targetable antigens available from mutations, thus demanding new personalized immunotherapies. Methods: The GAPVAC consortium realized an immunotherapy, for which personalized selection of 2 peptide-based actively personalized vaccines (APVAC1) per patient for treatment of newly diagnosed GB was based not only on whole-exome sequencing but also on human leukocyte antigen (HLA)-ligandome analyses providing insight into the actual presentation of relevant epitopes in the tumor. GAPVAC-101 (NCT02149225) enrolled 16 patients in a European phase I feasibility, safety, and immunogenicity trial integrated into standard of care. For APVAC1, up to 7 peptides were selected from a trial specific warehouse based on individual biomarker data. Vaccination (i.d.) with GM-CSF and poly-ICLC in 15 patients started with the 1st adjuvant cycle of temozolomide (TMZ). For APVAC2, analyses revealed a median of 36 somatic, non-synonymous mutations in the patients’ tumors. From the 4th TMZ cycle, 11 patients received APVAC2 with usually 2 matched outcome with tumor genotyping. Clinical trial information: NCT02454634.

Conclusions: Molecular profiling with WES and CMA were performed following surgery. Primary objective: to evaluate the feasibility of genotyping tumors in a time-frame to support real-time use in clinical trials. Comparisons with orthogonal genomic and functional methods were incorporated to inform best practices. Results: As of 1/30/18, 46 patients with GB enrolled among 5 sites. Median age was 60. WES and CMA were completed in 39 patients, with a median time between surgery and biomarker analysis completion of 51 days. Actionable findings, including activating BRAF and FGFR1 mutations were identified in 2 patients, and two tumors were reclassified as non-GB based on genomics. 26 patients with MGMT unmethylated GB were enrolled in INSIGHT, a companion randomized clinical trial of the German Neurooncology Working Group (NOA-16). First Author: Mehdi Touat, Dana-Farber/Cancer Institute, Harvard Medical School, Boston, MA

Background: Hot-spot point mutations in the gene for isocitrate dehydrogenase type 1 (IDH1R132H) are a frequent founder event in gliomas and other tumors. Preclinical studies have defined IDH1R132H as a clonal neoantigen presented on MHC class II to induce tumor-specific therapeutic T helper 1 cell responses. Methods: NOA-16 (NCT02454634) is a first-in-man, multicenter, phase I trial, which enrolled 33 patients with newly diagnosed WHO III and IV astrocytomas with IDH1R132H mutations. After completion of radiochemotherapy a total of eight vaccinations with an IDH1R132H peptide in incomplete Freund’s adjuvant produced at a central GMP site was to be administered subcutaneously with topical imiquimod over a period of 32 weeks together with maintenance temozolomide. The primary end points were safety and immunogenicity. Results: The safety dataset comprised 249 vaccines administered to 32 patients. One patient withdrew after screening. 29 patients received all eight vaccines. Vaccine-related adverse events (AE) were restricted to grade 1 reactions, according to common toxicity criteria for AE (CTCAE v4.0). Two serious AE were observed in two patients; one probably related to the peptide vaccine. 28/30 patients (93.3%) evaluable for immunogenicity displayed IDH1R132H-specific T cell (detected by ELISPOT assays in 24/30 (80%) or humoral (detected by ELISA in 26/30 patients (87%)) immunologic responses not detectable before vaccination. Until end of study (EOS, week 32), 4/32 (12.5 %) patients had progressive disease (PD) according to RANO criteria, all other patients (N = 28, 87.5%) had stable disease (SD). 12/32 (37.5%) patients displayed pseudoprogressions. Single-cell T cell receptor (TCR) sequencing allowed the identification of IDH1R132H-specific TCRs. IDH1R132H peptide vaccination displayed expected safety profiles and high immunologic activity warranting further development. Clinical trial information: NCT02454634.

Conclusions: The GAPVAC consortium realized an immunotherapy, for which personalized selection of 2 peptide-based actively personalized vaccines (APVAC1) per patient for treatment of newly diagnosed GB was based not only on whole-exome sequencing but also on human leukocyte antigen (HLA)-ligandome analyses providing insight into the actual presentation of relevant epitopes in the tumor. GAPVAC-101 (NCT02149225) enrolled 16 patients in a European phase I feasibility, safety, and immunogenicity trial integrated into standard of care. For APVAC1, up to 7 peptides were selected from a trial specific warehouse based on individual biomarker data. Vaccination (i.d.) with GM-CSF and poly-ICLC in 15 patients started with the 1st adjuvant cycle of temozolomide (TMZ). For APVAC2, analyses revealed a median of 36 somatic, non-synonymous mutations in the patients’ tumors. From the 4th TMZ cycle, 11 patients received APVAC2 with usually 2 mutated antigens per patient selected according to mutation, actual or putative HLA phenotype, being with regard to CD8 immunogenicity rate (51%, readout after in vitro culturation.) Mutated APVAC2 antigens induced predominantly CD4 responses of favorable TH1 type. Median PFS and OS were 14 and 29 months from diagnosis, respectively, in patients (N = 28, 87.5%) that received ≥1 APVAC2 vaccination (N = 15). Conclusions: Overall, the GAPVAC approach displayed expected safety profiles and high biological activity warranting further development. Clinical trial information: NCT02149225.

Background: Isocitrate dehydrogenase 1 and 2 mutations (mIDH1/2) occur in solid tumors including glioma, and result in production of the oncometabolite 2-hydroxylutarate (2-HG), promoting tumorigenesis. AG-881 is an oral, potent, brain-penetrant inhibitor of mIDH1/2 that reduces 2-HG by up to 98% in glioma models.

Methods: Patients (pts) with recurrent/progressive glioma and non-glioma solid tumors. No ALT/AST AEs. No ALT/AST which resolved to 98% in glioma models.

Results: As of Dec2017, 93 pts had received AG-881 (G: 52; NG: 41) and 20 remain on AG-881 (G: 19, NG: 1). Demographics: M/F = 40/53; median age = 51; median no. prior systemic therapies = 3 (range 1–8). 46 patients with GB enrolled among 5 sites. Median age was 60. WES and CMA were performed following surgery. Primary objective: to evaluate the feasibility of genotyping tumors in a time-frame to support real-time use in clinical trials. Comparisons with orthogonal genomic and functional methods were incorporated to inform best practices. Results: As of 1/30/18, 46 patients with GB enrolled among 5 sites. Median age was 60. WES and CMA were completed in 39 patients, with a median time between surgery and biomarker analysis completion of 51 days. Actionable findings, including activating BRAF and FGFR1 mutations were identified in 2 patients, and two tumors were reclassified as non-GB based on genomics. 26 patients with MGMT unmethylated GB were enrolled in INSIGHT, a companion randomized multi-arm trial comparing standard of care versus adjuvant CC-115, neratinib or abemaciclib in newly diagnosed GB (NCT02977780). Pre-defined biomarker groups (ERFR-, PI3K- and CDK4/6-positive) will be evaluated for their ability to predict outcome in each arm. 10 patients received standard of care, and 3 patients enrolled in other clinical trials. In a subset of patients, exploratory functional biomarker assays were generated on live cells from freshly resected tumors and patient-derived GB cell line models were derived. Updated outcomes and results of exploratory biomarker analyses will be presented at the conference. Prospectively generated genomic data will be made publicly available.

Conclusions: Molecular profiling with WES and CMA is feasible within a clinically acceptable time frame following surgery for patients with newly diagnosed GB. Genomic analyses conducted in a prospective manner can inform subsequent clinical trial analysis aiming at matching outcome with tumor genotyping.
2004
Oral Abstract Session, Fri, 2:45 PM-5:45 PM
Feasibility and benefit of molecularly-informed enrollment into early phase trials for patients with recurrent gliomas. First Author: Capucine Baldini, Gustave Roussy, St. Cloud, France.

Background: Recent reports showed that patients (pts) with recurrent glioma may be good candidates for early phase clinical trials (eACTs), however clinical benefit is often limited to a small subset of pts in all-comers design trials. We aimed to evaluate whether selecting pts through tumor genotyping is associated with better outcome in this population. Methods: From 2008 to 2017, individual records of pts enrolled in eACTs of cytotoxic therapies, who may benefit from this strategy.

Conclusions: The use of prospective genomics could increase the percentage of pts in eACTs. Molecular screening methods included immunohistochemistry and PCR-based assays, array CGH, next-generation sequencing, and RNA sequencing. Results: Seventy pts were enrolled, of whom 41/70 (58.6%) patients were molecularly oriented. Therapeutic targets included FGFR mutations/fusions (n = 11), BRAF (7) and IDH (15) mutations, MDM2 amplification (1) and mismatch repair deficiency (7). In addition, 34 pts participated in the MOSCATO 01 and 02 precision medicine study (NCT01566019), which allowed the identification of potentially actionable targets in 12/34 (35%) pts, of whom 4/12 (33.3%) received a molecularly-informed therapy. Grade 3/4 adverse events were reported in 6/70 (8.6%) pts. In the subgroup of IDH1/2-wild type high-grade tumors, response rate and disease control rate were 16.7% (3/18) and 55.6% (10/18) respectively in pts who were molecularly oriented, versus 0% (0/14) and 31.5% (5/14) in molecularly-unselected pts. There was no statistically significant difference in median PFS between molecularly-oriented and -unselected pts (2.83 months [95% CI 1.3-4.6] vs. 1.54 months [1.05-2.85], p=0.29).

Conclusions: A subset of pts with recurrent glioma may benefit from incorporating tumor genotyping to guide their enrollment in eACTs. Accelerating the use of prospective genomics could increase the percentage of pts who may benefit from this strategy.

2006
Oral Abstract Session, Fri, 2:45 PM-5:45 PM
Phase II study of pembrolizumab or pembrolizumab plus bevacizumab for recurrent glioblastoma (rGBM) patients. First Author: David A. Reardon, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA.

Background: Blockade of programmed-death 1 (PD-1) mediated immunosuppression has achieved meaningful benefit across many cancers. Vascular endothelial growth factor (VEGF), a highly upregulated proangiogenic growth factor in GBM tumors, can contribute to tumor-associated immunosuppression. We evaluated the safety and efficacy of pembrolizumab (P), a fully human IgG4 PD-1 blocking antibody, with and without bevacizumab (Bev) in rGBM patients. Methods: Bev-naive patients at 1st/2nd recurrence requiring ≤ 4 mg dexamethasone/day were randomized to receive P (200 mg IV Q3W) with (Cohort A; n = 50) or without (Cohort B; n = 30) Bev (10 mg/kg IV Q2W). The primary endpoint, PFS-6 per RANO, was assessed independently per cohort relative to historical benchmarks. Archival tumor PD-L1 expression and inflammatory gene expression signatures were explored as potential biomarkers.

Results: Grade 2 or 3 treatment related adverse events (TRAEs) occurring in ≥10% patients included: Cohort A: hypertension (50%), fatigue (18%), headache (16%), infection (14%) and proteinuria (14%); Cohort B – headache (30%), and fatigue (17%). There were no grade 4 or 5 TRAEs. With a median follow-up of 25.3 months, PFS-6 was: Cohort A: 26.0% (95% CI: 16.3, 41.5); Cohort B: 6.7% (95% CI: 1.8, 25.4). Median OS was: Cohort A: 8.8 months (95% CI: 7.7, 14.2); Cohort B: 10.3 months (95% CI: 8.5, 12.5). As of 14 Jan 18, 10 patients remain alive (cohort A – 7; cohort B – 3) including 2 receiving study therapy (both cohort A). Conclusions: P is well tolerated +/- Bev but has limited monotherapy activity for rGBM. The anti-tumor activity of P+standard-dosed Bev was comparable to historical Bev monotherapy data. Clinical trial information: NCT02337491.

2005
Oral Abstract Session, Fri, 2:45 PM-5:45 PM
Actionable targets involving FGFR receptors in gliomas: Molecular specificities, spatial distribution, clinical outcome and radiological phenotype. First Author: Anna Maria Di Stefano, Foch Hospital, Suresnes, France.

Background: to characterize clinical, molecular and radiological features of diffuse gliomas with FGFR3-TACC3 fusions or FGFR1 mutations, which are both actionable with new oral anti-FGFR inhibitors. Methods: We screened for FGFR3-TACC3 fusions 1112 gliomas (861 grade IV, 140 grade III and 111 grade II) by RT-PCR. We performed sequencing for hotspot FGFR1 mutations (N546 and K656) in 73 midline gliomas (8 grade II, 10 grade III, 51 grade IV), affecting cerebellum, spinal cord, brainstem, thalamus and diencephalon) and 479 hemispheric gliomas (170 grade IV, 151 grade III, 157 grade II). Results: We identified 50 gliomas (all IDH wild-type) with FGFR3-TACC3 fusion (45 grade IV, 2 grade III and 3 grade II). FGFR3-TACC3 fusion was mutually exclusive with EGFR amplification (p = 0.000) and co-occurred with CDK4 and MDM2 amplifications (p = 0.011 and p = 0.005). FGFR3-TACC3 positive glioblastoma patients had a longer median overall survival (OS) (40.1 months versus 19.0; p = 0.006). Multivariate analysis showed that FGFR3-TACC3 fusion is an independent predictor of better outcome for glioblastoma patients. Paired case-control analysis in pre-operative Magnetic Resonance Imaging MRI (2A FGFR3-TACC3 positive cases and 48 controls) by the VASARI vocabulary and sparse canonical correlation showed that FGFR3-TACC3 gene fusions have specific radiological features, are constantly unifocal and involve specifically cortico-subcortical regions. We identified recurrent FGFR1 mutations in 13 out of 73 midline gliomas with diverse locations and in only one hemispheric glioma with corpus callosum involvement. FGFR1 mutations occurred in both K27 mutated and K27 wild-type and were constantly IDH wild-type. FGFR1 mutations tended to be associated with younger age (p = 0.06) and ATRX loss (p = 0.05) and was an independent predictor of better outcome (median OS 45.0 months versus 13.8 months, p = 0.01).

Conclusions: gliomas with FGFR3-TACC3 gene fusions and FGFR1 mutations represent two specific entities with distinct anatomical, clinical and molecular features. They should be recognized because both alterations are eligible for currently ongoing anti-FGFR clinical trials.

2007
Oral Abstract Session, Fri, 2:45 PM-5:45 PM
Phase II study of pembrolizumab in leptomeningeal carcinomatosis. First Author: Priscilla Kalogi in Brasili nos, Massachusetts General Hospital, Boston, MA.

Background: Approximately 5-8% of patients with cancer develop leptomeningeal carcinomatosis (LMD). Median survival of patients with LMD is approximately 4-6 weeks and there are no effective treatment options. We performed a phase II study of pembrolizumab in LMD from any solid tumor malignancy (NCT02886585). Methods: The primary endpoint is the rate of overall survival at 3 months (OS3). A Simon two-stage design was used to compare a null hypothesis OS3 of 18% against an alternative of 43%. Ten patients were to be enrolled in the first stage. If 2 or more patients were alive at 3 months, an additional 8 patients would be enrolled. If at least 6 patients among the total of 18 patients were alive at three months, then the treatment would be deemed promising in the cohort. Serial CSF, blood samples and tumor samples were collected to elucidate the genomic and transcriptional determinants of immunotherapy response in central nervous system (CNS) lesions. Results: A total of 18 patients were accrued (15 with breast cancer, 2 with lung cancer and 1 with gastric cancer). The median follow-up of patients still alive was 2.9 months (range: 2.2 to 6.3 months). The percentage of patients with one or more grade-3 or higher adverse events that were at least possibly related to treatment is 33.3%. At the time of the data retrieval, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint.
Background: A Phase III study failed to demonstrate a therapeutic benefit of pembrolizumab in patients with recurrent glioblastoma. First Author: John Frederick De Groot, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX

Risk of CNS adverse events (CNS-AEs) for patients with non-small cell lung cancer (NSCLC) and melanoma brain metastases (BM) treated with CNS radiation (CNS-RT) and immune checkpoint inhibitors (CPIs). First Author: Michael Edward Devitt, University of Virginia, Charlottesville, VA

Background: CPIs are widely used in the treatment of both metastatic melanoma and NSCLC. BM frequently occur and are treated with CNS-RT. Since both BRAF/MEK and PD-1/PD-L1 can cause neuro-inflammation, we tested the hypothesis that concomitant treatment with CPIs and CNS-RT results in an increased risk of CNS-AEs. Methods: We identified patients with melanoma and NSCLC with BM treated with CNS-RT and seen at our institution between 2014 and 2016. Concomitant treatment with CPIs and CNS-RT was defined as administration of CPIs within 3 months before or after CNS-RT. CNS-AEs were defined as new or worsening edema on brain MRI without disease progression, new or worsening neurological deficit, or need to start or increase corticosteroids. A generalized linear model incorporated significant variables from a univariate analysis to model the incidence of CNS-AEs.

Results: We identified 213 cases of CNS-RT (NSCLC 167 [78%], GKR 2 [0.1%]), WBRT 63 [30%], and median 2 BM (1 to 20), median 1.9 mm max diameter (2 mm-74 mm)). Patients were 52% female with median age 61 (range 21-87), and ECOG 0-2 in 93% at time of CNS-RT. Risk of CNS adverse events (CNS-AEs) for patients with non-small cell lung cancer (NSCLC) and melanoma brain metastases (BM) treated with CNS radiation (CNS-RT) and immune checkpoint inhibitors (CPIs). First Author: Michael Edward Devitt, University of Virginia, Charlottesville, VA

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The recent successes of checkpoint blockade immunotherapy (CBI) and BRAFV600E-targeted therapy trials have generated exciting promise for revolutionizing the management of patients with advanced melanoma. However, the use of CPIs and BRAFV600E-targeted therapy either excluded or included disproportionately fewer cases of melanoma brain metastases (MBM), the survival benefit of these novel therapies for MBM remains unknown. Methods: The characteristics, management, and overall survival (OS) outcomes of patients who presented with cutaneous MBMs during 2010-2015 were evaluated using the National Cancer Database, which comprises approximately 70% of all newly diagnosed cancers in the U.S. OS was analyzed with risk-adjusted Cox proportional hazards and compared by Kaplan-Meier techniques. Results: 2,753 (36%) of patients presenting with stage 4 melanoma had MBMs. MBM patients who presented after the 2011 FDA approvals for CBI and BRAFV600E-targeted therapy demonstrated a 91% relative increase in 4-yr OS to 14.1% (95CI: 12.2-16.1) from 7.4% pre-approval (95CI: 5.3-10.0, p < 0.001). In the post-approval era, the proportion of MBM patients that received CBI rose from 10.5% in 2011 to 34.0% in 2015 (p < 0.001). Initial CBI in MBM patients displayed a 2.4x improved median and 4-yr OS of 12.4 mos (95CI: 10.4-15.8; vs. 5.2 mos, 95CI: 4.7-5.9, p < 0.001) and 28.1% (95CI: 22.1-34.4; vs. 11.1%, 95CI: 9.3-13.1). These benefits were particularly pronounced in MBM patients without extracranial metastases, in which CBI demonstrated improved median and 4-yr OS of 56.4 mos (95CI: 25.0-not reached; vs. 7.7 mos, 95CI: 6.7-8.7, p < 0.001) and 51.5% (95CI: 38.9-62.8%, vs. 16.9%, 95CI: 13.5-20.6) that persisted in MBMs that underwent resection or SRS. Conclusions: Using a large national cohort comprised of a “real-life” treatment population of MBMs, we demonstrate the dramatic improvements in OS associated with novel checkpoint blockade immunotherapies.
Background: MGMT promoter methylation status represents an important prognostic factor for GBM PTS in terms of progression free survival (PFS) and overall survival (OS). Quantitative pyrosequencing approach is a valid alternative to methylation-specific PCR but a cut-off value is still unclear. We performed a large, multicenter, retrospective study to identify a real cut-off value to discriminate its impact on clinical outcome in terms of PFS and OS. Methods: Retrospectively, from Italian neuro-oncology centers, we collected GBM PTS from 2005 to 2016 with assessment of MGMT promoter methylation by pyrosequencing approach evaluating CpG islands from 74 to 83. Other inclusion criteria were: confirmed histological diagnoses of GBM, ECOG PS ≥2, treatment with concomitant radiation therapy and temozolomide. Kaplan-Meier method was used to estimate the survival curves and ROC curve for defining cut-off value for PFS and OS. Results: 376 GBM PTS were enrolled; median age was 62 ys (25-86); ECOG PS was 0 in 129 PTS, 1 in 160 PTS, 2 in 87 PTS; 212 PTS (58%) had a complete resection. 67 PTS (18%) received a second surgery. Median PFS and OS was 8.6 and 14.3 months. The optimal cut-off value to identify a strong prognostic value of MGMT methylation status in terms of PFS was 0.72 (specificity 61%, accuracy 71%) and 24% of methylation (sensitivity 72%, specificity 61%, accuracy 71%), respectively. On multivariate analyses, corrected for age, KPS, type of surgery and second surgery, the MGMT cut-off values remained significantly correlated to longer PFS (HR = 0.5, 95% CI 0.3-0.9) and OS (HR = 0.47, 95% CI 0.3-0.6). Conclusions: From this large, multicenter study, we identify, by pyrosequencing approach, a strong prognostic value of MGMT methylation, in terms of PFS and OS. This value could be used as stratification factor in prospective clinical trials.

Background: Hypermutator genotype (HMGen) is seen in glioblastoma (GB) and lower-grade gliomas. It may be induced by temozolomide (TMZ) and leads to TMZ resistance. We describe demographics, mutational features, treatments and outcomes of HMGen gliomas. Methods: Retrospective review at MD Anderson between 02/2006-02/2017 identified 309 gliomas with tissue analyzed by next-generation sequencing (T200-1, Oncomine, FoundationOne). HMGen was defined as tumor mutation burden (TMB)-30 of 30 or more mutations (mut) per Mb, or displaying mut in mismatch repair (MMR) or DNA polymerase (Pol) genes. Results: 38 (12.3%) patients had HMGen. 25 (66%) were men. 19 (50%) had TMB-30, 10 (26%) had mut in Pol genes, 6 (16%) in MMR (1 had mut in both MLH and MSH6 genes), 1 had mut in both MMR and Pol genes and only 2 met all three criteria. GB (N = 26, 68%) was the most common tumor (N = 6, 23.1% IDH1-mut), followed by WHO grade III oligodendroglioma (N = 8, 21%), grade II astrocytoma (N = 3, 8%) and grade II oligodendroglioma (N = 1, 3%). HMGen was found as initial genotype in 17 (45%) cases, the rest after treatment with alkylating agents. Of those patients with de novo HMGen, Pol gene mut was most common (N = 9, 53%), followed by MMR mut (N = 4, 23.5%) and TMB-30 (N = 4, 23.5%). Of those 17, 15 (88%) were GB followed by WHO grade II gliomas: 1 oligodendroglioma with MMR mut (MSH6 gene) and 1 astrocytoma with TMB-30. For post-treatment HMGen, the most common alterations was TMB-30. The mean cumulative TMZ dose at HMGen diagnosis for GB, WHO grade II/III astrocytoma and grade II/III oligodendroglioma was 16g, 24g/28g, and 41g/29g, respectively with a mean monthly dose of 1.5-1.8g. Only 1 patient received CCNU (0.4g). For de novo and post-treatment HMGen GB IDH1-wildtype, the OS and PFS from HMGen diagnosis was 19.6/15 and 23.7/9.9 months (m) respectively. The latency interval from histopathologic GB to HMGen was 17.5 m and the total OS was 43.6 m. Of this subset group, 73% (N = 26) were alive at 24 months from diagnosis, the median OS was 15.4 months, and the median PFS was 7.5 months in historical controls. Estimated mOS for PEX is 15.4 months (95% CI 12.3, 20.7) vs. 18.9 months in controls. PEX was well tolerated, with most common drug-related toxicities including neutropenia and decreased ALT/AST. HMGen unmethylated patients comprised 60% of the patients, with estimated mOS of 13.8 months (95% CI 12.3, 20.7) vs. 68% and estimated mOS of 16.6 months in historical controls. HMGen methylated patients comprised 40%, and mOS not yet reached vs. 32% and estimated mOS of 23.5 months in historical controls. Tumors with high expression of monocyte/macrophage marker CD163 and macrophage stimulating factor CSF1R may be associated with better survival. We used TERT promoter mutation status as a marker for improving PFS and OS compared to robust, well-matched historical controls. Further investigation in relevant biomarker subgroups is ongoing. Clinical trial information: NCT01790503.
2016 Poster Discussion Session; Displayed in Poster Session (Board #174), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Safety and preliminary efficacy data from a phase I study of an implantable low intensity pulsed ultrasound (LIPU) device for disrupting the blood-brain barrier (BBB) in patients treated by chemotherapy for recurrent glioblastoma (GBM). First Author: Ahmad Ibdabaih, Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France

Background: The BBB limits the efficacy of many chemotherapies in GBM patients by blocking the passage of drugs to the brain. Two to four minutes of LIPU in combination with injection of micron-sized microbubbles can transiently disrupt the BBB to increase the passage of drugs such as carboplatin. Methods: This first-in-human, single arm, monocentric trial was performed at Hôpital Universitaire Pitié-Salpêtrière, Paris, France from 2014-2018. Recurrent GBM patients were implanted with (1) or (3) 1 MHz, 10-mm diameter cranial devices in burr holes during debulking surgery or during a dedicated procedure under local anesthesia. Ultrasound dose was escalated using a Simon titration design. The device was activated monthly to transiently disrupt the BBB before IV administration of carboplatin (AUC4-6). BBB disruption was visualized using MRI and patients were monitored clinically. Results: Twenty-seven patients were implanted with LIPU devices and 25 per-protocol were sonicated: 19 patients with (1) US emitter and six patients with (3) US emitters. In 85 ultrasound sessions, BBB disruption was visible on post-sonication T1w MRI for 72 soninations and was ultrasound dose dependent. A transient (≤24h) and permanent (≥48h) BBB disruption was observed in 61% and 40% of sessions, respectively. In events were observed: a partial seizure, two cases of transient edema (H1 and D15) and one transient facial palsy. No carboplatin-related neurotoxicity was observed. All patients treated with (1) emitter had tumor progression and 3/19 patients were alive. In this cohort, patients with or no or poor BBB disruption (n = 18) had a median PFS of 7 months and 12/18 patients were alive. In patients with clear BBB disruption (n = 11) had a median PFS of 15 weeks, and a median OS of 13 months. Conclusions: LIPU was well tolerated and may increase the effectiveness of drug therapies in the brain. The sonication of larger volumes of brain in recurrent GBM will be investigated in a future trial and may further enhance the observed effectiveness of this treatment modality. Clinical trial information: NCT02253212. Clinical trial information: NCT02253212.

2017 Poster Discussion Session; Displayed in Poster Session (Board #175), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

VXMO1 phase I study in patients with progressive glioblastoma: Final results. First Author: Wolfgang Wick, Neurology Clinic, DKFZ, DKTK, Heidelberg, Germany

Background: VXMO1 consists of an attenuated Salmonella typhi Ty21a carrying a plasmid encoding for vascular endothelial growth factor receptor (VEGFR)-2. The bacterium is a vector via the oral route of administration carrying the plasmid into the Peyers’s plaques. The vaccine elicits a systemic T-cell response targeting VEGFR-2. This trial examined safety and tolerability, clinical and immune response to VXMO1 after at least four vaccinations (10° or 10° colony-forming units (CFU)) in patients with progressive glioblastoma who have failed at least radiochemotherapy with temozolomide. Methods: Patients with progressive operable glioblastoma were subjected to VXMO1 in one oral administration each on day 1, 3, 5, and 7. In addition, VXMO1 was allowed to be administered in 4-weekly single doses every 4 weeks during the tumor follow-up period after surgery. Follow-up was done by weekly surveillance of local recurrence and physical examinations in the treatment period and 12-weekly thereafter T-cell immunomonitoring in the peripheral blood, and brain tumor immunohistochemistry. Results: Fourteen patients have been treated with VXMO1. Three out of them with additional nivolumab. Surgery has been performed in eight patients. Under VXMO1 treatment 119 adverse events, mostly unrelated to VXMO1, were observed after a median of 8 doses per patient. ELISPOT analysis showed a detectable VEGFR-2 response in 7 out 12 patients at 12 weeks. In the observation period of up to 20 months 7 patients are alive, 5 out of them survived for more than one year, 2 patients are ongoing at month 10. In one patient there was an objective and durable T1 response. Survival seemed to be correlated with a higher CDB/Treg ratio in progressive and primary tumors, with a median OS of 13 months. In treated patients with USP1 survival a decrease in intratumoral PD-L1 was observed arguing for combination of VXMO1 with an anti-PD-L1 checkpoint inhibitor. Conclusions: VXMO1 was safe and produces detectable specific peripheral immune responses as well as CDB/Treg ratio increase in post-vaccine tumor tissue. There was one patient with an objective response. As a next step, a combination study of VXMO1 and anti-PD-L1 checkpoint inhibitor has been launched. Clinical trial information: NCT02718443.

2018 Poster Discussion Session; Displayed in Poster Session (Board #176), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase I clinical trials evaluating olaparib in combination with radiotherapy (RT) and/or temozolomide (TMZ) in glioblastoma patients: Results of PARADIGM-Z. First Author: Anthony J. Chalmers, University of Glasgow, Glasgow, United Kingdom

Background: The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (O) has radio and chemosensitizing properties in GBM models. Clinical development of PARP inhibitors in combinations with RT and TMZ has shown promising results in terms of hematological toxicity and acute radiation toxicity. We studied pharmacokinetics (PK), safety and toxicity of O with RT and TMZ in three phase I studies. Methods: PARADIGM determined PK of O (AZ tablet formulation) in core and margins of recurrent GBM and maximum tolerated dose (MTD) of O with 42 days cycles of daily TMZ. PARADIGM determined phase II dose (RP2D) of O with 40 Gy 15 fractions of radiotherapy in newly diagnosed patients aged >70. PARADIGM-2 comprises two phase I studies of O+RT (60 Gy 30/6, MGMT unmethylated) or O+RT+TMZ (MGMT methylated) in newly diagnosed patients aged<70. Results: OPARATIC: 48 patients recruited; 27 underwent surgery, 36 receiving TMZ were evaluable. O detected in 71/75 tumor core specimens (27 patients); mean conc. 588nM (97–1374nM), and 27/28 tumor margin specimens (10 patients); mean conc. 500nM (97–1237 nm). Myelosuppression necessitated intermittent O dosing. MTD defined as ≤150 mg (OD) days 1-3 weekly plus TMZ 75 mg/m2 daily. For 36 evaluable patients receiving O/TMZ, progression-free survival at 6 months was 39%. PARADIGM: 16 patients (median age 72) treated in four O dose cohorts. One DLT (agitation grade 3) recorded (cohort 3, 100 mg BID). RP2D of O+40 Gy 5h in elderly GBM was 200 mg BID daily. Median overall survival 13.7 months (80% CI 6.3 – 11.7 months) at 12.9 months median follow up. PARADIGM-Z: 29 patients screened, 14 commenced study treatment. Three MGMT unmethylated patients completed cohort 1 (50 mg QID) with no DLTs and 4 recruited to cohort 2 (100 mg QID) with no DLTs to date. Seven MGMT methylated patients recruited to cohort 1 (100 mg x1 per week); 1 DLT reported to date (low platelets). Conclusions: O penetrates core and margins of recurrent GBM. Combination with radiotherapy is extremely well tolerated and randomized phase II evaluation is underway. Clinical trial information: NCT01390571.
Effect of dexamethasone in glioblastoma (GBM) patients on systemic and intratumoral T-cell responses induced by personalized neoantigen-targeting vaccination.

First Author: David A. Reardon, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: The impact of individualized neoepitope vaccination targeting neoantigens arising from tumor-specific mutations for GBM, a low mutation burden tumor with an immunologically cold tumor microenvironment, as well as that of concurrently administered dexamethasone (dex), are unknown.

Methods: Individualized vaccination of up to 20 synthetic, long neoepitope peptides with high predicted HLA binding affinity admixed with poly-ICLC, were administered subcutaneously using a prime-boost schedule after RT to newly diagnosed, TMZ unmethylated, at least partially resected, GBM patients without progression after radiation (RT) in our phase Ib study.

Results: 9 of 10 screened patients had sufficient (> 10) identified neo-epitope peptides. 8 patients without progression after RT received vaccine consisting of a median of 12 peptides (range, 7-20) beginning a median of 18.6 wks (range 16.0-23.2) after surgery. Adverse events were limited to infrequent grade 1/2 local reactions and fatigue. Median PFS and DS were 7.5 mths (90% CI: 6.2, 9.7) and 16.8 mths (90% CI: 9.6, 21.3). Evaluation of neoepitope-specific immune responses and tumor immune infiltrate analyses were performed on five patients with pre- and post-vaccination samples. Three patients on dex for post-RT edema during vaccine had no immune responses and no change in tumor volume for contrast 2 patients not on dex had robust, de novo immune responses against multiple predicted personal neoantigens including nonfunctional neoantigen-specific CD4+ and CD8+ T cells. These were enriched for memory and activated phenotypes as well as increased numbers of tumor-infiltrating CD4+ and CD8+ T cells. T cell receptor analysis from one patient identified identical clonotypes isolated from post-vaccination tumor tissue and peripheral blood including a clonotype specific for ARHGAP35, a neoantigen targeted by vaccination.

Conclusions: Individualized, multi-neoepitope vaccines are feasible, safe and capable of generating systemic and intratumoral immune responses in GBM patients that appear to be abrogated by dex. Clinical trial information: NCT02287428.

A unique MRI-based radiomic signature predicts hypermutated glioma genotype.

First Author: Islam Hassan, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Hypermutation is defined as the excessive accumulation of DNA mutation in cancer cells and is reported in several forms of cancer including low and high grade gliomas. Incidence of hypermutated genotype was associated with failure of DNA repair machinery such as mismatch repair (MMR) or disruption of DNA fidelity due to mutations in DNA polymerase genes (POLE and POLD). Hypermutated gliomas (mainly glioblastoma (GB)) are largely seen at recurrence with associated resistance to temozolomide therapy. Herein, we sought to identify an imaging-based signature for hypermutated gliomas using a radiomics-based approach.

Methods: In this IRB-approved retrospective study, we analyzed a total of 101 patients with primary gliomas from the University of Texas MD Anderson Cancer Center. Next generation sequencing (NGS) platforms (T200 and Foundation 1) were used to determine the Mutation burden status in post-biopsy (stereotactic/excisional). Patients were dichotomized based on their mutation burden; 77 hypomutated (< 30 mutations), 24 hypermutated (> 30 mutations or < 30 with MMR gene or POLE/POLD gene mutations). Radiomic analysis was performed on the conventional MR images (FLAIR and T1 post-contrast) obtained prior to tumor tissue surgical sampling; and a total of 2480 rotation-invariant radiomic features were extracted using: (i) the first-order histogram and (ii) grey level co-occurrence matrix. The Maximum Relevance Minimum Redundancy technique was used to select the most relevant radiomic features. ROC analysis and leave-one-out cross-validation (LOOCV) were used to assess the performance of the Support Vector Machine (SVM) classifier as and AUC, Sensitivity, Specificity, and p-value were obtained. Results: We found 100 radiomic features that can discriminate between hypermutated versus hypomutated gliomas, AUC 96.3% (CI: 90.2%-98.9%), Sensitivity 100%, Specificity 95%, p-value = 3.76e+6. Conclusions: Hypermutated gliomas has a unique radiomic quantitative signature that can be used to predict mutation burden regardless of tumor grade or histopathology.

Long-term stress risk of single-fraction photon-based stereotactic radiosurgery for meningioma.

First Author: Shearwood McClelland, Oregon Health and Science University, Portland, OR

Background: A recent randomized study of fractionated radiation therapy (RT) examining 44 subtotally resected/recurrent benign meningioma patients revealed that at median follow-up of 17.1 years, the risk of stroke following proton-photon RT was 20.5%; the average stroke developed 5.6 years following RT completion (Sanford et al., 2017). This stroke risk is up to 10 times higher than the 2.6% rate expected for the general population of ages 40-79 (Mozaffarian et al., 2015). The stroke rate following single-fraction stereotactic radiosurgery (SRS) has not been previously studied in meningioma patients. Methods: A PubMed database search for relevant articles examining SRS for meningioma with minimum mean/median follow-up of six years was undertaken. Stroke rate was assessed either from direct description in manuscripts, or from extrapolating post-SRS complications from reported clinical examinations (i.e. hemiparesis/weakness, pituitary dysfunction following treatment of cavernous sinus lesions). Results were then culled to determine an overall stroke rate. Results: Fourteen studies met inclusion criteria; 1,431 patients received photon-based SRS for meningioma with a sufficient long-term follow-up. Median mean follow-up ranged from 75-144 months. Operative resection prior to SRS occurred in 769/1377 patients (55.8%) for whom surgical history was reported. Twenty-four patients suffered a stroke following SRS, yielding a rate of 1.7%. Conclusions: The long-term stroke rate following single-fraction photon-based SRS for benign meningioma is no higher than that expected for the general population. The majority of patients underwent resection prior to SRS. These findings indicate that for patients with benign meningioma desiring to avoid the high stroke risk of fractionated proton-photon RT, SRS has a comparable stroke risk profile to observation. Such findings are pertinent for radiation oncology, neuro-oncology, and neurosurgery management of these patients.

Updated results of the INTELLANCE 2/EORTC trial 1410 randomized phase II study on Depatux-M alone, Depatux-M in combination with temozolomide (TMZ) and either TMZ or lomustine (LOM) in recurrent EGFR amplified glioblastoma (NCT02343406).

First Author: Martin J. Van Den Bent, Erasmus MC Cancer Center, Rotterdam, Netherlands

Background: Depatux-M is a tumor-specific antibody-drug-conjugate consisting of an antibody (ABT-806) bound to the toxin monomethylauristatin-F. In the primary analysis on EORTC 1410 we reported a trend (p = 0.06) towards improved overall survival (OS) in patients with EGFR-amplified (amp) recurrent glioblastoma treated with Depatux-M in combination with TMZ. Methods: Eligible were patients with centrally confirmed EGFRGlamp glioblastoma at 1st recurrence after TMZ chemo-irradiation, occurring ≥3 months after radiotherapy. Patients were randomized to either a) Depatux-M 1.0 mg/kg every 2 weeks intravenously, or b) the same treatment combined with TMZ 150-200 mg/m² day 1-5 every 4 weeks, or c) either LOM or TMZ (TMZ/LOM) depending on the time of relapse. Primary endpoint was OS. Pharmacokinetic (PK) sampling was done on day (d) 1 before and after dosing, d 4-7, d 1 course 2 before and after dosing, d 5-7 course 4, d 1 course 3, and then every 2 cycles. All available PK samples were used to calculate the Depatux-M average concentration during course 1 (CavgC1). The level of EGFRGlamp was determined using both qPCR, next generation sequencing and FISH. Results: An updated OS comparison of Depatux-M in combination with TMZ versus TMZ/LOM with longer follow-up, performed after 220 observed deaths using log-rank test and cox models stratified by stratification factors at randomization showed a HR of 0.68 (95%CI [0.48, 0.95]; p = 0.024) and 1-year OS rates of 40% versus 28%. In multivariate analysis including performance status, MGMT, surgery for the recurrence, time from last TMZ to relapse and lesion diameter, CavgC1 was a significant predictor for OS (HR 0.96, 95% CI [0.93, 0.98]; p = 0.0013). In Depatux-M treated patients, EGFR status (high vs low level amplification) did not correlate with OS. Conclusions: This updated OS analysis of Depatux-M in combination with TMZ confirmed the OS improvement in EGFRGlamp recurrent glioblastoma. In Depatux-M treated patients, higher drug levels during course 1 were associated with improved OS but high levels of EGFR amplification at first diagnosis were not. Clinical trial information: NCT02343406.
Depression and survival of glioma patients: A systematic review and meta-analysis. First Author: Nayan Lamba, Harvard Medical School, Boston, MA

Background: There is currently a lack of well-established meta-analyses examining the association between depression and patient survival in glioma patients. The aim of this meta-analysis was to study the effect of depression on glioma patients’ survival. Methods: A meta-analysis was conducted according to the PRISMA guidelines. PubMed, Embase, and Cochrane databases were searched for studies that reported depression and survival among glioma patients through 1/06/2016. Both random-effects (RE) and fixed-effect (FE) models were used to compare survival outcomes in glioma patients with and without depression. Results: Out of 619 identified articles, six were selected for the meta-analysis. Using RE model, the various measures of survival outcomes displayed worsened outcomes for both high and low grade glioma patients with depression compared to those without depression, with an overall pooled risk ratio for survival of 0.67 (95%CI: 0.46, 0.99; I² = 51.4%, P-heterogeneity = 0.06); an overall pooled standard mean difference for the overall survival time (in months) of -0.88 (95%CI: -1.89, 0.13; I² = 87.1%, P-heterogeneity = -0.01); and a pooled hazard ratio of death of 1.42 (95%CI: 1.00, 2.01; I² = 0%, P-heterogeneity = 0.85). Using the FE model, results were similar except for overall survival time, where the shorter survival time in glioma patients with versus without depression reached statistical significance (-0.70; 95%CI: -0.86, -0.53). Among high-grade glioma patients, preoperative depression diagnosis was associated with fewer months of survival compared to postoperative diagnosis, as shown under the FE model (P-interaction < 0.01), but not under the RE model (P-interaction > 0.1).

Conclusions: Among patients with either low or high grade glioma, depression was associated with significantly worsened survival regardless of time of diagnosis.

2027 Poster Session (Board #185), Sat, 1:15 PM-4:45 PM
Angiotensinogen gene silencing to predict bevacizumab response in recurrent glioblastoma patients. First Author: Thomas Urup, Rigshospitalet, Copenhagen, DK

Background: Bevacizumab in combination with chemotherapy has shown activity in recurrent glioblastoma patients. Patients who achieve response to bevacizumab have improved survival as well as quality of life. Recently, we found that low gene expression of angiotensinogen (AGT) was a predictive factor for bevacizumab response in recurrent glioblastoma patients. Because promoter methylation of AGT has been associated with AGT gene silencing, we investigated if AGT promoter methylation in tumor tissue predicts response to bevacizumab combination therapy in recurrent glioblastoma patients. Methods: The study includes 82 recurrent glioblastoma patients treated with bevacizumab combination therapy whom were both RANO response and biomarker evaluable. DNA methylation of 7 CpG sites in the CEBPA binding site (~200 bp from TSS) of the AGT promoter was measured using pyrosequencing. AGT gene expression in tumor tissue was measured by NanoString analysis. For each CpG site, methylation levels were associated with angiotensinogen gene expression using Spearman correlations and to treatment response using Mann-Whitney U test and logistic regression analysis. Results: Preliminary results on 58 of 82 patients analyzed: AGT gene expression was inversely associated with AGT promoter methylation on CpG site 1 (P = 0.049) and border line significant on CpG site 2 (P = 0.074). Compared to non-responding patients, responders expressed significantly higher methylation levels of CpG site 1 (P = 0.015), 2 (P = 0.013) and 3 (P = 0.045). DNA methylation levels at CpG site 4-7 were not associated with AGT gene expression or response. By univariate analysis, increased methylation of the AGT promoter region were predictive for bevacizumab response on CpG site 1 (2-fold increase: OR = 1.81; 95%CI: 1.02-3.23; P = 0.043) and on CpG site 2 (2-fold increase: OR = 2.08; 95%CI: 1.04-4.17; P = 0.040). Conclusions: Increased methylation of the AGT promoter regions is associated with AGT gene silencing and is predictive for bevacizumab response in recurrent glioblastoma patients. Updated results will be presented.
Contrast enhancement as a prognostic factor in IDH1/2 mutant glioma. 2029 Poster Session (Board #187), Sat, 1:15 PM-4:45 PM

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Effect of therapeutic pressure on stability of EGFR amplification in glioblastoma. First Author: Mannmeet Singh Ahluwalia, Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH

Background: Deputaxizumab mafodotin (depatux-m, formerly ABT-414) is an EGFR-directed antibody-drug conjugate being developed for treatment of EGFR-amplified glioblastoma (GBM). As therapeutic pressure engenders tumor adaptations, it is important to understand the stability of biomarkers targeted by precision medicine approaches such as deputax-m. Therefore, we assessed EGFR amplification (amp) and expression in longitudinally-sampled GBMs from patients (pts) treated +/- deputax-m to explore biomarker stability. Methods: Formalin-fixed, paraffin embedded GBM tumor tissue was analyzed from 68 patients who underwent at least 2 surgeries; EGFR amp was detected by in situ hybridization (e.g., FISH) or next-generation sequencing in all samples. Fifty-six pts did not receive deputax-m, among 12 pts who did, EGFR expression was also evaluated by RNA sequencing. Results: Of 56 pts who did not receive deputax-m, 35 (55%) had tumors harboring EGFR amp at 1st surgery (initial diagnosis); among those, EGFR amp was maintained at re-operation in 27 (87%), and not maintained in 4 (13%). None of the 25 cases without baseline EGFR amp acquired it at the 2nd surgery. Of 12 pts treated with deputax-m between surgeries, 9 cases harbored EGFR amp at baseline which was maintained in 4 (44%) at the 2nd surgery, all 4 of which had the highest levels of EGFR expression at baseline. Of the 3 cases without EGFR amp at baseline, none acquired amplification at the 2nd surgery, and all 3 had the lowest levels of EGFR expression at study entry. Conclusions: The presence of EGFR amp in GBM tissue at baseline was maintained in 2nd surgery in 87% of pts who received treatment other than deputax-m, and in 44% following deputax-m exposure. Therefore, deputax-m exposure appears to reduce EGFR amp maintenance (p = 0.0199 by Fisher’s exact test); accordingly, the therapeutic approach may influence EGFR status. In no case was EGFR amp acquired at recurrence, regardless of deputax-m therapy. Ongoing analyses of additional tumor samples will increase power and further examine concordance among EGFR amp assays.

2034 Poster Session (Board #119), Sat, 1:15 PM-4:45 PM

NKG2D chimeric antigen receptor-T cells to target GBM. First Author: Hong-jiu Dai, Nanjing Kaedi Biotech Inc, Nanjing, China

Background: GBM is the most common and the most lethal brain tumors with the 5-year survival rate of ~4% for patients over age 55. Recently people are exploring the potential of chimeric antigen receptor (CAR)-T cells in glioblastoma, yet the clinical outcome is limited. It’s reported that NKG2DLSs are widely expressed in glioma stem-like cells, which supports NKG2D system might play an important role in GBM therapy. Here we used NKG2D as antigen binding domain to construct a second generation of CAR (KD-025) for GBM treatment. Methods: U251 cell line as well as GBM cancer patient samples were evaluated for NKG2DLSs expression. The KD-025 CAR T cells showed antigen-specific stimulation by cytokine secretion and target cell lysis. U251 were used to establish in vivo sculean and xenograft models in NSG mice. Mice received a single treatment of 10 million KD-025 CAR-T cells intravenously. The main organs of mice were examined by hematoxylin and eosin (HE) staining after different doses of KD-025 administration. Results: NKG2DLSs were detected on U251 cells and most of screened glioma patient samples. The KD-025 expression was ~50% on the surface of T cells confirmed by flow cytometry. Co-incubation of KD-025 CAR-T cells with U251 cell specifically upregulates TNFs, IFNγ, IL-10 and IL-2 cytokines and strongly lysed tumor cells even at low E:T ratio (50-60% at 1:1, 70% at 10:1). Strikingly, KD-025 CAR demonstrate very potent anti-tumor activity in vivo. All the tumor cells are gone 14 days after single treatment of KD-025 CAR T cells. Regarding to T cell persistence, the CAR-T cells are barely detectable 24 days after injection, which is comparable with CD19 CAR in our experiments as well as published data. No obvious pathological changes were found in the tested organs. Conclusions: Our work with the KD-025 CAR contributes to the growing body of research committed to discovering a novel therapy for GBM. NKG2D ligands are highly expressed on human GBM samples. KD-025 CAR cells specifically recognize GBM cells and GBM and eliminate tumor in a xenograft mouse model with no obvious safety issue. The results support future clinical trial of KD-025 CAR in patients with GBM, where the need for effective treatment is great.

2035 Poster Session (Board #193), Sat, 1:15 PM-4:45 PM

A phase I/II clinical trial of autologous CMV-specific cytotoxic T cells (CMV-TC) for glioblastoma: Dose escalation results. First Author: Marta Penas-Prado, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX

Background: Cytomegalovirus (CMV) antigens are present in > 90% of GBMs but not in normal brain, and can be targeted as a tumor-specific antigen. CMV-TC present in GBM tumor tissue have their effector function suppressed. High functional CMV pp65 specific T cells can be expanded in vitro from peripheral blood (PB) of GBM patients. We have established GMP-compliant conditions for ex vivo expansion of polyclonal CD8+ and CD4+ CMV-TC from GBM patients. Methods: We explored 4 dose levels of autologous CMV-TC (from 5x10^4 cells to 1x10^6 cells) with a 3+3 design. CMV-TC were given after 3 weeks of lymphodepleting dose-dense temozolomide (dDTMZ, 100 mg/m2 for 3 weeks). Treatment was repeated q 6 weeks for a total of 4 cycles. Patients ≥18 years of age with KPS ≥60, CMV seropositivity, receiving ≤2 mg of dexamethasone daily, and any number of relapses were eligible. Imaging response was evaluated by MRI q 6 weeks. In vivo persistence and expansion of adoptively-infused CMV-TC was determined by dextramer staining and multiparameter flow cytometry in serially-sampled PB. Results: 27 patients were screened, of whom 15 underwent leukapheresis. Twelve patients (3 at each level) completed cycle 1. Median age 51 (27-65), median KPS 90; 9 were at 1st and 3 at 2nd relapse. MGMT was methylated in 5, unmethylated in 3, indeterminate or unknown in 4. IDH status was wildtype in 7, mutated in 3, indeterminate or unknown in 2. Number of cycles received was 4 in 4 patients, 2 in 3, and 1 in 5. No dose limiting toxicities (DLTs) were observed at any level. Complete radiographic response was observed in 1 patient, partial response in 1 patient, stable disease in 5 patients, and progressive disease in 5. Repeated infusions of CMV-TC were associated with a significant increase in circulating CMV+CD8+ T-cells. Conclusions: Adoptive infusion of CMV-TC after lymphodepleting chemotherapy with dDTMZ was well tolerated with no DLTs or serious CMV-TC related adverse events. The final dose level is currently being enrolled. Thereafter efficacy will be evaluated in expansion cohorts in newly diagnosed and recurrent GBM. The expansion in recurrent GBM will include correlative studies in tumor tissue after administration of CMV-TC. Clinical trial information: NCT02661282.

2036 Poster Session (Board #194), Sat, 1:15 PM-4:45 PM

Phase I study of afatinib and radiotherapy (RT) with or without temozolomide (TMZ) in newly diagnosed glioblastoma (GB). First Author: Frank Saran, The Royal Marsden NHS Foundation Trust, London, United Kingdom

Background: GB is a malignant primary incurable CNS tumor with poor prognosis. RT + TMZ is standard treatment for newly diagnosed GB suitable for radical treatment. ErbB pathway dysregulation has a role in the pathogenesis of GB and EGFR activation contributes to RT resistance. The irreversible ErbB family blocker afatinib has a manageable safety profile and modest activity in recurrent GB. This Phase I study assessed the feasibility of first-line afatinib + RT + TMZ in GB. Methods: This 3+3 dose-escalation study enrolled 36 pts with newly diagnosed GB. Treatment was stratified by MGMT promoter methylation status. Pts with promoter methylation received RT + TMZ + afatinib (20, 30, 40 mg/day) for 6 wks in RT period, the afatinib 40 mg/day + TMZ for up to 6 months before afatinib 40 mg/day until progression/undue AEs (maintenance period; Regimen M). As TMZ has limited benefit in pts with unmethylated MGMT, these pts received RT + afatinib then afatinib (Regimen U). Primary endpoint: MTD of afatinib + RT + TMZ. Secondary endpoints: AEs, ORR, PK. Results: In regimen M, 20 pts (median [range] age: 52.5 [25-66] yrs) were treated for median [range] 151 [62340] days (20 mg n = 7; 30 mg n = 6; 40 mg n = 7); of those evaluable for MTD, 1/6, 0/6 and 2/5 had dose-limiting toxicities (DLTs) in the RT period (2 grade [G] 4 thrombocytopenia and I G3 vomiting). Median afatinib + RT + TMZ exposure (16 mg/day, range 16 mg/day to 45 mg/day, G3 nausea, G1 diarrhea) was 134 days (median [range] 168 [1397] days) at 20 mg n = 3; 40 mg n = 13); of those evaluable for MTD, 0/3 or 1/6 had DLTs (1 G3 diarrhea) in the RT period. MTD of afatinib + RT was 40 mg/day. Common treatment-related AEs (TRAES) are shown in the Table. ORRs were 25% and 6% in regimens M and U, respectively. PK evaluation indicated that combination of afatinib with RT + TMZ had no influence on afatinib exposure. Conclusions: The MTD of afatinib + RT was 30 mg/day with TMZ and 40 mg/day without TMZ. The safety profile of afatinib + RT + TMZ was as expected, based on the known profiles of the individual agents. Common TRAES Clinical trial information: NCT00977431.

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Neurologist assessment in neuro-oncology (NANO) scale was developed as a standardized metric to objectively measure neurologic function in patients with brain tumors to complement radiographic assessment in defining overall outcome. The scale has been incorporated in various prospective studies to assess pts and to determine its utility. Methods: A multicenter, open label, phase II trial of pembrolizumab with and without bevacizumab in pts with recurrent glioblastoma (GBM) incor-
porated NANO scale as an exploratory endpoint. Neurologic examination by NANO was documented at baseline and each cycle until pts came off study. Statistical analyses including descriptive data analysis and gener-
alized linear models were performed using R (version 3.4.3). Results: Eighty
pts received treatment on study and underwent NANO evaluations. NANO compliance rate was 94%; of a total 388 expected NANO evaluations, 24 were missing. Of 80 pts, 7 missing NANO at baseline visit were excluded from analysis. Fifteen pts did not have end of treatment NANO evaluation. Of 73 pts, 35 (48%) had a normal neurologic examination at baseline by NANO. Two NANO domains (strength and language) accounted for the majority of variability in neurologic function over the course of study treatment. There was a significant correlation between NANO at each cycle and Karnofsky performance status score (p = 0.02). Nineteen pts were on dexamethasone at baseline; 42 required dexamethasone during study. Corticosteroid regimen (OR: 1.06, p = 0.001) and an increase in corticosteroid dose (OR: 2.6, p < 0.001) were associated with higher risk of NANO progression (PD). Eighteen pts (25%) met NANO criteria for PD, including 2 without PD on MRI. Three pts (4%) had a neurologic response per NANO criteria associated with stability on MRI. Conclusions: Evaluation of neurologic function by NANO was feasible in a multicenter prospective study in GBM pts with a high compliance rate. NANO was able to objectively track neurologic function throughout the trial including preservation of baseline status in non-progressors. Clinical trial information: NCT02337491.

Concordance between RTOG and EORTC risk factors in low grade gliomas: Who will remain standing in the ring at bell’s sound? First Author: Enrico Franceschi, Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy

Background: Low grade gliomas (LGG) are a heterogeneous group of brain primary tumors. The EORTC and the RTOG criteria are the most valuable scores to evaluate risk factors and for treatment decision. However, there is no data about concordance between criteria. Methods: We conducted an analysis on LGG patients treated in our Institution from 1998 to 2015. The population was stratified by RTOG criteria and whenever feasible we assessed the risk using both RTOG and EORTC criteria. Results: Median follow up (mFU) was 78.6 months. We evaluated 204 patients with histo-
logically diagnosed LGG. All the patients were stratified by RTOG criteria and a subgroup of 51 patients by both RTOG and EORTC criteria. The univariate analysis showed a statistically significant difference according to RTOG criteria (p = 0.01) for both OS and PFS. Low risk patients had a better OS compared to high risk group (211.0 vs 145.5 months, p = 0.01) and a longer PFS (60.0 vs 39.8 months, p = 0.005). The multivariate analysis confirmed that RTOG risk was an independent prognostic factor (p = 0.024). In the subgroup of 51 patients stratified by both RTOG and EORTC risk-factor criteria, the concordance was 54.9% (K = 0.113, p = 0.08). All the EORTC high risk patients (n = 25) were high risk also with RTOG criteria. Among the 26 EORTC low risk patients, only 3 (11.5%) were low risk with RTOG criteria, while 23 (88.5%) would have been deemed as high risk. In this population, after a FU or 91 months, no statistical difference regarding OS and PFS was documented applying either RTOG or EORTC criteria, probably due to the limited population. Conclusions: The concordance between RTOG and EORTC criteria is low, especially in the evaluation of low risk patients. So far, we cannot compare clinical trials adopting different risk criteria.
Phase II trial of SurVaxM combined with standard therapy in patients with newly diagnosed glioblastoma. First Author: Manmeet Singh Ahluwalia, Cleveland Clinic; Cleveland, OH.

Background: To determine 6-month progression-free survival (PFS-6), 12-month overall survival (OS-12) and immunologic response in newly diagnosed glioblastoma (nGBM) treated with concurrent temozolomide (TMZ) and radiation, followed by adjuvant TMZ and surfivin-targeted immunization with SurVaxM (SVM53-6/MS7-KLH). Methods: A single-arm, multi-center phase II trial was conducted in 63 evaluable patients with nGBM with HLA-A*02: A*03, A*11 and A*24 haplotypes and Karnofsky performance status ≥70. Patients (Pts) underwent craniotomy with near-total resection (< 1 cm³ residual contrast enhancement), followed by chemoradiation (Stupp) were eligible. Pts received 4 priming doses of SurVaxM (500 mcg) with Montanide and sargramostim (100 mcg) every 2 weeks, followed by adjuvant TMZ and maintenance SurVaxM every 12 weeks until progression. Immunogenicity of SurVaxM was assessed using expansion of survivin-specific CDB+ T-cells and survivin antibody (IgG) levels. Results: Interim analysis of the first 55 pts. Pts ranged in age from 20-82 yrs (median = 60), male/female = 32:23 with survivin tumor expression of 1-40% (median = 12%) by immunochemistry. PFS-6 was 96.3% (+2.8, -10.3) (n = 55) measured from diagnosis and 62.8% (+12.5, -16.2) (n = 43) from first immunization. OS-12 was 90.9% (+6.1, -16.5) (n = 33) from diagnosis and 70.8% (+14.1, -22.4) (n = 24) from first immunization. Median time to first immunization was 3.0 mo (1.9-4.0 mo). The regimen was generally well tolerated and immunogenic events were mild with no serious adverse events attributable to SurVaxM. The drug was highly immunogenic and produced survivin-specific antibody (IgG) titers and CDB+ T-cells detectable by survivin dextramers. IDH-1, MGMT methylation status, HLA class I haplotype, survivin expression levels, and the relationship of these variables to survival will be presented. Outcomes will be compared to historical patients receiving Stupp regimen, and Stupp plus Optune. Conclusions: Standard therapy plus SurVaxM appears promising in nGBM compared to standard therapy alone. The use of SurVaxM is safe in nGBM. A randomized, prospective trial of SurVaxM in glioblastoma is planned. Clinical trial information: NCT02455597.

Association of anticonvulsant prophylaxis in patients with primary and metastatic brain tumors and 1-year overall survival. A systematic review and meta-analysis. First Author: Timothy J Brown, The University of Texas Southwestern Medical Center, Dallas, TX.

Background: Despite high-quality evidence suggesting anticonvulsant prophylaxis in primary and metastatic brain tumors does not improve seizure outcomes, debate persists on the use of anticonvulsants in these patients. Valproic acid use has attracted particular interest due to its histone deacetylase and CYP2C9 inhibitory action. We sought to determine if the body of the world’s literature supports the use of anticonvulsant prophylaxis to improve survival in patients with primary or metastatic brain tumors. Methods: A systematic review of PubMed and EMBase was performed with MeSH headings to identify all studies of anticonvulsant prophylaxis in adult patients with primary or metastatic brain tumors. Data was extracted from the text of included studies or from survival curves. Statistics were performed using Cochrane ReviewManager software. Endpoints of interest were one-year overall survival. Results: Two-hundred seventy-six studies were reviewed. Eleven studies of 3767 patients with primary and metastatic brain tumors were included in the analysis of survival with any anticonvulsant, while ten studies of 3576 patients provided survival data with valproic acid. Compared to control, any anticonvulsant prophylaxis was associated with a relative risk (RR) of death of 0.88 [95% confidence interval 0.81-0.94, p = 0.0006]. Valproic acid compared to control was associated with RR of death at one year of 0.86 [95% CI 0.79-0.93, p = 0.002]. Eight studies of 3194 patients with glioblastoma associated a RR of death at one year of 0.86 [95% CI 0.75-0.99, p = 0.04] with any valproic acid prophylaxis compared to none. Two studies of 344 patients examined the effects of non-valproic acid anticonvulsant prophylaxis demonstrated no significant effect on the RR of death at one year, 0.90 [95%CI 0.79-1.03, p = 0.13], compared to control. Conclusions: In this meta-analysis of anticonvulsant prophylaxis in patients with primary and metastatic brain tumors, anticonvulsant prophylaxis was associated with a significant survival benefit at one year. This association appears to be driven primarily by valproic acid prophylaxis.
A randomized phase 2 trial of veliparib (V), radiotherapy (RT) and temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) glioblastoma (GBM). Feasibility, outcomes, (IUO; VERTU study). First Author: Mustafa Khasawar, Royal North Shore Hospital/University of Sydney, St Leonards, Australia

Background: TMZ offers minimal benefit in uMGMT GBM pts. V is synergistic with both RT and TMZ in preclinical models, safe when combined with either RT or TMZ clinically but the triplet (V+RT+TMZ) is poorly tolerated. This study examines a novel approach to patients with uMGMT GBM.

Methods: VERTU is a randomized Phase 2 trial comparing a (sequential arm) = RT (60gy/30 fractions) + V (200mg BID) followed by TMZ (150-200mg/m² D 1-5) + V (40mg bid, D 1-7) every 28 days for 6 cycles vs Arm B (Standard of care) = RT (60gy/30 fractions) + TMZ (75mg/m² daily) followed by TMZ (150-200mg/m² D 1-5) every 28 days for 6 cycles in pts with newly diagnosed uMGMT GBM. The study aims to randomize 120 pts (2:1 to the experimental arm). The primary endpoint is 6 months Progression Free Survival (6PFS) with multiple secondary and tertiary endpoints. Evaluation of feasibility and safety was planned after completion of RT in the first 60 pts (Stage 1). Acceptable feasibility and safety criteria for study continuation was defined as ≥70% of pts on the experimental arm completing 70% of the planned treatment with ≤30% of pts having any ≥ Grade (G) 3 Adverse Events (AEs). (ANZCTR #ACTRN12615000407594) Results: 60 pts have been randomized in Stage 1 (Arm A = 39, Arm B = 21). Patient characteristics (age, gender, performance status, and extent of resection) were well matched. All 39 pts in the experimental arm and all 31 pts in the standard arm completed the planned V treatment, receiving at least 70% of the full V dose and 80% of the planned RT dose. Eleven pts (28%) in the experimental arm experienced ≥ G3 AEs during concurrent treatment. The commonest severe AEs were seizures observed in 3pts in each arm, 7% in the experimental arm and 15% in the standard arm; followed by 1 pt in each arm experiencing grade 2 AEs, 5% in the experimental arm and 10% in the standard arm.

Conclusions: Stage 1 of VERTU satisfied the predefined feasibility and safety criteria and the study will continue until the accrual target (120pts) is reached (anticipated mid-2018). Efficacy endpoints will be analyzed and reported after completion of accrual. Clinical trial information: 12615000407594.

Updated results of REGOMA: A randomized, multicenter, controlled open-label phase II clinical trial evaluating regorafenib in relapsed glioblastoma (GBM) patients (PTS). First Author: Giuseppe Lombardi, Department of Clinical and Experimental Oncology, Medical Oncology 1, Veneto Institute of Oncology, IUOV-IRCCS, Padua, Italy

Background: There is no established treatment regimen for recurrent GBM. GBMs have activation of multiple signaling pathways in the tumor microenvironment, including the receptor tyrosine kinases, VEGFR, FGFR, and PDGF receptors. PDGFR, a receptor, is a multi-kinase inhibitor, inhibits these angiogenic kinases and the mutant oncogenic kinases KIT, RET, and B-RAF. Methods: We present, after the first analysis, the updated results of REGOMA trial. The primary aim of this trial was to assess REG activity in prolonging overall survival (OS) in PTS with relapsed GBM after surgery and Stupp regimen (α = 0.2, 1-sided; β = 0.2). Secondary objectives were PFS, disease control rate (DCR), safety, quality of life (Qol); exploratory objectives included analysis of metabolic tissue biomarkers as possible predictors of response. PTS with histologically confirmed GBM, ECOG PS 0-1, documented disease progression were randomized 1:1 to receive REG 160 mg/day (3 weeks on, 1 week off) or lomustine (LOM) 110 mg/m² (every 6 weeks) until disease progression or unacceptable toxicity. Tumor response was evaluated by brain MRI every 8 weeks according to the RANO criteria. Results: 119 PTS were randomized (n = 59 REG; n = 60 LOM) and stratified for surgery at re-recurrence; baseline characteristics, including MGMT methylation status, were balanced. Median age was 57.3 yrs; 27 PTS (22.7%) had surgery at recurrence, 22% and 23.3% in REG and LOM arm. At the time of the analysis (cut-off date: Dec 31, 2017), median follow up was 15.4 months(m), 99 PTS had died. Median OS was 7.4m (95% CI 5.8-12.0) for REG and 5.6m (95% CI 4.7-7.3) for LOM (HR = 0.50, 95%CI 0.38-0.65; p = 0.0007; 1-sided Log-rank test); 12 REG OS rates were 38.9% and 15.0% for REG and LOM. 6m-PFS rates were 16.9% and 8.3% (HR = 0.65; 95% CI 0.45-0.95; p = 0.0223) for REG and LOM, DCR was 44.8% and 21.1% (p = 0.009) for REG and LOM. Grade ≥ 3 adverse events were reported in 56% and 40% for REG and LOM, no treatment-related deaths were reported. Conclusions: In this phase II clinical trial, treating recurrent GBM with REG, we observed OS and PFS benefit in an open-label randomized trial versus LOM. Despite the limited sample size, these preliminary results are promising. A larger, longitudinal study of Qol quantification and its relationship to GBM is needed in our institution.
Preoperative and non-invasive prediction of chromosome arm 1p/19q codeletion in oligodendrogial tumors using MRI-based radiomics. First Author: Jingwei Wei, Chinese Academy of Sciences, Beijing, China

Background: Oligodendroglioma tumor (OT) is a main subtype of gliomas carrying poor prognosis. Fortunately, part of OT patients with chromosome 1p/19q codeletion show favorable response to chemo/radiotherapy and improved survival. Preoperative knowledge of 1p/19q codeletion could beyond doubt provide reasonable evidence for personalized treatment decision making. However, the 1p/19q co-deletion genotype is currently examined via invasive biopsy-based methods, which are highly risky causing neurologic deficit. Thus, it arouses an urgent need to develop a non-invasive approach for early prediction of 1p/19q codeletion. Hence, we used a new technique termed radiomics to perform the prediction on 1p/19q status using magnetic resonance imaging in this study. Methods: A cohort of 262 OT patients was collected from Beijing Tiantan Hospital and divided into training (n = 175) and validation (n = 87) datasets. We extracted 647 three-dimensional imaging features on T2-weighted images to describe the archetypal cancer phenotypes. Qualified features were selected by reproducibility and stability analysis. Random forest algorithm was finally adopted to perform the classification between 1p/19q codeletion and non-codeletion. Moreover, comparisons were explored between relevant clinical predictors and the proposed radiomics model. Results: The radiomics model demonstrated satisfactory performance on both the training and validation cohorts with areas under curve (AUCs) of 0.889 and 0.743, respectively. Among the top three most significant features, there were features with first-order intensity features (CoIf1_fos_kurtosis, ori_fos_skewness), and one textural feature (ori_glc, cluster_shade). The radiomics model outperformed the clinical factor: heterogeneous intensity, the AUCs of which were 0.580 and 0.616. When combining the radiomics features and the clinical factor together, it turned out to be the best predictive result with AUCs of 0.891 and 0.739. Conclusions: Our study highlights that radiomics model can effectively identify the 1p/19q codeletion in OTs by a non-invasive manner, thereby offering preoperative evidence for the treatment regime planning.

Non-invasive determination of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status in glioblastoma (GBM) using magnetic resonance imaging (MRI). First Author: Saima Rathore, Center for Biomedical Image Computing and Analytics, Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: MGMT promoter methylation is associated with better prognosis and increased benefit from temozolomide in patients with GBM. The methylation status of the MGMT promoter is typically determined by tissue-based polymerase chain reaction assays, which can be limited by inadequate specimen or assay failures. We hypothesized that multivariate analysis of quantitative imaging (QI) features, extracted from multi-parametric MRI (mpMRI), could enable the non-invasive determination of MGMT promoter methylation status. Methods: We performed a retrospective cohort study of 111 GBM patients at the University of Pennsylvania whose tumors underwent MGMT methylation testing (pyrosequencing across 4 CpG sites in the MGMT promoter) and for whom pre-operative structural mpMRI data (T1, T1-Gd, T2, and T2 FLAIR) were available. For each enhancing and non-enhancing tumor sub-region and its peritumoral edema/invasion, we extracted a diverse set of QI features comprising volumetric, morphologic, and texture characteristics, histogram-based signal profiling, and spatial distribution patterns. These features were multivariately integrated via a support vector machine to construct a non-invasive marker of MGMT promoter methylation that was quantitatively evaluated using a 10-fold cross-validation (CV). Results: 40 patients (36%) were positive for MGMT promoter methylation and 71 (64%) were negative. The accuracy of the non-invasive MGMT methylation marker was 88.28% (Specificity = 97.0%, Sensitivity = 75.0%, Area under the curve (AUC) = 0.80). The most predictive features were consistently selected across the 10-fold CV. Conclusions: Multivariate integrative analysis of QI features extracted from mpMRI yields an accurate, non-invasive marker of MGMT promoter methylation status in GBM. If validated in larger datasets, this marker may allow for early stratification of newly diagnosed GBM trial candidates by MGMT methylation status, non-invasive MGMT methylation testing in patients for whom tissue is inadequate, and potential monitoring of MGMT methylation status during treatment.
Background: Glioblastoma (GBM) remains an incurable disease that is associated with impaired immunity. Recently, immune checkpoint inhibitors (ICIs) have demonstrated efficacy in several solid tumors including brain metastases. This study evaluated the safety of anti-CTLA-4 (Ipilimumab; IPi) and anti-PD-1 (Nivolumab; NIVo) ICIs alone or in combination in newly diagnosed GBM during adjuvant temozolomide (TMZ) treatment. Methods: This is a single case study of IPi (3mg/kg), NIVo (3mg/kg), and the combination (1 mg/kg & 3 mg/kg respectively) followed by an expansion cohort for the combined treatment of adults with confirmed unifocal, supratentorial newly diagnosed GBM after gross or near total resection. Treatment with ICIs started after standard chemo-radiotherapy along with adjuvant TMZ; starting dosing of ICIs were at target with dose reduction planned for toxicity. The primary endpoint was the dose limiting toxicity (DLT) from the start of ICIs to 8 weeks after each in arm. A standard up-and-down design was used, with 6 evaluable patients enrolled at a given dose level. The dose level would be declared safe if no more than 1 of 6 had an DLT. Results: Thirty-two patients were enrolled at 9 individual dose levels, 6 to each arm and 14 to the expansion cohort. One patient treated, yielding 31 analyzable. Median age was 54 years (range: 23-74), 68% were male and 84% were white. Overall, treatment was well tolerated with a 16% rate of Grade 4 events; the combination did not have an increased toxicity rate and there was no reported Grade 5 event. One DLT was seen in each single-agent arm; one in the combination arm. Median follow-up time was 7.1 months (range: 0.5-21.3) for all analyzable patients, at which time 10 had progressed (32%) and 8 had died (26%). 7 due to disease progression and 1 due to pulmonary embolism. For the 18 patients who had at least 1-year follow-up, 6 on each arm, 3 died within 1 year, 1 on each arm. Conclusions: IPi and NIVo are safe and tolerable with similar toxicity profiles noted with other cancers when given with adjuvant TMZ for newly diagnosed GBM. These results provide necessary safety data justifying the performance of a subsequent trial to test the efficacy of ICIs in this disease. Clinical trial information: NCT02311920.

Correlation of immune infiltration of cytotoxic T cells and activated microglia in glioblastoma (GBM) post anti-PD1 therapy with response. First Author: Andrew Silverman, Columbia University Medical Center, New York, NY

Background: Glioblastoma (GBM) is an aggressive malignancy of the central nervous system with an abysmal prognosis. Recent advances in immuno-therapy, including anti-programmed cell death-1 (anti-PD1), has shown potential to improve outcomes for some GBM patients. In this study, we evaluate the immune cell densities in post-treatment biopsies from patients treated with anti-PD1 for refractory GBM. We hypothesized that density of both cytotoxic T lymphocytes (CTLs) and activated microglia is higher within the tumor microenvironment (TME) in patients who respond to anti-PD1. Methods: Formalin-Fixed, Paraffin-Embedded (FFPE) tumor samples from a preliminary cohort of five patients with GBM, 2 non-responders and 3 responders were analyzed using multiplex Immunofluorescence (qMIF). Response was classified as decrease in tumor volume by >50% and/or survival for 6 months without growth of tumor by >25%. Stains were sequentially applied, using Opal multiplexing/qMIF for CD3 (T cells), CD8 (cytotoxic T lymphocytes (CTLs), FOXP3 (regulatory T cells – Tregs), CD68 (microglia), HLA-DR (immune activation/tumor presentation), and SOX2 (tumor marker). Multispectral images (MSIs) were acquired using Vectra and analyzed using inForm software and R studio to evaluate density of immune phenotypes within the TME. Results: We find that post-treatment, the patients who responded to anti-PD1 have a significantly increased CTL/total CD68 density (p = 0.0393) and higher activated microglia CD68+HLA-DR+/total CD68 density (p = 0.0208), when compared to non-responders. Tregs were rarely seen in either subset of patients and had no significant correlation with response. Conclusions: Preliminary analysis demonstrates higher CTLs and activated microglia in the TME after treatment in patients with GBM who responded to anti-PD1 therapy. Analysis of a larger cohort of 17 patients with specimens at baseline, recurrence and post anti-PD1 is under way and will be presented at the meeting. This data would confirm that anti-PD1 can induce increased inflammation within the TME in GBM despite the blood brain barrier and suggest that further alteration of the immune TME may improve outcomes in GBM.

GEINO 1402: A phase Ib dose-escalation study followed by an extension phase to evaluate safety and efficacy of crizotinib in combination with temozolomide (TMZ) and radiotherapy (RT) in patients with newly diagnosed glioblastoma (GB); Results of the dose-escalation phase. First Author: Maria Martínez García, Hospital del Mar, Barcelona, Spain

Background: Crizotinib is an ALK, ROS-1 and c-MET inhibitor with an interest in the treatment of ALK, ROS-1 and c-MET positive non-small cell lung cancers. This study established the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of crizotinib in combination with RT and TMZ. Methods: Eligible patients received crizotinib with standard RT and TMZ and afterwards continued crizotinib daily with sequential adjuvant TMZ. Additional treatment with crizotinib beyond 6 TMZ cycles was allowed at the discretion of physician. Crizotinib MTD was determined using a standard “3+3” dose escalation design. Dose-limiting toxicities were observed during the first 12 weeks of therapy. Results: 12 patients (median age: 53.5, 33-60 y) were enrolled in 3 crizotinib cohorts (200 mg/QD, 250 mg/QD and 200 mg/BID). Most common adverse events (all grades) were: nausea (66.7%), asthenia (98.3%), transaminits (50%), neutropenia (50%), constipation (41.7%) and diarrhea (41.7%). Seventeen drug-related AEs ≥ G3 were reported, 5 neutropenia, 2 thrombopenia, 2 transaminitis, 1 asthenia, 1 lymphopenia, 1 constipation and 1 hypophosphatemia. 3 DLTs were observed (transaminits G3, neutropenia G4 and constipation G3); 0/3 in cohort 1 (200 mg/QD); 1/6 in cohort 2 (250 mg/QD) and 2/3 in cohort 3 (200 mg/BID). Median follow-up of 18.3 m (months) (5.4-34.5) and 8 events, median PFS was 16.8 m (95% IC: 8.2-25.3). Three patients died and median OS has not been reached. OS at 6 m was 92%, at 12m 80% and 60% at 24m. Conclusions: On the basis of the observed safety and tolerability, the dose regimen of crizotinib 250 mg/QD in association to standard RT and TMZ has been selected for further investigation in the extension phase. At this point, efficacy results, especially PFS, seem very encouraging. Funding for this study was provided by Pfizer, Inc, New York, USA Clinical trial information: NCT02270034.
2057 Poster Session (Board #215), Sat, 1:15 PM-4:45 PM
Prospective analysis of cancer stem cell drug response assay for glioblastoma patients.
First Author: Tulika Ranjan, Duke University Medical Center, Durham, NC
Background: Over the past 20 years even with the aggressive standard of care (Soc) Stupp treatment protocol the prognosis of glioblastoma (GBM) has only minimally improved from 12 to 14 months. This is due in large part to the presence of chemo- and radiation-resistant GBM cancer stem cells (CSCs) that contribute to tumor propagation, maintenance, and treatment resistance. We are using ChemID, a CLIA certified and CAP accredited drug response assay that identifies the most effective chemotherapies against CSCs and bulk of tumor cells from of a panel of potential treatments, offering great promise for individualized cancer management. A prospective study was conducted evaluating the use of the ChemID drug response assay in glioblastoma patients. Methods: Fresh tissue samples were collected for drug sensitivity testing from 61 glioblastoma patients enrolled in IRB approved protocol. Patients were prospectively monitored for tumor response, time to recurrence, progression-free survival (PFS), and overall survival (OS). Odds Ratio (OR) associations of 12-month recurrence, PFS, and OS outcomes were estimated for CSCs, bulk tumor and combined assay responses to treatment; sensitivities/specificities, areas under the curve (AUC) were examined. Results: The data suggests that ChemID guided treatment significantly enhanced tumor response. For every 5% increase in ex-vivo cell kill of CSCs by assay-guided chemotherapy, 12-month patient response (non-recurrence of cancer) increased 2-fold, OR = 2.2 (p = 0.01). Bulk of tumor assay was found to statistically superior to ChemID. The median recurrence time was 20 months for patients with a positive (> 40% cell kill) CSCs test versus only 3 months with a negative CSCs test, whereas median recurrence time was 13 months versus 4 months for patients with a positive (> 55% cell kill) bulk test versus negative. Similar favorable results for the CSC test were obtained for PFS and OS outcomes. Conclusion: The ChemID drug response assay has the potential to increase the accuracy of bulk tumor assays to help guide individualized chemotherapy choices. Glioblastoma cancer recurrence may occur quickly if the CSC test has a low ex-vivo cell kill rate, even if the bulk tumor test cell kill rate is high.

2058 Poster Session (Board #216), Sat, 1:15 PM-4:45 PM
Phase 2 trial of SL-701 in relapsed/refractory (r/r) glioblastoma (GBM): Correlation of immune response with longer-term survival. First Author: David M. Perea-Bon, Cleveland Clinic, Cleveland, OH
Background: SL-701 is a novel immunotherapy comprised of synthetic peptides designed to elicit an anti-tumor immune response against GBM targets: interleukin-13 receptor alpha-2, EphrinA2 and Survivin. Updated Phase 2 data are reported. Methods: Patients with r/r GBM HLA-A2+, bevacizumab (bev)-naive and KPS > 60, enrolled. Stage 1: SL-701 with adjuvants GM-CSF and imiquimod dosed biweekly for 6 months, then q28 days. Stage 2: SL-701 with adjuvant poly-ICLC dosed biweekly with bev (10 mg/kg) for 6 months, then q28 days. Primary objectives: safety, tolerability, investigator assessed objective response rate (ORR, RANO criteria) and 12-month OS rate (OS-12). SL-701 specific CD8+ T-cell frequency was assessed by flow cytometry. PBMCs were isolated by density gradient and stimulated for 4h with SL-701 peptides (1mg/ml/peptide) before intracelular staining with live/dead, CD3, CD4, CD8, IFNγ, TNFa, IL-2, and PD-1. Results: As of 2/7/18, 74 bev-naive patients received median of 8.5 SL-701 doses. Most frequent treatment-related adverse events (TRAEs) were fatigue (22%) and injection site reaction (18%). Grade 3 TRAE was fatigue (3%), no on-grade 4 TRAEs. In Stage 1, 1 partial response (PR) (duration: 78 weeks) and 15 stable disease (SD) (median 16 weeks; range: 1.3–99) seen in 46 patients. In Stage 2, 2 complete responses (CR) (duration: 30, 46 wks), 4 PRs (median 31 weeks; range 12–47) and 19 SDs (median 14 weeks; range 0.4–41) seen in 28 patients. OS-12: 43% (median 11.7 mos) in Stage 2 and 24% (median 11 mos) in Stage 1. 5 patients received bev, 1 PR and 4 SDs. Conclusion: SL-701 with immunostimulants, alone and in combination with bev, demonstrated durable and immunomodulated anti-tumor activity including multiple major responses. There is also a preliminarily promising survival tail in r/r GBM patients who received SL-701 with bev Further analyses ongoing; updated data to be presented. Clinical trial information: NCT02078648.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
2061 Poster Session (Board #219), Sat, 1:15 PM-4:45 PM
Dianhydrogalactitol in bevacizumab-refractory GBM: Further analysis of a phase 1-2 trial. First Author: Kent C. Shih, Sarah Cannon Research Institute/ Tenacious Oncology, Nashville, TN.

Background: Dianhydrogalactitol (VAL-083) is a first-in-class DNA-targeting agent with anticancer activity established in prior NCI-sponsored trials. We have previously reported results of DLM-10-001 (NCT01478178), a multicenter Phase 1-2 trial of VAL-083 in bevacizumab refractory GBM (BEV-rGBM), with median overall survival (mOS) of 8.35mo from BEV failure and an observed dose response. Here, we report further analysis of OS in DLM-10-001 from the start of treatment for patients (pts) receiving a clinically active dose of VAL-083 compared to pts receiving an inactive dose of the agent and two derived controls of historical and recent electronic medical records (EMR) data. Methods: 45 BEV-rGBM pts were enrolled across 10 cohorts at doses ranging from 1.5mg/m2 to 50mg/m2. Pts received VAL-083 IV on days 1, 2, 3 of a 21-day cycle. MTD was established at 40mg/m2/day. A clinically active dose of VAL-083 was determined at or below 40mg/m2 based on PK data and in vitro studies against GBM cell lines included pts from 20, 30 & 40 mg/m2 dose cohorts. OS in DLM-10-001 was calculated from the 1st dose of VAL-083. DLM-10-001 trial data are also compared to historical publications of BEV-rGBM, and recent EMR for BEV-rGBM pts receiving salvage therapy with TMZ, CCNU or carboplatin. mOS and hazard ratios (HR) were estimated by Kaplan-Meier and nominal p-values to compare survival curves by log-rank test (MedCalc Software v18). Results: OS for BEV-rGBM pts treated with a clinically active dose of VAL-083 (mOS = 7.9mo, 95% CI = 3.1-19.6mo) was superior to OS for pts receiving placebo (mOS of 7.3mo vs 1.9mo; HR = 0.362, p = 0.0005); and EMR data (mOS = 2.9mo, HR = 0.399, p = 0.011). There was no statistical difference between the control groups. Pts receiving a clinically active dose of VAL-083 demonstrated an OS benefit compared to placebo as an aggregate of the controls (mOS = 2.9mo, HR = 0.395, p = 0.0003). Conclusions: The results suggest a statistically significant and meaningful OS benefit for BEV-rGBM pts treated with a clinically active dose of VAL-083. While small sample size and retrospective nature of the analyses is limiting, the results warrant further exploration via a randomized trial. Clinical trial information: NCT01478178.

2062 Poster Session (Board #220), Sat, 1:15 PM-4:45 PM
Neurological death in patients with EGFR-mutant non-small cell lung cancer. First Author: Matthew Ramotar, Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.

Background: Patients with EGFR mutant non-small cell lung cancer (EGFRmNSCLC) have a high incidence of brain metastases (BM). We sought to determine the rate of neurologic death in EGFRmNSCLC patients diagnosed with brain metastases. Methods: A single-institution prospectively managed database identified 204 patients with EGFRmNSCLC treated for brain metastases between 2000 and 2016. We estimated actuarial survival rates using the Kaplan-Meier method. The incidence of neurologic death (ND) was determined using a competing risks analysis. ND was correlated to clinical and treatment variables using Fisher’s exact test. Survival was calculated from the date of BM diagnosis. We defined neurologic death as death due to brain metastases or leptomeningeal disease Results: Fifty-six percent of patients had BM at the time of initial diagnosis. The initial BM treatment was up front stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), or tyrosine-kinase inhibitor (TKI) alone in 22, 60, and 18 percent of patients, respectively. Two-year rates of OS in these subgroups were 64%, 38%, and 50%, respectively (p = 0.016). The 5-year rate of neurologic death was 38%. Thirty-four percent died of non-neurologic causes, 8% died of unknown causes, and the remaining patients were alive at last follow-up. Median survival (MS) was 19 months; MS in patients who died of non-neurologic causes and neurologic causes was 23, and 15 months, respectively. Of age, staging, BM at diagnosis, history of TKI therapy, initial treatment of BM, staging at diagnosis, and leptomeningeal disease at diagnosis (LMD), only LMD was significantly associated with ND (p = 0.047).

Conclusions: Neurologic death due to EGFRmNSCLC BM was more common in our cohort than has been previously reported, highlighting the need for dedicated studies focused on the best management of BM in this population.

2063 Poster Session (Board #221), Sat, 1:15 PM-4:45 PM
Impact of prior systemic therapy on lymphocytic infiltration in surgically resected breast cancer brain metastases. First Author: Andrew Bacotti, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Tumor infiltrating lymphocytes (TILs) have been positively correlated with response to systemic therapy and for triple negative and HER2+ subtypes and clinical outcomes in early breast cancer (BC) (Denkert C et al., Oncotarget 2015). Reactive glial cells actively participate in cytokine-mediated T cell stimulation (Fitzgerald DP et al., Clin Exp Met 2008). The impact of prior medical therapy (chemotherapy, endocrine therapy, and HER2-targeted therapy) on the presence of TILs and gliosis in human BCBM has not been previously reported. Methods: In order to determine the impact of prior medical therapy on the presence of TILs and other histopathologic variables, we examined prior treatment data for 133 patients who underwent craniotomy for resection of BMs from the electronic medical record. We examined the relationship between prior systemic therapy exposure and the histologic features of gliosis, necrosis, hemorrhage, and lymphocyte infiltration (LI) assessed by hematoxylin and eosin stain in BCBM resected at subsequent craniotomy in uni- and multivariate analyses (Prince G et al, Proc ASCO 2017, abstract 2072). Results: Complete treatment data were available for 122 patients, 36 of 114 patients (31.6%) who had received prior systemic treatment had BCBM LI while BCBM LI was observed in 6 of 8 patients (75%) who had not received systemic treatment (significant by Fisher’s exact test p = 0.02). There were no statistically significant relationships between prior systemic therapy and the three other histologic variables examined. Conclusions: This observation suggests that systemic therapy may interfere with the immune response to BCBM. This motivates clinical investigation of strategies to enhance LI for therapeutic benefit to improve outcomes for patients with BCBM. Analysis of these tissue samples to address the potential significance of the pattern of LI as well as relevant biomarkers is ongoing.

2064 Poster Session (Board #222), Sat, 1:15 PM-4:45 PM
Outcomes of lung cancer patients with leptomeningeal metastases in the targeted therapy era. First Author: Kathryn Sara Novel, Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY, US.

Background: Recent improvements in detection and molecular characterization of leptomeningeal metastasis from lung cancer (LC-LM) coupled with cerebrospinal fluid (CSF)-penetrating targeted therapies have substantially altered the management of this disease. In this new era, outcomes of patients harboring LC-LM are not well defined. This study identifies molecular and clinical characteristics of LC-LM and correlates these with clinical outcome. Methods: We retrospectively reviewed charts of 171 patients diagnosed with LC-LM between June 2009 and June 2017 at Memorial Sloan Kettering Cancer Center. Presence of targetable mutations (TM) in the primary tumor and CSF was determined by MSKCC IMPACT. Extent of radiographic involvement was scored by number of gadolinium-enhancing sites in eight locations. CSF studies included cytopathology, quantification of circulating tumor cells (CTCs), and cell free DNA (cfDNA) analysis. Kaplan-Meier survival curves were compared by log-rank analyses. Results: Median overall survival (OS) after LC-LM diagnosis (dx) was 125 days; 80/171 patients harbored a TM. At one year, 29% of patients with a TM were alive versus 12% of those without. Treatment of LC-LM with targeted therapies (TTx) was associated with improved OS (0 TTx = 70 days, 1 TTx = 109 days, 2+ TTx = 307 days; p < 0.0001). A subset of 93/171 patients underwent MRI brain, spine and CSF studies within 30 days of LM dx. Extent of radiographic involvement correlated with OS: 0-2 sites of disease OS = 113 days, 3+ sites OS = 75 days; p = 0.015. CTCs were analyzed in 15/171 patients. Fewer than 50 CTCs/mL correlated with OS of 377 days, versus OS 66 days for > 50 CTCs/mL. cfDNA was extracted from 20/171 patients. cfDNA concentration correlated with outcome; cfDNA < 0.025 ng/μL of OS = 231 days, vs cfDNA > 0.025 ng/μL OS of 60 days; p = 0.022. Conclusions: In this largest study of LC-LM, presence of a TM and treatment with TTx were associated with improved OS. Extent of radiographic involvement at dx was also a prognostic indicator. These findings support complete molecular characterization and CNS staging for clinical management, prognostication and clinical trial stratification of LC-LM.

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2065  Poster Session (Board #223), Sat, 1:15 PM-4:45 PM
Impact of apolipoprotein E (APOE) genotype on neurocognitive function (NCF) in patients with brain metastasis (BM): An analysis of NRG Oncology’s RTOG 0614. First Author: Jeffry Scott Weigel, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Whole brain radiotherapy (WBRT) is a common treatment for BM and is associated with decline in NCF. The APOE e4 allele is associated with increased risk of Alzheimer’s disease, and NCF decline after chemother-apy for non-CNS cancer, treatment for primary brain tumor, and in ir-radiated mouse models. APOE carrier status has not been evaluated as a risk factor for impaired NCF in patients with BM before and after WBRT.

Methods: RTOG 0614 treated adult patients with BM with 37.5 Gy of WBRT (+/- memantine), performed NCF testing (HVLT-R, TMT, COWA) at baseline, 8, 16, 24, and 52 weeks, and included an optional blood draw for APOE analysis. APOE alleles were evaluated by real-time PCR based SNP analysis using TaqMan genotyping. NCF test results were compared at baseline and over time with mixed effects models adjusted for baseline score, treatment arm, time, and interaction between time and APOE carrier status. A cause-specific Cox model for time to NCF failure was performed to assess the effects of treatment arm (memantine versus placebo) and APOE carrier status (e4 versus e4). Results: APOE results were available for 262 (n = 227/508) of patients. No pretreatment differences were detected between patients with APOE available versus not available. APOE e4 carrier status was evenly distributed between treatment arms (e4 positive = 29.5%). NCF test results did not differ by APOE e4 carrier status at baseline, but e4 carriers were less often tested and had a lower test completion rate. Mixed effects modeling showed that patients with an APOE e4 allele had better memory after WBRT compared to patients with an APOE e4 allele (HVLT-R Total Recall [estimate = 2.44, p = 0.026]). Delayed Recognition [estimate = 1.15, p = 0.024]). For time to NCF failure, treatment arm was a risk factor for a greater NCF at 12 months (HR = 7.15, 95% CI: 2.998, p = 0.0487) in favor of memantine; however, APOE e4 status was not (HR = 0.865, 95% CI: 0.606-1.233, p = 0.422).

Conclusions: Patients with an APOE e4 allele exhibited worse memory function after treatment with WBRT (+/- memantine), but no difference in time to NCF failure. APOE carrier status was not associated with NCF in patients with BM prior to WBRT. Clinical trial information: NCT00566852.

2067  Poster Session (Board #225), Sat, 1:15 PM-4:45 PM
Mutational complexity increases in lung adenocarcinoma (LADC) with the development of brain metastasis (BM). First Author: Mallaree Main, Department of Hematology-Oncology, West Cancer Center/University of Tennessee Health Science Center, Memphis, TN

Background: Up to 40% of LADC patients (pts) develop BM but little is known about the inciting molecular events. Methods: We compared mutational profiles of LADC BM pts with primary (P) LADC submitted to Caris Life Sciences from 2015-2017. Testing included next-generation sequencing (NGS) to get our institutional 95 cancer-related genes, PD-1 IHC and tumor mutational burden (TMB). NGS aberrations were test-defined as pathogenic (PATH), variants of undetermined significance or unclassified mutations (VUS). TMB was defined as: high (H; >16 mutations/megabase), intermediate (I; 7-16) and low (L; 0-6).

Results: 145 BM (57% female (f)) and 1145 P (58% f) cases were identified; BM median age was 64 (range 31-86) vs. 70 (25-90) in P pts. BM had 55 PATHs (38% pts) in 28 receptor tyrosine kinases (RTK) were observed in 117 BM (145 BM (57% female (f)) and 1145 P (58% f) cases were identified; BM median age was 64 (range 31-86) vs. 70 (25-90) in P pts. BM had 55 PATHs (38% pts) in 28 receptor tyrosine kinases (RTK) were observed in 117 BM (50% (24% vs. 23%) cases were similar. 143 BM and 1102 P pts had TMB data. BM cases were more-frequently TMB-H compared to P (39% (N = 56) vs. 12% (332), P < 0.0001) and less likely to be TMB-L (8% (12%) vs. 33% (366), P < 0.0001). 131 (92%) BM pts were TMB-I or H. Of 142 BM and 1060 P with PD-L1 testing, incidence of ≥1% (46% BM vs. 49% P) and ≥5% (24% vs. 23%) cases were similar. 327 VUS in 28 receptor tyrosine kinases (RTK) were observed in 117 BM (median 1 (0-12)) vs. 1648 VUS in 807 P pts (median 1 (0-13); 79% vs. 70%, P = 0.007). RTK VUS more frequently observed in BM included: 51 EP3A VUS (17% pts vs. 8%; P = 0.0002), 25 EP3A (15% vs. 8%; P = 0.004), 26 NTRK3 (14% vs. 6%; P = 0.0002) and 22 EP3A (13% vs. 6%; P = 0.0003), 151 NTRK1 and 12% (12% vs. 11%; P = 0.3). No significant difference was observed between BM specimen site and EGFR, KRAS, TMB and PD-L1 status.

Conclusions: While classic LADC biomarkers including PD-L1, EGFR and KRAS were similar between BM and P cases, nearly 40% BM pts were TMB-H (>25% more than P) and >90% either BM-I or H, indicating an incremental increase in BM development, suggesting immune checkpoint inhibitor use. In addition to STK1J1 PATHs, RTK VUS including NTRK3, EGFR, EP3A and EP3A were more-frequently mutated and warrant further evaluation as biomarkers or targets in BM.

2066  Poster Session (Board #224), Sat, 1:15 PM-4:45 PM
Incidence of treatment effect and characteristic MRI findings in immunotherapy-treated melanoma patients with brain metastases receiving stereotactic radiosurgery. First Author: Justin Lin Sovich, University of Michigan, Ann Arbor, MI

Background: Melanoma brain metastasis (MBM) treated with stereotactic radiosurgery or stereotactic body radiation therapy (SRS/SBRT) and immunotherapy may have higher rates of treatment-related injury including radiation necrosis, which can be difficult to differentiate from disease progression. Little is known about characteristic radiographic findings to guide decision-making. Methods: We identified all patients (pts) with MBM from the University of Michigan from 2012-2017 who were treated with SRS/SBRT. Pts receiving immunotherapy were compared to those who had not. Overall incidence of treatment-effect (TE) (pathologically confirmed or inferred by > 6 mos stable imaging) were calculated. We reviewed MRIs in pts with TE for conventional metrics including enhancement, T2 hyperintensity, and apparent diffusion coefficient (ADC) and perfusion parameters including calculated blood volume (rBV), blood flow (rBF, time to maximum (tMAX), and leakage (K2)). Results: 104 pts received SRS/SBRT and immunotherapy and 29 pts had not. Among the immunotherapy group, 16 had TE (6 pathologically confirmed, 10 by serial imaging) (15.4%). Of the 29 who did not receive immunotherapy, one had TE (pathologically confirmed) (3.4%). The observed risk difference was 12.0% (95% CI 2.4% to 21.6%). We reviewed MR findings for 18 lesions in 15 pts with TE, all of which had enhancement with T2 hyperintensity. Reliable ADC values were calculated for 10 lesions, average rADC ranged from 72 to 120%). Perfusion rBV was available for 9 lesions, with average rBV 1.63 (range 0.63 to 3.6). rBF 23.86 (9 to 54.5), tMAX 5.71 (0.99 to 27), and K2 -266.78 (-1110.6 to -36).

Conclusions: SRS/SBRT and immunotherapy resulted in higher absolute risk of treatment-related changes. MRI findings were consistent with existing data on radiation necrosis in glioblastoma multiforme which could help guide decision making in MBM. Comparative analysis on tumor progression in this population is ongoing and will be presented.

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Background: Brain metastases (BM) in patients (pts) with melanoma have improved, median survival remains 15 months. Several studies have demonstrated that among patients with melanoma BM receiving ICI. We hypothesized that texture analysis of contrast T1-weighted imaging may provide additional information about the radiographic features of BM that are associated with durable responses in a subset of pts. There are no prior reports of texture analysis in pts with BM.

Methods: Between 2010 and 2017, we retrospectively reviewed pts with measurable (>1.0 cm) melanoma BM on MRI who received ICI with or without concurrent radiation therapy (RT). Volume-of-interests were drawn around up to 5 BM per pt, and Haralick textures (n = 5), and Gabor edge features (n = 4) at angles (0, 30, 45, 90) and a bandwidth (γ = 2) were extracted for each lesion. Progression for BM was determined using RANO-BM; pts who died without repeat MRI were considered to have progressed. OS was calculated from date of ICI receipt. Cox regression was performed for each texture feature. Results: 88 pts with 196 total BM were identified. Median age was 63.5 (19-91), ECOG 0-5, 3-4, 2-2, 38% had elevated LDH, and 42% had prior systemic treatment. ICI was CTLA-4 monotherapy in 77%, PD-1 monotherapy in 9%, and PD-1 + CTLA-4 in 14%. 79% received concurrent RT (38% focal, 62% whole brain). Median OS was 5.4 months (0.3-80.9). Increased energy (HR = 1.04, 95%CI 1.01-1.07, p = 0.03) was associated with a poorer prognosis. There were no significant associations with classically radiosensitive tumors or prior or planned whole brain radiotherapy were detected. LMD pattern was categorized as either nodular or linear ("sugarcoating"). Results: The study cohort consisted of 147 pts. The most common primary sites were lung (40%), breast (24%), and melanoma (16%). The majority of pts received post-op SRS (94%) with breast patients often receiving HER-2 positivity (60%). The majority of resected BM (82%) extended to within 5 mm of the pial surface. Median time from initial SRS to 1st LMD was 5.6 months (interquartile range [IQR] 3.2 – 11). The median number of nodules was 2 (IQR 1 – 4), with a median distance of 2.5 cm from the surgical corridor (IQR 1.5 – 5.2). Most pts (60%) were symptomatic at time of LMD diagnosis, of which the most common symptoms were headache (58%), cranial nerve deficit (28%), and dizziness/balance issues (24%). Of the pts who required LMD treatment and had follow-up imaging (n = 101), 50% experienced 2nd LMD at a median of 5.5 months after 1st LMD (IQR 2.8 – 9.4). Of these, 68% were symptomatic at the time of 2nd LMD diagnosis, 58% had nodal LMD with a median of 1 nodule (IQR 1-3), and 70% underwent salvage therapy. Conclusions: In the first ever analysis of higher order MRI features in pts with melanoma BM receiving ICI, Haralick texture features are associated with both PFS and OS. Further research is required to determine whether these features are independently associated with OS in a multivariate analysis.
TPS2074  Poster Session (Board #230b), Sat, 1:15 PM-4:45 PM

Phase I/II study of laser interstitial thermotherapy (LITT) combined with checkpoint inhibitor for recurrent glioblastoma (rGBM). First Author: Andrew E. Sloan, University Hospital Case Medical Center, Cleveland, OH

Background: Glioblastoma (GBM) has a survival of only 3-5 months at recurrence. Salvage chemotherapy has been largely ineffective with PFS-6 rates of 10-15%. Bevacizumab’s impact on OS is modest at best. Thus, there is a pressing need for minimally invasive, approaches to debulk rGBM such as laser interstitial thermotherapy (LITT). Methods: Rationale for treating GBM with LITT: Laser interstitial thermotherapy (LITT) is a minimally invasive technique for ablating tumors percutaneously using thermal radiation which has demonstrated efficacy in several non CNS tumors. Subsequent studies reproduced the efficacy of LITT for glioma demonstrating that survival was consistently related to tumor volume and a minimal dose threshold. This suggested the possibility of an abscopal effect mediated by unmasking of tumor antigens by LITT as has been previously demonstrated for ionizing radiation (radiotherapy). Rationale for Immunotherapy for rGBM: GBM patients are known to have elevated levels of immunosuppressive cells such as Treg, M2 macrophages and MDSC, both in the tumor as well as in the systemic circulation. Rationale: Immunotherapy targeting co-inhibitory checkpoints such as CTLA-4 and PD-1 have proven highly effective for some solid tumors. The first trial targeting CTLA + PD-1 in rGBM demonstrated evidence of safety. Interestingly, targeting PD-1 concurrent with RT appeared to be synergistic and was effective in preclinical models. However, patients with rGBM have typically received maximum tolerated radiotherapy and are thus not candidates for additional RT off trial. We hypothesize that thermal radiation delivered using LITT technology interferes with tumor microenvironment, minimizing immunosuppression and re-introducing tumor neoantigens. The primary objective of this phase II trial is to estimate radiological response to LITT + pembrolizumab and compare this to that observed for LITT alone. Each patient will undergo a stereotactic biopsy followed by 200 mg pembrolizumab at various times before or after LITT. Secondary endpoints include a putative serum biomarker for GBM. Here we present the concept and the outcomes of the first patients in the study. Clinical trial information: NCT 03277638.

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2500 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Single agent activity of ZW25, a HER2-targeted bispecific antibody, in heavily pretreated HER2-expressing cancers. First Author: Funda Meric-Bernstam, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ZW25, a novel Azymetric bispecific antibody, targets HER2 domains ECD2 and ECD4, resulting in multiple differentiation mechanisms of action including increased tumor cell killing, blockade of ligand-dependent and independent growth, and improved receptor internalization and downstream activation of trastuzumab (T). In vivo, HER2-targeted activity in HER2-low to high expressing models. This Phase 1 study evaluated ZW25 single agent safety and anti-tumor activity. Methods: Part 1 (P1) evaluated ZW25 5, 10 and 15 mg/kg weekly and 20 mg/kg biweekly using a 3+3 design to identify a recommended dose (RD) for further study. Part 2 (P2) is ongoing and evaluating safety and efficacy in separate expansion cohorts, including HER2-high (IHC 3+ or 2+ + FISH+) breast (BC), gastric/esophageal (GE), and other cancers. Pts had to have progressive disease after standard of care, including HER2-targeted agents. Adverse events (AE), PK, and response per RECIST 1.1 (every 8 wks in pts with measurable disease) were assessed. Results: 33 pts have been treated in P1 and P2: 17 BC, 11 GE and 5 other cancers. HER2-high BC pts had prior T and T-DM1 (100%), pertuzumab (82%) and lapatinib (53%), with a median of 6 HER2-targeted regimens for metastatic disease. All GE pts had received prior T, with a median of 4 systemic tx. Safety and anti-tumor activity were similar across dose levels with no DLTs. The RD for Part 2 was 10 mg/kg weekly or 20 mg/kg biweekly. The most common AEs were diarrhea and infusion reaction, all Gr 1 or 2, with no tx-interruption. Other n=3

Conclusions: ZW25 is well tolerated with promising single agent antitumor activity in pts with heavily pretreated HER2-expressing cancers that have progressed after standard of care, including multiple HER2-targeted regimens. These data support the therapeutic potential of ZW25 and suggest that its unique MOA may overcome mechanisms of resistance to other HER2-targeted agents.

Clinical trial information: NCT02892123.

2502 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

A multi-histology basket trial of ado-trastuzumab emtansine in patients with HER2 amplified cancers. First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Human epidermal growth factor receptor 2 (HER2, ERBB2) amplification occurs in 2-5% of non-breast non-gastric cancers. Ado-trastuzumab emtansine is a HER2 targeted antibody drug conjugate that may have activity against a variety of cancers driven by HER2 amplification. Methods: Patients with HER2 amplified cancers were enrolled into a multi-histology basket trial of ado-trastuzumab emtansine, treated at 3.6 mg/kg every 3 weeks. The primary endpoint was overall response rate (ORR) using RECIST v1.1 or PERCIST. A Simon two stage optimal design was applied to each histology cohort with type I error rate under 2.7%, power of 89%, H0 10%, H1 40%. Other endpoints include duration of response (DOR), progression-free survival (PFS) and toxicity. HER2 amplification was identified by next generation sequencing (NGS), and tumors with adequate tissue were subsequently tested by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Results: 58 patients were treated across 8 cohorts of advanced lung, endometrial, salivary gland, biliary tract, ovarian, bladder, colorectal and other cancers. The median age was 63 (range 34-90) years, 72% were female. The median lines of prior systemic therapy was 2 (range 1-7). ORR was 26% (14/53 confirmed, 95% CI 15-40%), including 50% (3/6) for lung cancers, 22% (4/18, 2) for endometrial cancers, 100% (5/5, 3 CR) for salivary cancers, 17% (1/6) for biliary cancers, 17% (1/6) for ovarian cancers, not included are local regional intolerance testing confirmatory. Median DOR was 8.1 months (range 2-22+), median PFS was 3 months (95% CI 2-6). There was 1 (2%) grade 3 febrile neutropenia, but no treatment related deaths. The degree of HER2 amplification (NGS fold change 1.7 to 27.9) did not predict response. HER2 amplification by NGS correlated well with HER2/CEP17 ≥ 2 by FISH (40/41 tested) and HER2/CEP17 ≥ 3 (13/14 tested), and tumor linkage was seen in 2 patients who were tested IHC negative. Conclusions: Ado-trastuzumab emtansine showed efficacy in patients with HER2 amplified lung, endometrial, salivary gland, biliary tract and ovarian cancers as identified by NGS. This study has met its primary endpoint. Further development is warranted. Clinical trial information: NCT02679829.

2503 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Molecular analysis for therapy choice (MATCH) arm W: Phase II study of AZD4547 in patients with tumors with aberrations in the FGFR pathway. First Author: Young Kwang Chae, Northwestern University, Chicago, IL

Background: MATCH is a histology-agnostic signal finding trial targeting pathways in cancer. AZD4547 is a selective inhibitor of the fibroblast growth factor receptor (FGFR) 1-3 kinases. Methods: Patients (Pts) were screened by NGS for FGFR aberrations including amplification (≥7x), mutation, and fusion. 705558 (1.3%) of pts who underwent successful NGS evaluation were included (60% (651) of total 1069). Of these, 393 (61%) of tumors were treated in all treatment arms in arm W (July 2016 to June 2017). 50 pts received treatment with AZD4547 80mg PO twice a day until progression of disease (PD) or drug intolerance. Results: 39/50 (78%) were female, 45/50 (90%) were Caucasian with a median age of 62 years (range: 22-80). 25/50 pts (50%) had received more than three prior lines of treatment. The most common histologies were breast (n = 16), uterine (n = 7), and endometrial cancer (n = 4). Pts were divided into three groups: amplification (Arm n = 21), single nucleotide variant (SNV) (n = 20), or fusion (n = 9). Best confirmed response rate was 5% (all partial response, PR). 51% stable disease (SD), and 44% PD. All pts with PR had tumors harboring FGFR fusions; one with uterine transitional cell carcinoma (FGFR3-TACC3 F1717B) and the other with squamous cell carcinoma of cervix (FGFR3-TACC3 F1711). Six cases (2 PR and 4 SD) (SNV, 1 Amp, 1 fusion) out of 41 achieved a duration of response greater than 24 weeks (disease control rate, 15%). The 6-month progression-free survival rate is 17% (90% CI: 9.3-24.9); Amp 15% (90% CI: 4.8-38%); SNV 8% (90% CI: 2.3-28.8); and fusion 42% (90% CI: 19.4-94.9). Of 49 pts evaluable for adverse effects (AEs), 39 experienced any AEs (80%) with 19 having grade 3/4 AEs. 49% (24) of AEs were fatigue, 23% (11) nausea/vomiting, diarrhea, constipation, oral mucositis, anemia and liver function tests abnormality. Conclusions: AZD4547 demonstrated modest activity across various solid tumors with aberrations in FGFR pathway with acceptable toxicities. Further trials are warranted in tumors harboring FGFR fusions. Clinical trial information: NCT02465060.
Background: Crizotinib (criz) is registered for the treatment of patients (pts) with ALK+ or ROS1+ lung cancer. Criz targets (ALK, MET, ROS1) are also altered (translocation [t(lic], amplification [amp], mutation [mut]) in a wide range of malignancies (malg.) in adults and children. To generate high evidenced-based knowledge and to prevent off-label use, the French National Cancer Institute (INCa) launched the criz biomarker program: equal access to criz molecular diagnosis along with an exploratory phase II trial, to allow for a nationwide safe and controlled access to criz outside its indication. Methods: Biomarker identification was proposed to pts > 1 year old (yo) with an advanced disease among more than 15 malg. known to harbor a criz target alteration. If not eligible for any other trial, pts may enter one of the 22 cohorts defined by the type of tumor and target. Target response was evaluated every 2 months (mo) using RECIST criteria v1.1. The primary endpoint is the objective response rate (ORR) at 2 mo (complete + partial response). A two-stage Simon design is applied to each cohort. Results: From 08/2013 to 12/2017, 12836 pts from 186 centers have entered the biomarker program. Alterations found in pts were: ALK tlc, mut, amp, in 14/2053; 8/306, 10/1846; MET amp (> 6 copies/diploid genome) in 392/784(250/4127 NSCLC, 60/1232 glioblastomas, 28/939 colon, 33/546 esogastic, 7/635 ovarian, 3/82 kidney cancers); MET mut in 98/2697; ROS1 tlc in 80/4625 (NSCLC, cholangiocarcinoma, inflammatory myofibroblastic tumor (IMT)). Clinical trial information: NCT02034981. Overall, 235 pts (median age, 58 yo [1–82]) received criz (adult 250 mg bid; child 280 mg/m² bid). Conclusions: Criz displayed a wide antitumor activity in several MET, ALK and ROS1+ malg. Equal or superior efficacy was observed across France to molecular testing and targeted therapies outside their approved indication is feasible. Positive cohorts Pts analyzed CR/PR ORR % (IC95%)

| ALCL ALK tlc | 22 | 12 | 54 (34-75) |
| NSCLC MET amp | 37 | 6 | 24 (7-40) |
| ROS1 tlc | 20 | 5 | 25 (40-70) |
| MET mut | 27 | 6 | 22 (7-38) |
| Esogastic MET amp | 8 | 3 | 37 (10-74) |
| IMT ALK tlc / ROS1 tlc | 1 | 1 | 28 (5-70) |

Conclusions: Crizotinib demonstrated potent antitumor activity in various preclinical models. We evaluated safety, dose limiting toxicity (DLT), maximum tolerated dose (MTD), and preliminary antitumor activity of TAK-931 in pts with advanced solid tumors. Four schedules are being tested, and we report data from Schedule A: TAK-931 QD for 14 days on/7 days off in 21-day cycles. A Bayesian logistic regression model with overdose control was used to guide dose escalation and MTD estimation. Results: As of 14-Nov-2017, 25 Japanese pts (60% male; median age 59 [range 42–75] years) were treated with TAK-931 30 mg (n = 3), 40 mg (n = 3), 60 mg (n = 3), and 50 mg (n = 16: 7 pts in dose escalation, 9 pts in expansion). Pts received a median of 3 cycles (range 1–12). Most common any-grade adverse events (AEs) were nausea (n = 15), neutropenia (n = 12), decreased white blood cells (WBCs) (n = 8), decreased appetite, vomiting, and diarrhea (each n = 7). Most common grade 3 AEs were neutropenia (n = 11), decreased WBCs (n = 3), leukopenia, and decreased appetite (each n = 2). DLTs (grade 4 neutropenia) were observed in 2 of 3 pts at 60 mg; 50 mg was considered the MTD. Preliminary pharmacokinetics (PK) showed increased systemic exposure of TAK-931 in a dose proportional manner between 30 and 60 mg with minimal accumulation and mean terminal elimination half-life of 5.4 hours (15% CV). Dose-dependent inhibition of pMCM2, a direct substrate of CDC7, was observed in skin biopsies from most pts treated with TAK-931, which correlated well with drug exposure (R² = 0.6598). Partial responses were observed in pts with duodenal, esophageal, and cervical cancers (1 pt each) as well as prolonged stable disease of ~6 months in a bladder cancer pt and ~9 months in a pancreatic cancer pt. Conclusions: TAK-931 demonstrated an acceptable safety profile with early signs of clinical antitumor activity. Isolated neutropenia was the DLT with the tested schedule. Strong pharmacodynamic (PD) effects and PK–PD correlation provide clinical evidence of target engagement of TAK-931 in pts. Clinical trial information: NCT02699749.

Background: A phase I study was done to establish the safety, MTD and antitumor activity of the novel PARP 1/2 and Tankyrase 1/2 inhibitor, 2X-121 (E7449). A novel tumor agnostic molecular biomarker, 2X-121 DRP, was developed to identify responders and non-responders. Methods: Pts with advanced solid tumors were eligible. 2X-121 was administered orally, once daily (QD), continuously. Archival tumor samples were obtained from consenting patients. Following completion of the study the 2X-121 DRP was applied in a blinded manner following a pre-specified analysis plan. This biomarker is based on expression of 414 genes predictive of response to 2X-121. Results: 41 pts were treated at 6 dose levels: 50, 100, 200, 400, 800 and 600 mg QD. MTD were pancreatic (n = 13), ovarian (n = 5), breast (4), lung (n = 4), colorectal (n = 4) and other (n = 11). Fatigue is the dose limiting toxicity. The MTD is 600 mg QD. The most frequently reported ( > 30% of pts) TEAEs were fatigue, chromaturia, decreased appetite, nausea, diarrhea, constipation, and vomiting. Novel target validation and early evidence of clinical activity. First Author: Elizabeth Ruth Diamond, University of Colorado, Aurora, CO Background: PK/PD analysis of a drug is based on the change in the concentration of drug in plasma with time. This biomarker is based on expression of 414 genes predictive of response to 2X-121. 2X-121 was generally well tolerated at the MTD of 600 mg QD, with evidence of antitumor activity. The 2X-121 DRP predicted the responders irrespective of BRCA mutation status. Clinical trial information: NCT01618136.

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First Author: Kyniakos P. Papadopoulos, STARR, San Antonio, TX

Background: Hypoxia-inducible factor (HIF)-2a is a transcription factor that plays a central role in the hypoxic response pathway in tumor. HIF-2a heterodimerizes with HIF-1β and binds to hypoxic response elements in target genes. The first-in-class HIF-2a inhibitor, PT2385, demonstrated clinical activity in patients (pts) with clear cell renal cell carcinoma (ccRCC). PT2977 is a novel, orally administered selective small molecule HIF-2a inhibitor with improved potency compared to PT2385. PT2977 inhibited expression of HIF-2α target genes in tumor cells and induced regression in mouse xenograft models.

Methods: Pts with advanced solid tumors who had received at least 1 prior therapy were treated with PT2977 once daily (QD) in a Phase 1 dose-escalation trial to determine the recommended Phase 2 dose (RP2D) and evaluate safety, pharmacokinetics (PK) and pharmacodynamics (PD). Plasma PK were measured on days 1 and 15 and dose-dependent reductions from 8%-26%.

Results: Of 38 evaluable pts, 25 pts (65.8%) had stable disease and 40 pts (61.5%) had progressive disease. The most common all-grade AEs were fatigue (40%), edema (38%), headache (17%), and nausea (13%). Anemia (11%) was the most common Grade 3 AE; there have been no Grade 4 events. Exposure increased with dose along with dose-dependent reductions from 8%-26%.

Conclusions: PT2977 is well tolerated and has a favorable safety and PK/PD profile. Early evidence of clinical activity shows promise for HIF2a inhibition in the treatment of ccRCC. PT2977 is currently rolled in a 3+3 dose escalation study. MTL-CEBPA is administered as a 1-hr infusion, or 2-hour IV infusion (300, 600 or 900 mg/dose). Pts must have MF intralesional injection (75 mg/dose), subcutaneous or IV rapid bolus injection, or 2-hour IV infusion (300, 600 or 900 mg/dose). Pts must have MF plaques and/or tumors and could remain on concurrent stable treatment. Most common AEs in >15% of subjects were: fatigue, neutropenia, injection site pain, nausea, pruritus, and headache. Two AEs were deemed DLTs: Gr3 worsening pruritus and Gr 3 tumor flare. MTD has not yet been reached. Serum PK analysis shows a terminal half life of >24 hrs, with dose proportional C_{max} and AUC. Analysis of WBCs showed a significant increase of C/EBPα expression during treatment providing evidence of target engagement. Of 10 evaluable pts with HCC, 4 pts (40%) achieved one or more partial or complete clinical responses having an ongoing PR for 18 months associated with 73% decrease in tumour volume and reduction in IL-6, NF-κB and IFN-γ. Conclusions: Once weekly MTL-CEBPA therapy was well tolerated, shows promising activity and clinical response in patients with advanced HCC. Updated results for the dose escalation will be presented. Clinical trial information: NCT02716012.
Single agent activity of U3-1402, a HER3-targeting antibody-drug conjugate, in breast cancer patients: Phase 1 dose escalation study. First Author: Takahiro Kagawa, Department of Breast and Medical Oncology, National Cancer Center Hospital East, Chiba, Japan.

**Background:** U3-1402 is a human epidermal growth factor receptor 3 (HER3)-targeting antibody-drug conjugate (ADC) of high drug-to-antibody ratio (DAR: 7-8) with a novel linker and topoisomerase I inhibitor payload. HER3 is overexpressed in a variety of cancers, including colorectal, ovarian, prostate and urothelial cancer. This ongoing, Phase 1/2 study (NCT02989341) of U3-1402 in HER3-expressing metastatic breast cancer (MBC) is divided into three parts: dose escalation (Part 1), dose finding (Part 2), and dose expansion (Part 3).

**Methods:** In Part 1 of the ongoing study, the dose of U3-1402 was escalated based on dose-limiting toxicity data, guided by the modified Continuous Reassessment Method (mCRM). U3-1402 was administered via intravenous (IV) infusion in 21-day cycles. The primary objectives are to determine safety and tolerability of U3-1402, the maximum tolerated dose (MTD), and the recommended dose for Phase 2. AEs, PK, ORR per RECIST v1.1, and durability of responses were assessed. Efficacy- evaluable patients (pts) received at least one dose of U3-1402 and had pre- and post-treatment tumor assessments. **Results:** As of December 28, 2017, 21 evaluable pts (female, median age 59 years, ECOG 0-1, and ≥ 2 previous treatment regimens) have received U3-1402 at dose levels between 800 mg QD (resolved with 100 mg/kg of Roposumab) and 1200 mg QD or 3 mg/kg (resolved with procarbazine). Roposumab was discontinued due to PD and 1 pt discontinued due to Grade 2 neutropenia. Seventeen pts (80%) remain on treatment, including 6 pts (28%) who have remained on treatment for more than 6 months. HER3 IHC has been evaluated in 294 breast cancer pts, 87 (30%) showed high levels of HER3 expression. **Conclusions:** In a preliminary analysis of 21 pts, U3-1402 demonstrated antitumor activity in previously treated HER3 expressing MBC pts and treatment is associated with a manageable safety profile. Clinical trial information: NCT02989341.
Background: Differential response to tamoxifen observed in patients (pts) with hormone receptor-positive cancer may be due to variations in tamoxifen metabolism from CYP2D6 genetic polymorphisms that limit exposure to the active metabolite, z-endoxifen (Z). We conducted a phase 1 clinical trial with estrogen receptor imaging to determine the impact of Z and pharmacokinetics (PK) of oral Z. Methods: Adults with refractory gynecologic tumors, hormone-positive breast or other solid tumors, or desmoid tumors were eligible with ECOG performance status of 0-2 and adequate organ functions. Z was administered at 20, 40, 60, 100, 140, 200, 280, and 360 mg q day on a 28-day cycle. Estrogen receptor imaging with 16 alpha-[18F]-fluoro-17 beta-estradiol (FES)-PET was performed before dosing and, if positive, repeated during C1W1. Results: Median age of the 40 pts enrolled was 60 (range 21-80 yr) and 90% were female. MTD was not reached up to the targeted maximum dose of 360 mg/day. Of the 38 pts evaluable for response, 2 (fallopian tube and breast) had partial responses and 9 had 6+ cycles of stable disease. Pts stayed on study for 1-47+ cycles (average, 6 cycles; median, 2.5 cycles); two pts remain on treatment. Grade 3/4 adverse events occurring in ≥5% of pts were hypertension (13%), hyponatremia (8%), hypophosphatemia (8%), neutropenia (8%), dehydration (5%), and elevated lipase (5%). Mean Z serum levels increased with administered dose. Increases were seen in mean D1 (min 68.6 to 1309 ng/mL) and AUC0-24 (1084 to 20546 mg/L/hr) between doses of 20 and 360 mg/day. The elimination t1/2 was 30.6-55.9 hr, based on the AUC accumulation ratio of 2.4-3.9 over the 28-day dosing period. FES-PET from 9 pts were analyzed; FES-standard uptake values 2-5 days of 2. Conclusions: We established a targeted maximum dose of 360 mg/day Z and evidence of antitumor activity was observed. Oral Z administration produces Z plasma exposures well above those obtained after therapeutic doses of tamoxifen. Clinical trial information: NCT0273168. Supported in part by NCI Contracts CM52206 and HHSN261200800001E. Clinical trial information: 01273168.

A phase la/lb trial of the DNA-PK inhibitor M3814 in combination with radiotherapy (RT) in patients (pts) with advanced solid tumors: Dose-escalation results. First Author: Baukelien Van Triest, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: DNA-dependent protein kinase (DNA-PK), regulates one of the major pathways responsible for repair of DNA-strand breaks. The combination of RT and DNA-PK inhibitor M3814 is well tolerated and showed promising results against BTC. The combination of RT and DNA-PK inhibition (DNA-PKi) has been shown to be synergistic in preclinical studies. The purpose of this phase I trial is to explore the safety, tolerability, pharmacokinetic (PK) profile, and clinical activity of M3814 administered together with RT (Arm A) and chemorT (CRT; Arm B). Results for Arm A are reported. Methods: Pts with tumors or metastases in the head and neck region or thorax in need of palliative RT (30 Gy in 10 fractions) are enrolled in the dose escalation part la of Arm A to receive M3814, starting dose 100 mg. Dose escalation is aided by a Bayesian logistic regression model. Dose-limiting toxicity (DLT) is evaluated up to 3 weeks after RT. Rich PK sampling is performed during treatment. Tumor evaluation is performed every 6 weeks up to 6 months and every third month thereafter. BXQ-350 doses of 0.7, 1.1, 1.4, 1.8, or 2.4 mg/kg on days 1-5, 8, 10, 12, 15, 22 (cycle 1) and at 28-day cycles thereafter. Response was assessed at day 113 by RECIST (Arm A) or RANO/RECIST (Arm B). Results for Arm A: When reaching a maximum of 2-12 prior systemic therapies completed a median 2 (range, 1-6) cycles without DLTs or treatment-related severe adverse events (AEs). Moderately severe related AEs occurred in 3 (100%), 1 (33%), 1 (33%), and 2 (25%) Pt at 1, 1.1, 1.4, 1.8, and 2.4 mg/kg cohort doses, respectively. The most common treatment-related AEs was transient fatigue (n=4, 23.5%). At 2.4 mg/kg, 1 Pt had moderate blood pressure elevation. Best response in 7 Pt completing to day 113 was 1 PR (appendiceal carcinoma) at 2.4 mg/kg, and 6 SD (1 HGG Pt at 0.7 mg/kg had stable disease >12+ months, and had improved day 113 RANO/RECIST). BXQ-350 pharmacokinetics was dose proportional with half-life and Cmax, consistent with preclinical data. Conclusions: BXQ-350 showed clinical activity in heavily pre-treated patients with advanced solid and brain tumors. BXQ-350 has a tolerable safety profile with no significant DLT at the highest planned dose, supporting continued monotherapy dose expansion at 2.4 mg/kg. Clinical trial information: NCT 02895987.

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A phase I dose escalation study of hpV19, a novel humanized monoclonal antibody against VEGF-A, in patients with advanced solid tumors refactory to standard therapy. First Author: Dongmei Ji, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: hpV19 is a novel inhibitory mAb against VEGF with unique binding site different from that of Bevacizumab. This phase I study aimed to determine its dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and pharmacokinetics. Methods: hpV19 was infused in 23 patients via peripheral IV (PK) in patients with metastatic cancer (re-bleeding). Additional DLTs (1 patient per cohort) occurred at 4 mg/kg q2w (left ventricular failure), 8 mg/kg q2w (creatinine and urea increase and thrombocytopenia), 8 mg/kg 1 hr infusion q2w (nephrotic syndrome) and 12 mg/kg q3w (nephrotic syndrome). Based on these data, the MTD for hpV19 was determined at 12 mg/kg q2w (non-hematological). Toxicities were the most frequent grade 3 or above non-hematological or LFT abnormalities 9%, renal abnormalities 7.5%, hypertension 22.7%, dysphonia 18.2%, LFT abnormality 59%, renal abnormalities 7.5%, hypertension 22.7%, dysphonia 18.2%. LFT abnormalities 59%, renal abnormalities 7.5%, hypertension 22.7%, dysphonia 18.2%. LFT abnormalities 59%, renal abnormalities 7.5%, hypertension 22.7%, dysphonia 18.2%. LFT abnormalities 59%, renal abnormalities 7.5%, hypertension 22.7%, dysphonia 18.2%. LFT abnormalities 59%, renal abnormalities 7.5%, hypertension 22.7%, dysphonia 18.2%.

Conclusions: hpV19 was well tolerated with most AEs being consistent with prolonged inhibition of the VEGF pathway. Signs of single agent antitumour activity were observed and hpV19 is being further developed in lung cancer and multiple myeloma. Clinical trial information: NCT02194426.

Can VEGFA and ICAM1 polymorphisms predict response to bevacizumab? First Author: Christophe Le Tourneau, Institut Curie, Paris, France

Background: VEGFA and ICAM1 polymorphisms have been shown to be predictive of drug response. Although bevacizumab is widely used, there are still no available biomarkers. Given the need of individualized treatment approaches and the high cost of Bevacizumab, it is necessary to find biological predictors of response. The present study investigated the role of selected single nucleotide polymorphisms (SNPs) in VEGFA (Vascular endothelial growth Factor) and ICAM1 (Intracellular Adhesion Molecule 1) genes as response biomarkers. Methods: 46 patients with metastatic colorectal cancer (mCRC) treated with Bevacizumab and chemotherapy (fluoropyrimidines/oxaliplatin or irinotecan) as first-line treatment were enrolled. Selected VEGFA (rs2010963, 1570360, rs999947) and ICAM1 (rs4594, rs1799969) SNPs were detected using PCR-based Sanger sequencing (KAPABIOSYSTEMS, MA, USA). Statistical analysis was done using ANOVA and Kaplan-Meier Survival Analysis on SPSS software. Ethical committee of University Hospital of Patras approved study. Results: 61% of patients were males and 39% females, mean in agn was 64.5 (±8.6) years. ICAM1 genotype analysis was available in 27 patients. For rs999947 (A > C), the % genotype frequencies were 29.8% AA, 23.4% A, and 46.8% CC, while the rs1570360 (A > G) ones were determined to be equal to 10.6% AA, 23.4% A, and 66.6% GG. For rs2010963 (C > G), 12.7% CC, 27.7% CG, and 59.6% GG. 

Conclusions: Our findings suggest that rs699947, rs5498, and rs109063 serve as candidate response biomarkers. All three might be able to stratify patients, who may gain a long-term benefit towards the optimization of Bevacizumab therapy and achieving better-informed therapeutic outcomes.

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Evaluating fixed-dose regimens of seribantumab in patients with solid tumors.

First Author: Bambang Adiwijaya, Merrimack Pharmaceuticals, Inc., Cambridge, MA

Background: Seribantumab (MM-121) is an anti-HER2 human monoclonal antibody being tested as an anti-cancer therapy for patients with high expression of herculesin mRNA in NSCLC (SHERLOC study, 3g every 3 weeks (Q3W)+docetaxel) and in and in HR+ HER2- metastatic breast cancer (mBC) (SHERBOC study, 3g every 2 weeks (Q2W)+fulvestrant). Here we aimed to evaluate seribantumab dose regimens based on PK and safety.

Methods: Pharmacokinetic (PK) and safety were evaluated for fixed and weight-based dose: in NSCLC, 3g Q3W vs. 20 mg/kg Q2W; in mBC, 3 g Q2W vs. 40 mg/kg loading dose, followed by 20 mg/kg QW. PK was quantified using nonlinear mixed effect with the following covariates: sex, race, age, weight, dose, study, and hepatic functions. Adverse events (AEs) were evaluated for associations to PK and weight: Grade 1+ and 3+ diarrhea, fatigue, hypokalemia, hyperglycemia, nausea, pulmonary embolism, rash, stomatitis, and vomiting. Results: Seribantumab PK from 499 patients in 7 previous trials identified associations with sex and weight. Fixed and weight-based doses showed similar variability. With higher weight, weight-based dose resulted in higher exposure (average concentration [Cavg] and maximum concentration [Cmax]), and fixed dose resulted in lower exposure. Steady-state Cmax were higher with 3 g than with 20 mg/kg; these values were comparable to Cmax with 40 mg/kg. Steady-state Cavg were equal or higher for fixed dose than comparable weight-based dose. All doses tested had minimum concentrations (Cmin) higher than the nonclinical target concentration of 100 mg/L. Among AEs evaluated, significant associations with seribantumab exposure were observed for G1−diabetes, fatigue, nausea, rash, and stomatitis. Weight-based dose showed higher AE rates with increasing weight. Fixed dose is predicted to reduce AE rates in high-weight patients and to increase AE rates in low-weight patients with the latter having lower PK parameters than those in patients with higher weight.

Conclusions: The recommended dose of seribantumab is 3 g Q3W+docetaxel in NSCLC and 3 g Q2W+fulvestrant in mBC. The fixed dose of seribantumab allows acceptable concentrations and safety profiles and potentially reduces drug waste and dosing errors.
**2528 Poster Session (Board #354), Mon, 8:00 AM-11:30 AM**

**Plinabulin (Plin), a small molecule with anti-cancer activity and a novel mechanism of action (MoA) in docetaxel (Tax)-induced neutropenia: Phase (1/2a) dose-escalation trial from a head-to-head comparison (HPD)**

**Background:** Plin has clinical anticancer activity in combination with Tax (Mohanlal ASCO-SITC 2017, 18). Plin prevented Tax-induced neutropenia in a post-hoc analysis of a q 2 trial (Blayney ASH 2016). Plin is being studied in the prevention of chemotherapy(chemo)-induced neutropenia (CIN) induced by Tax/ admycin/cyclophosphamide in BC, by gemcitabine/abx in PC, by carboplatin/pemetrexed in NSCLC and irinotecan in CRC. We report final results of the q 2 portion of a prospective q 2/3 trial of Plin for CIN compared with Peg (NCT03102602; Study BPI 2358-105). The 105 study is designed to demonstrate non-inferiority (NI) of Plin vs Peg for duration of severe neutropenia (DSN) in q 3. Methods: Patients (Pts; n = 55) with lung cancer (NSCLC) were randomized to Tax 75 mg/m2 dose (D1) and either Peg 6 mg/ D2 or Plin 5, 10, or 20 mg/m2 D2. Plin was dosed on the same day of (30 min after) chemo. Absolute Neutrophil Count (ANC) was collected D1,2,3,6,7,8,9,10,15 and 21. Primary endpoints were DSN and grade (Gr) 4 neutropenia to establish recommended phase 3 dose (RP3D). The NI margin for DSN is 0.5 D1 and for Plin 0.54 D. Gr 3 HT was transient and not different among all groups (p < 0.18). Bone Pain occurred in 33% of pts with Peg and 11% with 20 mg/m2 Peg. Clinical trial information: NCT03102606. Conclusions: Plin 20 mg/m2, given 30 min after chemo with leukotriene antagonists, has similar myeloprotective effect vs Peg. Its post chemo recovery curve is shallower, broader and later compared with Peg, with median ANC staying within normal range, suggesting a different MoA to prevent CIN. Plin 20 mg/m2 is the RP3D based upon its protection against Gr 4 neutropenia and safety profile.

**2529 Poster Session (Board #355), Mon, 8:00 AM-11:30 AM**

**Phase 1/2a study of BAL101553, a novel tumor checkpoint controller (TCC), administered as 48-hour infusion in adult patients with advanced solid tumors.**

**Background:** BAL101553 is the produg of BAL27862, a small molecule TCC that binds microtubules and promotes tumor cell death by activation of the spindle assembly checkpoint. In a study of BAL101553 administered as a 2-h infusion on Days 1, 8 and 15 of a 28-day cycle (NCT01397929, Lopez et al. JCO 34, 2016; 2525), vascular toxicities were observed and appeared to be Cmax related. Nonclinical models indicate that the anti-proliferative effects of BAL27862 are AUC driven; this trial was intended to determine whether prolonged infusion reduces Cmax-related toxicity and increases the AUC at the recommended phase 2 dose (RP2D) (NCT02895360, Joerger et al. JCO 2017; TP52602). Methods: Patients with advanced solid tumors received 48-h infusions of BAL101553 using an elastomeric pump on Days 1, 8 and 15 of consecutive 28-day cycles using a 3+3 dose-escalation design to determine the maximum-tolerated dose (MTD). During Cycle 2, patients received BAL101553 orally on Days 15–21 instead of IV in order to assess oral bioavailability. Adverse events (AEs) were assessed by CTCAEv4.3 grade (G); tumor response by RECIST 1.1 every two cycles; pharmacokinetics were assessed during the first two cycles. Results: Phase 1 enrollment was completed with 20 patients (7M/13F; median age 60 years; median 3 prior chemotherapies) receiving IV BAL101553 at doses of 30, 45, 70 or 90 mg/m2. Dose-limiting toxicities included transient G3 hypotension at 70 mg/m2 and reversible G3 neutropenia at 90 mg/m2. G2 hallucinations and ataxia at 90 mg/m2. There were no relevant vascular toxicities. Of 16 evaluable patients, one had a confirmed partial response (ovarian cancer) and one had stable disease for 6 months (endometrial cancer). BAL27862 exposures (AUC) were near dose-proportional. At 70 mg/m2, the BAL2762 Cmax was 14.4 ng/mL and AUC was 144 ng•h/mL. Oral bioavailability was estimated to be > 80%. Conclusions: The MTD/RP2D of BAL101553 48-h infusion was 70 mg/m2. At this dose the AUC/Cmax ratio was ~4× higher compared to the 2-h infusion regimen at the RP2D of 30 mg/m2. There were indications of potential clinical benefits in patients with ovarian and endometrial cancers. Clinical trial information: NCT02895360.

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**2532** Poster Session (Board #358), Mon, 8:00 AM-11:30 AM  
**Palbociclib (P) in patients (Pts) with pancreatic cancer (PC) and gallbladder or bile duct cancer (GBC) with CDKN2A alterations: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. First Author: Tareq Al Baghdadi, Michigan Cancer Research Consortium, Ypsilanti, MI**  
**Background:** The TAPUR Study is a phase II multi-basket study that evaluates the anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations known to be drug targets. Results in two cohorts of PC and GBC pts each with CDKN2A loss or mutation treated with P are reported. **Methods:** Simon’s optimal two stage design was used to test the null hypothesis of 15% response rate versus the alternative of 35%. Power and alpha were set at 85% and 10%, respectively. Response was assessed per RECIST v1.1. This design requires 10 pts in stage 1 and if < 2 pts have objective response (OR) or stable disease (SD) at 16-weeks (wks), the cohort is closed. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. Genomic testing was performed using commercially available tests selected by clinical sites. Treatment was determined according to protocol matching rules based on the pre-defined genomic inclusion criteria. **Results:** Twelve pts were enrolled in the PC cohort from July 2016 to April 2017, but 2 were subsequently found to be ineligible due to minor deviations from inclusion criteria. Ten pts were enrolled in the GBC cohort from August 2016 to November 2017. All pts are included in the data analysis for demographics, safety, PFS and OS (Table 1). No ORs or SD at 16 wks were observed in the PC or GBC pts, the cohorts were therefore closed. The most common toxicity from P was thrombocytopenia. **Conclusions:** Monotherapy with P does not have clinical activity in PC or GBC pts with CDKN2A loss or mutation. Toxicity is similar to previous experience with P. These pts should be offered other treatments, including clinical trials. Clinical trial information: NCT02693535.

**Baseline demographics, clinical characteristics and outcomes by cohort.**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>PC (N = 12)</th>
<th>GBC (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male%</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>ECOG Performance Status, %</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Median yrs (range)</td>
<td>62 (52, 70)</td>
<td>63 (54, 81)</td>
</tr>
</tbody>
</table>

**Drug-related AEs, grades 3-4 (% of pts)**

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Palbociclib (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>25%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>25%</td>
</tr>
<tr>
<td>Fatigue/Weakness</td>
<td>25%</td>
</tr>
<tr>
<td>Nausea</td>
<td>33%</td>
</tr>
<tr>
<td>Periocular sensory neuropathy</td>
<td>0%</td>
</tr>
<tr>
<td>Nail loss/Onycholysis</td>
<td>0%</td>
</tr>
</tbody>
</table>

**2534** Poster Session (Board #360), Mon, 8:00 AM-11:30 AM  
**AUCtox: A new method to evaluate the safety of anticancer drugs. First Author: Vincent Launay-Vacher, Pitie-Salpetriere Hospital, Paris, France**  
**Background:** The evaluation of anticancer drugs safety currently relies on the NCI-CTCAE classification. Most often in clinical trials, attention is focused on severe adverse events (AE) i.e. grade 3 or more. However, AE of lower grades can have a significant deleterious impact, especially when recurrent or permanent. We aimed at defining a new method to better describe the impact of treatment on QoL. **Methods:** We developed and validated the AUCtox method combining the area under the curve of toxicities (AUCtox) that takes into account both the intensity and duration of toxicities, and the number of events. **Results:** AUCtox was calculated for any toxicity reported at least once. The association with QoL, evaluated by EQ-5D, can better detect the adverse events (AE). AUCtox: A new method to evaluate the safety of anticancer drugs.

**2535** Poster Session (Board #361), Mon, 8:00 AM-11:30 AM  
**Trends in oncology trials termination due to toxicity over a period of 16 years. First Author: Laura Vidal, Syneos Health, Barcelona, Spain**  
**Background:** Clinical research is a major aspect of drug development and requires patient participation. Family and friends are known to play a role in medical decision-making, the extent of which depends on factors such as timing (onset or end of the disease), type of disease, the legal situation (e.g., patients under guardianship, or minor), and cultural aspects. The role of the close circle in inviting patients to enroll in clinical trials therefore warrants further study. **Methods:** The French nationwide observational survey, EDIFICE 6, was conducted online from 26 June-28 July 2017 on a core sample of 12 046 individuals (age, 18-69 years). Representativeness was ensured by quota sampling on age, gender, profession, and stratification by geographical area and type of urban district. Multivariable stepwise logistic regression analysis was conducted to identify factors likely to incite close relatives of cancer patients to urge them to enroll in a clinical trial. The present analysis included 11 307 individuals with no history of cancer and focused on the question “If a person you are close to had cancer and was invited to take part in a clinical trial, would you encourage them to participate?” **Results:** Most respondents declared they would very likely (22%) or likely (61%) encourage someone close to enroll in a clinical trial. Of the 21 significant explanatory factors affecting this opinion, two were predominant: believing that clinical research leads to important advances (OR = 2.75; 95% CI [2.33-3.24], p < 0.001) and that progress is made rapidly (OR = 2.18; 95% CI [1.95-2.43], p < 0.001). Other factors related to the “advice-giver” were also significantly high such as: more male gender (OR = 1.79), being married (OR = 1.20), not being socially vulnerable (OR = 1.17), former smoker (OR = 1.16), and having short-term perspectives (OR = 0.96). **Conclusions:** A large proportion (83%) of close family and friends of cancer patients were seen to encourage them to take part in clinical trials. Greater awareness and a clear understanding of the numerous benefits of clinical research would likely further increase the number of individuals who are in favor of clinical trials.
**2536 Poster Session (Board #362), Mon, 8:00 AM-11:30 AM**

**Systematic review of pediatric oncology phase I trials: Toxicity and outcomes in the era of targeted therapies.**

First Author: Julia Wanda Cohen, Pediatric Oncology Branch, Children's Oncology Group, National Cancer Institute, National Institutes of Health, Bethesda, MD

**Background:** Historically, objective response rates (ORR) (CR/PR + PR) in pediatric phase I oncology trials have been <10%. With an increased emphasis on targeted treatment approaches, safety profiles and response rates may have changed. We analyzed outcomes of recent phase I pediatric oncology trials. **Methods:** Peer-reviewed phase I pediatric oncology trials published from 2012 through 2017 were identified through a PubMed search. Selection criteria included a pediatric population (median age ≥ 25 years), diagnosis of cancer (including CNS tumors), and a clear dose-escalation schema. Each publication was evaluated for therapy type (cytotoxic versus targeted, combination vs. single agent), trial design, patient characteristics, toxicity, and response. **Results:** Of 242 publications identified, 89 articles met the inclusion criteria. 46 (52%) incorporated targeted therapies. Total enrollment was 2187 patients; median age at enrollment/trial was 10 years (range 3-25 years). 1990 patients (91%) were evaluable for toxicity, of whom 256 (12.9%) experienced dose-limiting toxicity (DLT) with 3 study-related deaths (0.15%). Of 1703 patients, response in 787, 287 (16.8%) demonstrated a response (188 CR, 15 CRi, 84 PR). 31 (40%) of trials had no objective responses. Sixteen trials (21%) had an ORR ≥ 25% (leukemia trials: 9, solid tumor trials: 7), of which 8 were combination cytotoxic trials and 8 were targeted trials, the majority enrolling patients with the relevant target (e.g. CD19+targeted therapy for CD19+ disease). Comparison between the 46 targeted trials and the 43 cytotoxic trials demonstrated similar pooled rates of DLT (11.1% vs. 15.4%) and ORR (16.9% vs. 16.7%). **Conclusions:** Our systematic review of recent pediatric oncology phase I trials demonstrated a higher pooled ORR than rates previously reported without increased toxicity. A subset of trials with substantially higher ORR included combination cytotoxic trials and targeted trials with target specific enrollment, supporting earlier introduction of combinatorial approaches and inclusion of pediatric patients with the relevant target in early phase targeted trials.

**2537 Poster Session (Board #363), Mon, 8:00 AM-11:30 AM**

**A randomized Bayesian phase 1 design combining an MPS-1 inhibitor with paclitaxel: A strategy to improve determination of the incremental toxicity of a novel compound versus a well-established backbone therapy.**

First Author: Florence Arafat, Erasmus MC Cancer Institute, Rotterdam, Netherlands

**Background:** Here we present a study combining BAY1217389 (BAY), a potent MPS-1 kinase inhibitor with a backbone chemotherapy paclitaxel. Since we expected overlapping toxicities we sought to improve determination of the maximal tolerated dose (MTD) using a randomized phase 1 design with Bayesian dose modeling. We hypothesized that this approach may determine the MTD of BAY more accurately by limiting the impact of variability in dose limiting toxicities (DLTs) related to paclitaxel. **Methods:** Patients (≥18 years) were randomized to receive oral BAY with intravenous paclitaxel (experimental arm) or paclitaxel monotherapy (standard arm) in cycle 1. Dose escalation was guided by Bayesian modeling targeting a DLT-rate in the experimental arm of 10% over DLT-rate in the standard arm. PK profiles were determined for both BAY and paclitaxel. Simulations were performed to estimate MTD for several scenarios. **Results:** We were able to establish an MTD of 65 mg BAY using 50 patients in the dose-escalation part. As expected the main DLTs were hematologic toxicity. Grade ≥3 neutropenia was present in 20% of patients. Prior to dose 25 (preliminary) 3 study-related deaths were observed for BAY AUC0-12 on D8 (p<0.001) and not to paclitaxel AUC0-24 (p=0.1). To determine whether the randomization adds value to the study design we ran simulations comparing our randomized strategy using variable toxicity rate (5, 10, 20, 40%) for paclitaxel monotherapy with the 3+3 design. These data showed that the randomized design outperformed the 3+3 design. The 3+3 design underestimated the MTD as dose escalation was terminated more frequently at first dose for higher paclitaxel toxicity rate. **Conclusions:** Randomized Bayesian phase 1 dose escalation design was feasible with BAY plus paclitaxel. A major advantage of this design is the precise determination of an exposure-toxicity relation for the experimental drug. Moreover, simulations support our hypothesis that the randomized design was able to determine the MTD accurately regardless of variable toxicity rate for paclitaxel. This approach may improve dose determination in phase I combination trials. Clinical trial information: NCT02366949.

**2538 Poster Session (Board #364), Mon, 8:00 AM-11:30 AM**

**Successes and challenges faced by tissue collection during trials by oncology translational sciences.**

First Author: Simon Martimets, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

**Background:** The collection of tumor biopsies as part of clinical trials is critical with the growing integration of biopsies in clinical trial design. Tumor organ sites were per pair: bone (32%), lung (15%), prostate: 20.3% (range 0-80%), liver: 27% (0-60%; lung: 28.1% (0-60), no indication of organ site: 42.6% (range 1-90%). There was no indication of primary or metastatic tumour status. Processes to link meta-data collection (organ site or pathology report) with biopsies are in progress as well as encouragement to bone scan guiding when bone metastasis biopsies are necessary.

**2539 Poster Session (Board #365), Mon, 8:00 AM-11:30 AM**

**Prospective assessment of tumor biopsies as part of clinical trials: Patients’ (pts) perspectives.**

First Author: Sunu Lazar Cyriac, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

**Background:** Despite the increased inclusion of mandatory biopsies for clinical trials, there are scant data related to the perceptions and acceptability by pts. This study assessed the pre and post biopsy perceptions among gynecological cancer pts. **Methods:** A prospective study was conducted at Princess Margaret Hospital for pts with gynecological cancers. The study was approved by local ethics committee and enrolled pts planned for core tumors biopsies as part of clinical trials. A questionnaire was completed by pts prior to and 1 week post biopsy. The questionnaire assessed the Hospital Anxiety and Depression Scale (HADS), pts’ perceptions and experience. **Results:** 42 women completed the questionnaire at both time points. Median age was 63 years. Sites of biopsies were peritoneal nodules in 45%, liver in 24%, superficial lymphnodes (LN) in 17%, retroperitoneal LN in 7% and abdominal wall in 7%. 88% were Ultrasound guided, 8% was CT, and 4% as blind procedure. A risk threshold of less than 2% was considered acceptable for major complications, major bleeding or infection by 71%, 60% and 55% of pts, respectively. While 50% (21/42) of the pts reported that the biopsy didn’t impact their care, but helps research; only less than 10% felt it would impact their care. 71% (30/42) of the pts would allow their specimen to be used for future research. Most pts (98%) were agreeable for genetic testing of their specimen and wanted to be informed of significant findings. Table 1 shows the HADS result. The baseline score was normal in 81%. 91% (38/42) felt that the side effects and risks of biopsy were adequately explained before the procedure. One week after the biopsy, only 1 pt had major pain. 91% (38/ 42) of pts did not feel any embarrassment during the procedure. The majority of pts (91% [38/42]) were agreeable for a repeat biopsy for research. Table 1

<table>
<thead>
<tr>
<th></th>
<th>Pre Biopsy</th>
<th>1 week post Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS (Anxiety)(n = 42)</td>
<td>Normal</td>
<td>Borderline abnormal</td>
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<tr>
<td></td>
<td>Abnormal</td>
<td></td>
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<tr>
<td></td>
<td>34</td>
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<td></td>
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<td></td>
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</table>

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Accelerated vs. regular approval: Lessons learned from U.S. FDA oncology approvals. First Author: Thid Camero Leao, U.S. Food and Drug Administration, Silver Spring, MD

**Background:** This work categorizes the justifications for accelerated and regular approvals (AA and RA) of oncology products granted by U.S. FDA, based on endpoints other than overall survival (OS) that supported RA and pathways for AA conversion to RA. **Methods:** We reviewed FDA databases for approved oncology products for specific indications from January 2006 to November 2017. For each product and its indication, we reviewed the trial that supported its approval with respect to study population, trial design, endpoints, magnitude of the treatment effect and benefit-risk assessment. **Results:** Two hundred twenty-six new indications were granted, 159 (70%) received RA and 67 (30%) AA. OS was the primary endpoint supporting 40% of RAs. Non OS-endpoints that supported RA (60%, n = 95) included PFS (n = 51), response and response rate (n = 34), TTP (n = 4), DFS (n = 2), DFS (n = 2) and EFS (n = 2). The disease settings where non-OS endpoints were used included advanced breast cancer, multiple myeloma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, advanced solid tumors such as thyroid, renal cancer, NSCLC and rare cancers. Of the 67 indications granted under AA, response including hematologic response endpoints and pathological complete response was the basis for most of AA (88%, n = 59). Eight approvals were based on a time to event endpoint (12%; PFS, n = 7 and DFS, n = 1). We identified two pathways for AA to RA conversion based on 33 out of 67 AAs converted: (1) longer follow-up of the same trial that supported the AA demonstrating the sustained treatment effect (18%) and (2) additional confirmatory trial with primary endpoint that represented clinical benefit (82%). **Conclusions:** Our results provide clarity of FDA oncology approvals and useful information to stakeholders for efficient development of oncologic products.

Adverse events (AEs) in early phase cancer clinical trials. First Author: Grace Mishkin, National Cancer Institute, Rockville, MD

**Background:** AE reporting is required in the conduct of clinical trials for patient safety and to understand the toxicities from treatment interventions. This analysis used a uniquely comprehensive dataset of AEs from early-phase NCI trials to describe overall clinician-reported AE frequency and prevalence, as well as changes in frequency and prevalence over time. **Methods:** Data were used from early phase trials using NCI-sponsored agents with complete AE reporting. Patients ages 25+ with at least one AE were included. These AEs were collected for treatment courses started 2000-2016 and standardized to CTCAE v4.0. R was used for analysis. **Results:** Over this 17-year period complete AE reporting was available for 1,594 early phase clinical trials representing a wide range of disease areas and agents. There were 1,417,529 total AEs reported for 99,023 patients. There are 790 CTCAE terms, but the 15 most frequently reported AEs represented 48% of all AEs reported (Table 1). Grade 3 AEs represented 13.1% of the AEs for 2000-2003, but decreased to 9.9% for 2012-2016. **Conclusions:** These initial results from an extensive AE database show a small number of AE terms represent most AEs reported. The proportion of AEs which were grade 3 decreased over time, potentially due to changes in agents and improvements in supportive care. As more trials which include patient reporting of AEs are completed, joint analysis could lead to more comprehensive understanding of the tolerability of lower grade AEs. Analysis by agent class, patient age, and disease is ongoing.

### 15 most commonly reported ctcae terms

<table>
<thead>
<tr>
<th>CTCAE Term</th>
<th># AEs</th>
<th>% AEs (% in 1438936)</th>
<th># Patients</th>
<th>Patients (% in 59802)</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>10501</td>
<td>7.4%</td>
<td>36645</td>
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<tr>
<td>Anemia</td>
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<td>5.5%</td>
<td>27746</td>
<td>47.0%</td>
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<td>White blood cell decreased</td>
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<td>4.2%</td>
<td>21114</td>
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<tr>
<td>Nausea</td>
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<td>Platelet count decreased</td>
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<td>Diarrhea</td>
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<td>Peripheral sensory neuropathy</td>
<td>30118</td>
<td>2.2%</td>
<td>10166</td>
<td>17.6%</td>
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<tr>
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<tr>
<td>Vomiting</td>
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</table>

### Background:
BPM31510-IV is an Ubidecarenone (Coq10) containing IV nanodispersion targeting metabolic machinery in cancer, shifting bioenergetics from lactate dependency towards mitochondrial OxPhos and reversing the Warburg effect. This study evaluated the safety & tolerability of BPM 31510-IV alone or in combination with chemotherapy. The study design included PD sampling for multi-omic analysis to identify predictive markers of clinical benefit and patient stratification. **Methods:** Eligible patients were relapsed/refractory to standard therapy. The monotherapy arm received IV BPM 31501 for 6 d in continuous infusion in 28-d cycles, and combination arms (gemcitabine, 5-FU or docetaxel) were primed for 3 wks with BPM31510 prior to chemotherapy regimen followed by weekly dosing in a 6 wk cycle. Endpoints were safety, pharmacokinetics (PK) and pharmacodynamics (PD). Tumor response was evaluated at cycle 1 and then after every 2 cycles. **Results:** A total of 98 pts were enrolled. Thirty of 66 evaluable pts (45%) achieved stable Disease, for ≥ 2 cycles and 16/66 (24%) maintained a minimum of SD for ≥ 4 cycles. 99% patients receiving ≥ 1 treatment with BPM31510 experienced a TEAE. The most frequently experienced TEAEs were asymptomatic elevated APTT in 80% of pts, INR increased in 74%, PTT prolonged 64%, Anemia in 41%, fatigue in 24% and both AST increase & platelet decrease in 16% of pts, Molecular predictors of coagulation-related events prior to and 24h after 1st treatment with IP were identified. Biomarker candidates correlating with favorable clinical response & safety identified were independent of tumor type and prior therapy, suggesting a broad anti-tumor effect. Novel multi-omic panels with potential to stratify response before and 24h post treatment with AUC > 0.85 were identified. **Conclusions:** BPM31510-IV is well tolerated as monotherapy and in combination with standard chemotherapy agents. Clinical signatures with predictive potential of the safety and clinical response have been identified that will guide Phase 2/3 clinical development. Clinical trial information: NCT01957735.
Background: Experimental therapeutic oncology agents are often combined in an effort to circumvent tumor resistance to individual agents; most combination trials, however, fail to demonstrate sufficient safety and efficacy to advance to a later phase. The FACTS study collected survey data on phase 1 combination therapies to: 1) assess rates of advancement and regulatory approval, 2) identify factors associated with these rates, and 3) assess the degree that phase 1 trials were (pre)dictive of phase 1 clinical trial Design Task Force (CTD-TF) Guidelines. Methods: A 13-question survey collected data on phase 1 trial design, predefined expectations and criteria to assess success, biomarker information, and questions about the trials’ results and progress. Online surveys (N = 289, July-Dec. 2017) were emailed to Pts of early-phase NCI and/or industry trials; 263 emails (91%) were received and 114 surveys completed (43%). Two independent coders validated 10% of survey responses (N = 12) against manuscript publications (intercoder Reliability = 99%). Results: Phase 1 results indicated further investigation was warranted for 39.8% of combinations (95% CI: 30.8%, 48.8%). 29.4% of combinations (95% CI: 15.3%, 43.4%) progressed to phase 2 or further. 18.7% (95% CI: 5.90%, 31.4%) progressed to phase 3 or FDA approval. 12.4% (95 CI: 0.00%, 25.5%) achieved regulatory approval. Trial results where “clinical promise was observed” in phase 1 of the combination study were associated with higher rates of progression past each milestone compared to regulatory approval (OR = 1.9; 95% CI: 1.3, 2.8; p = 0.0002). The phase 1 study designs were concordant with CTD-TF Guidelines for 79.6% of the combinations (95% CI: 72.2%, 87.1%); most discordances occurred where no plausible pharmacokinetic or pharmacodynamic interactions were expected. Conclusions: “Clinical promise” of a combination may not necessarily align with the desired level of clinical activity; lower concordance between study designs of phase 1 trials of combination therapies and CTD-TF Guidelines was relatively high, raising more awareness of the best study design to use when no plausible pharmacokinetic or pharmacodynamic interactions are expected may be beneficial.

Background: Citarinostat is an oral, selective histone deacetylase 6 inhibitor that inhibits growth of solid tumor cell lines and exhibits potent synergy with Pac in preclinical studies. We conducted a phase 1b dose-escalation study evaluating the safety and preliminary antitumor activity of citarinostat (AST) and Pac in pts with AST. Methods: Pts with AST, including those who progressed on prior taxane therapy, were enrolled in a 3+3 escalation study. Cohorts: 1) 180 mg, 2) 360 mg, or 3) 480 mg oral citarinostat d1-21, all plus 80 mg/m2 Pac d1, 8, 15 in a 28-day cycle. If no maximum tolerated dose (MTD) was identified, an additional cohort was allowed. Primary endpoints: dose limiting toxicity (DLT), MTD, and citarinostat recommended phase 2 dose (RP2D). Key secondary endpoints: safety, efficacy, and pharmacokinetics (PK). Results: Of 20 pts enrolled (cohort 1 = 3 pts, cohort 2 = 5 pts, cohort 3 = 6 pts, additional 360 mg cohort = 6 pts), 15 had prior taxane therapy. No DLTs were observed; MTD was not identified. Citarinostat RP2D was established at 360 mg/day. At 480 mg, a higher incidence and severity of neutropenia were observed (1 grade 4; 1 grade 3; 1 grade 2) vs 360 mg (1 grade 1). Common (> 25%) treatment-emergent adverse events (TEAEs): anemia (50%), alopecia (40%), hypomagnesemia (40%), decreased appetite (35%), fatigue (35%), diarrhea (30%), nausea (30%), leucopenia (25%), dehydration (25%), and vomiting (25%). Peripheral neuropathy was observed in 30% of pts (15% grade 3; 8 Pac-related events, 1 Pac/citarinostat-related). Twelve serious TEAEs were reported in 8 patients. No deaths were observed under treatment. Citarinostat did not modify the overall safety profile of Pac. Two pts had confirmed partial response (PR); of 14 pts with stable disease, 2 had unconfirmed PR. In preliminary PK analysis, citarinostat exposure increased in a dose-proportional manner from 180 mg to 360 mg; however, a decrease in exposure was observed after dosing at 480 mg. Conclusions: Citarinostat plus Pac showed acceptable safety in heavily pretreated pts without any unexpected toxicities. Further investigations of efficacy are needed. Clinical trial information: NCT02955185.
NC19782: A phase 1 study of talazoparib in combination with carboplatin and paclitaxel in patients with advanced solid tumors. First Author: Anita Ahmed Turk, University of Wisconsin Carbone Cancer Center, Madison, WI

Background: Poly(ADP-ribose) polymerase (PARP) enzymes are involved in DNA repair and activated by DNA strand breaks. DNA damage from carboplatin is associated with activation of PARP. Preclinical data indicate that PARP inhibition and trapping potentiates the anti-tumor effect of platinum chemotherapy. Talazoparib (T) is an oral, selective PARP inhibitor. This phase 1 trial combines T with carboplatin (C) and paclitaxel (P).

Methods: Two dosing schedules are being investigated. C is administered on day 1 and P on days 1, 8, and 15 of a 21-day cycle. T (100-1000mg) is dosed once daily for days 1-7 (schedule A) or days 1-3 (schedule B) starting on day 1. Dose escalation is by 3+3 design. Key eligibility criteria include age 18+ with a solid incurable malignancy. Patients (pts) must have tumor type that is expected to respond to C + P or have BRCA germline or somatic mutation and adequate organ function. After 4-6 cycles of combination therapy, pts may continue the combination, change to P and intermittent T without P or change to T alone with continuous dosing. Each schedule will have a 6 pt dose expansion at the MTD. The starting dose for schedule A is the MTD from schedule B alone with continuous dosing. Each schedule will have a 6 pt dose expansion at the MTD. The starting dose for schedule B is the MTD from schedule A.

Results: Schedule A results are reported: 23 pts (median age 55 yrs [range 37-70]) have been enrolled. Primary malignancies include breast (9), ovarian (3), SSC of skin/oropharynx (4), pancreatic (1), and other (5). 10 pts have known gBRCA1/2 mutations. Dose level 3 (375mgC with C AUC 6 + P 80mg/m^2) exceeded the MTD with 2 of 3 pts (66.6%) showing limiting toxicities (DLTs). Expansion of dose level 2 (T 250mgC with C AUC 6 + P 80mg/m^2) confirmed this level as the MTD. Most common adverse events included neutropenia (grade 3-4: 73.9%), anemia (grade 3-4: 39.1%), and thrombocytopenia (grade 3-4: 30.4%). Pts were on study a median of 15 weeks (range 1-98+). Of 17 pts with measurable disease, 9 (52.9%) had stable disease; median time on study 5 cycles (range 3-10). DL3+ expanded for dose limiting toxicity: grade 4 hypophosphatemia and thrombocytopenia respectively (1pt, 4%). Other adverse events: grade 3 thrombocytopenia (6pts, 27%), leucopenia (5pts, 22%), lymphopenia (4pts, 18%). Maximally tolerated dose (MTD) at the combination (DL7) was 375mgC with C AUC 6 + P 80mg/m^2. This combination was tolerated with prolonged responses seen at lower dose T in combination with C+P. Clinical trial information: NCT02317874.

Conclusions: PLX51107 + carboplatin and paclitaxel is well tolerated in patients with advanced solid tumors. A dose expansion is planned with T 250mgC with C AUC 6 + P 80mg/m^2. The schedule A MTD and RP2D is T 250mgC with C AUC 6 + P 80mg/m^2. This combination was tolerated with prolonged responses seen at lower dose T in combination with C+P. Clinical trial information: NCT02317874.

PM1183: A phase 1/2 study of PLX51107, a small molecule BET inhibitor, in subjects with advanced hematological malignancies. First Author: Amita Patnaik, South Texas Accelerated Research Therapeutics, San Antonio, TX

Background: PLX51107 is an orally active small molecule inhibitor that exhibits low nanomolar potency in blocking interactions mediated by the four BET family proteins and a unique pharmacokinetic (PK) profile. We conducted a first-in-man 3+3 dose escalation study of PLX51107 in adult patients with relapsed/refractory solid tumors (lymphomas included) and AML to determine the recommended phase II dose (RP2D) (NCT02683395). Secondary endpoints included safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). Enrollment through Cohort 7 (160 mg QD) is ongoing as of January 2018. Results: 36 subjects with advanced solid tumors (median age 60.5 years) received PLX51107 in escalating doses from 20mg to 160mg QD and 60mg BID. Uveal Melanoma (n = 11) was the most common tumor type among others, biliopancreatic (3), esophageal (2), endometrial (2) and sarcoma (2). All patients had extensive hepatic metastasis are excluded going forward. Based on clinical toxicology data, the expected Maximum Tolerated Dose will be in the 200-250mg range. The BIQ dosing schedule was selected to move above exposure-observed. Clinical trial information: NCT02210364.

Conclusions: PLX51107 continues to enroll in dose escalation; patients with extensive hepatic metastasis are excluded going forward. Based on preclinical toxicity data, the expected Maximum Tolerated Dose will be in the 200-250mg range. The BIQ dosing schedule was selected to move above exposure-observed. Clinical trial information: NCT02210364.

Phase I trial of the triplet M6620 + veliparib + cisplatin in patients with advanced solid tumors. First Author: Geraldine Helen COS, Dana-Farber Cancer Institute, Cambridge, MA

Background: Ataxia-telangiectasia-related (ATR) protein kinase is known to repair the damage of DNA through the homologous recombination (HR) pathway, activating phosphorylation cascades that culminate in cell cycle arrest to allow time for DNA repair damage (DDR). M6620 is an ATR inhibitor with antitumor activity across a range of cell lines. Veliparib (ABT-888), an oral poly-(ADP-ribose)polymerase (PARP) inhibitor, plays a pivotal role in DDR response through the base excision repair pathway, with clinical evidence of antitumor activity in combination with cisplatin in BRCA mutation carriers. As DNA damage and antitumor activity of platinum results from DNA cross-links that stall replication forks and halt transcription, this trial evaluates if veliparib together with M6620 impair DNA repair by inducing a "BRCA null"-like phenotype that potentiates the antitumor activity of cisplatin.

Methods: Open label phase I trial of the M6620+veliparib-cisplatin combination; 3+3 design, 21-day cycle: cisplatin 40mg/m^2 intravenously (IV) Day 1 (Day 8 added from dose level (DL)3); M6620 (M) IV Days 2+9; Veliparib (V) orally twice a day. 1:1:1. Prior platinum, PARPi therapy permitted. Response: RECIST 1.1. Results: 23 patients/pts enrolled, 22pts evaluable for response. 3/22pts confirmed partial responses (PR) lasting >4 cycles (range 4-15): 1pt with BRCA-wildtype ovarian cancer (DL3), 1pt with esophageal cancer/biatalic loss of ATM (DL4); 1pt with NSCLC (NM). All remaining pts enrolled in study. 2/22pts had stable disease; median time on study 5 cycles (range 3-10). DL3+ expanded for dose limiting toxicity: grade 4 hypophosphatemia and thrombocytopenia respectively (1pt, 4%). Other adverse events: grade 3 thrombocytopenia (6pts, 27%), leucopenia (5pts, 22%), lymphopenia (4pts, 18%). Maximally tolerated dose (MTD) and recommended phase II dose (RP2D) for dose level (DL)3 was 170mg QD + 200mg, M 210mg/m2. Conclusions: combination is safe and shows antitumor activity in HR-compromised tumors. Planned biomarker assessment at MTD includes γH2AX, RAD51, p53B, and pATR in tumor biopsies and circulating tumor cells using a validated, quantitative immunofluorescence assay. Clinical trial information: NCT02723864.

Phase I trial of lurbinectedin (PM1183) in Japanese patients with advanced tumors. First Author: Shunji Takahashi, Cancer Institute Hospital of JFCR, Tokyo, Japan

Background: PM1183 (lurbinectedin, Zepsyre) is a new anticancer agent that inhibits activated transcription, induces DNA double-strand breaks leading to apoptosis and modulates tumor microenvironment. The recommended dose (RD) in non-Japanese patients (pts) is 3.2 mg/m^2 on Day 1 every three weeks (q3wk), with reversible myelosuppression as dose-limiting toxicity (DLT) and identified in dose limiting study (DLTs). Methods: Japanese pts with solid tumors (excluding OCR or CNS primary tumors), adequate organ function and ECOG PS 0-2 were treated at 3 different dose levels (DLs), 1.5 mg/m^2, 2.5 mg/m^2 and 3.2 mg/m^2, using a 3+3 design. Results: Fifteen pts (10 female / 5 male) were treated and evaluated for safety and efficacy. Median age was 52 years (38-65), albumin 4mg/dL (3.5-4.6) with 2 median previous lines (1-3). Tumors were, among others, biliopancreatic (3), esophageal (2), endometrial (2) and breast (1). 2 out of 4 pts on DL3 (3.2 mg/m^2) had a DLT consisting of a grade 4 neutropenia and a G3 neutropenia lasting > 7 days. Eight pts were treated at the RD established on 2.5 mg/m^2, with G2 neutropenia leading to dose reduction and dose delay in 1 pt each. Main adverse events at the RD were hematological with 1 pt (12.5%) presenting G3 neutropenia. Other Grade 4 toxicities included a non-drug related G4 hypokalemia (12.5%). Non-hematological toxicities were exclusively G1/2, including G2 ALT increase (50%), AST increase (25%), anorexia (25%), nausea (25%), fatigue (12.5%) and dyspepsia (12.5%). At RD, 1 pt (12.5%) with metastatic breast cancer achieved a durable partial response and 3 pts (37.5%) had confirmed stable disease. PK at RD (n = 6 pts) showed a similar behavior to non-Japanese pts, with a mean (standard deviation) total body clearance (CL) of 10.5 (4.5) L/h, half-life of 50.7 (18.1) h and volume of distribution at steady-state of 375.5 (172.0) L. Conclusions: The RD of PM1183 in Japanese pts is 2.5 mg/m^2 q3wk, with mild toxicity. Main DLTs were hematological. Hints of activity were observed in breast cancer. Japanese pts showed a similar CL to non-Japanese pts, but with a 26.5% lower distribution volume. A new cohort is exploring PM1183 3.2 mg/m^2 (non-Japanese RD) in Japanese pts receiving G-CSF support. Clinical trial information: NCT02210364.
Prior treatment with nab-paclitaxel is allowed. Status 0-1, and adequate renal, hepatic, and marrow function are included. Dosing (the day before, of, and after nab-paclitaxel). Pts going phase 1/2 study is evaluating the tolerability, anticancer activity, and chemotherapy resistance. Nonclinical and clinical studies have suggested that a GR antagonist (GRA) can enhance the efficacy of chemotherapy.

Background: Our preclinical data show that one mechanism of acquired resistance to anti-angiogenic therapy involves hypoxia correction, measured by decreased SUV (↓ SUV) on FDG-PET followed by mitochondrial up-regulation. ME344 is a potent inhibitor of mitochondrial respiration. The aims of this study were to assess 1) the fraction of HERNEBC patients that show ↓ SUV in response to single dose Bev and 2) if adding ME344 to Bev inhibits cell proliferation as determined by Ki67% decrease, a surrogate marker of efficacy in neoadjuvant breast cancer. Methods: Treatment-naive HERNEBC patients (T > 1 cm, any N, M0) received 15 mg/kg Bev on d0 and were then randomized 1:1 to ME344 10 mg/kg IV d8, 15 and 21 (arm A) or placebo (arm B) followed by physician’s choice of definitive therapy. FDG-PET was performed on d0 and d7 and tumor biopsy on day 0 and 28. The primary endpoint was Ki67% reduction from d0 to 28. A 40 patient sample size was powered to detect a 30% relative difference in Ki67% between arm A and B (alpha 0.05, beta 0.2). Threshold for hypoxia correction by PET was 10% (sUV). A predefined interim analysis was planned when 20 patients had completed treatment. Results: 19 patients were randomized (arm A/B: 7/7 LumA, 2/2 LumB, 1/0 TNBC). Baseline characteristics: Ki67 by IHC: mean 10.3% (1%-48%), age: mean 56 (44-75), T (8 T1, 10 T2, 1 T3), N (14 N0, 5 N1) and G (4 G1, 12 G2, 3 G3) were balanced between arms. 31% of patients experienced ↓ SUV > 10%. Mean absolute (relative) Ki67 decreases were 5.13 (29%) and 1.2 (9%) in arms A and B (P = 0.06). Patients with ↓ SUV > 10% experienced an absolute average Ki67 decrease of 16.6 vs. 2.3 in arms A and B (P = 0.19). Two G3 adverse events (high blood pressure) were reported (1 per arm) and deemed related to Bev. Conclusions: ME344 results in significant Ki67 reduction compared to placebo in HERNEBC patients exposed to single-dose Bev. This effect may be greater in those patients with Bev induced hypoxia correction. These clinical results are consistent with preclinical data suggesting that ME-344 can reverse resistance to anti-angiogenic therapy and warrant further studies to assess clinical efficacy of the combination. Clinical trial information: NCT02806817.

A phase 1/2 study of relacorilant + nab-paclitaxel (nab-pac) in patients (pts) with solid tumors: The dose-finding phase. This on-going A phase 1/2 study is evaluating the tolerability, anticancer activity, and Phase 2 dose of relacorilant + nab-pac. Nab-pac is administered weekly for 3 cycles. A predefined interim analysis was planned when 20 patients had completed treatment. Results: 19 patients were randomized (arm A/B: 7/7 LumA, 2/2 LumB, 1/0 TNBC). Baseline characteristics: Ki67 by IHC: mean 10.3% (1%-48%), age: mean 56 (44-75), T (8 T1, 10 T2, 1 T3), N (14 N0, 5 N1) and G (4 G1, 12 G2, 3 G3) were balanced between arms. 31% of patients experienced ↓ SUV > 10%. Mean absolute (relative) Ki67 decreases were 5.13 (29%) and 1.2 (9%) in arms A and B (P = 0.06). Patients with ↓ SUV > 10% experienced an absolute average Ki67 decrease of 16.6 vs. 2.3 in arms A and B (P = 0.19). Two G3 adverse events (high blood pressure) were reported (1 per arm) and deemed related to Bev. Conclusions: ME344 results in significant Ki67 reduction compared to placebo in HERNEBC patients exposed to single-dose Bev. This effect may be greater in those patients with Bev induced hypoxia correction. These clinical results are consistent with preclinical data suggesting that ME-344 can reverse resistance to anti-angiogenic therapy and warrant further studies to assess clinical efficacy of the combination. Clinical trial information: NCT02806817.

A phase 1/2 study of relacorilant + nab-paclitaxel (nab-pac) in patients (pts) with solid tumors: The dose-finding phase. This on-going A phase 1/2 study is evaluating the tolerability, anticancer activity, and Phase 2 dose of relacorilant + nab-pac. Nab-pac is administered weekly for 3 cycles. A predefined interim analysis was planned when 20 patients had completed treatment. Results: 19 patients were randomized (arm A/B: 7/7 LumA, 2/2 LumB, 1/0 TNBC). Baseline characteristics: Ki67 by IHC: mean 10.3% (1%-48%), age: mean 56 (44-75), T (8 T1, 10 T2, 1 T3), N (14 N0, 5 N1) and G (4 G1, 12 G2, 3 G3) were balanced between arms. 31% of patients experienced ↓ SUV > 10%. Mean absolute (relative) Ki67 decreases were 5.13 (29%) and 1.2 (9%) in arms A and B (P = 0.06). Patients with ↓ SUV > 10% experienced an absolute average Ki67 decrease of 16.6 vs. 2.3 in arms A and B (P = 0.19). Two G3 adverse events (high blood pressure) were reported (1 per arm) and deemed related to Bev. Conclusions: ME344 results in significant Ki67 reduction compared to placebo in HERNEBC patients exposed to single-dose Bev. This effect may be greater in those patients with Bev induced hypoxia correction. These clinical results are consistent with preclinical data suggesting that ME-344 can reverse resistance to anti-angiogenic therapy and warrant further studies to assess clinical efficacy of the combination. Clinical trial information: NCT02806817.

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
A phase Ib study of ADI-PEG 20 plus pembrolizumab in advanced solid tumors. First Author: Kwang-Yu Chang, National Institute of Cancer Research, National Health Research Institutes, Taichung, Taiwan.

Background: Arginine deprivation with pegylated arginine deiminase (ADI-PEG 20) has been shown to upregulate tumor programmed death-ligand 1 (PD-L1) expression and T cell infiltration. Current phase Ib study is to explore the feasibility of combining ADI-PEG 20 with pembrolizumab in patients with advanced solid tumors. Methods: Eligibility criteria included treatment-failure patients with measurable lesions. Pre-treatment tumor biopsy was required. In the “≤ 3” designed dose-escalation cohort, patients failed to receive ADI-PEG 20 36 mg/m² at day 1, 8 and 15, and pembrolizumab (1 mg/kg or 200 mg) at day 1, every 3 weeks to determine the maximum tolerated dose (MTD) of pembrolizumab for expansion cohort study. In the expansion cohort part, patients with platinum-failed HNSCC would receive both ADI-PEG 20 and pembrolizumab (at MTD) from day 1; while patients in translation cohort who were required to have < 50% PD-L1 expressing tumors would receive 3 doses of weekly ADI-PEG 20 and a post-ADI-PEG 20 biopsy before the start of combination treatment. The primary endpoint was safety and tolerability. Secondary endpoints included progression-free survival, overall survival, response rate, and the correlation between PD-L1 expression and T-cell infiltration after treatment with ADI-PEG 20 with and without pembrolizumab. Results: The recruitment of dose-escalation cohorts was completed between July 2017-January 2018. There was only one dose-limiting toxicity, grade 3 hepatitis, observed in a patient in 1 mg/kg dose level; while none in the 200 mg dose level. Among the (22.2%) who had partial response (PR) and four (44.4%) had stable disease. The two PRs were in thymus cancer and nasopharyngeal carcinoma, with both having 100% tumor baseline PD-L1 expression. The most common grade 3/4 adverse event (AE) was neutropenia, which occurred in seven patients. For serious AEs, two had neutropenic fever lasted less than one week. Three patients had injection site reaction (4.4%), and one had partial response due to tumor progression in the eighth week. The expansion cohorts are enrolling. Conclusions: Co-administration of ADI-PEG 20 and pembrolizumab is feasible. The major toxicity is neutropenia which is transient and manageable. Responses were observed with the regimen. Clinical trial information: NCT03294572.

Characterization of KEAP1-NRF2 genomic alterations across diverse tumor types: Co-occurring alterations, survival outcomes, and immune biomarkers targeting cancer metabolism. First Author: Shiraj Sen, The University of Texas Southwestern Medical School, Dallas, TX.

Background: CRISPR-Cas9-based genetic screening and metabolomic analyses have revealed that KEAP1-NRF2-mutated cancers depend on increased glutaminolysis and are vulnerable to glutaminase inhibition. However, alterations in KEAP1-NRF2 have yet to be clinically characterized. Methods: We analyzed clinical and next gen sequencing data from pts treated at MD Anderson Cancer Center and performed bioinformatic analyses of alteration frequency using TCGA data on cBio Portal to characterize KEAP1-NRF2 alterations and used Kaplan-Meier analysis to identify associations with overall survival (OS). Results: Among 189 pts with KEAP1 or NRF2 alterations (alts) at MDACC (97 with each, 5 with both), median age was 65 yrs (range: 18-89), 52% were females, 80% Caucasian, 11% Hispanic, and 5% African-American. KEAP1-NRF2 alts were most common in NSCLC (19%), cholangiocarcinoma (8%), breast (7%), and renal cell CA (7%). Mean number of co-occurring alts was 8 (range:0-73). We identified 69 unique alts in KEAP1, most commonly Q619del (11%) and V369A (9%), and 68 unique alts in NRF2, most commonly E79Q (6%) and G31A (6%). Median OS in the entire cohort was 966 days. Of the 1505 co-alts identified with KEAP1, most common were TP53 (57%), ARID1A/B/2 (55%), PIK3-encoding genes (37%), and NOTCH1 (29%). Of the 817 unique co-alts identified with NRF2 alts, most common were TP53 (52%), PIK3-encoding genes (36%), ARID 1A/B/2 (25%), and BRCA1/2 (19%). Co-alts in TP53, SWI/SNF complex, mTOR pathway, and NOTCH pathway genes did not impact survival. In TCGA, KEAP1-NRF2 alts were most common in NSCLC (26%), uterine (15%), breast (10%), and cholangiocarcinoma (9%). KEAP1-NRF2 alts were associated with decreased survival in lung adenocarcinoma (LUAD), 49 vs 33 months, log-rank p = 0.02. Conclusions: KEAP1-NRF2 alts are prevalent across diverse tumor types and associated with decreased survival in LUAD. They most frequently co-occur with alts in TP53, SWI/SNF complex, and mTOR pathway genes but these co-occurring alts did not impact survival in our cohort. A Basket trial of Glutaminase Inhibitor (BeGIN) CB839 in patients with KEAP1-NRF2 aberrant tumors is planned.

Identification of predictive and pharmacodynamic biomarkers associated with the first-in-class clinical pharmacology and experimental therapeutic. First Author: Mahlo M. Sachdev Dhawan, University of California San Francisco, San Francisco, CA.

Background: New non-coding RNAs, which appear to be involved in cell proliferation in animal cells, have been discovered by L.Burzio and co-workers. Andes-1537 is a short single stranded phosphorothioate-deoxyoligonucleotide which binds by base pairing to one of these newly discovered non-coding RNAs, named Antisense non-coding mitochondrial RNA (ASncmRNA). The resulting RNA-RNA hybrid is then hydrolyzed by two cellular RNases: RNase H and Dicer resulting in microRNAs. In vitro experiments with cells have shown Andes-1537 affects cancer cells by: a) inducing apoptosis by lowering the expression of anti-apoptotic proteins such as survivin b) decreasing proliferative signaling through inhibition of the expression of proteins such as cyclin D1 and cyclin B1, and c) inhibition of tissue invasion/metastatic proteins such as n-cadherin, B-catenin and metastasis inducing factors. Methods: The safety, tolerability, maximum tolerated dose (MTD), pharmacokinetic (PK) characteristics and efficacy of Andes-1537 was assessed in a phase 1 study. Patients with all solid tumors were enrolled in 5 cohorts at 1 mg/kg, 200 mg SC, 400 mg SC, 600 mg SC and 800 mg SC twice weekly. Results: 22 patients (14 M: 8F) with heavily pretreated solid tumors were enrolled in 5 cohorts. Two dose-limiting toxicities occurred at the 800 mg SC dose level both of which were injection site reactions: one precluding full cycle 1 dose delivery, and one involving grade 3 skin necrosis due to local inflammation and infiltration. No other grade 3/4 toxicities were seen. Grade 2 toxicities including injection site reactions and erythema. The MTD has been determined to be 600 mg SC twice weekly. Two patients (one with pancreatic cancer and one with cholangiocarcinoma) had stable disease on scans beyond six months. No partial or complete responses were seen with Andes-1537. PK data reveals a linear PK profile. Conclusions: Andes-1537 is a well-tolerated drug with a novel mechanism. It was determined to be tolerable at 600 mg SC twice weekly. An efficacy signal in pancreatic cancer and cholangiocarcinoma was seen at 200 mg dose level and thus dose expansion is under consideration. Clinical trial information: NCT02508441.
Background: SL-801 is a novel, oral, small molecule reversible inhibitor of Exportin-1 (XPO-1), a critical nuclear export protein overexpressed in many cancers. SL-801 has demonstrated potent in vitro and in vivo anti-tumor activity against a broad range of hematologic and solid cancers. SL-801’s reversible inhibition of XPO-1 may translate to selective activity and potential safety benefits. Interim results from the dose-escalation study are reported.

Methods: STML-801-0115 is a first-in-human, multicenter Phase 1 3×3 dose escalation study in patients with localized unresectable, or metastatic solid tumors resistant to or relapsed following standard therapy. Objectives are to evaluate safety and tolerability, identify maximum tolerated dose (MTD) or optimal doseregimen for further evaluation, and assess pharmacokinetics and preliminary anti-tumor activity. SL-801 is orally administered on days 1-4 and 8-11 of a 21-day cycle. Starting dose was 5 mg and is currently 55 mg (escalation ongoing). Results: As of 1/16/18, 31 pretreated patients (range: 1-11 prior therapies; 71% >3rd line) received SL-801 (16 females, median age 63 years [range: 39-76]). No dose limiting toxicity (DLT) has been identified in the highest dose reached. Measurable disease was observed in 12 patients (range: 0.5-1.5 cm). The common treatment-related adverse events included nausea (45%), vomiting (32%), diarrhea (19%), fatigue (26%) and decreased appetite (19%). Grade 3 TRAEs included nausea (n = 40, 45, 50 mg), vomiting (n = 1; 45 mg), fatigue (1; 45 mg), acute renal injury (n = 1; 30 mg), and neutropenia (n = 1; 10 mg). There were no grade 4 or 5 TRAEs. Nine patients had stable disease (SD) for 3-12+ cycles. Five patients, with GE junction, colon, neuroendocrine, basal cell, and breast cancer, had SD >6 months. Radiographic tumor shrinkage >10% was noted in 4 patients. Conclusions: SL-801 appears to be well tolerated in advanced solid tumors, and 29% of patients achieved SD as best response. Enrollment and dose escalation continue in an effort to identify an optimal dose and regimen. Clinical trial information: NCT02667873.

Dose escalation schema:

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Defactinib D1-21 (BID)</th>
<th>Pembrolizumab</th>
<th>Gemcitabine D1, B</th>
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</thead>
<tbody>
<tr>
<td>Level 1 (starting dose)</td>
<td>200 mg</td>
<td>200 mg</td>
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<td>Level 2</td>
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<tr>
<td>Level 5</td>
<td>400 mg</td>
<td>200 mg</td>
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</table>

Phase I clinical trial of the glutaminase inhibitor CB-839 plus cabazitabine in patients with advanced solid tumors. First Author: Andrew Wang-Gilliam, Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Colorectal cancers (CRCs) harboring a PIK3CA mutation demonstrated glutaminolysis in both in vitro and in vivo models, including those known to be fluoropyrimidine (F) resistant. CB-839 (CB) is an oral inhibitor of glutaminase, a key enzyme in glutamine metabolism. Preclinical studies further show that the combination of CB and a F is superior to either as a single agent, and can overcome F resistance. We conducted a phase I trial to assess the maximum tolerated dose and dose limiting toxicities (DLTs) of CB when given with cabazitabine (C). Methods: Patients with advanced solid tumors and disease progression on standard treatment, or for whom C is an acceptable treatment option, were enrolled. A standard 3+3 design was used to identify the RP2D. CB was given orally twice daily continuously and C was given IV once daily. Measurable disease was observed in 12 patients (range: 0.5-1.5 cm). The common treatment-related adverse events included nausea and vomiting (40%), diarrhea (35%), anorexia (30%), fever (25%), and myalgia (25%). No DLTs were observed, therefore the Level 5 dose was deemed to be the RP2D. Among the 15 patients evaluable for treatment response, 1 (7%) partial response, 8 (53%) stable disease and 6 (40%) disease progression were observed. The median time on treatment was 132 days for all evaluable patients, and 127 days in the 8 PDAC patients with the longest time on treatment being 290 days (1; 45 mg). 45 mg was the dose given to patients who progressed on gemcitabine and nab-paclitaxel. Paired biopsies in PDAC patients showed increased proliferating CD8+ T cells and decreased macrophages with treatment. Conclusions: The combination regimen is well tolerated. Dose Level 5 is the RP2D dose. The expansion cohort (PDAC only) is currently ongoing. Efficacy and correlative data is forthcoming. Clinical trial information: ACTRN12610000897066.

Dose escalation schema:

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<tr>
<td>Level 5</td>
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Phase I study of defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer. First Author: Andrea Wang-Gilliam, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: Focal adhesion kinase (FAK) is consistently hyperactivated in multiple tumor types including pancreatic ductal adenocarcinoma (PDAC). Our preclinical work showed that FAK and PD-1 inhibitors elicit significant tumor regression, and a maximal response is achieved by combining FAK and PD-1 inhibitors with gemcitabine, suggesting the need for a cytotoxic agent to bolster antigen presentation (Jiang H et al, Nature Medicine 2016). Methods: 16 eligible patients were being treated according to the dose escalation schema (Table 1). A 3+3 design is being used. The study has an expansion portion for PDAC patients at the recommended phase 2 dose (RP2D). The primary endpoint is to determine the RP2D. Secondary endpoints include safety, toxicity, objective response rate, progression-free survival and overall survival. The exploratory endpoints include developing a molecular and immune profile for treatment response. Results: The dose escalation cohort has been completed with a total of 20 patients with refractory solid tumors. The common treatment-related adverse events included nausea (50%), vomiting (40%), diarrhea (35%), anorexia (30%), fever (25%), and myalgia (25%). No DLTs were observed, therefore the RP2D dose was deemed to be the RP2D. Among the 15 patients evaluable for treatment response, 1 (7%) partial response, 8 (53%) stable disease and 6 (40%) disease progression were observed. The median time on treatment was 132 days for all evaluable patients, and 127 days in the 8 PDAC patients with the longest time on treatment being 290 days (1; 45 mg). 45 mg was the dose given to patients who progressed on gemcitabine and nab-paclitaxel. Paired biopsies in PDAC patients showed increased proliferating CD8+ T cells and decreased macrophages with treatment. Conclusions: The combination regimen is well tolerated. Dose Level 5 is the RP2D dose. The expansion cohort (PDAC only) is currently ongoing. Efficacy and correlative data is forthcoming. Clinical trial information: 02546531.
Pharmacokinetic (PK) and exposure-response (ER) analysis of pertuzumab (P) in patients (pts) with HER2-positive metastatic gastroesophageal junction area and gastric cancer (mGEJC/GC). First Author: Whitney Paige Kirschbrown, Genentech Inc., South San Francisco, CA

Background: The phase 2a, dose-finding JOSUHA study reported increased P clearance (CL; 37% lower P steady-state Cmin (Cmin,ss) in pts with HER2+ mGEJC/GC vs metastatic breast cancer (MBC). Based on these data, 840 mg q3w was selected for testing in the phase 3 JACOB study (NCT01774786) to achieve similar P concentrations (conc) to BC studies with the 840 mg q3w P dose. In JACOB, while there was evidence of pretreatment activity, addition of P to trastuzumab (H) and chemotherapy (CT) in 1L-line therapy did not significantly improve overall survival (OS) vs placebo (Pla)+H+CT (hazard ratio: 0.84 [95% CI 0.71–1.00], median OS 17.5 vs 14.2 months), in pts with HER2+ mGEJC/GC. Here we report the PK and ER analysis of P in JACOB.

Methods: PK samples were collected at Cycles 1–4, 6, and 8 (predose); Cycles 1, 2, 4 and 8 (postdose); and at follow-up. P+H peak and trough conc were summarized by descriptive statistics and % pts with a Cmin,ss > 20 µM (target conc) tabulated. PK exposure was compared across geographic regions. The Kaplan-Meier method and a log-rank test were used to assess OS across Cmin,ss quartiles. PK drug-drug interaction (DDI) was assessed using serum Cmin,ss geometric mean ratios. Results: Pts with ≥ 1 dose of P or H and ≥ 1 PK sample were included (P: n = 374 [P+H+CT]; H: n = 372 [P+H+CT] and 375 [Pla+H+CT]). Mean Cmin,ss Cycle 6 for P was 114±15.8 µM/L. 99.3% of pts had Cmin,ss for P ≥ 20 µM/L. There were no differences in OS across Cycle 1 and Cycle 6 (≤ 1) P Cmin,ss quartiles (Q1: 77.1, Q2: 6–39, Q3: 39.8–51.9, Q4: 51.9–110; n = 349, P = 0.52) and Q2: 0.075–1.00, median OS 17.5 vs 14.2 months), in pts with HER2+ mGEJC/GC. ER analysis showed no correlation between P trough conc and OS. PK data were consistent with prior GC (P: 840 mg) and BC (P: 840 mg/420 mg) studies and higher P CL in HER2+ mGEJC/GC vs other tumor types. Clinical trial information: NCT01774786.
### 2568 Poster Session (Board #395), Mon, 8:00 AM-11:30 AM

**Unexpected pharmacokinetics of evosofamidine observed in phase III MAESTRO study.**

**First Author:** Jack P. Higgins, Molecular Templates, Inc., Austin, TX

**Background:** Evosofamidine (Evo) is a prodrug of Br-IPM that is preferentially activated under hypoxic conditions. Hypoxia in locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC) is associated with disease progression and poor prognosis.

**Methods:** Gemcitabine (Gem) was evaluated with or without Evo in a randomized phase II (Ph 2) trial (N = 214) in US patients with advanced PDAC (NCT01144455). Two doses of Evo (240 mg/m² or 340 mg/m²) were tested with 340 mg/m² showing a significant improvement in ORR and PFS. MAESTRO was a double-blind, placebo-controlled phase III (Ph 3) trial (N = 693) of Evo + Gem versus Placebo (Pbo) + Gem in patients with locally advanced unresectable or metastatic PDAC (NCT01746979) using the same Ph 2 schedule and 340 mg/m² Evo dose. **Results:** Median OS in the Ph 3 study was 8.7 mo with Evo + Gem vs 7.6 mo with Pbo + Gem; HR = 0.84 (p = 0.059). Median PFS was 5.5 mo with Evo + Gem vs 3.7 mo with Pbo + Gem; HR = 0.77 (p = 0.004). The outcomes observed in the Ph 3 study (340 mg/m² dose) were similar to the 240 mg/m² dose Ph 2 outcomes (median OS = 8.7 mo; median PFS = 5.6 mo). Notably, a new ethanol-based formulation to improve drug product solubility was introduced after the Ph 2 study and before the start of the Ph 3 study. **Conclusions:** Comparison of the Evo PK profile from the Ph 3 and Ph 2 studies suggest the formulation change may have substantially reduced Evo serum exposure (Table 1). This reduction in Evo exposure could explain why the efficacy seen in the Ph 2 study at the 340 mg/m² dose was not replicated in the Ph 3 study. Evo is currently being tested at higher doses with the new formulation (ethanol-based) in an attempt to replicate the PK seen with the previous formulation at 340 mg/m². Clinical trial information: NCT01746979.

<table>
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<th>PK Parameters</th>
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</table>

AUC (mg/mL) = Area under the concentration-time curve from 0 to infinity; Cmax = maximum peak observed concentration; SD = standard deviation.

### 2570 Poster Session (Board #396), Mon, 8:00 AM-11:30 AM

**Gene expression and cytokine modulation in a first in human (FIH) study of pan BET inhibitor ABBV-075 in solid tumors.**

**First Author:** H. O’Neil, Indiana University School of Medicine, Indianapolis, IN

**Background:** ABBV-075 is an oral small molecule inhibitor of the BET family of bromodomain-containing proteins that function as regulators controlling many transcriptional programs required for cancer pathogenesis. ABBV-075 is an oral small molecule inhibitor of the BET family of bromodomain-containing proteins. ABBV-075 is currently being evaluated in a FIH study in advanced solid tumors (M14-546). Using a 3+3 dose escalation design, a total of 72 solid tumor patients were enrolled across 2 dose-escalating schedules. Dose-limiting toxicities were thrombocytopenia, fatigue, aspartate aminotransferase elevation, gastrointestinal bleed, and hypertension in the dose escalation phase.

**Methods:** In this report, pharmacokinetic (PK) and pharmacodynamic (PD) data are presented for 40 subjects. PD effect was measured in surrogate tissue (whole blood and serum), which was collected prior to therapy and at various time points post-dosing. Gene expression was evaluated by branched DNA assay. Soluble cytokines were analyzed by immunoassay (Myriad RBM’s InflammationMAP®).

**Results:** The observed Tmax varied at 2-4 hours post-dosing, Cmax and AUC increased dose-proportionally within the dose-range studies, mean T½ 13 - 32 hours. Exposure (Cmax) at day 8 correlated with decrease in platelet count on day 15 compared to baseline counts (Pearson correlation: -0.46, p = 0.032). HEXIM1 and DCXR gene expression increased, CD93 gene expression decreased at 6 hours post treatment. CD93 and DCXR demonstrated dose-dependent modulation. Statistically significant correlation was observed between gene modulation at 6 hours and drug exposure at day 8 (Pearson correlation: HEXIM1 = 0.435, CD93 = 0.375, DCXR = 0.541). Soluble BDNF expression demonstrated a dose and time-dependent decrease at cycle 2 and 3 compared to baseline (p < 0.0001).

**Conclusions:** We demonstrated target engagement in surrogate tissue via modulation of gene and soluble cytokine expression, both of which were dose dependent. Strong correlation was observed between drug exposure and gene expression modulation as well as thrombocytopenia, after ABBV-075 treatment. Correlation of these PD effects with adverse events and clinical response, are currently under investigation. Clinical trial information: NCT02391480.

### 2569 Poster Session (Board #395), Mon, 8:00 AM-11:30 AM

An open-label, randomized cross-over bioavailability and extension study of oral paclitaxel and HM30181 compared with weekly intravenous (IV) paclitaxel in patients with advanced solid tumours.

**First Author:** Christopher G. A. Jackson, Southern District Health Board, Dunedin, New Zealand

**Background:** Paclitaxel has poor oral bioavailability due to active excretion by p-glycoprotein (Pgp) on intestinal epithelial cells. An oral formulation would reduce IV access, avoid allergic reaction to cremophor, forego steroid premedication, reduce day stay, and improve convenience. With a lower Cmax, oral therapy may have toxicity advantages. Oraxol (Athens, USA) is a combination of HM30181, a novel, orally active, potent and specific inhibitor of Pgp with low systemic exposure and oral paclitaxel. We report the results of the first scheduled interim analysis of a bioequivalence study of Oraxol compared to IV paclitaxel, and the results of an extension study with repeat PK sampling after 4 weeks administration. **Methods:** We conducted a randomized crossover study at 3 sites in New Zealand. HM30181 15mg plus paclitaxel 205mg/m² was given PO on days 1-3 and compared to a single dose of IV paclitaxel (80 mg/m²) in patients (pts) with advanced solid tumours. PK blood samples were taken d1-9 for PO paclitaxel and d1-5 for IV paclitaxel. Pts who completed the initial study were eligible to enter an extension study on an open-label basis. Oraxol 205mg/m² d1-3 q1w with repeat PK sampling at week 4. **Results:** Paclitaxel PK was compared from the first 6 pts in the bioequivalence study, to 10 pts that were enrolled in the extension study. There was one treatment related SAE (tachycardia) which resolved. Treatment related toxicities were mostly GI and haematological, and manageable. One pt remains on study > 1 year without neuropathy. Clinical trial information: ACTRN12615000845949. **Conclusions:** Oraxol 61.5mg/m² PO d1-3 evaluated as AUC comparable to IV paclitaxel 80mg/m². This schedule of Oraxol is within predicted range needed to demonstrate bioequivalence. 4-week PK results show PO formulation is not altered with repeated dosing. A phase 3 study in patients with metastatic breast cancer is ongoing.

<table>
<thead>
<tr>
<th>Paclitaxel (80mg/m² N = 6)</th>
<th>Oraxol, Baseline (n = 6)</th>
<th>Oraxol Week 4 (n = 10) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mL)</td>
<td>5652 (1013)</td>
<td>5078 (1723)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2269.44 (227.11)</td>
<td>230.99 (133.84)</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>2493.4 (731.96)</td>
<td>2193.7 (707.14)</td>
</tr>
<tr>
<td>IC50 (50% CI)</td>
<td>0.67 (0.50)</td>
<td>0.101 (0.06)</td>
</tr>
</tbody>
</table>

Intra-subject CV (%) = 12.82.

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Impact of curcumin with and without (+/-) piperine on tamoxifen exposure.

First Author: Geradus Hussaarts, Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: Tamoxifen is extensively used as endocrine therapy for breast cancer. It is a prodrug that is primarily metabolized by CYP2D6 and CYP3A4, particular into endoxifen. In daily practice, the herb curcumin is widely used among patients (pts) because of its presumed anti-tumor effects. Preclinical studies show effects of curcumin on phase I and II drug metabolism, leading to altered plasma levels. We hypothesized that curcumin increases endoxifen exposure by affecting phase II metabolism. Therefore, we performed a randomized, 3-phase, cross-over study to compare tamoxifen exposure in breast cancer pts +/- curcumin, and with the addition of the bioenhancer piperine.

Methods: Pharmacokinetic sampling (PK) was performed in 15 pts at the 28th, 56th and 84th day of the trial. In the 28 days prior to PK, tamoxifen (20 mg qd) was either given alone, or combined with curcumin (1,200 mg TID), or with curcumin + piperine (10mg TID) in this order or vice versa. Genotyping was determined to perform log-transformed area under the curve (AUC). For multiple testing a Bonferroni correction was applied.

Results: Tamoxifen AUC0-24h decreased with 7.3% (95% CI: -0.5, 13.6%; p = 0.02) with curcumin and 13.0% (95% CI: -5.6, 19.9%; p = 0.002) with curcumin and piperine, compared to tamoxifen alone. Endoxifen AUC0-24h decreased with 8.9% (95% CI: -9.1, 16.3%; p = 0.029) and 13.5% (95% CI: -2.8, 23.0%; p = 0.15), respectively. CYP2D6 genotyping resulted in 6 intermediate metabolizers (IM), and 6 extensive metabolizers (EM). Interestingly, for pts with a EM phenotype, effects of curcumin on piperine on drug exposure (AUC0-24h) seemed to be higher than for IM phenotype pts (a decrease of 21.8% vs 4.8% for tamoxifen, and 22.6% vs 10.2% for endoxifen, respectively). Severe toxicities were not observed.

Conclusions: In contrast to our hypothesis, the exposure of tamoxifen and endoxifen significantly decreased by concomitant use of curcumin +/- piperine. Although limited effects in most pts, co-treatment with these herbs could reduce endoxifen levels below the threshold for efficacy, especially for EM phenotype pts. Clinical trial information: NTR6149.

Clinical pharmacology assessment of PF-06647020 (PF-7020), an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in adult patients (pts) with advanced solid tumors.

First Author: Dawei Xuan, Pfizer Early Oncology Development & Clinical Research, La Jolla, CA

Background: PF-7020, an ADC composed of humanized monoclonal antibody (Ab) against PTK7, auristatin payload, and valine-citrulline linker, is being investigated in the ongoing first in human Phase 1 study in pts with advanced solid tumors resistant to standard therapy. We present preliminary results of clinical pharmacology assessments of PF-7020, including phase pharmacokinetic (PK) analyses, and exploratory exposure-response analyses for efficacy and safety endpoints.

Methods: Non-proprietary PK analyses were conducted on data from dose escalation and expansion studies of once every 3 weeks dosing (Q3W). A semi-mechanistic model that integrates ADC, total Ab (TAB), and unconjugated payload (PL) was built to characterize PK. We explored the relationship between objective response rate (ORR, current 27%) in ovarian cancer pts (OVCA) and PF-7020 exposure (Cmin,C1D21) with logistic regression modeling. A semi-mechanistic PK-pharmacodynamic (PD) model was built to explore the relationship between PL concentrations and absolute neutrophil counts (ANC).

Results: As of Oct 24, 2017, 112 pts were treated with PF-7020 at doses of 0.2 – 3.7 mg/kg Q3W. PK exposure increased in a dose related manner, with a terminal half-life for PF-7020 of approximately 3 days at 2.8 mg/kg. Integrated PK model suggested that deconjugation and proteolytic degradation of ADC played major roles in elimination of PF-7020, and PL formation. A significant correlation was identified between ADC Cmin,C1D21 and OVCA ORR based on univariate analysis (P < 0.05); ORR increased with higher Cmin,C1D21, suggesting pts with lower exposures may benefit from increase in dose/dosing intensity. PK/ PD analysis suggests higher PL concentrations were associated with lower ANC. Conclusions: The PK exposure increased in a dose related manner, with a terminal half-life for PF-7020 of approximately 3 days at 2.8 mg/kg. Increase in PK exposure correlated with better clinical response in OVCA pts.

The PL exposure appeared to correlate with ANC profiles. The preliminary PK/PD analyses support evaluating PF-07020 under once every 2 weeks dosing (Q2W) in the ongoing study.

The clinical relevance of multiple DPYD polymorphisms on patients candidate for fluoropyrimidine based-chemotherapy. A case-control study in a Northern Italian setting.

First Author: Francesco Iachetta, Medical Oncology Unit, Clinical Cancer Center, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy

Background: Deletions polymorphisms in gene-encoding DPD (DPYD) may result in the severe reduction of DPD enzymatic activity that causes life-threatening toxicities when the standard dose of fluorouracil is used. DPYD*2A (WS14+1G>A) is the most common single-nucleotide polymorphism (SNP) associated with critical DPD deficiency. To enhance prevention of fluoropyrimidine toxicity, we assessed the potential clinical impact of additional DPYD polymorphisms.

Methods: In 2011, we began screening DPYD*2A in patients candidate for fluoropyrimidine based-chemotherapy. We planned a case-control study with all cases of DPYD*2A wild type who developed CTC-NCI-V.3 toxicity G3 and with a cohort of patients who did not present severe toxicities (ratio 1:1.5). The two groups were matched for tumour site, staging (I-III vs IV) and patient’s age. Then we tested the additional SNPs (c.2846A>T, c.1679T>G, c.2194G>A) using Real Time PCR.

Results: From 2011 to 2016 we screened 1,827 patients for DPD deficiency, of those 31 subjects (1.7%) showed DPYD*2A SNP. Complete clinical information was available only for 668 patients and of those, 146 (21.9%) developed severe toxicities (Case group). A control group was instead established with 220 patients who experienced no or mild toxicities. Fifty-three patients carried a variant in one of the additional SNPs: 35 subjects (66%) fell into the Case group and 18 (34%) into the Control group (OR 3.69, 95% CI 1.93-7.06, p < 0.0001). We confirmed that c.2846A>T > c.2194G>A was the most frequent SNP (12.5%, 46 of 366 pts) and showed a correlation with hematologic toxicity. In particular, neutropenia was observed in 50% of the patients carrying c.2194G>A (23 of 46) vs 21% of patients c.2194 WT (67 of 320) (OR = 3.75 95%IC 1.98-7.10; p < 0.0001). We confirmed that c.2826A>T (1.37%, 5 of 366 pts) was related to various toxicity (p = 0.0097) and c.1679T>G > 0.55% 2 of 366 pts) showed only gastrointestinal toxicity (p = 0.0027).

Conclusions: Our data suggested that additional DPYD polymorphisms could enhance prevention of fluoropyrimidine toxicity. c.2194G>A is the most frequent polymorphism and it resulted associated with neutropenia.
Deficiency of from reduced catabolism. This pharmacogenetic manifeststions typically as severe or fatal diarrhea, mucositis/stomatitis, myelosuppression and even rare toxicities as hepatic failure, esophageal ulceration, or ischemia following first or second dose of 5-FU. The most compelling reason to introduce routine testing is to avoid severe AEs in pts who receive 5-FU/CAP. 5-FU/CAP mutations are found in 50% of severe 5-FU toxicity cases.

Methods: We analyzed all pts who were tested for deficiency after toxicities from 5-FU/CAP, treated for GI cancers. DPD activity was evaluated by PBMC radioassay, genotyping of DPD, or 2'-13C uracil breath test after an informed consent. Demographics of pts, grades of toxicity, chemotherapy (dose, route) and outcomes were analyzed. Results: A total of 52 pts with DPD deficiency were identified (age range: 35–79 yrs, M:F = 1:3.1; Ethnicities: Caucasian (≥60%), African–American, unknown, Asian). Most commonly used regimens in decreasing order were infusion 5-FU, CAP and bolus. Excessive AEs included mucositis (70%), diarrhea (40%), cytopenias (40%), nausea/vomiting (30%), HFS or skin rashes (20%), neurotoxicity (12%) and cardiotoxicity (5%). 11/12 pts had low DPD activity (0.064 – 0.1 DPD/G) 2h (DPD/BSA c. 100G). DPD > 3.8% (c. 6.7G) 2h (DPD/BSA c. 100G) 1G > A (c.1905+1G > A, r39182920) 38%, D949V (c.2846A > T, rs67376798) 21%, C29R (r1801265) 4%, and Y186C (rs115233898, c.557 A > G) 2%. Univariate DPD confirmed DPD deficiency in 2 pts: DOB 50 of 49.4% and 52.5%. Re-challenge with CAP in 5 pts resulted in atypical or similar AEs. 6 pts received vistogard; 5 recovered. 3 pts died due to AEs.

Conclusions: DPD genotyping (+ TYMS) may identify ≥50% of pts, who are at greatest risk of AEs. At present, no formal recommendations regarding testing for DPD exist except warning on FDA website and prescription inserts.

Our data mandates the need for prospective studies to develop guidelines in pts receiving 5-FU/CAP.

Dihydropyrimidine dehydrogenase gene (DPYD) polymorphism among pts with 5-FU/capcitabine (CAP)-related adverse events (AEs): Experience of 2 decades. First Author: Nauman S Siddiqui, Tufts Medical Center, Boston, MA

Background: DPYD gene encodes DPD, the rate-limiting enzyme responsible for catabolism of 5-FU and is responsible for catabolism of 5-FU and is responsible for catabolism of 5-FU and is responsible for catabolism of 5-FU. DPYD is a target of 5-FU, 5-FC, and 5-FU/CAP, and is responsible for catabolism of 5-FU and is responsible for catabolism of 5-FU and is responsible for catabolism of 5-FU and is responsible for catabolism of 5-FU. DPYD activity was measured by PBMC radioassay, genotyping of DPYD, or 2'-13C uracil breath test after an informed consent. Demographics of pts, grades of toxicity, chemotherapy (dose, route) and outcomes were analyzed. Results: A total of 52 pts with DPYD deficiency were identified (age range: 35–79 yrs, M:F = 1:3.1; Ethnicities: Caucasian (≥60%), African–American, unknown, Asian). Most commonly used regimens in decreasing order were infusions of 5-FU, CAP and bolus. Excessive AEs included mucositis (70%), diarrhea (40%), cytopenias (40%), nausea/vomiting (30%), HFS or skin rashes (20%), neurotoxicity (12%) and cardiotoxicity (5%). 11/12 pts had low DPYD activity (0.064 – 0.1 DPYD/G) 2h (DPYD/BSA c. 100G). DPYD > 3.8% (c. 6.7G) 2h (DPYD/BSA c. 100G) 1G > A (c.1905+1G > A, r39182920) 38%, D949V (c.2846A > T, rs67376798) 21%, C29R (r1801265) 4%, and Y186C (rs115233898, c.557 A > G) 2%. Univariate DPD confirmed DPYD deficiency in 2 pts: DOB 50 of 49.4% and 52.5%. Re-challenge with CAP in 5 pts resulted in atypical or similar AEs. 6 pts received vistogard; 5 recovered. 3 pts died due to AEs.

Conclusions: DPYD genotyping (+ TYMS) may identify ≥50% of pts, who are at greatest risk of AEs. At present, no formal recommendations regarding testing for DPYD exist except warning on FDA website and prescription inserts. Our data mandates the need for prospective studies to develop guidelines in pts receiving 5-FU/CAP.
Vorolanib (CM082) in Chinese patients with advanced solid tumor: A phase 1, open-label, dose escalation study. First Author: Yan Song, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Vorolanib (CM082) is a potent and selective inhibitor of VEGFR and PDGFR, which is well tolerated from 20 to 400 mg without G3/4 treatment-related AEs (TRAEs) in patients in US. Here we present a phase I dose escalation study that assessed vorolanib in Chinese patients with advanced solid tumor. Methods: Patients with advanced solid tumors were enrolled to receive escalating dose of vorolanib once daily from 50 mg to 300 mg following the 3+3 design. Primary endpoints included evaluation of safety, pharmacokinetics, and maximum-tolerated dose (MTD) determination. Results: 19 patients were enrolled and treated, including 12 RCC. Most patients (n=18) have received at least one prior systemic treatments, in which 10 have been treated with VEGFR TKIs. No DLT was not achieved. The most common TRAEs were leukenkopnia (9/19), fatigue (9/19), diarrhea (8/19), neutropenia (8/19), and hypertension (8/19). G3 or higher events were seen in 7 patients across 100 to 250 mg dose cohort. PK analysis was shown in table 1. Partial response was seen in 1 RCC patients in higher doses, IVO was readily absorbed (median T_max 3 h). After peaking, IVO concentrations declined in a bi-exponential manner, with a mean terminal half-life of 72-138 h after a single dose. Dose-exposure nonlinearity of IVO from 50 mg to 1200 mg QD is suggested doubling of the dose would result in a ~30% increase in AUC. Steady state (SS) was reached within 14 days. Moderate accumulation was observed after 500 mg QD, with mean AUC and C_max accumulation ratios of 1.9- and 1.46-fold. IVO clearance was not altered by intrinsic patient factors. Concomitant administration of weak CYP3A4 inhibitors/inducers did not affect IVO clearance, though moderate/strong CYP3A4 inhibitors decreased IVO clearance and increased IVO SS exposure (AUC_0-24hr by ~56%; C_max by ~47%). Plasma 2-HG reduction reached a plateau within 14 days of dosing after multiple doses of 500 mg QD, and was reduced by ~90% over the range of IVO SS AUC in patients with newly diagnosed and previously treated myelofibrosis. IVO was well tolerated in patients harboring non-V600 BRAF mutation type. Conclusions: IVO demonstrated a long half-life suitable for QD dosing, moderate accumulation, and robust 2-HG inhibition in patients with mIDH1 myeloid malignancies. Intrinsic/extrinsic patient factors, including concomitant moderate/strong CYP3A4 inhibitors, did not significantly alter after IVO exposure. Clinical trial information: NCT02074839.

2585 Poster Session (Board #407), Mon, 8:00 AM-11:30 AM
Clinical pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with IDH1-mutant advanced hematologic malignancies from a phase 1 study. First Author: David Dai, Agios Pharmaceuticals, Inc., Cambridge, MA

Background: Mutant isocitrate dehydrogenase 1 (mIDH1) produces the oncometabolite D-2-hydroxylutarate (2-HG).ivosidenib (IVO) is a selective mIDH1 inhibitor under evaluation in patients with mIDH1 hematologic malignancies. This translational analysis explored the PK profile of IVO, the relationship between IVO exposure and 2-HG suppression, and the impact of intrinsic/extrinsic patient factors on IVO exposure from the phase 1 monotherapy study (NCT02074839). Methods: IVO was administered orally once (QD) or twice (BID) daily in continuous 28-day cycles. As of May 12, 2017, 258 patients had received IVO at doses ranging from 100 mg to 1200 mg QD in dose escalation (n = 78) and at 500 mg QD (n = 180) in dose expansion. IVO levels were assessed in plasma and 2-HG levels in plasma/bone marrow using LC-MS/MS methods. Results: After single and multiple doses, IVO was readily absorbed (median T_max 3 h). After peaking, IVO concentrations declined in a bi-exponential manner, with a mean terminal half-life of 72-138 h after a single dose. Dose-exposure nonlinearity of IVO from 50 mg to 1200 mg QD suggests doubling of the dose would result in a ~30% increase in AUC. Steady state (SS) was reached within 14 days. Moderate accumulation was observed after 500 mg QD, with mean AUC and C_max accumulation ratios of 1.9- and 1.46-fold. IVO clearance was not altered by intrinsic patient factors. Concomitant administration of weak CYP3A4 inhibitors/inducers did not affect IVO clearance, though moderate/strong CYP3A4 inhibitors decreased IVO clearance and increased IVO SS exposure (AUC_0-24hr by ~56%; C_max by ~47%). Plasma 2-HG reduction reached a plateau within 14 days of dosing after multiple doses of 500 mg QD, and was reduced by ~90% over the range of IVO SS AUC in patients with newly diagnosed and previously treated myelofibrosis. IVO was well tolerated in patients harboring non-V600 BRAF mutation type. Conclusions: IVO demonstrated a long half-life suitable for QD dosing, moderate accumulation, and robust 2-HG inhibition in patients with mIDH1 myeloid malignancies. Intrinsic/extrinsic patient factors, including concomitant moderate/strong CYP3A4 inhibitors, did not significantly alter after IVO exposure. Clinical trial information: NCT02074839.

2583 Poster Session (Board #409), Mon, 8:00 AM-11:30 AM
Phase 1/2 precision medicine study of the next-generation BRAF inhibitor PLX8394. First Author: A. Janku, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: First-generation BRAF inhibitors (BRAFi) show high response rates and prolonged survival in some BRAF(V600) mutant cancers; however, paradoxical activation of the RAF/MEK/ERK pathway promotes resistance and development of skin malignancies. PLX8394 is a next-generation, orally available small-molecule BRAFi that does not induce the RAF/MEK/ERK paradoxical activation from the downstream monomeric BRAF(V600) and dimeric BRAF(V600) protein. Methods: This is a phase 1/2 study of PLX8394 and cobasitab (cstat,150mg), a CYP3A4 inhibitor used to enhance PLX8394 exposure, to determine the safety, tolerability in subjects with refractory solid tumors (phase 1) and RECIST response rate in BRAF and dimer-dependent, RAS-independent BRAF(V600) mutant patients (phase 2). A hot-melt extrusion (HME) formulation of PLX8394 was used for this study. Results are reported as of January 8, 2018. Results: Phase 1: The RP2D was 900mg BID + cstat (Pro AACR-NCT161EORTC 2017, abst B176). A single DLT of reversible grade (G) 3 transaminists occurred in a subject treated with PLX8394 900mg BID + cstat. Cstat co-administration resulted in a 2-3-fold increase in PLX8394 systemic exposure. Of 13 evaluable BRAF(V600) mutated subjects, 3 (23%) achieved partial responses [colorectal cancer (42%), glioma (65%); both BRAFi naive, and ovarian cancer (62% previously treated with 3 lines of BRAFi/MEKi)]. Phase 2: Of 18 patients enrolled, 13 harbored BRAF(V600) mutation (melanoma (n = 5), colorectal (n = 4), glioblastoma (n = 2), thyroid (n = 2)) and 5 BRAF(V600) mutation [pancreatic (n = 2), and prostate, thyroid, and colorectal (each n = 1)]. No prior MAPK pathway inhibitors were permitted for non-melanoma subjects. G3 AEs included G3 transaminists and hyperbilirubinemia in one patient. Of 10 evaluable patients, 3 (30%, all with BRAF(V600) mutations) had stable disease (+7%, -10%, -14%, respectively). Efficacy and exploratory bio-marker analysis including transcription and cDNA analysis is on-going. Conclusions: PLX8394 + cstat has been well tolerated and shows promising activity in refractory solid tumors with BRAF mutations. This work was sponsored by Plexikon Inc. Clinical trial information: NCT02428712.
2584  Poster Session (Board #410), Mon, 8:00 AM-11:30 AM

Precision oncology: Results of a phase I study of M2698, a p70S6K/4E-BP1 inhibitor targeted agent in patients with advanced cancer and tumor PI3K/AKT/mTOR (PAM) pathway aberrations. First Author: Antonia Makris, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: M2698 is a potent and selective dual inhibitor of p70S6K and 4E-BP1 in the PAM pathway. M2698 has the advantages of being an oral, brain penetrant, PAM pathway inhibitor, which can mitigate the effects of the AKT feedback loop, a potential escape mechanism in tumors resistant to standard therapies. Methods: Patients (pts) with advanced cancer received once-daily oral M2698 300 mg: 9 dose levels in cycle 1, then a 21-day cycle 2 to dose escalation (DE) design was followed by an expansion phase (240 mg/day) in a pt population enriched with tumors that have PAM molecular alterations (+). PAM+ profiles, potential resistance markers (RM), including EGFR, KRAS and AKT2, safety and efficacy were investigated (cut-off Nov 2017). Results: From Dec 2012 to 3/2017, 66 pts were screened, 50 received M2698/DE (n = 40) and expansion n = 10); 18 men, 32 women, 78% were < 65 years old. Of these 50 pts, 44 were PAM+ (37 without RM, 7 with RM). M2698 was well tolerated. Adverse events were transient. The maximum tolerated dose was not reached at the maximum dose tested. Efficacy outcomes are shown in the table. In addition to these DE pts, PAM+ pts without RM subgroup had tumor control > 6 months (mo; range: 6.9–15.2 mo), whereas no pts in the PAM+ with RM subgroup had such prolonged tumor control. Clinical trial information: NCT01971515. PFS, progression free survival; SD, stable disease.

Conclusions: M2698 was well tolerated. PAM+ pts without RM were more likely to have sustained tumor control. Molecular characterization of tumor resistance signals may help identify patients who are likely to benefit from M2698.

2585  Poster Session (Board #411), Mon, 8:00 AM-11:30 AM

A phase 1 study of NOX66 in combination with carboplatin in patients with end stage solid tumours. First Author: Paul L. de Souza, University of Western Sydney School of Medicine, Liverpool, Australia

Background: NOX66 is under development as an enhancer of chemotherapy and radiotherapy across multiple tumour types. The primary mechanism of action of idronoxil (the active ingredient of NOX66) stems from its selective binding to ENOX2 - a tumour-specific NADH oxidase - inhibiting Sphin- gosine kinase activity within tumour cells and leading to inhibition of the PI3K/Akt pathway and induction of apoptosis. Here we report the results of the first-in-human study of NOX66 as monotherapy and in combination with carboplatin (carbo). Methods: 19 patients with metastatic end stage solid tumours were recruited to one of two dose cohorts, NOX66 400mg, and 800mg respectively. Following a monotherapy run in period (NOX66 administered PR, Day 1-14 followed by a 7 day break) patients received 6 cycles of combination therapy - NOX66 administered on Day 1-7 and intravenous carbo on Day 2 of a 28-day schedule. Carbo was administered at AUC4 for 3 cycles, followed by AUC4 for 3 cycles. Recruitment is complete, with last patient last visit scheduled for May 2018. Results: 16 patients have completed study treatment. Radiologic assessment of disease state is shown in the table below (Progressive Disease – PD; Stable Disease – SD; Partial Response – PR). 4 SAEs (including 3 deaths) were reported, none were considered related to NOX66. One Adverse Event (Grade 2 anaemia, NOX66 800mg + carbo AUC4) considered possibly related to NOX66 has been reported. Conclusions: NOX66 is well tolerated as a monotherapy and in combination with carboplatin. N = 4 or AUC = 6. Efficacy signals from this study warrant further investigation of NOX66 as a chemo-sensitizing agent. Clinical trial information: NCT02941523.

2586  Poster Session (Board #412), Mon, 8:00 AM-11:30 AM

A phase I study of LXH254 in patients (pts) with advanced solid tumors harboring MAPK pathway alterations. First Author: Nita Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CRAF is a key mediator of oncogenic mitogen-activated protein kinase (MAPK) pathway reactivation following MEK or BRAF inhibition. LXH254 is a BRAF and CRAF inhibitor with antitumor activity in MAPK-driven tumor models. This Phase I dose-finding study of LXH254 in pts with advanced solid tumors harboring MAPK pathway alterations is evaluating safety/tolerability and preliminary antitumor activity. NCT02607813. Methods: Primary objective: characterize the safety/tolerability of single-agent LXH254 and identify a recommended dose (RD)/schedule for future study. Secondary objectives: characterize antitumor activity (per RECIST 1.1) and PK. Dose escalation was guided by a Bayesian model-based approach. Eligible pts had advanced, pretreated solid tumors with MAPK pathway alterations. Results: At data cut-off 4 Dec 2017, 75 pts were enrolled in 9 dose cohorts: 100 (n = 4), 200 (n = 4), 300 (n = 5), 400 (n = 6), 800 (n = 12), 1200 mg QD (n = 12), and 200 (n = 7), 400 (n = 12), 600 mg BID (n = 13). Pts (ECOG PS 0/1, 41% male, median age 57 yrs) had lung (n = 16), colorectal (n = 14), ovarian (n = 12), melanoma (n = 12), or other (n = 21) cancers. Median duration of exposure was 7.7 vs; 59/79 (75%) pts discontinued treatment, due to disease progression (49 pts (65%), physician/pd decision (5 pts (7%)), death (3 pts (4%)), or AE (2 pts (3%)). Three DLTs were reported: platelet count decrease (Gr 4, 1 pt 1200 mg QD), pruritus and maculopapular rash (both Gr 3, 1 pt 600 mg BID). The most common (> 15%) drug-related, any-Gr AE's were rash (dermatitis acroemiform/rash/maculopapular rash, 53%), fatigue (20%), and nausea (20%). Gr 3 drug-related AEs occurred in 16% of pts, most frequently rash, myalgia, and increased lipase (2% (3%) pts each). Plasma peak drug concentration (Cmax) and exposure (AUC) after QD/BID oral doses increased approximately dose proportionally. There were two confirmed partial responses (with > 50% tumor size reduction) in pts with KRAS-mut and BRAF-mut cancers; stable disease was reported in 25/73 (33%) pts.

Conclusions: Oral LXH254 was well tolerated, all AEs were manageable, and preliminary antitumor activity was observed. The study is ongoing to establish a RD/schedule, and further establish antitumor activity. Clinical trial information: NCT02607813.

2587  Poster Session (Board #413), Mon, 8:00 AM-11:30 AM

Safety, tolerability, and antitumor activity of once-daily Wee-1 inhibitor AZD1775. First Author: Naoko Takebe, NCI/ NIH, Elkridge, MD

Background: Wee1 tyrosine kinase promotes G2 cell cycle arrest following DNA damage via inactivating phosphorylation of cyclin-dependent kinase 1. We are conducting a phase I study of the oral Wee1 inhibitor AZD1775 in patients (pts) with advanced solid tumors, examining twice daily (Arm A) and once daily (Arm B) schedules. Results for Arm A have been reported previously, and partial responses (PR) were observed in 2 pts with BRCA mutations only. Here, we present results for Arm B. Methods: AZD1775 was given orally once daily (GD) for 5 days during weeks 1 and 2 of a 21-day cycle (Arm B) or twice daily (BID) for 5 doses during weeks 1 and 2 (Arm A). Primary objectives were to determine safety, tolerability, and pharmacokinetics (PK). Secondary objectives were to assess pharmacodynamic (PD) biomarkers of DNA damage in tumor tissue and circulating tumor cells and evaluation of antitumor activity. Dose-limiting toxicity was evaluated during cycle 1, and response was defined by CT using RECIST 1.1. Results: Thirty-four pts have enrolled on Arm B; of the 28 assessable for response, 4 (14%) had a PR (3 ovarian, 1 endometrial) and 18 (64%) experienced stable disease (mean: 7.22 cycles). Of the 9 Arm B pts with confirmed BRCA mutations, 2 had a PR (22%; ovarian) and 6 had SD (67%; mean: 7.17 cycles). The maximum tolerated dose (MTD) for Arm B was 300 mg; dose-limiting toxicities were grade (g) 4 myelosuppression and g 3 fatigue. The type, rate, and severity of commonly observed g 3/4 toxicities were similar between Arms A and B, including (Arm A (%); Arm B (%)): anemia (28%; 24%), lymphopenia (20%; 35%), neutropenia (16%; 15%), and thrombocytopenia (12%; 12%), and fatigue (0%; 12%). Preliminary PD data indicate improved AZD1775 exposure (AUC and Cmax) for Arm B vs Arm A MTD cohorts. Conclusions: Once-daily AZD1775 is well tolerated, with toxicities comparable to twice-daily AZD1775. Plasma drug exposure was higher for the QD vs. BID MTD cohort. AZD1775 antitumor activity was observed in pts with and without known BRCA mutations. Accrual to Arm B is ongoing, as is PD analysis. Future whole-exome sequencing analyses may uncover additional predictive biomarkers. Clinical trial information: NCT01748825. Supported in part by NCI Contract HHSN261200800001E. Clinical trial information: 01748825.
2588 Poster Session (Board #414), Mon, 8:00 AM-11:30 AM
Dose finding study of varlitinib ± trastuzumab with carboplatin/paclitaxel in advanced solid tumors. First Author: Matilda Lee, National University Health System, Singapore, Singapore

Background: Varlitinib (V) is a reversible inhibitor of HER1/HER2/HER4. This is a phase 1b dose confirmation study to determine safety and early efficacy signals of V ± T combined with weekly P 80mg/m² and C AUC = 2 (NCT02396108).

Methods: Eligible patients had metastatic solid tumors. A 3+3 dose de-escalation study design was used and pharmacokinetic (PK) analyses of V and P were done.

Results: 37 patients (median age 56.8 years (18.1 – 73.8)) were enrolled in 9 cohorts with median 3 (0-14) prior lines of palliative therapies. PC + V 500mg BD cont (n = 10) was deescalated to 300mg BD intermittently (n = 4) due to DLTs, most commonly febrile neutropenia (FN) and electrolyte disturbances, and was deemed intolerable. Recommended dose (RD) was V 300mg BD int with P alone; addition of T to RD of P+V was safe with no DLTs (Table). 20/37 had HER2+ metastatic breast cancer (MBC) with median 4 (0-14) prior treatment lines. 7 achieved partial response (PR) and 3 stable disease (SD); 6 had disease control with single agent V for a median 7.0 more months (4.3 – 13.3) after chemotherapy ceased. 2/17 with other tumor types achieved PR (HER2- MBC = 1, NSCLC = 1). 3/10 patients (HER2+ MBC = 2) in the V 300mg BD int cohorts achieved PR. No correlation was seen between V and P mean AUC (ng.h/mL) in those with and without DLTs (Wilcoxon Rank vs 207/88, p = 0.21; P 488.2 vs 5197.6, p = 0.77). No interaction was seen between V dose/schedule with P PK.

Conclusions: The RD of V combined with P is 300mg BD int, and is active in HER2+ MBC. T can be added safely. The triple combination will be evaluated as neoadjuvant therapy in breast cancer. Clinical trial information: NCT02996108.

2590 Poster Session (Board #416), Mon, 8:00 AM-11:30 AM
Outcomes of patients with gene fusion driven cancers treated on early phase clinical trials. First Author: Russel Greensberg, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Gene fusions result in a constitutively activated tyrosine kinase that causes uncontrolled cell proliferation. Some fusions are actionable with multi-kinase inhibitors that are FDA approved or in development. We reviewed patients with gene fusions treated with a targeted agent in a large Phase 1 program. Methods: We reviewed charts of patients treated on trials with targeted therapy agents in our phase 1 clinic between 2009 and 2017. Targeted was defined as affecting either the fusion gene itself or a downstream pathway. Demographic information including diagnosis, age, sex, date of first dose on trial, date of progression, best response by RECIST, and date of death. Information on fusions was obtained from next generation sequencing or FISH performed as part of oncologic management. Results: A total 85 patients (M:F, 46:39) with gene fusions were identified and 59 (68.6%) were treated with a targeted agent. Tumors included sarcomas (N = 49, 57.6%), NSCLC (N = 17, 20%), cholangiocarcinoma (N = 7, 8.2%), salivary gland (N = 4, 4.7%), thyroid (N = 3, 3.5%), GBM (N = 2, 2.3%), HG neuroendocrine tumors (N = 2, 2.3%), colon and lymphoma (N = 1, 1.1%). Most common fusions were RET (KIF5B = 15, CCD62 = 2, Other = 1) and EWS-FLI1 (N = 12, 20%). Other fusion partners in our dataset included FGFR2/3 (N = 9, 15.3%), NTRK1/3 (N = 7, 11.9%), ALK (N = 3, 5.1%), ROS1 (N = 2, 3.4%), and BRAF (N = 1, 1.7%). Most therapies targeted the fusion itself except in sarcomas where downstream pathways (c-MET, IGFR1, nuclear redistribution) were targeted. Best response was CR in three patients (5%), PR in 12 patients (20%), and SD in 21 patients (35.6%) for a clinical benefit rate of 61%. Median PFS was 7.1 months, 95% CI [4.8,15.4] and OS was 19.6 months, 95% CI [10.8, 28.3] respectivley. Survival was similar with median overall survival (OS) of 14m. The PFS rate at 6, 12, and 18m was 22%, 11%, and 11% and the OS rate at 6, 12, and 18m was 83%, 70% and 28% respectively. Durable clinical response was observed in pre-Bev treated pts (1CR, 4 SD). The median OS for colon (n = 6) was not reached with 57% alive at 18m; median OS for lung (n = 9) was 13m with 13% alive at 18m. Better DCR was correlated with lower baseline PGF levels as well as increased level from baseline. Longer PFS was associated with higher than the median baseline values for VEGFR2, E-selectin and lower SDF-1x. Conclusions: Nin was well tolerated with Bev with no DLTs. Significant clinical activity was observed with Bev pretreated patients suggesting Nin can overcome Bev resistance. Clinical trial information: NCT02196930.

2591 Poster Session (Board #417), Mon, 8:00 AM-11:30 AM
Phase 1b trial of nintedanib in combination with bevacizumab in patients with advanced solid tumors. First Author: Ravi Kumar Paluri, University of Alabama at Birmingham, Birmingham, AL

Background: Vascular endothelial growth factor (VEGF) inhibitors have produced demonstrable but limited clinical benefit for various cancers. One mechanism of resistance includes revascularization secondary to up-regulation of alternative pro-angiogenic signals such as platelet derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFGR) pathways. Nintedanib (Nin) is an oral triple kinase inhibitor that blocks the VEGFR, PDGFR and FGFGR pathways and may improve antitumor activity by overcoming resistance to anti-VEGF therapies. This study evaluated the safety & tolerability (primary objective) of Nin in combination with bevacizumab (Bev). Methods: Patients (pts) were treated with escalating doses of Nin (150mg or 200mg oral twice daily) and Bev (15 mg/kg once intravenously every 3 weeks) until disease progression or unacceptable toxicity using standard 3 + 3 phase1 design. The plasma levels of anigogenic biomarkers were correlated with clinical outcomes. Results: Eighteen pts with advanced tumors (lung (9), colon (8) and cervical (1)) pretreated with at least two lines of chemo were enrolled. Fifty percent (9 patients) were pretreated with bev. The final dose of Nin was 200mg twice a day with no observed dose limiting toxicities (DLT). The common adverse events were fatigue (grade 1-3); nausea & diarrhea (grade 1-2). Two pts came off study due to grade 3 fatigue. The disease control rate (DCR) was 72% (1 CR, 1 PR & 11 SD). The median progression free survival (PFS) was 4 months (m), and median overall survival (OS) was 14m. The PFS rate at 6, 12, and 18m was 22%, 11%, and 11% and the OS rate at 6, 12, and 18m was 83%, 70% and 28% respectively. Durable clinical response was observed in pre-Bev treated pts (1CR, 4 SD). The median OS for colon (n = 6) was not reached with 57% alive at 18m; median OS for lung (n = 9) was 13m with 13% alive at 18m. Better DCR was correlated with lower baseline PGF levels as well as increased level from baseline. Longer PFS was associated with higher than the median baseline values for VEGFR2, E-selectin and lower SDF-1x.

Conclusions: Nin was well tolerated with Bev with no DLTs. Significant clinical activity was observed in Bev pretreated patients suggesting Nin can overcome Bev resistance. Clinical trial information: NCT02835853.
A phase I, open-label, multicenter dose escalation study to assess the safety, tolerability, and pharmacokinetics of AZD2811 nanoparticle in patients with advanced solid tumors. First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN

Background: Aurora kinases represent potential targets for anticancer therapy in solid tumors and hematological malignancies. The aurora B kinase inhibitor AZD1152 (barasertib) has shown benefit in patients (pts) with untreated AML versus low-dose AraC when given as a 7-day continuous infusion. AZD2811 nanoparticle is a novel, encapsulated slow release inhibitor of aurora kinases which offers superior pharmacodynamic profile compared to AZD1152 (Ashton S et al., Sci Transl Med 2016). AZD2811 nanoparticle mimics the AZD1152 7-day continuous infusion as a 2-hr infusion on Day 1 and 4, and resulted in increased efficacy preclinically. We report the first-in-man dose-escalation of AZD2811 in pts with advanced solid tumors (NCT02579226). The objectives were to determine the MTD, safety profile, dosing schedule and preliminary efficacy of AZD2811. Methods: Adult pts with advanced solid tumors were given AZD2811 nanoparticle IV on Day 1 and 4 every 28 days. Pts were enrolled according to a standard 3+3 design. Pharmacokinetics (PK) were assessed in cycle 1. Results: 24 pts were treated in 6 cohorts: 10mg (3 pts), 15mg (3 pts), 25mg (3 pts), 51 mg (3 pts), 100 mg (3 pts) and 200 mg (9 pts). Of these 24 pts, 20 pts discontinued due to disease progression, (1 pt) due to death, (1 pt) withdrew consent (1 pt), physician’s decision. Preliminary efficacy indicated one confirmed ongoing partial remission in cohort 6 at 16 months. In Cohorts 1-5, common treatment-related AEs (any grade) were diarrhea, nausea, and fatigue; in Cohort 6 (200 mg per infusion) common treatment-related AEs (any grade) were fatigue, decreased appetite, and neutropenia (5 pts, all grade 4 including 1 DLT of > 7 days without G-CSF), an expected pharmacodynamics marker of target engagement. There were no infections, fever of unknown origin or treatment-related deaths. AZD2811 total blood PK appears dose proportional with a t1/2 of 30-50 hours. Conclusions: AZD2811 nanoparticle is safe and well tolerated at a dose of 200 mg Day 1 and 4 every 28-28 days. A single day 1 infusion once every 21 days with G-CSF is also being investigated. Further safety and updated efficacy data will be reported at the annual meeting. Clinical trial information: NCT02579226.

A phase 1 study of novel dual Bcl-2/Bcl-xl inhibitor APG-1252 in patients with advanced solid tumors. First Author: Nehal J. Lakhan, START Midwest, Grand Rapids, MI

Background: We have developed a unique strategy to tactically reduce on-target platelet toxicity with APG-1252, a novel dual Bcl-2/Bcl-xL inhibitor, while maintaining strong in vivo antitumor activity. APG-1252 potently inhibits tumor growth in human cancer xenograft models including SCLC models while triggered significantly less platelet killing APG-1252 demonstrated a higher therapeutic index than ABT-263 in preclinical studies. Methods: This Phase I study (NCT03083011) enrolled patients with advanced SCLC or other solid tumors. In dose escalation, the patients received APG-1252 (10–400 mg) intravenously twice weekly for 3 weeks in a 28-day-cycle, until disease progression. Study objectives include safety (primary endpoint), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity assessed every 8 weeks per RECIST v1.1. Results: As of Jan 31, 2018, 13 patients (including 6 pts with SCLC) have been treated in 5 cohorts of APG-1252. Current dose level being explored is 160 mg. The median number of prior systemic anti-cancer therapies was 2 (range 1-6). The pts received a median of 2 cycles of APG-1252 (range 1-6). MTD has not been identified yet. TRAEs were reported in 10 pts (77%). The most common AE’s (reported in ≥10% of pts) included: arthralgia, AST/ALT increased, vomiting, and fatigue. All TRAEs were grade ≤ 2 in severity. There were no AEs leading to treatment discontinuation. No thrombocytopenia or other cytopenias have been observed six pts had ≥1 on-treatment tumor assessment. One confirmed partial response was observed in 1 patient with metastatic SCLC at the 40 mg dose, and the duration of response lasted for more than 6 cycles. PK analyses indicate that AUC and Cmax increase dose proportionally over 10-40 mg range on day 1, while AUC increases more than dose proportionally on Day 22. AUC at 40mg on Day 22 is close to in vivo efficacious exposure. Conclusions: APG-1252 was well-tolerated across all dose levels tested. No hematologic toxicity has been reported so far. Dose escalation and further evaluation of APG-1252 in patients with SCLC and other advanced solid tumors is ongoing. Clinical trial information: G3080311.

Safety and pharmacodynamics of the DRD2 antagonist ONC201 in advanced solid tumor patients with weekly oral administration. First Author: Mark N. Stein, Columbia University Medical Center, New York, NY

Background: ONC201 is a small molecule antagonist of DRD2, a G protein-coupled receptor overexpressed in several malignancies, that has prolonged antitumor efficacy in preclinical cancer models via induction of the CHOP/DR5-mediated integrated stress response pathway and caspase-dependent apoptosis. In addition to cytotoxic effects in tumor cells, DRD2 antagonism can induce the activation of NK and other immune cells. The first-in-human trial of ONC201 previously established a recommended Phase II dose (RP2D) of 625 mg once every three weeks. Here, we report the results of a Phase I study that evaluated the safety, pharmacokinetics (PK), and pharmacodynamics with weekly oral administration of ONC201. Methods: Patients ≥ 18 years of age with an advanced solid tumor refractory to standard treatment were enrolled. Dose escalation proceeded with a 3 + 3 design from 375 mg to 625 mg of ONC201. One cycle, also the dose-limiting toxicity (DLT) window, was 21 days. The primary endpoint was to determine the RP2D of ONC201 with weekly oral administration, which was subsequently confirmed in an 11-patient dose expansion cohort. Results: A total of 20 patients were enrolled: 3 at 375 mg and 17 at 625 mg of ONC201. The RP2D was defined as 625 mg with no DLT, treatment discontinuation, or dose modifications due to drug-related toxicity. Pharmacokinetic profiles were consistent with every three week dosing and similar between the first and fourth dose. Serum prolactin and caspase-cleaved cytokeratin-18 were detected, along with intratumoral induction of integrated stress response (CHOP/DR5), apoptosis (TUNEL) and infiltration of granzyme B + Natural Killer cells. Induction of cytotoxic cytokines and effector molecules was higher in patients who received ONC201 once every three weeks versus once every three weeks. Stable disease of ≥ 6 months was observed in several prostate and endometrial carcino patients. Conclusions: Weekly, oral ONC201 is well-tolerated and resulted in prolonged stable disease, intratumoral apoptotic signaling and enhanced immunostimulatory activity that warrants further investigation. Clinical trial information: NCT02250781; NCT02324621.
TPS2596: Poster Session (Board #422a), Mon, 8:00 AM-11:30 AM

The GATTO study: A phase I of the anti-MUC1 Gpatituzumab (GAT) in combination with the anti-EGFR Tomuzitumab (TO) in patients with EGFR positive solid tumors. First Author: Sebastian Ochsenreither, Charité Comprehensive Cancer Center, Berlin, Germany

Background: TO (CetuGEX) is a second-generation anti-EGFR antibody that specifically binds to EGFR and acts as a competitive antagonist at the ligand binding site. GAT (PankoMab-GEX) is a novel humanized monoclonal antibody, which recognizes the tumor-specific epitope of mucin-1 (TA-MUC1) expressed on tumor cells. Both antibodies are glyco-engineered to potentiate antibody-dependent cellular cytotoxicity (ADCC). Compelling preclinical evidence suggests a complex interaction between EGFR and cell surface expressed TA-MUC1 in driving cancerogenesis processes as well as shows a synergistic ADCC activity with the dual targeting of these molecules. Based on this evidence, this study aims to assess the tolerability, safety and preliminary activity of a combination with anti-EGFR and anti-TA-MUC1 glyco-engineered antibodies. Methods: The GATTO is an open label phase Ib dose evaluation study in patients with EGFR positive metastatic solid tumors, for whom no standard treatment is available. The proposed doses and schedule are 1400 mg Q2W for GAT and 1200 mg Q2W for TO. A staggered approach will be utilized in order to minimize the number of patients exposed and to evaluate the safety of the combination treatment. The first 6 patients will be enrolled into a safety run-in phase where the number of dose-limiting toxicities (DLTs) will be evaluated. Assuming that the safety criteria are met (ie. observation of 0 or 1 DLT), the dose will remain unchanged and further patients will be recruited to this dose level. If this is not the case, a stepwise dose reduction approach will be applied. The antitumor activity of the combined treatment will be evaluated as secondary endpoints including best overall response rate (ORR), duration of objective response, progression-free (PFS) and overall (OS) survival. Extensive pharmacokinetics (PK) and pharmacodynamic evaluations (serum and tissue biomarkers) will be also analyzed. As of January 2018, the study is ongoing and 2 patients have been treated. Clinical trial information: NCT03360734.

TPS2597: Poster Session (Board #422b), Mon, 8:00 AM-11:30 AM

AMC 095 (AIDS Malignancy Consortium): A phase I study of ipilimumab (IPI) and nivolumab (NIVO) in advanced HIV associated solid tumors (ST) with expansion cohorts in HIV associated solid tumors and classical Hodgkin lymphoma (cHL). First Author: Lakshmi Rajdev, Montefiore Medical Center, Bronx, NY

Background: Immune checkpoint blockade (ICB) using agents that target the priming phase (i.e. CTLA-4) and effector phase (e.g. PD-1) of host immunity, used individually or in combination, has emerged as a therapeutic strategy for cancers. Little is known about the safety, tolerability and efficacy of ICB in patients (pts) with HIV infection and cancer. Methods: AMC 095 (NCT02408861) is a multicenter, international phase I study of the PD-1 inhibitor, nivo alone or in combination with a CTLA-4 inhibitor, ipi, in 2 cohorts stratified by CD4 counts (Stratum 1: CD4 counts<200/uL and Stratum 2: CD4 count 200-200/uL) with additional expansion cohorts at the recommended phase II dose in pts with ST and cHL. The primary study objective is to determine the safety and feasibility of nivo alone and the nivo +ipi combination. Secondary objectives are to evaluate the effects of single agent nivo, and ipi+nivo, on HIV replication and immune function (HIV viral load in plasma using conventional assay, CD4+, and CD8+ cells), and to obtain preliminary information regarding response. Clinical trial information: NCT02408861. The trial was initiated in 8/15, as of 2/21/18, the study is ongoing, and 29 pts have been enrolled. Updated information on the safety and responses will be presented. Funded by the NCI Grant #UM1CA121947.

TPS2598: Poster Session (Board #423a), Mon, 8:00 AM-11:30 AM

MASTERCART key project: A basket/umbrella trial for rare cancers in Japan. First Author: Hitomi Sumiyoshi Okuma, National Cancer Center Hospital, Tokyo, Japan

Background: Establishment of standard therapies for patients with rare cancers have been poor compared to those of major cancers, due to lack of basis for clinical studies and investigations. The MASTER KEY Project is a biomarker driven basket/umbrella trial using a “master protocol”, aiming to find more efficient ways to evaluate treatments for rare cancers and to build a treatment development infrastructure by collaborating with industries. Similar studies including NCI–MATCH trial are ongoing; however, MASTER KEY Project is the first to be reported for such large scale trials that proceeds concurrently with a quality assured registry study focused only on rare cancers. Methods: The project is a two-stage structured study: the prospective registry study part and the multiple clinical trials (sub-study) part. Patients with advanced rare cancers/cancers of unknown primary/rare pathological subtypes of major cancers, who have priorly been evaluated by a molecular diagnostic testing, such as a validated next generation sequencing assay, are enrolled into the registry study. Rare cancer is defined as “annual incidence less than 6 cases per 100,000 population”. The primary objective of the registry study part is to collect consecutive data on biomarker, clinico-pathological background, and prognosis of rare cancers to build a large-scale database that is highly reliable as historical control data for future use in clinical trials of rare cancers. In the sub-studies, drugs are provided by various industries, who are collaborators, and could be approved or investigational agents. Sub-studies are placed under a “master protocol”, allowing new sub-studies to be added at any time. Each sub-study is ordinarily a single arm study and will enroll 5–20 patients with the appropriate biomarker of interest, regardless of histopathologic tumor type. Typically, the primary endpoint is response rate (set according to each sub-study), and Bayesian method will be used. A biomarker-negative sub-study will also be available so that all patients have a chance to be enrolled in a sub-study. The project opened in May 2017. As of Jan 2018, 154 of a planned 100 patients/year have been enrolled. There is one ongoing sub-study and three sub-studies will open in April 2018. Clinical trial information: UMIN000027552.

TPS2599: Poster Session (Board #423b), Mon, 8:00 AM-11:30 AM

A phase 1 dose escalation (DE) and cohort expansion (CE) study of ERY974, an anti-glypican 3 (GPC3) bispecific antibody, in patients with advanced solid tumors. First Author: Yoshitaka Ogita, Chugai Pharma USA, Berkeley Heights, NJ

Background: ERY974 is a bispecific T cell–redirecting antibody immunotherapy that redirects T cells to tumor cells by engaging CD3 on T cells and the glypican 3 (GPC3) antigen (which is selectively expressed on tumor cells). ERY974 T cell–dependent cellular cytotoxicity has been demonstrated in vitro and transient cytokine elevations have been observed in toxicology studies (Takahiro Ishiguro et al., Sci Transl Med 2017;9:eaal2491). The primary objective of DE is to determine the maximum tolerated dose (MTD) of ERY974 in patients with locally advanced or metastatic solid tumors expressing GPC3. The primary objective of CE is to assess ERY974’s preliminary anti-tumor activity. Methods: The study includes adult subjects with a life expectancy ≥ 3 months, histologically confirmed, measurable malignant solid tumors and/or metastatic disease not amenable to standard therapy, including patients with ≤ 1cm and ≤ 1 brain metastasis. Patients with interstitial lung disease, or acute/active chronic infection are excluded. ERY974 is administered IV and dosed weekly. DE occurs per an accelerated titration design (ATD), followed by a one-parameter logistic mode modified continual reassessment method (mCRM) to determine MTD (where the DLT occurrence rate is ≤ 0.25). The ATD and mCRM permit rapid dose escalation and determination of MTD while minimizing the number of subjects exposed to sub-therapeutic doses. Within DE, a flexible study design has been implemented to include a steeped increase in steroid administration and an ERY974 Fixed Day 1, Day 8 and Day 15 dosing regimen. Seven cohorts have completed without DLT and Cohort 8 began in December 2017. Additional measures will be implemented to help induce CRS tolerance. The CE will utilize a 2-stage design with futility analysis and will include the following 3 arms: GPC3+ gastric/gastroesophageal junction adenocarcinoma; GPC3+ squamous esophageal cancer; and other GPC3+ tumors. Clinical trial information: NCT02748837.

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A phase 1, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGD009 in combination with MGA012, both administered by IV infusion. Patients with B7-H3-expressing unselectable, locally advanced or metastatic solid tumors of any histology will be enrolled in the Dose Escalation Phase. Prior checkpoint inhibitor therapy is allowed. Dose escalation uses a 3+3 design, with patients treated every 2 weeks with escalating doses of IV MGD009 (starting dose 3µg/kg) and MGA012 at a dose of 3mg/kg in all cohorts. Cohort expansions will be limited to 6 tumor types (N=20/ cohort) treated at the maximum tolerated dose of the combination. Clinical trial information: NCT03406949.

A phase 1 study of MSC-1, a humanized anti-LIF monoclonal antibody, in patients with advanced solid tumors. First Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Leukemia Inhibitory Factor (LIF) is a pleiotropic cytokine involved in many physiological and pathological processes. LIF is highly expressed in a subset of tumors across multiple tumor types and shown to correlate with poor prognosis. LIF is hypothesized to contribute to tumor growth and progression by acting on multiple aspects of cancer biology, including immunosuppression of the tumor microenvironment (TME), and is a key regulator of cancer initiating cells (CICs), which are thought to underpin tumor growth, metastasis, and resistance to therapy. MSC-1, a first-in-class humanized IgG1 monoclonal antibody, is a potent and selective inhibitor of LIF. MSC-1 leads to robust STAT3 inhibition by disrupting the LIF signaling through the LIF receptor (LIFR). Blocking LIF with MSC-1 reprograms the TME through differentiation of immunosuppressive macrophages and modulation of several immune cell types. These findings form the basis of a robust therapeutic hypothesis, whereby MSC-1 treatment may lead to clinical activity in multiple cancer indications. Methods: The Phase 1 study of MSC-1 will enroll patients with advanced relapsed/refractory solid tumors. The study will employ an accelerated 3+3 escalation design to explore the safety, PK, immuno-regulatory activity and preliminary anti-tumor activity of MSC-1. Patients will receive treatment with MSC-1 intravenously once every 3 weeks until confirmed disease progression or intolerable toxicity. Four tumor specific expansion cohorts will be initiated once dose and schedule are established from dose escalation and include NSCLC, ovarian cancer, pancreatic cancer and a basket of advanced solid tumors; enrollment will be restricted to patients with LIF–High expression in their tumors using a diagnostic selection assay. Response will be assessed every 6 weeks per SY-1365 v1.1.

A phase 1, open-label, dose escalation study of MGD009, a humanized B7-H3 x CD3 DART protein, in combination with MGA012, an anti-PD-1 antibody, in patients with advanced solid tumors. First Author: Sadhna Shankar, MacroGenics, Inc., Rockville, MD

Background: T cells naturally undergo activation-induced upregulation of co-inhibitory pathways, which may limit the antitumor immune response. Blocking these inhibitory pathways may enhance the antitumor activity of CD3 bispecics. MGD009 is a clinical stage B7-H3 x CD3 DART protein designed to redirect T cells to kill B7-H3 expressing tumor cells. B7-H3, a member of the B7 family of immune regulators, is overexpressed in a variety of solid tumors and has limited expression in normal tissues. In preclinical studies, MGD009 causes T-cell infiltration, activation and expansion in the tumors. It upregulates PD-1 on T cells and PD-L1 on tumor cells and immune cells in vitro. Preliminary observations in patients enrolled in the ongoing phase 1 dose escalation trial with MGD009 alone indicate evidence of PD-1 up-regulation on both peripheral CD4 and CD8 T cells. MGA012 is an anti-PD-1 antibody under investigation in an ongoing Phase 1 clinical trial and has shown clinical responses. In vitro and in vivo studies have shown enhanced antitumor activity with the combination of MGD009 and MGA012 beyond that achieved with MGD009 alone. A combination approach that blocks checkpoint inhibition of T cells with MGA012, while recruiting cytotoxic and helper T cells to B7-H3-expressing tumors with MGD009, may show anti-tumor activity in a variety of tumors. Methods: This is a Phase 1, open-label, dose escalation, and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGD009 in combination with MGA012, both administered by IV infusion. Patients with B7-H3-expressing unresectable, locally advanced or metastatic solid tumors of any histology will be enrolled in the Dose Escalation Phase. Prior checkpoint inhibitor therapy is allowed. Dose escalation uses a 3+3 design, with patients treated every 2 weeks with escalating doses of IV MGD009 (starting dose 3µg/kg) and MGA012 at a dose of 3mg/kg in all cohorts. Cohort expansions will be limited to 6 tumor types (N=20/ cohort) treated at the maximum tolerated dose of the combination. Clinical trial information: NCT03406949.

A phase 1 multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety of SY-1365, a selective and potent covalent CDK7 inhibitor, in patients with tumors of any histology to evaluate PD endpoints in paired tumor biopsies. SY-1365 target engagement in PBMCs and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment. Biological impact of SY-1365 will be assessed by quantifying gene expression and induction of tumor cell apoptosis when feasible. This trial opened in May 2017. Clinical trial information: NCT03134638.

A phase 1 study of SY-1365, a selective and potent covalent CDK7 inhibitor, with initial expansions in ovarian and breast cancer. First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA

Background: SY-1365 is a selective and potent covalent CDK7 inhibitor. CDK7 activity has been implicated in various solid tumors with transcriptional dependencies. Recent preclinical studies have shown robust anti-tumor activity of SY-1365 in ovarian and breast cancer. In ovarian cancer, SY-1365 induced apoptosis in vitro and complete regressions in PDX models derived from heavily pre-treated patients (pts). In breast cancer, SY-1365 induced cell death in vitro across subtypes and displayed synergy when combined with fulvestrant in HR-positive models. These observations led to a change in the design of the expansion phase of this first-in-human study of SY-1365 to include a new focus on these tumors. The primary objectives of this study are to assess the safety and tolerability of SY-1365, and to determine dose-limiting toxicities, the MTD and the recommended Phase 2 dose. Secondary objectives include evaluation of pharmacokinetics and pharmacodynamic (PD) effects of SY-1365 in tumor and surrogate tissues, and assessment of preliminary antitumor activity. Methods: This is a multi-center, open-label Phase 1 trial with qualified pts. The dose escalation phase of the trial is open to solid tumor pts for whom standard curative or palliative measures do not exist or are no longer effective. SY-1365 is administered intravenously in two dose schedules, weekly and twice weekly for 3 weeks of each 4-week cycle. The expansion phase will evaluate preliminary antitumor activity in 3 ovarian cancer cohorts, either as a single agent or in combination with carboplatin, an HR+ breast cancer cohort in combination with fulvestrant in pts who failed treatment with a CDK4/6 inhibitor in combination with an AI, and a cohort in pts with tumors of any histology to evaluate PD endpoints in paired tumor biopsies. SY-1365 target engagement in PBMCs and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment. Biological impact of SY-1365 will be assessed by quantifying gene expression and induction of tumor cell apoptosis when feasible. This trial opened in May 2017. Clinical trial information: NCT03134638.

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TPS2604 Poster Session (Board #426a), Mon, 8:00 AM-11:30 AM

A phase 1 study evaluating the safety, pharmacology and preliminary activity of MM-310 in patients with solid tumors. First Author: Marc S. Ernstoff, Cleveland Clinic, Cleveland, OH

Background: Ephrin receptor A2 (EphA2) is expressed in cancer and stroma cells in a wide range of solid tumors. MM-310 is an EphA2-targeting lipoosomal form of a docetaxel produg. Preclinical investigation revealed a high correlation between EphA2 expression on cancer cells and MM-310 uptake. In vivo studies in multiple xenograft models demonstrated superior antitumor activity compared with standard of care agents, whereas toxicity analysis in rodents and non-rodent animal models revealed a favorable toxicity profile. The overexpression of EphA2 in a wide range of tumors, the high tumor specificity of MM-310 through the enhanced permeability and retention effect, and the EphA2 targeting support the investigation of MM-310 for potential clinical utility. Methods: This is a first-in-human, non-randomized, open-label Phase 1 study of MM-310 in patients with relapsed or refractory solid tumors. The clinical trial is divided into 3 parts. In the ongoing first part, MM-310 is assessed as a monotherapy, administered every 3 weeks at increasing dose levels (dose escalation), in patients with metastatic solid tumors, including urothelial carcinoma, gastric carcinoma, squamous cell carcinoma, non-small cell lung cancer, ductal adenocarcinoma, prostate adenocarcinoma, non-small cell lung cancer, small cell lung cancer, triple negative breast cancer, endometrial carcinoma and soft tissue sarcoma. The primary objective is to determine the maximum tolerated dose (MTD) of MM-310 monotherapy. Secondary endpoints include: characterization of dose-limiting toxicity profile, determination of pharmacokinetics and immunogenicity parameters, and assessment of preliminary activity of MM-310 monotherapy. In the dose-finding phase, the study uses a modified toxicity probability interval approach (mTPI) to determine the MTD of MM-310. After an MTD of monotherapy is established, an expansion cohort, and tol-totoxicity probability interval approach (mTPI) to determine the MTD of MM-310. After an MTD of monotherapy is established, an expansion cohort, and tol-

TPS2605 Poster Session (Board #426b), Mon, 8:00 AM-11:30 AM

First-in-human phase 1 study of DS-1062a in patients (pts) with advanced solid tumors (AST). First Author: Jacob M. Sands, Dana-Farber Cancer Institute, Boston, MA

Background: DS-1062a is a trophoblast cell-surface antigen 2 (TROP2)-targeting antibody drug conjugate. TROP2 is overexpressed in epithelial cancers, including non-small cell lung cancer (NSCLC), and its over-expression is associated with poor survival in solid tumors. In preclinical studies, DS-1062a showed promising antitumor activity and an acceptable safety profile in TROP2-positive tumors with a long half-life, allowing for every-3-week (Q3W) dosing. This dose escalation (ESC) and dose expansion (EXP) study will investigate DS-1062a in pts with ASTs (NCT03401385). Primary objectives are to determine the maximum tolerated dose and recom-mended dose for expansion (RDE) based on the dose limiting toxicity (DLT) rate (ESC) and assess safety and tolerability (ESC + EXP). Secondary objectives include pharmacokinetics (PK), antitumor activity and anti-drug antibody (ADA) incidence. Methods: In this multicenter, open-label study in the US and Japan, pts aged ≥18 (US) or ≥20 (Japan) years with unresectable relapsed or refractory advanced NSCLC are eligible regardless of TROP2 expression; other ASTs may be included if safety and efficacy in NSCLC is demonstrated. ESC will start at 0.27 mg/kg, followed by 21-day observation. Subsequent doses will be given Q3W. In EXP, pts will receive RDE Q3W. Pts will be treated until unacceptable toxicity, progressive disease, consent withdrawal or death. Endpoints include DLTs, adverse events (safety) and tumor response evaluated using RECIST v1.1 (efficacy). Pre-, on- and post-treatment tumor samples will be evaluated for TROP2 expression and other biomarker analyses. Immunogenicity will be assessed via ADA incidence and titer. Population PK and exposure-response analysis will be conducted. Pts will be enrolled in ESC using a modified continuous reassessment method and dose escalation with overlapping control, with at least 3 DLT-evaluable pts per dose level. For EXP, 40 pts with NSCLC and up to 40 pts with other solid tumors will be enrolled. Enrollment is open. Clinical trial information: NCT03401385.

TPS2606 Poster Session (Board #427a), Mon, 8:00 AM-11:30 AM

CD205-Shuttle study: A first-in-human trial of MEN1309/OBT076 an ADC targeting CD205 in solid tumor and NHL. First Author: Eva Garro-Calderon, Medical Oncology Department, Vall d’Hebron University Hospital; Molecular Therapeutics Research Group, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: MEN1309/OBT076 is a DM4-loaded Antibody Drug Conjugate (ADC), directed against CD205/Ly75, a type I transmembrane surface protein belonging to the macrophage mannose receptor family. CD205 is therapeutically relevant, because of its broad expression in multiple cancer types, its emerging role at facilitating metastatic invasion and its effective internalization upon antibody binding. Extensive preclinical evidence demonstrated MEN1309 antitumor activity in vitro, in xenograft and patient-derived xenograft (PDx) models. Methods: The CD205-Shuttle study is a two-step, open-label, multicenter, dose-escalation FIH study. Step 1 involves patients affected by different solid tumors, following an Accelerated Titration Design (ATD) whereby 1 patient per dose cohort is enrolled and the dose doubled at each cohort. If grade ≥2 toxicity is observed the trial design is expected to revert to a 3+3 scheme with a Fibonaci ascending dose scheme. Step 2 is designed to test MEN1309/OBT076 at minus 2 levels of the tolerated doses during Step 1 in patients with Non-Hodgkin-Lymphoma (NHL). Each dose level escalation will be subject to the assessment of the Cohort Review Committee (CRC). CD205-positive patients are selected by IFHC staining of archived tumor material. Patient with locally advanced or metastatic solid tumor in progression can be included if failed on ≥2 previous cancer treatments and if no standard therapy is available. The primary endpoint is to identify dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MEN1309/OBT076 administered by i.v. infusion once every 21-days. The secondary endpoints include assessment of pharmacokinetics (PK), immunogenicity, preliminary clinical efficacy of MEN1309/OBT076 and correlation with CD205 expression. Adverse Events (AE) will be graded according to NCI CTCAE v. 4.03. Responses will be evaluated according to RECIST v1.1 and Cheson criteria (2014). Study variables will be presented by dose-cohort and overall using appropriate descriptive statistics. The enrollment began in October 2017 in European sites; up to date 3 cohort levels have been achieved. NCT03403725. NOTE: First and Second Author equally contributed to this work Clinical trial information: NCT03403725.

TPS2607 Poster Session (Board #427b), Mon, 8:00 AM-11:30 AM

Phase 1b multi-indication study of the antibody drug conjugate anetumab ravtansine in patients with mesothelin expressing advanced or recurrent malignancies. First Author: Alex A. Adjei, Mayo Clinic, Rochester, MN

Background: Mesothelin expression is associated with poor prognosis in patients with a wide variety of tumors, including mesothelioma, pancreatic, gastric/gastroesophageal juncture, NSCLC, ovarian, triple-negative breast cancer, and thymic carcinomas. Anetumab ravtansine is a novel fully human antibody drug conjugate. TROP2 is overexpressed in five tumor types with high unmet medical need in patients pre-screened for mesothelin expression (NCT03102320). Methods: Eligibility criteria include: ≥18 years, unsuitable locally advanced or metastatic recurrent or relapsing disease, no prior (pancreatic adenocarcinoma) or one or more prior lines of therapy for their advanced stage of disease, and availability of tumor tissue for mesothelin expression testing as determined by the Ventana MSLN (SP74) immunohistochemistry assay. Mesothelin-positive patients with selected adenocarcinomas (gastric including gastro-esophageal junction, NSCLC, ovarian, triple-negative breast cancer, and thymic carcinomas) will receive anetumab ravtansine as monotherapy at 6.5 mg/kg IV on a 21-day cycle. Following a safety run-in phase (18-24 patients each), patients with pancreatic adenocarcinoma will receive anetumab ravtansine in combination with gemcitabine (1000 mg/m2 IV day 1 and 8 on a 21-day cycle). The primary objective is to determine response rate (ORR) of anetumab ravtansine in patients with mesothelin expression levels: high (≥30% positive tumor cells with moderate and stronger membrane staining intensity) and low-mid (<30% positive tumor cells with moderate and stronger membrane staining intensity). Secondary objectives include safety, disease control rate, duration of response, durable response rate, and progression-free survival. Approximately 350 patients will be enrolled. Clinical trial information: NCT03102320.

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A phase II trial of the DNA methyltransferase inhibitor, SGI-110 (guadecitabine), in children and adults with wild type GIST, pheochromocytoma and paraganglioma associated with succinate dehydrogenase deficiency and HLRCC-associated kidney cancer. First Author: Jaydila Del Rivero, Center for Cancer Research, NCI, NIH, Bethesda, MD

**Background:** Loss of activity of Krebs cycle components succinate dehydrogenase (SDH) complex or fumarate hydratase (FH) has been identified as a mechanism of tumorigenesis in SDH-deficient gastrointestinal stromal tumor, pheochromocytoma and paraganglioma (PHEO/PGL), and hereditary leiomyomatosis and renal cell cancer (HLRCC). Accumulation of the metabolites succinate or fumarate inhibits α-ketoglutarate-dependent dioxygenases leading to DNA hypermethylation in these tumors. Guadecitabine is a small molecule derivative of decitabine that acts as a DNA methyltransferase inhibitor. We hypothesize that guadecitabine will impact tumor growth by reversing DNA hypermethylation in tumors with Krebs cycle abnormalities (NCT03165721).

**Methods:** This single site, open label, phase II study uses a small optimal two-stage design to evaluate response in three groups of patients: SDH-deficient GIST, SDH-deficient PHEO/PGL and HLRCC-associated renal cell carcinoma. The primary objective is to assess the clinical activity (CR or PR) of guadecitabine in these patients. Adults and children (≥12 years of age) receive guadecitabine subcutaneously at a dose of 45mg/m²/day for 5 consecutive days on a 28-day cycle. Activity is assessed by imaging response of measurable disease using RECISTv1.1 using CT, MRI and/or PET. Toxicity is graded using version 4.0 of the NCI Common Toxicity Criteria. Guadecitabine-related toxicities ≥3 will be considered treatment limiting, unless they are reversible within 72 hours with supportive care. Following recovery from toxicity up to 2 dose reductions will be allowed. Initially 7 evaluable patients in each group will be enrolled and if 1 or more (14.3%) have a response, accrual will continue until a total of 21 patients have enrolled and at least 3 responses are observed among the 21 evaluable patients the agent will be considered worthy of further testing in this disease. Clinical trial information: NCT03165721.

Phase I study of the pan-HER inhibitor neratinib given in combination with everolimus, palbociclib or trametinib in advanced cancer subjects with EGFR mutation/amplification, HER2 mutation/amplification or HER3/4 mutation. First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Over expression and aberrant function of ErbB receptor tyrosine kinases (EGFR, HER2, HER3 and HER4) contributes to tumorigenesis. Multiple drugs targeting EGFR or HER2 are already approved for various cancers. In spite of clinical successes with EGFR or HER2 inhibitors, single agents are prone to drug resistance due to aberrant or compensatory activation of additional downstream signaling pathways. We sought to determine whether neratinib, a potent irreversible pan-HER tyrosine kinase inhibitor, would be safe and efficacious in combination with approved inhibitors of mTOR, CDK4/6, or MEK. Methods: This is an investigator-initiated, single-center, non-randomized, multi-arm phase I trial of subjects ≥18 years old with measurable advanced solid tumors with no curative therapeutic options and whose tumors harbor somatic mutations or amplifications in ErbB genes. Prior HER2 or ERG directed therapy are allowed. The study will have 3-arms: Arm 1: neratinib + everolimus, Arm 2: neratinib + palbociclib, Arm 3: neratinib + trametinib. Patients are selected for each arm at investigator’s discretion based on tumor type and molecular aberrations present. A standard 3 + 3 dose-escalation design will be utilized and patients will be recruited into five dose levels for each arm of the study. Additional subjects will be treated in dose-expansion cohort(s) once the MTD has been established. A treatment cycle is 28 days. Primary endpoint is determination of the maximum tolerated dose and dose limiting toxicities for each treatment arm. Secondary endpoints include pharmacokinetic and pharmacodynamic analysis along with preliminary anti-tumor efficacy. Prophylactic use of antiemetic medication is mandatory during first cycle. Imaging will be performed at 8 week intervals and response will assessed by RECIST v1.1. Enrollment to the study has already commenced. Clinical trial information: NCT03065387.
A phase 1a / 1b first-in-human, open-label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study of oral TP-0903, a potent inhibitor of AXL kinase, administered daily for 21 days to patients with advanced solid tumors. First Author: John Sarantopoulos, Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio, San Antonio, TX

Background: AXL kinase has emerged as a key regulator of the epithelial to mesenchymal transition (EMT), a process that enables cancer cells to develop migratory and invasive properties and acquire resistance to chemotherapeutics and targeted agents. AXL kinase is also known to serve to dampen the immune response to dying tumor cells. By activating EMT, AXL signaling allows cancer cells to engulf neighboring cancer cells undergoing apoptosis, reducing presentation of pro-inflammatory stimuli to the immune system. Consequently, the inhibition of AXL by TP-0903 may potentially reduce cancer cell metastasis, target cancer cells that demonstrate immunity to chemotherapeutics and activate the anti-cancer immune response. Methods: Patients with advanced solid tumors that are refractory or intolerant to established therapy have been enrolled in a standard 3+3 dose escalation trial of TP-0903 given orally once daily for 21 days of a 28-day cycle, with dose level 1, for 4 cohorts. Patients received TP-0903 for 4 weeks. Once the MTD has been reached, the study will be expanded into 5 cohorts of 20 patients each: 1) Patients on immunotherapy who demonstrate progression but are clinically stable, 2) EGFR + NSCLC having progressed on standard of care therapy, 3) platinum refractory/resistant ovarian, 4) BRAF, KRAS or NRAS mutated CRC with no standard therapy remaining, 5) BRAF, KRAS or NRAS mutated CRC with no standard therapy remaining. Efficacy and safety endpoints are primary objectives. The secondary objectives are PK, radiographic response, PD activity (e.g. GASC/AXL and other EMT markers), biological activity and RP2D. Key eligibility criteria include age ≥ 18 years, ECOG ≤ 1, adequate organ function, life expectancy of ≥ 3 months. The once-daily TP-0903 dose regimen is 150, 300, 600, 1200 mg, and 1200 mg as DLT enrollment into cohort 6 began January 2018. The primary objective is to determine the MTD and DLTs; secondary objectives are PK, radiographic response, PD activity (e.g. GASC/AXL and other EMT markers), biological activity and RP2D. Key eligibility criteria include age ≥ 18 years, ECOG ≤ 1, adequate organ function, life expectancy of ≥ 3 months. Once the MTD has been reached, the study will be expanded into 5 cohorts of 20 patients each: 1) Patients on immunotherapy who demonstrate progression but are clinically stable, 2) EGFR + NSCLC having progressed on ≥ 2 lines of TKIs, 3) BRAF, KRAS or NRAS mutated CRC with no standard therapy remaining, 4) Platinum refractory/resistant ovarian, 5) BRAF mutated melanoma that hasn’t responded to immunotherapy or combination BRAF/MEK inhibitor. Patients will be biopsied in each cohort to explore changes to the EMT phenotype. Clinical trial information: NCT02729298.

A modular, multi-arm, multi-part, first time in patient study to evaluate the safety and tolerability of the dual MET kinase/OCT2 inhibitor, OMO-1, alone and in combination with anti-cancer treatments, in patients with locally advanced, unresectable or metastatic solid malignancies. First Author: Elizabeth Ruth Plummer, Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, United Kingdom

Background: OMO-1, a highly selective, oral, small molecule MET kinase/OCT2 inhibitor, demonstrated single agent cellular and in vivo anti-tumor activity, including regression in MET driven xenograft models. Preclinical studies to identify optimal drug combinations Predicted efficacious exposures of OMO-1 were reached without clinically relevant adverse events in healthy volunteers, data from this study expedited the ongoing patient study. Methods: This novel study design consists of distinct study modules, each investigating a different hypothesis. Module 1, investigating OMO-1 monotherapy, commenced in Aug 2017. It consists of Part A (dose finding) and an optional Part B (cohort expansions in relevant clinical indications eg MET amplification or exon 14 skipping mutation). Part A is a traditional 3+3 dose escalation design. Part B expansions are powered to compare response rates to historical data. The option to start Part B and add further modules will be based on emerging data, a substantial protocol amendment being put in place before starting a new module. The dosing schedule/sequence of OMO-1 in each module may be adapted in response to emerging data. The maximum tolerated dose of OMO-1 for individual modules may differ based on the emerging safety profile for each combination. For all modules, Part A cohorts may be expanded by up to 12 additional patients, mandatory serial tumour biopsies will be taken and assessed for relevant PD biomarkers. This design allows one protocol to respond to emerging data, supporting studies in both monotherapy and multiple combinations, reducing the time to ‘first subject in study’ compared with multiple individual studies. It also allows investigators to pre-empt emerging data and changes to the treatment landscape. These challenges emphasize the need for flexible designs as the landscape of drug development continues to quickly evolve. Clinical trial information: NCT03138083.

An explorative phase 2 study of afatinib for advanced cancers carrying an EGFR, a HER2 or a HER3 mutation. First Author: Lore Decoster, UZ Brussel, Brussels, Belgium

Background: Next generation sequencing of solid tumors will increasingly reveal mutations in cancer genes, including EGFR, HER2 and HER3 mutations. Afatinib is a small molecule, which selectively and irreversibly inhibits EGFR, HER2 and HER4 and which blocks transphosphorylation of HER3. Afatinib monotherapy has shown activity in EGFR and HER2 mutated lung cancer and preclinical activity in rare HER3 mutated lung cancer. In addition, synergy has been reported between afatinib and paclitaxel. The aim of this Belgian multicentre multicohort basket trial is to study the activity of afatinib in cancers of any type with an EGFR, a HER2 or a HER3 mutation and to study the efficacy of adding paclitaxel to afatinib at disease progression, regardless of tumor type. Methods: This is a multicenter, open-label, phase 2 study of afatinib in three cohorts of patients with advanced cancer harbouring an EGFR mutation, a HER2 mutation or a HER3 mutation. For each cohort an optimal Simon’s two-stage design is used (p0 = 0.10; p1 = 0.30; alpha = 0.05; power 80%). The primary endpoint for each cohort is objective response as determined according to RECIST 1.1. Secondary endpoints are progression free survival, overall survival and toxicity. At progression, paclitaxel weekly will be added to afatinib and response rate, progression free survival and toxicity will be evaluated. In addition to genotype specific response determination, the activity of afatinib in each cancer type will also be evaluated. Rebiopsy will be performed at progression. Major eligibility criteria are: Patients with locally advanced or metastatic cancers harbouring an EGFR, HER2 or a HER3 mutation, excluding EGFR mutated lung cancer. Failure of at least one line of standard systemic therapy. ECOG performance status ≤ 2. Adequate organ function. This study is in progress and has currently recruited 4 patients (2 lung cancers, 2 breast cancers) in the HER2 mutated cohort. No patients have yet been recruited in the EGFR or HER3 mutated cohorts. EudraCT No.: 2016-003411-34 Clinical trial information: 2016-003411-34.
TPS2616  Poster Session (Board #432a), Mon, 8:00 AM-11:30 AM
A phase 2, open-label study of the combination of spartalizumab (PDR001) and LAG525 for patients with advanced solid tumors and hematologic malignancies. First Author: Sarina Ansz, Phi-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Spartalizumab is an immunoglobulin G4 humanized monoclonal antibody that binds with subnanomolar affinity to PD-1. LAG525 is an immunoglobulin G4 humanized monoclonal antibody that binds LAG-3 with low nanomolar affinity, inhibiting the LAG-3 interaction with MHC class II and potentially restoring the activity of antitumor effector cells and enhancing anti-PD-1 antitumor activity. Preclinical studies demonstrated that simultaneous inhibition of PD-1 and LAG-3 resulted in synergistic antitumor activity (Woo SR. Cancer Res. 2012). PDR001XUS01 will evaluate the clinical benefit of combination checkpoint blockade (CPB) with LAG525 plus spartalizumab across multiple tumor types that are associated with low response rates (overall response rate [ORR] < 30%) to monotherapy CPB. Methods: This phase 2, open-label, parallel-cohort study will enroll patients aged ≥18 years with documented progression of small cell lung cancer, gastric/esophageal adenocarcinoma, castration-resistant prostate adenocarcinoma, soft tissue sarcoma, ovarian adenocarcinoma, advanced well-differentiated neuroendocrine tumors, and renal cell carcinoma. A minimum of 5 patients and a maximum of 30 patients will be enrolled in each of the 7 tumor-type cohorts for a total planned enrollment between 35 to 210 patients. Patients will receive spartalizumab in combination with LAG525 administered intravenously every 3 weeks through treatment cycle 4, and in tissue biopsy samples of the primary endpoint (CBR) at 24 weeks of treatment. CBR will be assessed by RECIST 1.1 for solid tumors and the Revised Response Criteria for Malignant Lymphoma for lymphoma (Cheson BD. 2007). Secondary endpoints include ORR, time to response, duration of response, time to progression, and safety/tolerability. Accrual is ongoing. Clinical trial information: NCT03365791.

TPS2617  Poster Session (Board #432b), Mon, 8:00 AM-11:30 AM
A phase 2A open-label, multicenter trial of the safety and efficacy of LYC-55716, a first-in-class oral, small-molecule RORγ agonist to treat select solid tumors. First Author: Karen Kelly, University of California Davis Comprehensive Cancer Center, Sacramento, CA

Background: LYC-55716 is a first-in-class, oral, small-molecule agonist of the retinoic acid receptor-related orphan receptor γ (ROR-γ) under development as a novel immuno-ology agent for solid tumors. Preclinical evidence suggests that LYC-55716 alters immune cell anti-tumor effector functions and immunosuppressive mechanisms, leading to reduced tumor growth and enhanced survival. In the Phase 1 portion of an ongoing Phase 1/2A trial, LYC-55716 was well tolerated with no dose-limiting toxicities. Evidence of pharmacodynamic target engagement was demonstrated and disease stabilization with tumor reduction was noted in patients after failure of PD-1 therapy. The Phase 2A trial (NCT02929862) is underway in patients with advanced non-small cell lung, head and neck, gastrointestinal, renal cell, urothelial, and ovarian cancers. Methods: The Phase 2A portion of the trial will enroll ~70 adult patients who will receive 28-day treatment cycles of LYC-55716 administered twice daily. The primary endpoint is to determine the objective response rate (ORR). Secondary endpoints will include duration of response, progression-free survival, overall survival, safety, and pharmacokinetics. As an exploratory endpoint, immune-related biomarkers will be assessed in blood samples from all patients, taken at screening and every 2-4 weeks through treatment cycle 4, and in tissue biopsy samples of selected patients, taken at screening and 4-12 weeks after beginning cycle 1. The markers of interest will be evaluated on a NanoString platform and immunohistostaining. Results will be analyzed using descriptive and summary statistics. Clinical trial information: NCT02929862.

TPS2618  Poster Session (Board #433a), Mon, 8:00 AM-11:30 AM
Safety, dose tolerance, pharmacokinetics and pharmacodynamics study of CPX-POM in patients with advanced solid tumors. First Author: Scott James Weir, University of Kansas Cancer Center, Westwood, KS

Background: Ciclopirox (CPX) is an antifungal agent contained in a number of FDA-approved topical drug products. CPX possesses antitumor activity in a number of in vitro and in vivo preclinical models, however, its clinical utility is limited due to low oral bioavailability, gastrointestinal toxicity, and poor water solubility. Ciclopirox Prodrug (CPX-POM) selectively delivers its active metabolite, CPX, to the entire urinary tract following systemic administration. In a chemical carcinogen mouse model of bladder cancer, CPX-POM treatment resulted in significant decreases in bladder weight, a clear migration to lower stage tumors, dose-dependent reductions in Ki67 and PCNA staining, and inhibition of Notch 1 and Wnt signaling pathways. Methods: Study CPX-POM-001 (NCT03348514) is an ongoing US multi-center, Phase I, open-label, dose escalation study to evaluate dose-limiting toxicities (DLTs), define the maximum tolerated dose (MTD), and to determine the recommended Phase II dose of IV CPX-POM. Approximately 24 patients with any histologically- or cytologically-confirmed solid tumor type refractory to standard therapy, and also meet other standard Phase I eligibility criteria, will be enrolled in dose escalation cohorts. The MTD will be defined as the dose BELOW that dose which causes DLTs in ≥33% of patients. Safety and tolerability will be based on an assessment of adverse events, physical examinations, vital signs, electrocardiogram, clinical laboratory tests, ophthalmologic assessments, and concomitant medications. Single dose and steady-state pharmacokinetics of CPX-POM, CPX and ciclopirox glucuronide are being characterized in both plasma and urine. Urine 8-glucuronidase activity is also being determined. Single and multiple dose pharmacodynamics of CPX-POM are being characterized by measuring circulating biomarkers of Wnt and Notch cell signaling pathways. Enrollment began in January 2018 at a starting IV CPX-POM dose of 30 mg/m². Doses are currently being escalated in 100% increments until a ≥Grade 2 is encountered, at which point that cohort and all subsequent cohorts will follow a classical “3 + 3” dose escalation design. Clinical trial information: NCT03348514.

TPS2619  Poster Session (Board #433b), Mon, 8:00 AM-11:30 AM
First-in-human phase 1-2A study of CB-103, an oral Protein-Protein Interaction Inhibitor targeting pan-NOTCH signalling in advanced solid tumors and blood malignancies. First Author: Jose Manuel Perez Garcia, Medical Oncology Department (IOB), Quiron Hospital, Barcelona, Spain

Background: NOTCH signalling is a key development pathway whose aberrant activation is recognised to play an oncogenic role in human cancers. When NOTCH signalling is inappropriately activated by genetic alterations, it becomes an oncogenic driver for NOTCH-dependent cancers, while upregulation of NOTCH receptors is linked to resistance to standard of care. CB-103 is a new small molecule protein-protein interaction (PPI) inhibitor able to target assembly of the NOTCH transcription complex in the cell nucleus leading to downregulation of NOTCH target genes (c-MYC, CCND1, HES1) and inhibition of NOTCH signalling independently of NOTCH mechanisms of activation. CB-103 has demonstrated efficacy and tolerability in different preclinical tumor models derived from various NOTCH-driven cancer indications and in blood from NOTCH-activated leukemia pts. Methods: This study is a multi-centre, open label, non-randomised, phase 1-2A dose escalation study in adult patients (pts), with expansion arms of oral CB-103. Aim of phase 1 is to find the MTD/RP2D. The starting dose is targeting a plasma exposure (daily AUC) that has reasonable safety margin and allows reliable determination of pharmacokinetics (PK). An adaptive Bayesian logistic regression model for dose escalation is implemented in phase 1 to guide determination of MTD/RP2D. Full PK sampling profiles will be taken on days 1 & 8 of cycle one (28 days) and day 1 of cycle two. NOTCH-related PD and Biomarker exploratory analyses are planned on tumour biopsies, hair folliciles and blood samples (liquid biopsy). Administration schedule (once-daily) may be adapted depending on PK and safety. 3-6 eligible pts regardless of NOTCH pathway activation status are enrolled per dose group in phase 1, while pts in phase 2A will be selected for NOTCH pathway genetic alterations. Phase 2A will assess preliminary efficacy of CB-103 in expansion arms across different indications using Bayesian design. Enrollment into 1st dose group (15mg) started with first pt treated on 20Dec17: 7 pts registered with 2 screen failures, 1 discontinued due to early cancer progression and 4 in treatment in their first treatment cycle. Clinical trial information: NCT03422679.

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Phase 1 study of an oxidative phosphorylation inhibitor IM156 in patients with advanced solid tumors. First Author: Sun Young Rha, Severance Hospital, Seoul, Republic of Korea

Background: IM156 is a novel oral agent with a biguanide structure, which has anticancer activity through AMPK activation and reduction of oxidative phosphorylation. Inhibition of oxidative phosphorylation (OXPHOS) is detrimental to OXPHOS dependent drug resistant cancer cells which adapt metabolic shift upon cancer treatment or are intrinsically OXPHOS dependent cancer cells. OXPHOS dependent cancer cells are prone to energy stress such as OXPHOS inhibition that ultimately cause cancer cell death. Preclinical in vitro and in vivo experiments demonstrated that IM156 can be effective in glioblastoma, and other solid tumors. Therefore, a phase I dose-escalation study to determine safety and preliminary signals of activity of IM156 has been designed and activated (NCT03272256).

Methods: This is an open label, single center, dose-escalation study using the 3+3 design to determine the maximum tolerated dose and/or recommended phase 2 dose, dose limiting toxicities (DLT), safety, pharmacokinetics, pharmacodynamics and preliminary signals of anticancer efficacy of IM156 in patients with advanced solid tumors refractory to standard therapies. Eligible patients are adults with advanced solid tumors refractory to standard therapies with adequate performance status (ECOG ≤ 2) and organ function with measurable disease per RECIST 1.1 (or RANO for gliomas). IM156 is administered orally every other day starting on day 1 of each 28 days cycle. The study has total of 6 dose levels ranging from 100 mg to 1,800 mg and the dose escalation continues per 3+3 design as long as the proportion of DLTs, 33% (≤ 2/6). DLTs are evaluated during the first 28 days of therapy (cycle 1). Efficacy per RECIST 1.1 (RANO for gliomas) is evaluated every two cycles. Pharmacokinetics studies have been designed to determine Cmax, AUC, T1/2 and other parameters. Pharmacodynamics studies include PET scans with FDG and acetate probes, tissue and blood biomarkers including lactate levels. As of 2/8/18 the study enrolled 6 patients into two dose levels (100mg and 200mg respectively) and enrollment continues. Clinical trial information: NCT03272256.

Phase I study of procaspase activating compound-1 (PAC-1) for treatment of advanced malignancies. First Author: Oana C. Danciu, University of Illinois at Chicago, Chicago, IL

Background: Dysregulation in apoptotic pathways is a hallmark feature of cancer, offering opportunities for pharmacologic intervention in its treatment. Caspases, a family of proteases, play several roles in apoptosis. Caspase-3 catalyzes the intra-cellular proteolysis that characterizes part of the apoptotic process. Caspase-3 levels are low in many tumors including: glioblastoma; breast, colon, lung, and liver cancers; lymphoma; neuroblastoma; and melanoma. In contrast, procaspase-3, the precursor of caspase-3 is elevated in these tumors. We describe a phase I study of PAC-1, a drug that catalyzes the conversion of procaspase -3 to caspase-3. It induces apoptosis in tumor cell lines in vitro. In vivo activity has also been shown, when combined with alkylating chemotherapy, in rodent glioma models and in canines diagnosed with malignant glioma.

Methods: This Phase I dose escalation study has two components: the first (C1) to determine the maximum tolerated dose (MTD) of PAC-1 in advanced malignancies; the second (C2) to determine the MTD of PAC-1 when combined with temozolomide (TMZ) in patients with recurrent anaplastic astrocytoma (AA) or glioblastoma (GBM). A modified Fibonacci 3 + 3 design is used, expanding to nine subjects at the MTD level in each component. PAC-1 pharmacokinetics is assessed in all subjects during the first cycle. Secondary objectives include pharmacodynamics and correlations of PAC-1 activity with procaspase-3 expression in tumor tissue. Neurologic toxicity is closely monitored throughout the study. Inclusion criteria: diagnoses of advanced malignancies (C1) and recurrent AA or GBM (C2), ECOG PS 0-2, adequate organ function. Exclusion criteria: prior cytotoxic therapy in the last 3-6 weeks (varying with drug class) or uncontrolled chronic illness. Administration and design: For C1, PAC-1 (orally administered) is dosed at 75-1,000 mg daily on days 1-21 of each 28 day cycle. For C 2, the first PAC-1 dose is 375 mg daily with potential for escalation to 1,000 mg daily. TMZ, PO, is dosed at 150 mg/m2 daily, days 8-12, of each cycle. Enrollment to date for C1 is 27, (dose level 6); and for C2 is 4 (dose level 1). The study is open to accrual. Clinical trial information: NCT02355535.
ICONIC: Biologic and clinical activity of first in class ICOS agonist antibody JTX-2011 +/- nivolumab (nivo) in colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results. First Author: R. Siddiqui; Second Author: E. K. Chiles; Research Institute, Providence Cancer Institute, Portland, OR

Background: Preclinical studies demonstrate synergistic antitumor activity of PD-1 blockade and variol, a CD27 agonist antibody. Ph1 results were previously presented from a Ph1/2 study assessing the safety of nivo with variol; we now report Ph1/2 results for CRC and OVA. Methods: Pts with advanced, treatment refractory (anti-PD-1/L1 naïve) solid tumors received nivo (Ph1: 3 mg/kg; Ph2: 240 mg every two weeks (Q2W)). Ph1 cohorts also received variol at 0.1, 1, or 10 mg/kg Q2W. Ph2 cohorts received variol at 3 mg/kg Q2W (CRC and OVA), 0.3 mg/kg Q4W (OVA), or 3 mg/kg Q12W (OVA). Primary study objectives: safety (Ph1) and overall response rate (Ph2). Results: 42 CRC and 66 OVA pts received nivo and variol. Toxicity was consistent with the safety profile of each agent; treatment-related serious events occurred for 3 pts with CRC (mixed motor sensory neuropathy, pneumonitis, elevated ALT) and 2 pts with OVA (acute kidney injury, hepatitis, small bowel obstruction). Of 49 (Ph1, 41, Ph2) evaluable OVA pts, 5 (10%; all Ph2) had RECIST 1.1 Partial Response (PR) (19; 39%; 6 P1, 13 Ph2) and Stable Disease (SD; On-treatment biomarkers: revealed an increase in PD-L1 expression (p < 0.000), and B+ T cells (p < 0.005), which was more prevalent among pts with better outcome (PR or OR > 16 weeks of SD), p = 0.017 and p < 0.002. Of 41 (Ph1 21; Ph2 20) evaluable CRC pts, 2 (5%; 1 Ph1, 1 Ph2) had PR (Ph1 pt MSI-low, Ph2 pt MSI-high; both PD-L1 neg) and 7 (17%; 3 Ph1, 4 Ph2) had SD. 89% of CRC pts had PD-L1 high; both PD-L1 neg tumors at baseline. In contrast to CRC, increase in tumor PD-L1 expression or CD8+ T cells during treatment in CRC patients was infrequent, correlating with less overall clinical impact. Conclusions: Variol with nivo was well tolerated without evidence of additive toxicity. In OVA pts, treatment induced significant tumor changes that correlate with better outcome. Results of ongoing analyses of Ph2 data will be presented. Ph1 results provide a strong foundation for clinical development of nivo and variol and suggest a possible schedule on clinical outcome and biomarkers. The mechanisms that mediate the lack of tumor cell and PD-L1 increase in some pts are being explored by further tumor molecular profiling. Clinical trial information: NCT02335918.

A first-in-class, first-in-human phase 1 pharmacokinetic (PK) and pharmacodynamic (PD) study of Hu5F9-G4, an anti-CD47 monoclonal antibody (mAb). First Author: Branimir I. Sirk; Stanford University School of Medicine, Stanford, CA

Background: Hu5F9-G4 (5F9) is a humanized mAb that inhibits CD47, a don't eat me signal for macrophages, and can enhance tumor cell phagocytosis and T-cell priming. Preclinically, 5F9 is active against a wide range of tumors. Methods: Patients (pts) were enrolled in 3 dose escalation groups using a 3+3 design (NCT02640409). Part A (11 pts) defined 1 mg/kg of 5F9 as the optimal weekly (wk) 1 priming dose that was used subsequently in Parts B & C. Part B (14 pts) evaluated higher weekly (wkly) maintenance doses starting wk 2 and Part C (18 pts) evaluated an additional loading dose in wk 3. Safety, PK, PD and efficacy data are presented here. Results: In 58 pts (median age 60 y; median prior treatments 5) the most common tumor types were colorectal (CRC), ovarian, adenoid cystic breast, pancreatic, and squamous cell head & neck cancers. Using a priming + load/maintenance dose, no maximum tolerated dose (MTD) was reached in Part B where 14 pts received ≥ 20 mg/kg of 5F9 wky, nor in Part C where doses of 20 (7 pts), 30 (8 pts) and 45 mg/kg (3 pts) were well tolerated. Common Part C drug-related adverse events were fatigue, 50%, chills 50%, pyrexia 45%, anemia 39%, headache 34%, lymphopenia 28%, hemagglutination 17%, transient hyperbilirubinemia 17%, and myalgias 11%. Most AEs were Grade (Gr) 1 or 2 occurring in cycle 1 (28 days) with Gr 3+ being uncommon and no cumulative effects. Transient Gr 1/2 acute anemia due to CD47 blockade on older RBCs was common but was mitigated by the priming dose strategy. Saturation of nonlinear PK occurred at ≥ 10 mg/kg resulting in a prolonged t½; 14 days, 5F9 levels exceeding preclinical antitumor activity thresholds (200 µg/mL) and resulting in > 99% WBC CD47 receptor occupancy. The recommended Phase 2 dose is 1 mg/kg priming dose wk 1 followed by 30 mg/kg wky x 3 and then 30 mg/kg Q2W thereafter. Two pts (ovarian and fallopian tube cancers) had confirmed partial responses and were treated for 33 and 41 weeks, respectively. In 13 CRC pts treated at doses ≥ 20 mg/kg, 6 had stable disease with a median treatment duration of 18 wks. Conclusions: 5F9 prime + maintenance doses are well tolerated and demonstrate monotherapy antitumor activity. Clinical trial information: NCT02216409.

DURABILITY of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (pts) with refractory large B-cell lymphoma. First Author: Frederick Lundy Locke, Moffitt Cancer Center, Tampa, FL

Background: Axi-cel, an anti-CD19 CAR T cell therapy, demonstrated significant clinical benefit and a manageable safety profile for pts with refractory large B cell lymphoma in ZUMA-1 (Neelapu & Locke et al. NEJM.2017). These results led to its approval by the US FDA for the treatment of adult pts with relapsed or refractory large B cell lymphoma after ≥ 2 prior lines of therapy. Here, we examined responses over time in phase 2 of ZUMA-1. Methods: Pts with refractory large B cell lymphoma received 2 10^6 CAR T cells/kg after low-dose conditioning (Neelapu & Locke et al. NEJM.2017). Best objective response rates (BOR) were analyzed locally by investigators (local) and centrally by independent review committee (IRC; Cheson et al. J Clin Oncol. 2007); concordance was measured as the percentage of pts whose IRC matched local. Results: As of 8/11/17, median follow-up (f/u) was 15.1 mo for the 101 pts treated with axicel. While the BOR of 82% at primary analysis (PA; median f/u 8.7 mo) by local remained consistent (83%) at long-term f/u (LTU; median of 15.1 mo), complete response (CR) rates increased from 54% to 58% (Table). Out of 34 pts with partial response (PR) at 1 mo, 11 (32%) converted to CR by the LTU. High concordance (77% - 79%) was observed for objective response rates (ORR (CR + PR)) between local and IRC at all times assessed. Landmark analysis of progression-free survival (PFS) by response status (local) revealed that most of the 60 pts with disease control (stable disease or better) at 3 mo had prolonged disease control with a 73% - 12-month PFS rate. Of the 42 pts with CR and 9 with PR at 3 mo, the 12-mo PFS rates were 79% and 78%, respectively. Conclusions: Treatment with axicel induces high response rates in pts with refractory large B cell lymphoma. CR rates increased through the LTU, suggesting that responses deepen over time and that pts with PR can be converted as late as a year post-infusion. ORR at 3 mo may be prognostic for prolonged FSR. Drs Locke and Cheson equally. Clinical trial information: NCT02348216.
3004 Oral Abstract Session, Sat, 3:00 PM-6:00 PM
Treatment of metastatic human papillomavirus-associated epithelial cancers with adoptive transfer of tumor-infiltrating T cells. First Author: Sanja Stevanovic, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Adoptive T-cell therapy (ACT) is a promising cancer treatment modality. However, its study in epithelial cancers has been limited. Human papillomavirus (HPV)-associated cancers are difficult to treat epithelial malignancies for which better systemic treatments are needed. We conducted a clinical trial of ACT for the treatment of metastatic HPV-associated cancers. Methods: The clinical trial was a phase II design with two disease cohorts (cervical cancers and non-cervical cancers). Patients were treated with a single infusion of tumor-infiltrating lymphocytes (TIL), which were generated, when possible, from TIL subcultures with HPV-oncoprotein reactivity (HPV-TIL). HPV-TIL infusion was preceded by a lymphocyte-depleting conditioning regimen followed by systemic high-dose aldesleukin. Results: Objective tumor responses occurred in 5/18 (28%) patients in the cervical cancer cohort and 2/11 (18%) patients in the non-cervical cancer cohort. In the cervical cancer cohort, two patients experienced complete responses that are ongoing 53 and 67 months after treatment. Three patients experienced partial responses that were three months in duration. In the non-cervical cancer cohort, two responses were observed in a patient with anal cancer (four months duration) and a patient with oropharyngeal cancer (five months duration). The latter patient had previously been treated with six systemic anti-cancer agents. Multiple thoracic metastases responded completely after HPV-TIL infusion. A brain metastasis developed five months after treatment and was surgically resected. He is without evidence of disease 51 months after treatment.

Conclusions: HPV-TIL can mediate regression of metastatic HPV-associated cervical, oropharyngeal and anal epithelial cancers in some patients. These findings support the study of ACT for HPV-associated cancers and possibly other epithelial malignancies. Clinical trial information: NCT01585428.

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3006 Oral Abstract Session, Sat, 3:00 PM-6:00 PM
NKTR-214 (CD122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIWOT. First Author: Adi Diab, Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: PIWOT is an ongoing, open-label, phase 1/2 study of NKTR-214 (214; CD122-biased agonist) plus PD-1 inhibitor nivolumab (N) in patients (pts) with advanced cancers (MEL, RCC, NSCLC, TNBC, and UC). 214 monotherapy increases newly proliferative CD8+ T cells in tumors and increases cell surface PD-1 and PD-L1 expression, demonstrating a potentially synergistic mechanism with anti-PD-1 therapy. Methods: In P1 dose escalation, pts received 214 (0.003, 0.006 or 0.009 mg/kg) with N (240 mg or 360 mg) administered IV as outpatient Q2W or Q3W; in P2 expansion, the RP2D of 214 (0.006 mg/kg) with N (360 mg) Q3W was administered concurrently. Response was assessed Q8W by RECIST v1.1. Matched tumor samples were evaluated for changes from baseline in immune cell populations, gene expression, and T cell receptor repertoire. Tumor baseline and on treatment PD-L1 protein expression was assessed (28-8 IHC assay). Results: As of 7FEB2018, 162 pts (P1 = 38; P2, n = 124) were evaluable for safety. The most common TRAEs of all grades at the RP2D (> 25%) in pts were flu-like symptoms (63%), fatigue (39%), rash (38%) and pruritus (30%). G3+ TRAEs at the RP2D were 11%. No pts discontinued treatment due to TRAEs. A total of 60 IO-treatment naive stage IV pts (P1, n = 30; P2, n = 30) were efficacy evaluable (≥ 1 scan) (23 MEL, 24 RCC, 6 NSCLC, 4 UC, 3 TNBC). 22/30 P2 pts had only 1 scan. ORR (CR+PR) and DCR (CR+PR+SD) in 23 MEL (1L) pts was 52% and 78%. 18/23 MEL pts had known PD-L1 status. ORR was 5/9 (56%) for PD-L1(+) pts and 4/9 (44%) for PD-L1(-) pts. ORR and DCR in 24 RCC (1L) pts was 54% and 79%. 20/24 RCC pts had known PD-L1 status. ORR was 4/7 (57%) for PD-L1(+) pts and 7/13 (54%) for PD-L1(-) pts. ORR and DCR in 6 NSCLC (1L-2L) pts was 5/6 and 67%. 3/5 pts had known PD-L1 status. ORR was 3/5 (60%) in PD-L1(+) pts. ORR and DCR in 4 UC (1L) was 75% and 100%. ORR/DCR in 3 TNBC (1-2L) pts was 33%. In 60 evaluable pts, 32/32 responses are ongoing (0.3+ to 12.0+ mos) with 45/60 pts still on treatment. Conclusions: 214 plus N was well-tolerated with no new safety signals. Preliminary data is encouraging ORR and DCR responses observed in 5 of 5 tumor types in IO-treatment naive 1-2L pts. Updated data to be presented. Clinical trial information: NCT02983045.

3007 Oral Abstract Session, Sat, 3:00 PM-6:00 PM
Safety and activity of M7824, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with HPV-associated cancers. First Author: Julius Strauss, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Therapies targeting PD-L1/L1 have produced response rates of 15-20% in patients (pts) with HPV associated cancers (HAC) including cervical (cerv), anal or head and neck squamous cell carcinoma (HNSSC). Another potential target for these diseases is transforming growth factor-β (TGF-β) as genome wide association studies in HPV+ cancers have shown TGF-β to be significantly overexpressed. M7824 is a bifunctional fusion protein targeting PD-L1 and TGF-β comprised of a human IgG1 monoclonal antibody against PD-L1 fused to 2 extracellular domains of TGF-β receptor II, which functions as a TGF-β “trap”. We report data from pts with HAC on a fully dose escalated escalation portion of a phase 1 trial of M7824.

Methods: NCT02517398 is a phase I, 3+3-dose-escalation study. Pts received M7824 at 1, 3, 10, 20, or 30 mg/kg Q2W until PD or unacceptable toxicity. The primary objective was safety and maximum tolerated dose (MTD). A key secondary objective was best overall response per RECIST v1.1. Results: As of Feb 5, 2018, 16 pts with HAC (9 cerv, 4 anal and 3 HNSSC) were enrolled. HPV was confirmed in 23 MEL (1L) pts was 52% and 78%. 18/23 MEL pts had known PD-L1 status. ORR was 5/9 (56%) for PD-L1(+) pts and 4/9 (44%) for PD-L1(-) pts. ORR and DCR in 24 RCC (1L) pts was 54% and 79%. 20/24 RCC pts had known PD-L1 status. ORR was 4/7 (57%) for PD-L1(+) pts and 7/13 (54%) for PD-L1(-) pts. ORR and DCR in 6 NSCLC (1L-2L) pts was 5/6 and 67%. 3/5 pts had known PD-L1 status. ORR was 3/5 (60%) in PD-L1(+) pts. ORR and DCR in 4 UC (1L) was 75% and 100%. ORR/DCR in 3 TNBC (1-2L) pts was 33%. In 60 evaluable pts, 32/32 responses are ongoing (0.3+ to 12.0+ mos) with 45/60 pts still on treatment. Conclusions: 214 plus N was well-tolerated with no new safety signals. Preliminary data is encouraging ORR and DCR responses observed in 5 of 5 tumor types in IO-treatment naive 1-2L pts. Updated data to be presented. Clinical trial information: NCT02992743.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: ALT-803, an IL-15 superagonist, in combination with nivolumab in metastatic non-small cell lung cancer (NSCLC) patients and acquired resistance will lead to treatment failure in most responders. Cytokine therapy with IL-2/IL-15Rβ agonists has demonstrated durable responses in select solid tumors, though the response rates are low. There have been no published reports of combination trials of IL-2/IL-15Rβ agonists with anti-PD-1 immunotherapy. Methods: In this phase Ib/II trial NSCLC patients received anti-PD1 immunotherapy in combination with ALT-803, an IL-15 super-agonist. Eligibility criteria include measurable disease, no history of auto-immune disease, and ECOG performance status of 0 or 1. Nivolumab was administered IV every 14 days and ALT-803 was administered subcutaneously weekly for six months. The primary objective of the phase Ib study was to define safety, tolerability and to define a recommended phase II dose (RP2D) of ALT-803 in combination with nivolumab. Phase II enrollment is ongoing. Results: As of February 13, 2018, 38 subjects have been enrolled to trial. No dose-limiting toxicities have been observed. Common adverse events are injection site reactions and flu-like symptoms. The RP2D of ALT-803 is weekly subcutaneous 20 mcg/kg in combination with intravenous nivolumab 240mg every two weeks. The most common grade 3 adverse event, occurring in two patients each, was lymphocytopenia and fatigue. One patient had a confirmed partial response and 11 patients had stable disease lasting >6 months. The disease control rate was 91% (10 of 11) patients, with 27% (3 patients) partial responses or 5 toxicity was observed. Among patients in the phase Ib experience who had PD1 immunotherapy relapsed or refractory tumors, the disease control rate was 91% (10 of 11) patients, with 27% (3 patients) partial responses and 64% (7 patients) stable disease noted. Among 10 patients with PD-L1 negative tumors, the disease control rate was 70% with 30% partial response rate. Conclusions: The combination of nivolumab with ALT-803 can be safely administered in an outpatient setting. There is encouraging anti-tumor activity with the combination of nivolumab with ALT-803. Phase II study of the combination is ongoing. Clinical trial information: NCT02523469.

3008 Oral Abstract Session, Sat, 3:00 PM-6:00 PM
ALT-803, an IL-15 superagonist, in combination with nivolumab in metastatic non-small cell lung cancer: ongoing experience and biomarker development from a non-randomized, open-label, phase Ib/II trial.
First Author: John M. Wrangle, Johns Hopkins Univ School of Medcn, Baltimore, MD

Background: PD-1/PD-L1 blockade fails to yield a response in about 80% of untreated non-small cell lung cancer (NSCLC) patients and acquired resistance will lead to treatment failure in most responders. Cytokine therapy with IL-2/IL-15Rβ agonists has demonstrated durable responses in select solid tumors, though the response rates are low. There have been no published reports of combination trials of IL-2/IL-15Rβ agonists with anti-PD-1 immunotherapy. Methods: In this phase Ib/II trial NSCLC patients received anti-PD1 immunotherapy in combination with ALT-803, an IL-15 super-agonist. Eligibility criteria include measurable disease, no history of auto-immune disease, and ECOG performance status of 0 or 1. Nivolumab was administered IV every 14 days and ALT-803 was administered subcutaneously weekly for six months. The primary objective of the phase Ib study was to define safety, tolerability and to define a recommended phase II dose (RP2D) of ALT-803 in combination with nivolumab. Phase II enrollment is ongoing. Results: As of February 13, 2018, 38 subjects have been enrolled to trial. No dose-limiting toxicities have been observed. Common adverse events are injection site reactions and flu-like symptoms. The RP2D of ALT-803 is weekly subcutaneous 20 mcg/kg in combination with intravenous nivolumab 240mg every two weeks. The most common grade 3 adverse event, occurring in two patients each, was lymphocytopenia and fatigue. One patient had a confirmed partial response and 11 patients had stable disease lasting >6 months. The disease control rate was 91% (10 of 11) patients, with 27% (3 patients) partial responses or 5 toxicity was observed. Among patients in the phase Ib experience who had PD1 immunotherapy relapsed or refractory tumors, the disease control rate was 91% (10 of 11) patients, with 27% (3 patients) partial responses and 64% (7 patients) stable disease noted. Among 10 patients with PD-L1 negative tumors, the disease control rate was 70% with 30% partial response rate. Conclusions: The combination of nivolumab with ALT-803 can be safely administered in an outpatient setting. There is encouraging anti-tumor activity with the combination of nivolumab with ALT-803. Phase II study of the combination is ongoing. Clinical trial information: NCT02523469.

3009 Poster Discussion Session; Displayed in Poster Session (Board #223), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM
Cardiovascular adverse events in immune checkpoint inhibitor clinical trials: A U.S. Food and Drug Administration pooled analysis.
First Author: Laileh Amini-Kordestani, U.S. Food and Drug Administration, Bethesda, MD

Background: Immune checkpoint inhibitors (ICI) have been approved for numerous cancers and have transformed patient outcomes. There is a growing recognition of immune-related adverse events (AE), including cardiovascular (CV) AE. While rare cases of fulminant myocarditis have been reported, the full extent of CV AE remains unknown. Methods: This exploratory observational study pooled data from prospective ICI trials submitted to FDA in initial or supplemental Biologics License Applications until 1/2018. To systematically categorize CV AE, we combined CV MedDRA Preferred terms with a focus on the underlying pathology. Descriptive statistics were used to characterize the incidence of CV AE by exposure to ICI and calculate relative risks (RR) between arms of interest. To account for bias with respect to duration of exposure, we based our analyses on the first 6-month treatment window. Results: Within 59 trials (N = 21,664), ICI therapy was associated with higher rates of myocarditis, vasculitis, ischemia, arrhythmia, and pericardial disease compared to non-ICI therapy. When ICI were used in combination, CV AE increased across most categories compared to monotherapy. Five fatal cases of myocarditis were reported with ICI therapy. Conclusions: To our knowledge, this is the largest report of CV AE associated with ICI in clinical trials. Our results show that combination ICI therapy appears to be associated with an increase in incidence of CV AE relative to ICI monotherapy.

Vascular/PVD

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*not available due to 0 events in the Non-ICI group

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Background: LAG525 and spartalizumab (PDR001), humanized IgG4 mAbs, block binding of LAG-3 to MHC class I and PD-1 to PD-L1 and PD-L2, respectively. Preclinical studies show synergistic anti-tumor activity when blocking PD-1 and LAG-3. Here, we report dose escalation results from a Phase I/II study of LAG525 + spartalizumab in advanced malignant diseases. (NCT02460224). Methods: LAG525 was dosed Q2W (1–15 mg/kg, or 240/400 mg) or Q4W (3–10 mg/kg, or 400 mg); LAG525 + spartalizumab was dosed at 15 dose levels/schedules from 0.3 mg/kg LAG525 + 1 mg/kg spartalizumab Q2W to 1000 mg LAG525 + 400 mg spartalizumab Q4W. Phase I endpoints (dose-limiting toxicities (DLTs), additional safety, pharmacokinetics, efficacy, and biomarkers) were used along with an adaptive Bayesian logistic regression model guided by escalation with overdose control to support future study dosing. Baseline and on-treatment tumor samples were collected. Results: As of 31 Jul 2017, 115/119 pts (97%) receiving LAG525 and 99/121 pts (82%) receiving LAG525 + spartalizumab had discontinued treatment, primarily due to progressive disease (79% and 67%, respectively). DLTs occurred in 4 pts in each arm (LAG525 arm: Gr 3 intra-abdominal fluid collection, lipase increase, vomiting, Gr 4 acute kidney injury. Combination arm: Gr 3 hyperglycemia, pneumonitis, brain tumor edema, fatigue; Gr 4 intratumoral hemorrhage, autonomic nervous system dysfunction). Common (≥10%) related AEs were fatigue (10%) for LAG525 alone and fatigue (18%), diarrhea (15%), and nausea (12%) for the combination. Gr 3–4 related AEs were reported in 10 pts (8%) in the LAG525 arm and 10 pts (8%) in the combination arm. Approximately dose-proportional increases in LAG525 exposure were observed. LAG525 exposure was increased with spartalizumab, and titred for either arm. LAG525 + spartalizumab led to durable RECIST responses (11 PR, 1 CR) in a variety of solid tumors, including mesothelioma (2/8 pts) and triple-negative breast cancer (TNBC; 2/9 pts). In TNBC tumor biopsies, a trend in conversion of immune-cold to immune-activated biomarker profiles was observed with on-treatment tumor biopsies. Conclusion: Preliminary anti-tumor activity and immune profile modulation observed for LAG525 + spartalizumab. Phase II is ongoing in selected indications. Clinical trial information: NCT02460224.

Phase Ib/II study of lacnotuzumab (MCS110) combined with spartalizumab (PDR001) in patients (pts) with advanced malignancies. First Author: Aitana Calvo, Hospital General Universitario Gregorio Marañon, Madrid, Spain

Background: Tumor-associated macrophages mediate intrinsic/acquired resistance to programmed death-1 (PD-1) inhibitors; these cells can be reduced by inhibiting the colony-stimulating-factor-1 (CSF-1)/receptor pathway. Targeting CSF-1R with a monoclonal antibody (mAb) that developed a multivariate risk prediction model called the iSEND in a cohort as well as in aNSCLC pts treated with effective myeloid modulating agents. Treatment with IPI-549, a tumor macrophage-targeting agent, combined with nivolumab in advanced solid tumors. First Author: Ryan J. Sullivan, Massachusetts General Hospital, Boston, MA

Background: IPI-549 is a potential first-in-class, oral, selective PI3K-gamma inhibitor that in preclinical studies reprograms macrophages from an immune-suppressive to an immune-activating phenotype and can overcome resistance to checkpoint inhibitors. Methods: Ph 1b study IPI-549-01 (NCT02637531) is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunomodulatory activity of IPI-549 to determine its recommended Ph 2 dose (RP2D) and preliminary efficacy, as monotherapy and combined with nivolumab (nivo), in advanced solid tumors. Pre- and on-treatment blood samples were obtained for flow cytometry, gene expression, and serum analysis. Results: Initial combination dose-escalation results are reported. 31 pts (30 evaluable), median age 57 yrs and median 4 prior therapies (8 with prior anti-PD-1/L1 therapy), received IPI-549 20, 30, and 40 mg QD + nivo 240 mg Q2W in a 6+6 design. IPI-549 PK/PD were unaffected by nivo. The MTD was not reached. Most treatment-emergent adverse events (TEAEs) were Gr 1-2. The most common (≥2 pts) treatment-related TEAEs included rash (23%); pruritus (10%); and nausea, ALT increase, AST increase, and pyrexia (6% each), with no treatment-related deaths. 2 DLTs each occurred at IPI-549 30 mg (Gr 3 rash) and 40 mg QD (Gr 3 rash; Gr 3 AL/T AST increase). 2 pts demonstrated partial responses at 48 weeks (8 weeks from last dose), compared to 1 with melanoma and 1 with microsatellite-stable gallbladder carcinoma receiving IPI-549 30 and 40 mg QD, respectively. 40% of pts (n = 12) remained on study ≥12 weeks and 6 pts were ongoing at the O5 Feb data cutoff. Based on safety + PK/PD data, the RP2D was IPI-549 40 mg QD + nivo 240 mg Q2W. Clinical trials with IPI-549 showed evidence of immune modulation, including reduced immune suppression, including upregulation of IFN-g-responsive factors, such as PD-L1 and CXCL9/10, and dose-dependent re-activation/re-invigoration of exhausted PD1+CD8+CD45RA- T cells, evidenced by Ki67 increases. Conclusions: IPI-549 + nivo demonstrates favorable tolerability, early signs of clinical activity, and evidence of immune modulation. Combination expansion cohorts are enroling at the RP2D. Clinical trial information: NCT02637531.

Predicting outcomes of advanced non-small cell lung cancer patients treated with PD-1/PDL-1 inhibitors: Independent international validation of the iSEND model. First Author: Wungki Park, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Background: There is an unmet need for affordable and readily available biomarkers to predict outcomes to PD-1/PD-L1 inhibitors (PD-L1i). In a multinational prospective cohort study, we previously developed a multivariate risk prediction model called the iSEND in a cohort of 159 patients with nivolumab or pembrolizumab (nivolumab + pembrolizumab) in aNSCLC pts. We now validate this model in an independent international cohort confirming that it predicts outcomes of patients treated with PD-1/PD-L1i in the United States, France and Japan who received 2L+ PD-L1i. The outcomes for the iSEND Good, Intermediate, and Poor groups were compared. The performance was assessed using receiver operating characteristic (ROC) curves. Results: The median follow-up was 15.2 months (M) (95% Confidence Interval [CI]: 12.4-17.9). The median OS for iSEND Good, Intermediate, and Poor was 15.9 M (CI: 2.8-29.0), 12.4 M (CI: 9.6-15.1), and 4.0 M (CI: 3.0-5.0), respectively. The log-rank test was significant (p < 0.001). The median Progression Free Survival (PFS) was 2.6 M (CI: 2.0-3.1), 2.9 M (CI: 1.6-4.2), and 1.6 M (CI: 1.3-1.8), respectively. (Log-rank: p = 0.002) Time-dependent area under curves (AUC) of the iSEND model for OS at 6, 12, 18, 24, and 36 M were 0.63 (CI: 0.56-0.70), 0.50 (CI: 0.45-0.55), 0.50 (CI: 0.45-0.55), 0.50 (CI: 0.45-0.55), and 0.50 (CI: 0.45-0.55), respectively. The iSEND Good group had significant correlation with progressive disease compared to the iSEND Good group (HR: 2.7, CI: 1.2-6.1, p = 0.013). Conclusions: This study validates the iSEND model in an independent international cohort confirming that it predicts outcomes of patients treated with PD-L1i. Exploratory analyses of the iSEND Poor cohort as well as in anNSCLC pts treated with effective myeloid modulating combination strategy is strongly supported and underway.
Background: The aim was to develop a radiomic estimator of tumor infiltrating CD8 T-cells, to assess its association with tumor immune phenotype, and to evaluate outcomes of cancer patients enrolled in phase 1 trials of anti-PD-1/PD-L1 monotherapy. Methods: A radiomic signature of the expression of CD8 T-cells was trained using elastic-net method. Three independent cohorts were used for validation: (I) 119 patients from The Cancer Genome Atlas (TCGA) to validate the association with gene expression, (II) 100 tumors assumed as either immune-inflamed or immune-desert to analyze the association with the immune-phenotype, (III) 137 patients treated with anti-PD-1/PD-L1 monotherapy in phase 1 trials to assess clinical outcome. Clinical responses were defined according to RECIST1.1. Median value of the radiomic score was used to separate patients into two groups to assess the overall survival (OS). Results: The final radiomic signature kept eight features from the 83 initial ones, and was associated with the gene expression signature of CD8 T-cells in the TCGA validation set (AUC = 0.67, P = 0.002), and the infiltrated tumors in the assumed immune phenotype cohort (AUC = 0.76, P = 0.001). In the cohort of patients treated with immunotherapy, the radiomic score at baseline was higher in patients with objective response (CR + PR) or a controlled disease (SD + CR + PR) at 3 months (P = 0.049 and P = 0.050 respectively) and at 6 months (P = 0.025 and P = 0.013 respectively). OS was higher in patients with a high radiomic score. Conclusion: Radiomic score of CD8 T-cells was validated in three independent cohorts. It appears promising in estimating tumor immune phenotype and inferring outcomes of patients treated with anti-PD-1/PD-L1 in a non-invasive way.
Background: Colony stimulating factor 1 receptor (CSF-1R) signaling supports port recruitment, development, and maintenance of immune suppressive macrophages within the tumor. Combining anti-CSF-1R with anti–PD-L1 showed enhanced efficacy in preclinical models. Cabira, a humanized IgG4 monoclonal antibody, disrupts CSF-1R binding to ligands CSF-1 and IL-34, thus blocking receptor activation. We report immunohistochemistry (IHC) and transcriptomic evidence of on-target PD-C effects of cabira + NIVO in treated pts, as well as the first insight into genotypic characteristics of pancreatic tumors exhibiting a durable PR to PD-L1 + IHC (Wang et al. J Immunother Cancer 2017:5(suppl 2) (abst O24)). Methods: PD activity of cabira + NIVO in pts with advanced tumors treated in a phase 1b trial (NCT02526017) was evaluated using peripheral and tumor biomarkers. Results: Cabira + NIVO induced increases in serum CSF-1 and decreases in peripheral and tumor biopsy markers compared to baseline. DMR was determined as having at least one MMR protein expressed at 6%. There was no statistically significant correlation between PD-L1 expression and the presence or absence of dMMR as detected by IHC, consistent with the number of microsatellite instability tumor identified. Responses were observed across metastatic tumor types. Of note, in the 4 PRs observed in pts with pancreatic cancer, all were microsatellite stable (MSS) and low TMB. Conclusions: Orthogonal IHC and transcriptome-wide analyses demonstrated cabira-mediated CSF-1R blockade in the periphery and tumor microenvironment in pts with advanced cancer. Ongoing analyses include identification of transcriptomic signatures associated with response. This data support further clinical development of cabira + NIVO in multiple indications, including MSS pancreatic cancer (NCT0336216). Clinical trial information: NCT02526017.

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Abstract Background: Selecting appropriate biomarkers for immune checkpoint blockade (ICB) remains a clinical challenge. Quantitative biomarkers, for instance, PD-L1 expression or tumor mutation burden, are limited by their vague cut-off value, intra-tumor heterogeneity distribution and dynamic alterations. Qualitative biomarkers, including dMMR/MSI-H, are potent predictors, but merely a minority of patients harbor this abnormality. Therefore, a more prevalent biomarker would be highly desirable. In humans, DNA damage response (DDR) system is indispensable in maintaining genomic integrity. We hypothesize genetic mutations of DDR pathways may increase genomic instability and manifest as up-regulated neoantigen load and TMB, contributing to higher susceptibility to immune checkpoint blockade (ICBs).

Methods: Whole-exome sequencing data from 8552 solid tumors, across 29 cancer types from The Cancer Genome Atlas were included for analysis. The expression signatures of immune genes were compared across distinct DDR subgroups. Statistics concerning the correlation between DDR pathway mutations and treatment outcomes were evaluated in four cohorts treated with ICBs. Results: Mutations of HRR-MMR or HRR-BER pathways (defined as co-mut +) were correlated with higher neoantigen load and TMB. Co-mut + exhibited outcomes were evaluated in four cohorts treated with ICBs. Results: Co-mutations of HRR-MMR or HRR-BER pathways (defined as co-mut +) were correlated with higher neoantigen load and TMB. Co-mut + exhibited outcomes were evaluated in four cohorts treated with ICBs.

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Background: MK-1248 is a humanized IgG4 agonist monoclonal antibody (mAb) that targets GITR. GITR is expressed on regulatory T cells (Treg), resting CD4+ and CD8+ T cells, NK (natural killer) cells and NK T cells. Ligation of GITR decreases Treg-mediated suppression and enhances T cell proliferation, effector functions, and survival. Methods: MK-1248 was tested alone or in combination with pembrolizumab at a starting dose of 0.12 mg in both arms. Pembrolizumab dose was fixed at 200 mg. Both study drugs were administered intravenously every 3 weeks. Total number of intended doses of MK-1248 and pembrolizumab was 4 and 35, respectively. The study objective was to determine safety and tolerability, maximum tolerated dose (MTD), pharmacokinetic (PK), and pharmacodynamic (PD) profiles of MK-1248 as a monotherapy and in combination with pembrolizumab. Results: Data were available from 37 pts: 20 pts treated with MK-1248 monotherapy and 17 pts treated with MK-1248 + pembrolizumab combination therapy. Tumor types: colorectal cancer (8 pts), melanoma (5 pts), renal cell carcinoma (4 pts) and 20 pts with 16 other solid tumors. Maximum dose of MK-1248 tested: 170 mg (monotherapy) and 60 mg (combination). MK-1248 was well tolerated. Of the 37 pts treated, 36 pts (97.3%) had ≥1 adverse event (AE) and 17 pts (46.8%) had ≥1 treatment-related AE. Common AEs were: vomiting, anemia, decreased appetite, abdominal pain, cough, diarrhea, nausea, fatigue, headache and pyrexia. Infusion related reactions occurred in 6 (16.2%) pts who had grade 3 or 4 AEs (5, 81.1%) who were treatment-related. Serious adverse events (SAE) occurred in 6 pts (30.0%) in monotherapy arm and 5 pts (29.4%) in combination arm. No DLT or treatment-related deaths were observed. One CR and 2 PR were observed in the study. Conclusions: MK-1248 at the dose up to 170 mg as monotherapy and 60 mg in combination with pembrolizumab was well tolerated with no dose limiting toxicities or treatment-related deaths. Responses were observed when MK-1248 was administered in combination with pembrolizumab. Clinical trial information: NCT02553499.

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Pilot trial of an Indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor plus a multipeptide melanoma vaccine in patients with advanced melanoma. First Author: Craig L. Slingluff, University of Virginia School of Medicine, Charlottesville, VA

Background: Melanoma metastases limit infiltration and function of anti-tumor T cells in part by immunosuppression with IDO1. INCB024360 (epacadostat) is an IDO1 inhibitor that normalizes serum kynurenine/tryptophan (Kyn/Trypt) ratios. METL12.1 multipeptide vaccine induces CD8 T cell responses to melanoma antigens. A clinical trial was designed to test hypotheses that IDO1 inhibition (IDO1i) plus vaccination will result in high IDO1i will increase CD8 T cell infiltration into metastases and will enhance immune signatures in tumor, which will be further increased by the vaccine.

Methods: Patients (pts) with stage IIIb-IV melanoma were treated with INCB024360 days(d) 1-98 (300 mg po bid), and with METL12.1 emulsified in incomplete Freund’s adjuvant d21, 28, 35, 56, 77, 98. Prior checkpoint blockade therapy was allowed. Tumors were biopsied pre-treatment, d21, and d42, when feasible. Safety was assessed by CTCAE v4. The primary immunologic endpoint was tumor infiltration with CD8+ T cells. The biologic effect of INCB024360 on IDO1 function was assessed by serum Kyn/Trypt ratio. Clinical outcomes were assessed by RECIST 1.1, eligible pts were enrolled and treated. There were dose-limiting toxicities (DLTs) in 2 pts: grade 3 transaminase elevation, grade 3 syncope, both of which resolved. Six pts had all evident sites of disease resected in protocol biopsies and 1 had non-measurable disease. Of 4 pts with measurable disease beyond d42, best overall responses were PR (1), SD (3). INCB024360 reduced serum Kyn/Trypt ratios 44% (mean) by d21 (normalized in 10/11 pts). In 5 pts with evaluable biopsies d0 and d42, with multispectral immunofluorescence histology, CD8 T cell infiltration increased significantly to d42.

Conclusions: Combination therapy with INCB024360 and multipeptide vaccine was considered safe with transient DLTs in only 2 patients (18%). INCB024360 normalized serum Kyn/Trypt ratios in 91% of patients at 300 mg bid. Clinical activity was observed. There is evidence of enhanced CD8 T cell infiltration with the combination. Ongoing studies will assess the impact of INCB024360 on immune signatures and tumor infiltrating T cell function. Clinical trial information: NCT01961115.

Background: Previous studies have suggested the importance of dNLR and LDH as prognostic markers and indicators of inflammation in cancer and other inflammatory diseases. More recently, the lung immune prognostic index (LIPI), the combination of dNLR and LDH, was found to be associated with progression free survival (PFS) and overall survival (OS) in pts with NSCLC treated with ICi but not CCT suggesting its potential use as a predictive marker. We performed an exploratory retrospective analysis of LIPI on pooled clinical data from studies evaluating ICi in 2nd line nMSCC submitted to the FDA.

Methods: We identified 5 randomized, second line trials (N = 3399) evaluating ICi versus dacetaxel submitted to FDA between 2014-2017 for mNSCLC. Only pts with available dNLR/LDH data were included (71.8%). LIPI scores were calculated based on dNLR and LDH values per Mezquita et al. (JAMA Oncol. 2018). Univariate and multivariate analyses for PFS were performed.

Results: In the final analysis, 3638 ICI and 1072 CCT were evaluable for low (0), intermediate (1), and high (2) LIPI (TABLE). Conclusions: This exploratory retrospective analysis indicates that LIPI may be a prognostic biomarker for both ICI and CCT for 2nd line nMSCC.

#Poster Session (Board #249), Mon, 8:00 AM-11:30 AM

Exploration of baseline derived neutrophil to lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) in patients (pts) with metastatic melanoma treated with immune checkpoint inhibition (ICI) or cytokotox therapy (CCT). First Author: Dickran Garo Kazandjian, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Patients with melanoma are increasingly treated with immune checkpoint inhibitors (ICI) and cytokotoxic agents (CCT) and the proper selection of patients is of utmost importance. We aimed to explore the associations of baseline neutrophil to lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) with overall survival (OS) and progression free survival (PFS) in melanoma patients. dNLR and LDH are both used as inflammatory biomarkers and are often associated with prognosis and response to treatment. We aimed to determine the association of dNLR and LDH with clinical outcomes in melanoma patients treated with ICI or CCT. We performed a retrospective analysis of available dNLR/LDH data from 3638 ICI and 1072 CCT patients treated with ICI or CCT for 2nd line nMSCC.

Methods: We performed an exploratory retrospective analysis of LIPI on pooled clinical data from studies evaluating ICi in 2nd line nMSCC submitted to the FDA.

Results: In the final analysis, 3638 ICI and 1072 CCT were evaluable for low (0), intermediate (1), and high (2) LIPI (TABLE). Conclusions: This exploratory retrospective analysis indicates that LIPI may be a prognostic biomarker for both ICI and CCT for 2nd line nMSCC.

Background: Immune checkpoint inhibitors have improved survival in multiple malignancies, but genomic biomarkers for efficacy in microsatellite stable tumors are incompletely characterized. Methods: Tumor and germline whole exome sequencing (WES) from pre-treatment tumors in immune checkpoint-treated patients were assembled from 7 published studies and from 78 newly sequenced tumors (total n = 249). Tumor types included were melanoma (n = 151), non-small cell lung cancer (n = 57), bladder cancer (n = 27), head and neck cancer (n = 12), sarcoma (n = 1), and anal cancer (n = 1). The sequencing data were processed through a uniform pipeline, and the results were correlated with clinical outcomes to immune checkpoint therapy to identify tumor genomic features that contribute to response. RECIST (v1.1) was used to define responders as those with complete or partial response, and those with progressive disease as non-responders. Results: Although tumor mutational burden was correlated with response, its univariate predictive power in this cohort was low (AUC = 0.66). Further analyses identified additional correlates of response, including individual driver genes in kinase signaling and chromatin regulators, global mutational signatures, and specific HLA-restricted neoantigens. Copy number analysis corroborated associations between specific pathways and absence of response to immunotherapy, including increased copy number events in the interferon-γ pathway in nonresponders (19/123 vs 3/70, p = 0.034). However, many of these molecular features were interrelated and potentially confounded with one-another. Power simulations showed that significantly larger sample sizes are necessary to disentangle these features, highlighting the complexity of identifying genetic driver events that generate an immunoresponsive tumor environment. Conclusions: This study represents the largest analyses to date of SCSOs obtained from fresh tumors in patients treated with immune checkpoint inhibitors. This work defines a path for gathering insights from multiple cohorts, and advances hypotheses of biological mechanisms and biomarkers of response to immune checkpoint therapy for further study.
**3038 Poster Session (Board #252), Mon, 8:00 AM-11:30 AM**

Demonstration of anti-tumor immunity via intratumoral regulated platform ad-RTS-hIL-12 in advanced breast cancer and recurrent glioblastoma patients.

**Background:** Ad-RTS-hIL-12 (Ad) is a novel gene therapy candidate expressing IL-12 under the control of an orally administered activator ligand, veledimer (V), through a proprietary RheoSwitch Therapeutic System (RTS) gene switch. This platform reduces systemic toxicity and stimulates anti-tumor T cell immune response.

**Methods:** Two open label trials evaluated the tolerability of local inducible IL-12 expression in heavily pretreated patients with metastatic breast cancer (mBC) or recurrent glioblastoma (rGBM). Ad was administered as a single intratumoral injection with V 80 mg in mBC and 10-40 mg Qdx15 PO in rGBM. Results: We observed local expression of IL-12 and downstream IFNγ demonstrating biological activity with a mean increase in tumor cytotoxic T cells (CD3+CD8+)* baseline: 0.4 ± 0.2 to biopsy: 1.9 ± 0.8% cells with a mean reduction in Treg CD4+ FoxP3* baseline: 0.8 ± 0.4 to biopsy: 0.6 ± 0.3% cells. Sustained increases in tumor IFNγ were detected in both mBC (by biopsy at Day 42 post injection) and rGBM (biopsy range: 130-175 days post injection) while tumor IL-12 returned to baseline and systemic levels of IFNγ and IL-12 were undetectable. In mBC, injected and non-injected lesions (abscopal effect) turning cold tumors hot, with a good safety profile. This platform warrants further evaluation in multiple tumor types in mono- and in combination with immune checkpoint inhibitors. Clinical trial information: NCT02026271; NCT02423902.

**3039 Poster Session (Board #253), Mon, 8:00 AM-11:30 AM**

Outcomes by prior lines of therapy (LoT) in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cell) in patients (Pts) with refractory large B cell lymphoma.

**Background:** In ZUMA-1 (NCT02348216), axi-cell, an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, demonstrated significant benefit in patients (Pts) with refractory large B cell lymphoma with an objective response rate (ORR) of 82% (complete response (CR) 58%: Neelapu & Locke et al. NEJM. 2017). These results supported the recent approval of axi-cell by the US FDA for the treatment of adult pts with relapsed or refractory large B cell lymphoma after ≥ 2 prior lines of systemic therapy. Here, we assessed outcomes of axi-cell by prior lines of therapy (LoT) in pts from Phases 1 and 2 of ZUMA-1. Methods: Pts with refractory large B cell lymphoma were leukapheresed and received ≥ 2 × 10^6 CAR T cells/kg after low-dose conditioning (Neelapu & Locke et al. NEJM. 2017). Pts were evaluated by number of prior LoT 2 – 3 vs 4. Autologous stem cell transplant (ASCT) was considered a prior LoT. Results: As of 11/1/17, median follow-up was 15.4 mo for the 108 pts treated with axi-cell. Sixty-two (57%) pts had ≥2 prior LoT and 43 (40%) had ≥3 prior LoT. 9 pts with 3 prior LoT and 4 (40%) had ≥4 prior LoT. Median ages of 60 and 55 y, 65% and 47% of pts had EOCG performance status 0, and 84% and 42% of pts had ASCT. ORRs were 94% and 67% for pts with 2 – 3 and ≥ 4 prior LoT, respectively, with CR rates of 65% and 53%, 44% and 42% of pts had ongoing responses (as of the data cutoff (Table). Overall survival (OS) at 12 mo was 65% and 51% for pts with 2 – 3 and ≥ 4 prior LoT, respectively. Grade ≥3 treatment-emergent adverse events were reported for nearly all (100% and 93%) pts with 2 – 3 and ≥ 4 LoT, with similar rates of Grade ≥3 cytokine release syndrome (11% and 12%) and neurologic events (32% and 30%). There were 1 and 3 Grade 5 AE’s unrelated to disease progression in the 2 – 3 and ≥ 4 LoT groups, respectively. Conclusions: Axi-cell demonstrated long-term clinical benefit for pts with refractory large B cell lymphoma regardless of the number of prior LoT. Drs Locke and Neelapu contributed equally. Clinical trial information: NCT02348216.

**3040 Poster Session (Board #254), Mon, 8:00 AM-11:30 AM**

First-in-human study of HKK2455, a long-acting, potent and selective indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, in combination with moga-CLON (Mgcl), an anti-CCR4 monoclonal antibody, in patients (pts) with advanced solid tumors.

**Background:** IDO-1 inhibitors have shown antitumor activity in combination with immunotherapeutic agents in multiple cancers. HKK2455 is a novel and selective oral IDO-1 inhibitor. Unlike other inhibitors, HKK2455 inhibits IDO-1 apoenzyme, with long-lasting and potent activity. Moga is a monoclonal antibody with enhanced ADCD activity that has shown synergy with HKK2455 in preclinical models. Methods: Pts with advanced solid tumors received escalating doses of HKK2455 alone (0.3, 1, and 10 mg once daily) for 4 weeks (Cycle 0), followed by combination with 1 mg/kg weekly of IV Moga for 4 weeks (Cycle 1) and then on Days 1 and 15 (from Cycle 2) in a standard 3+3 Phase I design. Dose escalation was based on safety, tolerability, pharmacokinetics and IDO activity (kynurenine [Kyn] and tryptophan [Trp] levels and ex vivo Kyn production). Results: 21 pts were enrolled in cohorts that received HKK2455 at 0.3, 1, and 10 mg dose levels. No DLTs were observed. The most frequent adverse events (≥5%) included maculopapular rash,rash, dysphagia, thrombotic event, and tachycardia, none of which were considered related to HKK2455. One case of rash (Gr 3) was considered related to Moga but not a DLT. Plasma HKK2455 concentrations reached steady state by Day 8 (Cycle 0) and increased dose-dependently. Potent dose-dependent inhibition of IDO activity was demonstrated in plasma samples (67% and 66% inhibition in Kyn concentrations and Kyn:Trp ratio, respectively, compared to baseline) and ex vivo stimulation assays (> 95% inhibition in Kyn production) at 10 mg HKK2455, confirming target modulation. Four patients (n = 3 head and neck; n = 1 ovarian) from all dosing groups have achieved durable RECIST disease stabilization for more than 6 months, and one (salivary gland carcinoma) for more than 14 months. Conclusions: HKK2455 in combination with Moga is safe and well tolerated at all doses tested, suppresses Kyn production in a dose-dependent and sustained manner, and demonstrates early signals of antitumor activity. These data support the continued development of this promising combination. Clinical trial information: NCT02867007.

**3041 Poster Session (Board #255), Mon, 8:00 AM-11:30 AM**

Which is better in CD19 CAR-T treatment of r/r B-ALL, CD28 or 4-1BB? A parallel trial under the same manufacturing process. First Author: Peihua Lu, Hebei Yanda Lu Daopei Hospital, Langfang, China

**Background:** Second-generation CARs have been shown to improve the overall functional activity and persistence of CAR-T cells. KYMRIAH and YESCARTA used 4-1BB and CD28 co-stimulatory signaling domains, respectively. Methods: A parallel trial under the same manufacturing process to compare the CD28 and 4-1BB CD19 CAR-T. Results: This study enrolled 47 relapsed or refractory r/r B-ALL patients. 23 patients were leukapheresed and received 2 × 10^6 CAR T cells/kg in 3 treatment- LoT, with similar rates of Grade ≥ 3 cytokine release syndrome (11% and 12%) and neurologic events (32% and 30%). There were 1 and 3 Grade 5 AE’s unrelated to disease progression in the 2 – 3 and ≥ 4 LoT groups, respectively. Conclusions: Axi-cell demonstrated long-term clinical benefit for pts with refractory large B cell lymphoma regardless of the number of prior LoT. Drs Locke and Neelapu contributed equally. Clinical trial information: NCT02348216.

**3044 Poster Session (Board #256), Mon, 8:00 AM-11:30 AM**

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Ex vivo expanded multi-antigen-specific lymphocytes for the treatment of solid tumors. *First Author: Amy Houghtlin, Children’s National Medical Center, Washington, DC*

**Background:** Patients with solid tumors refractory to standard therapies have poor prognoses, and most salvage therapies are toxic and ineffective. Antigen-specific T cell therapies offer a promising alternative for targeted therapy with the ability to target multiple antigens in a single product. Hence, we hypothesize that patient-derived tumor-associated antigen-specific T cells (TAA-T) targeting WT1, PRAME, and survivin expressed by pediatric solid tumors can be safely administered to treat patients with relapsed/refractory disease. The objective of this phase I clinical trial is to determine the safety of administering TAA-T to these patients. The secondary objectives include determining disease response and tumor-specific immune reconstitution following infusion. *Methods:* T cells expanded from patient peripheral blood were stimulated weekly with antigen-presenting cells pulsed with an overlapping peptide library spanning the TAAas WT1, PRAME, and survivin. Following release testing, patients were infused with TAA-T on a dose escalation study, ranging from 1 x 10^6/m^2 (dose level 1) to 4 x 10^6/m^2 (dose level 3). Clinical and immune studies were performed post-infusion to monitor for adverse effects and assess immune and disease responses. *Results:* We have generated TAA-T products from 14 patients (age range 6-54 years) with relapsed/refractory solid tumors (neuroblastoma, osteosarcoma, Wilms tumor, Ewing sarcoma, soft tissue sarcoma, rhabdomyosarcoma). 14 patients have received a median of 2 (range 1-8) infusions without product-related adverse events or post-infusion EpIs. Epitope spreading was identified in 86% of responding patients. Preliminary outcome data (N = 10) show overall survival of 82% and event-free survival of 54% at 3 months. *Conclusions:* This unique immunotherapeutic has been well tolerated without causing life-threatening adverse events. Despite aggressive and multiply relapsed disease, 75% of patients demonstrated evidence of disease control and 84.6% of r/r B-ALL (84.6% of r/r B-ALL at 12 months after infusion). Cellular immunity was measured in PBMCsprev-infusion and post-infusion for the majority of pts. Preexisting/treatment-induced humoral and cell-mediated responses did not impact expansion or persistence of CARs in B-ALL, but 1% at baseline and postinfusion for the majority of pts. T-cell responses did not appear to impact translation expansion or persistence or pt outcomes. *Conclusions:* Preexisting/treatment-induced humoral and antigen-specific cellular immunity did not impact tisagenlecleucel expansion, persistence, nor efficacy. *Clinical trial information:* NCT02789228.

Immunogenicity of tisagenlecleucel in relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL) patients. *First Author: Karen Thudium Mueller, Novartis Institutes for BioMedical Research, East Hanover, NJ*

**Background:** Tisagenlecleucel, a chimeric antigen receptor (CAR) T-cell therapy, contains a murine single chain variable fragment (mCAR19) binding domain. Humoral immunity to anti-mCAR19 had no impact on safety or efficacy in pediatric r/r B-ALL patients (pts) (Mueller ASH 2017); immunogenicity in r/r B-ALL has not been studied. *Methods:* Tisagenlecleucel immunogenicity was measured in r/r B-ALL (ELIANA [NCT02435849, n = 75]; ENSIGN [NCT02228096, n = 29]) and r/r DLBCL (ULIJET [NCT02445248, n = 99]) 12 months after infusion. Cellular immunity was measured in PBMCs and tested for mCAR19 peptide-activated T cell responses by stimulated intracellular interferon-gamma production. Anti-mCAR19 antibodies (Ig) were measured by flow cytometry at baseline and after treatment. Treatment-induced Ig was defined as the ratio of postbaseline Ig levels to baseline. The impact of preexisting and treatment-induced Ig and T-cell activation on cellular kinetics, efficacy and safety were determined. *Results:* 84.6% of r/r B-ALL and 91.4% of r/r DLBCL pts had preexisting humoral immunogenicity. Treatment-induced humoral immunogenicity occurred in 34.6% of r/r B-ALL and 5% of r/r DLBCL pts. No relationship was found between tisagenlecleucel expansion (AUC0-28d) and preexisting humoral responses in r/r B-ALL (r² = 0.002) or r/r DLBCL (r² = 0.008), or treatment-induced humoral responses in r/r B-ALL (r² = 0.006). Results for Cmawere similar. Treatment induced humoral responses did not impact expansion or persistence of CARs in B-ALL, but sample size prevented correlation analysis in DLBCL as only 5% of pts had treatment-induced Ig. Preexisting humoral immunity did not appear to impact transgene persistence, duration of response, event-free survival or safety in either indication. T-cell responses were consistent over time with net responses <1% at baseline and postinfusion for the majority of pts. T-cell responses did not appear to impact transgene expansion or persistence or pt outcomes. *Conclusions:* Preexisting treatment-induced humoral and antigen-specific cellular immunity did not impact tisagenlecleucel expansion, persistence, nor efficacy. *Clinical trial information:* NCT02435849, NCT02228096, NCT02445248.
A phase I trial of T4 CAR T-cell immunotherapy in head and neck squamous cancer (HNSCC). First Author: Sophie Papa, Guy’s And St Thomas NHS Foundation Trust, London, United Kingdom

Background: Recent FDA approvals make CAR T-cell therapy a clinical reality for hematologic malignancy. Toxicity and antigen loss-mediated resistance remain problematic. Solid tumors impose additional challenges, foremost the paucity of safe targets. Moreover, CAR T-cells need to home to, penetrate and persist in an active state within a profoundly immunosuppressive tumor microenvironment. To address these issues, we developed T4-immunotherapy. T-cells that co-express: (i) TIE2G™, a CAR containing a promiscuous ErbB ligand coupled to a CD28+CD3ζ endodomain; and (ii) 4xβ, an IL-4-responsive chimeric cytokine receptor. TIE2G™ engages 8/9 ErbB homo/heterodimers, providing broad anti-tumor scope while minimizing risk of antigen escape. 4xβ enables IL-4-driven selective CAR T-cell enrichment/expansion during manufacture. Pre-clinical data demonstrate potent anti-tumor activity of T4-immunotherapy. However, risk of on-target off-tumor toxicity is significant, due to normal tissues low-level ErbB expression.

Methods: We undertook a Phase I dose-escalation trial of T4-immunotherapy in HNSCC. T4-immunotherapy was manufactured using a blood draw (40-130x10^6) in a two-week closed process using IL-4 as the sole cytokine stimulus post transduction. CAR T-cell dose was escalated through 5 cohorts from 1x10^7 -1x10^9 T4+ T-cells administered as a single treatment, by multifocal intra-tumoral injection without lymphodepletion. Results: Despite a lymphopenia rate of 62%, T4 manufacture was successful in 13/13 cases, yielding 2.5-7.5Bn T-cells (69+/-13% transduced). Treatment-related AEs were ≤ grade 2, with no dose-limiting toxicities (CTCAE V4.0). Frequent AEs were steroid-responsive tumor swelling, pain, pyrexias, chills and fatigue. Circulating T4+ T-cells were undetectable in all patients at all times. At 6-weeks, stable disease (SD) was seen in patients treated with ≥1x10^7 T4+ T-cells. Overall disease control rate was 69% (RECIST 1.1), despite rapidly progressing tumors on trial entry. Subsequent PD1 + oncolytic virus therapy in one patient achieved a rapid complete clinical response. Conclusions: These data demonstrate the safe intra-tumoral administration of T4 in patients with advanced HNSCC. Clinical trial information: NCT01818323.

Screening of neoantigen-specific T cells and establishment of T-cell receptor-engineered T cell implications for head and neck squamous carcinoma. First Author: Lili Ren, The University of Chicago, Chicago, IL

Background: Due to the high immune-suppressive condition in tumor microenvironment in growing tumors, the numbers of neoantigen-specific T cells is in general very limited. To improve adoptive T cell transfer (ACT) immunotherapy targeting neoantigens, we attempted to rapidly identify neoantigen-specific T cell receptors (TCRs) and establish T-cell receptor-engineered (TCR-engineered) T cells. Methods: To screen the neoantigen-specific T cells, we performed whole exome sequencing (WES) and transcriptome analysis, and selected candidate neoantigen epitopes to induce cytotoxic T lymphocytes (CTLs) in 20 patients with squamous head and neck cancer. 64 potential neoantigen peptides as well as 16 mirgenes, each of which were designed to express peptides carrying 20 somatic missense mutations, were examined for induction of neoantigen-reactive cytotoxic T cells in vitro using patient-derived dendritic cells and peripheral blood, or expanded TILs isolated from corresponding tumors. Neoantigen-specific T cells were screened by 4-1BB expression levels as well as ELISPOT assay and TCR sequences were determined using isolated T cell clones. We then cloned TCR cDNAs into T lymphocytes and generated the neoantigen-reactive TCR-engineered T cells. Results: We have so far confirmed 8 neoantigen-reactive T cells and established 6 TCR-engineered T cells which showed HLA-restricted neoantigen-reactive cytotoxic activity in vitro. We also tested HLA A*02:01 restricted engineering T cells with the antigen-negative humanized mouse model we generate previously, which showed very specialized antigen reactivity in vivo. Conclusions: We here demonstrate the establishment of a more effective and rapid protocol to generate neoantigen-specific T cells, identify neoantigen-specific TCRs for individual patients, and establish TCR-engineered T cells applicable for the clinical use.

ET190L1-ARTEMIS T cell therapy to induce complete remission of relapsed and refractory (rr) B-cell lymphoma with no cytokine release syndrome in the first-in-human clinical study. First Author: Zhi Tao Ying, Peking University Cancer Hospital & Institute, Beijing, China

Background: To ameliorate CRS commonly associated with CAR T-cell therapy, we developed a novel T cell therapy, the ARTEMIS platform, which functionally matches the potency of CAR-T cells, but triggers significantly less cytokine release upon target engagement. Herein we describe the first-in-human clinical studies of anti-CD19 ET190L1-ARTEMIS™ T cell therapy in rr B-cell lymphoma at multiple sites. Methods: Patients are assigned to 1 of 3 cohorts: single infusion of ET190L1-ARTEMIS™ T cells at 1, 3 or 6 x 10^6 cells/kg. The primary objective is to evaluate safety. Additional objectives include assessment of T cell engraftment and tumor response. Results: As of Jan 23, 2018, twelve heavily pretreated adult patients received autologous ET190L1-ARTEMIS™ T cells, 3 in the 1 x 10^6/kg cohort and 9 in the 3 x 10^6/kg cohort. Expansion of ARTEMIS T cells after infusion was observed in all patients. No CRS or neurotoxicity was observed. Plasma levels of IL-2, 4, 6, 8, 10, IFNg, TNFa, and GM-CSF were below detection at most time point post-infusion. Vital signs were normal except for 3 patients in the 3 x 10^6/kg cohort who had transient fever (37.5-39°C) from day 2 to day 4 post-infusion. One patient from the 1 x 10^6/kg cohort developed a transient skin rash. The overall response rate is 78% (7/9) (See Table 1). Six month follow-up data for the first 9 patients and early data from additional patients will be presented. Conclusions: In the studies, ET190L1-ARTEMIS™ T cell therapy demonstrated a favorable safety profile with no observed CRS or neurotoxicity and shows promising efficacy in rr lymphoma patients. Durability of the responses will be evaluated with longer follow-up. Based on its observed response rate and lack of CRS and neurotoxicity, the ARTEMIS platform is potentially a major improvement over existing CAR-T cell therapy.
3050 Poster Session (Board #264), Mon, 8:00 AM-11:30 AM
A phase I trial of PD-1 deficient engineered T cells with CRISPR/Cas9 in patients with advanced non-small cell lung cancer. First Author: You Lu, Department of Thoracic Oncology, Cancer Center, West China Hospital, West China School of Clinical Medicine, Sichuan University, Chengdu, China

Background: We performed the phase I clinical trial (NCT02793856) to assess safety of CRISPR/Cas9-mediated knockout of PD-1 gene in autologous T lymphocytes (PD-1-/- T) therapy in patients with metastatic non-small cell lung cancer (NSCLC). Methods: We assayed patients with advanced NSCLC with positive PD-L1 expression who had progressed after 3rd line standard therapeutic regimens. Two patients were enrolled in Pre-A cohort who received PD-1-/- T therapy with 2x10^6 cells/kg for one cycle and were observed for another cycle. Then 3 cohorts (A, B, C) enrolled 3 patients in each group receiving PD-1-/- T therapy with 1x10^7, 2x10^7, 4x10^7/kg in each cycle, respectively. Patients received PD-1-/- T therapy until disease progression or study withdrawal. Primary outcome was safety. Secondary end points were 8 weeks disease control rate (DCR) and progression-free survival (PFS). In exploratory analysis, expansion of de novo events on PD-1 editing region of T cells and CD3R3 region of T-cell receptor. Results: Nine patients were enrolled and eight patients received totally 17 cycles of PD-1-/- T therapy. Twenty-three adverse events (AEs) related to PD-1-/- T cell infusion occurred (Table 1). No 3-5 AEs were observed. Of note, one patient in Pre-A group suffered grade 1 arrhythmia (premature beat) lasting for 42.4 weeks. Seven patients were response evaluable. Two patients experienced stable disease (SD) with 17.6 and 22.0 weeks, respectively. Other 5 patients had progressive disease (PD). Eight-week DCR was 26.6%. In exploratory data, two patients with SD showed higher diversity of T cell repertoire in PBMC than other 5 patients with PD. Conclusions: Patients receiving PD-1-/- T therapy seemed safe. Further larger size studies are warranted to explore effective dose and related immune response. Clinical trial information: NCT02793856

3052 Poster Session (Board #266), Mon, 8:00 AM-11:30 AM
Clinical anti-lymphoma activity and toxicity of T cells expressing a novel anti-CD19 chimeric antigen receptor with fully-human variable regions. First Author: Jennifer N. Brudno, Experimental Transplantation and Immunology Branch, National Cancer Institute, Bethesda, MD

Background: T cells expressing chimeric antigen receptors (CARs) targeting CD19 have powerful activity against B-cell lymphoma. A limitation to CAR T-cell therapy for lymphoma is occurrence of toxicities, especially neurologic toxicities. Methods: We designed an anti-CD19 CAR with fully human variable regions (Hu19CAR). This CAR has CD8α hinge and transmembrane domains and a CD28 costimulatory domain; T cells expressing this CAR release relatively low levels of cytokines. A phase 1 dose-escalation trial was conducted to investigate the safety of Hu19CAR T cells and to assess efficacy for patients with previously treated B-cell lymphoma. Patients received cyclophosphamide and fludarabine chemotherapy to enhance CAR T-cell activity. Two days after the completion of chemotherapy, Hu19CAR T cells were infused. Results: Twenty patients have received Hu19CAR T-cell infusions. Of these patients, 75% had lymphoma that was chemotherapy-refractory or relapsed after autologous stem cell transplant. Patients received a median of 4 prior lines of therapy. The overall response rate is 75%, with 55% complete remissions (CRs). CRs were observed in patients with chemotherapy-refractory lymphomas and in patients with double-hit diffuse large B-cell lymphoma. Durations of response currently range from 1 to 17 months. Forty percent of patients are in ongoing remissions. Only one patient experienced greater than Grade 2 neurotoxicity (5%), which is a neurotoxicity rate lower than that of many anti-CD19 CAR trials. This patient had Grade 4 neurotoxicity which reversed in less than 24 hours with corticosteroid therapy. Three patients had Grade 3 cytokine release syndrome (CRS), and 1 patient had Grade 4 CRS; all other patients had Grade 2 or lower CRS. CRS and neurotoxicities resolved completely in all patients. Loss of CD19 expression by lymphoma cells was observed in 4 of the 8 patients who underwent biopsies of recurrent or residual lymphoma after Hu19CAR T-cell infusions. CAR T cells were detected in the blood of all patients at levels ranging from 4-2216 cells/μL. Conclusions: Hu19CAR T cells have substantial activity against recurrent lymphoma with a low rate of neurotoxicity. Clinical trial information: NCT02659943

3053 Poster Session (Board #267), Mon, 8:00 AM-11:30 AM
Impact of the influenza vaccination on cancer patients undergoing therapy with immune checkpoint inhibitors (ICI). First Author: Ragina Gopakrishnan, Vanderbilt University Medical Center, Nashville, TN

Background: Immune checkpoint inhibitors (ICIs) are standard of care for many cancer patients (pts). There have been conflicting reports on the effect of the influenza (flu) vaccines (flu-V) on pts being treated with ICI, and some suggest that flu-V may impact survival outcomes in ICI treated pts. Methods: We conducted a retrospective review of patients at Vanderbilt Ingram Cancer Center treated with ICI from 2010-2017. Data collected included age, gender, race, cancer type, comorbidities, type of ICI (single v. combo), time of drug administration, rate of flu-V on pts being treated with ICI, and some complications, rate of immune related adverse events (irAE) and admissions, and the impact of flu-V on PFS and OS. Statistical analysis was performed using Graph PAD prism and SPSS. Conclusions: Cases of B-ALL in the CD19 normal/bright group. However, prior CD19-targeted therapy was associated with a significantly higher rate (60%; p = 0.014) of NON and CD19NR compared to 25% in patients who did not receive prior CD19 targeted therapy. Immunophenotype of patients with CD19PR were identical to that of pre-therapy disease in 85% of cases, consistent with loss of CAR T cells as the etiology of those relapses. Blasts from CD19NR patients did not show any CD19-negative events by flow prior to CAR T cell therapy in 75% of cases suggesting that CD19-negative blasts may be de novo events. Conclusions: CAR T cell therapy is effective in B-ALL. Differences in CD19 expression prior targeted therapy is associated with increased non-response and relapse, likely due to CD19 escape. CD19PR after CAR T cell therapy are due to early loss of CAR T cells while CD19NR are likely due to expansion of de novo CD19-negative B lymphoblasts under treatment pressure.

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Safety and activity of programmed cell death-1 gene knockout engineered T cells in patients with previously treated advanced esophageal squamous cell carcinoma: An open-label, single-arm phase 1 study. First Author: Zhao Jing, Hangzhou Cancer Hospital, Hangzhou, China

Background: We designed the clinical trial to investigate the safety and activity of Programmed death-1 (PD-1) knockout engineered T cell in patients with advanced esophageal squamous cell carcinoma (ESCC). Methods: Patients (aged ≥18 years) with advanced ESCC whose disease had progressed after at least two systemic therapies were enrolled. Peripheral blood will be collected and PD-1 gene will be knocked out by clustered regularly interspaced short palindromic repeats (CRISPR)Cas9 in the laboratory. T lymphocytes will be selected, expanded and reinfused back into patients after about 2-3 weeks. Response was assessed 4 weeks after each infusion. Patients continued receiving treatment until disease progression, intolerable toxicity, or consent withdrawal. The primary endpoint was to evaluate the safety of PD-1 knockout engineered T cells treatment. Results: Between Mar, 2017, and Jan, 2018, we enrolled 21 patients who received at least one cycle PD-1 knockout engineered T cells treatment. Among 21 treated patients, 7 accepted only 1 cycle of cell infusion, 12 accepted 2 cycles, and 2 accepted 3 cycles. Up to the study cutoff date of Jan 31, 2018, the most common adverse events were transient fever (7 patients, the highest was 39.1°C) and chills (3 patients) and moderate skin rash (1 patient). No grade 3 or 4 adverse events were observed in the study. Of the 17 evaluable patients, no complete or partial responses were observed. 6 patients had stable disease, and 11 patients had progressive disease. Disease control rate was 35% (5/15) and median overall survival was 127 days (95% CI 45–209). During the trial, 10 cancer progression related deaths occurred. Immunofluorescence analysis showed that the PD-1 knockout engineered T cells could infiltrate into and persist for a durable time in ESCC that responded to therapy. Conclusions: The results showed that PD-1 knockout engineered T cells infusion might be an effective treatment in patients with heavily pretreated advanced ESCC. The treatment was well tolerated with no unexpected safety concerns. The regimen warrant further clinical investigation. Clinical trial information: NCT03081715.

Adaptive cellular immunotherapy with APN401, autologous cbl-b silenced peripheral blood mononuclear cells: Data from a phase I study in patients with solid tumors. First Author: Hans Loibner, Apeiron Biologics AG, Vienna, Austria

Background: Casitas-B-lineage lymphoma protein (c-b, an E3 ubiquitin ligase is an important intracellular checkpoint limiting activation of lymphocytes and NK cells. Silencing of c-b enhances T cell and NK cell antitumor activity in mouse tumor models and in vitro in human immune cells. APN401, an autologous cellular therapy consisting of ex-vivo c-b silenced PBMCs, was evaluated in patients with solid tumors. Methods: Patients with metastatic solid tumors not eligible for standard therapies were included. Patients with autoimmune disease or requirement for immunosuppressive drugs were excluded. PBMCs were obtained by leukapheresis and were transfected with c-b-siRNA ex vivo by electroporation, and 5, 10 or 50 x 10^9/PBMCs/kg were infused once shortly thereafter over 30 min. Results: 16 patients were treated with APN401. As a consequence of c-b silencing, all patient PBMC preparations produced enhanced amounts of cytokines IL-2 and IFN-g upon TCR stimulation in vitro. Moreover, evaluation of patient PBMC responses to common tumor antigens were stronger over the course of the follow-up period. Four patients (2 pancreas 1 renal cancer, 1 renal cancer) had stable disease as best tumor response during the study. The strongest response to tumor antigens was observed in the patient with the best objective clinical response (metastatic colon cancer; disease stabilization > 1 year). Infusions were well tolerated. Dose-limiting toxicities were not observed. Mild chills were the most commonly observed related adverse event, followed by mild anemia and fatigue. There were no immediate hypersensitivity or evidence for autoimmune adverse effects. Conclusions: Cbl-b-silenced PBMCs (APN401) from cancer patients respond to TCR stimulation and activation with tumor antigens. Strongest cell activation was seen in the patient with the best objective clinical response. 50 x 10^9/kg APN401 was safe and well tolerated. Multiple infusions of APN401 are currently clinically tested. Clinical trial information: NCT03087591.

Initial safety assessment of MAGE-A10^296TCR T-cells in two clinical trials. First Author: Vincent K. Lam, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MAGE-A10 is expressed in 10-50% of urothelial, melanoma, head and neck (HN), and non-small cell lung cancers (NSCLC). Affinity-enhanced autologous MAGE-A10^296TCR T-cells directed towards MAGE-A10 tumor antigen in the context of HLA-A^02 (SPEAR-T-cells) are being tested in 2 ongoing clinical trials (NCT02592577: NSCLC/NCT02989064: urothelial, melanoma, HNC). Methods: These first-in-human T-cell dose escalation studies utilize a modified 3+3 design to evaluate safety. Patients are enrolled after progression on at least one line of therapy. In the first treatment groups, lymphodepletion with Flu 30 mg/m^2/day and Cy 600 mg/m^2/day (NCT02989064) or Cy 600 mg/m^2/day (NCT02592577) is administered on days -7 to -5. The initial dose is 0.1 x 10^9 transduced cells; additional dose levels are 1 x 10^9 and 5 x 10^9. Dose-limiting toxicities (DLT) are determined regardless of attribution to cell infusion and adjudicated by a Safety Review Committee. Cohort expansion will occur at the maximum tolerated dose. Results: 8 patients were treated with 0.1 x 10^9 MAGE-A10^296TCR T-cells (29Dec17). Adverse events (AEs) in ≥3 patients included anemia, thrombocytopenia, lymphopenia, leukopenia, neutropenia, vomiting, constipation, dyspea and tachycardia. Grade (G) 3 AEs in ≥2 patients included thrombocytopenia, lymphopenia, leukopenia, neutropenia, anemia, pancytopenia, and hyponatremia; these were not reported as related to T-cell infusion. 1 event of cytokine release syndrome (CRS) and 1 increase in serum amylase were reported as related to T-cell infusion. SAEs included G5 disease progression, G4 CRS, G4 neutropenia, G4 thrombocytopenia, G4 sepsis, G4 abdominal pain, G4 supraglottic airway obstruction, G3 shortness of breath and G2 respiratory failure. There was 1 DLT of G4 CRS in a patient with NSCLC that resolved with tocilizumab and steroids. While no anti-tumor effects were observed at this dose, transduced cells were detectable in peripheral blood.

Conclusions: MAGE-A10^296TCR T-cells at the 0.1 x 10^9 transduced cell dose showed no evidence of on target or off target toxicity. 1 DLT of CRS was observed. The available data support continued investigation of MAGE-A10^296TCR T-cells at higher doses. Clinical trial information: NCT02592577; NCT02989064.

Association of efficacy and adverse events of special interest ofavelumab in the JAVELIN solid tumor and JAVELIN Merkel 200 trials. First Author: Karen Kelly, University of California Davis Comprehensive Cancer Center, Sacramento, CA

Background: Immune checkpoint inhibitors (ICIs) are associated with unique adverse events of special interest (AESIs), including infusion-related reactions (IRRs) and immune-related AEs (irAEs). It has been observed that patients (pts) responding to treatment might have a higher likelihood of AEs, potentially due to longer treatment duration. Understanding the association between AESIs and efficacy outcomes may improve the assessment of benefit/risk and thus aid in informed treatment decisions. Methods: We pooled and analyzed efficacy/safety data from NCT01772004 and NCT02155647. We performed an association analysis between response and IRRs. The association of efficacy and irAEs was analyzed using approaches that accounted for time dependency: Cox models analyzed overall survival under consideration of time-varying indicators for irAEs; multistate models were used to gain insight into underlying mechanisms. Results: 1783 pts were included in this analysis. 25.5% of pts had ≥1 IRR; 0.7% of pts had a grade 3-4 IRR. 97.3% of pts with IRRs had first onset during the first 3 infusions. No association between response and IRRs was observed. irAEs were observed in 16.8% of pts, most commonly hypothyroidism (6.7%) and rash (6.6%); grade 3-4 irAEs occurred in 2.7% of pts. 2.2% of pts discontinued avelumab treatment due to an irAE. An improved probability of survival was observed for pts who experienced irAEs (HR, 0.74 [95% CI, 0.61-0.88]). The multistate model did not suggest that occurrence of irAEs predicted response; however, responders were more likely to develop irAEs than others who remained on treatment. The discontinuation rate did not increase upon occurrence of irAEs. Conclusions: The overall incidence of AESI was low, and most grade was ≤ 2. The occurrence of IRRs did not impair the rate of response. The data suggest a survival benefit for pts who experienced an irAE; however, not having an AE did not preclude a response to avelumab. Continued awareness of irAEs may improve clinical outcomes in all pts, with particular vigilance needed if a pt is responding and remains on treatment. Clinical trial information: NCT01772004, NCT02155647.
3058 Poster Session (Board #272), Mon, 8:00 AM-11:30 AM

Circulating miRNA and extracellular vesicle containing miRNA as response biomarkers of anti PD-1/PD-L1 therapy in non-small-cell lung cancer.

First Author: Takehito Shukuya, The Ohio State University, Division of Medical Oncology, Columbus, OH

Background: Anti PD-1/PD-L1 antibody is a standard first or second-line treatment for advanced non-small cell lung cancer (NSCLC), and PD-L1 immunohistochemistry is used as a predictive biomarker for therapeutic response. However, because patients with lower PD-L1 expression also show durable response in NSCLC, and the usefulness of PD-L1 immunohistochemistry result has not been shown in the other malignancies, more accurate and non-invasive predictive biomarkers are needed. Circulating miRNA and that packaged in extracellular vesicles (EVs) are considered to play a role in intercellular communication among immune cells and between immune cells and tumor cells.

Methods: Pretreatment plasma of advanced NSCLC patients treated with single agent anti PD-1 or PD-L1 antibody was used in this study. Circulating miRNA was extracted from plasma by miRNAeasy kit. 26 circulating miRNAs were assessed by Bioanalyzer. In total, 26 circulating miRNAs were isolated using size-exclusion chromatography column (Izon), and miRNA was extracted by miRNAeasy kit. Modified small-RNA library construction was used to make small RNA sequencing libraries, and sequenced on a NextSeq 500 sequencer (Illumina). The sequencing results were analyzed by CEnvelope (http://srmalnary.systemsbiology.net/).

Results: Samples from 14 responders (patients who showed PR or SD ≥ 6 months) and 15 non-responders (who showed PD in RECIST) were analyzed. Extraction of EVs was confirmed by electron microscopy. Quality and quantity of circulating miRNA and EV encapsulated miRNAs were assessed by miRNAeasy kit. In 26 circulating miRNAs (p = 0.0030 – 0.049) and 4 EV associated miRNAs (p = 0.019 – 0.043) showed significant concentration differences between responders and non-responders. Of these, 2 miRNAs were in common. Conclusions: Circulating miRNA and EV containing miRNA have potential as predictive biomarkers for anti PD-1/PD-L1-L1 treatment response. We are in the process of identifying and validating circulating circulating miRNA and EV miRNA signatures associated with response to anti PD-1/PD-L1 therapy.

3059 Poster Session (Board #273), Mon, 8:00 AM-11:30 AM

Activity of ramucirumab (R) with pembrolizumab (P) by PD-L1 expression in advanced solid tumors. Phase 1a/b study in later lines of therapy.

First Author: Philip S. Haba, Yale University School of Medicine, New Haven, CT

Background: R (anti-VEGFR2) and P (anti-PD-1) are active in patients (pts) with previously-treated non-small cell lung carcinoma (NSCLC), gastric or gastroesophageal adenocarcinoma (G/GEJ) and uterine carcinosarcoma (UC). Because PD-L1 expression may be a predictive biomarker, we examined the effect of R + P in relation to PD-L1.

Methods: Eligible pts had progressive advanced or metastatic G/GEJ, NSCLC and UC, ECOG PS 0-1, and baseline tumor tissue. PD-L1 was assessed using the PD-L1 IHC 22C3 pharmDx assay, where the number of stained tumor cells (tumor proportion score; TPS) or tumor and immune cells (combined positive score; CPS) is relative to total tumor cells. PD-L1 positivity was defined by CPS ≥ 1% in G/GEJ and UC, and defined by TPS ≥ 1% in NSCLC.

Primary objective was safety and tolerability of R + P. Results: As of 31-July-2017, 92 pts received P 200 mg on Day 1 q3W with R at 10 mg/kg on Day 1 (G/GEJ, n = 17; NSCLC, n = 27; and UC, n = 24) or R at 8 mg/kg, Day 1 and 8 q3W (G/GEJ, n = 24). Baseline demographics and characteristics were as expected for an advanced, previously treated population. Median follow-up duration for G/GEJ, NSCLC, and UC, was 17.7 months (mo) and, 17.5 mo, respectively. The safety profile was consistent with that of each individual drug, with no additive toxicities. 84 (91%) of 92 pts were evaluable for PD-L1. Objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) by PD-L1 are shown in the table. 13 pts remained on study treatment (G/GEJ, n = 4; NSCLC, n = 8; and UC, n = 1). Clinical trial information: NCT02443324.

3060 Poster Session (Board #274), Mon, 8:00 AM-11:30 AM

Cost of inpatient admissions for immune-related adverse effects from immune checkpoint inhibitor therapy: A single center experience.

First Author: Jacqueline N. Chu, Massachusetts General Hospital, Boston, MA

Background: Immune checkpoint inhibitors such as anti-CTLA4 and anti-PD1 antibody is a standard first or second-line treatment for metastatic solid tumors. More recently, immune checkpoint inhibitor therapy: A single center experience.

Methods: Data were collected on metastatic solid tumors. More recently, immune checkpoint inhibitor therapy: A single center experience.

Results: The annual cumulative cost of all admissions for immune-related adverse effects was $1,990 to $6,674/day. Although total costs for immune-related adverse effects were less costly compared to other oncologic admissions, possibly because irAEs are more infrequent and less severe, irAE costs were significantly higher ($4,623/day vs. $8,257/day, p = 10-10). irAE cost by therapy was not significantly different. irAEs rose from $218,700 in 2011 to $1.3 million in 2016. However, the average cost of irAE admissions was significantly lower than that of non-irAE admissions ($1,249/day vs. $8,257/day, p < 0.001). irAE cost accounting system (TSI), to estimate total, variable, and direct costs, which were estimated at $1,000 to $4,000/day. Costs by organ varied from $1,990 to $6,674/day.

Conclusions: The annual cumulative cost of all admissions for immune-related adverse effects was significant at $1,990 to $6,674/day. Although total costs for immune-related adverse effects were less costly compared to other oncologic admissions, possibly because irAEs are more infrequent and less severe, irAEs are more costly compared to other oncologic admissions, possibly because irAEs are more readily identifiable. The added cost burden to usual oncologic care from irAEs may be less than anticipated.

3061 Poster Session (Board #275), Mon, 8:00 AM-11:30 AM

Velparib in combination with nivolumab and platinum doublet chemotherapy (OCEANS) in advanced gastroesophageal and urothelial carcinoma: A first single center experience.

First Author: Jeffrey Melson Clarke, Duke University Medical Center, Durham, NC

Background: Velparib (V), a PARP inhibitor, combined with platinum (Pt) doublet CT has shown promise in a Phase 2 study of nivolumab. Nivolumab (N), a PD-1 inhibitor, has demonstrated single-agent activity in relapsed NSCLC. This is the first study evaluating dose and safety of V combined with N + Pt + doublet CT. Methods: Phase 1, dose-escalation study (NCT 02944396) enrolled 26 pts with metastatic gastroesophageal cancers (G/GEJ) or urothelial carcinoma (UC). We evaluated 3 dose levels in each cohort, and no prior cytotoxic CT, anti-PD-1 or PARP. Primary objective was to establish the recommended Phase 2 dose (RP2D) of V combined with N (360 mg) and carboplatin (C, AUC 6)/paclitaxel (Pac, 200 mg/m2) or C(AUC 6)/Pem. 17% NR (n=1) for V + N + C/Pac. For V + N + C/Pem, best ORR, PFS, OS, and DLTs were as indicated. DLTs incl. hematologic and non-hematologic AEs delaying treatment (tx), requiring dose modifications, and attributed to V. Safety, PK, and anti-tumor activity by RECIST 1.1 were assessed.

Results: As of December 15, 2017, 17 pts (median age 61) with Stage IV NSCLC were enrolled (11 non-squamous for V + N + C/Pem; 1 non-squamous and 5 squamous for V + N + C/Pac). Median drug exposure was 105 d (range 3-284). Primary discontinuation of V occurred in 41% due to AE (2), PD (1), physician decision (1), pt withdrawal (1), death (1), or other (1). No DLTs were reported. Tt-emanent AEs incl. fatigue (47%), nausea (35%), anemia (35%) neutropenia (29%) and thrombocytopenia (29%). Grade 3/4 AEs additionally incl. febrile neutropenia, increased lipase, pneumonitis, and rash (6%). SAEs additionally incl. sinus arrhythmia, acute kidney injury, pleural effusion, pulmonary embolism, and sudden death (6%). ORR was 27% (95% CI 6, 61) for V + N + C/Pem and 17% (95% CI 64%) for V + N + C/Pem. For V + N + C/Pem, best response was PR (50%) or SD (50%). For V + N + C/Pac, best response was PR (50%). PK data will be presented. Conclusions: RP2D is 120 mg for V + N + C/Pac, and has not been determined for V + N + C/Pem (to date, highest tolerated dose is 200 mg). V combined with N + Pt doublet CT showed anticipated safety signals, with no additional toxicity of V when added to these regimens. Clinical trial information: NCT 02944396.

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Background: Pembrolizumab is currently approved for use in multiple cancer indications at a dose of either 200 mg or 2 mg/kg Q3W. An alternative extended dosing regimen would provide convenience and flexibility to patients and prescribers. Robust characterization of pembrolizumab pharmacokinetics (PK) and E-R relationships for efficacy and safety allow the use of model-based approaches to support alternative dosing regimens.

Methods: The dose for a Q6W schedule was selected by matching predicted exposures with the approved Q3W (200 mg and 2 mg/kg) regimens; efficacy and safety are bridged based on E-R assessments. Exposures were simulated using the established population PK model of pembrolizumab that adequately described PK across multiple tumor types. Regimens are compared on - A) Exposure metrics at steady state (Cmax,ss) and trough concentrations (Cmin,ss); B) Predicted clinical endpoints (e.g., objective response rate) in patients with multiple approved tumor types. Safety at the Q6W schedule is bridged by ensuring predicted peak concentrations at steady state (Cmax,ss) are below those at the mandated clinically administered and well-tolerated dose of 10 mg/kg Q2W.

Results: The 400 mg Q6W dosing regimen had similar predicted exposures (Cavg,ss or AUCss, geometric mean (GM) –1% higher) compared to those achieved at 200 mg Q3W. Less than 1% subjects had Cmin,ss lower than that for 200 mg Q3W. The GM of predicted Cmax,ss for 400 mg Q6W was ~65% lower than for 10 mg/kg Q2W, which is similar to the approved regimens and established E-R relationships for pembrolizumab over a 5-fold range of clinically tested doses, the clinical outcomes achieved with 400 mg Q6W are predicted to be similar as with 200 mg Q3W across tumor types. Conclusions: A 400 mg Q6W dosing regimen of pembrolizumab leads to exposures that are similar to the approved 200 mg Q3W dosing regimen. Based on the robust understanding of pembrolizumab clinical pharmacology, including well-established E-R profiles, such a less frequent dosing regimen is expected to produce similar efficacy, safety, and benefit-risk profile in all clinical treatment settings where 200 mg Q3W pembrolizumab is currently approved.

3064 Poster Session (Board #278), Mon, 8:00 AM-11:30 AM

Correlation between immune-related adverse events (irAEs) and efficacy in patients with solid tumors treated with immune checkpoint inhibitors (ICIs), First Author: Mariona Riudavets, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Background: ICIs are associated with irAEs. We describe the incidence of irAEs in patients with solid tumors receiving ICIs and its correlation with efficacy. Methods: We retrospectively analyzed all patients with solid tumors receiving ICIs in our center. ICIs were graded according CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free survival (PFS) and overall survival (OS). Analyses were performed using SPSS v24 package. Results: From March 2014 to January 2018, 178 patients received ICIs. Median age was 64.1 (33-88) years, 72% were male. Most frequent tumors were lung (63.5%), bladder (14.6%) and melanoma (11.8%). 96% presented advanced disease. Most common used ICIs were nivolumab (38.2%), pembrolizumab (28.7%) and atezolizumab (17.4%). ICIs were used as monotherapy (74.7%) or in combination with ICI (3.4%), chemotherapy (17.4%) or targeted therapies (4.5%). Median duration of immunotherapy was 6.9 [0.7-46.3] months. 95 (53.4%) patients developed 158 irAEs with a median number per patient of 1.2 [0-4]. Most frequent irAE was rash (24.7%) followed by diarrhea (17.7%), hypothyroidism (9.5%), arthritis (6.9%), hyperthyroidism (3.8%), pneumonitis (3.2%) and mucositis (3.2%). Median time to the onset irAEs was 53.2 [11-490] days. 12 (6.7%) patients presented grade (G) 3-4 irAEs: 5 G-3 diarrhea, 2 G-3 liver dysfunction, 1 G-3 pneumonitis, 1 G-3 hyperlipidemia, 1 G-3 mucositis, 1 G-3 arthritis and 1 G-3 nephritis. There were 2 (1.1%) treatment-related deaths due to pneumonitis. 21.3% patients required steroids for irAEs management. 8.4% patients discontinued treatment due to irAEs. 73.9% irAEs had improved at the time of analysis. OS was superior in patients with advanced disease experiencing irAEs: 37.3 [95%CI, 19.2-51.4] vs 7.8 [95%CI, 4.9-10.8] months (p < 0.0001). Similarly, PFS was longer: 7.9 [95%CI, 4.4-11.4] vs 2.6 [95%CI, 2.0-3.2] months (p < 0.0001).

Conclusions: There was a significant correlation between presence of irAEs and outcomes in patients with advanced solid tumors treated with ICIs.

3065 Poster Session (Board #279), Mon, 8:00 AM-11:30 AM

A meta-analysis to indirectly compare the safety and efficacy of PD-1 and PD-L1 antibodies across solid tumors using a Bayesian hierarchical model, First Author: Mythili Koneru, Eli Lilly and Company, New York, NY

Background: Many PD-1/PD-L1 mAbs are in development across a broad range of tumors. The expanded literature provided an opportunity to address a critical question: if PD-1 mAbs targeting the receptor have a different safety/efficacy profile than the PD-L1 mAbs targeting the ligand. Direct comparison of these mAb would be ideal but highly unlikely. Methods: We performed a meta-analysis using a Bayesian model to provide indirect comparison based on data in the public domain including PubMed and key medical conference abstracts (eg ASCO, ESMO etc.). Key inclusion/exclusion criteria include patients 1) with any specific solid tumor, 2) PD-L1 status if tested using one of the approved assays, 3) received one of the approved mAbs as a monotherapy, and 4) with disclosure date between June 4th, 2013 and June 6th, 2017. The search resulted in about 70 clinical trials in 31 tumors and 12,025 patients. The endpoints include ORR, PFS and overall G3/4 AE rate for safety. Results: For efficacy, in all solid tumors except for HNSCC, ORR is slightly greater for PD-1 than PD-L1 mAb, with the largest odds ratio (OR) in 2L+ NSCLC favoring the PD-1 mAb [OR_{PD-1} = 19.8% vs OR_{PD-L1} = 16.5%, OR = 1.27, 95% CI = (0.96, 1.70)] and the smallest OR in 1L HNSCC favoring the PD-L1 mAb [OR_{PD-L1} = 27.4% vs. OR_{PD-1} = 28.7%, OR = 0.975, 95% CI = (0.38, 1.50)]. Overall, there is 81% posterior probability that ORs are equivalent for PD-1 and PD-L1 mAbs. For safety, the OR of PD-1 vs PD-L1 mAbs is numerically higher for PD-1 than PD-L1 mAb (OR = 1.48, 95% CI = (0.19, 12.39)) across tumors. Overall, there is 79% posterior probability that the safety profile in terms of G3/4 AE rate is equivalent for PD-1 and PD-L1 mAb.

Conclusions: There was no significant difference between PD-1 and PD-L1 mAbs across tumors. The ORs for ORR, PFS and Gr 3/4 AE rate are greater when the information was analyzed across tumor types, the small magnitude of the difference relative to the variability across tumor types suggests strong interchangeability of efficacy and safety profile of the antibodies targeting either PD-1 or PD-L1. Ultimately, the variability within this class of antibodies is not likely to be clinically meaningful.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: The occurrence of severe, acute limiting toxicity in patients receiving anti-PD-1 monoclonal antibodies, such as nivolumab, is largely unpredictable. Sarcopenia was found associated with anti-CTLA4 acute toxicity (Daly LE et al, Br J Cancer 2017). We studied the clinical and pharmacological parameters influencing nivolumab toxicity, including body composition.

Methods: From June 2015 to December 2016, all consecutive patients treated with nivolumab in our institution were prospectively included. We studied the relationship, using logistic regression, between muscle mass, assessed by computed tomography and by Jainmahasan formula, nivolumab trough levels (Cmin) assayed using ELISA method, and the occurrence of grade 3 or 4 toxicity or any toxicity leading to treatment discontinuation (ALT). Univariate and multivariate analysis were made for parameters associated with nivolumab concentration.

Results: Out of 92 patients, 81 were analyzable for body composition and 84 for nivolumab pharmacokinetics. The population included 63% males, median age 65 years, a majority had lung cancer (72%). We observed 20 ALT including 4 pneumonitis and 4 colitis in 20 (21.7%) patients and 825 (2.4%) nivolumab infusions. The ALT events were more frequent in sarcopenic patients (OR = 3.29, 95% CI: 0.96-11.28, p = 0.06). Sarcopenic overweight patients were the most susceptible to experience ALT (OR = 5.08, CI: 0.53-48.9, p = 0.1), as already reported in our group using the same definition (Couturier et al, Invest N Drugs, 2017). The nivolumab Cmin was 17.0 ± 5.9 µg/mL on day 14. In multivariate analysis, low nivolumab Cmin was independently associated with hypoalbuminemia (< 35g/L) (OR = 0.03, 95% CI: 0.002-0.34, p = 0.005) and sarcopenia (OR = 0.13, 95% CI: 0.03-0.54, p = 0.04) (Figure 1). The recycling of albumin and nivolumab is both mediated by the neonatal Fc receptor (FcRn) and therefore albumin levels may reflect the abundance and efficiency of FcRn.

Conclusions: Body composition influences both nivolumab pharmacokinetics and acute toxicity.

Can body composition (BC) be predictive for outcomes and severe toxicities (ST) in metastatic solid tumors patients (pts) treated with checkpoint inhibitor (CPI)? An analysis of 145 patients.

First Author: Sophie Cousin, Institut Bergonié, Bordeaux, France

Background: BC parameters have previously been associated with treatment toxicities, and worst outcomes in metastatic solid tumors pts. We studied association between BC parameters and their changes, with ST and outcomes in pts receiving CPI. Methods: Pts consecutively treated with CPI between December 2013 and December 2016 in our institute (Institut Bergonié, Bordeaux, France) for metastatic solid tumor and with a baseline computed tomography (CTo) scan <28 days before CPI beginning were included. BC parameters were assessed with Slice-O-Matic software v4.3 (Tomovision, Montreal, Canada), using third lumbar vertebra as standard landmark, normalized for height (cm2/m2). Results: 145 pts were included (73 female, median age: 62); 124 had a CT scan after 2 months of CPI (CT2). Tumor type was non small cell lung cancer in 80 (55%) pts. 68 pts had received >1 line of chemotherapy before CPI treatment. Before CPI treatment was: anti-PD-1, anti PD-L1, anti PD-L1/CTLA-4 combination in 113, 13, and 19 pts, respectively. ST included: Grade III-V toxicity according to NCI-CTC v4.0, unscheduled hospitalization, definitive CPI treatment discontinuation. 15 pts (10.3%) had ST. None of the baseline clinical, nutritional, and BC parameters was associated with ST. In multivariate analysis, subcutaneous adipose tissue index (SATI) decrease -10% between CTo and CT2 was significantly associated with occurrence of ST (OR=6.3, p=0.027). Median Overall survival (OS) was 402 days. Median progression free survival (PFS) was 86 days. In multivariate analysis, 3 BC-related parameters were significantly associated with worse OS: body mass index < 25 (HR=2.375, p=0.030), Skeletal muscle index (SMI) decrease >-10% (HR=4.603, p<0.001), and visceral adipose tissue index (VATI) decrease >-10% (HR=8.470, p=0.030). Only SMI decrease >-10% was predictive of PFS (HR=3.643, p=0.001).

Conclusions: Our results demonstrate that body composition is associated with clinical outcomes of cancer patients treated with CPI. Early decrease of SATI is predictive of ST whereas early decrease of skeletal muscle index and of VATI are associated with worse OS.
3070 Poster Session (Board #284), Mon, 8:00 AM-11:30 AM
Comparative analysis of durable responders on immune checkpoint inhibitors (ICI) versus other systemic therapies: A meta-analysis of phase III trials. First Author: Elvire Pons-Tostivint, Department of Medical Oncology, Institut Curie, Paris, France

Background: Durable responses have been reported with ICI. We aimed at quantifying the proportion of patients experiencing a durable response on ICI, and comparing it to the proportion observed with other systemic therapies including targeted therapy and chemotherapy. Methods: We retrieved all phase III trials that included at least one ICI arm. The proportion of durable responders was evaluated for each treatment arm, and the proportion of patients who had a progression-free survival (PFS) exceeding 3 times the median PFS. The proportion of patients who experienced an overall survival (OS) that exceeded 2 times the median OS was also estimated in each arm, from the published survival curves. The impact of the tumor type and the line of treatment were evaluated. Groups were compared using the Mann-Whitney test. Results: 20 phase III trials involving 12.834 pts (8275 in ICI arms) treated for 8 different types of cancer in 44 treatment arms were retrieved. Median follow up was 15 months [range: 5.6-36.6]. Treatment was ICI alone, chemotherapy, a tyrosine kinase inhibitor, a vaccine, a placebo and ICI + chemotherapy in 24 (54.5%), 5 (1.2%), 3 (2.3%), 2 (4.5%), and 3 (7%) arms. The mean median PFS was 3.8 [95%CI: 3.4-7.1] vs 3.5 months [95%CI: 2.9-4.1] in the ICI alone arm and in the control arms. Mean median OS was 13.9 [95%CI: 10.6-17.2] vs 9.7 months [95%CI: 7.8-11.6] in the ICI alone arm and in the control arms (p = 0.01). The proportion of patients who experienced a durable PFS exceeding 3 times the median PFS was 24.6% [95%CI:20.9-28.3] vs 11% [95%CI:8.5-13.5] in the ICI alone and control arms, respectively (p < 0.0001). The proportion of patients who survived longer than 2 times the median OS was 29.7% [95%CI: 28-31.3] in the ICI alone group vs 21.8% [95%CI: 19-24.4] in the control group (p = 0.0001). These results were similar even in patients treated beyond the first-line metastatic setting and in non-melanoma tumor types. Conclusions: The proportion of patients experiencing a durable response was more than twice higher on ICI than on other treatments, even in patients treated beyond the first-line metastatic setting and in non-melanoma tumor types.

3072 Poster Session (Board #286), Mon, 8:00 AM-11:30 AM
Preliminary interim results of the first-in-human, dose-finding PROCLAIM-CX-072 trial of the PD-L1 Probody therapeutic (Ph-Tx) CX-072 (0.3 mg/kg) with nivolumab (ipi) in patients (pts) with advanced solid tumors. First Author: Rachel E. Sanborn, Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR

Background: CX-072 is a Pb-Tx directed against programmed cell death ligand 1 (PD-L1), designed to be preferentially activated by tumor-associated proteases but not in healthy tissue. Preclinically, the combination of a PD-1 Pb-Tx with an anti-CTLA-4 antibody showed comparable efficacy but improved safety compared to the non-Pb-Tx combination control. This dose-escalation cohort of CX-072 + ipi in pts with advanced solid tumors was designed to examine the safety and tolerability of combination therapy. Preliminary safety and antitumor activity are reported. Methods: In this ongoing phase 1-2 study (NCT03013491), pts receive CX-072 + ipi in a concomitant dosing schedule (study Part B1). Eligible pts are PD-1, PD-L1, and CTLA-4 inhibitor naive. Planned doses are CX-072 0.3-30 mg/kg every 3 wk and ipi 1 mg/kg every 3 wk for 4 doses then N 3 mg/kg every 2 wk, or 3 doses then N 3mg/kg every 2 wk, or S 50 mg/d orally for 4 wk (6-wk cycle). Exploratory HRQoL analyses were conducted on RCC-specific symptoms from the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) and general cancer symptoms assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) instruments. Analyses used t tests (change from baseline (BL) analysis) and mixed-model repeated measures (MMRM; using a pre-defined 6-m landmark). Results: A total of 847 IP risk pts were randomized (N-I, 425; S, 422). HRQoL assessment completion rates were >80% in the first 6 m. Statistically significant differences in change from BL on FKSI-19 total scores (mean BL scores: 60.1 [N-I; 59.1 (13)] vs 60.7 [S] favoring N-I were observed at all but 2 post-BL time points through 2 years of follow-up (P<0.05). MMRM analysis found a statistically significant difference between arms at 6 m favoring N-I in FKSI-19 total score and most subscores (table). Change from BL results for the FACT-G trended in a similar direction, with N-I scores exceeding those in the S group arm throughout 2 years of follow-up. Similarly, MMRM of FACT-G total scores showed significant benefit of N-I at 6 m. Conclusions: In addition to the OS benefit and superior safety profile, descriptive data suggest that N-I offers significant and sustained HRQoL improvement vs S in IP risk pts with untreated aRCC. Clinical trial information: NCT02231749.

MMRM analysis: FKSI-19.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Difference</th>
<th>N-I vs S (95% CI)</th>
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<tr>
<td>Total</td>
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<tr>
<td>DRS</td>
<td>0.75 (0.10-1.40)*</td>
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<tr>
<td>CRS-Physical</td>
<td>1.19 (0.28-2.11)</td>
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<tr>
<td>DCS-Emotional</td>
<td>0.10 (0.00-0.27)</td>
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<tr>
<td>Treatment side effects</td>
<td>1.09 (0.79-1.38)*</td>
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<tr>
<td>Functional well-being</td>
<td>0.35 (−0.14 to 0.84)</td>
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*P<0.05 CI, confidence interval; DRS, disease-related symptoms

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3074 Poster Session (Board #288), Mon, 8:00 AM-11:30 AM

Single-cell RNA-sequencing and -imaging of melanoma ecosystems reveals sources of resistance to immune checkpoint blockade. First Author: Benjamin Izar. Dana-Farber Cancer Institute, Boston, MA

Background: While immune checkpoint blockade (ICB) produces durable responses in some patients with melanoma, most patients derive no clinical benefit, and the molecular underpinnings of ICB resistance (ICR) are elusive.

Methods: We applied single-cell RNA-sequencing (scRNA-Seq) to > 10,000 malignant and non-malignant cells derived from 31 melanoma tumors, including 15 from patients with ICB, 15 treatment-naïve patients, and 1 patient with clinical response. We applied a novel data-driven method to systematically map cancer programs that promote ICR and T cell exclusion.

Results: We demonstrate that cancer cell-autonomous ICR programs identified by scRNA-Seq predict comprise several putative mechanisms of resistance, including several that have previously not been described. In addition to functional implications, we generated a clinically applicable signature that was predictive of clinical response (per RECIST criteria) and progression-free survival (PFS): one of patients who underwent RNA-seq of matched pre-treatment and progression (ICR) specimens; and another of 112 melanoma patients with pre-treatment RNA-seq who receive anti-PD1-1 monotherapy. This scRNA-Seq derived predictive signature was superior to all interrogated previously published signatures. Furthermore, we demonstrated that pharmacological reversal of these oncogenic cell states can be achieved by CDK4/6 inhibition, and explored the impact of this treatment in melanoma at the single cell level. To determine the role of T cell exclusion from the TME as a potential mechanism of ICR, we performed spatially resolved 2D-plex single-cell analysis of matching FFPE specimens from 16 patients who also underwent scRNA-seq. While the integration of these data sets is pending, the presented analytical platforms provide a promising approach to understanding drug resistance within preserved tumor ecosystems.

Conclusions: Our study provides a high-resolution landscape of oncogenic ICR states, identifies clinically predictive signatures, and forms a basis to developing novel therapeutic strategies that could overcome ICR-resistance in melanoma.

3076 Poster Session (Board #290), Mon, 8:00 AM-11:30 AM

Association between PD1 mRNA and response to anti-PD1 monotherapy across multiple cancers. First Author: Laila Panesar. Immunotherapy and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

Background: In advanced cancer, the overall response rate (ORR) following anti-PD1 monotherapy is variable (0% to 50%). Here, we hypothesized that this observation is partly explained by different amounts of the drug target (i.e. PD1) in the tumor. Methods: RNA-seq data from 10,078 tumors representing 34 cancer-types were obtained from TCGA. The expression of PD1 and 566 immune-related genes/signatures were evaluated. Correlations between each gene/signature and ORRs reported in the literature were calculated. We included only studies of anti-PD1 monotherapy that enrolled at least 20 patients (pts) who were not selected for PD1L1 expression. To translate the in-silico findings to the clinical setting, we analyzed the expression of PD1 mRNA using the nCounter platform in 69 formalin-fixed paraffin embedded (FFPE) tumor samples from 16 cancer-types. Finally, we performed spatially resolved 2D-plex single-cell analysis of matching FFPE specimens from 16 patients who also underwent scRNA-seq. While the integration of these data sets is pending, the presented analytical platforms provide a promising approach to understanding drug resistance within preserved tumor ecosystems.

Conclusions: Our study provides a high-resolution landscape of oncogenic ICR states, identifies clinically predictive signatures, and forms a basis to developing novel therapeutic strategies that could overcome ICR-resistance in melanoma.

3075 Poster Session (Board #289), Mon, 8:00 AM-11:30 AM

Phase 1 open-label, ascending dose trial of AGEN1884, an anti-CTLA-4 monoclonal antibody, in advanced solid malignancies: Dose selection for combination with PD-1 Lorcaterol. First Author: Brooklyn A. Wilky. Sylvester Comprehensive Cancer Center, Miami, FL

Background: AGEN1884 is a novel fully human IgG1 monoclonal antibody targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Objective: Assess the safety, maximum tolerated dose, and pharmaco kinetic (PK) and pharmacodynamic characteristics of AGEN184 in patients with advanced or refractory solid malignancies. Methods: Patients (≥18 years old) with relapsed/refractory lymphoma or solid cancers without curative treatment options received AGEN1884 at 0.1, 0.3, 1, 3, or 6 mg/kg in a “3+3” trial design. An additional 10 patients were enrolled in both 1 and 3 mg/kg dose expansion cohorts. AGEN1884 was administered intravenously (IV) every 3 weeks for 4 doses and then every 3, 6, or 12 weeks at the Investigator discretion. Results: As of 03 Jan 2018 data cutoff, 33 patients were enrolled in the following cohorts: 0.1 mg/kg (n = 5, 2 not evaluable [NE] for dose-limiting toxicity [DLT]), 0.3 mg/kg (n = 3, 1 mg/kg [100% MTD]), 1 mg/kg (n = 12, 2 NE for DLT) and 3 mg/kg (n = 3, median age 61 years [range 26–88], baseline ECOG scores were 0 [N = 4], 1 [N = 25], unknown [4], with a median of 10 [range 3–26] prior therapies. As of Jan 2018, no DLTs have been reported. Immune-related adverse events were reported in 10 (30.3%) of patients as follows: 0.1 mg/kg (1 [20.0%]), 0.3 mg/kg (1 [33.3%]), 1 mg/kg (1 [100%]), and 3 mg/kg (6 [50%]) and included hypophysitis, colitis, diarrhea, rash and pruritus. Most were mild–moderate consistent with published reports of other PD-1/PD-L1 agents. 6 patients were discontinued due to disease progression or AE’s but none related to treatment. Of 11 subjects evaluable for response, 1 with angiosarcoma treated at 0.1 mg/kg attained a CR at 7 months after achieving a PR. Three subjects with SD: 1 at 0.3 mg/kg with adenoid cystic carcinoma at Week 21 who had SD at 5 months, 1 with breast cancer with SD at 21 and 1 with invasive metastatic breast cancer at Week 12 on study. Conclusions: AGEN1884 was well tolerated at 0.1, 0.3, 1 and 3 mg/kg dose levels. Enrollment continues at 6 mg/kg. Updated safety and PK data will be presented. A starting dose level of 1 mg/kg has been selected for combination with PD-1 blockade. Clinical trial information: NCT02694822.

3077 Poster Session (Board #291), Mon, 8:00 AM-11:30 AM

Impact of immune checkpoint inhibitor dose on toxicity, response rate, and survival: A pooled analysis of dose escalation phase 1 trials. First Author: Shiraj Sen. The University of Texas Southwestern Medical School, Dallas, TX

Background: PK and PD studies demonstrate drug exposure and target saturation of immune checkpoint inhibitors (ICI) at doses below MTD. MTD remains a primary endpoint in ICI phase 1 trials and the optimal dosing to minimize toxicity and optimize response remains unclear. Methods: We analyzed clinical data from pts treated in phase 1 ICI dose escalation trials at MD Anderson Center for Targeted Therapy. Patients were stratified into a low-dose (LDG) (<33% MTD), medium dose [MDG] (34–66% MTD), high dose [HDG] (67–100% MTD), or very high dose [VHDG] (>100% MTD) group. Groups were compared for irAE, PFS, OS, ORR (CR + PR), and DCR (CR + PR + SD > 6 months). Results: Among 90 pts treated with escalating doses of ICI (57 CTLA-4 and 33 PD1-based) between April 2013 and December 2016, median age was 59 years (range: 20-86 years) and 37 (41%) were females. The most common tumor types treated included renal cell carcinoma (n = 23; 25%), melanoma (n = 16; 18%), sarcoma (n = 10; 11%), and GIST (n = 10; 11%). PFS in the LDG (n = 16) was 2.76 months (mo) (95% CI 1.48-NA), MDG (n = 21) was 2.76 mo (95% CI 1.48-NA), HDG (n = 36) was 2.46 mo (95% CI 1.84-3.29), and VHDG (n = 17) was 3.68 mo (95% CI 2.76-NA). Log rank p = 0.22. OS in LDG was 6.18 mo (95% CI 3.45-NA), MDG was 17.05 mo (95% CI 3.94-NA), HDG was 5.16 mo (95% CI 4.24-7.62), and VHDG was 7.49 mo (95% CI 5.59-NA). Log rank p = 0.0070. In all evaluable patients, ORR in LDG, MDG, HDG, and VHDG was 0%, 6%, 6%, and 12% (p = 0.47) and DCR was 62%, 71%, 41%, and 81% (p = 0.027), respectively. irAE rates in LDG, MDG, HDG, and VHDG were 6%, 10%, 17%, and 29% (p = 0.045). Conclusions: Despite a dose-dependent increase in irAE, we identify no improvement in PFS, OS, or DCR with escalating doses of ICI administered in phase 1 trials but did detect an improvement in ORR. Prospective dose-exposure-response relationships and biomarker-driven RP2D are warranted on all ICI dose-escalation phase 1 trials. Lower doses may reduce toxicity and cost without compromising disease control or survival.

Dosing PFS, months (95% CI) OS, months (95% CI) ORR (%) DCR (%) irAE (%)

<table>
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<th>Dose</th>
<th>PFS</th>
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<th>ORR</th>
<th>DCR</th>
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<td>LDG</td>
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<td>VHDG</td>
<td>3.68 (2.76-NA)</td>
<td>7.49 (5.59-NA)</td>
<td>12</td>
<td>29</td>
<td>25</td>
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Phase II open-label, multi-centre study of bemcentinib (BGB324), a first-in-class selective AXL inhibitor, in combination with pembrolizumab in patients with advanced NSCLC.

Background: Bemcentinib (BGB324) is a first-in-class, oral, potent and highly selective inhibitor of the AXL tyrosine kinase currently in phase II clinical development across several cancer types. AXL over-expression has been observed in pts failing PD-1 therapy in several cancers whereas AXL inhibition via bemcentinib has shown synergistic effect with checkpoint blockade in pre-clinical models of NSCLC.

Methods: In this single-arm, two-stage Phase 2 study, pts with documented Stage IV lung adenocarcinoma progressed on a single line of platinum-based chemotherapy chemotherapy and – if applicable – at least one line of licensed therapy for EGFR mutations or ALK re-arrangements received 200 mg/d bemcentinib po and 200 mg/ q3wk pembrolizumab iv. Patients were required to consent to a fresh pre-treatment biopsy. Tumour assessments were done 9-weekly. The primary endpoint was objective response. Predefined secondary endpoints included disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety. Tumour biopsies were analysed for PD-L1 and AXL, and infiltrating immune cells. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in patients pre-dose and at C2D1.

Results: As of February 2018, 13 pts (median age 66 years) initiated therapy and 11 pts remain on treatment. Combination therapy was well tolerated with the overall serious adverse event profile being similar to that reported for pembrolizumab monotherapy. 1 of 4 pts (25%) who had reached their first scan showed a PR and another patient (22%) had SD. There were no grade 4 treatment-related events. Dose reduction from 200 to 100 mg/d of bemcentinib as a consequence of adverse events was required in 12% of patients.

Conclusions: Combination treatment of bemcentinib and pembrolizumab was well tolerated. A preliminary analysis of response to combination treatment during the first stage of this study as well as biomarker correlation will be presented at the meeting. Clinical trial information: NCT03184571.

Safety and efficacy results from a phase I dose-escalation trial of Nintedanib in combination with pembrolizumab in patients with advanced solid tumors (PEMBIB trial).

First Author: Andreea Varga, Gustave Roussy Cancer Campus, Villejuif, France

Background: We aimed to determine the safety and activity of the nintedanib +pembrolizumab combination. Nintedanib is an oral angiokinase inhibitor targeting the vascular endothelial, platelet-derived and fibroblast growth factor receptors as well as RET. Pembrolizumab is a highly selective, humanized monoclonal IgG4 antibodies targeting the vascular endothelial, platelet-derived and fibroblast growth factor receptors as well as RET. Pembrolizumab is a highly selective, humanized monoclonal IgG4 antibodies targeting the PD-1 receptor expressed by T cells.

Methods: PEMBIB is a monocentric phase Ib trial which evaluated escalating doses of nintedanib (Dose level 1 (DL1) = 150 mg BID; DL2 = 200 mg BID) in combination with intravenous flat dose of pembrolizumab at 200 mg every 21 days in patients with advanced solid tumors using the rolling 6 design. A lead-in monotherapy of nintedanib was performed 7 days prior starting pembrolizumab. The primary objective was to establish MTD of this combination based on DLT occurrence during the first 4 weeks (28 days since C1D1) and to determine the recommended phase 2 dose (RP2D).

Results: As of November 24, 2016, 13 patients (12 evaluable for DLT) have been enrolled in the escalation part: 2 cervical carcinoma, 1 malignant pleural mesothelioma, 1 peritoneal mesothelioma, 1 gastric adenocarcinoma, 1 renal carcinoma, 1 neuroendocrine tumor, 1 nasopharyngeal cancer. The median age was 54, of these 50% were male, all ECOG 0 (83%) or 1. There were no grade 4-5 toxicities. The adverse events reported for more than 2 patients were alanine & aspartate aminotransferase increase, fatigue, anorexia, diarrhea, nausea, vomiting, hypothyroidism. Three dose-limiting toxicities of liver enzymes elevation were observed in 200 mg BID nintedanib thus recommending 150 mg BID nintedanib for the phase II part. Three patients have developed an objective RECIST partial response (ORR = 25%).

Conclusions: Toxicity was consistent with the safety profile of each drug. Additional data for safety and efficacy is being further evaluated in the expansion part of this trial. The efficacy of the combination is currently further explored in 8 expansion cohorts of 30 patients. Clinical trial information: NCT02856425.

Autoimmune genetic variants as germline biomarkers of response in melanoma immunotherapy treatment.

First Author: Vylyny chat, New York University School of Medicine, New York, New York, USA

Background: Immune checkpoint inhibition (ICI) has improved clinical outcomes for metastatic melanoma patients. However, – 60% of patients do not respond to ICI and 65-80% experience immune-related adverse events (irAEs). Currently, the personalized biomarkers predicting ICI efficacy or toxicity are limited. Given the link between immunotherapy, irAEs and autoimmunity, we investigated if the baseline genetic susceptibility to multiple autoimmune diseases can modulate clinical efficacy of ICI.

Methods: By performing a comprehensive search of autoimmune genome wide association studies, we identified 25 SNPs, each associated with at least 3 autoimmune diseases. Using the Agera MassArray, we genotyped 25 SNPs in 389 Caucasian metastatic melanoma patients receiving ICI treatment (N = 214 anti-CTLA4, N = 175 anti-PD1) at one of our collaborative centers. Multivariate logistic regression adjusting for age at treatment and gender was used to test for association of germline variants with ICI efficacy.

Results: We identified two variants previously associated with multiple autoimmune diseases that may predict ICI efficacy: rs1893217 in PTPN2 (OR = 0.35; 95%CI = 0.17-0.73; p = 0.009) and rs17388568 was associated with clinical benefits in anti-CTLA4 and anti-PD1 ICI, respectively. These variants predict efficacy in opposite direction - rs1893217 was associated with anti-CTLA4 treatment resistance while rs17388568 was associated with delayed disease progression.

Conclusions: Our study reports two autoimmune germline variants as potential biomarkers of anti-CTLA4 or anti-PD1 ICI efficacy in melanoma and suggests that underlying genetic susceptibility to autoimmunity may play an important role during ICI treatments. rs1893217 in PTPN2, involved in cytokine signaling, has been associated with collagen disease, inflammatory bowel, rheumatoid arthritis and type 1 diabetes. Similarly, rs17388568 was mapped to important immune-related genes (IL2, IL21 and ADAD1) and associated with allergy, colitis and type 1 diabetes. Additional genetic and functional validation of these findings is underway in a large collaborative setting.

Role of melanoma cell-intrinsic RIG-I and STING signaling for checkpoint inhibitor-mediated anticancer immunity.

First Author: Simon Heidegger, Klinikum rechts der Isar, Technical University Munich, Munich, Germany

Background: Strong inter-individual variation in clinical response to immune checkpoint inhibitors (ICB) including anti-CTLA-4 remains a major challenge, but the molecular pathways that modulate ICB efficacy remain ill defined. Methods: Using CRISPR/Cas9 technology to generate melanoma cell lines that lack nucleic acid receptors or downstream signaling molecules together with available genetically deficient mouse models, we addressed the importance of nucleic acid receptor signaling in both tumor and host cells for the efficacy of anti-CTLA-4 immunotherapy.

Results: We demonstrate that anti-CTLA-4 immunotherapy relies on melanoma cell-intrinsic activation of the cytosolic RNA receptor RIG-I (DDx58) but not the DNA sensing adaptor protein STING. Mechanistically, RIG-I signaling induced caspase-3-mediated tumor cell death, cross-presentation of tumor-associated antigen by CD103+ dendritic cells, subsequent expansion of tumor antigen-specific CD8+ T cells and the accumulation of CD8+ T cells within the tumor tissue. These processes were independent of tumor-cell derived type I IFN (IFN-I), but additionally required host STING, Mavs and IFN-I signaling. Consistently, therapeutic targeting of RIG-1 with 5’-phosphorylated-RNA in both tumor and non-malignant host cells potently augmented the efficacy of CTLA-4 checkpoint blockade.

Conclusions: Our data are consistent with the finding that expression of RIG-I in human melanomas has been associated with clinical benefit to CTLA-4 blockade and identify activation of RIG-I/STING signaling in tumors and their microenvironment as a crucial component for checkpoint inhibitor-mediated immunotherapy of cancer. These findings not only nominate tumor intrinsic RIG-I activity as potential biomarker for treatment response to checkpoint inhibitors, but predict that targeting this pathway may serve as a basis for the development of new combined modality approaches to increase the response rate of checkpoint inhibitor-based immunotherapy, particularly in individuals that do not have a sufficient spontaneous antitumor T-cell immune response.
Allo-immunity and graft rejection after checkpoint inhibitor therapy (CPI) in solid organ transplant (SOT) recipients. First Author: Noha Abdel-Wahab, Section of Rheumatology & Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The safety of CPI in patients (pts) with prior SOT was never fully assessed because they were always excluded from clinical trials due to the risk of allo-immunity and organ rejection, and being on immunosuppressive therapy (IST). Methods: We identified from pharmacy records pts who had received CPI between January 2004 and June 2017 at our institution (n = 4,406). Claims data were obtained for all pts from 6 months prior to first infusion to last follow-up or death. ICD 9 & 10 diagnostic codes were used to identify pts with organ transplant (n = 173). Medical records were reviewed to identify SOT pts. We systematically reviewed the literature databases through September 2017 to identify similar pts. Results: A total of 24 pts were retrieved, 6 from institutional databases and 18 from literature. Median age of CPI after SOT was 8 (1-25) years. Most received anti-PD1 agents (79%).

Conclusions: Neurologic irAEs are uncommon but potentially fatal toxicities of immune checkpoint blockade (ICB). Their incidence, clinical and pathologic features, and association with therapy received are poorly understood. Methods: An IRB approved retrospective study was conducted to identify neurologic irAEs of all patients (pts) treated with ICB (anti-CTLA4, anti-PD1, anti-PDL1 monotherapy or in combination) from January 2010 to August 2017 at our institution. Clinical, radiologic, and pathologic features of neurotoxicity were collected. We excluded pts with primary CNS tumors or neurologic symptoms that were attributable to their CNS disease. Results: Of 4,864 pts who received anti-CTLA4, anti-PD1, or anti-PDL1 either as monotherapy or in combination, neurologic irAEs developed in 81 (1.67%; 95% CI, 1.34% to 2.06%). Clinical, radiographic, and radiologic features of neurotoxicity were diverse. Time to onset ranged from 3 days to 17 months with a median of 2 doses (1 to 20) received. The incidence was higher with combination therapy versus monotherapy (36 of 1,448 [2.49%] v 45 of 3,416 [1.32%]; P = 0.0047), and there was no significant difference in incidence among pts age ≤ 65 at time of treatment versus pts age > 65 (41 of 2,705 [1.90%] v 40 of 2,159 [1.85%]; P = 0.3692).

Efficacy and immune modulation by BXCL701 a dipheridyl peptide inhibitor, NKTR-214 a CD122-biased agonist monoclonal antibody, in motion pancreatic tumors. First Author: Luca Rustelli, bioncel therapeutica, Branford, CT

Background: BXCL701 targets DPP8/9 and stimulates migration and cytotoxicity of T and NK cells in addition to targeting fibrolast activator protein (FAP) which forms an immunological barrier to the tumor microenvironment. NKTR-214 is a CD122-biased agonist designed to provide sustained signaling through the heterodimeric IL2 receptor pathway (IL2Rβγc) to preferentially activate and expand effector CD8+ T and NK cells. NKTR-214 has demonstrated robust anti-tumor activity when combined with anti-PD1 in multiple murine tumor models and recently, with nivolumab in multiple human cancers. We hypothesized that BXCL701 could further potentiate NKTR-214/anti-PD1 anti-tumor activity by removing fibrotic barriers to immune cells. Methods: NKTR-214, BXCL701 and anti-PD1 were dosed in mice bearing established (~100mm³) murine pancreatic tumors (Pan02) as single agents, doublets and the triplet (0.8mg/kg q9d, 20 qw2 respectively). Tumors were profiled using IHC and multiplex serum cytokine/chemokine analysis. Tumor-free mice were re-challenged with either Pan02 or murine lung tumor (LLC). Results: Of the mice treated with the triplet combination, 100% became tumor-free (9/9) by day 21. These animals remained tumor free for more than 60 days when a subset were re-challenged with new tumor cells. Of these, 5/6 mice rejected tumor regrowth suggesting durable immunity after the triplet therapy. IHC of the tumors from satellite animals sacrificed on day 3 revealed that the triplet significantly reduced FAP expression while increasing the number of immune cell infiltrates in the tumor. Conclusions: The triplet of NKTR-214, BXCL701 and anti-PD1 provided 100% tumor-free mice in established pancreatic tumors with concomitant reduction in FAP expression. The results suggest that removal of fibrotic barriers to immune infiltration is an important mechanism for overcoming immune escape by tumors otherwise resistant to immune therapy. These results provide therapeutic rationale for treatment of pancreatic cancer patients with this triple combination.

Phase 1/2 open-label, multiple ascending dose trial of AGEN2034, an anti-PD-1 monoclonal antibody, in advanced solid malignancies: Results of dose escalation. First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: AGEN2034 is a fully-human IgG4 monoclonal anti-body antagonist targeting Programmed Cell Death Protein-1 (PD-1). The objective was to assess safety, MTD, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AGEN2034 in patients (pts) with advanced, refractory malignancies. Analyses of PD-1 receptor occupancy on circulating CD8+ and CD4+ effector memory T lymphocytes was completed. Methods: Thirty pts were enrolled in escalating dose cohorts of 1, 3, and 10 mg/kg. AGEN2034 is administered intravenously qw2 for up to 2 years with cohorts evaluating qw2 dosing at 6 and 10 mg/kg. Twenty of 30 pts had treatment-related adverse events consistent with this drug class were observed of pneumonitis, colitis, diarrhea, rash and pruritus. 21 of 30 pts had treatment-related adverse events (TRAEs). 13 subjects (43%) discontinued (dc) due to disease progression and 2 pts dc due to TRAEs of hepatitis (n = 1) and pneumonitis (n = 1). In 25 evaluable heavily pre-treated pts, three partial responses (two confirmed) were noted in patients with cervical, ovarian and breast cancers in 1mg/kg and 3mg/kg cohorts. At the time of data cut-off, 13 patients had stable disease, including 5 of 5 with ovarian cancer. AGEN2034 demonstrates a dose-proportional Cmax of 19.6 µg/mL at 1 mg/kg and 73.6 µg/mL at 3 mg/kg in 12 patient samples analyzed in the first two cohorts. Average PD-1 receptor occupancy on circulating CD8+ and CD4+ effector memory T lymphocytes (n = 18) demonstrated > 59% saturation at all dose levels at day 15. Conclusions: AGEN2034 is a pharmacologically active, well-tolerated PD-1 antagonist antibody, demonstrating early signals of clinical activity in cervical and ovarian cancers. PK and RO results are comparable to commercial PD-1 antagonists. A phase 2 expansion in pts with relapsed/refractory cervical cancer is underway. Clinical trial information: NCT03104699.
Characterization of immune related hepatitis (irH) from immune checkpoint inhibitors (ICIs). First Author: Justine Vanessa Cohen, Massachusetts General Hospital, Boston, MA

Background: Immune related hepatitis (irH) occurs in a subset of patients receiving ICIs. Although the pathologic features of irH have been described, no studies have correlated the histologic findings on liver biopsy with steroid responsiveness. Methods: 25 patients with cancer (22 melanoma, 1 cutaneous squamous cell carcinoma, 1 glioblastoma, 1 non-small cell lung cancer) who had a liver biopsy for elevated transaminases were included. 23 patients received anti-PD-1, anti-CTLA4 or a combination of ICI with a non-ICI agent. 2 patients underwent biopsies after targeted therapy. Liver biopsies were reviewed for pattern of injury. Steroid response and requirement for secondary immunosuppression was determined from clinical notes. The pattern of hepatic injury was correlated with response to steroids. Results: 15 biopsies showed evidence of lobular injury that was often centrilobular, but in some was panlobular, with a histiocytic inflammatory response. In 6, the histiocytes formed granulomas that were loose, well-formed, or fibrin ring type. 5 of the 15 had central vein endothelialitis. Another 3 patients had mild lobular or portal inflammation without typical features of irH. 2 patients had cholestatic patterns, with portal edema, duct injury, and a bridging necrosis. 3 remaining patients had non-inflammatory patterns of hepatic injury such as hepatocyte cytoplasmic rarefaction. 19 (76%) patients required steroids and 6 (24%) required secondary immunosuppression. 11 (73%) of the 15 cases with characteristic irH were steroid responsive (resolution of transaminases within ~2 months). The 2 cholestatic cases were less responsive to steroids (one required > 2 months of steroids and the other required secondary immunosuppression). Patients with fatty liver and non-inflammatory injury had variable response to steroids. Conclusions: ICI hepatitis has a characteristic pattern of lobular injury with histiocytic infiltration, granuloma formation, and endothelialitis on liver biopsy is highly likely to be steroid responsive. A cholestatic pattern of injury predicts less steroid responsiveness. Non-inflammatory hepatic injury on liver biopsy has variable steroid responsiveness.

Pelareoep to promote the expression of a IFN-gamma-related gene signature that elicits response to checkpoint blockade therapy. First Author: Grey A Wilkinson, Oncolytics Biotech Inc., Calgary, AB, Canada

Background: A clinical study in patients (pts) with metastatic breast cancer (mBC) treated with pelareoep resulted in significant improvements in overall survival. Clinical studies with checkpoint blockade inhibitors (CBIs) have also resulted in noteworthy clinical responses in a small subset of mBC pts. In pts who do not respond to CBIs, the absence of IFN-γ signaling in the tumor microenvironment has been proposed as a key mediator of innate resistance. IFN-γ signaling upregulates the expression of checkpoint ligands and promotes lymphocyte activation and infiltration to the tumor microenvironment. Thus, the expression of IFN-γ-related genes can be used to both facilitate and predict response to CBIs. Given pelareoep’s known capacity to promote an infiltrated tumor phenotype, we hypothesised that pelareoep could also stimulate the expression of IFN-γ-related genes associated with response to CBIs. Methods: Cells lines derived from breast cancer (BC; MCF7, T47D, MD-231), colorectal cancer (CRC; HT-29, SW620), hepatocellular carcinoma, (HCC; SNU-387) and non-small cell lung cancer (NSCLC; H522) were infected with pelareoep at a multiplicity of infection equal to 50. We examined changes in gene expression and conducted cell viability assays at 6, 12, and 18 hours post-infection (including a non-infected control). To monitor changes in gene expression we employed a 780-gene panel (nanoString) to monitor for changes in the expression of key IFN-γ-related and other immunity-related genes. Results: All cell lines were susceptible to pelareoep induced cytopathic effect. Strikingly, BC and HCC cells lines significantly upregulated IFN-γ-related genes while CRC and NSCLC cell lines demonstrated only a modest and variable ability to promote IFN-γ pathway activation. Moreover, BC and HCC cells lines also upregulated key chemokines that are known to promote response to immunotherapy. Conclusions: These results suggest that various tumor types are amenable to immune priming for CBIs therapy with pelareoep. The role of pelareoep in the treatment of BC and HCC deserves further investigation, particularly in combination with other immunotherapies.

Identifying new biomarkers and targeted molecules for immunotherapy using targeted RNA next generation sequencing. First Author: Wanlong Ma, NeoGenomics Laboratories, Aliso Viejo, CA

Background: Predictive biomarkers for selecting of patients who may benefit or experience serious adverse effects from checkpoint blockade therapy are urgently needed. These biomarkers may vary from one type of tumor to next. Developing a broad approach for the discovery of new tissue-specific predictive biomarkers may also help guide combination therapy. We used targeted RNA sequencing for the discovery of biomarkers that are correlated with PD-L1 expression. We used RNA sequencing of 1385 genes to profile tissues from solid tumors and lymphomas and correlated RNA levels with PD-L1 expression as detected by IHC in tumor and inflammatory cells. Results: After normalization, adjusting for group effect and multiple hypothesis testing, 21 genes correlated with PD-L1 expression; fourteen genes correlated positively and 7 correlated negatively. Using the first principle component, we demonstrated that these 21 genes are highly redundant in predicting levels of IHC PD-L1 expression and practically any one can be used as a biomarker. Using LASSO to develop a multivariable model, we demonstrated that RNA levels of CD274, PLAU (uPA), and RAC1 are independent biomarkers predictive of IHC PD-L1 expression. Conclusions: RNA expression, measured using targeted NGS, is a reliable alternative to IHC PD-L1 expression testing. We showed that RNA levels of CD274, which codes for PD-L1, and 20 other genes can be used interchangeably in predicting IHC PD-L1 expression. Further, as RNA expression of PLAU and RAC1 are independent from CD274, targeting PLAU and RAC1 in combination with PD-L1 inhibitors potentially may augment the therapeutic effects of anti-PD-L1 therapy.
3091 Poster Session (Board #305), Mon, 8:00 AM-11:30 AM
Phase I trial of BMS-986253, an anti-IL-8 monoclonal antibody, in patients with metastatic or unrespectable solid tumors. First Author: Julie Marie Collins. National Cancer Institute, Bethesda, MD.

Background: BMS-986253 is a novel fully human monoclonal antibody that binds to and inhibits IL-8, a chemokine that promotes immune escape and tumor progression. High serum IL-8 levels correlate with poor prognosis in various cancers (Sanmamed et al. Clin Cancer Res. 2014). IL-8 stimulates recruitment of myeloid-derived suppressor cells (MDSCs) and promotes epithelial-mesenchymal transition (EMT) in tumors conferring resistance to immune-mediated killing (David et al. Vaccines 2020). We hypothesize that IL-8 inhibition shown the ability of BMS-986253 to reduce mesenchymal features in cancer cells leading to enhanced susceptibility to NK and T cell-mediated lysis, and to decrease the frequency of granulocytic MDSCs in xenograft models. Decreases in serum IL-8 were also associated with response to anti-PD1 therapy in a small cohort of patients with melanoma and NSCLC (Sanmamed et al. Ann Oncol. 2017). Methods: Patients with metastatic or unrespectable locally advanced malignant solid tumors were treated with BMS-986253 monotherapy at 4, 8, 16, or 32 mg/kg IV in a Phase I, open-label, 3+3 dose-escalation study. The primary objective was to determine the safety and tolerability and establish a recommended starting dose (RSD).

Pharmacokinetics and changes in serum cytokine levels including IL-8 were also evaluated. Results: Amongst 15 patients, no serious treatment-related adverse events (TRAES) were observed and MTD was not identified through 32mg/kg. TRAEs occurred in 5 pts (33%), and all were Grade 1 or 2. No TRAEs were Grade 4 or 5. Reductions in serum IL-8 levels were observed at all dose levels. Changes in serum cytokines including IL-8 and IL-10 were assessed q4 cycles (range, 1-16) of SEA-CD40 at doses 0.6-60 mcg/kg on Day 1 (n = 38), or 30 mcg/kg on Days 1 and 8 (n = 10) IV q3 wks. SEA-CD40 maximum concentrations increased dose-proportionally (10-60 mcg/kg; Day 1 dosing), with mean half-life estimates of 32-95 hrs and no accumulation upon repeat dosing. Dose-limiting toxicities occurred in 5 pts; all were infusion-related reactions (IRRs). Treatment-emergent AEs in 25% of pts were IRR (69%), chills (65%), fatigue (54%), nausea (52%), vomiting (35%), and dyspnea and headache (27% each). No treatment-related G3 AEs were reported. Chemokine/cytokine changes and associated immune-trafficking changes observed in the peripheral blood and tumor microenvironment support the proposed mechanisms of action. Best response in 34 efficacy-evaluable pts was PR (basal cell carcinoma) and 10 SD, for a 32% disease control rate (DCR) in CR-PR-SD by RECIST. 5 pts had confirmed disease control as assessed at Cycle 8 (6 mos). Conclusions: SEA-CD40 monotherapy shows clinical (32% DCR) and biological activity in heavily pre-treated pts with advanced solid tumors. SEA-CD40 has a generally tolerable safety profile; strategies to manage AEs are being evaluated as dose escalation continues at defined MTD. Combination therapy dose escalation (SEA-CD40 + pembrolizumab) in solid tumors is underway, as is monotherapy dose escalation in lymphomas. Clinical trial information: NCT02536469.

3092 Poster Session (Board #306), Mon, 8:00 AM-11:30 AM
Single intravenous preoperative administration of the oncolytic virus Pexa-Vec to prime tumor immunity. First Author: Alan Anthony, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background: Oncolytic viruses (OV) constitute a promising modality of cancer therapy. Intra-tumoral administration has yielded encouraging clinical results, but restricted the use of OV to tumors that are readily accessible. Pexa-Vec, a Thymidine Kinase–Deactivated Vaccinia Virus expressing GM-CSF, has been shown previously to successfully target tumor tissue after intra-tumoral administration (Breitbach C.J. et al., 2011). Herein, we report data on the immunostimulatory effects of a single intravenous (i.v.) administration of Pexa-Vec prior to surgical resection in patients with advanced solid tumors.

Methods: Patients with operable tumors received a single i.v. administration of 1x10^7 plaque forming units of Pexa-Vec, 14 days prior to surgical resection. Up to six blood samples were collected pre- and post-injection for each patient. Tumor tissue was collected at surgery for histologic and translational assessments. Results: The study included 3 patients with metastatic melanoma and 5 with colorectal cancer metastases to the liver (CRLM). Pexa-Vec injection was well tolerated in all cases. Histologic examination of tumor tissue indicates the presence of virus in tumor at the time of surgery. Of the 3 evaluable CRLM, 2 show signs of inflammation and fibrosis, within the background liver. Phenotyping of peripheral blood mononuclear cells showed robust activation of Natural Killer (NK) and professional antigen presenting cells (CD14+), as well as CD4+ and CD8+ cells, with high CD69 expression. Functional assays revealed increased patient NK cell degranulation in the presence of tumor cell lines consistent with cellular killers. Pexa-Vec induced a significant elevation of serum cytokines associated with immune response including IFNα, IL3, IL12p40, IL16, IL18. Conclusions: When administered intravenously, Pexa-Vec exhibited a selective persistence in tumor tissues suggesting a targeted oncolytic action in the tumor. Concur- rent anti-OV-VectoChimericA (OV-ve) targeting resulted in robust immune activation of both innate and adaptive immune cells. These data strongly support the rationale for sequential JX-594 and anti-PD-1 vino-immunotherapy, which is the focus of the ongoing study, NCT03071094. Clinical trial information: ISRCTN13913966.
Pharmacodynamic and clinical activity of RGX-104, a first-in-class immunotherapy targeting the liver-X nuclear hormone receptor (LXR), in patients with refractory malignancies. 

**Methods:** We are conducting a Phase 1 clinical trial in advanced, refractory solid tumors. 

**Results:** RGX-104 was dosed orally in 23 patients with a broad array of tumors on 5 cohorts at doses ranging from 120 mg QD for 3 of 4 weeks to 200 mg BID continuously. Following single dosing, PK analysis demonstrated high inter-patient variability with 1.6-fold, from 6 – 8 hr. 

**Conclusions:** A Patient with a platinum-refractory, high-grade neuroendocrine carcinoma expressing MUC1 has demonstrated low toxicity and encouraging antitumor activity. Our data supports further clinical evaluation in a larger study cohort. 

Clinical trial information: NCT02922764.

First-in-man study of Ad-sig-hMUC-1/ecdCD40L vector vaccine in cancers expressing MUC1 has demonstrated low toxicity and encouraging antitumor activity. We report results of the first-in-class LXR-agonist RGX-104 in advanced cancer patients. RGX-104 was well tolerated with dose escalation to 160mg BID and demonstrated robust PD effects on ApoE expression and relevant immune cell populations. Dose escalation with a PD-1 inhibitor has begun with plans to study RGX-104 both as monotherapy and in combination with a PD-1 inhibitor in select malignancies. 

Clinical trial information: NCT02922764.

Conclusions: irAEs from immune checkpoint inhibitors can result in prolonged hospitalizations, need for immunosuppressive, inpatient mortality, and high readmission rate. The number of admissions for irAEs has increased from < 0.5% to 2% over the last 5 years. The most common irAEs were gastrointestinal (43.9%), pulmonary (16%), hepatic (15%), neurologic (8.9%), endocrine (7.1%), rheumatologic (4%), dermatologic (3%), cardiac (3%), renal (1.8%), and allergic (1.9%).

**Conclusions:** The national burden of irAEs has increased significantly in the recent years, but comfort level in managing these complications is low. Consequently, there is a critical need for coordinated multidisciplinary approach, comprehensive provider education, and translational research programs for early detection and intervention.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Utility of comprehensive genomic profiling (CGP) for personal cancer vaccine development via neoantigen analysis. First Author: Dana Vyzum, KEW, Inc., Cambridge, MA

Background: Cancer vaccines against neoantigens have shown promise in treating advanced stage cancers [1,2]. Typically, detection of somatic mutations underlying neoantigen expression is done using WES, a cost and time-ineffective platform for routine clinical use. Here, we assess the feasibility of a large NGS panel for use in cancer vaccine development through discovery of somatic mutations and prediction of neoantigen load.

Methods: Various patient tumor samples with a range of mutational loads (n = 30; mean: 84 mutations, range: 34-248) were profiled using CANCERPLEX, a 435-gene panel for identifying clinically-relevant genomic alterations in cancer [3]. For each mutation, all possible 9- and 10-mer peptides were enumerated. For mutations that result in novel open reading frames (neoORF), peptides overlapping the entire neoORF were considered. The 28 most frequent HLA-A and HLA-B alleles in the Caucasian, African, and Asian populations were used. Peptides were computationally evaluated for binding to HLA using the NetMHCpan-3.0 algorithm [4]. For each neoantigen, the rank relative to the collective mutant and wildtype 9- or 10-mers was determined. Neoantigens were classified as strong binders if rankmutant/rankwt relative to the collective mutant and wildtype 9- or 10-mers was determined. This algorithm-dependent distribution suggests that certain HLA alleles are better binding partners for potential neoantigens or preferential for certain peptide. Conclusions: The high number of neoantigens identified suggests that CGP is a feasible alternative to WES for cancer vaccine development. CANCERPLEX accurately detects somatic mutations [3] thus enabling prediction of tumor neoantigens, an emerging biomarker in immunotherapy [5]. Future studies incorporating HLA transcription testing with CGP are warranted to further establish the platform for cancer vaccine development.

ZUMA-2: Phase 2 multicenter study evaluating efficacy of kte-c19 in patients with relapsed/refractory mantle cell lymphoma. First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Mantle cell lymphoma (MCL) is an aggressive B cell malignancy, and accounts for ~6% of non-Hodgkin lymphomas. Despite high initial response rates, MCL is generally considered incurable, as almost all patients (pts) eventually progress (Cheah et al. J Clin Oncol. 2016). Bruton tyrosine kinase (BTK) inhibition can lead to high rates of prolonged responses in relapsed/refractory (R/R) MCL, as noted with ibrutinib (Wang et al. NEJM, 2013) and acalabrutinib (Wang et al. Lancet. 2017). However, many pts develop ibrutinib-resistance and outcomes to salvage regimens (including investigational agents) are poor with a response rate of 32% and median overall survival of 8.4 months (Cheah et al. Ann Oncol. 2015). This phase 2, multicenter, open-label study examines efficacy and safety of KTE-C19, an autologous anti-C19 chimeric antigen receptor (CAR) T cell therapy, in pts with R/R MCL who have progressed on prior chemotherapy, an anti-CD20 antibody, and a BTK inhibitor. Methods: ZUMA-2 (NCT02601313) is enrolling pts with R/R MCL sequentially into 2 separate dose level cohorts (~40 pts each). After leukapheresis and manufacturing, pts will receive conditioning chemotherapy with fludarabine 30 mg/m^2/d and cyclophosphamide 500 mg/m^2/d x 3 d and then receive a single infusion of KTE-C19 cells at a dose of 0.5 x 10^9 CAR T cells/kg. The primary endpoint is objective response rate by Independent Review Committee assessment; secondary and exploratory endpoints include duration of response, progression-free survival, overall survival, incidence of adverse events and levels of CAR T cells and cytokines in blood. Eligible adult pts with pathologically confirmed R/R MCL and an ECOG of 0-1 must have received ≤ 5 prior therapies that must have included an anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib. Pts who received an autologous stem cell transplant or prior CD19-directed therapy or those with clinically significant infection or a history of central nervous system lymphoma or central nervous system disorders are not eligible. Accrual is ongoing. Clinical trial information: NCT02601313.
A phase 1 multicenter study evaluating the safety and efficacy of MHC class II-restricted MAGE-A3/6 T-cell receptor engineered T cells (KITE-718) in patients with advanced cancers. First Author: Psaltis, Panagiotis, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Melanoma-associated antigens 3 and 6 (MAGE-A3/6) are among the most commonly expressed cancer testis antigens in a variety of tumors and are associated with poor disease prognosis. Antitumor activity, including partial and complete responses, has been observed with MHC class II-restricted T-cell receptor (TCR)-engineered T cells targeting MAGE-A3 and MAGE-A6 (Lu et al. J Clin Oncol. 2017). In this study, the safety and antitumor activity of KITE-718, an autologous TCR-engineered T cell therapy targeting MAGE-A3/6, will be evaluated in HLA- DPB1*04:01-positive patients with advanced cancers. Methods: Phase 1A of the study (NCT03193970) uses a single-patient dose-escalation scheme to evaluate safety and determine the recommended Phase 1B dose of KITE-718, enrolling up to 30 patients. Phase 1B will include 45 patients with non-small cell lung cancer, urachal cancer, and all other MAGE-A3/6-positive tumors treated at the recommended KITE-718 dose. For both portions of the study, after leukapheresis patients may receive optional bridging therapy prior to conditioning chemotherapy. After manufacture in a sterile cyclophosphamide and fludarabine conditioning chemotherapy followed by KITE-718 at a dose of 1 × 10^6 to 1 × 10^7 TCR-transduced T cells/kg. Following KITE-718 infusion, patients will receive daily subcutaneous IL-2 therapy for a maximum of 14 days. The primary endpoint for Phase 1A is incidence of adverse events as defined as dose-limiting toxicities. The primary endpoint of the Phase 1B study is investigator assessment of objective response rate per modified RECIST v1.1 or IMWG criteria. Secondary endpoints include duration of response, progression-free survival, overall survival, and safety. Patients aged ≥ 18 y must be HLA- DPB1*04:01-positive, have relapsed/refractory MAGE-A3/6-positive advanced solid tumors, have adequate bone marrow and organ function. Patients amenable for loco-regional therapy or with history of stroke, myocardial infarction, or symptomatic deep vein thrombosis/pulmonary embolism are not eligible. The study is open and accruing patients. Clinical trial information: NCT03193970.

A phase 2 study to assess the efficacy and safety of autologous tumor infiltrating lymphocytes (TIL, LN-145) alone and in combination with anti-PD-L1 inhibitor durvalumab in patients with locally advanced or metastatic NSCLC. First Author: Sylvia Mina Lee, University of Washington - Seattle Cancer Care Alliance, Seattle, WA

Background: Adoptive cell therapy with TIL has demonstrated durable complete responses in immunogenic tumors with high mutational burden. Durvalumab, which enhances T-cell antitumor cytotoxicity through blockade of the PD-1/PD-L1 pathway, has shown clinical activity in NSCLC. Despite recent advances in the treatment of NSCLC using checkpoint inhibitors, the majority of patients do not respond, leaving an unmet need to improve therapeutic outcomes, warranting this investigation of TIL therapy alone and in combination with durvalumab. IOV-LUN-201 is a phase 2 multicenter, open-label study designed to evaluate the efficacy and safety of autologous LN-145 therapy alone or in combination with durvalumab, for previously-treated, anti-PD-1/PD-L1-naïve NSCLC patients. Methods: LN-145 is a preparation of TIL extracted from surgically-resected tumors and manufactured in a 22-day process at a central GMP facility. LN-145 infusion is preceded by a non-myeloablative lymphodepletion regimen of cyclophosphamide and fludarabine, and followed by up to 6 infusions of IV IL-2. Cohort 1 patients receive LN-145 therapy alone. Patients in Cohort 1 who do not receive LN-145 or those who progress following LN-145 therapy can receive durvalumab 1500 mg IV Q4W until progression or unacceptable toxicity. Cohort 2 patients receive durvalumab 2 weeks prior to and 2 weeks after tumor harvest, and then following LN-145 infusion resume durvalumab 1500 mg IV Q4W until progression or unacceptable toxicity. Patients unable to receive LN-145 are allowed to receive durvalumab alone. Patients ≥ 18 years of age must have confirmed stage III/IV NSCLC and have received ≥1 line of prior systemic therapy, including anti-PD-1/anti-PD-L1. Other major eligibility criteria include: minimum of 2 tumor lesions, adequate organ function, and ECOG PS 0 or 1. Primary endpoints are efficacy as defined by ORR and safety of LN-145 as a single agent or in combination with durvalumab; secondary endpoints are DOR and PFS per RECIST 1.1, and OS. Key exploratory objectives include: ORR, OS, DOR and PFS per RECIST 1.1, and OS. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
**TPS3108**  Poster Session (Board #318b), Mon, 8:00 AM-11:30 AM

Evaluating immune checkpoint inhibition in solid tumor patients with homogeneous recombination repair deficiency.

**First Author:** Fernando Manuel Vargas Madueno, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

**Background:** Recent studies have shown that patients with mismatch repair deficiency have an increased response rate to immune checkpoint inhibitors (ICI). This led to the tissue-agnostic FDA approval of pembrolizumab (PEM). Stemming from this, we are investigating the interplay between homologous recombination (HR) repair deficiency, another mechanism of DNA repair, and solid tumor response to ICI using an all-inclusive functional immunofluorescence assay of the Fanconi Anemia pathway (FATS1) that we developed and which can be performed in paraffin embedded tumors.

**Methods:** This is a phase 2 open-label single center trial evaluating the role of PEM in patients with metastatic solid tumors who have progressed on first-line standard of care chemotherapy and for whom PEM does not have an FDA approved indication. FATS1 will be performed in all patients, as well as stool analyses for microbiome composition evaluation. We hypothesize that FATS1 negative tumors will be associated with improved responses. Other eligibility criteria include measurable disease by imaging, 18 years of age or older and no previous exposure to ICI. Patients with known microsatellite instability (MSI) high tumors are not eligible. The trial plan to evaluate the immune-related objective response rate (iORR) achieved in patients with FA Repair Pathway functionally competent and functionally deficient tumors. Secondary objectives include 20-week progression free survival and overall survival. Other exploratory objectives include evaluation of the mutation load, markers of neo-antigenicity, T-cell receptor clonality, and immune checkpoint analyses (before and after treatment) and alterations in HR repair genes. We will utilize a two-stage phase II trial design to detect an iORR ≥ 20% in the whole population tested vs. the null hypothesis that the true iORR ≤ 5%, representing a response by chance alone, or other infrequent unknown mechanisms. An interim analysis requires that at least 2 of the first 20 evaluable patients enrolled have an objective response. If this occurs, we will accrue 19 additional patients for a total of 39. Enrollment is ongoing and seven patients are currently on treatment. Clinical trial information: NCT03274661.

**TPS3109**  Poster Session (Board #319a), Mon, 8:00 AM-11:30 AM

Phase 1b/2 study of nivolumab in combination with an anti-IL-8 monoclonal antibody, BMS-986253, in a biomarker-enriched population of patients with advanced cancer.

**First Author:** Ignacio Melero Bermejo, Clínica Universidad de Navarra, Pamplona, Spain

**Background:** Interleukin 8 (IL-8) is a chemokine that has been suggested to play a predominant role in tumor immune escape by promoting an immunosuppressive tumor microenvironment (TME). High levels of serum IL-8 are associated with a poor prognosis in various tumors (Sammand, MF, et al. Clin Cancer Res. 2014;20:5697-5707), such as melanoma, non-squamous small cell lung cancer (NSCLC), and renal cell carcinoma, and decreases in serum IL-8 levels have been suggested to be associated with response to anti-PD-(L)1 therapy with nivolumab in a small cohort of pts with melanoma and NSCLC (Sanmand, MF et al. Ann Oncol. 2017;28:1998-1999). Preclinical studies showed synergistic antitumor activity by combining anti- CXCR2 with anti-IP-1 vs either agent alone in mouse. BMS-986253 is a fully human-sequence IgG1x anti-IL-8 monoclonal antibody that abrogates signaling through both IL-8 receptors (CXCR1 and CXCR2), resulting in a complete blocking of IL-8 mediated pathway, and as such, can be used to assess the mechanistic role of this pathway in IO resistance. Here we describe the interim analysis of the phase 1b/2 study of the combination of BMS-986253 plus nivolumab in a biomarker-enriched population of pts with advanced cancers (NCT03400332).

**Methods:** This is a 2-part study with an enrollment of 260 target selected pts, aged ≥ 18 y with advanced solid tumors. Pts must have ≥ 1 measurable lesion at baseline per RECIST v1.1. Outcomes include safety, tolerability, efficacy, pharmacokinetics, immunogenicity of BMS-986253 plus nivolumab, and measurement of serum IL-8 levels at baseline and during treatment. This study will also explore various peripheral and intra-tumor pharmacodynamic effects of blocking IL-8 in a target selected pt population. Clinical trial information: NCT03400332.

**TPS3110**  Poster Session (Board #319b), Mon, 8:00 AM-11:30 AM

A phase 3, randomized, open-label, multicenter study to compare the efficacy and safety of tislelizumab, an anti-PD-1 antibody, versus chemotherapy as first-line treatment in patients with advanced hepatocellular carcinoma.

**First Author:** Shukui Qin, People’s Liberation Army (PLA) 81 Hospital, Nanjing, China

**Background:** Advanced hepatocellular carcinoma (HCC) accounts for 70% of diagnosed HCC. Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death receptor-1 (PD-1). Furthermore, tislelizumab was specifically engineered to minimize FcγR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors, including HCC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been established for tislelizumab.

**Methods:** This global, phase 3, randomized, multicenter, non-inferiority study (NCT03412773) was designed to evaluate the efficacy and safety of tislelizumab compared with sorafenib as a first-line treatment of advanced HCC. Adult patients, aged ≥ 18 years, with unresectable, histologically confirmed HCC, an ECOG score 0-1, Child-Pugh A classification, BCLC Stage C disease or BCLC Stage B disease that has relapsed after locoregional therapy, and who have not received prior systemic therapy, are being enrolled. Approximately 640 patients from 100 international centers will be randomized (1:1) to receive tislelizumab 200 mg IV Q3W or sorafenib 400 mg orally BID. The primary outcome of this non-inferiority study is overall survival (OS) of patients treated with tislelizumab compared with OS of patients treated with sorafenib; secondary outcomes include objective response rate, progression-free survival, duration of response, time to progression, and quality-of-life outcomes. Safety/tolerability assessments include monitoring adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms. Clinical trial information: NCT03412773.

**TPS3111**  Poster Session (Board #320a), Mon, 8:00 AM-11:30 AM

A phase 3, randomized, open-label study to compare the efficacy of tislelizumab (BGB-A317) versus chemotherapy as second-line therapy for advanced, unresectable/metastatic esophageal squamous cell carcinoma (ESCC).

**First Author:** Lin Shen, Peking University Cancer Hospital & Institute, Beijing, China

**Background:** Approximately 40% of patients (pts) with esophageal cancer are diagnosed with advanced unresectable or metastatic disease; the 5-year survival rate for advanced disease is < 5%. Inhibition of programmed cell death protein-1 (PD-1) has demonstrated promising antitumor activity and manageable safety in pts with advanced unresectable or metastatic ESCC. Tislelizumab (also known as BGB-A317), a humanized IgG4 monoclonal antibody, has high affinity and specificity for PD-1. Tislelizumab was specifically engineered to minimize FcγR binding on macrophages, thus abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in pts with solid tumors, including ESCC. A recommended phase 2 dose of 200 mg administered IV every 3 weeks (Q3W) has been established for tislelizumab.

**Methods:** This phase 3, randomized study (NCT03430843) was designed to evaluate the efficacy, safety, and tolerability of tislelizumab compared with chemotherapy for second-line treatment of advanced unresectable/metastatic ESCC. Adult pts, aged ≥ 18 years, with histologically or cytologically confirmed ESCC that has progressed with first-line therapy, have ≥ 1 measurable/evaluable lesion, ≥ 1 measurable lesion at baseline per RECIST v1.1. Outcomes include safety, tolerability, efficacy, pharmacokinetics, immunogenicity of BMS-986253 plus nivolumab, and measurement of serum IL-8 levels at baseline and during treatment. This study will also explore various peripheral and intra-tumor pharmacodynamic effects of blocking IL-8 in a target selected pt population. Clinical trial information: NCT03400332.
A phase 3, open-label, multicenter, randomized study to investigate the efficacy and safety of tislelizumab, an anti-PD-1 antibody, versus docetaxel in patients with advanced non-small cell lung cancer (NSCLC) who have progressed on a prior platinum-containing regimen. First Author: Dingzhi Huang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers and has a poor prognosis in later stages. Although lung cancers are not typically immunogenic, recent studies of immune checkpoint inhibitors have shown efficacy in patients with advanced NSCLC. Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death receptor-1 (PD-1). Furthermore, tislelizumab was specifically engineered to minimize FcγR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with solid tumors, including NSCLC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been identified for tislelizumab. Methods: This phase 3, randomized, multicenter study (NCT03358875) assessed the efficacy, safety, and tolerability of tislelizumab compared with docetaxel in the second- or third-line treatment of NSCLC. Adult patients aged ≥18 years with locally advanced or metastatic NSCLC (Stage IIIb or IV, squamous or non-squamous), who have progressed on ≥1 prior platinum-containing therapy, have adequate hematologic and end-organ function, and an ECOG performance score ≤1 are eligible to enroll. Patients with a known EGFR sensitizing driver mutation or ALK rearrangement are excluded. Approximately 800 patients from ~100 global clinical sites will be randomized (2:1) to receive tislelizumab 200 mg IV Q3W or docetaxel 75 mg/m² IV Q3W. Randomization will be stratified by histology, line of therapy, and PD-1 ligand tumor cell expression (< 25% vs ≥25% [PD-L1-1]). Co-primary endpoints are overall survival in the intent-to-treat population and in the PD-L1+ population; secondary endpoints include objective response rate and health-related quality-of-life outcomes. Clinical trial information: NCT03358875.

A phase 3, double-blind, randomized study of pamiparib versus placebo as maintenance therapy in patients with inoperable, locally advanced, or metastatic gastric cancer that responded to platinum-based first-line chemotherapy. First Author: Fortunato Cicardiello, University of Campania “Luigi Vanvitelli”, Naples, Italy

Background: Gastric cancer is the fifth most common cancer, and is the third leading cause of cancer deaths worldwide. A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD. Pamiparib (previously known as BGB-290) is a selective PARP1/2 inhibitor that crosses the blood-brain barrier, has shown potent DNA–PARP trapping, and has demonstrated robust antitumor activity in preclinical models. In early phase clinical studies (NCT02361723; NCT03339915), pamiparib was generally well tolerated and showed promising antitumor activity. These studies also established 60 mg orally twice daily as the recommended pivotal dose. Methods: This double-blind, placebo-controlled, randomized, multicenter phase 3 study (NCT03427814) conducted in Asia, Australia, Europe, and North America is designed to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in ~540 patients with advanced gastric cancer who have responded to first-line, platinum-based chemotherapy. Patients who are ≥18 weeks after their last platinum dose of first-line chemotherapy will be randomized 1:1 to receive either pamiparib 60 mg twice daily or placebo. Patient randomization will be stratified by genomic loss of heterozygosity status (ie, high versus low), region, and ECOG status. Radiologic assessments will be centrally evaluated per RECIST every 8 weeks after first dose. The primary endpoint is progression-free survival; key secondary endpoints include safety/tolerability, overall survival, objective response rates, and PFS by RECIST. Clinical trial information: NCT03427814.

A phase 1/2 study investigating safety, tolerability, pharmacokinetics, and preliminary antitumor activity of anti-PD-L1 monoclonal antibody bgb-A333 along with single-agent tislelizumab in patients with advanced solid tumors. First Author: Jayesh Desai, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia

Background: Programmed cell death-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), play critical roles in the immune modulation of tumor progression. Tisilezumab is a humanized IgG4 monoclonal antibody against PD-1. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors at the recommended dose of 200 mg administered every 3 weeks (Q3W). BGB-A333 is a humanized IgG1 monoclonal antibody against PD-L1 which increased functional activities of human T cells in vitro studies, and showed antitumor activity in various cancer xenograft models. BGB-A333 blocks the interaction between PD-L1 and CD80 (B7-1), which in turn release the inhibitory signals to T-cells, enhances T-cell expansion, and prevents T-cell energy induction. Therefore, a combination of anti-PD-1 and anti-PD-L1 can potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments. Methods: This open-label study (NCT03379259) consists of two phases, each phase consisting of two parts. Phase 1 is designed to investigate the safety and tolerability of the BGB-A333 RP2D alone or in combination with tislelizumab. Phase 1A (BGB-A333 dose escalation) will follow a 3+3 design to establish the RP2D of BGB-A333. Phase 1B (combination dose confirmation) explores safety and tolerability of IV BGB-A333 (determined from dose escalation) in combination with IV tislelizumab (200 mg Q3W). Phase 2 is designed to evaluate the antitumor activity of BGB-A333 alone and in combination with tislelizumab. Phase 2A (BGB-A333 dose expansion) will enroll patients into two cohorts: non-small cell lung cancer and urothelial carcinoma. Phase 2B (combination dose expansion) will enroll patients with specific tumor types, which will be chosen based on data from phase 2A and other studies. The primary endpoint of the phase 2 study is overall response rate. Clinical trial information: NCT03379259.

PROPEL: A phase 1/2 trial of NKTR-214 (CD122-biased agonist) combined with anti-PD-1 (pembrolizumab) or anti-PD-L1 (atezolizumab) in patients (pts) with advanced solid tumors. First Author: Daniel A. Vaena, West Cancer Center, Germantown, TN

Background: NKTR-214 is an investigational cytokine designed to target CD122 (IL-2Rβ) expressed on immune cells (CD8+ T cells and NK cells) in order to expand these tumor-killing cells. NKTR-214 monotherapy increases newly proliferative CD8+ T cells and NK cells in tumors and increases cell surface PD-1 and PD-L1 expression, demonstrating a potentially synergistic mechanism with anti-PD-1 therapy. NKTR-214 plus nivolumab resulted in rapid tumor responses in pts with metastatic melanoma (mM), non-small cell lung cancer (mNSCLC), and renal cell carcinoma. Given the early efficacy data and favorable safety profile of NKTR-214 plus nivolumab, PROPEL will evaluate the clinical benefit, safety and tolerability of NKTR-214 combined with pembrolizumab or atezolizumab. Methods: PROPEL (NCT03138889) will approximately enroll 60 pts in 2 separate arms concurrently. The first arm will evaluate NKTR-214 plus pembrolizumab in up to 30 select pts with locally advanced or m, mNSCLC, or locally advanced or metastatic urothelial bladder cancer (UBC) within the FDA-approved pembrolizumab indications and dosing regimen. The second arm of this study will evaluate NKTR-214 plus atezolizumab in up to 30 select pts with locally advanced or metastatic UBC or mNSCLC within the FDA-approved atezolizumab indications and dosing regimen. NKTR-214 is administered intravenously over 30–60 minutes 3 weeks in an outpatient setting; the first studied dose of NKTR-214 will be 0.006 mg/kg. The primary objectives are to evaluate safety and tolerability and to define the maximum tolerated dose or recommended phase 2 dose of NKTR-214 combined with pembrolizumab or atezolizumab. The secondary objectives are to evaluate preliminary anti-tumor activity and efficacy by assessing overall survival and progression-free survival. In addition, the study will assess the immunological effects of treatment and the association between efficacy measures and PD-L1 expression in tumors. Treatment may continue beyond progression if there is clinical benefit as determined by the investigator. Enrollment is ongoing in the U.S. Clinical trial information: NCT03138889.
A phase Ib study evaluating the safety and tolerability of durvalumab in combination with eribulin in patients with HER-2-negative metastatic breast cancer and recurrent ovarian cancer. First Author: Takashi Kojima, Department of Gastroenterology and Hepatobiliary Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Recent studies have revealed only modest responses to single-agent immune checkpoint blockade in metastatic breast cancer (MBC) and recurrent ovarian cancer (ROC) patients as compared to other more immunogenic tumors. Methods to improve response employing the rational combination of cytotoxic chemotherapy with immunotherapies have shown promise. Eribulin (E), a novel microtubule inhibitor, is an effective single-agent chemotherapy in metastatic breast cancer with promising results observed in ovarian cancer patients. Preclinical studies have shown that E may induce intratumoral vascular remodeling through novel anti-vascular activity. It is hypothesized that the combination of E with durvalumab (D), a PD-L1 inhibitor, will result in increased T cell infiltration and activation leading to improved systemic and tumor site immune responses. Methods: This is a single center Phase Ia study to evaluate the safety, dose-limiting toxicity (DLT) rate, and the recommended phase II combination dose of E with D. Patients must have metastatic HER-2 negative MBC or ROC, adequate organ function, no prior treatment with E or anti-PD-L1, and are to receive durvalumab therapy with no more than 5 prior lines. A 3+3 dose-escalation design is employed to evaluate 3 dose levels of E given by intravenous (IV) injection. The starting dose is 1.1mg/m² with dose escalation to 1.4mg/m² on day 1 and day 8 of a 21-day cycle. In the event that multiple DLTs are observed at the initial dose level, a dose de-escalation to 0.7 mg/m² will be utilized. A fixed dose of D (1.12g by IV) is given on day 1 of each cycle. Secondary objectives include preliminary evaluation of anti-tumor activity as measured by objective response rate, progression-free survival, and overall survival. Responses will be assessed per iRECIST every 9 weeks. Patients will be treated until unacceptable toxicity or disease progression. Results: Enrollment began in May 2017. As of January 2020, 23 patients have been enrolled in part 1. 29 patients were enrolled in part 2. Patients planned to be treated with E and D up to 50 mg/m² will be treated in a “3+3” cohort-based dose escalation design of DSB-301 (1x10¹⁰VP on cohort 1, 1x10¹¹VP on cohort 2 and 1x10¹²VP on cohort 3) with pembrolizumab (200mg/body q3w). DSB-301 is administered at day 1, day 15, and, Day 29 by intratumoral injection and pensilumab is administered at day 8 and then every 28 days thereafter. Primary endpoint is dose limiting toxicity. Secondary endpoint is response rate, progression free survival, and rate of adverse event. Phase Ib part was designated to evaluate the safety and efficacy of the recommended dose DSB-301 selected in phase Ia part in combination with pembrolizumab in 10 patients. We will also investigate biomarker study using paired samples of both tumor biopsy and blood. The patient enrollment has been started in October 2017. Clinical trial information: NCT03172819.

A phase III Trial of CRISPR-Cas9-mediated PD-1 knockout Epstein-Barr virus cytotoxic lymphocytes (EBV-CTLs) for advanced stage EBV-associated malignancies. First Author: Jia Wei, The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: EBV associated malignancies exhibit high amplification of PD-L1 as distinguished from EBV non-associated malignancies (Kim et al. Gastroenterology 2015; Chen et al. Clinical Cancer Research 2013). The up-regulation of PD-L1 restricts antitumor effect of EBV-CTLs by immune tolerance and results in poor prognosis of patients. Our previous work has generated PD-1-disrupted CTLs by CRISPR-Cas9 system which could up-regulate IFN-γ production and enhance cytotoxicity in tumor cell lines and mouse model (Su et al. Oncoimmunology 2016). Methods: This phase III prospective single center clinical study (clinicaltrials.gov NCT03044743) was designed to evaluate the safety of PD-1 knockout EBV-CTLs in treating EBV positive advanced stage malignancies. Patients included should be pathologically verified EBV positive stage IV gastric carcinoma, nasopharyngeal carcinoma or lymphoma progressed after standard treatment with measurable lesions. Patients will be divided into three groups and receive 2 to 4 cycles of cell therapy according to their tolerance. PD-1 knockout EBV-CTLs from autologous origin will be generated and 2 x 10¹⁰/kg of specific T cells will be infused in one cycle. Each cycle is divided into three administrations, with 20%, 30% and 50% respectively. To modify immune microenvironment, Fludarabine at 30mg/m² and cyclophosphamide at 300mg/m² will be administered 3 days (intravenous injection, i.v.) before cell infusion. Interleukin-2 will be given daily (i.v.) from the first day of the cell infusion for 5 consecutive days at the dose of 4000,000 international unit (IU)/day to sustain the survival of infused T cells. The adverse events will be evaluated after each cycle by Common Terminology Criteria for Adverse Events (CTCAE v4.0) as primary endpoint. Progression-free survival (PFS), the duration of the normalization of tumor marker and immunological markers will be evaluated as the secondary endpoints. Immunological markers will continuously be examined every 2 cycles. Clinical trial information: NCT03044743.

An open label phase I study to evaluate the safety and efficacy of OBP-301 with pembrolizumab in patients with advanced solid tumors. First Author: Toshio Kubo, Center for Clinical Oncology, Okayama University Hospital, Okayama, Japan

Background: PD-1 blockade showed promising efficacy in facilitating tumor shrinkage for broad type of cancer patients, but objective response rates are very limited. The antitumor potential of oncolytic adenoviruses has been demonstrated in preclinical and clinical studies. In addition to the specific killing of cancer cells via oncolytic virus, these agents prompt the immune system to stimulate an antitumor immune response. OBP-301 is an oncolytic adenovirus in which gene is modified to be able to selectively replicate in cancer cells by introducing human telomerase reverse transcriptase (hTERT) promoter. Further antitumor effect will be expected activating of two different antitumor immunity by using OBP-301 in combination with pembrolizumab. Therefore, we initiated phase I study to evaluate the safety and efficacy of OBP-301 with pembrolizumab. Methods: The major eligibility criteria is patients with advanced or metastatic solid tumor not responded to or intolerant of standard chemotherapies, and with possibility of intratumoral injection. History of anti PD-1/PD-L1/PD-L2 antibody treatment is acceptable. Patients must have metastatic HER-2 negative MBC or ROC, adequate organ function, must have metastatic HER-2 negative MBC or ROC, adequate organ function, or disease progression. Optional blood samples will be collected at various time points for quantification and characterization of immune responses and evaluation for potential biomarkers of response. We estimate accrual of 6-12 patients. Clinical trial information: NCT03430518.
Clinical trial information: NCT02608385.

Methods: HUDSON is a multi-centre, international multi-arm umbrella study that will 1) evaluate therapies to reverse ICI-resistance and 2) define mechanisms of ICI-resistance in NSCLC patients who have progressed following standard-of-care platinum and ICI based therapies. HUDSON is a platform study that consists of two groups; a biomarker matched and a biomarker non-matched group. Within the biomarker matched group, different cohorts will test 1) homologous recombination repair (HRR) defects and 2) LKB1 aberration for response to durvalumab and olaparib (PARP inhibitor), 3) ATM deficiency for response to durvalumab and AZD6738 (ATR inhibitor) and 4) RICTOR amplification for response to durvalumab and vistusertib (mTORC1/2 inhibitor). In the bio- marker non-matched group, cohorts will test durvalumab in combination with either i) olaparib, ii) AZD9150 (STAT3 inhibitor) or iii) AZD6738. New cohorts will be added as new translational hypotheses are established. Translational research will be performed on serial peripheral blood samples (including ctDNA) and tumour biopsies. HUDSON enrols ICI-resistant refractory patients in a signal searching manner. Biomarker matched and non-matched groups will be opened simultaneously, and all eligible patients can be allocated a treatment option irrespective of their tumour profile. Enrolment is ongoing. Clinical trial information: NCT03334617.

Methods: Pembrolizumab 200mg IV Q3W is to be used to assess radiated tumor progression. Control (defined as CR, ORR ≥ 20%) will be calculated by the Kaplan Meier method and compared between partially irradiated tumors and completely irradiated tumors with PR, or SD) will be calculated by the Kaplan Meier method and compared. HUDSON enrolls refractory patients in a signal searching manner. Biomarker matched and non-matched groups will be opened simultaneously, and all eligible patients can be allocated a treatment option irrespective of their tumour profile. Enrolment is ongoing. Clinical trial information: NCT03341948.
Regorafenib and nivolumab combination therapy for advanced and metastatic solid tumors: Phase I clinical trial (EP01603).

First Author: Shota Fukushima, Division of Cancer Immunology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan

Background: Immune checkpoint inhibitors (CPIs) have shown promising efficacies in several types of malignancies. However, still around half of patients with most tumor types experienced disease progression at the initial tumor assessment. One possible reason for resistance to CPIs is suspected to be based on interaction with cancer niche which include suppressive immune cells such as myeloid-derived suppressor cells (MDSC), regulatory T cells (Tregs) and tumor-associated macrophages (TAMs). Previous in vivo study showed that selective inhibition of VEGF pathway with anti-VEGF antibody or anti-VEGF tyrosine kinase inhibitors (TKIs) suppress tumor growth and decrease MDSC, Tregs and TAMs. In addition, suppression of stem cell factor (SCF)-mediated signaling through c-Kit also decreases MDSC expansion and tumor angiogenesis, which may overcome resistance to CPIs. Therefore, we initiated phase I study to assess efficacy and safety for the combination of nivolumab and regorafenib as a multi-kinase inhibitor targeting both VEGF and SCF signaling. Methods: The main eligibility criteria is patients with unresectable recurrent solid tumor who are refractory or intolerant to standard chemotherapy. Primary objective is to examine the safety and tolerability of repeated dosing of regorafenib and nivolumab and to investigate the maximum tolerated dose (MTD) and recommended dose (RD). Dose escalation cohort was designed to determine the recommended expansion cohort dose in a “3+3” cohort-based dose escalation design of regorafenib (80 mg once daily for 21 days on 7 days off on level 1, 120 mg on level 2 and 160 mg on level 3) with nivolumab (3.0 mg/kg q2w). In expansion cohort, approximately 30 patients with selected solid tumors such as gastric, colorectal, hepatocellular carcinoma will be enrolled at the RD. We also investigated several biomarkers using pre- and post-treatment samples from both biopsied tumor and blood. First three patients were enrolled and treated in level 1 as of January 2018. Clinical trial information: NCT03406871.

TPS3125

A phase I/II study of regorafenib (R) plus avelumab (A) in digestive tumors.

First Author: Sophie Cousin, Institut Bergonié, Bordeaux, France

Background: Several preclinical studies have shown that simultaneous blockade of programmed death/programmed death-ligand 1 (PD/PD-L1) and neoangiogenesis induces systemic anti-tumour effect in vivo. R is a multikinase inhibitor approved for the treatment of metastatic colorectal (CRC) and gastro intestinal stromal tumor (GIST). A is a PD-L1 inhibitor approved for the treatment of Merkel carcinoma. We hypothesized that R in association with A could be synergistic and feasible in patients (pts) with tumors of the digestive tract. Methods: This is a multicenter, prospective phase I/II trial assessing R+A in 4 cohorts of pts with advanced pretreated: A) CRC not MSI-H or MMR-deficient, B) GIST, C) Oesophageal/gastric carcinoma, D) Biliary tract/ hepatocellular carcinoma. Primary objectives are to determine the recommended phase II dose (RP2D) of R+A in phase I, and assess the best overall response defined as per RECIST v1.1 with A+R in phase II. In phase I, 2 doses of R will be investigated: 120mg, 160mg, daily, 3 weeks on/1 week off with fixed dose of A: 10mg/kg every 2 weeks. In phase II, all pts will received the RP2D of R with A. Main eligibility criteria are: -adult pts with metastatic, histologically confirmed tumor of 1 of the 4 cohorts, with measurable, pretreated disease. -Evaluation of progression after = 1 previous line of systemic therapy (primary endpoint is toxicity according to NCI-CTCAE v4.0 and incidence rate of DLT at each dose level during the first 28 days; I); antitumor activity in terms of best overall response (II). Secondary endpoints encompass: Objective Response Rate (ORR), Progression Free Survival (PFS), Growth modulation index, 6-months OS and Overall Survival + PK for R. A prespecified cohort (I) on (I) mandatory blood samples at baseline/on treatment, archived tumor tissue, (II) on optional biopsy at Baseline/after 4 weeks of R+A focusing on TAM, Lymphocytes infiltrates, PD-L1, VEGFR, PDGFR, HIF1alpha expression. Phase I will follow a classical 3+3 design with 2 dose levels and a maximum of 12 pts. A Bayesian approach will be used in phase II with a maximum sample size of 50 pts/cohort. At each update of interim analysis, a stopping rule for inefficacy will recommend stopping the trial if there is a high predictive probability (>80%) that ORR is < or = to the futility bound p0 = 0.20%. Clinical trial information: NCT03475953.

TPS3127

A study of REGN3767, an anti-LAG-3 antibody, alone and in combination with cemiplimab (REGN2810), an anti-PD1 antibody, in advanced cancers.

First Author: Kyriakos P. Papadopoulos, START, San Antonio, TX

Background: Lymphocyte activation gene 3 (LAG-3) is an immune checkpoint receptor with a biological role in T cell regulation. Analysis of immune cell infiltrates from human tumors show that a subset of CD4+ and/or CD8+ cells co-express LAG-3 and PD-1 and may be associated with decreased T-cell effector function and tumor escape (Baithch et al et al. J Clin Investig. 2011;121:2350-2360; Jie HB et al. Br J Cancer, 2013;109:2629-2635.). Preclinical models provide evidence that dual inhibition of LAG-3 and PD-1 blockade offer synergistic anti-tumor effects and suggest a promising immunotherapy combination that warrants clinical investigation (Woo SR et al. Cancer Res. 2012;72(4): 917-927). This first in human study will evaluate the safety and efficacy of REGN3767 alone and in combination with cemiplimab in advanced malignancies. Methods: Phase 1 study enrolling patients with advanced malignancies. Dose escalation phase employs a modified 3+3 (4+3) design to assess the tolerability and pharmacokinetics (PK) of REGN3767 monotherapy and in combination with cemiplimab. Monotherapy is exploring 4 escalating REGN3767 dose levels. Combination is exploring 3 escalating REGN3767 dose levels. After tolerability and PK evaluation, doses of REGN3767 will be selected for monotherapy and combination therapy tumor-specific expansion cohorts. Solid tumor expansion cohorts will enroll per Simon’s two-stage design to evaluate safety and preliminary efficacy. Lymphoma expansion cohorts will enroll 15 patients. Patients who are on PD-1/PD-L1 therapy naive and experienced are eligible for separate cohorts. Patients previously exposed to anti-LAG-3 therapy are not eligible. The primary objectives are the determination of the recommended phase 2 dose (RP2D, dose escalation) and ORR (dose expansion). Secondary objectives include characterization of PK and immunogenicity in all patients, as well as anti-tumor efficacy in dose escalation, and safety in dose expansion. This trial is actively enrolling eligible patients in the US, UK, Ireland, and South Korea. Clinical Trial Information: NCT03005782.
TPS3128  Poster Session (Board #328b), Mon, 8:00 AM-11:30 AM
Phase I study of recombinant interleukin-15 in combination with checkpoint inhibitors nivolumab and ipilimumab in subjects with refractory cancers.
First Author: Gerard Neel, O’Shea_CymaBC fka Covid-19 Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Interleukin-15 is a stimulatory cytokine. Recombinant human IL-15 (rhIL-15), a nonglycosylated single-chain peptide, increased circulating CD8+T-cells, NK cells and inflammatory cytokines in clinical trials (Conlon et al, 2015, JCO). Simultaneous in vivo administration of IL-15 with anti-CTLA-4 and anti-PD-1+L1 is associated with increased levels of tumor antigen-specific CD8+T cells and T-cell tumor lytic activity, increased antigen-specific IFN-γ release, decreased tumor growth, and improved mouse survival; as well as inhibition of suppressive functions of CD4+CD25+ and CD8+CD122+ regulatory T-cells (Yu et al, Proc Natl Acad Sci. 2012). Therefore we postulate the combination of checkpoint inhibitors+rhIL-15, which act on different stages of T-cell activation, will enhance anti-tumor immune responses through T-cell expansion, differentiation, and cytotoxic activity. Methods: Open label phase I trial of the rhIL-15+ipilimumab+nivolumab combination following a 3+3 design, with safety lead-in doubles of rhIL-15+nivolumab (Cohort A) or rhIL-15+ipilimumab (Cohort B). Estimated enrollment: 45 patients (pts). 42-day cycles: rhIL-15 administered subcutaneously on days 1-8 and 22-29 for the first 4 cycles only; nivolumab intravenously (IV) day 8, 22 and 36; ipilimumab IV day 1. Pts must be ≥18 years of age, have histologically confirmed solid tumors that have progressed on standard of care therapy, ECOG PS ≤2. Pts with treatment related metastasis or stable disease >4 weeks will not require steroids/anti-seizure medication, and who do not respond on any 2/3 agents, are eligible. Exclusion criteria include grade3 immune related adverse events during prior checkpoint inhibitor treatment, active/chronic autoimmune disease, systemic steroid use or HIV/hepatitis infection. Currently, cohort A has enrolled 3 patients with 3 planned patients. Safety data from cohort A will be presented. Results: Of the 24 patients treated, 22 achieved a partial response (PR), 2 stable disease (SD), 0 progressive disease. 7 patients achieved a complete response (CR). All patients achieved a decrease in tumor burden. No treatment related Grade 4 events were observed. Conclusions: The combination of checkpoint inhibitors+rhIL-15, which act on different stages of T-cell activation, will enhance anti-tumor immune responses through T-cell expansion, differentiation, and cytotoxic activity.

TPS3129  Poster Session (Board #329a), Mon, 8:00 AM-11:30 AM
The "INSIGHT" trial: An explorative, open-label phase I study to evaluate the feasibility and safety of intra-tumoral, intra-peritoneal, and subcutaneous injections of IMP321 (i.e. IL-15 fusion protein), for advanced stage solid tumor entities.
First Author: Daniel Wilhelm Mueller, Institute of Clinical Cancer Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany

Background: The INSIGHT study evaluates feasibility and safety of intra-tumoral and intra-peritoneal injections of IMP321 (mono-agent) for the treatment of advanced stage solid tumors as well as to generate first efficacy data. This proof-of-concept data could build the basis for further clinical studies exploring the therapeutic potential of active immunotherapy with IMP321 by direct injection into the tumor mass or the peritoneal space. Furthermore, safety and efficacy of combining standard-of-care (SOC) chemomunotherapyes with IMP321 subcutaneous (s.c.) injections in various solid tumor entities will be assessed. IMP321 is a soluble form of the LAG-3 T-cell surface receptor with a dual mode of action (MOA) consisting of activation of antigen presenting cells (primary MOA) and prevention of exhaustion of activated T-cells (secondary MOA at high local concentration). Methods: This is a prospective investigator initiated phase I trial consisting of three strata. Stratum B: Pretreated patients with solid tumors and additional peritoneal carcinomatosis receive q2w intra-tumoral IMP321 injections via direct injection or a silicon catheter. Both strata performed in phase 1 were analyzed in a per-protocol analysis. Results: Of the 20 patients treated, 12 achieved a partial response (PR), 4 stable disease (SD), 4 progressive disease. No treatment related Grade 4 events were observed. Conclusions: The combination of checkpoint inhibitors+rhIL-15, which act on different stages of T-cell activation, will enhance anti-tumor immune responses through T-cell expansion, differentiation, and cytotoxic activity.

TPS3130  Poster Session (Board #329b), Mon, 8:00 AM-11:30 AM
A sequential cohort study of combination immunotherapy with BRN-bachuray vaccine, M7824, AL-ATL03 and epacadostat in metastatic castration-resistant prostate cancer (mCPRC) (QuEST1). First Author: Jason M. Redman, National Cancer Institute, Bethesda, MD

Background: Vaccine and checkpoint inhibitor monotherapies infrequently produce objective responses in mCPRC. Combination immunotherapy that 1) facilitates immune recognition of tumor, 2) increases number and function of tumor directed effector cells, and 3) decreases immune suppression in the tumor microenvironment (TME), is a promising strategy to improve outcomes in mCPRC. In pursuit of safety and efficacy, this Quick Efficacy Seeking Trial (QuEST1) will add immunotherapies to sequential study arms. QuEST1 first combines the BRN-Bachury vaccine, targeting a tumor antigene specific T-cell receptor (TCR) hinge region, with four doses of the immune checkpoint inhibitor pembrolizumab (M7824) targeting PD-L1 and TGF-β. It is planned to enroll 1 of 3 planned pts. Assessment of intrinsic apoptosis biomarkers, PD-L1 activity. Therefore we postulate the combination of checkpoint inhibitors+rhIL-15, which act on different stages of T-cell activation, will enhance anti-tumor immune responses through T-cell expansion, differentiation, and cytotoxic activity. Methods: Open label phase I trial of the rhIL-15+ipilimumab+nivolumab combination following a 3+3 design, with safety lead-in doubles of rhIL-15+nivolumab (Cohort A) or rhIL-15+ipilimumab (Cohort B). Estimated enrollment: 45 patients (pts). 42-day cycles: rhIL-15 administered subcutaneously on days 1-8 and 22-29 for the first 4 cycles only; nivolumab intravenously (IV) day 8, 22 and 36; ipilimumab IV day 1. Pts must be ≥18 years of age, have histologically confirmed solid tumors that have progressed on standard of care therapy, ECOG PS ≤2. Pts with treatment related metastasis or stable disease >4 weeks will not require steroids/anti-seizure medication, and who do not respond on any 2/3 agents, are eligible. Exclusion criteria include grade3 immune related adverse events during prior checkpoint inhibitor treatment, active/chronic autoimmune disease, systemic steroid use or HIV/hepatitis infection. Currently, cohort A has enrolled 3 patients with 3 planned patients. Safety data from cohort A will be presented. Results: Of the 24 patients treated, 22 achieved a partial response (PR), 2 stable disease (SD), 0 progressive disease. 7 patients achieved a complete response (CR). All patients achieved a decrease in tumor burden. No treatment related Grade 4 events were observed. Conclusions: The combination of checkpoint inhibitors+rhIL-15, which act on different stages of T-cell activation, will enhance anti-tumor immune responses through T-cell expansion, differentiation, and cytotoxic activity.

TPS3131  Poster Session (Board #330a), Mon, 8:00 AM-11:30 AM
A phase 1/2 study with birinapant in combination with pembrolizumab.
First Author: Russell J. Schilder, Thomas Jefferson University Hospital, Philadelphia, PA

Background: Birinapant is a bivalent SMAC mimetic with activity against multiple members of the inhibitor of apoptosis protein (IAP) family including cIAP1 and has demonstrated tolerability with robust and durable target engagement in advanced cancers. Synergistic effects of combining birinapant with immune checkpoint inhibitors have been demonstrated in preclinical models, consistent with the reported role of cIAP1 in tumor cells and immune cells (Beug et al., 2017). Based on these observations, a phase 1/2 trial with birinapant and pembrolizumab has been initiated (NCT02587962). Methods: In the dose escalation part of this multi-center phase 1/2 study, patients > 18 years with advanced solid tumors without further suitable standard therapeutic options are eligible for inclusion. The primary objective is to determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant in combination with pembrolizumab using a standard 3+3 design. The secondary objective is to assess efficacy by RECIST 1.1. The doses of birinapant to be evaluated are 5.6, 11, 17 and 22 mg/m² IV on day 1 and 8 in addition to pembrolizumab 200 mg on day 1 in a 21-day cycle. RP2D will be proposed by the safety review committee. The phase 2 part plans to include 111 patients. The primary objective is to assess the clinical activity of birinapant and pembrolizumab, measured as ORR by RECIST in separate cohorts of microsatellite stable colorectal (N = 28), ovarian (N = 27) and cervical cancer (N = 26). Simon’s two-stage design yields a type I error rate of 0.05 and statistical power of 0.80 for each of the three cohorts using a one-sided test based on true response rates of 20% (colorectal cancer), 25% (ovarian cancer) and 30% (cervical cancer). The study will also evaluate an exploratory cohort consisting of five patients with each small cell lung cancer, cholangiocarcinoma, gastroesophageal cancer, mesothelioma, head and neck squamous cell carcinoma (check-point inhibitor-naïve and experienced). The phase 2 secondary objectives are safety and tolerability, tumor response, progression-free and overall survival. Exploratory objectives will assess tumor response by RECIST, pharmacokinetics, pharmacodynamics and predictive biomarkers. Clinical trial information: NCT02587962.
Phase 1, multicenter, open-label study of single-agent bispecific antibody T-cell engager GBR 1342 in relapsed/refractory multiple myeloma. First Author: Joshua Ryan Richter, John Theurer Cancer Center, Hackensack, NJ

Background: Therapeutic advances have improved outcomes in multiple myeloma but patients eventually relapse, requiring treatment with agents that are active in refractory disease. CD38, a transmembrane glycoprotein upregulated on myeloma cells, is a validated disease target as evidenced by the anti-myeloma activity of daratumumab (an anti-CD38 monoclonal antibody). However, not all patients respond and many eventually develop progressive disease to daratumumab monotherapy. GBR 1342, a CD3xCD38 bispecific antibody engineered (using Glenmark’s BEAT platform) to direct T-cells to CD38-expressing myeloma cells, has the potential to overcome the limitations of existing therapies. In preclinical studies, GBR 1342 redirected the cytotoxic potential of T-cells to human myeloma cell lines in vitro and in mouse xenograft models. This ongoing, 2-part, first-in-human study aims to: (1) evaluate the safety and maximum tolerated dose (MTD) of GBR 1342 monotherapy in subjects with relapsed/refractory multiple myeloma (> 3 prior therapies); and (2) further elucidate the safety, tolerability, and preliminary clinical activity of GBR 1342 at the MTD. Methods: In Part 1, intravenous GBR 1342 is administered on Days 1 and 15 in 28-day treatment cycles at escalating doses (Table). The first 4 cohorts consist of a single-subject cohort. Subsequent cohorts use a 3+3 enrollment design. In Part 2, 65 evaluable subjects will be treated at the MTD identified in Part 1 until disease progression or unacceptable toxicity occurs. Primary endpoints include AE (frequency, severity), number of dose-limiting toxicities during Cycle 1 (Part 1), and objective response to GBR 1342 (Part 2). Secondary endpoints include pharmacokinetics and anti-tumor activity of GBR 1342 (progression-free and overall survival). Nijhof IS et al. Blood 2016; doi.org/10.1182. Clinical trial information: NCT03309111.

Dose escalation scheme (doses in ng/kg):

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TPS3133 Poster Session (Board #331a), Mon, 8:00 AM-11:30 AM
HepVac-101 first-in-man therapeutic cancer vaccine phase II/I clinical trial for hepatocellular carcinoma patients. First Author: Luigi Buonaguro, HCCS INT Fondazione, Naples, Italy

Background: HCC is the third leading cause of death from cancer globally with an extremely variable 5-year survival rate. The HepVac-101 phase II/I, first-in-man, therapeutic cancer vaccine single-arm clinical trial is performed as part of the HepVac project, funded by the European Commission’s 7th Framework Program under the Grant Agreement Nr. 602893 (www HepVac.eu). The HepVac-101 trial identification numbers are NCT03203005 (Clinical trials.gov) and 2015-003389-10 (EudraCT). Methods: The therapeutic cancer vaccine IMA970A is a multi-peptide-based HCC vaccine composed of 16 newly discovered and overexpressed tumor-associated peptides (TUMAPs) directly identified from resected HCC tissues. Of these TUMAPs, 7 are restricted to HLA-A*02, 5 to HLA-A*24 and 4 to HLA class II. CVB102 is a novel RNA based immunostimulatory agent inducing a balanced Th1/Th2 immune response. A total of 40 patients with very early, early and intermediate stage of HCC are enrolled to be treated with a single pre-vaccination infusion of low-dose cyclophosphamide, followed by 9 intradermal vaccinations consisting of IMA970A plus CVB102. The study drugs are applied without concomitant anti-tumor therapy, in order to reduce risk of tumor recurrence/progression in patients having received all indicated standard treatments and without evidence of active disease. The primary endpoints of the HepVac-101 clinical trial are safety, tolerability, and immunogenicity. Secondary/exploratory endpoints are additional immunological parameters in circulation, infiltrating T-lymphocytes in tumor tissue, biomarkers in blood and tissue, DFS/PFS and OS. Once safety of this vaccination approach has been established in the first 10 patients the addition of a checkpoint inhibitor will be considered. Suitable patients enrolled at very early, early and intermediate stage of HCC are invited to participate in a trial extension investigating an actively personalized vaccine (APVAC). The HepVac-101 trial is conducted in 6 centers located in 5 European countries. Five centers are actively recruiting patients. As of the time of abstract submission, 4 HCC patients have been screened for HLA haplotype and 1 is eligible for vaccine. Clinical trial information: NCT03203005.
Phase I/II study of BSK01, an artificial intelligence-driven, peptide-pulsed, mature DC immunotherapy for solid and hematological malignancies. First Author: Leonardo Mirandola, Kiromic, Inc., Houston, TX

Background: Despite advances in understanding the biology of hematologic malignancies (HM) and solid malignancies (SM), and the availability of new treatment options, many patients with HM and SM remain incurable. Since the majority of cancer patients display a defective immune response to tumor antigens, the ex vivo activation of dendritic cells (DC), through their exposure to tumor associated antigens, is an attractive and active area of investigation. The choice of the target antigen and the identification of immuno-dominant and immunogenic peptides to drive powerful and specific cellular responses against tumor cells are crucial for the success of cancer vaccines. We have developed a powerful artificial intelligence (AI) computational platform, K.A.I., capable of collecting, normalizing, and analyzing data from multiple data sources, and to prioritize target antigens and immune-dominant peptides for any given malignancy. Methods: Currently, we are conducting 4 clinical trials for solid and hematologic malignancies, both in the consolidation and re-fractory settings. We hypothesize that treatment of patients with HM or metastatic SM using autologous DC pulsed with immuno-dominant tumor-specific peptide antigens will result in antigen-specific CD4+ T-cell and/or CD8+ CTL responses without significant toxicities. We also hypothesize that the responses generated against specific antigens may translate into clinical anti-tumor activity. Primary Objective: Phase I (6 subjects). To determine safety of intradermal/subcutaneous DC vaccine therapy, low-dose cyclophosphamide and GM-CSF, in patients with metastatic SM or HM. Secondary Objective: Phase II (up to 17 subjects). To determine immune responses associated with intradermal/subcutaneous DC vaccine therapy, low-dose cyclophosphamide and GM-CSF, in patients with metastatic SM or HM who demonstrate a response, or whose disease remains stable, after conventional first-line systemic therapy, or who have failed conventional systemic therapy. The study population is currently drawn from patients at various clinical institutions following contractual agreements. Clinical trial information: NCT02709993; NCT02705703; NCT02224599; NCT02223312.
Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of the PETACC-6 trial.

First Author: Hans-Joachim Schmoll, Martin Luther University, Halle, Germany

Background: The PETACC-6 trial investigated the role of oxaliplatin in combination with preoperative capecitabine-based chemoradiation (CRT) and postoperative capecitabine (CT) to improve disease-free survival (DFS) in locally advanced rectal cancer. Methods: Between 11/2008 and 09/2011, 1090 patients with rectal adenocarcinoma within 12 cm from the anal verge, T3a/T3b and/or node-positive, with no evidence of metastatic disease, to be randomized either resectable at the time of entry or expected to become resectable, to 5 weeks preoperative CRT with capecitabine, followed by 6 cycles of adjuvant capecitabine without (arm 1) or with oxaliplatin (arm 2) (before and after surgery). The primary analysis was intent-to-treat and adjusted for stratification factors (clinical T category, nodal status, distance from the tumor to the anal verge and method of locoregional staging) except the center.

Results: An early release of DFS after a medium follow-up of 31 months per recommendation of the IDMC, did not show any difference between arms (adjusted HR = 1.04, 95% CI: 0.81 -1.33, P = 0.781) (Schmoll H et al, Proc ASCO 2014).

We now report on the long-term results for DFS and OS. At median follow-up of 68 months, respectively 157 vs.156 DFS events and 97 vs. 109 deaths were observed in arm 1 and 2. In each arm, 58 patients died due to progressive disease. There is no difference in DFS between arms (adjusted HR = 1.02, 95% CI: 0.82-1.28, P = 0.835) nor in OS (adjusted HR = 1.17, 95% CI: 0.89 - 1.54, P = 0.262), 5-year DFS was 71.3% (95% CI: 67.1% - 75.0%) in arm 1, vs. 70.5% (95% CI: 66.3% - 74.3%) in arm 2, 5-year OS was 83.1% (95% CI: 79.5% - 86.1%) in arm 1, vs. 80.1% (95% CI: 76.2% - 83.4%) in arm 2. No major heterogeneity of the results for DFS according to baseline factors was identified except for the subgroup of non-german patients (N = 357) vs. german patients (N = 737) (p = 0.02 for Cochran’s Q test). Adjusted HR was 1.27 (95% CI: 0.96-1.68, p = 0.091) in favor of oxaliplatin in german patients while adjusted HR was 0.65 (95% CI: 0.44 – 0.97, p =0.033) in favor of oxaliplatin in non-german patients. Conclusions: Long-term results confirm that the addition of oxaliplatin to capecitabine plus radiotherapy does not improve significantly DFS and OS in T3/4 and/or node-positive patients who had available follow-up and obey the treatment protocol, 130 (6.4%) in FOLFOX arm vs 97 (5.9%) in the FL arm (HR 0.63 (95% CI, 0.43–0.93, p = 0.018) by intention-to-treat analysis. In the subgroup analysis for DFS, patients with ypStage III (HR 0.59 (0.38-0.92), p =0.019), ypN1b (HR 0.35 [0.14-0.83], p= 0.017), ypN2 (HR 0.47 [0.22-0.99], p=0.048), high grade histology (HR 0.28 [0.08-0.97], p =0.045), minimally regressed tumor (HR 0.40 [0.19-0.86], p = 0.016), absence of lymphovascular (HR 0.55 [0.33-0.86], p = 0.01), male gender (HR 0.62 [0.39-0.98], p = 0.039), and younger than 65 years (HR 0.64 [0.42-0.97], p =0.034) benefited more from FOLFOX than FL. The 5-year overall survival (OS) rate was 78.1% in the FOLFOX arm vs 76.4% in the FL arm (HR 0.73 [0.45-1.19], p= 0.21). In the subgroup analysis for OS, those with ypN2 (HR 0.42 [0.18-0.96], p =0.04) and minimally regressed tumor (HR 0.42 [0.19-0.97], p = 0.043) benefited more from FOLFOX than FL. Conclusions: Adjuvant FOLFOX clearly demonstrated improved DFS in rectal cancer patients with ypStage II/III after preoperative CRT. Subgroup analyses provided additional information on the selection of adjuvant candidates. Clinical trial information: NCT00807911.

Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial.

First Author: Yanhong Deng, Sun Yat-sen University, Guangzhou, China

Background: The FOWARC trial compared FOLFOX6 with or without Radiation in neoadjuvant treatment of locally advanced rectal cancer to 5-FU chemoradiotherapy. First results of early secondary endpoints have been published (Deng et al., JCO 2016). Here we present the primary endpoint, disease-free survival (DFS) at 3 years. Methods: Between 01/2011-02/ 2015, patients with rectal cancer within 12 cm from the anal verge, clinical stage II-III were randomly assigned to received 5-FU with radiation(RT) (FU-RT arm), or receive mFOLFOX6 with RT (FOLFOX-RT arm), or receive 4-6 cycles of mFOLFOX6 alone (FOLFOX arm), peri-operative RT was allowed if needed. The primary endpoint was DFS at 3 years defined as the interval from randomization to incomplete surgical resection, locoregional or metastatic recurrence or death, whichever occurred first. Results: A total of 495 patients were randomly assigned to three arms at 1:1:1 ratio. 418 patients who had available follow up and obeyed the treatment protocol, 130 in FU-RT arm, 142 in FOLFOX-RT arm and 146 in FOLFOX arm. The local recurrence rate was 10.0%, 8.5% and 8.9% respectively. After a median follow-up time of 45.2 months, 35 patients in FU-RT arm had a DFS-related event, as compared with 37 patients in FOLFOX-RT arm (HR 1.031, 95% confidence interval 0.657 to 1.620), and 41 in FOLFOX arm (HR 0.960, 95% confidence interval 0.615 to 1.497). The rate of DFS at three years was 76.4±3.8% in FU-RT arm, 77.8±3.5% in FOLFOX-RT arm and 75.7±3.6% in FOLFOX arm (P = 0.961 by the exact stratified log-rank test). The rate of OS at three years was 93.7±2.2% in FU-RT arm, 92.0±2.3% in FOLFOX-RT arm and 92.2±2.3% in FOLFOX arm (P = 0.961 by the exact stratified log-rank test). Conclusions: FOLFOX with or without radiation did not significantly improved DFS in patients with advanced rectal cancer. However, FOLFOX alone seems to have identical local recurrence rate and 3-DFS and 3-OS compared to standard FU-RT. Clinical trial information: NCT01211210.

Adjuvant FOLFOX clearly demonstrated improved DFS in rectal cancer patients with ypStage II/III after preoperative CRT. Subgroup analyses provided additional information on the selection of adjuvant candidates. Clinical trial information: NCT00807911.
Plasma HER2 (ERBB2) copy number to predict response to HER2-targeted therapy in metastatic colorectal cancer. First Author: Alberto Bardelli, Istituto di Candiolo, Fondazione del Piemonte per l’OncoLOGIA, IRCCS, Candiolo, Italy

Background: The rate of HER2 (ERBB2) copy number amplification (CNA) in metastatic colorectal cancer (mCRC) ranges from 2-13%. HERACLES, a phase II trial of trastuzumab and lapatinib (T+L) in HER2-positive mCRC showed response rates of 30%, suggesting HER2 as a viable target in this population. Cell-free circulating tumor DNA (ctDNA) next-generation sequencing (NGS) may be an option for ERBB2 CNA determination when biopsy is infeasible or tissue is insufficient. Here we determine the sensitivity of plasma DNA (pCNA) detection using a cDNA NGS assay and suggest a cutoff predictive of response to HER2-targeted therapy. Methods: Pre-treatment and progression plasma samples (N = 48) from 26 HER2 FISH-positive patients in the HERACLES study were tested using the Guardant360 assay. We correlated ERBB2 pCNA with progression free survival (PFS) and best objective response (BOR) on T+L. To establish a threshold for absolute pCNA predicting response, we analyzed ERBB2 CN relative to panel-wide CNA profile and clonal driver co-occurrence in 89 consecutive mCRC samples tested with Guardant360. Results: 46/47 samples with detectable ctDNA were ERBB2-amplified based on cDNA (2.55-122 copies; PPA = 96%, 95% CI 85-99%). A threshold of ≥3 copies of ERBB2 in circulation allowed identification of 94% of FISH-positive patients, while excluding 86% of all co-occurring KRAS, NRAS, and BRAF driver mutations in the larger clinical cohort. HERACLES patients below this threshold had reduced PFS (median 4.6 vs. 11.1 months, p = 0.10). Above the threshold, plasma ERBB2 CNA strongly correlated with BOR (r = 0.5) but weakly with PFS (r = 0.37). Conclusions: The ctDNA platform utilized correctly identified 96% of samples as ERBB2-amplified and accurately predicted HER2-targeted therapy response rates. Based on the HERACLES and large clinical cohorts, a cutoff of 3 copies of ERBB2 in plasma is proposed to select patients who will benefit from targeting HER2.

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Oral Abstract Session, Tue, 9:45 AM-12:45 PM
3507 Actionable fusions in colorectal cancer using a cell-free circulating tumor DNA (ctDNA) assay: First Author: Katherine Clifton, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The presence of gene fusions affects clinical management of patients (pts) with NSCLC, GIST, and CML. Likewise, identification of actionable fusions provides another potential approach to offering effective therapies to pts with advanced colorectal cancer (CRC). Here we detail the frequencies and clinicopathological features of gene fusions in CRC using a comprehensive ctDNA NGS assay. Methods: Pts with advanced, pre-treated CRC underwent molecular profiling using a plasma-based ctDNA NGS assay (Guardant360), which includes testing for fusions in FGFR2, FGFR3, RET, ALK, NTRK1, and ROS1. Correlations between fusions and clinicopathological features were measured using Fisher’s exact test. Relative frequencies of genomic alterations (point mutations, indels, and splice variants) were compared according to fusion status using an unpaired t-test. Results: 45 unique fusions were detected in 41 of 4290 pts tested (0.96%, 95% CI 0.70-1.3%). RET (N = 16, 0.37%), FGFR3 (N = 13, 0.30%), ALK (N = 10, 0.23%), NTRK1 (N = 3, 0.07%), ROS1 (N = 2, 0.05%), and FGFR2 (N = 1, 0.02%). Among pts with multiple fusions (N = 4 total), RET fusions accounted for 3, all subclonal. Fusions were detected at a median variant frequency of 0.31% (IQR, 0.11-1.5%). FGFR2 fusions were associated concomitant RET mutations (OR 3.5, P = 0.03). All NTRK1 fusions were KRAS/NRAS/BRAF wild-type. Genomic alterations were more common for the fusion-present cases than non-fusion cases (mean 10.2 vs. 5.1, P < 0.0001). Conclusions: This is the first large series in CRC patients to demonstrate that plasma-based detection of a broad array of actionable fusions is practical. Fusion presence was associated with a higher mutation frequency, also characteristic of microsatellite instability in CRC. Since these fusions are actionable in other solid tumors, our data provide rationale to utilize ctDNA testing for fusion testing in CRC.
Per protocol analysis and final OS update of the FIRE-3 (AIO KRK-0306) study comparing FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab. First Author: Sebastian Stintzing, Ludwig Maximilian University of Munich, Munich, Germany

Background: FIRE-3 compared 1st-line therapy with FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS ex2 wt mCRC patients (pts). Extended RAS analysis showed RAS wild type (RASwt) in tumors of 400 pts. Median RAS wt protocol analyses were done in all patients that received at least 3 cycles of chemotherapy and who had at least one CT scan following baseline allowing to evaluate of objective response rate (ORR) as the primary endpoint. ORR and early tumor shrinkage (ETS) were compared using Fisher’s exact test. Overall survival (OS) was compared using Kaplan-Meier estimation and log-rank tests. Follow up was calculated using the inverse Kaplan-Meier method. Hazard ratios (HR) were estimated according to the Cox proportional hazard method.

Results: With data cutoff of July 24th 2017, a total of 400 pts with RASwt tumors were evaluable. The median follow-up time was 70.8 months and 85.3% of OS events have occurred. Of the 400 pts, a total of 351 (87.8%) were evaluable according to the per protocol pre-specified analyses. The final efficacy data is shown in the table below. Conclusions: In the per-protocol analysis of RASwt pts treated in FIRE-3, a significantly higher ORR was demonstrated for FOLFIRI plus cetuximab compared to FOLFIRI plus bevacizumab. This advantage relates to a significantly longer OS after more than 85% of OS events had occurred. Clinical trial information: NCT00439397.

### Table 1: OS Analysis

<table>
<thead>
<tr>
<th>RASwt population</th>
<th>FOLFIRI CET</th>
<th>FOLFIRI BEV</th>
<th>p</th>
<th>RASwt evaluable population</th>
<th>FOLFIRI CET</th>
<th>FOLFIRI BEV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI CET N=199</td>
<td>68.4</td>
<td>48.9</td>
<td>p</td>
<td>70.0</td>
<td>50.3</td>
<td>p</td>
<td>0.004*</td>
</tr>
<tr>
<td>FOLFIRI BEV N=201</td>
<td>65.3</td>
<td>58.7</td>
<td>0.18</td>
<td>76.9</td>
<td>64.8</td>
<td>0.01*</td>
<td>0.81</td>
</tr>
<tr>
<td>ETS, %</td>
<td>10.4</td>
<td>10.5</td>
<td>0.58*</td>
<td>10.5</td>
<td>10.7</td>
<td>0.80*</td>
<td>HR: 0.95</td>
</tr>
<tr>
<td>mPFS, mo</td>
<td>25.1</td>
<td>22.6</td>
<td>0.01*</td>
<td>25.6</td>
<td>26.1</td>
<td>0.97</td>
<td>HR: 0.75</td>
</tr>
<tr>
<td>mOS, mo</td>
<td>33.1</td>
<td>21.6</td>
<td>p</td>
<td>32.5</td>
<td>26.1</td>
<td>0.87</td>
<td>HR: 0.95</td>
</tr>
<tr>
<td></td>
<td>24.1</td>
<td>16.2</td>
<td>0.16</td>
<td>25.1</td>
<td>22.6</td>
<td>0.97</td>
<td>HR: 0.75</td>
</tr>
</tbody>
</table>
| CET = cetuximab; BEV = Bevacizumab; ETS = Extent of tumor shrinkage at week 6; mPFS = median progression-free survival; mOS = median overall survival; “= two-sided Fisher’s exact test; “= two-sided log-rank test of P<0.05.

3510 Poster Discussion Session; Displayed in Poster Session (Board #3), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

REVERE: Randomized Phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan—Biomaer analysis. First Author: Yasuyoshi Tsuji, Department of Medical Oncology, Tomo Hospital, Sapporo, Japan

Background: REVERE demonstrated longer overall survival (OS) with the therapeutic sequence of regorafenib (R) followed by cetuximab (C) compared to the reverse sequence (C-R) at baseline in patients (pts) with pretreated metastatic colorectal cancer (mCRC; median OS 17.4 vs. 11.6 months, HR 0.61; Shitara K, et al. GI Symposium University of Texas MD Anderson Cancer Center, Houston, TX)

Methods: We analyzed biomarker data from plasma and serum samples of 101 pts with RAS wild-type (RASwt) at baseline were enrolled in the study to assess the relationship between the rMAF of ctDNA and the half-life of 3.4 mo and 6.9 mo, respectively. Our model predicts that at the time of progression only 30% of the cells in the tumor carry a mutation in RAS. This suggests that the remaining 70% are in a quiescent state and will be reactivated in response to therapy or other oncogenic alterations. Conclusions: We identified that RAS and EGFR MT alleles decay exponentially over time since last EGFR. These results provide a molecular explanation for the efficacy of EGFR rechallenge therapies after a period of EGFR inhibition. The half-life of these clones may help guide timing of rechallenge therapies and the monitoring of ctDNA. Further studies are needed to validate these results and suggest that a subclinical tumor population may be exerting resistance through paracrine mechanisms. These data will be validated on an external dataset.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
ABSTRACT WITHDRAWN
Background: Adjuvant CT in stage III CC prevents recurrence by eradicating minimal residual disease (MRD) not visible on imaging. However, many patients (pts) will not have MRD and not all pts with MRD will benefit from adjuvant CT. In this study, we determined (i) if the presence of ctDNA following surgery was predictive of recurrence following CT; (ii) if ctDNA could be used to determine the effectiveness of CT during treatment and (iii) if the presence of ctDNA following CT completion was predictive for later recurrence. Methods: Serial plasma samples from stage III CC pts planned for adjuvant CT were collected post-surgery, during CT and at treatment completion. Somatic mutations in individual tumors were identified via massively parallel sequencing of 15 genes commonly mutated in colorectal cancer. Personalized Safe-SeqS assays to quantify ctDNA in plasma samples were designed. Clinicians were blinded to ctDNA results. Results: 95 pts were enrolled from Nov-2014 to May-2017, median age was 64 years. All received adjuvant CT and 19 (20%) had recurred at a median follow-up of 21.1 months. We observed an inferior recurrence-free survival (RFS) in the 19 of 95 pts (20%) with positive ctDNA post-surgery (HR, 3.5; p = 0.004). ctDNA status changed from positive to negative in 10 of 17 pts (59%) after 2 months of CT, and remained negative (50%) at CT completion. Superior RFS was observed when ctDNA became undetectable after CT (HR 5.1; p = 0.02). Conversely, ctDNA status changed from negative to positive after CT in 6 of 71 pts (8%) and was associated with an inferior RFS (HR 5.3; p = 0.006). Finally, inferior RFS was seen in the 15 of 89 (17%) with positive ctDNA after adjuvant CT completion (HR, 7.14; p < 0.001). Conclusions: ctDNA can reveal the presence of residual metastatic cancer cells not apparent on imaging in stage III CC patients. Serial analysis of ctDNA can define subsets of pts benefiting or not benefiting from CT and is therefore a real-time marker of adjuvant treatment efficacy in solid tumors. Further studies are needed to determine if ctDNA analysis can guide a personalized and risk adjusted approach to the initiation and modification of adjuvant CT in stage III CC.

3518 Poster Discussion Session; Displayed in Poster Session (Board #11), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM
RFA: Randomized phase II study comparing induction (I) mFOLFOX6 with or without aflibercept followed by chemoradiation (CRT) and total mesorectal excision (TME) in high risk rectal cancer. GEMCAD 14-02 trial. First Author: Carlos Fernandez-Martos, Instituto Valenciano De Oncologia, Valencia, Spain

Background: Pre-clinical studies suggest that VEGF-Flt-4 blockade can have a role in the preoperative treatment of rectal cancer but how to combine it with chemotherapy (CT) and/or CRT remains controversial. Increased risk of postoperative morbidity has been reported with preop anti VEGF/CRT combination. Aflibercept (Aflib) acts as a soluble receptor that binds to human VEGF-A, VEGF-B, PlGF. We hypothesized that administering Aflib/FOLFOX followed by CRT would improve pathological complete response (pCR) without compromising wound healing. Methods: Between 1/2015-2017, pts selected with centrally reviewed magnetic resonance (mr) imaging with middle or distal third, nrT3/T4/T2 rectal adenocarcinoma were randomly assigned (2:1), stratified by mr extramural venous invasion and mrT4 mFOLFOX6 with (arm 1) or without Aflib (arm 2) prior to standard CRT (capecitabine with 50.4 Gy in 28 fractions) and TME. The study was designed to perform a hypothesis testing with an alpha = .2 and beta = .2. Results: 115/65 pts were assigned to arm 1/arm 2. The pCR rate (ypT0N0) in pts who underwent curative surgery was achieved in 25/103 (24.2%); (95%CI 16.36-33.71) in arm 1 and 9/65; 14.5% (CI 6.86-25.78) in arm 2 (p = 0.1335 Preoperative grade 3-4 toxicity occurred in 50% in arm 1 and 23% in arm 2 during the I period (difference mostly due to hypertension). Overall postoperative complications were similar between both arms (14.7% and 12.3%). Six cycles of I CT were administered in 92% and 95% and 90% and 96% completed CRT in arm 1 and 2 respectively. R0 resection rate was 87.3% and 88.7%. Conclusions: The addition of aflibercept to mFOLFOX6 led to a significantly greater pCR compared with mFOLFOX6 alone in patients with high-risk rectal cancer. The experimental arm showed higher toxicity during the I phase, with similar toxicity afterwards and no increase in surgical complications. Funding: Sanofi Clinical trial information: NCT023340949.
Final overall survival (OS) analysis of first-line (1L) FOLFOX-4 + cetuximab (cet) in patients (pts) with RAS wild-type (wt) metastatic colorectal cancer (mCRC) in the phase 3 TAILOR trial. First Author: Shukui Qin, Nanjing Bayi Hospital, Nanjing, China

Background: The survival advantage conferred by the addition of cet to FOLFOX chemotherapy was verified in TAILOR, the first prospective, randomized, phase 3 study of the addition of cet to 1L FOLFOX in pts with RAS wt mCRC. We previously presented the primary analysis of the TAILOR trial, with fewer OS events. Here, we provide the final OS results for this trial.

Methods: TAILOR was an open-label, randomized, multicenter, phase 3 trial with a modified intention-to-treat (mITT) population of 593 pts from China that evaluated FOLFOX-4 + cet in RAS wt mCRC. The primary endpoint was progression-free survival (PFS) time; secondary endpoints include OS time, overall response rate (ORR), and safety/tolerability. Results: An updated analysis (performed after 84% of events occurred) verified the survival advantage of the addition of cet to FOLFOX-4 (Table). Additionally, >77% of pts in the cet + FOLFOX-4 arm reached >80% dose intensity of cet, confirming that cet + FOLFOX-4 has high compliance. There were no new or unexpected safety findings. Finally, 59.6% and 56.0% of pts in the cet + FOLFOX-4 and cet+ FOLFOX-4 arms, respectively, received subsequent antiangiogenic therapy after treatment discontinuation (54.4% and 49.5% received any chemotherapy, and 17.6% and 27.0% received any targeted therapy). Clinical trial information: NCT01228734. Conclusions: The TAILOR study met all its endpoints, confirming cet in combination with FOLFOX-4 as an effective standard-of-care option for pts with RAS wt mCRC. We acknowledge that OS findings for the mITT population are likely influenced by the low percentage of pts who received further lines of treatment after progression on their 1L regimen, suggesting regional differences in access to anticancer therapy.

Efficacy outcomes

<table>
<thead>
<tr>
<th>Cet + FOLFOX-4 (n = 193)</th>
<th>FOLFOX-4 (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
</tr>
<tr>
<td># events</td>
<td>156</td>
</tr>
<tr>
<td>Median</td>
<td>174</td>
</tr>
<tr>
<td>HR (95% CI); vs. FOLFOX-4</td>
<td>1.40</td>
</tr>
<tr>
<td>(95% CI: 1.04-1.87)</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI); vs. FOLFOX-4</td>
<td>0.81</td>
</tr>
<tr>
<td>(95% CI: 0.64-1.04)</td>
<td>p = 0.15</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6.8-10.9</td>
</tr>
<tr>
<td>OSR by investigator, %</td>
<td>66.3</td>
</tr>
<tr>
<td># events</td>
<td>165</td>
</tr>
<tr>
<td>Median</td>
<td>142</td>
</tr>
<tr>
<td>HR (95% CI); vs. FOLFOX-4</td>
<td>0.92</td>
</tr>
<tr>
<td>(95% CI: 0.78-1.08)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>OR (95% CI); vs. FOLFOX-4</td>
<td>5.4</td>
</tr>
<tr>
<td>(95% CI: 3.9-7.5)</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>OR (95% CI); vs. FOLFOX-4</td>
<td>2.893</td>
</tr>
<tr>
<td>(95% CI: 1.98-4.361)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Conclusions: The survival advantage conferred by the addition of cet to FOLFOX-4 (Table). Additionally, >77% of pts in the cet + FOLFOX-4 arm reached >80% dose intensity of cet, confirming that cet + FOLFOX-4 has high compliance. There were no new or unexpected safety findings. Finally, 59.6% and 56.0% of pts in the cet + FOLFOX-4 and cet+ FOLFOX-4 arms, respectively, received subsequent antiangiogenic therapy after treatment discontinuation (54.4% and 49.5% received any chemotherapy, and 17.6% and 27.0% received any targeted therapy). Clinical trial information: NCT01228734. Conclusions: The TAILOR study met all its endpoints, confirming cet in combination with FOLFOX-4 as an effective standard-of-care option for pts with RAS wt mCRC. We acknowledge that OS findings for the mITT population are likely influenced by the low percentage of pts who received further lines of treatment after progression on their 1L regimen, suggesting regional differences in access to anticancer therapy.

Optimizing treatment strategy for advanced rectal cancer in the West and Japan: Results from an international multicenter cohort study. First Author: Akira Ouchi, University of Texas MD Anderson Cancer Center, Houston, TX

Background: The treatment strategies for locally advanced rectal cancer in the West and Japan have evolved through divergent philosophies - pre-operative chemoradiation (CRT) and total mesenteric excision (TME) in the West and upfront TME with lateral pelvic node dissection (LPND) in Japan. The purpose of this study was to compare these approaches. Methods: Consecutive patients with >T3 rectal cancer located ≥12 cm from the anal verge and diagnosed between 1998 and 2013 at 3 tertiary cancer centers (1 US and 2 Japan) were identified. Only patients who received preoperative CRT+TME in the US and those who underwent TME+LPND based on tumor location in Japan were included. The primary outcome was cumulative rate of local recurrence (LR) and secondary outcomes included relapse-free survival (RFS). Results: A total of 1597 patients (836 US and 761 Japan) met study criteria and were analyzed. Adjuvant chemotherapy was given to 88.4% in the US and 24.4% in Japan. Five-year cumulative risk for LR was 4.6% in the US and 6.7% in Japan (HRadj 0.58 [95% CI 0.30-1.13]). Overall RFS was longer in the US on univariate analysis (HR 2.09 [1.64-2.66], p < 0.001), but after adjustment for yp stage and relevant covariates, did not differ from Japan (HRadj 0.89 [0.66-1.19]). Following CRT and TME in the US or TME+LPND in Japan, 63.4% and 21.2% of stage cII patients were downstaged, respectively. On stage stratified adjusted analysis, there were no differences in RFS for stage cII and (yp)I subgroup; meanwhile RFS in stage cII subgroup was significantly longer in the US, but did not differ for stage (yp)II subgroup (Table). Conclusions: This is the first comparison of a large cohort of patients treated by CRT+TME, and TME+LPND within dedicated cancer centers in the US and Japan. Overall the rates of local recurrence were lower than historically reported. These results suggest good outcomes can be achieved without CRT for some stage cII patients but that neoadjuvant CRT is associated with improved survival for stage cII patients who are downstaged.

RFS HRadj (95% CI) p
Stage cII 1.40 (0.73-2.68) 0.30
Stage (yp)II 1.28 (0.53-3.11) 0.57
Stage cII 2.54 (1.79-3.61) < 0.001
Stage (yp)II 0.86 (0.61-1.21) 0.41

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**3525** Poster Session (Board #18), Sun, 8:00 AM-11:30 AM

**Change in CEA as an early predictor of progression to first-line systemic therapy in metastatic colorectal cancer. First Author: Pat Gulhati, University of Texas MD Anderson Cancer Center, Houston, TX.**

**Background:** Carcinoembryonic antigen (CEA) levels are used in conjunction with imaging to monitor response to systemic therapy in pts with metastatic colorectal cancer (mCRC). We sought to identify a threshold for change in CEA from baseline that can predict progressive disease (PD) at first restaging scan in mCRC pts receiving first-line therapy. **Methods:** Pts from trials collected in ARCAD database were included if baseline CEA was ≥10 ng/mL and repeat CEA was available within 14 days of first restaging scan. Optimal cutoffs for CEA change were identified by ROC analysis. Prediction performance of cutoffs was evaluated by sensitivity, specificity, and negative predictive value (NPV). Analyses were conducted by treatment class: chemotherapynone (chemo) and chemotherapy plus anti-VEGF antibody (anti-VEGF). **Results:** 2828 pts from 7 trials [M: 60%/40%; median age: 61 yrs; EGOG PS 0-1: 97%] with mCRC [55% pts with ≥2 metastatic sites] treated with systemic therapy were included. In chemo group (n = 957), median percent change of CEA from baseline to first restaging was -53.1% and +23.6% for pts with CR/PR/SD and PD, respectively. Optimal cutoffs based on sensitivity and specificity (AUC cutoff) or 99% NPV are shown in the table. The optimal AUC cutoff for differentiating PD from CR/PR/SD on first restaging was -7.5% for chemotherapy and -62.0% for anti-VEGF group. A drop in CEA less than optimal AUC cutoff was significantly associated with higher risk of PD at 1st restaging; ORadj = 6.51; anti-VEGF group. A drop in CEA less than optimal AUC cutoff was significantly associated with progression on first restaging was -7.5% for chemotherapy and -62.0% for anti-VEGF respectively. In anti-VEGF group (n = 1355), median percent change of baseline to first restaging was -53.1% and +23.6% for pts with CR/PR/SD and PD, respectively. In chemo group (n = 957), median percent change of CEA from baseline to first restaging was -7.5% and +23.6% for pts with CR/PR/SD and PD, respectively. **Conclusions:** In this study, we conducted a retrospective, multi-institutional study to validate the quality of a novel 55-gene classifier (55GC) for Stage II CC and compared 55GC subtypes with the CMS categories. **Methods:** We collected formalin-fixed, paraffin-embedded cancer specimens from 232 patients with Stage II CC who underwent curative surgery (RO) without adjuvant chemotherapy at 10 institutions between 2009 and 2012. Tissue sections were prepared from each specimen and subjected to DNA microarray measurement. **Results:** Using the 55GC, patients were classified as having the MSI-like subtype in 27%, CIN-like in 41%, and stromal in 32% of the cases. The 5-year recurrence-free survival (RFS) rate of patients with the MSI-like, CIN-like, and stromal subtype cancers was 88.5%, 83.3%, and 71.2%, respectively (stromal vs. others: p = 0.0049). Multivariable analysis by Cox proportional hazard model revealed that stromal subtype (hazard ratio, 2.3; p = 0.0063), pT4, and the number of lymph nodes examined (<12) were independent poor prognostic factors. The overall concordance rate between 55GC and CMS was 72%: 29% (18/62) of the MSI-like subtype, 79% (75/95) of the CIN-like subtype, and 98% (74/76) of the stromal subtype were judged as CMS1, CMS2/3 and CMS4, respectively. The 5-year RFS rate of patients with CMS1, CMS2/3 and CMS4 was 100%, 86.3%, and 73.0%, respectively (CMS4 vs. others: p = 0.005). **Conclusions:** 55GC is a useful and reproducible grading system for recurrence risk stratification of Stage II CC.

**3526** Poster Session (Board #19), Sun, 8:00 AM-11:30 AM

**A validation study of stratification by the 55-gene classifier for assessing recurrence risk in stage II colon cancer: The 55 STAR study (UMIN23879).** First Author: Shigeki Yamauchi, Gastrointestinal Surgery, Saitama Medical University International Medical Center, Hidaka-Shi, Japan. **Background:** Cancer subtypes classified by DNA microarray data have shown excellent abilities in predicting patient prognosis; in particular, consensus molecular subtypes (CMSs) are regarded as the most robust classification system with clear biological interpretability. Recently, we performed an unsupervised clustering analysis using a public database and selected the expression of 55 genes to construct a discriminant model with the aim of classifying colon cancer (CC) into three subtypes: “microsatellite instability (MSI)-like”, “chromosomal instability (CIN)-like”, and “stromal”; the recurrence rates of these subtypes were shown to be different (p = 0.001). In this study, we conducted a retrospective, multi-institutional study to validate the quality of a novel 55-gene classifier (55GC) for Stage II CC and compared 55GC subtypes with the CMS categories. **Methods:** We collected formalin-fixed, paraffin-embedded cancer specimens from 232 patients with Stage II CC who underwent curative surgery (RO) without adjuvant chemotherapy at 10 institutions between 2009 and 2012. Tissue sections were prepared from each specimen and subjected to DNA microarray measurement. **Results:** Using the 55GC, patients were classified as having the MSI-like subtype in 27%, CIN-like in 41%, and stromal in 32% of the cases. The 5-year recurrence-free survival (RFS) rate of patients with the MSI-like, CIN-like, and stromal subtype cancers was 88.5%, 83.3%, and 71.2%, respectively (stromal vs. others: p = 0.0049). Multivariable analysis by Cox proportional hazard model revealed that stromal subtype (hazard ratio, 2.3; p = 0.0063), pT4, and the number of lymph nodes examined (<12) were independent poor prognostic factors. The overall concordance rate between 55GC and CMS was 72%: 29% (18/62) of the MSI-like subtype, 79% (75/95) of the CIN-like subtype, and 98% (74/76) of the stromal subtype were judged as CMS1, CMS2/3 and CMS4, respectively. The 5-year RFS rate of patients with CMS1, CMS2/3 and CMS4 was 100%, 86.3%, and 73.0%, respectively (CMS4 vs. others: p = 0.005). **Conclusions:** 55GC is a useful and reproducible grading system for recurrence risk stratification of Stage II CC.

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3529 Poster Session (Board #22), Sun, 8:00 AM-11:30 AM
Impact of the type and modalities of preoperative chemotherapy on the outcome of liver resection for colorectal liver metastases: A LiverMetSurvey study. First Author: Yuchi Guo, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France

Background: Prognostic factors of survival have been extensively reported after resection of colorectal liver metastases (CLM). However, a specific analysis of patients submitted to preoperative chemotherapy (PCT), with the real impact of type and modalities of PCT on patient outcome is lacking.

Methods: The study population consisted of a multicentric cohort of patients who received PCT before resection of CLM within a 20-year period and whose data were prospectively collected in the LiverMetSurvey. Patients were analyzed in terms of intentions of PCT including neoadjuvant (N-CT) and conversion (C-CT) chemotherapy. Overall survival (OS) rates were analyzed by Kaplan-Meier method and compared using the log-rank test. The distribution of potential prognostic factors for OS including age, sex, siedness of primary tumor, timing of metastases, tumor number, diameter of largest CLM, CEA, bilaterality, and type and number of PCT cycles were analyzed by Cox regression model. Results: Of 7,202 eligible patients, N-CT was submitted in 4,422 (61.4%) for resectable and C-CT in 2,780 patients (38.6%) for unresectable CLM. In N-CT, 5-year OS of ImCloneca decreased compared to the oxaliplatin-based (Oxa)-PCT (40.9% vs. 47.8%, p < 0.01). The 5-year OS was not different with or without targeted therapy (41.1% vs. 47.0%, p = 0.12). As for C-CT, the 5-year OS was comparable between In- and Oxa-PCT (32.2% vs. 32.9%, p = 0.32), and also not different with regard to the use of targeted therapy (p = 0.47). On multivariate analysis, In-PCT was associated with worse OS in N-CT (HR = 1.46 [1.02-1.52], p = 0.02) but not in C-CT (p = 0.89). Use of targeted therapy was not associated with OS for both N-CT and C-CT (p = 0.53, p = 0.06, respectively). PCT > 6 cycles in N-CT (HR = 1.46 [1.23-1.76], p = 0.04) and > 8 cycles in C-CT (HR = 2.39 [1.73-3.30], p < 0.01) were associated with worse OS. Conclusions: For resectable CLM with N-CT, Oxa-PCT is associated with better survival compared to In-PCT. For unresectable CLM with C-CT, the type of PCT did not influence the outcome, provided that resection is achieved for both. For the shorter, the PCT, the best is the survival after surgery.

3530 Poster Session (Board #23), Sun, 8:00 AM-11:30 AM
Multicenter phase III trial of BB1608 and pembrolizumab combination in patients with metastatic colorectal cancer (SCOOP Study): EPCO1503. First Author: Eiji Shinozaki, Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: The anti-PD-1 antibody pembrolizumab provided an objective response rate of 28-57% in patients (pts) with Microsatellite Instability-High (MSI-H) metastatic colorectal cancer (mCRC) vs 0% in pts with Non-MSI-H. The WNT/b-catenin signaling has been reported to prevent anti-tumor immunity and promote resistance of anti-PD-1/PD-L1 antibodies. Furthermore, STAT3 has been known to be a key driver of the immune evasion. This study investigates efficacy and safety of the combination of BB1608, which blocks phosphorylated STAT3 and downregulates WNT/b-catenin signaling, with pembrolizumab in pts with mCRC. BB1608 480mg BID with pembrolizumab was determined as RP2D in the phase I part (Kawazoe A, et al, ASCO-GI 2018). Here, we present the preliminary results of the ongoing phase II part. Methods: Phase II part was composed of Cohort A (MSI-H) and Cohort B (Non-MSI-H). The main eligibility criteria was pts with mCRC not responded or intolerant to standard chemotherapies. Primary endpoint was Immune-related objective response rate (iORR) determined by irRECIST. Sample size for Cohort A with 10 pts was determined in an exploratory manner. In Cohort B, according to a null hypothesis and alternative hypothesis; iORR = 5% and 20%, estimating required sample size was 40 pts with a one-sided alpha of 5% and power of 90%. Results: From Feb 2017 to January 2018, 10 pts were enrolled in Cohort A, and 37 pts in Cohort B. As of October 2017, tumor response was evaluated in 38 pts in Cohort A and 22 pts in Cohort B, respectively. Two out of the 3 pts in Cohort A showed confirmed partial response. Among 12pts with right-sided colon in Cohort B, one patient showed confirmed partial response with remarkable decline of CEA level, and two pts showed stable disease lasting more than 16 weeks. Immunochemistry before treatment demonstrated high levels of C-CT and PD-L1 in the tumor samples from the patient with partial response. No severe or unexpected adverse events occurred up to the present. Conclusions: BB1608 with pembrolizumab showed preliminary efficacy signals with acceptable toxicity for MSI-H as well as Non-MSI-H mCRC pts with right-sided primary. Clinical trial information: NCT02851004.

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3533 Poster Session (Board #26), Sun, 8:00 AM-11:30 AM
Circulating tumor DNA (ctDNA) as an early marker to monitor clinical benefit of regorafenib and TAS-102 in patients with metastatic colorectal cancer (mCRC). First Author: Paula Assis Lima Pereira, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Utilization of ctDNA has been rapidly adopted as a predictive diagnostic in advanced Non-Small Cell Lung Cancer and indications in GI cancers may be emerging. We aimed to evaluate ctDNA as an early biomarker of efficacy of new therapies for mCRC. Methods: mCRC patients (pts) who consented to a genomic matching protocol and had started a new line treatment with regorafenib or TAS-T102 were eligible. Droplet digital PCR (ddPCR) assays were performed using 3 mL of plasma samples from pts with tumors harboring RAS mutations (BioRad). Serial plasma samples also underwent transposable element (RE) based multiplexed qPCR assay using 300 µL of plasma, a DNA Integrity Index (DII) was calculated using a ratio of long to short DNA fragment size measurements (Innogenetics). Progressive disease (PD) by ctDNA, defined as any increase in allele frequency (AF) by ddPCR and any decrease in DII by RE-qPCR, was compared to RECIST at first restaging. Results: 40 mCRC pts were included. 16 pts were treated with regorafenib and 31 with TAS-102 (7 pts received both drugs). Therefore, 47 treatment regimens were included in this study with serial monitoring completed in 22 treatments with ≥ 2 serial plasma samples. At baseline, the median AF by ddPCR was 18.1%, and the median DII was 0.112. A moderate correlation was seen between baselines CEA and AF by ddPCR (r = 0.43; p = 0.056). The sensitivity and specificity of ddPCR in detecting PD by RECIST was 61.5% (95%CI: 32% - 83%) and 100% respectively. RE-qPCR had a sensitivity of 90% (95%CI: 79% - 97%) and specificity of 100%. Unlike ddPCR which was limited to monitoring patients with common mutations in KRAS and NRAS, the DII was successfully obtained in all patients. There was no false-positive in either assay. Serial change in CEA was more sensitive (77.6%), but less specific (16.8%). Conclusions: Methods: First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Woodville, Australia

Background: In the RAS wt population of APEC, q2w cetuximab combined with first-line FOLFOX or FOLFIRI achieved an overall response rate (ORR), median progression-free survival (PFS), and median overall survival (OS) similar to those reported in prior first-line pivotal studies involving weekly cetuximab. In this subgroup analysis, we evaluated the impact of tumor side in mCRC patients who received first line mCRC. Methods: A nonrandomized phase 2 trial conducted in the Asia-Pacific region, with ORR as the primary endpoint. Patients with KRAS exons 2 wt tumors received q2w cetuximab + investigator’s choice of FOLFOX or FOLFIRI. Tumor side was categorized in evaluable patients with RAS wt tumors (left [L]-sided = splenic flexure, descending sigmoid, colon, and rectum; right [R]-sided = appendix, cecum, ascending colon, hepatic flexure, and transverse colon). Results: Among 167 patients with RAS wt mCRC, 159 were evaluable for tumor side; 130 (81.8%) had L-sided and 29 (18.2%) had R-sided mCRC. Baseline characteristics in the tumor side subgroups reflected the known differences between L- and R-sided mCRC: indeed, 95.4% and 75.9% of patients had BRAF wt disease, respectively. Efficacy data are summarized in the Table. Conclusions: Consistent with prior first-line pivotal studies with weekly cetuximab, a prognostic effect of tumor side in patients receiving first-line q2w cetuximab was confirmed in APEC. In patients with R-sided mCRC, ORR remained ≥ 50%, and response rate was comparable to that of L-sided mCRC. Taken in line with prior evidence showing that use of cetuximab may be appropriate when rapid tumor shrinkage is the goal. These hypothesis-generating data raise the possibility of a synergy between cetuximab and irinotecan in patients with R-sided tumors, although numbers are small. Clinical trial information: NCT00778830.

3534 Poster Session (Board #27), Sun, 8:00 AM-11:30 AM
Impact of primary tumor side on outcomes of every-2-weeks (q2w) cetuximab + first-line FOLFOX or FOLFIRI in patients with RAS wild-type (wt) metastatic colorectal cancer (mCRC) in the phase 2 APEC trial. First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Woodville, Australia

Background: In the RAS wt population of APEC, q2w cetuximab combined with first-line FOLFOX or FOLFIRI achieved an overall response rate (ORR), median progression-free survival (PFS), and median overall survival (OS) similar to those reported in prior first-line pivotal studies involving weekly cetuximab. In this subgroup analysis, we evaluated the impact of tumor side in mCRC patients who received first line mCRC. Methods: A nonrandomized phase 2 trial conducted in the Asia-Pacific region, with ORR as the primary endpoint. Patients with KRAS exons 2 wt tumors received q2w cetuximab + investigator’s choice of FOLFOX or FOLFIRI. Tumor side was categorized in evaluable patients with RAS wt tumors (left [L]-sided = splenic flexure, descending sigmoid, colon, and rectum; right [R]-sided = appendix, cecum, ascending colon, hepatic flexure, and transverse colon). Results: Among 167 patients with RAS wt mCRC, 159 were evaluable for tumor side; 130 (81.8%) had L-sided and 29 (18.2%) had R-sided mCRC. Baseline characteristics in the tumor side subgroups reflected the known differences between L- and R-sided mCRC: indeed, 95.4% and 75.9% of patients had BRAF wt disease, respectively. Efficacy data are summarized in the Table. Conclusions: Consistent with prior first-line pivotal studies with weekly cetuximab, a prognostic effect of tumor side in patients receiving first-line q2w cetuximab was confirmed in APEC. In patients with R-sided mCRC, ORR remained ≥ 50%, and response rate was comparable to that of L-sided mCRC. Taken in line with prior evidence showing that use of cetuximab may be appropriate when rapid tumor shrinkage is the goal. These hypothesis-generating data raise the possibility of a synergy between cetuximab and irinotecan in patients with R-sided tumors, although numbers are small. Clinical trial information: NCT00778830.

3535 Poster Session (Board #28), Sun, 8:00 AM-11:30 AM
Induction chemotherapy (CT) with FOLFRINOX or FOLFOX/FOLFIRI, plus cetuximab (CET) or bevacizumab (BEV) by RAS status, in patients (pts) with primarily unresectable colorectal liver metastases (CRLM): Results of the randomised UNICANCER PRODIGE 14-ACCORD 21 (METHEP-2) trial. First Author: Marc Ychou, Institut du Cancer de Montpellier (ICM), Univ Montpellier, Montpellier, France

Background: pts with unresectable CRLM who respond to induction CT allowing curative-intent liver surgery have longer overall survival (OS) than pts who do not. Triplet (3-) over doublet (2-) CT, combined with CET or BEV, are often used in this setting. However, the best CT regimen remains to be determined. Methods: METHEP2 assessed whether 3-CT (FOLFRINOX) compared to 2-CT (FOLFOX or FOLFIRI), combined with CET or BEV (by KRAS/RAS status), would increase R0/R1 liver-resection rate in pts with initially unresectable CRLM. Randomization was stratified by KRAS (amended to RAS) status, meta-versus synchronous CRLM, and reason for non-resectability (technical vs. oncological). It was designed to demonstrate a 20% increase in the R0/R1 liver-resection rate (2-CT arm, 50% vs. 3-CT arm, 70%); bilateral = test, 5%; p = 10%. Results: 256 pts were included, 126 in the 2-CT arm (FOLFIRI; 56: FOLFOX, 70 and in the 3-CT arm. KRAS and RAS were mutated in 91 pts (35.5%) and in 109 pts (42.6%), respectively. After a median follow-up of 45.6 months (mo), RO/R1 liver resection was achieved in 74/130 pts (56.9%; 95%CI: 48-66) in the 3-CT arm vs. 61/126 pts (48.4%; 95% CI: 39-57) in the 2-CT arm (p = 0.17). The odds for R0/R1 resection were higher in the 3-CT than in the 2-CT arm (OR, 1.8; 95%CI, 1.1-2.7; p < 0.02) when using a logistic regression model adjusted on stratification factors. Median OS was 42.9 mo in the 3-CT arm vs. 37.6 mo in the 2-CT arm (HR = 0.80; 95%CI, 0.54-1.16). Efficacy by targeted agent was as follows: R0/R1 cases: 153 (56.2%; 95%CI: 48-64) and 49/103 (47.6%; 95% CI: 38-58), objective response: 120/153 (78.4%; 95%CI: 71-85) and 58/103 (56.3%; 95% CI: 46-66), mPFS: 12.8 mo (95%CI: 11.6-13.1) and 10.7 mo (95% CI: 9.7-13.1); OS: 43.6 mo (95% CI: 40.0-51.8) and 34.2 mo (95% CI: 27.8-40.4), for CET- and BEV-treated pts, respectively. Conclusion: Despite not reaching the primary endpoint, FOLFRINOX tends to be superior to FOLFOX/FOLFIRI, combined with CET or BEV, in terms of RO/R1 liver-resection rate in pts with initially unresectable CRLM. Clinical trial information: NCT01442935.
Background: In resected CLM, randomized studies of Ox CT have not demonstrated improvements in overall survival (OS) and Ox CT has not been compared to non-Ox CT. The aim of this study was to assess the impact of Ox CT regimens on OS in patients that have undergone resection of CLM in a real world setting. Methods: Patients who underwent resection of CLM in the provinces of Alberta and British Columbia, Canada were identified from 1996-2016. Perioperative (pre and/or post) CT regimens were reviewed and categorized as Ox, non-Ox CT or no CT. OS was measured from the time of metastatic diagnosis to death or last follow-up using the Kaplan-Meier method. CT regimens were compared using the log-rank test and a Cox regression model, adjusting for possible confounders including age, gender, primary tumor sidedness and the presence of synchronous metastatic disease. Results: 516 patients were identified who underwent R0 resection of CLM for mCRC, including 205 that received Ox CT, 129 non-Ox CT and 182 with no CT. Of these patients, 24% and 56% received pre-operative and post-operative CT, respectively. 70% of these patients received a fluoropyrimidine (5-FU or capecitabine), 40% oxaliplatin, 13% irinotecan, 7% received bevacizumab and 1% panitumumab. Median age of these patients was 64, with 60% male and 57% demonstrating synchronous metastatic disease and 38% right-sided primary. The median OS for patients receiving Ox CT was 98 months, for non-Ox CT 60 months and no CT 56 months, p = 0.024. After adjusting for potential confounders with a Cox proportional hazard model, patients who received Ox CT had a lower risk of death HR of 0.65 (95% CI 0.48-0.87, p < 0.01). Among patients who underwent Ox CT group did not have HR, 0.84 (95% CI 0.62-1.13, p = 0.25) compared to no CT. Conclusions: Perioperative Ox CT appears to improve OS in conjunction with R0 resection of CLM in this multi-institutional population based study. This observation provides further evidence supporting the role of Ox CT in the management of resectable colorectal cancer. Ox CT should be considered in patients that undergo R0 resection of CLM, in favor of non-Ox CT. The addition of biologic agents to CT remains limited. Further studies should evaluate the optimal timing and duration of perioperative CT.

3541 Poster Session (Board #34), Sun, 8:00 AM-11:30 AM

Effect of time to resection of colorectal liver metastases on recurrence risk.
First Author: Emerson Yu-sheng Chen, Oregon Health and Sciences University, Portland, OR

Background: Resection of colorectal liver metastases (CRLM) with perioperative chemotherapy is curative in only 20-30% of patients. There are no biomarkers or robust clinical predictors that can effectively select patients curable by resection. The time interval from diagnosis of liver metastasis to hepatic resection (time to resection, or TTR) has not been studied to risk stratify patient. Who would benefit? Methods: A retrospective analysis of patients who underwent resection for CRLM from 2003 to 2017 was conducted at our institution. Patients were categorized as: 1) no evidence of disease (NED) or 2) disease relapse or death. NED patients with < 1 year follow-up were excluded. Factors including TTR (short = < 3 months; intermediate = 3-6 months; and long = > 6 months) were compared between the two groups (all p < 0.05 unless noted). Logistic regression was used to identify factors associated with NED. Results: We identified 264 patients with a median follow-up of 30 months. Of these, 60% presented with synchronous liver metastases, 42% had bilateral liver disease, and 76% received preoperative chemotherapy. Preoperative MRI was performed in 19% of patients. R0 resection was achieved in 88%. Overall, 27% of patients were NED at one year. Patients with intermediate TTR had a higher proportion of NED compared to short TTR and long TTR (45% vs. 27% vs. 28%). Primary tumor location, grade, metastachronous CRLM, and response to chemotherapy were not associated with NED. Long TTR was associated with synchronous CRLM, bilateral disease, and more liver lesions compared to intermediate and short TTR. On multivariate analysis, patients with long TTR (OR: 0.65), older age (OR: 0.97), more liver lesions (OR: 0.80), and positive resection margin (OR: 0.08) were less likely to achieve NED. Preoperative MRI use was predictive of NED (OR: 2.6). Conclusions: Intermediate TTR is associated with NED status at > 1 year when compared to short TTR. This suggests liver resection should wait 3-6 months to assess for more indolent tumor biology. Lack of benefit seen with long TTR was likely due to high tumor burden in our dataset. Use of preoperative MRI may better quantify extent of liver involvement to help select patients who will benefit from resection. Analysis is ongoing.
Background: Both patients with and without prior targeted therapy can benefit from fruquintinib treatment. Safety profile. The benefits seen may have been achieved by good disease control and according to baseline clinical characteristics.

Methods: The FRESCO Study is a randomized, double-blind, phase III trial with mCRC, previously untreated, ECOG PS 0-1, age 18-75, were randomized to treatment with B alone or B+Fluoropyrimidine (C or FU). Sample size of experimental arm was calculated according to Simon's two-stage design, with A vs B in rate of 0.05 and 0.90 power. With null hypothesis ORR 32% and alternative hypothesis ORR 48%, 46 pts had to be accrued in the first stage, for a final number of 80 pts. Study design was formally non-comparative, but exploratory comparison between arms was performed. Results: One-hundred thirty-two pts were randomized (45 arm A: B; 87 arm B: O). The main clinical characteristics of the entered pts were well balanced. ORR (Arm A vs B) was 55.6% vs 48.3% (p = 0.43). With a median follow-up of 47.2 months, PFS was 10.0 vs 9.9 months (HR 0.96, 95% CI 0.96-1.1; p = 0.84) and OS was 29.8 vs 25.0 months (HR 1.21, 95%CI 0.77-1.92; p = 0.41). Main G3-4 toxicity rates (Arm B vs A) were: thrombocytopenia 2/2, anemia 2/4, neutropenia 6/3, nausea 9/5, vomiting 2/3, diarrhea 7/7, neurotoxicity 2/2 and hyponatremia 2/2.

Conclusion: GOIM study 2802 showed that the XELOX2+B regimen is active as FOLFOX4+B in pts with mCRC. Given the extreme tolerability and convenience of administration of therapy, XELOX2+B appears to be indicated even in frail or elderly patients. Clinical trial information: 2010-022091-31.
A phase 1 expansion study of trifluridine and tipiracil (FTD/TPI) in combination with irinotecan (IRI) and bevacizumab (BEV) in patients with metastatic colorectal cancer (mCRC). First Author: Anna M. Varghese, McMaster University, Hamilton, ON, Canada

Background: FTD/TPI is an oral antineoplastic agent that was developed to overcome resistance to fluoropyrimidines. FTD/TPI is approved for use in previously treated patients with mCRC. This Phase I expansion study investigated the safety, pharmacokinetics (PK), and preliminary efficacy of FTD/TPI and IRI with BEV. The dose-escalation phase determined the maximum tolerated dose of FTD/TPI and IRI to be FTD/TPI 25 mg/m² and IRI 180 mg/m². Methods: Patients aged ≥18 years with mCRC with disease progression following ≥1 line of chemotherapy were included. Patients who had required any prior IRI dose reductions, dose delay, or growth factor support in the first 8 weeks of treatment with IRI were excluded. FTD/TPI was had required any prior IRI dose reductions, dose delay, or growth factor support in the first 8 weeks of treatment with IRI were excluded. FTD/TPI was administered at 25 mg/m² twice daily on days 1-5 of 14-day cycles with IRI 180 mg/m² preceded by BEV 5 mg/kg on day 1 of each 14-day cycle. PK samples were collected on days 1-3 of cycle 1. Results: Twenty-four patients with mCRC were enrolled; 67% were female and the median age was 55.5 years (range 19-73). The median number of prior regimens was 4; all patients received prior fluoropyrimidine and oxaliplatin. Patients were IRI-naïve, and 5 patients were BEV-naïve. Grade ≥3 adverse events were reported in 20 patients (83%); the most common were neutropenia (33%), leukopenia (25%), diarrea (13%), and hypertension (13%). Based on RECIST v1.1 of the 24 evaluable patients, 3 had a partial response and 17 experienced stable disease (57%). The median duration of response was 7.9 months (95% CI 5.1, 13.4). PK analysis did not show any significant correlation between the plasma concentrations of FTD/TPI and IRI or their metabolites. Conclusions: No new safety findings or cumulative adverse events were reported with the addition of BEV to FTD/TPI and IRI. Preliminary efficacy results indicate promising anti-tumor activity using FTD/TPI and IRI with BEV for patients who had failed a median of 4 prior regimens with most having had prior IRI. This triple chemotherapy combination warrants further evaluation in patients with mCRC. Clinical trial information: NCT01916447.

FOLFIRINOX plus cetuximab (CET) or bevacizumab (BEV) in patients (pts) with initially unresectable colorectal liver metastases (CRLM). First Author: Evelyne Lopez-Crapez, Institut regional du Cancer de Montpellier ICM, Montpellier, France

Background: The treatment of metastatic colorectal cancer (mCRC) pts with BRAF-mutated tumors is a major challenge for physicians. They account for 5-10% of all CRC cases. BRAF-mut tumors: A subgroup analysis of the UNICANCER PRODIGE 14-ACCORD 21 (METHEP2) trial. First Author: Evelyne Lopez-Crapez, Institut regional du Cancer de Montpellier ICM, Montpellier, France

Methods: This trial assessed whether 3-CT (FOLFIRINOX) compared to 2-CT (FOLFOX or FOLFIRI), combined with CET or BEV (by KRAS exon 2/RAS status), would increase R0/R1 liver resection rates in pts with initially CRLM. As an exploratory analysis, we assessed the outcome of the subset of BRAF-mut mCRC pts. Results: 256 pts were included. KRAS exon 2 and RAS (KRAS/ NRAS: exon 2, exon 3, exon 4) were mutated in 91/256 pts (35.5%) and in 9/218 pts (50%), respectively. The R0/R1 liver resection rate was 57% in the 3-CT arm vs. 48% in the 2-CT arm. mPFS was 12.8 mo in the 3-CT arm vs. 11.5 mo in the 2-CT arm (HR, 1.05; 95% CI 0.79-1.39). mOS was 42.9 mo in the 3-CT arm vs. 37.6 mo in the 2-CT arm (HR, 0.80; 95% CI, 0.56-1.16). Nine out of 230 (3.9%) mCRC pts were BRAF-mut. 8/9 pts received CET and 1 (in the 2-CT arm) received BEV as the targeted agent. Efficacy results in the 2-CT (n = 4) vs. the 3-CT (n = 5) arm were as follows: objective tumor response, 0/4 vs. 4/5; R0/R1 resection, 0/4 vs. 2/5; mPFS, 1.8 vs. 6.1 mo; and mOS, 6.6 vs. 21.3 mo. Conclusions: In this small series, pts with BRAF-mut tumors treated with 3-CT plus a targeted agent had better PFS and OS than those treated with 2-CT plus a targeted agent. Moreover, intent-to-treat survival outcomes in the 3-CT plus a targeted agent group suggested a survival benefit vs. the 2-CT arm. Further studies are needed to confirm these results. Clinical trial information: NCT01442935.

Proteomic profiling of phosphatidylinositol 3-kinase (PI3K) altered metastatic colorectal cancer (mCRC) after protein kinase B (Akt) inhibition. Insulin like growth factor 1 receptor (IGF1R) mediates adaptive resistance. First Author: Malika Nusrat, Cancer Medicine Fellowship Program, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: We have reported earlier that Akt inhibition is clinically ineffective as monotherapy in PI3K altered (PIK3CA mutant or PTEN loss) mCRC patients (pts). The reasons for this are unknown yet vital for developing effective treatments. We hypothesized that mCRC evades Akt inhibition via adaptive signaling activation. Methods: KRASwt PI3Kmut altered mCRC pts were treated with single agent oral Akt inhibitor, MK2206 (200 mg/week), on a CTEP-sponsored clinical trial (n = 18). Metastases were biopsied at baseline and on day 15. Pt derived xenografts (PDXs) were established for a co-clinical trial with either MK2206 or carbox (30% Captisol) for 3 weeks. Signaling pathways were profiled by reverse phase protein array (RPPA) on tumors from pts and PDXs, as well as on 2 CRC cell lines (KM12L4 and SW480) treated with MK2206. Protein levels from treated and untreated samples were compared by paired or student’s t-test, or ANOVA as applicable. Results: Out of 18 pts, 16 progressed and 2 had stable disease. Similarly, all treated PDXs progressed after a brief response. RPPA data was available for 15 paired biopsies, 9 treated PDXs and 10 control PDXs. MK2206 adequately inhibited pharmacodynamic (PD) markers (including pAkt T308 and pAkt S473) in PDXs, with a similar but nonsignificant trend in pAkt in pts’ biopsies. In cell lines, IGF1R rose after 24 hours and was maintained up to 7 days (P < 0.01). Similarly, treated PDXs had increased IGF1R, insulin receptor beta (INSRB) and HER3 levels (P < 0.05 for all). MK2206 did not affect MAPK signaling. Conclusions: Akt inhibition with MK2206 in mCRC induces adaptive upregulation of receptor tyrosine kinases, namely IGF1R but also HER3 and PDGFR, resulting in reactivation of the Akt pathway. Combined analysis of cell lines, PDXs and pts’ samples allows in-depth interrogation of adaptive resistance and identifies rational combination therapies worthy of future investigation.
3550 Poster Session (Board #43), Sun, 8:00 AM-11:30 AM
Folate gene expression in treatment response to 5-FU and leucovorin in advanced colorectal cancer. First Author: Bengt Gustavsson, Surgical Oncology Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden

Background: Folates are a group of water-soluble, B-vitamins that are involved in DNA and RNA synthesis, cell proliferation, and cell growth. 5-fluorouracil (5-FU) and leucovorin (LV) are widely used chemotherapy agents for colorectal cancer (CRC). Folates without sufficient co-factor (5,10-methylenetetrahydrofolate) and weak inhibition of the target gene thymidylate synthase (TYMS) may lead to poor response to 5-FU + LV combination chemotherapy.

Methods: Tissue samples of primary tumors were obtained at surgery from patients with metastasizing CRC (n = 143) prior to FLV-based chemotherapy. Folate pathway genes were analyzed using real-time quantitative PCR (qPCR) as paired primary and metastatic tissue samples from patients with metastatic CRC.

Results: Significant positive correlations between folate genes expression and survival were found. After adjustment in a multiple Cox analysis of all analyzed genes, only ABCB3 remained significant (p = 0.002). The ABCB3 protein is involved in outward transport of folates, and has preference for 5-formyltetrahydrofolate. This folate inhibits the first conversion step of LV to co-factor. High expression of ABCB3 may therefore cause a high conversion rate of LV to co-factor, and enhanced inhibition of TYMS. After Cox analysis, ABCB3 expression levels were divided into tertiles; the low, intermediate and high tertiles had identical outcomes and were combined. The high expression group had a median PFS of 10.1 months compared to 6.5 months among patients in the low expression group. Conclusions: Folate-related genes predict response to treatment with FLV in stage III and IV CRC. Outcome study after direct treatment with the co-factor deficient antitumor regimen is warranted.

3552 Poster Session (Board #45), Sun, 8:00 AM-11:30 AM
A phase II study of nintedanib and capcitabine in refractory metastatic colorectal cancer. First Author: Patrick McKay Boland, Roswell Park Cancer Institute, Buffalo, NY

Background: Nintedanib is a vascular endothelial growth factor (VEGFR), platelet-derived growth factor (PDGFR), and fibroblast growth factor receptor (FGFR) inhibitor. The combination of both variables should allow optimal anti-angiogenesis and anti-metastatic activity in patients with refractory metastatic colorectal cancer.

Methods: A phase I/II study of nintedanib and capcitabine was conducted. Eligible patients were 18 years of age or older, with histologically proven metastatic colorectal cancer, ECOG PS of 0 or 1, progression/intolerance to a previous regorafenib was exclusionary. The primary endpoint was 18- month progression-free survival (PFS).

Results: Forty patients were enrolled across 2 dose levels. Nintedanib 200 mg po bid and Capecitabine 1000 mg/m2 po bid was established to be the RP2D. 36 patients were treated at the RP2D and evaluable for efficacy. The 18 week progression free survival (PFS) was 36% (13/36 patients), p = 0.0922, indicating a statistically significant increase in PFS over historic control. No responses were observed; 19 (53%) patients experienced SD. Median PFS was 3.3 months. Median OS was 7 months. 16 (44%) patients received two chem regimens. 30% were able to continue on therapy.

Conclusions: The combination of Capcitarbine and Nintedanib was well tolerated. Efficacy compares favorably to historical data with regorafenib or TAS-102 monotherapy and is similar to results from other international multi-kinase TKIs and fluoropyrimidines in the refractory setting. Further investigation is warranted. This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Boehringer Ingelheim Pharmaceuticals, Inc. Clinical trial information: NCT02393795.

3553 Poster Session (Board #46), Sun, 8:00 AM-11:30 AM
Association between genotypes, clinical scores and survival outcome in metastatic colorectal cancer. First Author: Moreno Reinaldo, Hospital Clinic Barcelona, Barcelona, Spain

Background: Several prognostic clinical scores for metastatic colorectal cancer (mCRC) exist; GEMCAD GERCOR K¨ ohne are useful for treatment guidance. Next generation sequencing (NGS) allows the evaluation of multiple genes including VEGFR, PDGFR, and FGFR with preclinical efficacy in bevacizumab resistant metastatic colorectal cancer.

Methods: Mutations were analyzed in 98% of patients using NGS. Genotype was defined as Complex: 1) BRAF mutant 2) NRAS 3) RTK-RAS-PI3K+/-p53 negative 4) RTK-RAS-PI3K+/-p53 wild-type 5) p53 wild-type 6) SMAD4 mutant 7) FBXW7 mutant. A Cox proportional hazard model was built to adjust for tx selection bias based on stage at diagnosis (dx), number and site of met, type of first-line chemotherapy (chem), and curative resection of met. Results: In total, 913 pts were registered in the database and 416 (45%) fulfilled the molecular criteria. From these pts, 98% received two chem regimens, 70% anti-EGFR tx, 60% anti-angiogenic tx and 45% had surgery of met. Clinical variables associated with poor OS after anti-EGFR tx were older age at dx, single met site and surgery of met (p < .05). The only factor linked to preference for anti-EGFR tx as 1st line was year: 30% from 2010-2014 and 56% from 2015-2016 (p < .01). In anti-EGFR treated pts not eligible to curative surgery of met (n = 152), OS in pts with left-sided prim (spinal flexure-rectum, 85% of all cases) was 47.5 months and in those with right-sided prim (cecum to transverse, 15%) it was 33.6 months (HR = 1.26, CI95% 0.8-2.1, p = .27). The same was true for right-sided prim (HR = 1.4, CI95% 0.8-3.2, p < .36; interaction p = .32). Conclusion: In a real-world cohort before the “sidedness” era we found that anti-EGFR sequence did not affect OS of pts with left-sided prim, but 1st line therapy was preferred setting in more recent years. Only 15% of molecularly-selected pts have poor outcome right-sided prim, limiting subgroup analysis.

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3554 Poster Session (Board #47), Sun, 8:00 AM-11:30 AM
What is the prognostic impact of BRAF mutation in patients undergoing resection of colorectal liver metastases? Results of nationwide intergroup (ACHBT, FRENCH, AGEO) cohort of 240 patients.
First Author: Jean-Baptiste Bachet, Hospital Pitié-Salpêtrière, Paris, France

Background: BRAF mutation is associated with poor prognosis in patients with metastatic colorectal cancer. In patients with resectable colorectal liver metastases (CRLM), the prognostic impact of BRAF mutation is unknown and the benefit of surgery is debated. This study aims to evaluate oncologic outcome of patients undergoing liver resection for BRAF-mutated CRLM.

Methods: From 2012 to 2016, 66 patients underwent resection for BRAF-mutated LM in 24 centers. Case-matched comparison was made with 183 patients who underwent resection for BRAF-wild type CRLM during the same period. The matching criteria were: synchronous or metachronous CRLM, initially resectable or unresectable CRLM, univ- or bilobar distribution, and number (≤ or > 4) of CRLM. Patients with extra-hepatic disease were excluded.

Results: Mean follow up was 28.7 ± 19.8 months after surgery. The 1- and 3-year disease-free survival (DFS) rates were 46.1% and 19.3% in BRAF-mutated and 55.4% and 27.8% in BRAF-wild type patients (p = 0.430). In multivariate analysis, BRAF mutation was not a predictor of worse DFS (p = 0.574; OR: 1.1295%CI: 0.74-1.71). The 1- and 3-year overall survival rates after surgery were 93.5% and 54.3% in BRAF-mutated and 95.8% and 82.9% in BRAF-wild type patients (p = 0.004). The median survival after disease progression was 23.0 months (11.4-34.9) in BRAF-mutated and 44.3 months (35.9-52.6) in BRAF-wild type patients (p = 0.049). Multiple disease progression was more common in BRAF-mutated than in BRAF-wild type patients (48 vs 30%, p = 0.034) and was less likely to be surgically treated with curative intent (27% vs 42%, p = 0.085).

Conclusions: Our results support the interest of surgical therapy of BRAF-mutated resectable CRLM as BRAF mutation by itself does not increase the risk of relapse after surgery. By analogy to non-metastatic CRC, BRAF mutation has a negative impact on survival in patients who relapse after resection of LM.

3556 Poster Session (Board #49), Sun, 8:00 AM-11:30 AM
Apatinib as a salvage treatment for refractory metastatic colorectal cancer.
First Author: Xiaofeng Chen, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Apatinib, an oral VEGFR2 inhibitor, has been approved as third line treatment for metastatic gastric cancer in China. The aim of this study was to evaluate the efficacy and safety of apatinib, in the treatment of refractory metastatic colorectal cancer patients who failed from two or more lines of chemotherapy.

Methods: In this open-label, single-arm, phase II study, patients were treated with apatinib in daily dose of 500 mg, po, in the third - or more line setting. Capture sequencing was dynamically performed to identify somatic variants in circulating tumor DNA (ctDNA) with a panel of 1021 cancer related genes. The primary endpoint was progression-free-survival (PFS) and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Interim analyses was applied as predefined.

Results: From June 01, 2016 to December 31, 2017, 26 patients were enrolled. The median FOF of the whole group was 3.9m (95% CI: 2.1-5.4). Patients with PS 0-1 had longer PFS than those with PS 2 (4.17m vs 1.93m, p = 0.0014). Patients without ivy metastasis also had longer PFS than those who had liver metastasis (5.87m vs 3.33m, p = 0.0274). Median overall survival was not reached, 10-month survival rate was 55%. The common side effects of apatinib were hypertension, hand-foot syndrome, proteinuria and diarrhea. The incidence for grade 3-4 related AEs was observed in 3 patients, and two deaths occurred on study.

Conclusions: Apatinib monotherapy showed promising efficiency for refractory colorectal cancer patients, especially in patients with PS 0-1 or no liver metastasis. TMB is a potential prognostic biomarker. In addition, tumor molecular burden may be a predictor in serial monitoring of tumor load. Clinical trial information: NCT03190616.

3555 Poster Session (Board #48), Sun, 8:00 AM-11:30 AM
A phase III/II trial of cabozantinib (C) with or without panitumumab (P) in patients (pts) with RAS wild-type (WT) metastatic colorectal cancer (mCRC). Clinical outcomes in pts with RAS amplification (amp) detected in ctDNA
First Author: Jingquan Jia, Duke University Medical Center, Durham, NC

Background: MET amp is a well described driver of acquired EGFR antibody (Ab) resistance. Blood-based genomic profiling of cell free (cf)DNA is a safe and efficient means to identify pts with acquired MET amp. To determine whether a MET targeting strategy is feasible and clinically active in pts with MET amp RAS WT mCRC, we studied pts treated with an anti-c-MET multikinase inhibitor (C) combined with an anti-EGFR Ab (P) or (C) alone.

Methods: Pts with RAS WT mCRC were enrolled in 2 cohorts: 1) C+P combination (C+P); or 2) C monotherapy (C) (NCT02008383). Peripheral blood was sequenced for up to 73 single nucleotide variants, insertions/deletions, fusions, and amplifications, including MET amp (Guardant360, Guardant Health). Pts enrolled in the C+P cohort received retrospective cfDNA profiling for MET amp. Pts enrolled in the C cohort were prospectively screened for MET amp; only those pts with MET amp in blood were treated in the C cohort.

Results: 64/65 pts (98%) had detectable cfDNA (C+P = 13; C = 51). MET amp was identified in 12 pts (18%) (C+P = 4, C = 8). Among pts with MET amp detected in blood the median copy number was 2.6 (range 2.3-6.4). 8 pts with MET amp received treatment (C+P = 4, C = 4); 7 pts were evaluable for efficacy (C+P = 4, C = 3). 1 pt (C+P cohort) had a RECIST PR, and this pt had low grade EGFR and MET co-amp (MET = 2.3 copies; EGFR = 2.2 copies). 4/7 pts (57%) had a reduction of measurable RECIST target lesions, 3 of whom received at least 1 RECIST PR = 1, SD = 2, PD = 1 (27% reduction) received C. 3/4 pts in the C+P cohort had EGFR and MET co-amp, 2 of these pts had a reduction in RECIST lesions (PR = 1; PD = 1). No evaluable pts in the C cohort had EGFR and MET co-amp. Conclusions: This study demonstrates the feasibility of utilizing cfDNA to identify MET amp in pts with RAS WT mCRC, with the potential to identify pts with MET co-amp. Our results have shown that the role of EGFR co-amp, and the additive value of combined EGFR blockade remain to be determined. Clinical trials utilizing cfDNA to identify and treat MET amp mCRC are ongoing. Clinical trial information: NCT02008383.

3557 Poster Session (Board #50), Sun, 8:00 AM-11:30 AM
First Author: Nilofor Saba Azad, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: In studies reported to date, no objective responses have been observed with PD-1 inhibitors in advanced/metastatic CRC (mCRC) pts with microsatellite stable (MSS)/mismatch repair proficient (pMMR) tumors. About 95% of mCRC pts have this phenotype; additional strategies are needed to improve effectiveness of immunotherapies in these pts. Entinostat (ENT), an oral, class I-selective histone deacetylase inhibitor, enhances anti-PD-1 activity by downregulation of immunosuppressive cell types in the tumor microenvironment in vivo and has shown promising activity with pembrolizumab (PEMBRO) in pts with melanoma and lung cancer. This study evaluates the safety and efficacy of ENT + PEMBRO in MSS/pMMR CRC pts.

Methods: This study is a multi-cohort, Simon 2-stage, phase II trial. Main eligibility criteria for pts in the CRC cohort are: documented MSS/pMMR status, ≥1 prior regimen in the metastatic setting, and no prior anti-PD-(L)1 therapy. All pts received ENT 5 mg PO QW + PEMBRO 200 mg IV Q3W. The primary endpoint is objective response rate (ORR) as assessed by irRECIST. Results of the first stage are reported. Results: 16 pts were enrolled in Stage I with a median age of 58 (range 36-68) and 4 lines of prior therapy. Median follow up is 4.7 mos. To date, 2 pts had documented pseudoprogression (1 subsequently became a confirmed PR). As of data cutoff, 6 pts (1 PR, 5 SD) remain on study (median time on treatment of 18 wks). Common (> 15%) treatment-related AEs include fatigue (37.5%), arthralgia (18.8%), and increased alkaline phosphatase (18.8%). Grade 3/4 related AEs were observed in 3 patients, and two deaths occurred on study — one due to sepsis secondary to cholangitis and the other due to progression. Serial blood and pre-treatment biopsies were obtained in all pts, with paired post-treatment biopsies in a subset of pts. Evaluation of PD-L1 expression, gene expression, myeloid and lymphoid compartments in biopsies is in progress. Conclusions: ENT + PEMBRO demonstrates acceptable safety and encouraging preliminary activity in a small cohort of MSS/pMMR CRC pts, a population in which objective responses have not been reported with PD-(L)1 monotherapy. Clinical trial information: NCT02437136.
EORTC-ESSO 1409 GITGC: A prospective colorectal liver metastasis database with an integrated quality assurance program (CLIMB). First Author: Carmela Aves Caballero, EORTC, Brussels, Belgium

Background: The European Organization for Research & Treatment of Cancer & European Society of Surgical Oncology joined forces to build an infrastructure for surgical quality assurance (QA) in clinical trials (SUR-CARE) and advance the surgical research agenda in Europe. Benchmarking is a critical step to achieve this. Their first project is CLIMB, a prospective study to evaluate complications and identify indicators for improvement in surgery for unresectable or borderline resectable colorectal liver metastases (CRLM). Methods: CLIMB (NCT02218801) opened in 2015 in 9 countries and 14 specialised centres for liver surgery. Eligible patients were registered after multidisciplinary evaluation and before surgery. Primary endpoint was 30 and 90 day surgical complication rate. On-site visits and central review ensured prospective data inclusion of the following: biomarker, imaging, chemotherapy, surgery, complications graded by Clavien-Dindo classification and survival. Data until post op day 90 were analysed but long term outcome will be reported after all patients were followed for two years after registration. Results: Among 210 patients registered, 126 (60%) who had at least one liver surgery were analysed. 73% had left-sided, 95.2% had synchronous primary and liver metastasis, 19.8% had extra-hepatic lesions and CRLM. Most patients (N = 95, 75.4%) had one stage liver surgery while 30 (23.8%) had two stage liver surgery, 10 of whom had ALPS. Overall complication rates for one stage was 53.7% (95% CI (43%, 64%)), 17.9% (95% CI (11%, 28%)) with grade=3 and 93.5% (95% CI (78, 99%)) for two stage, 46.7% (95% CI (28%, 66%), grade=3 including two deaths. Intra-abdominal, wound and urinary tract infections, bile leak and post hepatectomy liver failure grade A were most commonly reported over-all. Conclusions: CLIMB prospectively collected data from complex surgery for unresectable colorectal liver metastasis. Patients who had more grade=3 complications. Harmonizing standards in multidisciplinary evaluation, biomarker testing and imaging may improve this outcome. SUR-CARE will use these indicators to develop trials with enhanced QA methods to improve cancer surgery. Clinical trial information: NCT02218801

Avelumab and cetuximab in combination with FOLFOX in patients with previously treated metastatic colorectal cancer (MCRC): Results of the safety run-in phase of the phase II AVETUX trial (AIO-KRK-0216). First Author: Alexander Stein, Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany

Background: Single agent PD-1/L1 inhibition is efficacious in mismatch repair deficient tumours - about 5% of MCRC patients (pts). For the remaining MCRC pts the role of immunotherapy still needs to be determined. FOLFOX and cetuximab in combination with avelumab (AVETUX regimen) in 1st line RAS/BRAF wildtype MCRC is currently evaluated in a phase II trial independent of mismatch repair status (NCT03174405). Methods: This is a single arm exploratory investigator-initiated trial planned to include 43 pts to receive mFOLFOX6 and cetuximab in combination with avelumab (AVE) (10mg/kg day 1 from cycle 2 onwards). Primary endpoint is 12 months progression-free survival rate. Secondary endpoints are response rate, tolerability and translational research evaluating tissue and serial ctDNA. A safety analysis was planned after the 15th patient has passed 2 months to inform about tolerability. Results: As of 1st February 2018 24 of 43 pts were enrolled and treated with the AVETUX regimen at 6 German sites. The safety analysis of the run-in phase was conducted on the 1st of February after a median of 3.2 months of treatment. The following adverse events were noted: 19/5 grade 3/4 (CTC AE 4.03) in 9 patients, including neutropenia (n = 11/4), nausea (n = 3), and infection (n = 3/1), mostly related to chemotherapy with only two grade 3 AE related to AVE. In 7 out of 15 patients 9 SAEs (one related to AVE), were noted including one case of grade 3 hepatitis, which resolved quickly with steroid treatment, 4 infections/fever, one diarrhea and three nausea (in one patient). Despite the relatively high absolute rate of G3/4 toxicity and SAES, adverse events were manageable and did not relevantly impact on treatment feasibility. Two pts developed uncomplicated fever the day after the first infusion of AVE, both among the highest T cell infiltrated tumors. The IDMC recommended trial continuation based on these safety data. Updated safety and translational data and efficacy results will be presented at the meeting. Conclusions: The interim safety analysis has supported the feasibility of the AVETUX regimen in 1st line MCRC. The trial is ongoing. Clinical trial information: NCT03174405.
### 3562 Poster Session (Board #55), Sun, 8:00 AM-11:30 AM

Update survival analysis from a multicenter, randomized phase 3 study on the optimization of the combination of bevacizumab with FOLFIRI/XELOX in patients with metastatic colorectal cancer (mCRC). First Author: Hidetoshi Danno, Avallone, Istituto Nazionale Tumori Fondazione G. Pascale, Naples, Italy  

**Background:** Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, approved in combination with chemotherapy in the treatment of mCRC. It has been hypothesized that the schedule of administration might be critical and that anticipating bevacizumab to chemotherapy might improve treatment efficacy. Present analysis updates 2016 findings.  

**Methods:** mCRC pts, <75 yrs, ECOG PS ≤1, were randomized (1:1) to receive standard (S) administration of bevacizumab (5mg/kg d1 Q14) with chemotherapy (mFOLFOX/OXXEL regimen for 12 cycles) vs experimental (E) bevacizumab given whenever 4 days before chemotherapy (same dose and cycles number). Pts could receive maintenance bevacizumab with fluoropyrimidines until disease progression or unacceptable toxicity. Primary endpoint was the objective response rate (ORR). With 80% power and 2-tailed alpha 0.05, an expected 20% increase in response rate, 230 pts were planned. Analyses were based on the intention to treat. Correlative studies on biomarkers and FDG-PET were also planned. Results: From May 2012 to Dec 2015, 230 pts, randomised to E (n = 115) and S (n = 115) arm, Median age was 62 yrs (IQ range 53-68), 79% were PS 0, 93% were not pretreated, 53% had a single metastatic site, 71% had a left primary site (71% and 74% in E and S, respectively), 54% were RAS-mutant (47% and 62% in the S and E arm, respectively), 54% were RAS-mutant (47% and 62% in the S and E arm, respectively), 54% were RAS-mutant (47% and 62% in the S and E arm, respectively). ORR was 54% in both arms (p = 0.89). With a median follow-up of 42 months, 209 PFS events and 150 deaths were reported. Median PFS was 10.5 and 11.7 months (HR 0.80, 95% CI: 0.61-1.06; multivariate adjusted p = 0.12) and median OS was 23.8 and 29.1 months (HR 0.70, 95% CI: 0.51-0.97; multivariate adjusted p = 0.03), in the S and E arm, respectively. Distribution of patients receiving treatment after progression was similar across the arms. Conclusions: Anticipating bevacizumab to chemotherapy does not improve ORR and PFS, but results associated with a significantly longer OS. Further studies are required to confirm whether this schedule might improve treatment efficacy in mCRC patients. Supported by the Italian Ministry of Health. Clinical trial information: NCT01718973.

### 3564 Poster Session (Board #57), Sun, 8:00 AM-11:30 AM

Health related quality of life in elderly or frail patients with advanced colorectal cancer treated with dose reduced capecitabine. First Author: Daniel Adam Breadner, Schulich School of Medicine and Dentistry, London, ON, Canada  

**Background:** Palliative chemotherapy’s role is to prolong survival while minimizing treatment toxicities to preserve or improve quality of life. We recently published a phase 2 trial of dose reduced capecitabine in elderly or frail patients with advanced colorectal cancer (aCRC). We herein provide a robust analysis of the HRQoL data from our trial.  

**Methods:** A single arm multi-centered phase II trial of dose reduced capecitabine in elderly or frail patients. Capecitabine was given at 2000 mg/m2 days 1-14 q21 days; or 1500 mg/m2 for patients with prior treatment. Capecitabine was randomized to E (n = 115) and S (n = 115) arm. EARLY was similar across the arms. Distribution of patients receiving treatment after progression was similar across the arms. Conclusions: Anticipating bevacizumab to chemotherapy does not improve ORR and PFS, but results associated with a significantly longer OS. Further studies are required to confirm whether this schedule might improve treatment efficacy in mCRC patients. Supported by the Italian Ministry of Health. Clinical trial information: NCT01718973.

### 3565 Poster Session (Board #58), Sun, 8:00 AM-11:30 AM

Prognostic impact of residual HPV ctDNA detection after chemoradiotherapy for anal canal carcinoma. First Author: Luc Cabel, Institut Curie, Paris, France  

**Background:** Chemoradiotherapy (CRT) is the current standard of care for patients diagnosed with locally advanced anal squamous cell carcinoma (ASCC), but some patients will present a local and/or a distant relapse during follow-up. We previously reported the analytical validity of HPV circulating tumor DNA (HPV ctDNA) detection by droplet digital PCR in HPV-related cancers. The current study aimed at analyzing residual HPV ctDNA levels during CRT in locally advanced ASCC.  

**Methods:** We analyzed prospectively collected samples from patients with HPV16 or HPV18 ctDNA detection as previously published with droplet digital PCR. Results: 36 stage II-IV ASCC patients were included. HPV-ctDNA detection had a sensitivity of 89% (n = 32/36). All 4 patients with no ctDNA detected had a stage I ASCC (detection rate 33% versus 100% for higher stage, p = 0.001). In patients with detectable ctDNA before CRT, median ctDNA levels were significantly associated with lymph node(s) status: the median ctDNA level was 102 copies/ml (range 8.7-933) in N+ ASCC vs 32 copies/ml (range 3-1350) in N- ASCC (p = 0.026). Among 18 patients with available paired samples (before and after CRT), only 3 (17%) displayed residual detectable HPV-ctDNA at the end of CRT.  

**Conclusions:** This is to our knowledge the first proof of concept study assessing the prognostic value of ctDNA after CRT in locally advanced ASCC. In most patients, HPV-ctDNA can be detected before CRT but drops below detection limits during CRT. We show here that residual ctDNA levels at the end of CRT are associated with a very poor outcome, suggesting the use of HPV-ctDNA as tool to select high-risk patients that may be eligible for further systemic treatments.
Phase II study of panitumumab, 5-fluorouracil, mitomycin-c and radiotherapy treatment in patients with non-metastatic squamous cell carcinoma of the anal canal.

Jaime Feliu, Hospital Universitario La Paz, Madrid, Spain

Background: More than 80% of squamous cell carcinoma of the anal canal (SCC) express epidermal growth factor receptor (EGFR). VITAL was a phase II, multicentre, single arm study, which aimed to evaluate efficacy and safety of the addition of panitumumab (Pmb) to fluorouracil (5-FU), mitomycin C (M) and radiotherapy (RT) standard treatment in patients (PTS) with non-metastatic squamous cell carcinoma of the anal canal (AC) and is associated with significant toxicity. We determined a modified schedule, FOLFCIS, and performed an integrated clinical and genomic analysis of advanced AC.

Methods: We reviewed all patients with metastatic or recurrent locally advanced AC treated with first line FOLFCIS chemotherapy at Memorial Sloan Kettering Cancer Center (MSK) between January 2007 and July 2017. FOLFCIS, which is essentially FOLFOX with cisplatin substituted for oxaliplatin, consisted of cisplatin 40 mg/m² day 1, leucovorin 400 mg/m² day 1, 5-FU 400 mg/m² day 1, 5-FU 1000 mg/m²/ d days 1 and 2 in a 14-day cycle. Forty-one advanced AC patients underwent targeted next generation tumor sequencing of >300 genes (MSK-IMPACT), including 23 of the patients treated with FOLFCIS. Results: Fifty-three AC patients (48 metastatic; 5 unresectable, locally advanced) received first line FOLFCIS during this period; all were platinum naive. Median age was 59 years, and 32% had metastatic disease at diagnosis. Thirteen patients (25%) received multimodal treatment for metastatic disease. Administered dose intensity of both cisplatin and 5-FU was > 70%. Response rate was 48% (95% CI, 32.6 - 63). With a median follow up of 41.6 months, progression free survival (PFS) and overall survival (OS) were 7.1 months (95% CI, 4.4 - 8.6) and 22.1 months (95% CI, 16.9 - 28.1), respectively. Among all advanced AC, most frequent genomic alterations consisted of chromosome amplifications (17p, 8q), EGFR mutations (19p, 20p, 21p), TP53 mutation, YAP1 amplification, and TERT promoter mutations appeared enriched in HPV-negative AC. No genomic alteration correlated with response or resistance. Conclusion: FOLFCIS treatment was effective and safe as first line chemotherapy in advanced AC patients and represents an alternative treatment option for patients with AC.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: CALGB 80405 is a phase III clinical trial of FOLFOX/FOLFIRI with randomly assigned cetuximab/bevacizumab. Novel causal machine learning approaches to the study dataset may lead to valuable insights into CRC prognosis and management of CRC progression. Methods: Using a Bayesian causal machine learning and simulation platform, we built an ensemble of network models for overall survival (OS). We used 78 baseline clinical and demographic variables for 947 patients with wild-type KRAS tumors. Causal modeling identifies the set of conditional dependencies between variables leading to outcomes. Building an ensemble of causal models estimates model uncertainty and identifies key drivers by model consensus as measured by ensemble frequency (f). Counterfactual simulations were performed on this ensemble to identify causal drivers of disease. Results: Key causal variables of OS (f > 50%) include primary tumor side (f = 85%), aspartate aminotransferase (AST) and hemoglobin (HGB) concentrations (f = 100%, 91%), and tumor sites: local primary and intra-abdominal metastases (f = 85%, 89%). Counterfactual simulations, controlling for confounders, suggested a significant causal effect of the following variables on driving OS: AST (median hazard ratio (HR) = 1.3, 75th vs. 25th percentile value; 10th -90 th percentile interval: 1.2-1.4), HGB (0.8, 0.7-0.9), primary side (1.5, 1.0-1.7; right vs. left), and tumor sites (present vs. absent): local primary (1.3, 1.0-1.5), intra-abdominal (1.4, 1.1-1.6) and liver (1.1, 1.0-1.4) metastases. AST was a stronger biomarker of OS in patients with liver metastases (1.6, n = 705) than without (1.2, n = 242). Conclusions: Primary side, AST, HGB, and tumor sites (local primary, intra-abdominal, and liver) play a central role as independent drivers/biomarkers of OS. Availability of these measures at baseline will allow better risk stratification at initiation of treatment. Clinical trial information: U10CA180821, U10CA180882.

3570 Poster Session (Board #63), Sun, 8:00 AM-11:30 AM
Causal modeling of CALGB 80405 (Alliance) to identify network drivers of metastatic colorectal cancer (CRC). First Author: Rahul K Das, GNS Healthcare, Cambridge, MA

3571 Poster Session (Board #64), Sun, 8:00 AM-11:30 AM
Night shift work duration and risk of colorectal cancer according to IRS1 and IRS2 expression. First Author: Yan Shi, Chinese PLA General Hospital, Beijing, China

Background: Although accumulating evidence supports an association between night shift work and an increased risk of colorectal cancer (CRC), the mechanism remains elusive. Notably, metabolic disorders, including insulin resistance, play an important role in both CRC development and other chronic diseases caused by circadian disruption. IRS1 (insulin receptor substrate 1) and IRS2 are the primary mediators of insulin-dependent mitogenesis and could respond to the metabolic microenvironment. We therefore hypothesized that the risk of CRC in night shift workers might be different according to IRSs expression level. Methods: Among 77,470 eligible women with available night work data in the Nurses’ Health Study, we documented a total of 1,397 physician-confirmed CRCs during 24 years of follow-up, of which 304 and 308 had available data on IRS1 and IRS2, respectively. We used duplication method Cox proportional hazards regression analysis for competing risks data to calculate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for each CRC subtype. We measured tumor IRS1 or IRS2 protein expression by immunohistochemistry. Results: Compared with women who never worked night shifts, those working a rotating night shift for 15 years or more had a trend of increased overall risk of CRC (P trend= 0.06, multivariable HR = 1.20, 95%CI, 0.99 to 1.45). For the same comparison, longer of night shift duration was associated with a higher risk of IRS1-positive tumors (multivariable HR = 1.81, 95%CI 1.32 to 2.48) and IRS2-positive tumors (multivariable HR = 1.42, 95%CI 1.06 to 1.92). IRS1-negative tumors (multivariable HR = 1.13, 95%CI 0.71 to 1.80, P trend= 0.56, P heterogeneity for IRS1 subtypes = 0.02). The corresponding multivariable HRs were 2.69 for IRS2-positive tumors (95%CI 1.48 to 4.89, P trend= 0.001) and 0.90 for IRS2-negative tumors (95%CI 0.54 to 1.51, P trend= 0.72, P heterogeneity for IRS2 subtypes = 0.038). Conclusions: Working 15 years or more of rotating night shift was associated with higher risk of CRC with IRS1-positive or IRS2-positive, but not negative tumors. This molecular pathological epidemiology data suggest a potential role of insulin receptor substrate in mediating carcinogenesis induced by night shifts.

3572 Poster Session (Board #65), Sun, 8:00 AM-11:30 AM
Impact of MLH1, PMS2, MSH2, and MSH6 alterations on tumor mutation burden (TMB) and PD-L1 expression in 1,057 microsatellite instability-high (MSI-H) tumors. First Author: Mohamed E. Salem, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC

Background: MSI-H tumors are associated with higher TMB. We examined the yet uncharacterized relationship between TMB and individual MMR gene alterations in MSI-H tumors. Methods: MSI-H was determined by examining altered microsatellite loci (MSI) using NextGen sequencing (cut-off : > 46) on a 502-gene panel. TMB was calculated by enumerating somatic missense mutations. MMR protein expression was evaluated by IHC. ANOVA and chi-square tests were used for comparisons. Results: A total of 1057 MSI-H tumors (283 colorectal cancer (CRC); 449 endometrial cancer (EC); and 325 others from 29 cancer types) were examined. High TMB (> 17 mutations/megabase (mt/MB)) was seen in 74% of tumors. MSI-H CRC had the highest TMB compared to MSI-H EC and “all others” (mean TMB: 39 vs. 23 vs. 31 mt/MB, respectively; P < 0.0001). There was no difference in TMB between BrafV600E mutant and wild type MSI-H CRC (38.7 vs. 39 mt/MB). In general the most frequently altered (IHC loss or mutation) MMR genes were MLH1 and PMS2 (72% and 83%; CRC, 90% and 95%; EC). MSH2 and MSH6 were more frequently altered in CRC than EC (21% vs. 5% and 49% vs. 28%, respectively; P < 0.0001). In CRC, MSH2 and MSH6 were more frequently altered in left than right sided MSI-H tumors (45% vs. 12% and 67% vs. 40%; P = 0.01). Overall MSH2 or MSH6 alterations were associated with a higher TMB (48.5 and 40 mt/MB, respectively) than MLH1 or PMS2 (27 mt/MB for both; P < 0.0001). Tumors with MSH2/6 alterations (4%) had a higher TMB compared to those with MLH1/PMS2 (39%) (co-)alteration (50 vs. 24 mt/MB; P < 0.0001). PD-L1 overexpression was seen at a higher frequency in tumors with MSH2 (23%) than MLH1 (16%), MLH1 (16%), or PMS2 (14%); P = 0.01. MSH2/6 alterations in EC were associated with higher MS alterations (MSH2, 88; MSH6, 73; MLH1, 68; PMS2, 68; P < 0.0001), while all genes were equal in CRC. MSH2 alterations were associated with higher frameshift mutation rates in 36 genes in EC, and in different 10 genes in CRC. Conclusions: TMB varies significantly across MSI-H tumors, MSH2/6 alterations were associated with a significantly higher TMB than MLH1/PMS2 across several cancer types. No MSI alterations associated with MSH2/6 were tumor-type specific.

3573 Poster Session (Board #66), Sun, 8:00 AM-11:30 AM
Association between density of tumor infiltrating lymphocytes and disease-free survival (DFS) in patients with resected stage I-III colorectal cancer in the FACS randomized trial. First Author: Sian Alexandra Pugh, University of Southampton, Southampton, United Kingdom

Background: Accumulating evidence demonstrates an association between density of tumor infiltrating lymphocytes and outcome in colorectal cancer (CRC). This study sought to assess the prognostic utility using an accurately staged cohort of patients followed up in a clinical trial. Methods: Observational analysis of data from the FACS (follow-up after CRC surgery) trial after 5 years of follow-up. All patients had undergone treatment with curative intent for stage I-III primary CRC, with microscopically clear margins, no evidence of metastases on axial imaging and CEA < 10μg/l following completion of treatment. Immune cell densities were quantified in the centre (CT) and in logistic (LM) of all tumors for CD3 and CD45RO. For each tumor region high (Hi) and low (Lo) CD3 and CD45RO densities were determined according to the median of the cohort to investigate association with disease free survival (DFS). Results: Tumor samples have been analyzed from 297 patients per decade to which the combined 5 year DFS is 83% (left sided CRC 81%, right sided CRC 85%). High densities of CD3 and CD45RO positive cells in both tumor regions were associated with a superior outcome: CD3+HI+C45RO+Hi 94% 5yr DFS vs CD3+LO+C45RO+Lo 81%, HR 0.36 95% CI 0.15-0.89 p = 0.04. This difference was most notable in left CRC: CD3+HI+C45RO+Hi 96% 5yr DFS vs CD3+LO+C45RO+Lo 78%, HR 0.13 95%CI 0.04-0.41 p = 0.02. In right sided CRC the difference was not significant: CD3+HI+C45RO+Hi 91% 5yr DFS vs CD3+LO+C45RO+Lo 83%, HR 0.70 95%CI 0.17-2.89 p = 0.62. Conclusions: In a well characterized and followed up cohort of CRC patients within a clinical trial we have demonstrated that CD3+HI+C45RO+Hi left sided tumors have a significantly better outcome. The potential for these data to impact on the need for clinical follow-up in patients with left sided CRC should be examined in a prospective study. Clinical trial information: NCT019147.
3576 Poster Session (Board #69), Sun, 8:00 AM-11:30 AM
Polyorphism in the circadian clock pathway to predict outcome in patients with metastatic colorectal cancer (mCRC): Data from TRIBE and FIRE-3 phase III trials. First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA
Background: The clock machinery comprises a complex network of transcription-translation feedback loops which regulates the circadian expression of target genes involved in key cellular functions. The disruption of circadian clock is associated with cancer risk and progression, and recent studies have suggested a possible role of core clock genes in colorectal cancer (CRC) development. However, the role of genetic variants in the circadian clock on CRC risk is still unclear.

Methods: Genomic DNA from blood samples of 215 participants (median age: 62 years; n = 220) with metastatic colorectal cancer (mCRC) from three trials (FIRE-3 n = 235, TRIBE n = 320, MAVERICC n = 235). Cox proportional hazards regression was performed to assess the association between polymorphisms in 11 clock pathway genes (CRY1-2, RORa), and population stratification was assessed using the GenABEL package in R. The exploratory analysis was performed with a Bonferroni correction threshold for genome-wide significance ($\alpha = 0.05/11 = 0.0045$).

Results: In total, 1,064 primary CRCs were examined. In the discovery cohort (n = 220), the overall population carrying the 3 genetic variants had a higher risk of overall survival (OS) and progression-free survival (PFS) compared to LT (32% vs. 6.9%, P = 0.003), and KMT2D (4.5% vs. 0%, P = 0.003), and KMT2D (4.5% vs. 0%, P = 0.003). In the discovery cohort, the overall population carrying the 3 genetic variants had a higher risk of OS and PFS compared to LT (32% vs. 6.9%, P = 0.003), and KMT2D (4.5% vs. 0%, P = 0.003), and KMT2D (4.5% vs. 0%, P = 0.003).

Conclusions: Our data identify a new promising prognostic biomarker for OS and PFS among patients with mCRC, and population genetic differences may contribute to disparities in survival by ancestry.

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3578  Poster Session (Board #71), Sun, 8:00 AM-11:30 AM

Results from a phase I study of andecaliximab in combination with FOLFIRI and bevacizumab in patients with second line metastatic colorectal cancer. First Author: Zev A. Wainberg, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Matrix metalloproteinase 9 is highly expressed in several malignancies, including metastatic colorectal cancer (mCRC) and is an adverse prognostic feature. In preclinical colorectal cancer models, inhibition of MMP-9 was associated with tumor growth inhibition. Andecaliximab (ADX) is a chimeric antibody directed against MMP-9 engineered to inhibit the enzyme. Our goal was to determine the safety and tolerability of combination therapy with FOLFIRI and bevacizumab with ADX, and to assess preliminary antitumor activity.

Methods: This was a phase I, open-label, dose escalation study to determine the MTD and pharmacokinetics of ADX in combination with 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) and bevacizumab (AV). Patients with mCRC who progressed on first-line therapy were eligible to receive ADX plus FOLFIRI and bevacizumab. Participants were randomized in a 1:1 ratio to receive ADX 10mg/kg body weight or 20mg/kg body weight on days 1, 8, 15, 22, and 29, FOLFIRI, and bevacizumab. Treatment cycles were repeated every 28 days.Safety, tolerability, and antitumor activity were assessed.

Results: 44 patients were enrolled (25 in the 10mg/kg arm and 19 in the 20mg/kg arm). Of these, 25 patients were evaluable for response. The most common adverse events were fatigue (39%), nausea (31%), diarrhea (27%) and vomiting (22%). Three treatment-related grade 3-4 adverse events were reported: acute pancreatitis, abdominal pain, and severe anemia. No patients required dose reduction. Partial responses were observed in 2 patients and stable disease was observed in 16 patients. The median number of cycles administered was 6.

Conclusions: The combination of ADX with FOLFIRI and bevacizumab was safe and effective. The activity of the combination appears encouraging in 2nd line treatment of metastatic colorectal cancer. Updated data will be presented at the time of the presentation. Clinical trial information: NCT01803282.

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3579  Poster Session (Board #72), Sun, 8:00 AM-11:30 AM

Comparison of chemotherapy use, cost, and survival in patients with metastatic colorectal cancer in Western Washington and British Columbia. First Author: Todd Yezefski, University of Washington School of Medicine, Seattle, WA

Background: The high frequency of negative phase III oncology trials following positive phase II results indicates a need for improved metrics which assess treatment effect. Vol-PACT is an ongoing private-public partnership launched to collect source imaging data from phase III trials with a goal of developing improved methods of assessing therapies in randomized clinical trials. With phase III industry sponsored datasets received and more expected, Vol-PACT is among the largest collective cancer imaging databases with fully annotated measurements of target, non-target, and new lesions.

Methods: Images from 4 phase III trials in metastatic colorectal cancer (mCRC) were evaluated and benchmarked against 4 phase III trials in other solid tumors. Lesions were measured directly on CT images using semi-automated algorithms. Four metrics quantifying change from baseline through 2 cycles (week 8-16) were evaluated: RECIST response rate, percent change over time, absolute change over time, and log change over time. For other trials they were 0.80, 0.94, 0.95, respectively. Across the full set of 8 trials, observed correlations were 0.64, 0.93, and 0.90.

Conclusions: Continuous response metrics derived from original CT images correlated strongly with PFS HR across mCRC and other solid tumors. Lesions were measured directly on CT images using semi-automated algorithms. Four metrics quantifying change from baseline through 2 cycles (week 8-16) were evaluated: RECIST response rate, percent change over time, absolute change over time, and log change over time. For other trials they were 0.80, 0.94, 0.95, respectively. Across the full set of 8 trials, observed correlations were 0.64, 0.93, and 0.87. The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

3580  Poster Session (Board #73), Sun, 8:00 AM-11:30 AM

Prognostic value of tumour infiltrating lymphocytes in stage II colon cancer. A national population-based study. First Author: Ann Christina Eriksson, Danish Colorectal Cancer Center South, Vejle Hospital, Vejle, Denmark

Background: Patients with high-risk stage II colon cancer (CC) may benefit from adjuvant chemotherapy, but additional prognostic markers are needed for better treatment stratification. We investigated the prognostic value of tumour infiltrating lymphocytes (TILs) in a true population-based cohort of patients with stage II CC.

Methods: A total of 573 patients were included, representing all patients operated for stage II colon cancer in Denmark in 2002. Tumour blocks representing the deepest invasive part of the primary tumour were used for analysis. CD3+ and CD8+ TILs at the invasive front were evaluated by immunohistochemistry on whole tumour sections. The invasive area was manually outlined, and Visiopharm Integrator System software was used for quantification. Data were dichotomized for comparison with clinical data. The prognostic value was investigated in Cox proportional hazard models for recurrence-free survival (RFS) and overall survival (OS).

Results: Low CD3+ or CD8+ TILs were significantly associated with poor RFS and OS, (p = 0.0021 and p = 0.0009, respectively, log-rank test). In multiple Cox regression analysis low CD3+ and CD8+ TILs were associated with reduced RFS with hazard ratio (HR) 1.386 (95% CI 1.039-1.850), p = 0.026, and HR 1.394 (95% CI 1.029-1.890), p = 0.032, respectively. Across the full set of 8 trials, observed correlations were 0.64, 0.90, 0.93, and 0.87. The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

3581  Poster Session (Board #74), Sun, 8:00 AM-11:30 AM

Early response metrics for predicting trial outcomes: A report from volumetric CT for precision analysis of clinical trials (Vol-PACT). First Author: Patrick Hilden, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Imaging is the analysis of data from emerging immunotherapy trials. Other trials, and may be more informative than RECIST response categories. From original CT images correlated strongly with PFS HR across mCRC and other trials, and may be more informative than RECIST response categories. Development of metrics based on volumetric measurements are ongoing, as is the analysis of data from emerging immunotherapy trials.
Genome-wide association with survival in stage II-III colon cancer clinical trials (NCCTG N0147, Alliance for Clinical Trials in Oncology, NSABP C-08, NRG Oncology). First Author: Kathryn Pinney, Harvard T.H. Chan School of Public Health, Boston, MA

Background: Many genetic variants have been identified as associated with colorectal cancer (CRC) risk; few have been associated with CRC survival. Identification of variants associated with survival may further explain the biology of disease progression and aid in outcome prediction. We performed a genome-wide association study (GWAS) in 2 CC clinical trials to identify genetic variants associated with overall survival (OS). Methods: We included patients from N0147, a phase III adjuvant trial in stage III CC patients, and C-08, a phase III trial comparing adjuvant therapy regimens for patients with stage III CC. 4974 samples were genotyped with the Illumina HumanOmniExpress + Exome array, consisting of 964,193 SNPs. Genotypes were imputed using 1,000 Genomes Project data. We calculated OS as time from randomization to death from any cause and used Cox proportional hazards regression to evaluate association of each SNP with OS, adjusting for age, sex, treatment arm and principal components. Analysis was performed in N0147 and C-08 separately; results were combined in a fixed-effects meta-analysis. Results: Follow-up after diagnosis was similar in both trials: median OS for N0147 and C-08 was 1678 days (IQR = 1238-2071) and 2224 days (IQR = 1901-2494), respectively. A locus on chromosome 7p15.2 was significantly associated with improved OS. The most significant variant at this locus, rs76766811 (p = 1.59e-8), is exceedingly rare in this primarily European American population but much more common in African Americans (AAs) (~19%). When the analysis is stratified by self-reported ancestry, the signal is only present in AAs (n = 359) (HR = 0.30, 95% CI: 0.21-0.43, p = 1.81e-10). Conclusions: This GWAS nested within 2 CC trials identified rs76766811 on 7p15.2 as significantly associated with OS among AAs. This finding should be confirmed in additional study populations, particularly focusing on identifying variants associated with survival in AAs. Support: NIH R01 CA176722, U10CA-180868, -180821, -180822, U10CA-189667, U24CA-196067, PA DoH (which disclaims certain responsibilities), Genentech, Inc., Sanofi-Synthelabo Inc.

Prognostic value of CD73 expression in resected colorectal cancer liver metastasis. First Author: Nouredin Messaoudi, Research Centre of the Centre hospitalier de l’Université de Montréal (CRCHUM), Montreal, QC, Canada

Background: As approximately 80% of patients recur and die of their cancer after undergoing curative-intent resection of colorectal cancer liver metastasis (CRLM) combined with systemic chemotherapy, novel prognostic biomarkers and therapeutic targets are needed to improve outcomes. We investigated in CRLMs whether the expression of the cell-surface enzyme CD73, rate limiting for the degradation of extracellular AMP into immune-suppressive adenosine, could define a subset of patients with distinct prognosis. Methods: A tissue microarray-based analysis of 391 CRLMs resected in 214 patients (2011-2014) and followed prospectively until 10/2017. Each CRLM was arrayed with 1,532 CC. Tumor budding at invasive margin was defined as single or cluster of ≤4 tumor cells. We divided the cohort into training and validation sets. Optimal cutpoints were identified; associations with 3-year disease-free survival (DFS) were evaluated by multivariable Cox regression. Results: TIL and tumor budding cutpoints identified in training set were confirmed in validation set for prognosis. Patients whose tumors had low (≤ 3) vs high TILs were significantly more likely to have higher T, N stage, low histologic grade, left sidedness, worse performance status, non-mutated BRAF, and proficient (p) MMR. Tumors with high budding (> 3) had higher T, N stage; most had pMMR. Overall, significantly shorter DFS was found for tumors with low TILs [HR = 1.74 (95% CI 1.35, 2.24), p < .0001] or with high budding [HR = 1.37 (1.13, 1.67), p = .0011]. When combined, low TILs plus high budding showed poorer DFS (HR = 2.07 (1.50, 2.88), p < .0001). Similar results were found for pMMR tumors (Table). Within dMMR, patients whose tumors had low (≤ 3) vs high TILs had significantly shorter DFS (HR = 2.14; p = 0.0173); budding was not prognostic. Table: Conclusions: Low TILs and budding were each validated as markers of poor prognosis in FOLFOX-treated stage III CC, indicating that reduced anti-tumor immunity and an EMT phenotype increase tumor aggressiveness. Whereas TILs and budding each stratified pMMR tumors by DFS, only TILs were prognostic in dMMR tumors and identified the subset with poorest survival.

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The impact of skeletal muscle and adipose tissue on long-term survival in patients with each resectable colorectal cancer. First Author: Michael B. Sawyer, Cross Cancer Institute, Edmonton, AB, Canada

Background: Computed tomography-derived body composition parameters are emerging prognostic factors in colorectal cancer. This study aimed to determine the roles of sarcopenia, myosteatosis and adiposity as independent and overlapping parameters in resectable colorectal cancer patients. Methods: This was a retrospective cohort study from a prospectively collected database. It included all adult patients with early-stage colorectal cancer, who underwent curative resection from 2007-09. All patients were seen in a tertiary care cancer center in Northern Alberta. Computed tomography-derived quantification of skeletal muscle and adipose tissues were used to determine cohort-specific cut-offs for sarcopenia, myosteatosis and total adiposity using an optimal stratification analysis. Multivariable Cox proportional hazards models were performed to assess for associations between body composition parameters and overall, disease-free and cancer-specific survival. Results: In the 968 patients included, there were a total of 254 disease recurrences and 350 deaths. Body mass index and computed tomography-derived measures of adiposity did not result in worse survival outcomes. Sarcopenia was independently predictive of worse overall (HR = 1.45; 95% CI 1.16, 1.84), recurrence-free (HR = 1.32, 95% CI 1.00, 1.75) and cancer-specific survival (HR = 1.46, 95% CI 1.09, 1.94) in a multivariate model. Myosteatosis was also independently predictive of overall survival (HR = 1.53, 95% CI 1.19, 1.97). In a multivariate model considering joint effects of sarcopenia and myosteatosis, the presence of both parameters predicted the worst overall (HR = 2.23, 95% CI 1.62, 3.06), recurrence-free (HR = 1.53, 95% CI 1.06, 2.21) and cancer-specific survival (HR = 2.40, 95% CI 1.69, 3.42). Conclusions: Sarcopenia and myosteatosis are independent predictors of worse survival in early-stage colorectal cancer. Their joint effect is highly predictive of reduced overall, recurrence-free and cancer specific survival. Sarcopenia and myosteatosis represent prognostic factors that may be easily integrated into clinical practice.
Prognostic immune scoring of colorectal cancer liver metastasis with MHC class-I expression combined to T cell quantification. First Author: David Henault, Research Centre of the Centre hospitalier de l’Université de Montréal (CRUCHM), Montreal, QC, Canada

Background: Approximately 80% of patients recur after curative-intent resection of colorectal cancer liver metastasis (CRLM) and systemic chemotherapy. Immune profiling may help prognostication to individualize follow-up and lead to novel therapeutic strategies. We tested whether adding major histocompatibility class I (MHC-I) expression to T cell immune scoring in CRC could group patients with distinct prognosis. Materials and Methods: Biopsy microarray analysis of 391 CRLMs resected in 214 patients (2011-2014) followed prospectively until 10/2017. Each CRLM arrayed with twelve 0.6 mm punch biopsies, 6 at the interface (IF) with normal liver and 6 intratumoral (IT). Automated quantification of CD3+ cells and MHC-I surface area stained by immunohistochemistry. We tested associations between immune, clinicopathological, and time to recurrence (TTR) and disease specific survival (DSS) outcome variables. Results: The mean patient age was 62.7 years, 78.5% received pre-operative chemotherapy (mean of 6 cycles), and a median of 2 CRLMs/patient were resected. The median TTR and DSS were 15.4 and 56.7 months respectively. Pre-operative chemotherapy was associated with higher CD3 infiltration and lower MHC-I expression at IF and IT. Good pathological response to chemotherapy (Rubbia-Brandt TRG score 1-2-3) compared to lack of response (TRG 4-5) was associated with higher CD3 infiltration but no significant histopathological difference in MHC-I expression. CD3 immune scoring integrating the IF and IT areas had no prognostic value. MHC-I expression prognostically stratified patients with CD3hi but not CD3low CRLMs. Compared to the rest of the cohort, patients with at least one CD3hiMHC-Ihi CRLM (n = 35, 16.4 %) had significantly shorter median TTR (8.3 vs. 17.1 months, p < 0.001) and DSS (Actuarial 61.5 months vs. 96.9 months, p < 0.001). CD3hiMHC-Ihi CRLMs were found in 41.2% of recurrent CRLMs in patients without this type of metastasis at first recurrence. CD3hiMHC-Ihi CRLMs were an independent predictor of poor outcomes by multivariate analysis. Conclusions: CD3hiMHC-Ihi CRLMs may identify patients with poorly immunogenic tumors associated with worst outcome and suboptimal response to systemic chemotherapy.


Background: The local microenvironment of a tumor plays an important role in colorectal cancer (CRC) progression. A desmoplastic stroma surrounding the tumor, characterized by excessive collagen deposition, can result in reduced drug delivery into the tumor, leading to poor prognosis and lack of therapy response. Here we present a new class of liquid biopsy proteins, reflecting collagen formation (desmoplasia) and evaluate their prognostic use in CRC. Methods: Pro-peptides from collagen type III (PRO-C3) and collagen type VI (PRO-C6) were measured with ELISAs in patient sera of patients with metastatic CRC (mCRC) and 40 healthy donors. Biomarker levels in patients and healthy donors were compared using unpaired, two-tailed Mann-Whitney test. The biomarkers were further evaluated by univariate Cox-regression analysis for their association with overall survival (OS) and progression-free survival (PFS). Results: Serum levels of PRO-C3 and PRO-C6 were significantly elevated in patients with mCRC compared to healthy donors (PRO-C3: 11.5 ng/mL vs. 6.8 ng/mL, p < 0.0001, PRO-C6: 8.0 ng/mL vs. 5.9 ng/mL, p < 0.0001). The median OS was 266 or 213 days in biomarker high patients (75th percentile) vs. 1330 or 979 days in biomarker low patients (25th percentile) for PRO-C3 (HR 8.7, 95%CI 2.7-28.2) and PRO-C6 (HR 6.8, 95%CI 2.3-20.3), respectively. The median PFS was 251 or 267 days in biomarker high patients (75th percentile) vs. 329 or 496 days in biomarker low patients (25th percentile) for PRO-C3 (HR 2.3, 95%CI 0.7-7.1) and PRO-C6 (HR 2.6, 95%CI 0.8-9.0), respectively. Conclusions: This study evaluated the prognostic use of a new class of liquid biopsy biomarkers, namely small peptides originating from the tumor microenvironment that are released into the circulation as a consequence of tumorigenesis. High serum levels of PRO-C3 and PRO-C6 (collagen formation) were significantly associated with poor OS and shorter PFS in patients with mCRC. This may suggests that increased collagen deposition around the tumor, limits cancer therapy delivery into the tumor, resulting in a lack of response to therapy.

Prognostic significance of number versus location of positive mesenteric lymph nodes in node positive colon cancer. First Author: Kozo Kataoka, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan

Background: Metastasis to locoregional lymph nodes (LN) is one of the most powerful predictors of recurrence free survival (RFS) in colon cancer (CC). Debate persists on the prognostic value of the location of positive LN in addition to the positive lymph node ratio (LNR) or the number of invaded LN (LN+). The recently introduced technique of complete mesocolic excision (CLEM) presupposes a prognostic role of removal of high level (apical) LN. We analyzed the prognostic significance of positive LN location in a cohort of CC patients who underwent extensive (D3) lymphadenectomy. Methods: Colon cancer patients from Kanagawa Cancer Center, Japan, who underwent extensive (D3) lymphadenectomy from 2000 to 2016 were analyzed. Lymph nodes were classified according to anatomical location as paracolic (L1), intermediate (L2), or along the main vascular trunk (L3). RFS were adjusted with their trends over the groups. Univariate and multivariate Cox proportional hazards models were used to evaluate the association of LN count and L level (L1, L2 and L3) with RFS. Results: 843 patients were included and 446 were node positive of whom only 25 (6.6%) had positive L1 vs. 95%CI 0.8-9.0), respectively. Conclusions: In this cohort of patients who underwent standard extensive (D3) lymphadenectomy for CC, apical (L3) lymph nodes are incidentally invaded and were a significantly worse RFS. The anatomical location of invaded nodes adds no prognostic information to T-stage and LNR. These findings question the value of standard extensive lymphadenectomy in CC.

Adjuvant chemotherapy and survival outcomes in diabetic patients with colon cancer: A population-based analysis. First Author: Shiru Lucy Liu, BC Cancer Agency, Vancouver, BC, Canada

Background: Diabetes can pose challenges when using adjuvant chemotherapy (AC), as specific cytotoxic drugs, including oxaliplatin, may potentiate certain diabetic complications, such as neuropathy. We performed a provincial analysis of resected colon cancer patients to evaluate the prevalence of diabetes, type of chemotherapy used, and survival outcomes. Methods: We examined 5,440 patients with resected stage 2 or 3 colon cancer who were diagnosed from 2004 to 2015 in Alberta. Baseline patient, tumor, and treatment characteristics were compared between those with and without diabetes. Survival analysis was conducted based on Kaplan-Meier methods. Results: 608 patients (11%) had uncomplicated diabetes (UDM) and 436 (8%) patients had diabetes with complications (CDM), defined as neuropathy or other micro/macrovascular end-organ damage. CDM patients were older and had worse Charlson comorbidity index (p < 0.001). While 34% of UDM patients and 35% of non-diabetic patients received AC, only 15% of CDM patients received AC (p < 0.001). Among those who received AC (N = 1574), an oxaliplatin-based regimen was given to 45% and 52% of UDM and non-diabetic patients, respectively, but only 35% of CDM patients (p = 0.001). Kaplan-Meier analysis revealed significantly worse overall survival (OS) in the CDM group when compared to the UDM or non-diabetic groups (p < 0.001). Of those treated with AC however, there were no statistical differences in OS (p = 0.188) or cancer-specific survival (CSS) (p = 0.461) across all groups regardless of diabetes or complication status (see Table). Result of oxaliplatin was associated with improved OS among patients with stage 3 disease compared to monotherapy (p = 0.006). Conclusions: Patients with CDM are less likely to receive AC; however, patients treated with oxaliplatin-AC appear to have similar survival outcomes as their UDM and non-diabetic counterparts.
Clinico-pathological and molecular characterisation of BRAF mutant metastatic colorectal cancer (mCRC): Are all mutations created equal?

**Background:** Functional studies on preclinical models (Yao, Nature 2017) identified 3 classes of BRAF mutations: activating-RAS-independent BRAF mutations signaling as monomers (class 1-BRAFV600E) or as dimers (class 2-codons 601/597) and RAS-dependent BRAF mutants with impaired kinase activity (class 3-codons 594/596). While clinico-pathological and molecular features of class 1 mutation are well known, limited data are available with regard to class 2 and 3 mutations, due to their rarity in CRC. **Methods:** Clinico-pathological, molecular and outcome data from BRAF mutated mCRC patients were collected. A group of BRAF wild-type (wt) patients was included as control. IHC analyses were performed to determine the consensus molecular subtypes (CMS). Clinical features were compared by chi-square or fisher’s exact test. PFS and OS were evaluated by Kaplan-Meier and log-rank test. **Results:** Class 1, 2 and 3 included 92, 12 and 13 patients respectively. BRAF wt patients were 540. No clinico-pathological differences were observed comparing class 1 to class 2 BRAF mutated. Conversely, BRAF class 3 mutated were more frequently left sided (p = 0.0028), well differentiated (p = 0.0120), pN0 (p = 0.0359), and with no peritoneal metastases (p = 0.0176) compared to class 1. With regard to CMS, class 2 and 3 tumors were all assigned to CMS2-3. Class 1 tumors were assigned to CMS1, 2 or 3 in 39%, 44% and 17% of cases. **Conclusion:** Mutations signaling as monomers (class 1-BRAF mutant) are associated with worse outcome compared to BRAF wild type (N = 540) and class 2 and 3 mutations, due to their rarity in CRC.
Background: HER2 amplification (HER2*) in metastatic colorectal cancer (mCRC) is associated with resistance to anti-EGFR antibodies and response to HER2 targeted therapies. This study assessed the diagnostic criteria on HER2* mCRC among four groups (GI-SCREEN-Japan, SWOG-Japan, HERACLES-Italy, and Korea) and harmonized the criteria for patient enrollment in clinical trials that target these patients (pts). Methods: Samples from 475 and 16 pts with mCRC were used in exploratory and validation cohorts, respectively. We assessed HER2 status by immunohistochemistry (IHC) and HER2/CEP17 ratio and gene copy number (GCN) by fluorescence in situ hybridization (FISH) and copy number variations (CNV) by targeted next-generation sequencing (NGS) panel. OCA by ThermoFisher and AMC v3 by illumina were used in exploratory and validation cohorts, respectively for the cross-validation of NGS panels. Results: The consensus diagnostic criteria for HER2* mCRC was reached; IHC 3+ or IHC 2+ and HER2/CEP17 ratio by FISH ≥ 2.0, and tumor content > 10% for surgically resected specimens (separate quantity criteria were established in each group). The median GCN and CNV for pts who met consensus criteria for HER2* was 10.9 and 27.7 compared to 2.5 (P < 0.0001) and 3.5 (P < 0.0001), respectively in pts who were HER2+. These findings were validated in validation cohort (GCN: 16.2 ± 2.4, P = 0.0002; CNV: 42.9 ± 2.0, P = 0.0003). GCN also showed strong correlation in CNV both cohorts (exploratory: 0.90, validation: 0.97; P < 0.0001). CNV in cross validation of OCA and AMC v3 also showed strong correlation (r: 0.97, P < 0.0001). The CNV for pts verifying the consensus criteria was more than 4.0 in the two cohorts. The accuracy of the IHC/FISH criteria was validated for mCRC pts, providing cross-validation of NGS panel. Conclusions: Results verify the HER2 classification consistency between CNV by NGS and IHC/ FISH by harmonizing diagnostic criteria for HER2*. This strategy can help establish diagnostic criteria for HER2* cancer by allowing for different methodologies to be used for pts screening for trial eligibility.

3596 Poster Session (Board #89), Sun, 8:00 AM-11:30 AM
A prospective cohort study in colorectal cancer assessing the relationship between post-surgery detection of methylated BCAT1 or IKZF1 and a risk for residual disease and survival. First Author: David Murray, Clinical Genomics Technologies Pty Ltd., North Ryde, Australia

Background: The methylated ctDNA biomarkers BCAT1 and IKZF1 are common events in colorectal cancer (CRC), play a role in its development and drugs targeting BCAT1 are available. As these biomarkers disappear from blood after surgery in most patients, a prospective study was conducted to assess the relationship between their persistence post-surgery and presence of and risk for residual disease as well as survival. Methods: ctDNA status using these biomarkers was determined within 12 mo of initial surgical resection. Detection of either marker was related by logistic regression and survival analysis (Cox proportional hazards) to pathologically-determined presence or risk of residual disease (“RD”, margins involved, metastases present or nature of node involvement) and to recurrence-free survival. Results: 172 CRC patients were tested for the biomarkers and then followed for a median 37.1mo (IQR 22.6-49.8) during which 23 experienced recurrence and 10 died from CRC. 28 (16%) were ctDNA positive post-surgery. Univariate analysis showed that a positive result was more likely if any of three markers of RD was present (OR 7.7, 95% CI: 2.3-25.0; p = 0.001), while increasing number of lymph nodes (OR 8.3, 95% CI: 1.8-37.7 p = 0.004) and involved peritoneum (OR 3.8, 95% CI: 1.6-9.2 p = 0.003) where also associated with a positive result. Multivariate modeling with adjustment for treatment status at time of venesection indicated that features of RD was an independent predictor of post-surgery ctDNA status; cases with 3 features (margins or apical node involved, distant metastases) were 5.3 times (95% CI: 1.5-18.4, p-value = 0.008) more likely to be positive. Modelling recurrence-free survival showed that post-surgery ctDNA positivity was associated with an increased risk of recurrence (HR 3.8, 1.5-9.5, p = 0.004). Conclusions: CRC cases positive for these ctDNA biomarkers within 12 months of surgery are at increased risk of residual disease and subsequently for recurrence. This has implications for adjuvant therapy and monitoring of cases; randomised studies are now indicated to determine if such can provide survival benefit. Clinical trial information: 1261100318987.

3597 Poster Session (Board #90), Sun, 8:00 AM-11:30 AM
Prognostic impact of BRAF V600E mutation in patients with non-metastatic colorectal cancer with microsatellite instability – a systematic review and meta-analysis. First Author: Sashidhar Manthravadi, University of Kansas Medical Center, Kansas City, KS

Background: Colorectal cancer (CRC) displaying high levels of microsatellite instability (MSI-H) has been associated with improved survival in colorectal cancer. MSI-H CRC is also known to be enriched in V600E mutations in the BRAF gene (BRAF-Mut). BRAF-Mut is a known adverse prognostic factor in patients with non-metastatic MSI-low CRC. However, the prognostic role of BRAF V600E mutations in non-metastatic MSI-H CRC remains unclear. Methods: Following PRISMA guidelines, a systematic review of PubMed and Embase was performed from inception through January 2018 to identify studies which described the impact of BRAF-Mut on outcomes in patients with non-metastic MSI-H CRC. Summary hazard ratios (HR) with 95% confidence intervals (CI) for overall survival (OS) recurrence-free survival (DFS) were estimated using a random effects model and heterogeneity was estimated using the inconsistency index (I²). Results: After reviewing 988 reports, 8 studies which described the association between BRAF status and outcomes in non-metastatic MSI-H CRC were selected for inclusion. These were reported from Europe, North America and Asia. A total of 1164 patients with MSI-H CRC were included of whom 553 were found to carry BRAF V600E mutation. Data regarding RFS and OS for BRAF-Mut vs BRAF-Wild type was provided in 5 and 8 studies respectively. No association was found between BRAF-Mut and DFS in patients with non-metastatic MSI-low CRC. However, the prognostic role of BRAF V600E mutations in non-metastatic MSI-H CRC remains unclear. Conclusion: Following PRISMA guidelines, a systematic review of PubMed and Embase was performed from inception through January 2018 to identify studies which described the impact of BRAF-Mut on outcomes in patients with non-metastatic MSI-H CRC. Summary hazard ratios (HR) with 95% confidence intervals (CI) for overall survival (OS) recurrence-free survival (DFS) were estimated using a random effects model and heterogeneity was estimated using the inconsistency index (I²). However, our results suggest that BRAF-Mut and the majority were considered clonal by allele frequency (defined as > 25%). The mutation locations were broadly distributed, although 10 recurrent (hot-spot) regions were identified. ARID1A mutations were associated with MSI-H status (OR = 8.1, 95% CI 4.9-14.8; p < .001), with PIK3CA mutations (OR = 2.8, 95% CI 2.1-3.9; p < .001), and BRAF mutations (OR = 3.1, 95% CI 2.2-4.4; p < .001) but had inverse correlation with TP53 mutations (OR = 0.5, 95% CI 0.4-0.7; p < .001). Of note, 18/23 (74%) of tumors with ARID1A mutations were classified as consensus molecular subtype-1 (CMS-1) with OR of 17 (95% CI 4.8-63.7; p < .001). The mutations were associated with a DNA damage response (DDR) transcription factor activity. ARID1A mutations were more common in early stages (OR = 1.83, 95% CI 1.09-3.07; p = 0.019) and right-sided tumors (OR = 1.66, 95% CI 1.01-2.71; p = 0.034). There was no association between ARID1A mutation and race, gender, age at the time of diagnosis, grade, or presence of distant metastases. Conclusions: This is the largest study evaluating ARID1A mutations in CRC. The majority of mutations appear to be truncating and clonal, suggesting that they have functional significance. ARID1A-mutated tumors demonstrate enrichment of wild-type TP53 but they are more likely to have MSI-H, PIK3CA and BRAF mutations. The transcriptional signature may indicate future therapeutic strategies for this subgroup.
Background: Colorectal cancers (CRC) with dMMR typically have abundant TILs identified by CD3+ and CD8+ T cells has not been adequately studied in clinical trials. Densities of CD3+ and CD8+ TILs were higher in dMMR tumors compared with pMMR tumors. CD3+ IM (cutpoint) n (%) HR adj P_adj 5y OS rate

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Adjusted indications: T, N, grade, BRAF/KRAS, tumor side, age, smoking

3600 Poster Session (Board #93), Sun, 8:00 AM-11:30 AM
Total neoadjuvant treatment versus chemoradiotherapy in locally advanced rectal cancer: A propensity score analysis from two prospective phase II clinical trials. First Author: Jianwei Zhang, Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

Background: Neoadjuvant chemoradiotherapy (CRT) is still the standard of treatment for locally advanced rectal cancer, but it delays systemic chemotherapy, leading to high incidence of distant metastases. To enhance systemic chemotherapy and improve the outcome of rectal cancer, totally neoadjuvant therapy (TNT) has been investigated recently. Here, we aimed to compare the efficacy of TNT with CRT in locally advanced rectal cancer. Methods: A total of 180 patients with clinical stage II or III locally advanced rectal cancer who received either total neoadjuvant treatment (n = 79) or CRT (n = 101) followed by total mesorectal excision (TME) were identified from two prospective clinical trials (NCT01211210 and NCT02217020) in our institutional database. Propensity score analysis was performed to mitigate selection biases. The TNT group and CRT group, respectively. Grade 3/4 Leukopenia (21.5% vs. 60.8% vs. 35.4%, respectively (p = 0.001). Grade 3/4 neutropenia was the most common (33.9%). Results: Of the 180 patients, the pathologic complete response (pCR) rate was 21.7%. Following propensity score matching, each group contained 79 patients. The baseline characteristics were well balanced. The pCR rate of TNT group and CRT group was 34.2% vs. 15.2%, respectively (p < 0.005). And the tumor downstaging rate was 60.8% vs. 35.4%, respectively (p = 0.001). Grade 3/4 neutropenia was the more common in TNT group, which was 30.4% vs. 8.9% (P = 0.0007) in the TNT group and CRT group, respectively. Grade 3/4 Leukopenia (21.5% vs. 12.7%, P = 0.14) and thrombocytopenia (5.1% vs. 11.4%, P = 0.15) was similar between the two groups. Conclusions: TNT showed higher pCR rate and tumor downstaging rate than that of CRT, which was a promising strategy for improving outcome of rectal cancer, although the grade 3-4 adverse events were a bit higher in TNT group. But this finding requires further analysis from long-term survival data. The phase III study comparing TNT with CRT is ongoing.

3601 Poster Session (Board #94), Sun, 8:00 AM-11:30 AM
Association of adverse events (AEs) with outcomes in early stage colon cancer (CC): An analysis of 10,695 CC patients from the ACCENT database. First Author: Winson Y. Cheung, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

Background: Initial dosing of adjuvant chemotherapy (ACT) is largely based on body surface area, but studies show that drug metabolism can vary significantly across patients. ACT-related toxicities may serve as proxies for these pharmacodynamics and pharmacokinetic variations. Thus, AEs may predict for treatment efficacy and survival. In some tumors, dose titration individualized with consideration of recurrence risk, regimen, and toxicity. Here we considered the influence of age, gender, and PS on the outcomes of patients who received FOLFOX-based adjuvant therapy (N = 3270; NCT01150045). Methods: Using stratified Cox proportional hazard models we stratified the IDEA cohort by stage (≤ 70 or > 70), gender, and PS (0 v 1/2), testing for interactions with subgroups and duration of Rx. Results: Overall, DFS results comparing 3 vs. 6 months of Rx did not significantly differ across age, gender or PS subgroups. However, significant (sign) interactions were detected within subgroups (Table). For pts ≤ 70 who received CAPOX, 3m Rx was as good as 6m (HR 0.9). 6m of Rx is required for pts ≤70 (HR 1.16) with FOLFOX and may be best for pts >70 on either regimen (p = .068, 3 way interactions). It was found that gender influenced the impact of risk group on the duration comparison (p = .078, 3 way interaction); 3m Rx was as good as 6m for male low-risk (HR 0.94) but 6m is required for high risk male (HR 1.18). For females, risk group did not alter the relative merits of 3 vs 6m of Rx. The biologic and clinical rationales for the differences observed within certain subgroups need to be explored before they are used to make treatment choices. Clinical trial information: NCT01150045.
Impact of adjuvant chemotherapy in higher risk stage II colon cancer with a deficient mismatch repair (dMMR)/microsatellite instability (MSI-H) profile. First Author: Prunella Louise Blinman, Concord Repatriation General Hospital, Concord, NSW, Australia

**Background:** The optimal duration of ACT following surgery for colon cancer remains controversial. SCOT is an international, randomised trial that compared 3 months versus 6 months of ACT in this setting. We sought the survival benefits that patients participating in SCOT judged necessary to make extra 3 months of ACT worthwhile. **Methods:** SCOT participants from Australia & New Zealand completed a validated questionnaire 3 and 18 months after randomisation to elicit the minimum survival benefit each participant judged necessary to make it worthwhile having ACT for 6 months rather than 3 months. Standardised hypothetical scenarios used the following baseline survivals with 3 months of ACT: life expectancies (LE) of 5 years (5Y) and 15 years (15Y), and 5-year survival rates (SYS) of 65% and 85%. Comparisons were non-parametric, 2-sided, and considered statistically significant if p < 0.05. **Results:** Questionnaires were completed by 160 participants, 82 allocated 3 months ACT, and 78 allocated 6 months ACT. ACT was FOLFOX in 121 (75%), XELOX in 39 (25%), and the mean age was 64. Preferences varied substantially among participants, and did not differ according to their allocated treatment group. The median survival benefits judged necessary to make the extra 3 months of ACT worthwhile were an extra: 3 years beyond a LE of 5Y; 3 years beyond a LE of 15Y; 15% beyond a 65% SYS; and 5% beyond an 85% SYS. Preferences were similar at 3 months and 18 months. Participants with symptomatic peripheral neuropathy (132, 82%) judged a median benefit of 18 months after randomisation to elicit the minimum survival benefit each participant judged necessary to make it worthwhile having ACT for 6 months rather than 3 months than the estimates of the benefits based on the IDEA meta-analysis.

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3606  
Poster Session (Board #99), Sun, 8:00 AM-11:30 AM
Who should undergo pelvic node dissection after neoadjuvant chemoradiation for rectal cancer?

First Author: Sanghol Malakorn, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The optimal surgical strategy for rectal cancer patients with suspected lateral pelvic lymphadenopathy (LPN) in unknown. Despite the use of neoadjuvant chemoradiation (CRT), lateral compartment treatment failure has emerged as an important clinical problem. The purpose of this study was to evaluate association between preoperative LPN size on imaging and disease diagnosed at pathology in order to determine the indication for lateral pelvic lymph node dissection (LPND).

Methods: Rectal cancer patients with lateral pelvic node metastasis who underwent TME with LPND between 2006 and 2017 were identified from the institutional database of a tertiary cancer center and their medical records were retrospectively reviewed for information regarding patient, tumor, and treatment. Indication for LPND was suspected LPN based on CT or MRI. Patients with locally recurrent cancers at presentation were excluded. Primary outcome was rate of pathologic LPN positivity. Associations between LPN size on post-neoadjuvant CRT imaging and pathologic lateral pelvic lymph node positivity were evaluated. Results: A total of 70 patients who underwent TME & LPND met criteria and were analyzed. The median number of LPN evaluated per patient was 3 (IQR 1–5) per patient. The mean LPN size before and after CRT was 15.7 ± 12.7 mm and 11.0 ± 10.0 mm, respectively and the minimum size of positive LPN was 6 mm on post-treatment imaging. Overall, a total of 56 of 256 LPN were positive (22%). Twenty patients (28.6%) had only ≤5 mm LPN after CRT; none were positive at pathology. Among 50 (71.4%) patients with LPN, 5 mm was strongly associated with pathologically positive LPN but with no patients with size ≤5 mm had positive LPN at pathology. Following LPND no patients with positive LPN developed local recurrence. Therefore, patients with LPN ≥5 mm on post-CRT MRI should undergo TME with LPND.

3607  
Poster Session (Board #100), Sun, 8:00 AM-11:30 AM
Mesorectal excision with or without lateral lymph node dissection for clinical stage II/III rectal cancer: Long-term follow-up data of Japan Clinical Oncology Group study JCOG0212.

First Author: Mitsuhiyo Ota, Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan

Background: We conducted the non-inferiority study of mesorectal excision (ME) alone to ME with lateral lymph node dissection (LLND) for clinical stage II/III rectal cancer without lateral pelvic lymph node enlargement. Non-inferiority of ME to ME with LLND was not confirmed in terms of efficacy in the primary analysis of the long-term follow-up data. In this study, we report median follow-up of 84 months for all randomized patients. Methods: Eligibility criteria included clinical stage II/III; main lesion located in the rectum with the lower margin below the peritoneal reflection; no lateral pelvic lymph node swelling larger than 10 mm. After surgeons had confirmed R0 resection by the ME procedure, patients were randomized intraoperatively to ME alone or ME with LLND. The primary endpoint was relapse-free survival (RFS), with a non-inferiority margin for the hazard ratio (HR) of 1.34. The planned sample size was 700 with a power of 75% and a one-sided alpha of 5%. Results: A total of 701 patients enrolled from 33 institutions were randomized to ME+LLND (n = 351) or ME (n = 350) between June 2003 and August 2010. The 7-year RFS was 71.1% and 70.7% in the ME+LLND group and the ME group, respectively. The HR was 1.09 (95% CI: 0.84-1.42) (non-inferiority P = 0.064). In subgroup analysis shown in the table, RFS of clinical stage III patients in the ME+LLND group was significantly better than that of those in the ME group (HR: 1.49 [95% CI: 1.02-2.17]). Conclusions: Long-term follow-up data supported that the non-inferiority of ME to ME with LLND was not confirmed in terms of efficacy in the primary analysis. ME with LLND is recommended especially for clinical stage III patients who do not undergo preoperative chemoradiotherapy. Clinical trial information: NCT00190541.

Characteristics | HR (95% CI) | p value
--- | --- | ---
Sex | | |
Male | 0.95 | 0.69-1.29
Female | 1.03 | 0.75-1.43
Pathologic stage | | |
II | 1.94 | 1.39-2.72
III | 1.54 | 1.02-2.36
Tumor size | | |
≥5 cm | 1.30 | 0.86-1.91
<5 cm | 0.88 | 0.61-1.28
Disease-free survival | | |
OS | 1.30 | 0.86-1.91
RFS | 1.27 | 0.91-1.77
Death from anal verge | 1.54 | 1.02-2.36

Subgroup analysis of RFS

3608  
Poster Session (Board #101), Sun, 8:00 AM-11:30 AM
Predicting treatment outcome of rectal cancer patients undergoing neoadjuvant chemoradiotherapy by ctDNA: The potential use of ctDNA Long-term follow-up and organ-sparing approach.

First Author: Lifeng Yang, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Neoadjuvant chemoradiotherapy (nCRT) is widely accepted for the treatment of locally advanced rectal cancer (LARC). Watch & wait (W&W) strategy can improve life quality, but needs strict patient selection. We aimed to analyze the ctDNA status of patients during nCRT treatment to predict the long-term efficacy. Methods: Patients with rectal cancer who received nCRT plus organ-sparing surgery were included. Plasma samples were collected pretreatment, in the middle of nCRT, post-nCRT, and post-surgery samples, with ctDNA status measured by digital PCR. Results: ctDNA status changed in irregular patterns. ctDNA status goes up during nCRT, all ctDNA status at zero before the end of nCRT, which was consistent to pCR. Conclusions: ctDNA analysis could potentially be used to guide patient selection for W&W strategy or adjuvant chemotherapy.

3609  
Poster Session (Board #102), Sun, 8:00 AM-11:30 AM
Reasons for urban-rural differences in colon cancer outcomes: A population-based study.

First Author: Nicholas Adam Bosma, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

Background: Previous studies showed that rural patients with colon cancer tend to have worse overall survival (OS). In the US, this disparity is due in part to poorer healthcare access or lack of insurance in rural populations. It is unclear what drives this disparity in single payer healthcare systems. Methods: Patients diagnosed with colon cancer from 2006 to 2017 in a large Canadian province were identified. Demographics, disease, treatment, and outcome data were collected. Using residential postal codes, we classified patients as living in urban, regional, or rural areas. OS was measured from the time of diagnosis to death and analyzed using the Kaplan-Meier method. Multivariate Cox regression models were used to assess the impact of residence on outcomes, while adjusting for measured confounders. Results: We included 6,163 patients: 3,691 in urban, 639 in regional, and 1,779 in rural areas. Median age at diagnosis was 71 years, with 52% men, 51% stage II disease, 54% left-sided colon cancer, and 5% Charlson score 0. In comparison, there were more younger patients (p = 0.033) and more right-sided colon cancers (p = 0.042) in urban areas. In addition, urban patients experienced shorter times from diagnosis to surgery (p < 0.001), but longer delays from surgery to adjuvant chemotherapy (p = 0.002) (see Table). In survival analysis, median OS among urban, regional, and rural populations was 104, 83, and 94 months, respectively (log-rank p < 0.001). After adjusting for measured confounders and observed variations in baseline characteristics across patient populations, residence continued to predict for OS (HR 1.3, 95% CI 1.1-1.4, p < 0.001) for regional and HR 1.1, 95% CI 1.0-1.2, p = 0.040) for rural, when compared to urban. Conclusions: Urban-rural differences in colon cancer survival persist, even in settings with universal healthcare coverage. These findings may be partly driven by a younger population and more expedited surgical intervention in urban populations, but they do not fully explain the disparities.

Characteristics | HR (95% CI) | p value
--- | --- | ---
Sex | | |
Male | 0.95 | 0.69-1.29
Female | 1.05 | 0.88-1.26
Charlson score | | |
0 | 1.00 | 1.00
1 | 1.54 | 1.22-1.96
2 | 1.60 | 1.33-1.94
3a | 1.03 | 0.68-1.56
4 | 1.03 | 0.68-1.56
Tumor size | | |
≤5 cm | 1.00 | 1.00
>5 cm | 1.30 | 0.86-1.91
Disease-free survival | | |
OS | 1.10 | 1.00-1.22
RFS | 1.10 | 1.00-1.22
Death from anal verge | 1.10 | 1.00-1.22

Subgroup analysis of OS
Prognostic impact of CDX2 in stage II colon cancer: Results from two nationwide cohorts. First Author: Terben Hansen, Danish Colorectal Cancer Center South, Vejle Hospital, Vejle, Denmark

**Background:** The aim of the present study was to validate the prognostic impact of CDX2 in stage II colon cancer and confirm its clinical potential.

**Methods:** Individual patient data and formalin fixed, paraffin embedded tumor tissue were collected from two unbiased, population-based cohorts representing all patients operated for stage II colon cancer in Denmark in 2002 and 2003. The CDX2 expression was evaluated by immunohistochemistry on whole tumor sections. Patients were classified into three groups, of CDX2 expression: positive, intermediate, and negative, for comparison with the clinical data. The endpoint was disease free survival (DFS).

**Results:** A total of 1,157 patients was included. We found a significant difference in overall survival of CDX2 positive compared to the intermediate and negative groups. A higher proportion of patients with CDX2 expression showed improved overall survival and disease free survival compared to the intermediate and negative groups. This result was also confirmed by Kaplan-Meier analysis.

**Conclusions:** CDX2 expression in stage II colon cancer is an independent prognostic factor. The use of CDX2 in the clinical setting may help to identify patients with better prognosis and potentially benefit from adjuvant chemotherapy.
Effects of proton pump inhibitors (PPIs) on FOLFOX and XELOX regimens in colorectal cancer (CRC). First Author: Grace Wong, Cross Cancer Institute, Edmonton, AB, Canada.

Methods: First-line adenocarcinoma chemotherapy options for stage II-III CRC include XELOX (capecitabine (cape), oxaliplatin) and FOLFOX (oxaliplatin, leucovorin, 5FU). Cape is an oral 5FU prodrug, and recent studies suggested that PPIs may detrimentally affect cape efficacy. Conversely, some literature postulates that PPIs may negatively impact CRC itself. Our primary objective was to compare 3-year recurrence-free survival (RFS) rates between XELOX-treated PPI-users and non-PPI users, and FOLFOX-treated PPI patients and non-PPI users. Our main secondary objective was to compare overall survival (OS).

Results: 23.4% of XELOX-treated pts and 28.0% of FOLFOX-treated pts used PPIs concurrently with treatment. 3-year RFS was significantly lower in XELOX-treated pts than non-PPI pts (69.5 vs. 82.6%, P = 0.029).

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TPS3618  Poster Session (Board #109b), Sun, 8:00 AM-11:30 AM
First-line treatment with panitumumab plus FOLFIRI in elderly patients with RAS/BRAF wild-type unresectable metastatic colorectal cancer and good performance status: OPALO trial. First Author: Jaime Feliu, Hospital Universitario La Paz, Madrid, Spain

Background: Approximately 60% of colorectal cancer (CRC) patients are ≥ 70 years, of whom 50-60% already have metastasis at the time of diagnosis. Available data indicate that elderly patients with good performance status may, like younger patients, benefit from intensive treatment approaches. The objective of this trial is to assess the efficacy and safety of first-line therapy with panitumumab + FOLFIRI in elderly patients with RAS/BRAF wild-type unresectable metastatic colorectal cancer and good performance status. Methods: OPALO is a phase II, single-arm, multicentre clinical trial. Primary objective: progression-free survival (PFS) at one year. Main eligibility criteria: 1. Patients ≥ 70 years; 2. colorectal carcinoma with unresectable metastatic disease; 3. RAS/BRAF wild-type status; 4. Independence in activities of daily living (ADL) based on the Katz Index and in instrumental activities of daily living (IAL) based on the Lawton Index; 5. To have one or no comorbidity according to the Charlson Comorbidity Index; 6. Patients starting therapy with FOLFIRI + panitumumab with a treatment aim other than achieving potential resectability of the disease. Treatment: all patients are receiving panitumumab (6 mg/kg) plus FOLFIRI every two weeks. Tumour response is evaluated every 8 weeks till disease progression. A blood sample is taken at baseline and at the time of disease progression to determine the RAS/BRAF mutation status. Statistical design: a sample size of 80 patients is deemed adequate (assuming a precision of 11.45%, a two-sided type I error of 5%, and a follow-up rate of 10%). The recruitment of patients has begun in October 2017.

TPS3619  Poster Session (Board #110a), Sun, 8:00 AM-11:30 AM
ABT-165 plus FOLFIRI vs bevacizumab (bev) plus FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine/oxaliplatin and bev. First Author: Keren A. Wainberg, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: The dual variable domain immunoglobulin ABT-165 targets human vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4). Combined VEGF and DLL4 blockade increased inhibition of cutaneous xenograft growth of human colon cancer-derived cell lines vs blockade of either axis alone. In vivo, ABT-165 plus chemotherapy (CT) induced tumor regression with improved efficacy, vs anti-VEGF monoclonal antibody plus CT. In a phase 1 study, a tolerable recommended phase 2 dose was identified for ABT-165 plus FOLFIRI and showed promising efficacy. This phase 2 trial in progress assesses the efficacy/safety of ABT-165 plus FOLFIRI vs bev plus FOLFIRI in pts with second-line mCRC. Methods: This is an open-label, multicenter, phase 2 randomized (1:1) trial (NCT03368859) in pts (>18 years; Eastern Cooperative performance status: 0–1) with historically/cytologically confirmed mCRC who progressed after fluoropyrimidine/oxaliplatin and bev. ABT-165 (2.5 mg/kg) plus FOLFIRI (irinotecan: 180 mg/m²; leucovorin: 400 mg/m²; fluorouracil bolus: 400 mg/m², infusion: 2400 mg/m²) or bev (5 mg/kg) plus FOLFIRI are given intravenously on day 1 of each 14-day cycle, until disease progression/intolerable toxicity. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), and safety. Exploratory endpoints include biomarkers predictive for efficacy/safety, correlation of DLL4 levels with PFS, OS, and disease progression, pharmacodynamic effects, and the efficacy/safety-exposure relationships in the ABT-165 arm. The hazard ratios of PFS and OS comparing the 2 groups are estimated using the Cox proportional hazard model. Kaplan-Meier methodology is used to estimate the PFS and OS curves, median PFS and OS, and their 90% confidence intervals. Safety is assessed by ABT-165 exposure, adverse events (AEs), laboratory data, all deaths, and changes in laboratory data and vital signs. Archival tissue is collected and evaluated for DLL4 expression and angiogenesis signature. Approximately 100 pts are planned to be enrolled, with recruitment initiated in January 2018. Clinical trial information: NCT03368859.

TPS3620  Poster Session (Board #110b), Sun, 8:00 AM-11:30 AM
A randomized phase II study of trastuzumab and pertuzumab (TP) compared to cetuximab and irinotecan (CETIRI) in advanced/metastatic colorectal cancer (mCRC) with HER2 amplification: S1613. First Author: Kanwal Pratap Singh Raghab, Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite advances in systemic therapy, few patients are cured, creating a large unmet need for strategies targeting novel signaling and resistance pathways. The HER2 pathway, which has been successfully targeted in breast and gastric cancer, is one such unique potential target in mCRC. HER2 amplifications (HER2amp) have been identified in a small but distinct subset (6-8%) of KRAS wild-type mCRC. HER2amp is associated with resistance to anti-EGFR therapy (cetuximab/panitumumab) and short progression-free survival (PFS) (< 3 mos.). (Raghab ASCO 2016). Preliminary clinical data (MyPathway Study) has shown promising activity of dual-anti-HER2 inhibition using TP in HER2amp and KRAS wild-type mCRC (Response rate 52%, 95% CI 31 - 72%; and median PFS 5.7 months, 95% CI 4 – 12 mos.) (Hurwitz GIASCO 2017). Methods: S1613 is a multicenter, randomized phase 2 study assessing efficacy of TP relative to CETIRI in HER2amp mCRC. This is a 2 step study. All anti-EGFR naive mCRC patients (pts) without known activating mutations in KRAS/NRAS/BRAF will be screened in step 1 for HER2amp by a central lab using immunohistochemistry and dual-probe in-situ hybridization. Screening can be performed at any time, even during treatment on 1st/2nd line of therapy. If HER2amp positive, pts will be randomized in step 2 after progression on 1st/2nd line of therapy to either TP (pertuzumab (840mg loading dose + 420mg every 3 weeks) and trastuzumab (8mg/kg loading dose + 6mg/kg every 3 weeks)) or CETIRI (irinotecan (180 mg/m² IV every 14 days) and cetuximab (500 mg/m² IV every 14 days)). Prior cetuximab is allowed. Crossover to TP will be allowed after progression on CETIRI arm. A total of 122 eligible patients will provide 80% power to detect an increase in median PFS to 5.1 months from 3 months (HR 0.59) based on a two-sided type I error of 5%, 33 months of accrual and 7 months of follow-up. The primary endpoint of PFS will be analyzed in all eligible patients per intent-to-treat. Randomization will be stratified by prior use of irinotecan and HER2/CEP17 ratio. The study is now activated and open to enrollment to all NCI - NCTN institutions. Clinical trial information: NCT03365882.

TPS3621  Poster Session (Board #111a), Sun, 8:00 AM-11:30 AM
Physical activity program in patients with metastatic colorectal cancer who receive palliative first-line chemotherapy: A randomized controlled phase III trial. (ACTIVE-2 SAKK 41/14). First Author: Viviane Hess, University of Basel and University Hospital Basel, Medical Oncology, Basel, Switzerland

Background: Exercise has become a main focus of basic and clinical research worldwide during the current pandemic of physical inactivity. A clear link between inactivity and cancer incidence/relapse has been established, particularly for colon cancer, the third most common cancer. However, whether exercise has an impact on disease course and survival in advanced disease is unknown. Exercise modifies key host factors that are determinants of chemotherapy efficacy such as metabolic and immunologic tumor microenvironment, drug tolerability and treatment adherence. Thus, we aim to assess whether a supervised exercise program concomitant to first-line palliative chemotherapy for patients with metastatic colorectal cancer (mCRC) enhances chemotherapy efficacy and, therefore, increases survival and decreases symptom burden as compared to patients treated with chemotherapy alone. Methods: Patients with newly diagnosed mCRC are stratified (pre-diagnosis physical fitness, RAS-mutational status, primary tumor location, alkaline phosphatase levels) and randomly assigned to undergo standard systemic treatment and care-as-usual or standard systemic treatment combined with a 12-week structured physical activity (PA) program with twice weekly supervised, heart-rate guided interval training on a bike ergometer. Both groups undergo regular imaging with CT/MRI in order to assess the 1st endpoint of progression-free survival (PFS), i.e. the time between diagnosis and disease progression or death. Radiologists who are blinded to the group assignment will review imaging. A total of 439 events occurring in 524 patients will be needed to show a clinically meaningful HR of 0.75 for PFS with 80% power and an α of 0.03. Co-primary endpoint is self-reported symptom burden as measured by the revised Edmonton Symptom Assessment Scale (eSAS). 50 patients from 17 Swiss and Austrian Centers have been randomized. A planned feasibility analysis of the first 40 patients is ongoing. Clinical trial information: NCT02597075.

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TPS3622
Poster Session (Board #111b), Sun, 8:00 AM-11:30 AM
PRODIGE 52-UCGI 29-CCTG/CO.27 (IROCAS): A multicenter, international, randomized phase III trial comparing adjuvant modified mFOLFOX6 in patients with high-risk stage III (pT4 and/or N2) colorectal cancer (a UNICANCER GI-PRODIGE trial).
First Author: Jaafar Bennouna, Centre Hospitalier Universitaire Nantes, Digestive Oncology, Nantes, France

Background: According to the IDEA trial (Shi et al. ASCO 2017;LBA1), 6-month adjuvant chemotherapy should remain the standard in stage III T4 or N2 colon cancer. The relatively poor survival in this high-risk subgroup (3-year disease-free survival (DFS) rate, 66%) and the potential synergistic efficacy of 5-fluorouracil (5-FU), oxaliplatin, and irinotecan (demonstrated in stage IV colon and pancreatic cancers) suggest FOLFIRINOX as a regimen of particular interest in this setting. Methods: This multicenter, international, phase III trial (NCT02967289) conducted in 47 centers in France and Canada, plans to include 640 patients, aged 18 to 70 years, ECOG performance status ≤1, within 42 days (start treatment, within 56 days) after curative-intent R0 surgical resection of a pT4N1 or pT1-4N2 colon adenocarcinoma. Patients are randomized (1:1; minimization method) between adjuvant mFOLFOX6 (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², and 5-FU 2.4 g/m² over 46 h) or mFOLFOX6 (oxaliplatin 85 mg/m², leucovorin 400 mg/m², 5-FU bolus 400 mg/m² then 2.4 g/m² over 46 h), every two weeks for 24 weeks (12 cycles). Patients will be followed up for 5 years after the end of adjuvant chemotherapy. A gain of 9% in 3-yr DFS (primary endpoint) is expected (74% in the experimental arm vs. 65% in the control arm; α = 5% two-sided log-rank test; 1-b, 80%). Secondary endpoints include 2-yr DFS, overall survival, and toxicity. Since April 2017, 49 patients have been enrolled to date (accrual period, 4 years). Clinical trial information: NCT02967289.

TPS3623
Poster Session (Board #112a), Sun, 8:00 AM-11:30 AM
Phase I trial of TAS-102 and concurrent radiation therapy for patients with locally recurrent, unresectable or metastatic, rectal cancer.
First Author: Joleen Marie Hubbard, Mayo Clinic, Rochester, MN

Background: After primary therapy for rectal cancer (chemotherapy, surgery, and/or radiotherapy), 7-10% of patients will develop locally recurrent disease. Re-irradiation +/- resection of recurrent rectal cancer is possible for select patients. Trifluridine/tipiracil (TAS-102) is a combination nucleoside analog and thymidine phosphorylase inhibitor (TPI) with activity in colorectal cancer refractory to fluoropyrimidines. Trifluridine has a similar mechanism of action as the fluoropyrimidines, which are known radiosensitizing agents, and pre-clinical data shows TPI can potentiate the effects of radiation on colon cancer cell lines. TAS-102 in combination with radiation therapy may have a synergistic effect treating recurrent rectal cancers in patients previously exposed to a fluoropyrimidine. The primary objective of this trial is to determine the maximum tolerated dose and dose-limiting toxicity of TAS-102 when administered in combination with concurrent radiation therapy in patients with locally recurrent rectal cancer. Methods: This is a phase I trial with a standard 3 + 3 dose escalation design (see table). All patients will receive TAS-102 administered PO twice daily on days 1-5 and days 8-12. All patients will also receive radiation therapy at a dose of 300 cGy/day, for a total dose of 3000 cGy in 10 fractions, Monday through Friday for days 1-5 and days 8-12. Patients ≥ 18 years with histological confirmation of locally recurrent rectal adenocarcinoma within the pelvis after primary therapy are eligible. Patients with pelvic disease that is resectable or unresectable and metastatic disease outside the pelvis are allowed. Patients with the first occurrence of rectal cancer amenable to treatment with trimodality therapy will be excluded. Prior treatment with TAS-102 and cancer treatment ≤ 28 days prior to registration is not allowed. Patients with prior pelvic radiation therapy > 54 Gy are ineligible. This trial is currently accruing patients to the first cohort. Clinical trial information: NCT03297710.

Dose Level | Dose | **TAS-102 Dose (2X daily)**
---|---|---
1 | -57% | 15 mg/m²
0* | -43% | 20 mg/m²
1 | -29% | 25 mg/m²
2 | -14.3% | 30 mg/m²
3 | 100% | 35 mg/m²

*Starting dose. **Round dose to the nearest 5 mg. Maximum dose 80 mg.

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Background: Metastatic pancreatic cancer (mPC) still harbors a dismal prognosis (5-year overall survival [OS] <5%). Our previous trial (PRODIGE-ACCORD11) has demonstrated the superiority of 6-month [m] chemotherapy with FOLFIRINOX over gemcitabine in terms of progression-free survival (PFS) [6.4 vs. 3.3 m; HR: 0.47; 95% CI: 0.37-0.59; p <0.001] and OS [11.1 vs. 6.8 m; HR: 0.57; 95% CI: 0.45-0.73; p <0.001], at the expense of higher toxicity, notably cumulative, often limiting, peripheral neuropathy with oxaliplatin. In this randomized Phase II trial, we aimed to assess an alternative sequential strategy in mPC. Methods: Patients (pts) were randomized to receive either 6m FOLFIRINOX (arm A), 4m FOLFIRINOX followed by LV5FU2 maintenance treatment for controlled pts, and treatment reintroduction at disease progression (arm B), or a sequential treatment alternating gemcitabine and FOLFIRI3 every 2m (arm C). The primary endpoint was to evaluate the 6m-PFS rate (HR: 30%, H1: 45%, Fleming design) in order to select the best therapeutic strategy for a future Phase III clinical trial. Results: Between Jan 2015 and Nov 2016, 273 pts (mean age: 63 years; range: 40-76) were enrolled (A: 91; B: 92; C: 90). The median durations of treatment were 5.1, 6.2, and 4.4 m in A, B, and C respectively. Grade 3/4 neurotoxicity occurred in 10% of pts in arm A and 19% of pts in arm B. Median ratio of oxaliplatin was 83% in A and 92% in B. 6m-PFS rates were 47% in A, 44% in B, and 34% in C. 4m objective response rates were 35% in A, 41% in B, and 17% in C. Median PFS was respectively 6.3, 5.7 and 4.5 m in A, B and C. Median OS was 10.1 in A, 11.2 in B and 7.3 m in C. The median duration of first maintenance therapy in B was 3.3 m (range: 0.03-22.6). Conclusions: Maintenance with LV5FU2 appears to be feasible and effective in patients with mPC controlled after 4m of induction chemotherapy with FOLFIRINOX. Severe neurotoxicity rate was higher in the maintenance therapy arm, likely because of higher cumulative oxaliplatin dose. Conroy NEJM 2011. Clinical trial information: NCT02392377.

Background: Patients (pts) with advanced HCC and elevated AFP have a poorer prognosis compared to the general HCC population, and need effective, well tolerated treatment options. Increased VEGF and VEGFR2 expression is associated with high AFP expression in HCC tumors. Ramucirumab (RAM), a human IgG1 mAb, inhibits activation of VEGFR2. REACH-2 was designed to confirm the benefit of RAM treatment observed in the REACH study in pts with baseline AFP ≥400 ng/mL. Methods: Eligible pts were ≥18 yrs, had HCC with BCLC stage C or B disease refractory or not amenable to locoregional therapy, baseline AFP ≥400 ng/mL, Child-Pugh A, ECOG PS 0 or 1, adequate hematologic and biochemical parameters, had progressed on or following, or were intolerant to sorafenib. Pts were randomized (2:1) to receive RAM 8 mg/kg iv or placebo (PL) Q2W plus best supportive care, until disease progression or unacceptable toxicity. Primary endpoint was overall survival (OS). Secondary objectives included progression-free survival (PFS), objective response rate (ORR) per RECIST v1.1 and safety. Results: 292 pts were randomized to RAM (197) or PL (95). Baseline characteristics were generally balanced between arms. RAM treatment significantly improved OS (median OS 8.5 m vs 7.3 m PL; HR 0.710; 95% CI 0.531, 0.949; p <0.0199). RAM significantly improved PFS (median PFS 2.8 mo vs 1.6 mo PL; HR 0.452, 95% CI 0.339, 0.603; p <0.001). ORR was 4.6% RAM vs 1.1% PL (p=1.156) and disease control rate (ORR + stable disease) was 59.9% RAM vs 38.9% PL (p=0.006). Grade ≥3 adverse events occurring in ≥5% pts in the RAM arm were hypertension (12.2% RAM, 5.3% PL) and hyponatremia (5.6%, 0%). Conclusions: REACH-2 met its primary endpoint showing a significant survival benefit, with RAM treatment reducing the risk of death (29%) in pts with HCC and AFP ≥400 ng/mL who progressed on or were intolerant to sorafenib. Treatment was well tolerated, with a safety profile consistent with the established profile for single agent RAM. REACH-2 is the first positive phase 3 study conducted in a biomarker-selected pt population with HCC. Clinical trial information: NCT02435433.

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A randomized study of temozolomide or temozolomide and capetebactine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). First Author: Pamela L. Kunz, Stanford University School of Medicine, Stanford, CA

**Background:** Patients with advanced pancreatic neuroendocrine tumors (pNETs) have few treatment options that yield objective tumor regression. Somatostatin analogues, everolimus, and sunitinib yield prolonged progression-free survival (PFS) but low response rates (RRs). Retrospective and small, prospective studies suggest that temozolomide-based therapies may have activity and the combination of temozolomide and capetebactine (TC) is associated with high RRs and relative long PFS. However, there are no randomized, prospective studies of these agents and this trial was initiated to establish a role for the combination of TC. **Methods:** E2211 was a two-arm, randomized, phase II trial comparing T (200 mg/m^2 PO QD days 1-28 every 42 days) or the control group (8 cycles of S-1 at 80-120 mg/body on days 1-14 of each cycle, and then 4 further cycles of S-1 at 80-120 mg/body on days 1-28 every 42 days) or the control group (8 cycles of S-1 at 80-120 mg/body on days 1-28 every 42 days). Block randomization was performed by a central interactive computerized system stratified by the institution, stage (IIIA, IIIB, or IIIC) and histological type (differentiated or undifferentiated). The sample size of 1,100 was necessary to detect a 7% increase in the 3-year RFS, the primary endpoint, in the S-1/docetaxel group (HR 0.78, 2-sided alpha = 0.05, beta = 0.2). The secondary endpoints were OS, TTF and safety. **Results:** At the planned second interim analysis, the 3y RFS of the S-1/docetaxel arm (65.9%) was significantly superior to that of the S-1 arm at 49.6% (HR 0.632, 99% CI: 0.400~0.998, p = 0.0007), and the independent data and safety monitoring committee recommended termination of the trial. S-1/docetaxel suppressed all types of recurrences including hematogenous, lymphatic and peritoneal. Although grade 3 adverse events including leukopenia, neutropenia, stomatitis and anemia were more frequent, postoperative S-1/docetaxel was safe and manageable. **Conclusions:** Postoperative adjuvant S-1/docetaxel after D2 gastrectomy is recommended as the new standard of care for patients with pStage III GC. Clinical trial information: NCT01824875.

A randomized phase III study comparing S-1 plus docetaxel with S-1 alone as a postoperative adjuvant chemotherapy for curatively resected stage III gastric cancer (JACCRO GC-07 trial). First Author: Yasuhiro Kodera, Nagoya University, Nagoya, Japan

**Background:** Although postoperative adjuvant chemotherapy with S-1 is among the standard treatments for curatively resected stage III gastric cancer (JACCRO GC-7, a randomized controlled trial [JACCRO GC-7, a randomized controlled trial](#). The treatment was well-tolerated with expected AEs and higher rates of mucositis, neutropenia, and cytopenia. Anorexia, stomatitis and anemia were more frequent, postoperative S-1/docetaxel was safe and manageable. **Conclusions:** Postoperative adjuvant S-1/docetaxel after D2 gastrectomy is recommended as the new standard of care for patients with pStage III GC. Clinical trial information: NCT00103377.

Chemo-prevention of esophageal cancer with esomprazole and aspirin therapy: Efficacy and safety in the phase III randomized factorial ASPECT trial. First Author: Janusz Jankowski, University of Central Lancashire, Preston, United Kingdom

**Background:** iobenguane (I-131 MIBG), has been developed for the treatment of iobenguane-avid malignant (metastatic) or recurrent or unresectable pheochromocytoma or paraganglioma (PGL). **Methods:** MIBG-avid PGL patients (pts) ineligible for curative surgery or chemotherapy, and on a stable antihypertensive regimen for tumor-related hypertension were enrolled. Pts received a dosimetric dose (111-222 MBq) followed by up to 2 therapeutic doses (each at 296 MBq/kg to a maximum of 18.5 GBq) approximately 3 months (mths) apart. Pts were followed for 12-mths (efficacy period) and an additional 4 years for long-term follow-up. The primary endpoint was defined as proportion of pts with at least 50% reduction, including discontinuation, of all antihypertensive medications lasting ≥6 mths beginning during the efficacy period. Secondary endpoints included objective tumor response (ORR) by RECIST and overall survival (OS). **Results:** Of 81 pts enrolled, 74 pts received a dosimetric dose of AZEDRA. 68 pts received 1 therapeutic dose (full analysis; FA) and 50 received two (per protocol; PP). At study entry, 52% (35/68) had prior surgery and systemic therapy (I-131 MIBG) and/or chemotherapy for PGL. 50% (32/64) of evaluable pts had lung and/or liver metastases at baseline. The primary endpoint was met by 25% (95% CI 16%-37%) of FA and 32% (95% CI 21%-46%) of PP pts, achieving pre-specified success criteria. For ORR, 23% and 30% of FA and PP populations achieved partial response (PR). The 12-month OS was 91% in FA pts. Median OS was 36.7 mths (95% CI 29.9, 49.1), and median survival appeared similar in pts with and without lung/liver metastasis at baseline (42.6 and 41.1 mths, respectively). The most common (≥50%) treatment-emergent adverse events were myelosuppression, nausea, and fatigue. No acute drug-related hypertensive events were observed. **Conclusions:** Updated results from this pivotal phase 2 study suggest that AZEDRA is an efficacious and safe treatment for an ultra-orphan disease with no approved therapies in the United States. Clinical trial information: NCT00874614.
Phase III study comparing triplet chemotherapy with S-1 and cisplatin plus docetaxel versus doublet chemotherapy with S-1 and cisplatin for advanced gastric cancer (JCOG1013). First Author: Yasuhide Yamada, National Cancer Center Hospital, Tokyo, Japan

Background: Doublet chemotherapy with S-1 and cisplatin (CS) is one of the standard first-line chemotherapy for advanced gastric cancer. Triplet chemotherapy with docetaxel added to CS (DCS) showed a promising activity associated with feasible toxicities in a phase II study. We conducted a phase III study, JCOG1013, to investigate whether DCS improved overall survival (OS) compared with CS. Methods: Patients with previously untreated, human epidermal growth factor receptor 2 negative or unknown, unresectable or recurrent gastric adenocarcinoma, performance status 0 to 1, and adequate organ function were eligible. They were randomly assigned to receive CS (S-1 40-60 mg orally twice a day for 3 weeks, cisplatin 60 mg/m² on day 1, S-1 40-60 mg orally twice a day for 2 weeks, repeated every 4 weeks) or DCS (docetaxel 40 mg/m², cisplatin 60 mg/m² on day 1, S-1 40 mg/m² on day 8, repeated every 5 weeks), or DCS (docetaxel 40 mg/m², cisplatin 60 mg/m² on day 1, S-1 40-60 mg orally twice a day for 2 weeks, repeated every 4 weeks). The primary endpoint was OS. A total of 740 patients were required to detect an increase in median OS from 13.5 months in the CS arm to 16.5 months in the DCS arm, corresponding to a hazard ratio (HR) of 0.8435, with a one-sided alpha of 5% and power of 80%. Results: From April 2012 to March 2016, 741 patients were enrolled in total (CS 371, DCS 370). Median OS was 14.2 and 15.3 months for DCS and CS, respectively (HR 0.995; 95% confidence interval [CI] 0.86-1.15; p = 0.92). The overall response rate was 59.3% for DCS and 56.0% for CS (p = 0.50). The most common adverse events of grade 3 or 4 were neutropenia (DCS 58.5%, CS 32.1%), febrile neutropenia (DCS 7.5%, CS 5.7%), and diarrhea (DCS 7.0%, CS 7.4%). Conclusions: Addition of docetaxel to CS failed to improve OS in patients with untreated advanced gastric cancer. Therefore, CS remains the standard treatment for first-line chemotherapy for advanced gastric cancer. Clinical trial information: UMIN000007652.

A randomized phase II study of weekly paclitaxel + trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT). First Author: Akikata Makiyama, Department of Hematology/Oncology, Community Health Care Organization Kyushu Hospital, Kitakyushu, Japan

Background: Trastuzumab (Tmb) is a key drug for HER2-positive breast and gastric or gastro-esophageal junction cancer (G/EJG) cancer. While continuous use of Tmb beyond progression (TPB) showed a benefit in HER2-positive metastatic breast cancer, it has not been studied in HER2-positive G/EJG cancer. We compared weekly paclitaxel alone (P) with weekly paclitaxel plus Tmb (PT) in patients (pts) with HER2-positive advanced G/EJG cancer progressing during Tmb-containing therapy. Methods: Pts with HER2-positive advanced G/EJG cancer progressing during first-line chemotherapy with Tmb + fluoropyrimidine + platinum were enrolled, and randomized to receive either P (80mg/m², day 1, 8, 15, q4w) or PT (P + initial Tmb 80mg/kg followed by 60mg/kg, q3w). The primary endpoint was progression-free survival (PFS). Major secondary endpoints included overall survival (OS), response rate, safety, and translational biomarker research. A total of 69 events was required to achieve 80% power for one-sided log rank test with 10% significance level, expecting median PFS of 3.0 months for P and 6.0 months for PT. Results: From December 2012 to October 2016, 91 pts were randomized to P (n = 45) or PT (n = 44). Median PFS was 3.19 (95% CI 2.86-3.48) and 3.68 (95% CI 2.76 to 4.53) months in the P and PT arms, respectively (HR = 0.91, 95% CI 0.67-1.22, p = 0.33). Median OS was 9.95 months in the P arm and 10.2 months in the PT arm (HR = 1.23, 95% CI 0.75-1.91, p = 0.20). In the P and PT arms, the overall response rates were 29% and 23% (p = 0.70), and the disease control rates were 71.1% and 61.5% (p = 0.47), respectively. PT treatment was associated with longer PFS in pts whose interval between the last Tmb administration and the randomization ≥30 days (HR = 0.45, 95% CI 0.21-0.96), but not in pts < 30 days (HR = 1.40, 95% CI 0.82-2.37). Safety was comparable between the two arms. HER2-positive gastric cancer tissues from 16 pts before the study entry was lost in 69%. Conclusions: TPB strategy failed to improve PFS in pts with HER2-positive advanced G/EJG cancer. Clinical trial information: UMIN000002927.

Survival outcomes from CALGB 80803 (Alliance): A randomized phase II trial of PET scan-directed combined modality therapy for esophageal cancer. First Author: Karyn A. Goodman, University of Colorado, Denver, CO

Background: We evaluated use of early PET response after induction chemotherapy (CT) to direct changing to alternative CT during preoperative chemoradiation (CRT) among patients (pts) with resectable esophageal and gastro-esophageal junction (GEJ) adenocarcinomas who are PET nonresponders. We previously reported the primary endpoint of improving pathologic complete response (pCR) in PET nonresponders; pre-specified efficacy criteria were met for improvement in pCR rates with changing CT during CRT. We now report survival outcomes by PET response status. Methods: 257 pts enrolled, underwent baseline PET and were randomized to 1 of 2 induction CT arms: modified FOLFOX-6 (oxaliplatin, leucovorin, 5-FU) days 1, 15, 29 or carboplatin/paclitaxel (PC) days 1, 22, 29. Repeat PET was performed days 36-42; change in maximum standardized uptake value (SUV) from baseline was assessed. PET nonresponders (SUV: PET-NR) crossed over to alternative CT regimen during CRT (50.4 Gy/35 fractions). PET responders (SUV: PET-R) continued on same CT during CRT. Pts underwent surgery at 6 weeks post-CRT. Overall survival (OS) was measured from randomization to death from any cause; 2-year (yr) OS rates were estimated using the Kaplan-Meier method. Results: 240 eligible pts received protocol treatment and 222 had an evaluable repeat PET. With median follow-up of 35.9 months (95% CI: 33.1-42.4), median OS was 34.4 mo (95% CI: 28.4-49.7) and 2-yr OS was 61.8% (95% CI: 55.7-68.5%). Median OS for PET-R was 42.0 mo (95% CI: 31.0, not estimable [NE]) and for PET-NR was 27.4 mo (95% CI: 20.3, NE). OS follow-up continued with median follow-up of 6.8 mo (10.3-32.4) with final analysis performed at 565 events: 36.7%/63.2% (ECOG 0/1), 71.2%/27.9% (ME), 74.6%/25.4% (histological tumor response (HR) 0.99; 95% CI 0.86-1.10; p = 0.8596), respectively. The mPFS was 3.55 vs 3.65 m in PET-R and PET-NR arms (HR 1.01 [95% CI, 0.86-1.20] p = 0.8596), respectively. The overall incidence of adverse events (AEs) was 98.6% vs 96.6% in PET-R and PET-NR arms without any additive toxicity. AEs ≥ Grade 3 occurred in 62.9% vs 59.7% in PET-R and PET-NR arms, with ≥ Grade 3 diarrhea in 16.0% vs 1.4%, respectively. Conclusions: A randomized, placebo-controlled phase 3 trial of NAPA + PTX did not improve OS or PFS in pts with gastric and GEJ adenocarcinoma. Addition of NAPA to PTX was tolerable. Clinical trial information: NCT02178956.
4013 Poster Discussion Session; Displayed in Poster Session (Board #202), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

A multi-center, randomized, prospective study evaluating the optimal radiation dose of definitive concurrent chemoradiation for inoperable esophageal squamous cell carcinoma. First Author: Yanjun Xu, Zhejiang Cancer Hospital, Hangzhou, China

Background: To determine the optimal radiation dose for definitive concurrent chemoradiation in esophageal squamous cell carcinoma (ESCC) using modern radiation technology. Methods: Pathologically confirmed ESCC patients with stage IIA/IVA were randomized into high-dose (50Gy) and low-dose group (45Gy). The total radiation doses were delivered 2 Gy per fraction, 5 fractions per week, by intensity-modulated radiation therapy (IMRT). Concurrent weekly docetaxel (25 mg/m²) followed by cisplatin (25 mg/m²) and 2 cycles consolidation chemotherapy with docetaxel 70mg/m² plus cisplatin 25mg/m² day 1-3 were administered. The primary endpoint was local/regional progression-free survival (LRPFS). Results: From April 2013 to May 2017, 305 patients were randomized into the high-dose (n = 152) and low-dose group (n = 153). There were no significant differences in gender, age, KPS, clinical stage, location, the length of tumor between the two groups. The radiotherapy completion rate was 87.5% (133/152) and 95.4% (146/153) in the high and low dose groups respectively (P = 0.002). The concurrent weekly chemotherapy completion of receiving 5, 4, 3 weeks drugs were 61.2% (93/152), 66.7% (102/153); 21.1% (32/152), 20.9% (32/153); 17.8% (27/152), 12.4% (19/153) (P = 0.406). There was no significant difference in the completion of 5FU, 45.5% (9/152) and 45.5% (7/153) (P = 0.998). The median follow-up of the two groups was 24/152, 17.5% (24/151) in the high-dose and low-dose group, respectively. The 1, 2-year LRPFS rate was 86.4% (131/152) and 85.1% (130/153) respectively.

4014 Poster Discussion Session; Displayed in Poster Session (Board #203), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Randomized phase III study of gemcitabine plus S-1 combination therapy versus gemcitabine plus cisplatin combination therapy in advanced biliary tract cancer: A Japan Clinical Oncology Group study (JCOG1113, FUGA-BT). First Author: Makoto Ueno, Department of Gastroenterology, Hepatology and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan

Background: Gemcitabine (GEM) plus cisplatin (GC) is the standard of care for patients with advanced biliary tract cancer (BTC). However, GC is considered to be toxic because of nausea, vomiting, and appetite loss, and inconvenient due to requiring hydration before and after administration. GEM plus S-1 (GS) was reported to be promising with preferable efficacy and acceptable toxicity profile. This phase III study aimed to confirm the non-inferiority of GS to GC in terms of overall survival (OS). Methods: Eligibility criteria included chemotherapy-naïve patients with recurrent or unresectable biliary tract adenocarcinoma (gastricbladder, intrahepatic biliary tract, extrabiliary biliary tract, or ampulla of Vater), an ECOG-PS of 0–1, and adequate organ function. In the GC arm, 1 g/m² of GEM and 25 mg/m² of cisplatin was infused on days 1 and 8 of a 21-day cycle. In the GS arm, 1 g/m² of GEM was infused on days 1 and 8, and S-1 60, 80, or 100 mg/day according to body-surface area was administered from days 1 to 14 of a 21-day cycle. The primary endpoint was OS and the secondary endpoints included progression-free survival (PFS), response rate (RR), adverse events (AEs), clinically relevant AEs predefined as any of grade 2 or above, adequate hydration, vomiting, oral mucositis, and diarrhea. The sample size was calculated to be 350 with a one-sided alpha of 5%, a power of 80%, non-inferiority margin of 1.155 in terms of hazard ratio (HR). Results: From May 2013 to March 2016, 354 patients were enrolled. The non-inferiority of GS to GC was demonstrated (HR 1.36, 95% CI: 0.91–2.03, p-value = 0.139), and the lower boundary of the 95% confidence interval (CI), 0.78 to 1.15; P = 0.046 for non-inferiority. Median PFS was 5.8 months in GC and 6.8 months in GS (HR 0.86, 95% CI, 0.70–1.07). RR was 32.4% in GC and 29.8% in GS. Both treatments were generally well tolerated. Clinically relevant AEs were observed 35.1% in GC and 29.9% in GS. Correlation of GS demonstrated non-inferiority to GC in OS by a log-rank test and was considered as new convenient option of standard of care without hydron for advanced BTC. Clinical trial information: UMIN000010667.

4015 Poster Discussion Session; Displayed in Poster Session (Board #204), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Phase 2 trial of the IDO pathway inhibitor indoximod plus gemcitabine / nab-paclitaxel for the treatment of patients with metastatic pancreatic cancer. First Author: Nathan Bahary, University of Pittsburgh Medical Center Cancer Center Pavilion, Pittsburgh, PA

Background: The indoleamine 2,3-dioxygenase (IDO) pathway is a key counter-regulatory mechanism that is exploited by tumors to prevent and evade immune surveillance. Inhibitors of IDO action, such as indoximod, are an increasingly validated class of potential cancer therapeutics. Methods: Single arm study with indoximod (1200mg BID continuous) plus G / N (1000mg/m² / 125mg/m² q week x3 per 4-week cycle). Patients had treatment naïve mPCA or 1st line therapy after previous resection and adjuvant therapy. Treatment continued until disease progression or toxicity. Primary endpoint was an improvement in median overall survival (mOS) from a historical 8.5 months for G / N to 12.1 months (HR 0.70). Secondary endpoints included overall response rate (ORR) by site review RECIST 1.1. An expansion cohort enrolled patients undergoing pre and post-treatment (end Cycle 2) tumor biopsies. Results: A total of 135 patients initiated treatment in Phase 2 including 36 in the biopsy group. 104 were efficacy evaluable (EE) per the pre-specified definition of completing one cycle of therapy with one-on-treatment imaging study. The ORR in the EE was 46.2% (48/104) with 1% CR (1/104) and 45.2% PR (47/104). The mOS in the EE was 10.9 months. Combination was generally well tolerated with fatigue, nausea, and anemia being the most commonly observed adverse events. Immuno-histochemical analysis by immunohistochemistry from biopsy samples (n = 11) indicate responders had increased intra-tumoral CD8 density after 2 cycles of therapy compared to non-responders (p = 0.030). Conclusions: EE patients had a mOS of 10.9 months and ORR of 46.2%; responding patients had an increased intra-tumoral CD8 density. The study did not meet the pre-specified primary endpoint of a 50% increase in PR (p value = 0.141). Progression-free survival showed similar trend (16.39 vs 10.09 months, p-value = 0.1049) and (16.39 vs 10.38 months, p-value = 0.3778), respectively. No increase in serious adverse events or delay in wound healing post-surgery was observed in Arm A vs Arm B. Conclusions: These findings indicate that pamrevlumab may be a new convenient option of standard of care without hydration for advanced BTC. Clinical trial information: NCT01937208.

4016 Poster Discussion Session; Displayed in Poster Session (Board #205), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Effect of anti-CTGF human recombinant monoclonal antibody pamrevlumab on resectability and resection rate when combined with gemcitabine/nab-paclitaxel in phase 1/2 clinical study for the treatment of locally advanced pancreatic cancer patients. First Author: Vincent J. Picozzi, Virginia Mason Hospital and Medical Center, Seattle, WA

Background: Pancreatic ductal adenocarcinomas exhibit high degree of desmoplasia with extensive connective tissue growth factor (CTGF) expression and extracellular matrix production. CTGF overexpression is associated with aberrant fibrous tissue in mouse model, in which progression of tissue adhesions was inhibited by pamrevlumab. We hypothesize that pamrevlumab, an anti-CTGF antibody, may influence resectability of locally advanced pancreatic cancer (LAPC) by inhibiting effects of CTGF. Methods: Pamrevlumab + gemcitabine/Nab-paclitaxel (GN) Arm A vs G/N (Arm B) was given to treatment-naïve LAPC patients to improve resection rate and overall survival (OS). Patients (N = 37) were randomized 2:1 in Arm A vs Arm B. Patients who completed 6 cycles of treatment underwent resectability assessment per protocol criteria (NCCN, CA 19-9, PET, RECIST) and, if found eligible, under went re-resection. No adjuvant therapy was given; second line therapy was administered per investigator discretion. Results: In the ITT population, a higher percentage of patients discontinued treatment in Arm B (46.2% vs Arm A (25%), mainly due to disease progression or adverse events. More patients normalised PET in Arm A (35%) vs Arm B (23%). Thirty percent of patients overall had best objective RECIST response (CR + PR). More patients were eligible for surgery and were resected in Arm A vs Arm B; 70.8% vs 15.4% and 33.3% vs 7.7%, respectively. Improvement in OS was noted in patients eligible for surgery vs not (27.7 vs 18.4, p-value = 0.0766) and in patients operated vs not (N = 20 vs N = 16 months, p-value = 0.045). Progression-free survival showed similar trend (16.39 vs 10.09 months, p-value = 0.1049) and (16.39 vs 10.38 months, p-value = 0.3778), respectively. No increase in serious adverse events or delay in wound healing post-surgery was observed in Arm A vs Arm B. Conclusions: These findings indicate that pamrevlumab may be a new convenient option of standard of care without hydration for advanced BTC. Clinical trial information: NCT02210559.

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Conclusions:

95%CI 0.38-0.83; p = 0.004). Median TTUP was 20.6 and 26.7 months in the T and TS groups (HR = 0.56, 0.87; p = 0.006), respectively. The number of OS events has not reached.

Methods: In this randomized, open label, multicenter, comparative trial (NCT01217034), patients with unresectable HCC, Child-Pugh score ≤7, ECOG performance status 0-1, no vascular invasion (VI), no extrahepatic spread (EHS), size ≤10 cm and number ≤10 and adequate organ function were randomized 1:1 (stratification by institution, Milan criteria in or out, and number of previous TACE 0 or 1 to 2) to T or TS. In TS group, sorafenib 400 mg once daily was pretreated for 2-3 weeks prior to TACE followed by 800mg once daily during on-demand conventional TACE sessions until the time of unTACEable progression (TTUP), which was defined as the time to the date of a state when TACE continuation is not possible due to untreated tumor progression, deterioration to Child-Pugh C or appearance of VI/EHS. Co-primary endpoints are PFS and OS. Multiplicity is adjusted using a gatekeeping hierarchical testing. PFS event in this trial was defined as death or time to TTUP. Key secondary endpoints were time to progression and safety. PFS is expected to 40% extension from 18 months (control arm) to 25 months, target HR was 0.71, with a power of 0.80.

Results:

The trial was conducted in 33 institutions and a total of 156 patients were randomized to T (n = 76) or TS (n = 80). Median PFS in the T group and TS group was 13.5 and 25.2 months (HR = 0.59, 95%CI 0.41-0.87; p = 0.004). Median TTUP was 13.5 and 26.7 months in the T and TS groups (HR = 0.57, 95%CI 0.35-0.92; p = 0.02), respectively. There was no unexpected toxicity. Conclusions: Sorafenib in combination with TACE significantly improved PFS for patients with unresectable HCC. Adverse events were consistent with the known safety profile with previous TACE combination trials. Clinical trial information: NCT01217034.

Caboxtantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: Results from the randomized phase 3 CELESTIAL trial. First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center, New York, NY

Background: C, an inhibitor of MET, VEGFR, and AXL, has previously shown activity in pts with advanced HCC. In this open-label, randomized, double-blind, global, phase 3 trial (NCT01908426), evaluable P (n = 1725) and treated pts were randomized 2:1 (C vs P stratified by etiology, geographic region, and presence of extrahepatic spread) to receive either C (60 mg qd) or P (thus C was randomized in 1745 pts). Primary endpoint was overall survival (OS). Secondary endpoints were OS, progression free survival (PFS), and safety in pts with advanced HCC previously treated with sorafenib. Here we report on/evaluation of clinical, pharmacokinetic (PK), and safety data. C was significantly superior to P in OS (HR: 0.67, 95%CI 0.58-0.78; p = 0.0001) with median OS duration of 12 mo (Kaplan Meier) and median response duration was not reached (3.1 - 12.5+ mo). Best response was CR in 1 pt (one Arm). C had a favorable PK and safety profile, with 72% of pts experiencing grade 3 or 4 adverse events (predominantly grade 3) with higher incidence in the C versus P groups (10% vs 2%). Subgroup analyses of OS and PFS by baseline characteristics will also be presented.

Results: As of 1 Jun 2017, 707 pts were randomized, and 484 deaths had occurred (317 out of 470 for C; 167 out of 237 for P). Baseline characteristics were balanced between the arms: median age was 64 years, 82% were male, 38% had HBV, 24% had HCV, 25% enrolled in Asia, 85% had EHS/VWI, and 27% had received 2 prior systemic regimens for advanced HCC. The study met the primary endpoint at the second planned interim analysis with median OS 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63-0.92; p = 0.0049). Median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36-0.52; p < 0.0001), and OS was 47% vs 40% (p = 0.0086). The most common grade 3/4 adverse events (predominantly grade 3) with higher incidence in the C vs P arm included hand-foot skin reaction (17% vs 0%), hypertension (16% vs 2%), increased aspartate aminotransferase (12% vs 7%), fatigue (10% vs 4%), and diarrhea (10% vs 2%). Subgroup analyses of OS and PFS by baseline characteristics will also be presented. C was significantly superior to P in the safety profile. Both studies had a similar safety profile with manageable adverse events. C was well tolerated by both OS and PFS vs P in previously treated pts with advanced HCC. Adverse events were consistent with the known safety profile of C. Clinical trial information: NCT01908426.

Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): Global OPTIMIS final analysis. First Author: Markus Peck-Radosavljevic, Medical University of Vienna Klagenfurt am Wörthersee, Vienna/Klagenfurt, Austria

Background: TACE is often used to treat unresectable HCC (uHCC). However, there is no globally accepted consensus on the indication and definition of TACE failure. It is critical to reassess the risk/benefit of continuing TACE after failure as it may delay or prevent pts from receiving subsequent treatments. Methods: OPTIMIS, an international, prospective, observational study, enrolled pts with uHCC for whom a decision to treat with TACE was made at study entry. Practice patterns, safety, subsequent treatments, and outcomes data were collected. TACE ineligibility was defined and consistent with international and regional guidelines. Data were analyzed using descriptive statistical methods.

Results: Overall, 1650 pts received TACE; 529 pts (32%) were BCLC stage C, 118 (7%) had extrahepatic spread, and 123 (7%) had portal vein thrombosis. At inclusion visit, 636 pts (39%) received TACE despite being TACE ineligible according to protocol-specified criteria. After first TACE, the proportion of pts with chronic liver function deterioration (worsening in CTCAE grade 3–50 mo after TACE) ranged from 11% to 29% across assessed liver parameters. Complete and partial response rates to first TACE (N=1650) were 14% and 26%, respectively, which decreased by second (10% and 16%; n=1002), third (10% and 15%; n=580), and fourth (8% and 17%; n=338) TACE. Proportion of pts who received the number of TACE procedures: 18%, 21%, 25%, and 27% for first, second, third, and fourth TACE, respectively. In total, only 507 pts (31%) became TACE ineligible during the study. Of those 507 pts, 47 (9%) received sorafenib at the time of TACE ineligibility and 460 (91%) received sorafenib later or not at all. Considerable imbalances between the 2 cohorts were observed; a propensity score analysis is planned to analyze overall survival from TACE ineligibility. Conclusions: These results indicate that real-world TACE use appears to deviate from treatment guidelines. This heterogeneity highlights the need for a globally accepted consensus on the indication and definition of TACE failure. These observations also indicate the importance of monitoring liver function in pts receiving TACE. Clinical trial information: NCT01933945.

Pembrolizumab (pembro) in patients with advanced hepatocellular carcinoma (HCC): KEYNOTE-224 update. First Author: Andrew X. Zhu, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA

Background: Initial results from KEYNOTE-224 (NCT02702414), an open label, phase 2 trial showed that pembro, an anti-PD-1 antibody, was active and safe in pts with advanced HCC previously treated with sorafenib. Here we report final clinical outcomes and updated safety data. Methods: Pembrolizumab (200 mg IV Q3W for 2y or until disease progression, unacceptable toxicity, withdrawal of consent or investigator decision) was administered to 104 pts (95% CI, 9.8 to 24.9, n = 17) and similar across differing etiologies; 66% of responders had duration ≥12 mo (Kaplan Meier) and median response duration was not reached (3.1 - 12.5+ mo). Best response was CR in 1 pt (1%). PR in 16 (15.4%), SD in 47 (45.2%) and PD in 34 (32.7%); DCR was 61.5%. Median DFS (95% CI) was 4.9 mo (3.4 to 7.0) and OS was 12.9 mo (9.7 to NA). PFS and OS 12 mo rates were 25.4% and 53.6%, respectively. Safety was similar to that observed in other trials in other indications. Immune-mediated hepatises occurred in 3 (2.9%) pts; no cases of HBV/HCV flare were seen. Higher PD-L1 CPS in tumor and immune cells was associated with higher ORR and longer PFS, while PD-L1 CPS in tumor cells alone and GEP showed less robust associations with outcomes. Conclusions: These results support further clinical investigation of pembrolizumab in advanced HCC. PD-L1 CPS was associated with clinical response to pembrolizumab while results for PD-L1 CPS and GEP were less robust; further study is needed to better define these relationships. Clinical trial information: NCT02702414.
4021 Poster Session (Board #210), Sun, 8:00 AM-11:30 AM
Two novel registry-based prediction models for overall survival in patients with metastatic esophageal or gastric cancer. First Author: Héctor van den Bornl, Academisch Medisch Center, Amsterdam, Netherlands

Background: Prediction models for decision-making in oncology are increasingly being used, but few are available for esophagogastrectomy cancer, particularly in the metastatic setting. The aim of this study is to construct prediction models for overall survival in patients with metastatic esophageal or gastric cancer. Methods: Data from patients with metastatic esophageal (N = 8670) and gastric (N = 4804) cancer diagnosed in the period 2005-2015 were retrieved from the nationwide Dutch cancer registry. Multivariable Cox-regression models, extended with treatment interactions, were created to predict overall survival. Multiple imputations were used to handle missing data. Predictor selection was performed via the Akaike Information Criterion (AIC) and was extended by a Delphi consensus among experts in the field of palliative esophagogastrectomy cancer. Validation was performed with an 11-fold temporal validation. Both the concordance-index (c-index) and calibration were used to assess model quality. Results: The Delphi consensus yielded seven important predictors of survival and are shown with the AIC-selected predictors in Table 1. The c-indices show consistent discriminative ability during validation, i.e., 0.71 and 0.68 for respectively the esophageal and gastric cancer models. There is close agreement between predicted and observed survival, with an error of 1.7% and 2.2% for respectively the esophageal and gastric cancer models. Conclusions: The models yield fair discriminative and high calibration levels, and provide a good foundation for further investigation in clinical practice to determine their added value in decision-making.

Overview of selected predictors in the esophageal and gastric cancer models (8. selected during Delphi consensus).

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Response evaluation criteria in Solid Tumors (RECIST) version 1.1.

4022 Poster Session (Board #211), Sun, 8:00 AM-11:30 AM
Oxaliplatin plus cetuximab (XELOX) in the perioperative treatment of locally advanced gastric adenocarcinoma in combination with D2 gastrectomy (NEO-CLASSIC). First Author: Yunsu Liu, Zhongshan Hospital, Fudan University, Shanghai, China

Background: This multicenter, open-label study (NEO-CLASSIC) evaluated the efficacy and safety of oxaliplatin and cetuximab (XELOX), plus gastrectomy, in localized resectable gastric cancer. Methods: Patients aged 18–75 years with histologically confirmed gastric adenocarcinoma (stage T1-3/N+1-3, M0, or T4aN+M0) were given eight cycles of XELOX (four preoperatively, four postoperatively). Each 3-week cycle comprised capecitabine 1000 mg/m2 twice daily on days 1–14, and oxaliplatin 130 mg/m2 as an intravenous infusion over 2 hours on day 1. Curative D2 gastrectomy was scheduled 2–4 weeks after the last preoperative cycle. Results: Fifty-five patients were enrolled, and one was excluded because of screening failure. R0 resections were achieved in 45 of 54 intent-to-treat patients (93.3%), and four patients received R1 resections. There were no complete responses, 27 (50.0%) partial responses, 24 cases (44.4%) of stable disease, and 3 (5.6%) of progressive disease. The objective response rate was 50.0%. Median follow-up was 31.9 (range 17.4–48.1) months: 29 patients (54.7%) had disease progression, and median progression-free survival was 23.9 (95% confidence interval: 4.0, 31.5) months; median overall survival was not reached. Fifty-four patients completed 209 cycles of preoperative chemotherapy; 42 patients received 133 cycles of postoperative chemotherapy. The rate of grade 3–4 adverse events was 8.5% (29/342 cycles); the most frequent events were neutropenia (9/342 cycles) and leukopenia (14/342 cycles). Conclusions: These findings suggest that combination therapy with cetuximab and oxaliplatin as neoadjuvant chemotherapy, followed by D2 gastrectomy, is effective in late-stage, locally advanced gastric cancer. Clinical trial information: NCT01880632.

Clinical response in the intent-to-treat population (n = 54). Response evaluation criteria in Solid Tumors (RECIST) version 1.1.

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<th>% patients</th>
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<td>Disease control rate</td>
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4023 Poster Session (Board #212), Sun, 8:00 AM-11:30 AM
Final analysis of single-arm confirmatory study of diagnostic endoscopic resection (ER) plus selective chemotherapy (CRT) for stage I locally advanced squamous cell carcinoma (ESCC). JCOG0508. First Author: Keiko Minashita, Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan

Background: For clinical stage I submucosal (cT1b-SM) ESCC, surgery is the standard treatment and CRT is optional. We conducted a single-arm confirmatory study of diagnostic ER plus selective CRT for cT1bN0M0 ESCC and reported the 3-year survival at 2016 ASCO Annual Meeting. We will report the final data of survival analysis after 5-year follow-up with a cutoff date of Aug 2017. Methods: Clinical stage I ESCC (cSM1-2, N0M0), tumor size ≤ 5 cm and circumference ≤ 3/4 was eligible. After ER, additional treatment was selected based on the histological evaluation: Group A, pT1a with negative resection margin and pT1a with LVI-prophylactic CRT; Group C, pT1b with positive resection margin - definitive CRT. CRT consisted of concurrent 2 courses of chemotherapy (5-fluorouracil and cisplatin with 4-week interval, and radiotherapy of 41.4 Gy/23 fr (Group B) or 50.4 Gy/28 fr (Group C). Primary endpoint was 3-year overall survival (OS) of Group B. The sample size was 82 for primary analysis, with one-sided alpha of 0.05 and power of 90%, based on the expected and threshold 3-year OS as 90% and 80%. Final analysis was planned after 5-year follow-up for all pts. Results: Between Dec 2006 and July 2012, 177 pts were enrolled from 23 institutions in Japan. 176 pts underwent ER and Group A/B/C were 74/87/15, respectively. The 3- and 5-year OS of Group B was 90.8% (95% CI; 84.1-94.8) and 89.7% (95% CI; 81.9-94.5). The 3- and 5-year OS of all pts was 92.6% (90% CI; 88.6-95.3) and 90.9% (95% CI; 85.6-94.3). Twenty pts relapsed (Group A; 1 primary, 1 distant LN, Group B; 4 primaries, 8 regional LNs, 2 distant, Group C; 2 regional LNs, 2 distant), 7 pts underwent salvage esophagectomy. Univariable analysis in 83 pts of Group B showed that vascular invasion, one course of chemotherapy, SM2 with LVI had lower progression-free survival. Conclusions: Five-year survival data was comparable to that of surgery or CRT for c stage I ESCC. Vascular invasion, one course of chemotherapy, SM2 with LVI may be a risk factor of recurrence for prophylactic CRT after ER. Clinical trial information: JUMIN000000953.

4024 Poster Session (Board #213), Sun, 8:00 AM-11:30 AM
Updated report of a randomized phase III trial comparing 4 and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1). First Author: Masanori Terashima, Shizuoka Cancer Center, Nagazumi, Japan

Background: Postoperative S-1 for 1 year (corresponding to 8 courses) is one of standard adjuvant chemotherapies for p-stage II gastric cancer. We reported 4-courses of S-1 was inferior to 8-courses of S-1 in terms of relapse-free survival (RFS) for p-stage II gastric cancer at the first planned interim analysis (ESMO2017). Here, we report the updated results of this trial. Methods: Patients with p-stage II except T1Nany and T3NO (7th edition of TNM), performance status 0-1, R0 resection were randomized either 8-courses or 4-courses. Primary endpoint was RFS. The total sample size was determined to be 1,000 with a non-inferiority margin of hazard ratio (HR) of 1.37, with one-sided alpha of 5% and power of 80%. Results: Between Feb 2012 and Mar 2017, 590 (295 in each arm) patients were enrolled and analyzed. Proportion of patients in treatment of S-1 at 6 months was 76.9% for the 8-courses and was 80.1% for the 4-courses, and that at 12 months was 59.3% in 8-courses. The RFS at 3 years was 89.8% for 4-courses and 93.1% for 8-courses (HR 1.84, 95% CI 0.93-3.63). The overall survival at 3 years was 92.6% for 4-courses and 96.1% for the 8-courses (HR 3.34, 95% CI 1.22-9.12). The cumulative incidence of recurrence at 3 years was 7.7% for the 8-courses and 5.5% for the 4-courses (HR 1.59, 95% CI 0.75-3.39). For safety analysis, 8 patients who did not receive the protocol treatment were excluded. Adverse events were mild in both arms, but slightly less frequent in the 4-courses arm than in the 8-courses arm. Conclusions: The updated primary results confirmed that non-inferiority of 4-courses S-1 were not demonstrated in RFS. S-1 adjuvant chemotherapy for p-stage II gastric cancer should be continued for one year considering the efficacy, acceptable toxicities, and high compliance. Clinical trial information: UMIN000007306.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Immunotherapy with the PD-1/PD-L1 inhibitors has produced potent long-lasting antitumor activity in patients with esophageal cancer. However, as responses are observed in only a fraction of patients and treatment responses are sometimes transient, additional strategies to reverse elements of immune suppression imposed by cancer are needed. IDO1 is the primary enzyme that generates immunosuppressive metabolite, and IDO1 inhibitors are being intensively developed and tested in clinical trials for various human cancers. Nonetheless, prognostic and immunological features of PD-L1 and IDO1 expressions remain still unknown in esophageal cancer. Methods: Using a non-biased database of 305 curatively resected esophageal cancers, PD-L1 expression, IDO1 expression, CD8 expression, and FOXP3 (a maker of Treg) were evaluated by immunostaining. The term “prognostic marker” is used throughout this article according to the RE-MARK Guidelines. Results: Compared with PD-L1 negative cases (n = 252), PD-L1 positive cases (n = 53) showed significantly worse overall survival (log-rank P = 0.016; hazard ratio (HR); 1.7: 95% confidence interval (CI); 1.08-2.61; P = 0.024; multivariate HR: 1.69. 95% CI: 1.05-2.67; P = 0.033). The effect of PD-L1 was not significantly modified by any clinical factors (P > 0.05 for all interactions). Second, IDO1 expression was significantly correlated with poor overall survival (log-rank P = 0.0041), low CD8 expression (P = 0.044) and high counts of FOXP3 positive cells (P = 0.02). Importantly, a stratification based on PD-L1 expression and IDO1 expression was also significantly associated with overall survival (log-rank P = 0.0013); both positive cases experienced unfavorable clinical outcome compared with other cases. Conclusions: PD-L1 and IDO1 expressions were associated with clinical outcome in esophageal cancer patients. In addition, the subgroups defined on the basis of PD-L1 and IDO1 status possessed diverse prognostic features. PD-L1 and IDO1 expressions in esophageal cancer may serve as a predictive tissue biomarker and may be used for patient selection in clinical trials of drugs targeting the PD-L1 pathway and IDO1.
Biomarker study for trastuzumab continuation beyond progression in a randomized phase II trial of weekly paclitaxel + trastuzumab in patients with HER2+ (pre-T) advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum (WJOG7112G).

Background: WJOG7112G study, comparing paclitaxel plus trastuzumab (PT; n = 64) with paclitaxel alone (P; n = 45), did not demonstrate survival benefit of trastuzumab continuation beyond progression (TBP) in HER2-positive gastric or gastro-esophageal junction cancer. As a collaborative study, we analyzed biomarkers possibly associating with TBP efficacy.

Methods: We prospectively collected tumor tissues and serum samples after progression of prior chemotherapy from patients enrolled into the WJOG7112G trial. HER2 status in tumor tissue was examined by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). HER2 amplification in serum cell-free DNA (cfHER2amp) was assessed by droplet PCR. Serum level of neuregulin-1 (NRG1), a ligand of HER3 and an activator of HER2 heterodimerization, was measured by ELISA.

Results: Tumor tissues and serum samples were collected from 18 (P; n = 10, PT; n = 8) and 68 (P; n = 33, PT; n = 35) patients, respectively. IHC 3+, 2+, and FISH positive tumors were 3 (17%), 3 (17%), and 8 (44%), respectively. All IHC 3+ and 2+ tumors were FISH positive except 1 unevaluable tumor. cfHER2amp was positive in 41 (60%) patients (n = 21, PT; n = 20). There was no benefit of TBP in progression-free survival (PFS) regarding HER2 status. Both cfDNA-HER2 amplification (hazard ratio (HR) 0.93, 95% CI 0.49 - 1.76, and HR 0.81, 95% CI 0.36 - 1.85, respectively). Serum NRG1 was detectable in 16 (24%) patients, and significantly associated with shorter survival in patients treated with PT (median PFS: 2.6 and 3.8 months, log-rank test p = 0.045, median OS: 7.4 and 10.9 months, p = 0.013). Two thirds of patients lost HER2 positivity after the progression of prior trastuzumab-containing chemotherapy. Serum cfHER2amp was not associated with the efficacy of TBP. NRG1 might be a resistant marker to TBP in HER2 positive gastric or gastro-esophageal junction cancer. Clinical trial information: UMIN000009297.
A phase II study of perioperative intraperitoneal paclitaxel plus S-1/paclitaxel for curatively resectable gastric cancer with serosal invasion: The GAPS study. First Author: Seiji Ito, Aichi Cancer Center Hospital, Aichi, Japan

Background: The prognosis of gastric cancer with serosal invasion is extremely poor. Despite various perioperative adjuvant therapies, peritoneal recurrence is still difficult to control. Since the clinical efficacy of intraperitoneal (IP) paclitaxel (PTX) was suggested for the treatment of gastric cancer with peritoneal metastasis and positive cytology, IP PTX is a promising strategy for curatively resectable gastric cancer with serosal invasion. This multicenter, phase II study evaluated the efficacy and safety of IP PTX plus S-1/PTX for this target. Methods: Eligibility criteria included pathologically confirmed gastric adenocarcinoma with serosal invasion, but no peritoneal or distant metastases. Patients received three courses of preoperative IP PTX plus S-1/PTX (IP PTX 20 mg/m², intravenous PTX 50 mg/m² on days 1 and 8, and S-1 80 mg/m²/day on days 1-14, q3 weeks) followed by D2 gastrectomy, and they then received three courses of IP PTX plus intravenous PTX postoperatively. The primary endpoint was the proportion of the completion of protocol treatment (% protocol completion). Secondary endpoints were safety, overall survival, and the response rate (RR). The sample size was estimated to be 50 cases, under the hypothesis of expected % protocol completion of 80% and threshold % protocol completion of 60% with one-sided testing at the 2.5% significance level and power of 80%. Results: Between May 2014 and August 2016, 51 patients were enrolled. Among the 51 eligible patients with a median age of 66 years, 41 completed the protocol treatment (80.4% completion; 95% confidence interval 66.9-90.2%, p = 0.0016). During perioperative chemotherapy, grade 3/4 neutropenia occurred in 31.4%, and grade 3/4 non-hematological adverse events occurred in 19.6%. The incidence of adverse events related to surgery was 19.1%. There were no treatment-related deaths. Median follow-up for long-term survival is continuing. The clinical RR of preoperative chemotherapy was 71.4% (5/7). The pathological RR (residual tumor < 2/3) was 68.1% (32/47). Conclusions: Perioperative IP PTX plus S-1/PTX is a safe and promising treatment for gastric cancer with serosal invasion.

Clinical trial information: UMIN000013109.

Oxaliplatin, 5FU and nab-paclitaxel as neoadjuvant regimen in patients with resectable oesogastric adenocarcinoma: A GERCOR phase II study (CALGAD). First Author: Sarah Sophie Watson, Institut Mutualiste Montsouris, Paris, France

Background: Peri-operative chemotherapy is the standard of care in Resectable OesoGastric Adenocarcinoma (ROGA), with several validated regimens such as Cisplatin-5FU, FOLFOX, ECOrx, or FLOT. Nanoparticle-bound (Nab) paclitaxel is active in OGA. Tumor regression grade (TRG) is an objective parameter for assessing efficacy of neoadjuvant chemotherapy (NACT). The study objective was to evaluate TRG with Nab-paclitaxel combined with FOLFOX in ROGA patients (pts). Methods: HER2-negative ROGA pts over 18 yrs received Nab-paclitaxel (150mg/m²) and FOLFOX (oxaliplatin 85 mg/m²; 5FU 2400mg/m² over 48h, and leucovorin 400mg/m²) on D1 q2w for 6 cycles in preoperative setting. 6 postoperative cycles were followed by 2 cycles of Nab-paclitaxel (100 mg/m²; Day 1) with RAM (8 mg/kg, Days 1, 8) or placebo (PBO; Days 1, 8) in Part A (21-day cycle); patients received paclitaxel (80 mg/m²; Days 1, 8, 15) and RAM (8 mg/kg, Days 1, 15) in 8 Arms. Randomized, double-blind, phase 2 study of S-1 plus oxaliplatin (SOX) with or without ramucirumab (RAM) as first-line therapy followed by paclitaxel plus S-1 as second-line therapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma (AGC). First Author: Kei Muro, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Background: RAM (a human IgG1 antibody against vascular endothelial growth factor receptor-2) plus paclitaxel has been found to improve overall survival compared with paclitaxel alone as second-line therapy in patients with AGC. This Asian phase 2 study (RAINSTORM) assessed whether adding RAM to SOX as first-line therapy could improve progression-free survival (PFS). Methods: Chemotherapy-naïve patients with AGC who were randomized to receive SOX (5-1: 80-120 mg/day, twice daily, Days 1-14; oxaliplatin: 100 mg/m², Day 1) with RAM (8 mg/kg, Days 1, 8) or placebo (PBO; Days 1, 8) in Part A (21-day cycle); patients received paclitaxel (80 mg/m²; Days 1, 8, 15) and RAM (8 mg/kg, Days 1, 15) in Part B (28-day cycle). PFS (primary endpoint), objective response rate (ORR), disease control rate (DCR), and safety for Part A are reported. The PFS hazard ratio (HR) was estimated using a stratified Cox regression model, with a stratified log-rank test. P-value of < 0.2 interpreted as RAM+SOX being a useful regimen for first-line therapy in patients with AGC. Results: RAM+SOX (n = 96) did not show an improvement in PFS compared with PBO+SOX (n = 93) (median PFS: RAM+SOX, 9.4 vs. PBO+SOX, 10.6 months; HR: 0.98, 95% CI: 0.80-1.20; P = 0.80). Among patients with measurable disease, the ORR was 52.6% and 50.0% (odds ratio [80% CI]: 1.37 [0.84, 2.24]; P = 0.420), and the DCR was 90.9% and 87.0% (odds ratio [80% CI]: 1.53 [0.68, 3.43]; P = 0.501), in the RAM+SOX (n = 55) and PBO+SOX (n = 54) arms, respectively. The most common treatment-emergent adverse events in both arms were peripheral sensory neuropathy (RAM+SOX: 58.3%; PBO+SOX: 75.3%), decreased appetite (56.3%; 62.4%), and nausea (56.3%; 39.8%). The most common adverse events of special interest in the RAM+SOX arm (vs PBO+SOX arm) were bleeding/ hemorrage events (37.5% vs 23.7%), hypernephrosis (29.2% vs 12.9%), and proteinuria (25.0% vs 15.1%). Conclusions: Addition of RAM using a new starting dose regimen (8 mg/kg, Days 1 and 8 every 21 days to a standard SOX regimen did not improve PFS in patients with AGC. Clinical trial information: NCT02539225.
**4037 Poster Session (Board #226), Sun, 8:00 AM-11:30 AM**

**Psychiatric comorbidities among esophageal cancer survivors in South Korea: A nationwide population-based, longitudinal study.** First Author: Jaesung Heo, Department of Radiation Oncology, Ajou University School of Medicine, Suwon, Korea, Republic of (South)

**Background:** Esophageal cancer has a relatively poor prognosis (< 15% overall 5-year survival), owing to a lack of initial symptoms and delayed diagnosis. Also, patients with this fatal cancer tend to have a high rate of mental disorders. The psychological problems could cause treatment compliance and could increase mortality in cancer survivors.

**Methods:** The aim of this longitudinal study was to analyze the prevalence of mental disorders among esophageal cancer survivors using claims data in South Korea. We confirmed mental disorders in a nationwide cohort of 8,879 patients who were diagnosed with esophageal cancer between January 1, 2010 and December 31, 2014. We categorized the prevalence of mental disorders based on the age and the time of diagnosis.

**Results:** In esophageal cancer, a total of 738 patients were diagnosed with a mental disorder, 1 year prior to the cancer treatment. Of these patients, 231 were diagnosed with depression (31.3%) and 245 with anxiety (33.2%) during their first visit. The overall frequency of mental disorders peaked within 2 months after the cancer treatment. The highest rate of increase after treatment was confirmed in stress reaction/adjustment disorders. As age and sex were a significant predictive factor for mental disorders (p = 0.05). Female patients were at a higher risk for mental disorders (hazard ratio: 1.30, p = 0.002), whereas patients with initial treatment as surgery were more likely to have mental disorders compared with radiotherapy (hazard ratio: 1.55, p < 0.001).

**Conclusions:** Incidence of cardiotoxicity (2.1%) was detected and it was not related to survival. HFSR + 4.07, 3.06 of life for esophageal cancer survivors. Diagnosis and intervention for psychological distress could increase the quality of life for esophageal cancer survivors.

### The frequency of mental disorders in esophageal cancer survivors (N = 8,879).

<table>
<thead>
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<th>Age</th>
<th>Total number of esophageal cancer</th>
<th>Mental disorder</th>
<th>Substance abuse</th>
<th>Depressive disorder</th>
<th>Anxiety disorder</th>
<th>Stress/adjustment disorder</th>
<th>Somatoform/conversion disorder</th>
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<td>129</td>
<td>231</td>
<td>232</td>
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**4039 Poster Session (Board #228), Sun, 8:00 AM-11:30 AM**

**Development of non-hematological adverse events in apatinib-treated gastric cancer after their association with clinical outcome: Results from a phase IV study.** First Author: Yi Ba, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

**Background:** Apatinib, a multicenter Phase IV study, is conducting to evaluate apatinib as third-line or beyond therapy in a routine practice setting of gastric cancer patients (pts). **Methods:** This analysis was undertaken to evaluate the non-hematological adverse events (AEs), and to explore their potential associations with survival.

**Results:** This analysis was based on 1,468 pts as of 12/21/2017. The most common non-hematological AEs were hypertension (HTN: 22.8%), proteinuria (PTN: 18.1%), fatigue (16.7%), diarrhea (11.9%) and hand-foot-skin reaction (HFSR: 9.7%), irrespective of the relationship with medication. They were not correlated with progression free survival (PFS); however, pts with diabetes or HFSR had a statistically longer overall survival (OS) (8.41 vs. 6.14 mos, p = 0.0458; 8.31 vs 5.98 mos, p < 0.0001) (Table). After adjusting for baseline characteristics and treatment dose, presence of HFSR was an independent predictor for prolonged OS (p = 0.004).

**Conclusions:** Occurrence of HFSR could be an effective prognostic factor for OS of esophageal cancer survivors.

### Relationship between non-hematological AEs and survival.

<table>
<thead>
<tr>
<th>Substance</th>
<th>PFS, 95%CI (mos)</th>
<th>OS, 95%CI (mos)</th>
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<td>PTN</td>
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<td>5.78, 4.92-7.23</td>
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<td>Fatigue</td>
<td>4.27, 3.81-4.76</td>
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<td>Diarrhea</td>
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**4040 Poster Session (Board #229), Sun, 8:00 AM-11:30 AM**

**Role of neoadjuvant chemotherapy or chemoradiotherapy in oesophageal carcinoma.** First Author: Herui Ya, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

**Background:** The role of neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACR) in patients with oesophageal carcinoma continues to be debated. This study aimed to assess the comparative efficacy and safety of NAC or NACR for oesophageal carcinoma. **Methods:** Randomized clinical trials reporting on NAC or NACR with local operable oesophageal carcinoma were identified. The primary endpoint was overall survival (OS). All trial results were combined and analysed using a fixed or random-effects meta-analysis. Quality of evidence was appraised with GRADE criteria. The PROSPERO registry number is CRD42017072242. **Results:** 40 trials with 8,393 patients were included. High-quality evidence indicated that NAC was associated with a significant benefit on OS (hazard ratio [HR] 0.86, 95% CI 0.80 to 0.92; p < 0.000) and relapse-free survival (RFS) (HR 0.78, 95% CI 0.72 to 0.84; p = 0.0000) versus surgery alone, with an absolute difference at 5 years of 10% (6 to 13), and the treatment effect on survival was especially in favor of adenocarcinoma (HR 0.81, 0.72 to 0.91), but no significant difference in squamous-cell carcinoma ( SCC) (HR 0.93, 0.81 to 1.08). High-quality evidence revealed that treatment with NACR, as compared with surgery alone, prolonged OS (HR 0.74, 95% CI 0.67 to 0.81; p = 0.0000) and RFS (HR 0.74, 95% CI 0.65 to 0.84; p = 0.0000), corresponding to an absolute difference at 5 years of 14% (9 to 20), with similar survival for different histological types of tumor: 0.73 (0.65 to 0.83) for SCC and 0.73 (0.62 to 0.93) for adenocarcinoma. There was moderate-quality evidence that the overall direct and indirect comparison of NACR with NAC showed a survival advantage (HR 0.83, 95% CI 0.73 to 0.94; p = 0.0044), with results for SCC (HR 0.74, 0.63 to 0.89) and for adenocarcinoma (HR 0.74, 0.63 to 0.89). **Conclusions:** The SWOG study confirmed that a significant clinical benefit is evident for NACR in both adenocarcinomas and SCC of the esophagus, and NAC in patients with adenocarcinoma of the oesophagus. To our knowledge, this is the first evidence-based finding which provided advantage of NACR over NAC in patients with oesophageal carcinoma.

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Laparoscopic-assisted versus open D2 distal gastrectomy for advanced gastric cancer: Five-year overall survival and morbidity results from a randomized phase II multicenter clinical trial (COACT 1001). First Author: Young Woong Kim, National Cancer Center, Goyang, Korea, Republic of (South)

Background: For advanced gastric cancer (AGC), D2 gastrectomy is the standard treatment. However, a laparoscopic D2 gastrectomy (LG) is technically challenging surgery. Our previous report of COACT 1001 study, which is randomized phase II study to evaluate the feasibility of LG compared with open surgery (OG) for AGC, showing primary endpoint of non-compliance of lymph node dissection and three-year disease-free survival supported role of LG for AGC. Herein we report five-year overall and disease-free survival outcome of the study. Methods: Patients with cT2-4a and cN0-2 (AJCC 7th staging system) distal gastric cancer were randomly assigned but not blindly assigned to LG or OG groups. Patients were followed up for recurrence and survival for 5 years. Results: Between Jun 2010 and Oct 2011, 204 patients were enrolled and underwent either LGD (n = 105) or ODG (n = 99). Of those, 196 patients (100 in LADG and 96 in ODG) were included in the intention-to-treat analysis. There were no significant differences in the five-year overall survival between LG and OG groups (85.1% vs 84.1%, respectively; p = 0.749). In the subgroup analysis, five-year overall survival was not different in between the groups according to the clinical stage (stage I: 95.7% vs 95.5%; p = 0.988, stage II: 96.1% vs 84.6%; p = 0.057, stage III: 48.3% vs 74.1%; p = 0.156) and pathological stage (stage I: 97.5% vs 94.4%; p = 0.512, stage II: 100% vs 90.8%; p = 0.059, stage III: 48.7% vs 72.7%; p = 0.151, stage IV: 100% vs 0%; p = 0.181). Five-year disease-free survival also was not significantly different between two groups (74.5% vs 78.7%, respectively; p = 0.604). The trend of overall and disease-free survival was favorable for LG in stage II but OG in stage III. Conclusions: LG was feasible for AGC based on the five-year overall and disease-free survival rate. Further research should be done in large scale for stage III gastric cancer. Clinical trial information: NCT01988204.

Methods: A cohort of 491 patients who underwent R0 resection for locally-advanced gastric cancer between 2000 and 2009 at 12 institutions in northern Japan from the Northern Japan Gastric Cancer Consortium was included. H. pylori infection status was assessed from paraffin-embedded formalin-fixed samples. Overall survival (OS) and disease-free survival (DFS) in surgery-only (Surgery) and adjuvant chemotherapy (S1) groups were analyzed. A propensity score matching was employed to control for confounding factors by indication. To evaluate the local immune response with curative intent, the infectious mechanism is crucial since the potential effect may result in a survival benefit for life-threatening diseases. To understand the potential risk, we investigated the impact of PDT on survival in a post-hoc analysis. Results: Study blinding was continued until final OS data-lock. Investigators could choose any treatment for PDT. To compare OS from randomization as well as from the start of second-line (2L) treatment (Landmark OS), PDT were categorized into RAM or Non-RAM containing, RAM- paclitaxel (PTX), or All Others. Analyses were stratified by ECOG PS, primary tumor location, disease measurability & geographic region. Results: 326 pts were randomized to chemo+RAM (8 mg/kg iv D1, D8, every 21 d) & 319 pts to chemo+PL (ITT, N = 645). The primary endpoint of investigator-assessed PFS was met (HR, 0.75; 95% CI 0.61-0.94; p = 0.011; median, 5.7 vs 5.4 mo) while no OS benefit was observed (HR, 0.96; 95% CI 0.80-1.16; p = 0.68; median, 11.2 vs 10.7 mo). 150 pts (46%) in the RAM arm received PDT compared to 164 (51%) in the PL arm. Subgroup results are summarized in Table. Conclusions: PDT use was balanced in both arms. OS from Randomization and Landmark OS is numerically higher in patients who received RAM containing PDT compared to Non-RAM PDT. Despite the small sample size, the results are consistent with previously described OS benefit with RAM+PTX as 2L therapy. Clinical trial information: NCT02314117.

**Summary of PDT** Results (any subsequent line).

<table>
<thead>
<tr>
<th>Median months</th>
<th>Median months</th>
<th>n</th>
<th>Median months</th>
<th>Median months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PDT pts</td>
<td>13.4 (12.6, 15.2)</td>
<td>314</td>
<td>All Non-PDT pts</td>
<td>7.1 (6.5, 7.8)</td>
</tr>
<tr>
<td>OS from Randomization</td>
<td>16.2 (13.7, 16.7)</td>
<td>40</td>
<td>Non-RAM Containing</td>
<td>13.2 (11.9, 16.3)</td>
</tr>
<tr>
<td>OS from Randomization</td>
<td>14.9 (12.6, 18.9)</td>
<td>53</td>
<td>Non-RAM Containing</td>
<td>13.0 (11.4, 15.0)</td>
</tr>
<tr>
<td>Landmark OS</td>
<td>16.3 (15.0, 16.6)</td>
<td>37</td>
<td>All Others</td>
<td>14.0 (11.8, 16.2)</td>
</tr>
<tr>
<td>Landmark OS</td>
<td>8.6 (5.2, 10.9)</td>
<td>46</td>
<td>All Others</td>
<td>6.8 (5.5, 7.8)</td>
</tr>
</tbody>
</table>

\* = overall, the most frequent PDTs included: PTX, RAM, & irinotecan in both arms.
Background: Gastric cancer (GC) is one of the most common tumors in China. The ToGa study has shown trastuzumab in combination with fluoropyrimidine plus cisplatin prolonged overall survival (OS) in patients with HER2-positive advanced GC (AGC). Although docetaxel plus capcitabine (DX) is a standard regimen for AGC, combination of trastuzumab plus DX has not been studied. In this study, the efficacy and safety of trastuzumab in combination with DX was evaluated in Chinese patients with HER2-positive advanced GC.

Methods: This phase II, multi-center, open label, single arm study enrolled patients with HER2-positive metastatic gastric or gastro-esophageal junction adenocarcinoma who have not received prior treatment for metastatic disease. Patients were treated with trastuzumab (8 mg/kg loading dose followed by 6 mg/kg on day 1), capcitabine (1000mg/m² twice daily, d1-14) and docetaxel (60mg/m² on day 6) for 3 cycles. Primary endpoint is progression-free survival (PFS) and secondary endpoints are objective response rate (ORR), OS and toxicity profiles.

Results: 67 patients with AGC were enrolled from 14 centers and 64 patients were in Full Analysis Set (FAS). The median OS was 8.1 months (95% CI: 5.6-12.8) and the median OS was 20.9 months (95% CI: 15.1-33). Response was evaluated in 59 patients (5 missing in FAS), five patients achieved CR and thirty-five patients achieved PR, the ORR was 67.8%. In 67 patients who received at least one cycle of treatment, the most common adverse events of grade 3 or above were neutropenia (17.9%), leucopenia (19.4%), hand-foot syndrome (9%), febrile neutropenia (4.5%) and anemia (3%).

Conclusions: Combination of trastuzumab and docetaxel/capcitabine is a well-tolerated and highly effective regimen in patients with HER2-positive advanced gastric cancer. Clinical trial information: NCT02004769.
4049 Poster Session (#238), Sun, 8:00 AM-11:30 AM
Pembrolizumab for patients with previously treated metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: Phase 2 KEYNOTE-180 study. First Author: Masashi A. Shirah, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY
Background: Effective therapy for patients (pts) with metastatic esophageal cancer progressing after at least 2 lines of prior therapy is an unmet need. The phase 2, open-label, KEYNOTE-180 (NCT02559687) study evaluated the activity of pembrolizumab (pembro) in pts with previously treated, advanced/metastatic adenocarcinoma (EAC) or squamous cell carcinoma (ESCC) of the esophagus or Siewert type 1 adenocarcinoma (EAC/SC) with metastatic esophageal junction. Methods: Eligible pts with metastatic esophageal cancer, ≥2 prior lines of therapy, and tumor samples evaluable for biomarker expression, received pembro 200 mg Q3W for up to 2 years, or until disease progression, unacceptable toxicity, or withdrawal. Tumor response was assessed Q2W (RECISTv1.1, central review). PD-L1+ pts had combined positive score ≥10 using IHC (22C3 antibody). Primary endpoint was objective response rate (ORR). Secondary endpoints included safety, DOR, PFS, and OS. Results: Of 121 pts enrolled (Jan 12, 2016 to March 21, 2017), 100 (83%) were male, median age was 65 years (range 33-87), 63 (52%) had ESCC, and 58 (48%) had PD-L1+ tumors. As of September 18, 2017, median duration of follow-up was 5.8 mo (range, 0.2-18.3). ORR (CR+PR) was 10% (95% CI, 5%-17%); 12 (10%) pts had PR, 25 (21%) SD. Median DOR was not reached (IQR range, 1.9+ mo to 14.4+ mo), and median PFS was 2 mo (95% CI, 1.9-2.1) with 6-mo PFS rate of 16% (95% CI, 10-23). Median OS was 5.8 mo (95% CI, 2.2-12) with 12-mo OS rate of 32% (95% CI, 20-37). In ESCC, ORR was 14% (95% CI, 7-25), and in EAC ORR was 5% (95% CI, 1-14). In PD-L1+ pts, ORR was 14% (95% CI, 6-25) and in PD-L1- pts ORR was 6% (95% CI, 2-16). Overall, 15 (12%) pts had treatment-related grade 3-5 AEs. Five (4%) pts discontinued due to a treatment-related AE. There was one treatment-related pneumonitis death. Pembro provided durable clinical benefit with manageable safety for pts with heavily pretreated esophageal cancer. A phase 3 study, KEYNOTE-181 (NCT02564263), to evaluate the activity of pembro versus standard therapy in pts with metastatic esophageal cancer progressing after first-line therapy is ongoing. Clinical trial information: NCT02559687.

4051 Poster Session (#240), Sun, 8:00 AM-11:30 AM
A single-arm confirmatory study of definitive chemoradiotherapy (dCRT) including salvage had trastuzumab in patients (pts) with clinical cStage II/III EC: Pembrolizumab (pembro) versus standard treatment (ST) for pts refusing surgery (S) in Japan based on the previous trial (JCOG9906). However, poor survival, high incidence of late toxicities, and severe complications of salvage S are problems. We conducted this trial of CRT modifications including salvage treatment to reduce CRT toxicities and facilitate salvage treatment to improve survival. Methods: EC pts hoping esophage preservation as initial treatment, with cStage II/III (UICC 6th, non-T4), PS 0-1, and age 20-75 years were eligible. Chemotherapy (CT) was CDDP (75 mg/m² on days 1, 29) and 5-FU (1000 mg/m²/d on days 1-4, 29-32). RT was administered to a total dose of 50.4 Gy with elective nodal irradiation of 41.4 Gy. Good responders after dCRT received additional 1-2 cycles of CT. For residual or recurrent disease, salvage endoscopic resection (ER) or S was performed based on the prespecified criteria. The primary endpoint was 3-year OS. Key secondary endpoint was salvage treatment related toxicity. The sample size was 95, with one-sided alpha of 5% and power of 80%, expected and threshold 3-year OS as 55% and 42%. Results: From 4/2010 to 8/2014, 96 pts were enrolled, two were ineligible and 94 were included in efficacy analysis (Mif, 84/10, Age, median 63 (range 48-75); cStage IIA/IIB/IIC, 22/38/4). Two cycles of CT and RT were completed in 93 pts (99%). Complete response was achieved in 55 pts (59%). Salvage ER and S were performed in 5 (5%) and 25 pts (27%). RT resection of salvage S was achieved in 19 (76%). 3-year OS was 74.2% (90% CI 65.9-80.8%). 3-year progression-free survival and esophagectomy-free survival were 57% (95% CI 46.3-66.3%) and 65% (95% CI 52.5-72.4%). No complications occurred after salvage ER. Five pts (20%) showed ≥ grade 3 operative morbidities and 1 treatment related death due to bronchus-pulmonary artery fistula occurred after salvage S. Only 9 pts (9.6%) showed grade 3 late toxicities. Conclusions: This combined modality treatment of dCRT for salvage treatment could be a new standard treatment for EC pts hoping to esophage preservation. The sample size was 95, with one-sided alpha of 5% and power of 80%, expected and threshold 3-year OS as 55% and 42%.

4052 Poster Session (#241), Sun, 8:00 AM-11:30 AM
Companion of clinical outcome and safety after minimally invasive esophagectomy: Ivor Lewis versus McKeown—A real-world multicenter observational study from China. First Author: Yang Liu, Department of Thoracic Surgery, Chinese PLA General Hospital, Beijing, China
Background: Ivor Lewis (Iv) and McKeown (Mc) are two commonly used minimally invasive esophagectomy. Currently, there are limited data to compare effectiveness and safety between Iv and Mc in China. Methods: We conduct the study based on a national collaborative prospective esophageal cancer (EC) database (designed by LinkDoc Technology Co, Ltd.), EC patients who underwent Iv or Mc esophagectomy from Jan.2010 to Jun.2017 and pathologically confirmed stage I–III with middle thoracic and lower thoracic esophagus were enrolled. Log-rank test was used in the comparison of the two surgery groups. And Cox’s proportional hazard models and logistic regression were used in the factors analyses. Results: Total 1862 patients (1447 males and 415 females) were enrolled, mean age of 61.4±8.7.9. Among the patients, there were 97.2% squamous cell carcinoma, 1% adenocarcinoma and 1.8% others. 667 were performed with Iv esophagectomy and 1195 patients with Mc esophagectomy. Number of lymph nodes examined was 14.1±9.02 in Iv group, compared with 21.5±11.57 in Mc group, p<0.05. Recurrence rate was 12.3% in Iv group and 7.6% in Mc group, p<0.05. The 5 years overall survival (OS) was 51% in Iv group and 59% in Mc group, p<0.05. Multivariate analysis showed that risk factors for EC recurrence after esophagectomy include operation type (Iv vs Mc, odds ratio 1.70, CI 1.187-2.430), N stage and T stage, p<0.05. Operation type (Iv vs Mc, HR 1.49, CI 1.153-1.928), N stage and T stage were hazard factors for OS in analysis of multivariate Cox’s proportional hazard models, p<0.05. Especially, for the subgroup diagnosed as stage T3 at middle thoracic esophagus, Recurrence and OS were significantly different according to surgery type. Median blood loss was 300 mL in Iv group compared with 200 mL in Mc group, p<0.05. Post-operative complications was significantly less in Iv group, p<0.05. Conclusions: Our data showed that Mc is preferred with better lymphadenectomy, lower recurrence and improved survival compared with Iv, especially for patients diagnosed as stage T3 at middle thoracic esophagus. And the survival rate was significanly improved than the surgery type of Mc.
**4053** Poster Session (Board #242), Sun, 8:00 AM-11:30 AM

Final results of a phase 3 study of comparing paclitaxel plus 5-fluorouracil versus cisplatin plus 5-fluorouracil in chemoradiotherapy for locally advanced esophageal squamous cell carcinoma (ESCC) patients. This trial aimed to assess the efficacy and safety of the paclitaxel plus 5-FU (TF) regimen compared to cisplatin plus 5-FU (PF) regimen for ESCC patients. **Methods:** ESCC patients presenting with stage IIIa to IVa were enrolled in a prospective multicenter phase II study. Patients were randomized to either TF or PF group. Patients in TF group were treated with 5 cycles of weekly TF (5-FU 300 mg/m², cisplatin 50 mg/m², d1) in CCR followed by 2 cycles of monthly TF (5-FU 1800 mg/m², cisplatin 75 mg/m², d1) in consolidation chemotherapy. Patients in PF group were treated with 2 cycles of CCR followed by 2 cycles of consolidation chemotherapy with PF (cisplatin 25 mg/m²/d, d1-5, plus 5-FU 1800 mg/m², d1-28). The radiotherapy dose was 61.2 Gy delivered in 34 fractions. The primary end-point was the 3-yr OS. **Results:** 436 ESCC patients (217 assigned to TF group and 219 assigned to PF group) in 6 centers were recruited between April 2012 and July 2015. Median follow-up of patients who survived was 44.6 months (IQR 29.3–72.0). The 3-yr OS was 57% in TF group and 51% in PF group (HR 0.91; 95% CI 0.69-1.18; P = 0.46). No significant differences were recorded in 3-yr DFPS or 3-yr LFPS between TF and PF groups (44.3% vs. 45.3% and 48.8% vs. 49.8%, respectively). TF group had a significant higher incidence of grade 3-4 leukopenia (31.3% vs. 18.3%), dermatitis (5.1% vs. 1.4%), and pneumonitis (9.7% vs. 3.2%), and significant lower incidence of anemia (0.5% vs. 3.2%), thrombocytopenia (0.5% vs. 13.7%), fatigue (6.9% vs. 19.6%), anorexia (1.4% vs. 14.6%), nausea (1.4% vs. 14.2%), and vomiting (2.3% vs. 18.0%) in PF group. There were anorexia (7.5% vs. 9.7%), fatigue (6.9% vs. 20.6%), and anemia (1.4% vs. 3.2%) in TF group died of acute pneumonitis. 1 (0.5%) patient in TF group and 2 (0.9%) patients in PF group died of delayed pneumonitis. **Conclusions:** TF might be an option used in CCR in ESCC patients with a different type of side effects compared with PF, although it did not significantly prolong OS. Clinical trial information: NCT01991139.

**4054** Poster Session (Board #243), Sun, 8:00 AM-11:30 AM

The activity of crizotinib in chemo-refractory MET-amplified esophageal adenocarcinomas: Results from the AcSé-crizotinib program. **First Author:** Thomas Auaric, Department of Gastroenterology, Saint Louis Hospital, Paris, France

**Background:** Crizotinib (czb) is only registered for treating ALK and ROS1-translocated lung cancer. However, Czb is also a MET inhibitor. Several malignancies are characterized by MET amplification (amp). Czb activity in MET-amplified (+) tumors was explored within the French National Cancer Institute (INCa) AcSé program. This included access to tumor molecular diagnostic tests and an exploratory multi-tumor 2-stage design phase II. We herein report the results in patients (pts) with esophageal MET+ adenocarcinomas (adenok). **Methods:** MET expression, on formalin-fixed, paraffin-embedded tumor samples, was screened in 127 centers and analyzed in 28 regional molecular genetic centers. MET+ was evaluated by FISH in tumor samples with IHC scores ≥2+. Pts with tumors showing ≥ 6 MET copies, whatever the METCEN7 ratio, were eligible. Pts were treated with czb 250 mg BID. A two-stage Simon design was planned with a 90% power to detect an objective response rate (ORR) at 8 weeks (w) (CR+PR) above 30% against a 10% rate at the 10% level. The disease control rate (DCR) (CR+PR+SD) was assessed at 16 w. Responses were assessed every 8 w. **Results:** Of 120 pts enrolled in the trial, median age was 62 years (48–80), WHO performance status 0 in 2 pts, 1 in 5 and 2 in 1 pt. At the cut-off date, 1 pt was still treated. Both Czb and chemotherapy were well tolerated. Encouraging efficacy was observed 3 PR and 1 SD, giving an ORR = 42.8% [6.1-79.4]. At 16 w, DCR = 50% [95% CI: 40-60] was achieved in 3/6 evaluable pts. Czb was well tolerated with only 6 grade ≥3 AE pts. The most common AEs, mainly grade 1, were anorexia (76.7%), mild fatigue (54.2%), nausea (12.5%), and vomiting (10%). Grade 3-4 AEs were anorexia (25.8%), fatigue (1.4%), nausea (12.5%), and vomiting (6.2%). grade 3-4 AE of interest (AOI) was fatigue (62.5% for each), vomiting-fatigue-loss of appetite-visual disturbances were significantly lower in TF vs PF group at 3 yr (79% vs. 57%, HR 0.91; 95% CI 0.69-1.18; P = 0.46). The 3-yr OS was 72.0%. The 3-yr OS was 57% in TF group and 51% in PF group (HR 0.91; 95% CI 0.69-1.18; P = 0.46). There were 3 (1.4%) patients in TF group died of acute pneumonitis. 1 (0.5%) patient in TF group and 2 (0.9%) patients in PF group died of delayed pneumonitis. **Conclusions:** TF might be an option used in CCR in ESCC patients with a different type of side effects compared with PF, although it did not significantly prolong OS. Clinical trial information: NCT02034981.

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2017, a total of 144 Patients were protocol eligible with 74 assigned to the
Results:
was 3-year overall survival (OS).
point was 3-year disease-free survival (DFS), and the secondary end point
followed by another 4 cycles of XELOX after RT (CRT arm). The primary end
plus 45 Gy radiotherapy (RT) with capecitabine concurrently, and then
patients after D2 gastrectomy.
Methods:
XELOX combined with concurrent CRT in the treatment of gastric cancer
trial was designed to compare capecitabine plus oxaliplatin (XELOX) versus
Comparing XELOX with nCRT, we conducted a multi-center, randomized, controlled trial to compare 3-year disease-free survival (DFS) rates after laparoscopic distal gastrectomy with D2 lymphadenectomy and open surgery for advanced gastric cancer. Methods: Between September 2012 and December 2014, we randomly assigned 1056 patients with clinical stage T2, T3, or T4a gastric cancer, without bulky nodes or distant metastases to undergo either laparoscopic or open distal gastrectomy with D2 node dissection in a 1:1 ratio. The primary end point was 3-year DFS rate. Results: At 3 years, the DFS rate were 76.5% in the laparoscopic group and 77.8% in the open group; the hazard ratio (HR) for recurrence was 1.069. The 3-year overall survival rates were similar in the two groups (83.1% in the laparoscopic group and 85.2% in the open group; HR for death, 1.162). The clinical recurrence types were comparable between two groups (P = 0.213). Conclusions: The long-term oncological outcomes of laparoscopic distal gastrectomy with D2 lymphadenectomy were non-inferior to those of the conventional open surgery for the patients with advanced gastric cancer. (CLASS-01 trial) Clinical trial information: NCT01690309.

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Selumetinib plus docetaxel as second-line chemotherapy in KRAS mutant, KRAS amplified or MEK signature gastric cancer patients: with or without low MEK signature

Methods: Selumetinib was administered orally 75mg twice a day continuously. Docetaxel was administered as an IV infusion over 1 hour at 60 mg/m2 every 3 week of a 21 days schedule. The primary objective was to investigate response rate (RR) and secondary objectives were to perform pre-planned analysis using ctDNA and tumors to identify an optimal biomarker for selumetinib. Results: Twenty seven patients who were identified through the VIKTORY screening to harbor KRAS mutation, KRAS amplification or MEK signature were enrolled onto the study. Of 27 patients, 12 had GC harboring KRAS mutation and two KRAS amplification. The remaining 13 patients were KRAS wild type with either low MEK signature (N = 7) or high MEK signature (N = 6). Only 1 of 12 KRAS mutant patients was KRAS signature. Of 25 patients who received the study drug, there were 7 partial responses (PRs), 8 stable diseases (SDs), 6 progressive diseases (PDs) and 4 non-evaluable diseases. The overall RR for the study combination was 28.0% (95 CI, 0.12 – 0.49). The most commonly observed any grade adverse events (AEs) were diarrhea (7/43 or 16.3%), rash (7/43 or 16.3%) and second common AE was diarrhea (5.5%) which was all grade 1/2. In bio-marker analysis, the two patients with had typical KRAS mutation (G12) or KRAS amplification with high MEK signature achieved a PR from selumetinib/docetaxel. However, three with atypical KRAS mutation (i.e. A146T/G12D/R136C) or RAS gene alterations. Especially, the specific subset of patients with patients with KRAS mutation or KRAS amplification with high MEK signature were likely to benefit from selumetinib/docetaxel. Clinical trial information: NCT02448290.

Conclusions: Selumetinib plus docetaxel as second-line therapy revealed the useful efficacy and tolerable safety in GC patients with MEK signature or RAS gene alterations. Especially, the specific subset of patients with patients with KRAS mutation or KRAS amplification with high MEK signature were likely to benefit from selumetinib/docetaxel. Clinical trial information: NCT02448290.
Investigation of PD-L1 expression and response to pembrolizumab (pembro) in gastric cancer (GC) and cervical cancer (CC) using combined positive score (CPS) and tumor proportion score (TPS). First Author: Karina Kulangara, Dako North America, Agilent Technologies, Carpinteria, CA

Background: TPS, the percentage of viable tumor cells with partial or complete membrane staining at any intensity, has been invaluable for assessing PD-L1 expression in non-small cell lung cancer (NSCLC) and identifying patients (pts) likely to respond to anti-PD-1/PD-L1 therapy. However, TPS has limited utility beyond NSCLC. We investigated the predictive value of TPS and CPS and their association with response to pembro in pts with GC and CC. Materials and Methods: Tumor samples from pts with previously treated GC (KEYNOTE-059, NCT02335411) or CC (KEYNOTE-158, NCT02628067) were analyzed for PD-L1 expression per an investi-gationally-use-only-labeled version of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). Response was assessed per RECIST v.1.1 by independent review. External reproducibility of CPS, the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100, was assessed. Results: Response, prevalence, positive predictive value (PPV), and negative predictive value (NPV) for CPS and TPS at cutoffs of 1 (TPS1, CPS1) and 10 (TPS10, CPS10) are shown in the table. Response to pembro was significantly associated with CPS (P = 0.024) in GC, whereas response to pembro was significantly associated with CPS (P = 0.008) and TPS (P = 0.023) in CC. Intersite and interobserver overall agreement assessments of external reproducibility for CPS were 92.0% (95% CI, 87.4-96.3) and 96.6% (95% CI, 94.0-98.7), respectively, in GC and 95.0% (95% CI, 92.0-97.7), respectively, in CC. Conclusions: CPS is a robust, reproducible scoring method that identified more responders than did TPS in GC and CC. Further investigation of CPS in cancers beyond NSCLC is warranted. Clinical trial information: NCT02335411 and NCT02628067.

Phase III study of intraperitoneal/intravenous adjuvant chemotherapy compared to intravenous chemotherapy in stage III gastric cancer. First Author: Yang Yang, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University and Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: Peritoneal metastasis is detected as any part of the metastasis in more than 50% of surgically resected stage III gastric cancers. However, little is known about the role of HER2 and HER3 in the non-metastatic disease in European population. Methods: Immunohistochemical expression of HER2 was analyzed using DAKO-HercepTest kit and gene amplification using DAKO-Duocish kit; both were scored according to published criteria. HER3 expression was analyzed using HER3 clone DAK-H3-ICH/HER3 patients with 0-1+ were classified as HER2 negative, patients with 2+ and negative Duocish as equivocal and 3+ or 2+ with positive Duocish as positive. HER3 pts were classified as negative if 0-1+ or positive 2+ by two independent observers. Six subtypes according to HER2 and HER3 status were defined. Results: Subtypes distribution with known HER2 and HER3 status proposes a classification in 6 groups with clinicopathologic characteristics and survival was analyzed retrospectively. Results: 106 pts diagnosed between Jan-2007 and Jun-2014 were analyzed. Subtype distribution was: HER2-Her3 (+) (56.6%), HER2 equivocal/HER3 (–) 9 pts (8.5%), HER2 (–) HER3 (+) (15.1%), HER2 equivocal HER3 (+) (6.6%), HER2 (+) HER3 (+) (7.5%) and HER2 (+) HER3 (+) (5.7%). HER2 had a significant association with DFS: HR 0.26, 95%CI 0.16-0.43, p < 0.001; DFS: HR 0.56, 95%CI 0.36-0.87, p = 0.008; 4-year DFS: 33%, 95%CI 0.40-0.90, p = 0.01). This difference was confined to the subgroup with adenoid histology (OS: HR 0.28, 95%CI 0.16-0.47, p < 0.001; DFS: HR 0.26, 95%CI 0.16-0.43, p < 0.001). In the SCC subgroup, OS and DFS were similar (OS: HR 1.30, 95%CI 0.48-2.64, p = 0.77; DFS: HR 0.91, 95%CI 0.43-1.94, p = 0.82). Using multivariable re-gression with AIC backward selection, the only retained univariate treatment factors were treatment modality (p < 0.001) and histology (p = 0.002). Conclusions: Our findings support preferential use of trastuzumab therapy for pts with adenoid histology given superior OS and DFS, whereas trastuzumab and trastuzumab therapy appeared comparable in pts with SCC histology. Pending confirmation in larger series with longer follow-up, these findings suggest differential treatment algorithms for locoregional esophageal and GEJ cancer based on tumor histology.
Circulating tumor DNA dynamics in resectable gastric cancer. First Author: Alessandro Leali, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD.

Background: There is an unmet need for predictive biomarkers of clinical outcomes in resectable gastric cancer (RGC) treated with perioperative chemotherapy. We have used targeted error correction sequencing (TEC-Seq) to analyze DNA from circulating tumor DNA (ctDNA) patients enrolled in the CRITICS study (NCT00471863). Methods: We prospectively isolated cell-free DNA (ctDNA) from plasma of 115 patients with stage IB-IIIA RGC enrolled in a phase III trial of perioperative chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy. Samples were collected prior to neoadjuvant treatment (baseline), as well as prior to and after partial or total gastrectomy. Pathologic responses to neoadjuvant chemotherapy were assessed using tumor regression grade (TRG). Tumor-derived alterations were analyzed using TEC-Seq at the indicated timepoints. Results: Patients had a median follow-up of over 60 months. Initial analyses of 84 plasma samples from 52 patients revealed median levels of ctDNA of 9.8 ng/ml (0.8-123.0). We detected 259 somatic mutations in 34 genes. Patients with tubular adenocarcinoma had higher ctDNA concentrations than signet-ring cell carcinoma, with median mutant allele fractions (MAFs) of 0.25% vs. 0.16%, respectively (P < 0.001). ctDNA levels were reduced after neoadjuvant chemotherapy, with MAFs declining from 0.22% to 0.15% (P < 0.001). TRG 1-3 responses were associated with longer median overall survival (OS) (not reached (NR) vs. 39.4 months, HR = 0.25; 95% CI = 0.06-0.96, P = 0.02). We observed a trend for longer OS and EFS among patients with detectable ctDNA at baseline who were treated with perioperative chemotherapy (median OS NR vs. 37.4 months, HR = 0.39; 95% CI = 0.14-0.96, P = 0.02, respectively). Conclusions: Our study shows that ctDNA levels differ between histologic subtypes of gastric cancer. The presence of detectable ctDNA at baseline may provide a predictive real-time biomarker of neoadjuvant chemotherapy benefit in patients with resectable disease. Additional ctDNA analyses at all timepoints will be presented. Clinical trial report: NCT00471863.

4070 Induction chemoradiotherapy for esophageal cancer: Comparing CROSS regimen with cisplatin/5-FU. First Author: Abraham Geller, Harvard Medical School, Boston, MA.

Background: While trimodal therapy with neoadjuvant carboplatin/paclitaxel (CP) has demonstrated superiority over surgery alone for treatment of locally advanced esophageal cancer (LAEC), its superiority to alternative regimens is yet unproven. Here we directly compare CP against cisplatin/5-FU (CF), the historical standard, as a component of trimodal therapy for LAEC.

Methods: Patients receiving trimodal therapy with either CP or CF for LAEC as part of a single institution from 2002 to 2017 were included in this retrospective study. Clinical data, treatment regimen, and tumor response were obtained from medical records. The primary outcome was pathologic complete response (pCR). Secondary outcomes were overall (OS) and disease-free survival (DFS), calculated from the date of surgery until death (OS & DFS) or first recurrence (DFS only). Primary outcomes were measured with logistic regression; survival was estimated with Kaplan-Meier and Cox Proportional Hazards models. Patient characteristics were compared with Student's t and chi square tests. Results: 326 patients were included in this study. 187 patients (57%) received CP; 139 patients (43%) received CF. Mean follow-up was 33.8 months. The CF group was older (mean age 64 vs. 62, P = 0.01) and had a higher rate of hypertension (49% vs. 35%, P = 0.02) than the CF group. Distribution of tumor stages was similar between groups (P = 0.3). CF was associated with improved pCR compared to CP in both univariate (OR 1.8, P = 0.02) and multivariate (OR 2.2, P = 0.01) analysis. CF showed improved median OS compared to CP (42 vs. 29 months, HR = 0.53; 95% CI = 0.18-1.6, P = 0.2, respectively). Conclusions: CF is an effective and well-tolerated trimodal regimen for LAEC.

Gastrointestinal (Noncolorectal) Cancer
**4074 Poster Session (Board #263), Sun, 8:00 AM-11:30 AM**

Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). First Author: Stacey Stein, Yale School of Medicine, New Haven, CT

**Background:** Advanced HCC is a lethal cancer with a high unmet medical need. Single-agent immunotherapy with PD-L1/PD-1 blockade or treatment (Tx) with anti-angiogenic bevacizumab (bev; anti-VEGF) has shown modest activity in HCC. We hypothesized that the combination of atezolizumab (atezo; anti–PD-L1) + bev results in a greater clinical benefit due to the additional immunomodulatory effects of bev (increased DC maturation, enhanced T-cell infiltration, reduced MDSCs and T-reg/Tumor-Irinys that create a more favorable tumor microenvironment that potentiates the effi-
cacy of atezo.

**Methods:** Patients (pts) with unresectable or metastatic HCC who were naive to systemic Tx were enrolled in a Phase Ib study cohort (NCT02715531). Pts received atezo (1200 mg) + bev (15 mg/kg) IV every 3 weeks until loss of clinical benefit or unacceptable toxicity. The primary objective was to assess the safety and tolerability of the combination. Secondary efficacy endpoints included ORR, PFS, DOR and time to pro-
gression (TTP) per RECIST v1.1; and OS.

**Results:** As of the data cutoff (October 24, 2017), 26 pts were evaluable for safety. Tx-related all-grade AE's occurred in 21 pts (81%). Tx-related grade 3-4 AEs (n = 10; 35%), most commonly hypertension (n = 5 (19%)). No grade 5 AEs were observed. Two pts (8%) experienced 3 Tx-related grade 3 serious AEs (autoimmune encephalitis, mental status change and intra-abdominal hemorrhage). Immune-related AEs requiring corticosteroid Tx occurred in 3 pts (12%). Among A safety population, efficacy-evaluating and confirmatory analysis, 13 pts (62%) regardless of HCC etiology, region (Asia or US), baseline a-
fetoprotein levels (≥ or < 400 ng/mL) or extrahepatic spread of the tumor. The median AEs for FDS, DOR, TTP and OS have not yet been reported.

**Conclusions:** The combination of atezo + bev is safe and tolerable. New safety signals were identified beyond the established safety profile for each agent. The confirmed rate of 62% suggests that atezo + bev in combination has synergistic clinical activity. Expansion of this HCC cohort and evaluation of atezo + bev in a Phase III study are under way. Clinical trial information: NCT02715531.

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**4076 Poster Session (Board #265), Sun, 8:00 AM-11:30 AM**

A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable or metastatic hepatocellular carcinoma (HCC). First Author: Masafumi Ikeda, National Cancer Center Hospital East, Kawasaki, Japan

**Background:** LEN is a multikinase inhibitor of VEGFR 1, 2, and 3, FGFR 1, RET, and KIT that showed noninferiority with respect to overall survival (OS) compared with sorafenib in the first-line treatment of pts with uHCC in a phase (Ph) 3 trial (REFLECT). PEM is an anti-PD-1 monoclonal antibody that has shown promising activity in HCC. An ongoing Ph 1b study of LEN + PEM has shown promising activity in several solid tumor types. We report preliminary results from a Ph1b trial of LEN + PEM in pts with uHCC. *Methods:* In this open-label, multi-center study, pts with uHCC, BCLC stage B (not eligible for transarterial chemo-
embolization) or C, Child-Pugh class A, and ECOG PS ≤ 1 received LEN (body weight ≥ 60 kg: 12 mg/day; < 60 kg: 8 mg/d) daily and 200 mg PEM IV once every 3 wks. Tolerability was evaluated by assessing dose-limiting toxicities (DLTs) during the first cycle in pts who were ineligible for other therapies (3+3 design; Part 1). Once tolerability of the combination was confirmed, additional pts with no prior systemic therapy for uHCC were enrolled (Part 2). The primary endpoint was safety. Secondary and exploratory endpoints included OS, and objective response rate, progression-free survival, and time to progression using modified RECIST (mREC-
IST). Tumor assessments of complete or partial responses (CR or PR) were confirmed ≥ 4 weeks after initial response. **Results:** As of December 1, 2017, 18 pts had received LEN + PEM (Part 1: n = 6; Part 2: n = 12). Pts had BCLC stage B (n = 6) or C (n = 12), Child-Pugh scores of 5 (n = 14) or 6 (n = 4), and 4 pts (22%) had received prior sorafenib. No DLTs were reported in Part 1. All 18 pts remained on study. Tumor responses were confirmed (≥ 4 weeks after initial response). **Conclusions:** LEN + PEM was well tolerated with encouraging antitumor activity in pts with uHCC. Clinical trial information: NCT03006926.

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**4075 Poster Session (Board #264), Sun, 8:00 AM-11:30 AM**

Anti-programmed death-1 antibody SHR-1210 (S) combined with atapinib (A) for advanced hepatocellular carcinoma (HCC), gastric cancer (GC) or esophageal squamous cell carcinoma (ESCC) in a phase 1b trial. First Author: Jian-Ming Xu, Cancer Center, 307 Hospital, Academy of Military Medical Sciences, Beijing, China

**Background:** A phase 1 (P1) study to assess the safety and efficacy of combination of S, a fully human IgG4 monoclonal antibody against PD-1 with PD-L1/PD-L2 plus Apatinib (A), a VEGFR2 inhibitor in patients (pts) with advanced HCC, GC, ESCC cancer. **Methods:** In P1 a dose escalation, pts received 125, 250, 500mg, QD, 5 pts per cohort) and S (200 mg, Q2W) until unacceptable toxicity, disease progression. In phase 1b cohort ex-
pansion, pts received A at recommended P2 dose (RP2D) + S (200 mg, Q2W). Response was evaluated by RECIST v1.1. **Results:** At the cut-off data (Feb. 2, 2018), 42 pts (P 1a, n = 15; P2, n = 27) were enrolled. Median prior lines of therapy in HCC and GC were 1 and 2, respectively. In P1a stage. DLTs (all grade 3 pneumonia) were observed in A 500mg cohort. The RP2D was A 250mg + S. In P1b stage, the median treatment duration was 19 wks (range, 2-57 wks). 19 pts (58%) had ≥ 3 treatment-related adverse events (TRAEs). The ≥ 10% grade 3 TRAEs were hypertension (18%), increased AST (13%) and ALT (12%). These ESs were manageable, only 1 pt discontinued treatment due to TR grade 3 hyperbilirubinemia. There were no TR- deaths. The ODR and DCR in 36 evaluable pts in all 3 cohorts were 30.6% (n = 11) and 83.3% (n = 30), respectively. All 11 responses occurred in A 125mg (n = 1) and 250mg (n = 10) cohorts. Among 18 HCC pts (14 evaluable: A 125mg cohort: n = 4; A 250mg cohort: n = 10), all responded with median survival follow-up, 8.3 mo), confirmed partial responses occurred in 13 pts (62%) regardless of HCC etiology, region (Asia or US), baseline a-
fetoprotein levels (≥ or < 400 ng/mL) or extrahepatic spread of the tumor. The median estimates for FDS, DOR, TTP and OS have not yet been reported.

**Conclusions:** The combination of atezo + bev is safe and tolerable. New safety signals were identified beyond the established safety profile for each agent. The confirmed rate of 62% suggests that atezo + bev in combination has synergistic clinical activity. Expansion of this HCC cohort and evaluation of atezo + bev in a Phase III study are under way. Clinical trial information: NCT02942329.

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**4077 Poster Session (Board #266), Sun, 8:00 AM-11:30 AM**

A multicenter, single arm phase II trial of a small molecule immune-modulator in hepatocellular carcinoma pts Safety, overall survival, immune dynamics, and PD-L1 expression in advanced hepatocellular carcinoma. First Author: Yang Sun, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

**Background:** HCC was characterized with high heterogeneity and immune 

tolerogenic*. Despite of immune checkpoint inhibitors have demonstrated promising results with improved overall survival, a significant fraction of advanced HCC patients are still left with limited treatment options and poor survival. The purpose of this study is to determine the safety, clinical activity and immune dynamic biomarkers of a small molecule icariin, IL-6/STAT3 immune-modulator in advanced HCC. **Methods:** Major eligibility criteria include histologically confirmed unresectable HCC patients with Child-Pugh Class A or B liver function. Total of 70 advanced HCC patients were enrolled and administered with 600 mg b.i.d. Primary endpoints were TTP, sec-
ondary endpoints were safety, OS, and DCR. Local disease control was defined as no progressive disease (PD) by RECIST. Kaplan-Meier analysis was utilized for OS assessment. Immune dynamic of NLR, IL-6 and baseline PD-L1 expression of immune cells was evaluated, retrospectively. **Results:** There was no grade III drug related AE observed in all enrolled 70 advanced HCC patients. Objective response evaluation in per-protocol population showed PR (1.6%), SD (32.8%) and PD (59.0%) and median overall survival (OS) 254days (95% CI, 172-296). DCR was achieved 34.4% (95% CI, 22.7-47.7%); Median OS for the PD-L1-positive (n = 9) and negative (n = 24) subgroups were 389 (95% CI, 80-522) vs. 286.5days (95% CI, 135-482), for IL-6-advantage (n = 23) subgroups were 295(95% CI, 235-509) vs. 178days (95% CI, 135-296), respectively. Conclusions: Icariin has demonstrated its favorable clinical safety and immune-modulation clinical efficacy. The improved OS was implicated in the subgroups of advanced HCC patients including PD-L1-positive immune cell expression. Both safety and immune-response efficacy are warranted for the phase III trial. Clinical trial information: NCT01972672.
Phase I dose-finding study of OPB-11107, a novel STAT3 inhibitor, in patients with advanced hepatocellular carcinoma. First Author: Changhoon Yoo, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of (South), Korea

Background: The signal transducer and activator of transcription 3 (STAT3) signaling pathway might be a promising therapeutic target for hepatocellular carcinoma (HCC).

Methods: This study was a multicenter, open-label, non-comparative, dose escalating phase I study of OPB-11107, an oral STAT3 inhibitor, in patients with advanced HCC who failed on sorafenib. Continuous dosing (daily administration: 50 mg to 400 mg) and intermittent dosing (4-days on/3-days off administration: 300 mg to 900 mg) regimens were evaluated and the dose-limiting toxicities (DLTs), maximal tolerated dose (MTD), and recommended dose (RD) were the primary endpoints. Results: A total of 33 patients (19 for continuous dosing and 14 for intermittent dosing) were enrolled. One patient experienced a DLT with grade 3 dizziness, but the MTD was identified in neither the continuous nor the intermittent dosing cohorts. The RDs were determined to be 250 mg for the continuous dosing regimen and 600 mg for the intermittent dosing regimen. There was no treatment-related death; 6 patients (18%) had grade 3-4 toxicities including thrombocytopenia (6%), fatigue (3%), and dizziness (3%). No patients achieved complete or partial responses and the median progression-free survival was 1.4 months (95% confidence interval, 0.8-2.8). Conclusions: OPB-11107 was well tolerated in patients with advanced HCC after sorafenib failure, but only showed limited preliminary efficacy outcomes. Further investigation of the role of the STAT3 signaling pathway in HCC and the development of biomarkers for STAT3 inhibitors are warranted. Clinical trial information: NCT01942083.

Poster Session (Board #267), Sun, 8:00 AM-11:30 AM

Phase II trial of sorafenib plus doxorubicin (SD) in patients (Pts) with advanced hepatocellular carcinoma (HCC) after progression of disease (PD) on sorafenib (S). First Author: Imane H. El Dika, Memorial Sloan Kettering Cancer Center, New York, NY

Background: SD may synergistically improve outcome after PD on S by promoting ASK-1 mediated apoptosis through RAF-1 inhibition. In a prior retrospective analysis of 14 pts who in the lack of other choices of therapy received SD after PD on S, progression free survival (PFS) and overall survival (OS) were 3.4 and 10.1 months (m) respectively. Methods: A non-randomized, open label, single institution, single arm phase II study of SD in pts with histologically confirmed advanced HCC. Eligibility: RECIST 1.1 radiologic PD on S, ECOG 0-1, Child-Pugh A, and adequate major organ function. Therapy: S 400mg twice a day (once a day if bilirubin (B) ≥1.3mg/dl ≤3mg/dl) and D 60mg/m2 (30mg/m2 if B ≥1.3 mg/dl ≤3mg/dl) on day 1 of 3-week cycle. Cross-sectional imaging was performed every 3 cycles. The primary endpoint was OS at 6m (OS6), based on Simon two-stage design, unacceptable OS6 50%, acceptable OS6 72%, type I and II errors 5% and 15% respectively. Secondary endpoints included PFS, OS, response rate by RECIST 1.1, and associations between duration of prior S and OS and PFS. Baseline and on-treatment biopsies evaluated ASK-1 and p-ERK expression levels (separate report). Results: N = 30 pts enrolled. The majority were male (86%), median age 64 years (range 24-82), 16 pts had hepatitis (53%), OS6 was 76.6% (95%CI: 57.2-88.1%). Median doses of D and S were 94mg and 380mg respectively. OS was 8.6% (95%CI: 7.3-12.1) and PFS was 3.6% (95%CI: 2.4-4.4) m. There were 3 (10.7%) partial responses and 17 (60.7%) stable disease. Median duration of prior S treatment was 3.3 m (range: 0.9-27) m. Neither OS nor PFS were associated with previous S duration (p value 0.11 and 0.15 respectively). Grade 3-4 adverse events occurring in ≥10 pts: neutropenia (16%), febrile neutropenia (10%), lymphopenia (43%), anemia (10%), thrombocytopenia (10%), elevated AST (23%) and ALT (10%), hypophosphatemia (10%), and fatigue (10%). There was no treatment related death. Conclusions: Despite the study meeting its primary endpoint, SD resulted in significant toxicity and a median OS of 8.6 m. Based on front-line evaluation of SD and the results reported herein, further development of SD in HCC is not warranted Clinical trial information: NCT01840592.

Poster Session (Board #268), Sun, 8:00 AM-11:30 AM

Phase Ib study of binimetinib (MEK162) in combination with capcetabine in gemcitabine-pretreated advanced biliary tract cancer. First Author: Jon Wand, Amy, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of (South), Korea

Background: In biliary tract cancer (BTC), RAS/RAF/MEK/ERK pathway is known to be activated in up to 20-40%. Binimetinib (MEK162) is allosteric MEK1/2 inhibitor, which shows preclinical activity in BTC. Interestingly, MEK inhibitor and 5-FU shows synergistic effects in BTC cells. With that, we conducted phase Ib study of binimetinib and capcetabine in gemcitabine-pretreated BTC patients. Methods: This study consists of dose escalation (DE) part and expansion (EX) part. Binimetinib (B) and capcetabine (C) were dosed twice daily, 2 weeks/1 week on/off. In DE part, 3 dose levels (DL) were tested (DL1: B 15mg, C 1000 mg/m²; DL2: B 30mg, C 1000 mg/m²; DL: B 30mg, C 1250 mg/m²) with 3+3 design. The primary end point was max immunotolerated dose in DE part and 3-month progression free survival (PFS) rate (3m-PFSR) in EX part. Results: In DE part, 9 patients (3 per DL) were recruited and there was no dose limiting toxicity up to DL3. Recommended phase 2 dose (RP2D) was determined as DL3. In EX part, 25 patients were enrolled. Median age was 63 years (range 48-73); Primary tumor origins were gallbladder (29.4%), intrahepatic (29.4%), extrahepatic (26.5%), and ampulla of vater (14.7%). 25 (73.5%) and 9 patients (26.5%) were 75th-line and 3rd-line setting, respectively. Of 34 evaluable patients, 6 (17.6%) and 20 patients (58.8%) showed partial response and stable disease (SD). Response rate and disease control rate were 17.6% (95% CI. 4.8-30.4) and 76.5% (95% CI. 62.1 - 90.7). Median PFS and overall survival (OS) were 3.9 m (95% CI. 3.0 - 4.8) and 8.0 m (95% CI. 4.9 - 11.1). 3m-PFSR was 61.3%. 60% of patients with SD showed prolonged SD (> 12 weeks). In biomarker study, RAS/RAF/MEK/ERK pathway activated patients showed longer PFS (5.4 m vs 2.6 m, p = 0.03). OS (10.8 m vs 5.3 m, p = 0.02) and OS6 (10.3 m vs 6.3 m, p = 0.01) in non-activated patients. Most of adverse events were grade 1/2 and manageable with G3 anemia (11.8%) and G3 fatigue (5.9%). Conclusions: RP2D of binimetinib and capcetabine combination is binimetinib 30mg, capcitabine 1250mg/m², twice daily, 2 weeks on/1 week off. This combination shows acceptable tolerability and promising antitumor efficacy, especially in RAS/RAF/MEK/ERK pathway activated BTC patients. Clinical trial information: NCT02773459.

Poster Session (Board #270), Sun, 8:00 AM-11:30 AM

A phase II study of ramucirumab for advanced, pre-treated biliary cancers. First Author: Jonathan Mizrahi, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Biliary cancers (BC) have no clear second-line therapy in advanced disease after progression on standard of care gemcitabine and cisplatin. Angiogenesis has been shown to be a potential target for BC, and ramucirumab, FDA-approved for treatment of advanced gastric, lung and colon cancer, is a novel monoclonal antibody that targets VEGFR2 to inhibit tumor-induced angiogenesis. Methods: We conducted a single arm, single institution, single institution, single arm phase II study. Eligibility criteria included patients (pts) with advanced BC, ECOG PS 0 or 1, who had received at least 1 prior regimen containing gemcitabine. Pts were treated with IV ramucirumab at a dose of 8 mg/kg every 2 weeks, and restaging imaging was performed every 8 weeks until progression. The primary endpoint was progression free survival (PFS). Secondary endpoints included overall response rate (ORR), disease control rate (DCR), overall survival (OS) and toxicity (tox) of ramucirumab. Exploratory endpoints included correlating baseline gene expression profile and pre- and post-therapy CT imaging features with tumor response. Results: 43 of a planned 50 pts were enrolled, 42 receiving treatment. The cohort had a median age of 59.9 yrs (range 42-77), ECOG PS 0/1 (15/26), male/female (20/22), intrahepatic cholangiocarcinoma/extraperitoneal gallbladder (23/9/10), median prior therapies = 1 (range 1 to 5). Pts received a median number of 6 cycles. There were 9 (21%) grade 3 toxicity including anorexia, dehydration, hypertension, hypoproteinemia, proteinuria and vomiting. No grade 4 toxicity was observed, and no pts were taken off study due to tox. 5 pts required dose reductions. After a median follow-up of 3.44 months, the median PFS and OS were 2.73 months (95% CI: 1.91-8.03) and 6.31 months (95% CI: 4.7 - not reached). Of 34 pts evaluable for response, ORR = 0% and DCR = 44%, with 6 pts on treatment for > 24 weeks. Analysis of the correlative endpoints is ongoing. Conclusions: Ramucirumab as a single agent was well-tolerated and resulted in a PFS similar to that achieved with more toxic chemotherapy regimens used in the refractory setting. Furthermore, a minority of ramucirumab-treated patients (13%) experienced prolonged PFS > 24 weeks, warrants further investigation of this agent in refractory BC. Clinical trial information: NCT02520141.

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4082 Poster Session (Board #271), Sun, 8:00 AM–11:30 AM
Multi institutional phase II trial of single agent regorafenib in refractory advanced biliary cancers. First Author: Richard D. Kim, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: There is currently an unmet medical need for patients with advanced biliary cancer (BC) who have failed one prior gemcitabine based systemic therapy. Regorafenib is an oral multikinase inhibitor that targets both receptor tyrosine kinases (RTKs), as well as the tumor cell proliferation/survival signaling pathways (RAS/RAF/MEK/ERK). Methods:Pts with histologically proven BC who progressed on at least one line of systemic therapy received regorafenib (80mg PO daily) until toxicity or patient choice. Results:Thirty nine pts received at least 1 dose of regorafenib of whom 32 pts were evaluable for efficacy. Twenty pts failed 1 line of therapy and 12 pts failed 2 lines of therapy. Median age was 62 (range: 27-88) years and the primary sites of tumor were intrahepatic cholangiocarcinoma (ICC) (60%) and gallbladder (12%). 7 pts were considered evaluable for efficacy if patients received more than 1 cycle of regorafenib. Seven pts were not evaluable because one pt withdrew consent, 5 pts expired due to clinical progression within a month and 1 pt due to toxicity. For 32 evaluable pts, 6 month OS was 50% (95% CI: 32.1%-67.6%), 12 month OS was 35% (95% CI: 22.5%-53.7) and 18 month OS was 35% (95% CI: 16.2%-52.3). Median PFS was 3.7 months (95% CI: 2.3-5.5) and median OS was 9.9 months (95% CI: 3.7-20.1). PR was achieved in 2 (6.2%) pts, SD in 18 (56.2%) pts with DCR of 62.4%. The overall toxicity profile was as expected with grade 3/4 AE of 71.8%. The most common adverse events were fatigue (56.4%) and hypertension (53.8%). Dose modification was required in 49% of the patients. Plasma samples were collected in all pts with planned correlative studies underway. Conclusions: The primary endpoint was met in this study. Further randomized trials are warranted to confirm the efficacy. Clinical trial information: NCT02115542.

4084 Poster Session (Board #273), Sun, 8:00 AM–11:30 AM
Selumetinib (Sel) and cisplatin/gemcitabine (CisGem) for advanced biliary tract cancer (BTC): A randomized trial. First Author: Hafith Esmail, Sunnybrook Cancer Centre at Sunnybrook Health Sciences Centre, University Health Network, Toronto, ON, Canada

Background: Sel (AZD6244, AR142866) is an oral MEK inhibitor, with preclinical evidence of synergy with Gem in BTC. CisGem is standard first-line treatment for advanced BTC. This trial assessed the efficacy of Sel in continuous or sequential combination with CisGem in first-line advanced BTC. Methods:This randomized, multicentre phase II trial (NCT02151084) enrolled patients (pts) with advanced cholangiocarcinoma (CC) or gallbladder cancer (GBC). CisGem was given at standard doses. Sel started at 75mg BID, daily (continuous – Arm A) or day 1-5, 8-19 every 21 days (sequential – Arm B). CisGem was given at standard dose (80mg/m^2) starting dose was increased to 50mg BID for toxicity concerns after 32 enrolled pts (protocol amendment). Primary endpoint was % change in RECIST tumor size of 48 evaluable pts; Arm A or B vs Arm C. Secondary endpoints: PFS, OR, disease control rate (DCR) and toxicity. Results: 57 pts were enrolled; 29 female, 22 intrahepatic CC, 16 extrahepatic CC and 19 GBC. Baseline characteristics were similar across arms. Mean change in tumor size was not significantly different between either Sel arm and the control arm (Arm A p = 0.37, Arm B p = 0.53 (Table). There were no significant differences in other efficacy endpoints. Toxicities appeared more frequent in Arm A; dose intensity of Gem and Sel were lower. More pts in Arms A and B stopped treatment due to toxicity than Arm C. Conclusions: Adding Sel to CisGem failed to improve tumor response at 10 wks, or prolong survival, but added toxicity and led to lower dose intensity. Expansion of biomarkers may identify a group of patients that benefit, but it should not be studied further in unselected BTC. Clinical trial information: NCT02151084.

4085 Poster Session (Board #274), Sun, 8:00 AM–11:30 AM
ADi-PEG 20 and FOLFOX6: A phase 1 study in pts (pts) with advanced hepatocellular carcinoma (HCC). First Author: James J. Harding, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Arginase depletion interferes with pyrimidine metabolism as well as DNA damage repair pathways, and preclinical data indicate that pairing pegylated arginine deaminase (ADi-PEG 20) with fluoropyrimidines or platinum enhances cytotoxicity in vitro and in vivo in arginine auxotrophs. NCT02642913, an open-label, single arm phase 1 trial of ADi-PEG 20 and FOLFOX6 for treatment-refractory HCC and other advanced gastrointestinal (GI) tumors was based on a 3+3 dose escalation design. The primary objectives were to define safety, tolerability, and the recommended phase 2 dose (RP2D). An HCC expansion cohort was used to define best overall response rate (ORR). Secondary objectives included progression-free survival (PFS), overall survival (OS), and exploration of pharmacodynamics and immunogenicity. Eligible patients were treated with intravenous FOLFOX6 biweekly at standard doses and ADi-PEG 20 intramuscularly weekly at 18 (Cohort 1) or 36 mg/m^2 (Cohort 2 and RP2D expansion). Results: 27 pts enrolled—23 advanced HCC (and 4 other GI). HCC cohort median age 64 (44-77) years old (100% Child Pugh A, 100% failed prior SORA). No dose limiting toxicity was observed and the RP2D for ADi-PEG 20 was 36 mg/m^2 weekly with FOLFOX6. Common adverse events (AEs) any grade: thrombocytopenia, neutropenia, leukopenia, anemia, and fatigue. Among 23 HCC pts, the most frequent treatment related grade 3 AE was neutropenia (47.8%), thrombocytopenia (34.7%), leukopenia (21.7%), anemia (21.7%), and lymphopenia (17.4%). The ORR for 23 HCC pts was 21.7% (95% CI: 95.7-43.7). Median PFS and OS were 7.3 and 14.5 months. Arginine levels (Mean ± S.D. baseline 81 ± 7.8, week 1 0.9 ± 0.2 in PAR) were depleted with therapy despite the emergence of low levels of anti-ADi-PEG 20 antibodies. The degree of arginase depletion, presence of antibodies, and archived tumor arginase/nitric oxide synthetase-1 levels did not correlate with response. Conclusions: Concurrent ADi-PEG 20 and FOLFOX6 is safe with favorable efficacy compared to historic controls. The HCC cohort expanded to a phase 2A phase with the combination in the third-line. Clinical trial information: NCT02102022.
Phase II study of pembrolizumab in advanced, unresectable hepatocellular carcinoma. First Author: Lynn G. Feun, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL

**Background:** Recently, checkpoint inhibitors have shown modest activity in patients (pts) with advanced, unresectable hepatocellular carcinoma (HCC). In multicenter trials with nivolumab and pembrolizumab, the response rates have been reported to be 14% and 16%, respectively. We report a prospective single-institution investigator-initiated clinical/ translational study of pembrolizumab in advanced HCC. **Methods:** A phase II trial is ongoing, with pembrolizumab administered at a fixed dose of 200 mg every 3 weeks for 3 cycles. Endpoints: 1) primary: confirmed overall response (ORR); 2) secondary: RECIST 1.1 was used to assess response. Time to tumor progression (TTP) and median OS were estimated along with the corresponding 95% confidence interval. **Results:** Twenty-six patients have been treated and 21 were evaluable for response at this time. Ten of the 21 patients had prior sorafenib. Seven had hepatitis C and 1 had hepatitis B. Sixteen had extrahepatic metastases. The median TTP was 3 months (95% CI: 2-7) and median OS was 14 months (95% CI: 3- not estimable). In terms of both arms, the response rates were 41% and 28% for C vs P in pts who had received only prior S based on duration of prior S (N = 98) (51 patients in C arm, 47 in P arm); median OS 3 mo, 141 (28%) for 3 to < 6 mo, and 217 (44%) for ≥ 6 mo. ORR: Confirmed partial response (cPR) in 5 (19%) (N = 43) and 6 (13%) (N = 44) for C and P, respectively. Disposition: 20 pts discontinued for PD, 1 for Gr2 irAE neuropathy, 1 for unrelated AE; 5 remain on treatment. Median cycles: 6 (range 2-28+). ORR: Confirmed response (cPR) in 5 (19%) (95% CI: 3-34%) (1 MSI, 4 MSS); cPR or stable disease (SD) ≥ 6 months in 9 (33%). PFS: 35% (95% CI: 15-54%); median OS: not reached. Endocrine irAE, CA 19-9 changes ≥ 50%, hepatitis C virus (HCV), and TMB were associated with efficacy in univariate analyses. PD-L1+i+ ≥ 1% was present in 3/10 (30%) pre-treatment samples but was not associated with ORR or PFS; additional PD-L1 results are pending. Conclusions: PEM induction GM-CSF is safe and well-tolerated in ABC. Prolonged responses and PFS in MSS ABC along with candidate biomarkers warrant further study in larger sample. Clinical trial information: NCT02703714.

**2088**

Outcomes in patients (pts) who had received sorafenib (S) as the only prior systemic therapy in a phase 3 CELESTIAL trial of cabozantinib (C) vs placebo (P) in advanced hepatocellular carcinoma (HCC). First Author: Robin Kate Kelley, University of California San Francisco, San Francisco, CA

**Background:** The efficacy of immune checkpoint inhibition (CPI) has not been established in ABC. The combination of CPI plus the myeloid cytokine GM-CSF was safe with prolonged overall survival (OS) compared to CPI monotherapy in melanoma. This phase 2 trial evaluates the safety, efficacy, and biomarkers of PEM in combination with 2 cycles of low dose induction GM-CSF in ABC (NCT02703714). **Methods:** Design: Simon’s 2-stage. Key eligibility: ABC after > 1 standard therapy, no prior CPI, bilirubin ≤ 1.5xULN. Treatment: PEM 200 mg IV Q3 weeks plus GM-CSF 250 µg SC days 1-4 Q3 weeks for 2 cycles. Endpoints: 1) Overall response rate (ORR) by RECIST 1.1 with H0 5% vs. H1 20%. 2) Safety, progression-free survival at 6 months (PFS6). OS, tumor PD-L1 expression. Exploratory: CA 19-9 levels, tumor microsatellite instability (MSI), TMB, tumor mutation burden (TMB), tumor and peripheral immune cell profiling. **Results:** Accrued has completed with 27 patients enrolled 5/2016-9/2017: Stage I/II 9/18; F/M 13/14; median age 61; intra-/extra-hepatic 74%/26%; stage IVA/B 85%, III/II 15%; median prior therapies 2 (range 1-6); MSI/MSS/unknown 1/97; TMB high/low/unknown 5/1/11. Adverse events (AE): Related ≥ grade (Gr)3 AE in 2 (7%) (1 each immune-related (ir)AE of Gr4 diabetes mellitus and Gr3 fever); irAE requiring steroids in 3 (11%); endocrine irAE in 8 (30%). Disposition: 20 pts discontinued for PD, 1 for Gr2 irAE neuropathy/arthralgia, 1 for unrelated AE on remain on treatment. Median cycles (range 2-28+). Correlative studies including hepatitis B and C titers, IL1B, IL2, IL12, IL6, TGF beta, gamma interferon, and PD-L1/PD-1 staining are ongoing and will be presented. Conclusions: Pembrolizumab has activity in advanced ABCHCC patients, including those with extrahepatic metastases. Toxicity was generally well tolerated and reversible. A set of immunological markers as well as PD-L1/PD-1 staining is being investigated as possible indicator for response. Clinical trial information: NCT02658019.

**2089**

Outcomes of patients (pts) who had received sorafenib (S) or placebo (P) in advanced hepatocellular carcinoma (HCC) (N = 100). First Author: Kabir Modi, Mayo Clinic, Jacksonville, FL

**Background:** Cholangiocarcinoma (CCA) has limited treatment options. Genomic analyses have led to development of targeted therapies now in several clinical trials, and may enable the discovery of new treatment options. However, biopsy often yields limited tissue, thus hampering tissue-based profiling opportunities. Data regarding circulating tumor DNA (ctDNA) plasma analysis in CCA during real time clinical practice is limited. **Methods:** We performed ctDNA NGS analysis in patients with advanced CCA (January 2015 – December 2017). ctDNA analysis was performed using Guardant360, which detects single nucleotide variants, amplifications, fusions, and specific insertion/deletion mutations in up to 73 different genes. Seventeen samples were performed on previous panel versions (3 on a 54-gene, 1 on a 68-gene, and 13 on a 70-gene panel) The mutant allele fraction (MAF) for detected alterations was calculated relative to wild type in ctDNA. Actionability was defined as possible treatments within OncoKB levels I-IV and R1. The study was conducted in accordance with Mayo Clinic Institutional Review Board requirements. **Results:** Among 104 patients and 115 total samples, ctDNA NGS revealed at least one genomic alteration (excluding variants of uncertain significance (VUS) and synonymous mutations) in 80 patients (77%). Median number of alterations per patient was 3.1 (range, 0-23). The total number of unique alterations was 389, with the most commonly altered genes being: TP53 (84 alterations, 22%), followed by KRAS (34 alterations, 9%), FGFR2 (31 alterations, 8%), ARID1A (20 alterations, 5%), APC and PIK3CA (16 alterations each, 4%). Amplifications were noted in 14 genes, including BRAF, CCND1, CCND2, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, MET, MYC, PDGFRα, and PIK3CA. Fusions of FGFR2 were seen in 3 cases. Potentially actionable alterations were seen in 63 of the 104 patients (61%). ctDNA plasma profiling of patients with advanced CCA is a feasible alternative method to gather comprehensive genomic data. Further study of responses to ctDNA NGS-guided over tissue-graded targeted therapy is needed to define the best means to optimize outcomes in CCA.

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**Background:** The incidence of HCC generally increases with age, although the age of onset varies depending on disease etiology and geographic region (Yang, Nat Rev Gastroenterol Hepatol 2010). In the phase 3 CELESTIAL trial (NCT01908426), C, an inhibitor of MET, VEGF receptors, and AKT, improved overall survival (OS) and progression-free survival (PFS) compared with placebo (P) in pts with previously-treated advanced HCC. Overall survival was 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63–0.92; p = 0.0049), and median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36–0.52; p < 0.0001). Here, we evaluate clinical outcomes based on age in the CELESTIAL trial. Methods: 707 pts were randomized 1:1 to receive C (60 mg qd) or P. Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, ECOG PS ≤1, and must have received prior sorafenib. Randomization was stratified by disease etiology, geographic region, and extent of disease. Outcomes were analyzed for subgroups based on age (<65 years and ≥65 years). Results: Median age at baseline was 64 years; 51% of pts were <65 years old. Elevation of HBV was more frequent in pts <65 years (52% vs 22%), while elevation of HCV occurred at a similar frequency in both age groups (24%). Asian race and enrollment in Asia were more frequent in pts <65 years vs ≥65 years (46% vs 21% Asian race; 35% vs 14% enrolled in Asia). Median OS was 9.6 mo for C vs 7.7 mo for P (HR 0.81, 95% CI 0.62–1.05) for pts <65 years old and 1.1 – 8.3 mo for P (HR 0.74, 95% CI 0.56–0.97) for pts ≥65 years old. Median PFS was 5.0 mo for C vs 1.9 mo for P (HR 0.45, 95% CI 0.35–0.57) for pts <65 years old and 5.4 mo for C vs 2.0 mo for P (HR 0.46, 95% CI 0.35–0.59) for pts ≥65 years old. The discontinuation rate due to treatment-related adverse events in pts ≥65 years old was lower in the C arm (11% vs 22%), while the percentage of pts with any dose reduction (61% vs 64%) and the median average daily dose of C (37 mg vs 34 mg) were similar in both age groups. The most common grade 3/4 adverse events in both age groups were consistent with those in the overall population. Conclusions: C improved OS and PFS vs P in pts with previously-treated advanced HCC irrespective of age category. Clinical trial information: NCT01908426.

**Impact of cholangiocarcinoma (CC) molecular heterogeneity on outcome during first-line chemotherapy and access to targeted therapies in early clinical trials (CT).** First Author: Helena Verduguer, Vall d’Hebron University Hospital, Barcelona, Spain

**Background:** CC has poor prognosis and limited therapeutic options beyond first-line therapy. It is molecularly heterogeneous with several gene alterations (alt) that can be matched to targeted treatments in CT. We investigated the impact of CC molecular profiling in the clinics. Methods: From 2011 to 2017, we identified 165 patients (pts) with advanced CC - 129 intrahepatic CC (ICC) and 36 extrapancratic CC (ECC) - whose analyses were analyzed in our center with NGS tests (124 had fusion panels). We retrospectively collected outcome information and access to CT. Results: Most pts were diagnosed at stage IV (67%) and received first-line gemcitabine plus platinum (80%). Most common alt found in ICC were mutations (mt) in TP53 (19%), IDH1 (14%), CDKN2A (9%), IDH2 (7%), ATM (7%), BAP1 (6%), PIK3CA (6%), KRAS (6%), NRAS (5%), BRAF (4%) and fusions in FGFR2/3 genes (3%). In ECC, we found mt in TP53 (28%), CDKN2A (11%), PTEN (11%), PIK3CA (6%), BRC2 (6%) and mt or amplifications (amp) in ERBB2 (11%). With a median follow up of 56 months (m), median overall survival (OS) of the overall population was 23 m, with no differences between ICC and ECC (p = 0.83). There was statistically significant difference in OS between pts with TP53 mt vs TP53 wild type (wt) tumors (28 m vs 15 m, HR 1.8, p = 0.01). During first-line therapy, median progression free survival (PFS) was 6.6 m in TP53 mt and 3.8 m in TP53 wt patients (HR 2.3, p < 0.05). In pts ≥65 years (46% vs 21% Asian race; 35% vs 14% enrolled in Asia), median OS was 4 m; 2 pts (8%) achieved a partial response (1 MET amp;1 BRAF mut) and 14 (61%) had stable disease as best response. Conclusions: Higher OS and PFS in pts with targetable gene alt and OS or PFS during first-line therapy. Future therapies may confer clinical benefit. Molecular profiling of CC is of growing interest to improve the knowledge of this disease and its therapeutic opportunities.

**Understanding quality of life in hepatocellular carcinoma patients. First Author: Stacie Hudgens, Clinical Outcomes Solutions, Tucson, AZ**

**Background:** Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer causing morbidity and adversely affects quality of life (QoL) from serious symptom burden. Methods: HQRQoL collected in a multicenter, randomized, open-label, Phase 3 study compared first-line systemic treatment lenvatinib (LEN) to sorafenib (SOR) in unresectable HCC, were evaluated descriptively. Key QoL outcomes for patients progressing earlier than ninths months and ≥3 months were modeled longitudinally and summarized using area under (AUC) the time curve analyses. The difference in AUC was calculated with contrasting domain parameter estimates of a mixed model with time, group, time*group, and a random intercept at baseline and Day 1 each cycle through Cycle 18. Results: 954 patients were randomized to LEN (N = 478) or SOR (N = 476). Trial outcomes: median OS LEN (13.6 mos) vs SOR (12.3 mos), HR 0.92, 95% CI, 0.79–1.06; median PFS 7.4 vs 3.7 mos, respectively (HR 0.66; 95% CI, 0.57–0.77; P < 0.0001). Baseline HRQoL outcomes (e.g. EORTC QLQ-C30, HCC18, and EQ-5D) markedly favored LEN on sex life (dif = -0.4244), fatigue (dif = -0.2021). Differences in symptoms related to jaundice, body image, and fever was minimal between treatment arms (dif ≥0.05). Conclusion: More patients experienced disease progression earlier on therapy with SOR compared to LEN. In our analysis baseline QoL was more severely impacted HCC patients who progress earlier while on therapy, suggesting that patients treated with LEN have an added benefit in terms of QoL as progression occurred later compared to SOR treated patients. Functional and symptom differences in QoL measures, while not statistically significant, also favored patients treated with LEN. Clinical trial registration: NCT01761266.

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**4094** Poster Session (Board #283), Sun, 8:00 AM–11:30 AM
Additional value of tumour growth rate (TGR) in patients (pts) diagnosed with well-differentiated neuroendocrine tumours (NETs) achieving RECIST-defined stable disease (SD): Subgroup analysis of the 262ENET study. First Author: Angela Lamarca, Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom

**Background:** Response evaluation with RECIST has limitations when applied to slow growing malignancies with low objective response rates, such as NETs, when most pts achieve SD as best response. TGR represents the percentage of change in tumour volume per month and is postulated to overcome such limitations. **Methods:** Pts from 7 centres with advanced, grade (G) 1/2 NETs from the pancreas (P) or small bowel (SB) initiating systemic treatment (ST) or watch and wait (WW) and who achieved SD as best response were eligible. Baseline and follow-up scans were retrospectively reviewed for TGR calculation (%/month) at 3 (+/-1) months (m) of study entry (TGR <0). A previously identified TGR <0 cut-off of 0.8 %/m was applied to assess impact of TGR on progression-free survival (PFS) (Kaplan-Meier/ Cox Regression). **Results:** Out of 222 pts in the GREPONET study, 81 were eligible and included in this analysis: 54.3% SB, 45.7% P; 87.7% meta-

**4095** Poster Session (Board #284), Sun, 8:00 AM–11:30 AM
Assessing prognosis of neuroendocrine neoplasms: Results of a collaborative multinational effort including over 10,000 European patients—The ENETS registry. First Author: Ivan Borbath, Department of Gastroenterology, Cliniques Universitaires Saint-Luc, Bruxelles, Belgium

**Background:** Global European high quality epidemiologic data on Neuroendocrine Neoplasms (NE) are lacking. There is limited knowledge on the contribution of prognostic factors on patient (pt) management. **Methods:** The multinational ENETS registry (www.enets.org/the_registry.htm) was launched in 2015. To date, data from 7 countries (Belgium, Czech republic, Germany, Greece, Poland, Spain, Switzerland) were analyzed, including age, gender, primary site, functional syndrome, WHO grade, stage according to TNM/ENETS, treatment modalities and overall survival (OS). **Results:** High quality data from 10,102 pts are presented. Median age at diagnosis is 59 y (10-102y), female represent 48%. Pancreas (2722 pts, 26%) and small intestine (2123 pts, 21%) NEN are the most frequent primaries. Functional syndrome is present in 26.9% of pts, 80% being carcinoid syndrome. Stage at diagnosis (n = 5297 pts) is IV in 46%, III in 16%, II in 11% and I in 27%. WHO grading (n = 7400) is G1 in 48%, G2 in 36% and G3 in 16%. Among metastatic pts (46% of total), liver is the most frequent site (77%), followed by lymph nodes (48%), bone, lung and peritoneum (10-15%). Surgery was performed in 23%, somatostatin analogues were given to 1/3 of pts, chemotherapy to 20%, molecular targeted therapies to 8% and PRRT to 9%. Median OS of all pts is 178 months. Five-year and 10-year OS are 74.5% and 60.9% respectively. OS is influenced by grade (G1: 279 months, G2: 167m, G3: 18m) and stage (I: Not reached, II: 233m, III: 160m, IV: 8m). Independent predictors of OS are primary site, functional syndrome and stage are independent predictors of OS; grade 2 vs grade 1 (HR 1.49, p < 0.001), grade 3 vs grade 1 (HR 7.56, p < 0.001), stage 3 vs stage 1 (1.59, p < 0.001) and stage 4 vs stage 1 (HR 3.99, p < 0.001). **Conclusions:** This analysis represents the largest multinational dataset of NEN patients to date, and highlights the contribution of WHO grading (Ki67) for predicting patients’ prognosis. In addition, it provides valuable information on patients’ demographics, tumor characteristics and applied therapies.

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Background: GEP-NETs are rare malignancies and their molecular characteristics are largely undefined. Here, we explored the underlying biology of GEP-NETs and the differences between gastrointestinal (GI) and pancreatic (PNET), high grade (HG) and low grade (LG) tumors. Methods: GEP-NETs were analyzed using NextGen sequencing (NGS) on 47 genes. NGS on somatic mutations, immunohistochemical analysis, and in-situ hybridization. Tumor mutation load (TML) was calculated based on somatic nonsynonymous missense mutations, and microsatellite instability (MSI) was evaluated by NGS of known MSI loci. Results: In total, 724 GEP-NETs were examined and categorized by location and grade: GI (N = 459), PNET (N = 226), LG (N = 135), and HG (N = 336). Demographics were as follow: female/male 51%/49%, median age 59 (19-90 yr). Among LG tumors, most frequently mutated genes were ATRX (13%), ARID1A (10%) and MEN1 (10%). Among HG, TPS3 (51%), KRAS (30%), APC (27%), ARID1A (23%) and RB1 (11%). Immune-related biomarkers showed lower prevalence in LG tumors compared to HG: TML-high 1% vs 7% (P = .05), MSI-H 0% vs 4% (P = .04), PD-L1 overexpression 1% vs 6% (P = .03). Compared to LG, HG NETs showed a higher mean TML (9.5mut/MB v 5.1, P < .0001), higher mutation rate in BRAF (5.4% v 0%, P < .0001), KRAS (29.4% v 2.6%, P < .0001) and PIK3CA (7% v 0.3%, P < .0001). When compared to GI, PNET carried significantly higher frequency of MEN1 (25.9% v 0%, P < .0001), FOXO3 (8.6% v 0.8%, P = .005), ATRX (20.6% v 2.0%, P = .007), and TSC2 (26.3% v 0.0%, P = .007), but lower frequency of mutations in APC (1.0% v 13.8%, P < .0001). Comparison between LG GI vs LG PNET is reported in the table. Conclusions: Significant molecular differences were observed in GEP-NETs by tumor location and grade, indicating differences in carcinogenic pathways and biology, as well as response to therapy. HG tumors may benefit from immune therapy over LG tumors. Mutations in several targetable genes may provide novel therapeutic options and suggests the utility of genomic profiling in this tumor type.

**Table: Gene Mutation Rates in LG and HG NETs**

<table>
<thead>
<tr>
<th>Gene</th>
<th>LG GI</th>
<th>HG PNET</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>0%</td>
<td>24%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ATRX</td>
<td>3%</td>
<td>5%</td>
<td>0.005</td>
</tr>
<tr>
<td>ARID1A</td>
<td>0%</td>
<td>5%</td>
<td>0.005</td>
</tr>
<tr>
<td>FOXO3</td>
<td>3%</td>
<td>12%</td>
<td>0.005</td>
</tr>
<tr>
<td>KRAS</td>
<td>0%</td>
<td>7.5%</td>
<td>0.005</td>
</tr>
<tr>
<td>TSC2</td>
<td>2%</td>
<td>2.2%</td>
<td>0.047</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>0%</td>
<td>56%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PR</td>
<td>4%</td>
<td>17%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TOP2A</td>
<td>0%</td>
<td>2%</td>
<td>0.005</td>
</tr>
<tr>
<td>TS</td>
<td>6%</td>
<td>13%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**MEN1**

**ATRX**

**ARID1A**

**FOXO3**

**KRAS**

**TSC2**

**CTNNB1**

**PR**

**TOP2A**

**TS**

**Figure 1: Values for 2015**

**2015: Gastrointestinal (Noncolorectal) Cancer**

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Clinical outcomes in patients with baseline renal dysfunction in the NETTER-1 study: 177Lu-Dotatate vs. high dose octreotide in progressive midgut neuroendocrine tumors. First Author: Jonathan R. Strosberg, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Might potential nephrotoxicity be a risk for therapy with 177Lu-Dotatate? Among patients randomised in the NETTER-1 study, nephrotoxicity and treatment efficacy were evaluated in the two study arms (177Lu-Dotatate (177Lu) vs. high-dose octreotide (Oct)) according to renal function categories at baseline (no dysfunction eCrClC-G ≥ 60 ml/min vs. mild dysfunction eCrClC-G = 50 – 59.99 ml/min vs. moderate dysfunction eCrClC-G < 50 ml/min).

Methods: Changes in renal function were assessed in the two arms per the three baseline categories, and analysed via Fisher’s exact test. The primary endpoint of the NETTER-1 study, progression-free survival (PFS), was evaluated after classifying the patients according to the baseline renal function categories (impaired vs. normal at baseline). Results: There were 93 patients with normal renal function, 11 with mild baseline renal dysfunction and 13 patients with moderate dysfunction in the 177Lu arm. Equivalent numbers were seen in the Oct arm (85 with normal function, 16 with mild and 9 with moderate dysfunction; p = 0.41825 for imbalance between the two study arms). The rates of deterioration of renal function over baseline (based on the two study arms for each of the three categories of baseline renal function), were similar (p = 0.70695; 1.0000; 1.000, respectively). In patients with no renal impairment in baseline (no dysfunction eCrClC-G ≥ 60 ml/min vs. mild dysfunction eCrClC-G = 50 – 59.99 ml/min vs. moderate dysfunction eCrClC-G < 50 ml/min), the NETTER-1 study did not show any evidence of nephrotoxicity associated with 177Lu treatment, even in patients with mild to moderate baseline impairment in renal function. Long-term analysis of renal function will be performed after classifying the patients according to the baseline renal function categories (impaired vs. normal at baseline).

Optimal cut points for Ki-67 proliferative index in predicting survival in high grade neuroendocrine tumors. First Author: Robert A. Ramirez, Louisiana State University Health Sciences Center, New Orleans, LA

Background: High grade (HG) neuroendocrine tumors (NETs) are rare neoplasms with limited literature regarding their prognostic course. HG-NETs generally demonstrate aggressive behavior. We hypothesized that patients diagnosed with HG-NETS with a Ki-67 proliferative index of ≥55% will have a worse prognosis. Methods: Records of patients with HG-NETs seen at our clinic between June 1, 2012 and June 1, 2017 were retrospectively reviewed. Demographics, pathologic characteristics, prior and treatment data were collected. Overall survival (OS) was measured from date of high-grade diagnosis to either the date of death or the study cutoff date (December 31, 2017). Subset analysis was performed based on Ki-67 at initial HG-NET diagnosis (< 55%, ≤55%) as well as Ki-67 at initial NET diagnosis (< 20%, > 20-54%, ≥55%). Results: Fifty-five patients were included in our study. Eleven patients were initially diagnosed with low/intermediate grade NETs (Ki-67 < 20%) and subsequently transformed to HG-NETs (Ki-67 > 20%) after progression. Median OS for the entire group was 18 months (m). The 6, 12 and 24m survival rate was 89%, 62%, and 40% respectively. A significant survival advantage was shown in patients with Ki-67 < 55% as shown in the table (p < 0.05) Survival did not vary significantly between primary tumor site. Low/intermediate (L/I) grade patients who transformed to HG-NETs had a median OS from HG diagnosis of 43m with 6, 12 and 24m survival rate of 100%, 82% and 64% respectively which was a significant compared to the entire cohort (p < 0.05).

Conclusions: Using a Ki-67 value of 55% is useful in conforming prognosis in patients with HG-NETs. Interestingly, patients who were initially diagnosed with L/I grade NETs and transformed to HG survived longer than those with an initial HG diagnosis. Treatment options for HG-NETs should take into account Ki-67 values.

Pembrolizumab (P) monotherapy in patients with previously treated metastatic high grade neuroendocrine neoplasms (HG-NENs). First Author: Namrata Vijayvergia, Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA

Background: There is currently no standard therapy for metastatic HG-NENs after progression on platinum based therapy and available chemotherapy is of limited benefit. Given the promising activity of checkpoint inhibitors in small cell lung cancer, we initiated a phase I trial of P (PD-1 mhibitor) in pts with previously treated metastatic HG-NENs. Methods: A prospective, open-label, phase 2 trial, for which pts with metastatic, histologically confirmed HG-NENs (Ki67 > 20%), excluding lung/thymus origin, were eligible after prior platinum based therapy. Other eligibility criteria included ECOG PS 0–1, adequate hematological, hepatic, and renal function. PT selection was not based on PD-L1 expression but archival tissue was mandated for correlative testing of immunophenotype. P was administered at a dose of 200 mg every 3 weeks intravenously and with radiographic evaluation was conducted every 9 weeks. The primary endpoint was overall response rate. Results: Between 11/2016 and 1/2018, 21 pts (11 males/ 10 females) were enrolled from two institutions and received at least one dose of P, thus completing accrual. Grade 3 toxicities were observed in 6 pts (28%) with 4 (19%) at least possibly related to P (elevated liver enzymes, fatigue, hypercalcemia and hyperkalemia). Other common grade 1-2 toxicities observed include fatigue (32%), diarrhea (26%) and nausea/vomiting (37%). Efficacy analyses and correlative studies are underway and will be presented at the meeting. Conclusions: P as a single agent can be safely administered to pts with advanced HG-NENs with similar toxicity profile as described previously for this agent. Efficacy data and correlative analysis will be presented at the annual meeting. Clinical trial information: NCT02939651.

Optimal cut points for Ki-67 proliferative index in predicting survival in high grade neuroendocrine tumors. First Author: Petur A. Vena, Renuka V. Iyer, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Serotonin is the cause of carcinoid symptoms and can signal the formation of fibroblasts via fibroblast growth receptors (FGFR). Nintedanib is an oral inhibitor of the FGFR pathway and several angiogenic signaling pathways thought to drive carcinoid tumor progression. We hypothesized that nintedanib may slow tumor progression in pts with progressing carcinoids in a phase 2 study. Methods: Thirty pts with unmetastatic/metastatic carcinoids on stable dose of somatostatin analogue for ≥12 months were included in our study. Eleven patients were initially diagnosed with low/intermediate grade NETs and transformed to HG survived longer than those with an initial HG diagnosis. Treatment options for HG-NETs should take into account Ki-67 values.
4104 Poster Session (Board #297), Sun, 8:00 AM-11:30 AM
Targeting advanced pancreatic cancer with activated T cells armed with anti-CD3 x anti-EGFR bispecific antibody. First Author: Lawrence G. Lum, Emily Comin Cancer Center, Charlottesville, VA

Background: Conventional chemotherapy (CT) for advanced pancreatic cancer (PC) is associated with dismal response rates and poor survival. Arming anti-CD3 activated T cells (ATC) with anti-CD3 x anti-EGFR bispecific antibody (EGFRBi) makes every ATC into a non-MHC-restricted EGFR-specific cytotoxic T lymphocyte. Engagement of CD3 on T cells and EGFR on PC cell lines leads to cytokine secretion, proliferation, cytotoxicity by ATC, and inhibition of tumor growth. Methods: We report on 9 LAPC and MPC patients (pts) (5 phase I and 4 phase II/III pts). In our phase I study at Karmanos Cancer Institute (KCI) on NCT0140874, EGFRBi-armed T cells (EGFR BiT cells) were used to target EGFR in 5 pts with unresectable or metastatic PC in a phase I dose escalation involving 3 weekly infusions of 10, 20, and 40 x 10^6 BiT cells per infusion followed by a booster infusion 3 months later for up to 80 x 10^6 BiT cells if they were stable or better. In a phase II study performed at KCI on NCT02620865 and continued at the University of Virginia (UVA) on NCT03269526, 4 pts received two infusions per week of 10^6 EGFRBi BiT cells for 4 weeks for a total of 8 x 10^10. Results: Following the BiT cells infusions in the phase I study at KCI, one pt was stable for 6.5 months and 2 pts who progressed after the infusions developed complete responses (CRs) to subsequent CT. Remarkably, pt IT20104 who was stable for 1 year on capecitabine had a “flare” or “pseudoprogression” after 3 BiTs infusions, but subsequently achieved a CR to capecitabine and has been off therapy for 1 year (40.8 months after enrollment). The median overall survival (OS) in 5 pts was 31.0 months (13.6, 14.5, 31.0, 40.8 (CR) and 42.5 months after enrollment) with the median time to progression (TTP) of 7.0 months. In summary, 5 of 5 pts in the phase I survived > 1 year. In the phase II study, two pts have stable disease at 2.3 and 21.5 months, respectively. The median OS is 31.0 months for all 9 patients. Conclusions: While these patients are selected, these results are promising. Targeting PC with EGFR BiT cells may improve OS in a small series of pts. The series provides evidence for anti-tumor activity of EGFR BiT cells and, in addition, the BiTs infusions may enhance tumor responses to subsequent CT. Clinical trial information: NCT01420874.

407 Poster Session (Board #296), Sun, 8:00 AM-11:30 AM
Gemcitabine plus nab-paclitaxel until progression or given sequentially with 5-fluorouracil plus irinotecan (FOLFIri3) for first-line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC). A randomized phase II study (PRODIGE 37-FIGREMAX), First Author: Julien Taitel, Sorbonne Paris Cité, Paris Descartes University, Department of Gastroenterology and Digestive Oncology, Georges Pompidou European Hospital, Paris, France

Background: Chemotherapy is effective in mPDAC but new approaches are still needed to improve patients (pts) survival and quality of life. We have previously published successful results of a sequential treatment strategy of gemcitabine followed by an intensified FOLFIri regimen with good efficacy and tolerability results. In the present study, we tested the same sequence with the new gemcitabine + nab-paclitaxel (G+A) first-line standard therapy. Methods: We randomized chemotherapy-naive pts with proven mPDAC, bilirubin levels ≤ 1.5 ULN and performance status (PS) 0-2 to receive in alternate G+A (MPACT regimen) (2 months (mo)) and FOLFIri3 (FIGREM regimen) (2 mo; arm A) or G+A alone (arm B). The primary objective was to increase the 6-mo progression-free survival (FPS) rate from 40% (HO) to 60% (H1; binomial exact method; required 124 pts). Analyses were done in preplanned modified intent-to-treat (mITT, pts who received at least one dose of treatment) and per-protocol (PP, pts reaching the 2 mo treatment switch) populations. Results: Between Nov 2015 and Nov 2016, 127 pts were enrolled. Mean age was 64 years (range: 38-76), PS was 0/1/2 in 37/5/11%, 2 no major imbalance for baseline characteristics was noted between arms. Main grade 3-4 toxicities per pt (%) were (arms A/B): diarrhea (13/2), nausea/ vomiting (9/2), neutropenia (7/0), febrile neutropenia (2/0), hypothyroidism (2/0), and peripheral neuropathy (13/20). No toxic deaths occurred. Best objective response rates (mITT) were A: 40% (95%CI, 28-54) and B: 25% (95%CI, 15-38), 6-mo FPS rates were A: 45% and B: 23% in mITT (n = 122; HR: 0.70; 95%CI, 0.48-1.03) and A: 60% and B: 30% in PP (n = 90; HR: 0.57; 95%CI, 0.34-0.95). Grade 3-4 toxicities in the arms were (A/B): diarrhea (7/0), febrile neutropenia (1/0), neutropenia (7/0), and neuropathy (13/20). Conclusions: The FIGREMAX strategy with G+A followed by FOLFIri3 every 2 mo, appears to be feasible and effective, with manageable toxicities and decreased neurotoxicity, in patients with mPDAC able to reach >2mo of treatment for their disease. 1-Troutouille EJC 2014 2-Von Hoff NEJM 2013 clinical trial information: NCT02927201.
4110 Poster Session (Board #299), Sun, 8:00 AM-11:30 AM
Phase 1b/2 trial of cancer stemness inhibitor nabapucasin (NAPA) + nab-paclitaxel (nPTX) and gemcitabine (Gem) in metastatic pancreatic adenocarcinoma (mPAC). First Author: Teresa S. Szabo, CanStem111P, Mayo Clinic, Phoenix, AZ

Background: NAPA is an oral investigational agent, hypothesized to inhibit cancer stemness pathways, including STAT3 pathway implicated in cancer stem-cell viability. We report updated data in a study of mPAC patients (pts) (NCT02231723) treated with NAPA + nPTX + Gem, including a subgroup of pts eligible for enrollment in the ongoing phase 3 study (NCT02993731, CanStem111P).

Methods: A phase 1b/2 multicenter study in mPAC pts was done to assess the recommended phase 2 dose, PFS, OS, and the rate of anticancer activity of NAPA + nPTX + Gem, including a subgroup of pts eligible for enrollment in the ongoing phase 3 study (NCT02993731, CanStem111P).

Conclusions: Of 59 study pts, 47 (79.7%) were treatment-naïve, and 12 (20.3%) had prior adjuvant therapy. There were no notable PK interactions or dose-limiting toxicities. The most common adverse events included grade 1 diarrhea, neuropathy, pyrexia, and grades 1/2 nausea and fatigue. Among all 59 pts, median OS was 40% (95% CI 31-49%) with median OS 21.3 (95% CI 17-26) months. 2-year OS for evaluable pts (19%) pts did not proceed to surgery. 92 (81%) pts had surgery; 83 (73%) during the neoadjuvant phase and overall. 22 (19%) pts did not proceed to surgery. 92 (81%) pts had surgery; 83 (73%) were resected with PD for resectable PDAC. 2-year OS for evaluable pts was 40% (95% CI 31-49%) with median OS 21.3 (95% CI 17-26) months. 2-year OS for resected pts was 52% (95% CI 37-59%) with median OS 25.4 (95% CI 22-30) months. Conclusions: For resectable PDAC, neoadjuvant therapy provides 2-year OS similar to pts able to receive standard adjuvant therapy. Importantly, futile PD was avoided in 27% pts. Further evaluation of neoadjuvant therapy in resectable PDAC is warranted as more active chemotherapy regimens emerge. Support: U10CA180821, U10CA180882; Clinical trial information: NCT00733746.

4111 Poster Session (Board #300), Sun, 8:00 AM-11:30 AM
A phase 1/2, open-label dose-escalation study of liposomal irinotecan (nal-IRI) plus 5-fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (OX) in patients with previously untreated metastatic pancreatic adenocarcinoma (mPAC). First Author: Andrew Peter Dean, St. John of God Hospital, Subiaco, Australia

Background: nal-IRI+5-FU/LV+OX (NAPOX) is being evaluated in patients with mPAC, with promising antitumor clinical activity of NAPOX. Dose escalation and expansion is ongoing. Clinical trial information: NCT02551991.

Conclusions: nal-IRI+5-FU/LV+OX (NAPOX) is being evaluated in patients with mPAC in a phase 1/2, open-label dose-escalation study. The current study (NCT02551991) is a phase 1/2, open-label trial to assess the safety, tolerability, and dose-limiting toxicities (DLT) of nal-IRI+5-FU/LV+OX (NAPOX) for the first-line treatment of patients with mPAC and to determine Phase 3 dosing. Method: NAPOX is being evaluated in patients > 18 years with previously untreated mPAC, with an ECOG performance status ≤ 1 and adequate organ function. Three of 4 dose-escalation cohorts of NAPOX, dosed on day 1 and 15, have been initiated. Safety and tolerability are the primary endpoints of this study, with assessment of exploratory efficacy signals. Results: As of 10 Nov 2017, 24 patients (Cohort A: n = 7; Cohort B: n = 7; Cohort C: n = 10) have received ≥ 1 dose of NAPOX (median age: 66.0 yrs, range: 44-78 yrs). 5 patients reported ≥ 1 DLT (Cohort A: n = 2/7; Cohort B: n = 1/7; Cohort C: n = 2/10). The most frequent treatment-emergent adverse events (TEAEs) were gastrointestinal (GI) disorders (Cohort A: 71%; Cohort B: 71%; Cohort C: 60%). Grade 3 or 4 TEAEs were GI disorders (Cohort A: 43%; Cohort B: 14%; Cohort C: 50%) and neuropathy (Cohort A: 43%; Cohort B: 29%; Cohort C: 40%). The best overall response was partial response (PR) in 6/24 patients (Cohort B: n = 3/7; Cohort C: n = 3/10). In Cohort B the (lowest and most tolerable cohort), n = 57 pts reached disease control (PR or stable disease > 16 weeks), with n = 47 pts were treated for > 24 weeks. Conclusions: NAPOX has shown a well-tolerated dose and promising antitumor clinical activity of NAPOX. Dose escalation and expansion is ongoing. Clinical trial information: NCT02551991.

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4115 Poster Session (Board #304), Sun, 8:00 AM-11:30 AM
Geographic and ethnic heterogeneity in the BRCA1/2 pre-screening population for the randomized phase III POLO study of olaparib maintenance in metastatic pancreatic cancer (mPC).
First Author: Taliya Golan, Institute of Oncology, Sheba Medical Center, Ramat Gan, Israel

Background: Germ-line mutations in BRCA1/2 (gBRCAm) can cause defective repair of double-strand DNA breaks and are a risk factor for mPC. The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib exploits homologous recombination repair deficiency in BRCAm tumors to produce synthetic lethality. Its efficacy is being evaluated in the POLO trial (NCT02184195). It is unknown how geography and ethnicity impact uptake of gBRCAm pre-screening in mPC.

Methods: POLO is an international, ongoing, placebo-controlled trial to determine efficacy of olaparib (tablet formulation) maintenance monotherapy in gBRCAm pts with mPC. Mandatory pre-screening involves gBRCA testing by Integrated BRACAnalysis (Myriad Genetic Laboratories/MGL). The current analysis includes pts with gBRCAm previously identified by MGL or via pre-screening. Demographicclinical history data were collected at enrollment.

Results: 2206 pts from 12 countries were tested between 10/14 and 12/17. Pre-screening identified 130/2179 (6.0%) with a new gBRCAm; 27 additional pts had a previously known gBRCAm that were confirmed by Myriad testing. Of the total 159/2206 (7.2%), Pre-screened pts were 57.2% male; 21% had early-onset mPC (Age in yrs: <33: 0.6%; 33-49: 20.3%; 50-64: 49.4%; 65-88: 29.7%). gBRCAm pts were younger (57.9 vs. 61.1 yrs). The countries with the highest rates of new gBRCAm by pre-screening were: USA 37/288 (12.8%), Israel 26/230 (11.3%), France 24/293 (8.1%), Germany 17/262 (6.5%), Italy 15/250 (6.0%), Spain 14/244 (5.1%), and Korea 13/249 (5.1%). Outside US and Israel (populations enriched in Ashkenazi Jews), gBRCAmwas newly identified in 96/1668 (5.7%). All pts with a known gBRCAm were White; all gBRCAm in African American/Asian/Hispanic pts (n = 19) were first identified by pre-screening. Conclusions: 6-7% unselected mPC have gBRCAm, with the highest rates in the USA, Israel, France, Germany, Italy, Spain, and Korea.

4116 Poster Session (Board #305), Sun, 8:00 AM-11:30 AM
Potentially curative combination of TGF-b1 inhibitor losartan and FOLFIRINOX (FFX) for locally advanced pancreatic cancer (LAPC): R0 resection rates and preliminary survival data from a prospective Phase II study.
First Author: Janet E. Murphy, Massachusetts General Hospital, Boston, MA

Background: FFX is under study in LAPC for its potential for curative resection, but the downstaging rate remains low. Preclinical data suggest that inhibition of the renin-angiotensin system with losartan reduces TGF-b1 activity, enhancing intratumoral penetration of chemotherapy by remodeling desmoplasia and improving perfusion. This study investigated the R0 resection rate of FFX/losartan in LAPC. Methods: LAPC pts (per NCCN criteria), ECOG PS 0-1 were enrolled in a single institution NCI-sponsored phase II study (NCT01821729). Pts received 8 cycles FFX/losartan. If the tumor was radiographically resectable after chemotherapy, pts received short-course chemoradiation (CRT) in 5 fractions (protons 25 GyE, capecitabine 825 mg/m2 bid). If the tumor still abutted vasculature, pts received CRT to 50.4 Gy with a vascular boost to 58.8 Gy. Primary endpoint was R0 resection rate. Secondary endpoints were mPFS, mOS and circulating biomarkers of losartan activity. Results: 50 pts enrolled from 8/2013 to 7/2017. One pt withdrew consent, and 49 pts were evaluable for this analysis. Median age was 63y (42-78), tumor size was 41mm (18-68). Tumor was in the pancreatic head in 31 (63%) of pts, 39 pts received 8 cycles of FFX/losartan, while 10 had fewer than 8 cycles due to progression (4), losartan intolerance (3), and toxicity (3). Grade 3 or greater toxicity occurred in 25 (51%) pts, including diabetes, thrombocytopenia, nausea, and neutropenia/febrile neutropenia. No single grade 3-4 toxicity occurred in more than 14% of pts. 46 pts (92%) of CRT; 7 pts (14%) of short-course CRT; 33 pts (66%) had long-course CRT. 39 pts underwent attempted surgery, with 34 pts resected. R0 resection was achieved in 30 pts (61% of evaluable pts, 88% of resected pts), with R1 resection in 4 pts. Overall mPFS was 17.5 months and mOS 31.4 months. Among resected pts, mPFS was 21.3 months and mOS was 33.0 months. Biomarker analyses showed superior OS in pts with lower plasma levels of HGF at baseline. Conclusions: FFX/losartan achieved a remarkably high (61%) R0 resection rate in LAPC pts. A multi-center randomized Phase II trial is planned.
Clinical trial information: NCT01821729.

4117 Poster Session (Board #306), Sun, 8:00 AM-11:30 AM
Nab-paclitaxel plus S-1 followed by S-1 maintenance therapy as a first-line strategy for advanced pancreatic adenocarcinoma.
First Author: Yan Shi, Chinese PLA General Hospital, Beijing, China

Background: Growing evidence support maintenance therapy (MT) offer clinical benefit in pancreatic, colorectal and lung cancers. In our phase II trial, nab-paclitaxel plus S-1 (NPS) showed encouraging objective response rate (ORR) as first-line treatment in advanced pancreatic adenocarcinoma (APAC), in which S-1 was an option as MT after NPS. Our observational study aims to evaluate the effectiveness and tolerability of stratagically using S-1 MT after NPS in APAC.

Methods: Between Jan 2014 and Oct 2017, 122 patients with APAC treated with NPS were included in this observational study. In patients without progression after at least 4 cycles of NPS (nab-paclitaxel, 240mg/m2 every 3-week; S-1, 80-120 mg/d by per body surface area on day 1-14 of each 21-day cycle) treatment discontinued due to any reasons, S-1 monotherapy was allowed to be given as MT at physician’s discretion according to patients’ desire and ECOG performance status. Patients were followed up every 2 months until death. ORR, progression-free survival (PFS), overall survival (OS) and safety were measured. Results: In 8 locally advanced and 14 metastatic APACs, ORR, median PFS and OS were 49.2%, 7.5 (95%CI 6.0 to 9.0m) and 10.7 months (95%CI 8.6 to 12.8m), respectively. Total 84 patients had no progression after a median of 4 cycles of NPS (2 to 8 cycles), in which 49 had a median of 4-cycle S-1 MT (1 to 32 cycles). Median FFS and OS in patients with S-1 MT were 10.4 months (95% CI 9.7 to 12.9m) and 16.7 months (95% CI 14.5 to 18.9m) compared to 5.1 months (95% CI 4.7 to 5.5m) and 8.1 months (95% CI 6.4 to 9.8m) without S-1 MT (P = 0.001). In patients with stable disease (n = 31), MFS and mOS in S-1 MT group were 10.4 (95% CI 6.9 to 13.9m) and 16.4 months (95% CI 13.8 to 19m) compared to 5.2 (95% CI 4.3 to 6.1m) and 8.1 (95% CI 6.7 to 9.5m) without S-1 MT (P < 0.05). Survival rates were 79.1% and 65.7% at 1 year, 61.9% and 33.4% at 2 years in patients with or without S-1 MT, respectively. S-1 MT group had a higher incidence of grade 3 or 4 leukopenia/neutropenia (20.4%) compared to 12.8% in the group without MT. Conclusions: Maintenance with S-1 after NPS was effective and well tolerated in APAC, which offered a new first-line strategy for APAC with a promising OS and PFS.
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Safety, efficacy and pharmacodynamics (PD) of MEDI9447 (oleclumab) alone or in combination with durvalumab in advanced colorectal cancer (CRC) or pancreatic cancer (panc). First Author: Michael J. Overman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Oleclumab is a human mAb that binds to CD73 and inhibits production of immunosuppressive adenosine. This is a first-in-human study to investigate the safety, efficacy, and pharmacodynamics of oleclumab alone or in combination with durvalumab in patients (pts) with advanced panc or MSS-CRC. Methods: A 3+3 dose-escalation design was followed in which pts received one of 4 escalating doses of oleclumab IV with or without durvalumab 10 mg/kg IV Q2W until disease progression, followed by study expansion with high dose of oleclumab plus durvalumab 10 mg/kg Q2W. AE and tumor response (RECIST v1.1) were assessed. Free soluble CD73 and cell surface CD73 on lymphocytes were measured by ELISA and flow cytometry, respectively. Tumoral CD73 was centrally assessed by an in situ enzyme assay and IHC. Results: The initial dose-escalation and PD exploration enrolled 42 monotherapy and 24 combination pts with no reported DLTs. The minimum target serum concentration was exceeded at the top 2 doses. Sustained decrease in free soluble CD73 and CD73 on peripheral T cells was demonstrated across all doses and pts. Decreased CD73 enzymatic activity was observed in all evaluable frozen tumor biopsy samples (n = 4) 20 days after treatment with the top 2 doses of oleclumab. Treatment with oleclumab alone decreased tumoral CD73 expression (5/9) while increasing CDB+ TILs in all 5 samples. Subsequently, durva + oleclumab high dose was selected for expansion in 2/1 CRC (2 pts) and 2/20 panc (2 and 3L) pts; SD was observed in 2/21 CRC and 3/20 panc (6.5%), AST (6.5%), and ALP (6.5%). PR was observed for 1/21 CRC (5L) and 2/20 panc (1 and 3L) pts; PR was observed in 2/21 CRC and 3/20 panc pts. Duration of treatment for subjects with disease control was 84-322 days (CRC) and 28-232 days (panc). Treatment is ongoing for 1 CRC (322 days) and 2 panc pts (140 and 182 days). Conclusions: Treatment with oleclumab and durvalumab has a manageable safety profile and PD consistent with mechanism of action. Combination therapy has encouraging clinical activity in pan and potentially in CRC pts. Clinical trial information: 02503774.

4125 Poster Session (Board #314), Sun, 8:00 AM-11:30 AM
Adjuvant treatment for resected sub-centimeter T1 pancreatic cancer. First Author: Walid Labib Shaib, Winship Cancer Institute of Emory University, Atlanta, GA

Background: The standard of care for pancreatic cancer (PC) patients with resected stage I to III is adjuvant chemotherapy. The role of adjuvant treatment for sub-centimeter T1 stage is unknown. This study evaluated treatment patterns in surgically resected PC and no prior therapy. Patient demographics, tumor histology, treatment modalities, and survival trends were examined between 2004 and 2013. Adjuvant therapies were analyzed. Kaplan-Meier analysis and the log-rank tests were performed to determine the unadjusted association between overall survival (OS), size and treatment. Results: A total of 964 patients met criteria for inclusion. The median age was 66 (32-90). Majority were Caucasian (N = 807, 83.7%); 53.5% were female (N = 515), and moderately differentiated (N = 447, 46.4%). Tumors of 1-cm constituted 71.2% (N = 666), 28.8% < 1 cm (N = 178). Majority had negative surgical margins (N = 887, 93.3%). Patients who received surgery alone were 48.3% (N = 466); 27.5% received adjuvant chemotherapy (N = 265), and 22.6% had adjuvant chemotherapy and radiation (N = 218). Patients with < 1 cm tumors who received adjuvant chemotherapy had a median OS that was not reached v. 85.3 mo who received surgery alone (P = 0.41). In patients with 1-2 cm tumors, the OS for patients who received adjuvant treatment was 70.7 mo v. 38.8 mo for patients who received surgery alone (P < 0.0001). The 12-mo, 24-mo, and 60-mo survival was 93.2%, 75.6% and 53.6% respectively, v. 72.5%, 61.0%, and 31.0%, respectively, for patients who received surgery alone. These results of adjuvant therapy for tumors < 1 cm v. 1-2 cm are parallel for patients who received adjuvant chemotherapy (P = 0.08), and any adjuvant radiation (P = 0.15). Conclusions: This is the first report of adjuvant treatment analysis for resected PC patients with sub-centimeter stage I disease. Adjuvant treatment does not appear to improve survival in sub-centimeter T1, stage I PC.

4126 Poster Session (Board #315), Sun, 8:00 AM-11:30 AM
Precision medicine for pancreatic cancer patients: preliminary results from the know your tumor program. First Author: Emanuel Petricoin, George Mason University, Manassas, VA

Background: To demoratize the implementation of precision medicine (PM) in the care of pancreatic cancer patients, the Know Your Tumor (KYT) program was initiated US-wide using a turn-key PM operating system that produces a treatment decision support tool/report. Methods: Tumor samples were obtained for 640 patients from 287 high-volume academic and local community-based practices across 6 US states. Oncologists performed an institutionalized workflow within an IRB-approved registry protocol from patient intake through multi-omic molecular profiling, integration of treatment history followed by computational analysis to produce a treatment decision support tool of patient-tailored therapeutic options. Longitudinal outcome is collected on every patient along with treatment decisions, and patient experience. Results: Tumor samples were adequate for next-generation sequencing in 96% and immunohistochemistry in 91% of patients. KRAS mutations were identified in 92% of pancreatic ductal adenocarcinomas. A tumor board reviewed the results for each patient and found actionable genomic alterations in 50% of patients with (27% highly actionable) and actionable proteomic alterations (excluding chemopredictive markers) in 5%. Actionable alterations commonly found were in DNA repair genes (BRCA1/2 or ATM mutations, 8.4%) and cell cycle genes (CDKN1A/2/3 or CDK4/6 alterations, 8.1%). A subset of samples was assessed for actionable phosphoprotein markers. At date, 126 (19.7%) patients have utilized a molecularly matched therapy. Patients with highly actionable biomarkers who received matched therapy (n = 17) had a median progression-free survival (PFS) of 4.1 months, significantly longer than patients without highly actionable biomarkers (n = 72; PFS = 2.8 months; adjusted P-value = 0.03). Conclusions: A comprehensive PM system can be implemented in community and academic settings and can provide actionable findings observed in ~25% of pancreatic cancers. Patients whose tumors have highly actionable molecular alterations and who receive matched therapy demonstrated significantly increased PFS. Our findings support expansion and further prospective evaluation of precision oncology in pancreatic cancer.
4127 Poster Session (Board #316), Sun, 8:00 AM-11:30 AM
Chemotherapy and radiotherapy application for pancreatic cancer in Europe and USA: An international population-based study. First Author: Lei Huang, German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: The role of chemotherapy in the treatment of pancreatic cancer (PaC) has been well-established, while radiation plays ambiguous roles. This large-scale international population-based study aimed to investigate the trends and variations in the application of chemotherapy and radiotherapy for PaC in Europe and the US and to explore the application determinants.

Methods: Population-based data from multiple European national cancer registries and the US Surveillance, Epidemiology, and End Results (SEER)-18 database during 2003-2014 were analyzed. Temporal trends and geographical variations in the application of chemotherapy and radiotherapy were quantified using age standardization. Associations between treatment and demographic and clinical characteristics were assessed using multi-variable logistic regression.

Results: A total of 141,533 PaC patients were analyzed. From 2003-2005 to 2012-2014, chemotherapy application rates increased in most countries and more strongly among resected cancers, while radiation rates were generally low with a slight decline or no obvious trend. In 2012-2014, 13.1% (Estonia) to 64.4% (Belgium) of patients with resected PaC and 18.1% (Slovenia) to 60.0% (Belgium) of those with unresected cancer underwent chemotherapy. Radiation was administered in 2.6% (the Netherlands) to 26.7% (the US) of resected and 0.7% (the US) to 6.2% (Belgium) of unresected tumors. Strong temporal and geographical variations were observed. Patterns and strengths of the associations between treatment and demographic and clinical characteristics differed between countries and treatment stages, and location differed substantially between resected and unresected diseases and varied greatly across countries. Conclusions: Administration of chemotherapy but not radiotherapy for PaC increased during the last decade in Europe and the US. The evidence from randomized trials majorly supporting chemotherapy does not seem to have been implemented into the wider clinical practice in many countries. The uptake strongly varied between countries, highlighting the need for standardization in PaC treatment to improve patient care.

4129 Poster Session (Board #318), Sun, 8:00 AM-11:30 AM
High prevalence of hereditary cancer syndromes and outcomes in adults with early-onset pancreatic cancer. First Author: Maria Fernanda Montiel, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Most patients with Pancreatic Ductal Adenocarcinoma (PDAC) are diagnosed over the age of 65. Individuals diagnosed under the age of 60 are considered to be early-onset and potentially at high risk for a genetic predisposition. We aimed to determine the prevalence of germline mutations among early-onset PDAC, as well as their influence in prognosis.

Methods: A High Risk Cohort (HRC) and a General Cohort (GC) were included in this study. The HRC patients were patients with PDAC who met referral criteria for genetic counseling and were seen at The University of Texas MD Anderson Cancer Center (MDACC) from 2005-2016. The GC patients had metastatic PDAC and were seen at MDACC between 2010-2016. Either gene-specific (targeted) or panel DNA germline sequencing for the 13 most common genes associated with pancreatic cancer (ATM, APC, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PMS2, PALB2, STK11, EPCAM, PMS2) was performed. Survival outcomes were analyzed with respect to germline mutation status and age by using Kaplan-Meier curves. Results: A total of 409 patients underwent genetic testing (277 from High Risk and 132 from General Cohort). As expected, the HRC had higher prevalence of germline mutations compared to the general cohort: 17.3% vs 6.81%. The most common mutations in both cohorts were in BRCA1/2 and MMR genes. Patients younger than 60 years old had significantly higher prevalence of germline mutations in both the HRC (OR: 1.93 +/-1.03-3.70, P: 0.039) and GC (4.78 +/-1.10-32.95, P: 0.036). With respect to clinical outcomes, the GC patients with germline mutations had significant higher median survival as compared to patients without mutations, 18.2 months vs 9.2 months respectively (HR: 0.44, 95% CI of HR: 0.25-0.76, P= 0.030). In the HRC, only patients older than 60 years old with mutations had better overall survival compared to the group without mutations (HR: 0.40, 95% CI of HR: 0.20-0.80, P= 0.038). Conclusions: Germline mutations are highly prevalent in patients with PDAC of early-onset and can be predictive of better outcomes. Considering emerging screening strategies for relatives carrying susceptible genes as well as impact on therapy choices, genetic counseling and testing should be encouraged in young onset PDAC.

4128 Poster Session (Board #317), Sun, 8:00 AM-11:30 AM
DNA repair deficiency, genomic instability and immune profiling in a phase 1 study of locally advanced pancreatic cancer patients treated with veliparib, gemcitabine and radiotherapy. First Author: W. Seiwatz, G. Schattner. Genomic Oncology Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Background: A phase I trial of veliparib (V), gemcitabine (G) and radiotherapy (RT) was conducted to determine the maximum tolerated dose (MTD) and clinical activity in patients with and without DNA damage repair (DDR) defects. Methods: LA patients were treated with weekly G (1000 mg/m2), daily RT (8 Gy/15 fractions) and daily V 20 mg BID for 3 cycles escalated per Bayesian method followed by standard chemotheraphy. DAVID was used to interpret differential gene expression. Cox regression model was used to identify DDR pathways associated with survival. Next generation sequencing (NGS) identified genetic mutations involved in DDR, tumor mutation burden (TMB) and microsatellite instability (MSI) status. Blood samples were interrogated for PAR protein and cytokines using an ELISA and electro-chemiluminescent array, respectively. The log-rank test was used to evaluate differences in PFS and OS. Results: 34 patients were enrolled from 2013 to 2016. MTD of veliparib was 40 mg BID with gemcitabine 400 mg/m2 and RT (30 Gy/15). 12 patients experienced DLT (93.3% lymphopenia, 8.3% neutropenia). Median PFS and OS were 10 and 15 months, respectively. Gene expression analysis identified DDR defects in 50% of patients. Median PFS and OS were significantly higher for these biomarker positive patients (17 vs. 8 mos, p < .01; 22 vs. 12 mos, p < .001, respectively). NGS identified 10 DDR mutations which were not prognostic of outcome. Clonal DDR defects (TMB) were identified in 63% of patients. Conclusions: The combination of V, G and RT was well tolerated. DDR alterations were identified in a large proportion of patients and were associated with improved PFS and OS. Whereas most patients were MSS and had low TMB, those with higher levels of pro-inflammatory cytokines were likely to harbor DDR alterations which were associated with improved outcomes. Clinical trial information: NCT03245541.

4130 Poster Session (Board #319), Sun, 8:00 AM-11:30 AM
Outcome driven persona-typing for precision oncology: Beyond a genomics-oriented view to tumor biology. However, a multi-omic view to tumor biology and more accurate outcome prediction is emerging. Combining this with treatment history, clinical-epidemiological data, and outcome data may provide patient-specific descriptors that in N-dimensional space constitute population-based “personas” that share common outcome destinies and identify response predictors to any given therapy. Methods: We utilized our database from 919 pancreatic adenocarcinoma patients within our ongoing registry study as a feasibility study. Clinical exome (315 genes by NGS) and proteomic data (24 proteins by IHC) as well as previous and current treatment history, epidemiological data and outcome data were collected on every patient. Overall Survival (OS) was calculated and 10 individual outcome “personas” were created that spanned short-term survival (< 6 months) to long term survival (32-110 months). Statistical analysis of individualized gene, protein, specific treatment type, disease stage, location, age, gender, ethnicity, was used to determine key principal components that significantly (p < 0.05) described each outcome persona to create a unique persona-type identifier. Results: Proteomic information was significantly associated with outcomes more frequently than genomic information (p = 0.02). Longest term outcome personas (OS > 32 months) were characterized by increased PD1 and decreased TS protein levels along with increased frequency of BRCA2 genomic alterations and treatment with off-label targeted therapy. Shorter term personas (OS < 6 months) were described by high TS protein levels along with genetic alterations in MYCL1, MYS3T, VEGFA, ZNF703 and KEL. Conclusions: Personas-typing can be used to define and map key characteristics that associate with survival and specific treatment. In the future, individual patients can be mapped to predefined personas that could more accurately describe outcome destiny and optimized/personalized therapy options.
An investigator initiated multicenter phase II study of paclitaxel, ramucirumab with nivolumab as the second-line treatment in patients with metastatic gastric cancer. First Author: Tomohiro Nishina, Shikoku Cancer Center, Matsuyama, Japan

Background: Paclitaxel (PTX) and ramucirumab (RAM) is a standard regimen as the second-line treatment for metastatic gastric cancer (mGC). In the phase III ATTRACTION-2 trial, nivolumab (NIVO) significantly improved overall survival (OS) over placebo for metastatic gastric cancer (mGC) patients (pts) refractory to standard therapies. In preclinical models, anti-angiogenesis agents with immune-checkpoint inhibitors demonstrated enhanced activity against cancer cells compared with either drug alone. Methods: We are conducting a phase II study to determine the recommended phase II dose (RP2D) and evaluate the efficacy, safety and biomarkers of the combination regimen of PTX, RAM with NIVO in pts with mGC as the second-line treatment. Key eligibility criteria are: mGC pts who were refractory or intolerant to fluoropyrimidine and platinum in the first-line treatment, and had no prior immunotherapy; an age of 20 years or older; ECOG performance status of 0-1; and controllable hypertension. Phase I is designed to determine RP2D in the dose de-escalation design of NIVO (q4w, 3 mg/kg on days 1 and 15 or level 1 and 1 mg/kg for level 1) with fixed doses of PTX and RAM (Arm A: 80 mg/m² on days 1, 8, and 15 and 8 mg/kg on days 1 and 15, respectively). Primary endpoint is progression-free survival (PFS) rate at 6 months in pts treated with RP2D. Using a single stage binomial design, this study requires 43 pts, with a PFS rate at 6 months of 50% deemed promising and 35% unacceptable (one-sided alpha = 0.1; beta = 0.25). 35 patients have been enrolled since Feb 2017. Clinical trial information: UMIN000025947.

Methods: This is a prospective, multicenter, randomized, investigator initiated phase II trial. Patients with advanced gastric or esophagogastric junction cancer will be randomized 2:1 to FOLFIRI (irinotecan 180 mg/m²; 5-FU 400 mg/m²; leucovorin 400 mg/m²; 5-FU 2400 mg/m² on day 1 and 15 of a 28-day cycle) plus ramucirumab 8mg/kg every two weeks (Arm A) or paclitaxel 80 mg/m² (days 1, 8, 15 of a 28-day cycle) plus ramucirumab 8mg/kg every two weeks (Arm B). Primary endpoint of the trial is OS after 6 months, based on the ITT population. The experimental therapy (FOLIRI + Ramucirumab; n = 67) is considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounts to 65% or more, as this corresponds to the efficacy of the standard ramucirumab-paclitaxel regimen according to the RAINBOW study in the western population. Secondary endpoints are progression-free survival, response rate, safety and tolerability. Currently (Jan 2017) 40 of planned 111 patients are randomized. Clinical trial information: NCT03081143.

A randomized phase 2, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-positive gastric cancer. First Author: Kensei Yamaguchi, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: There is no HER2-targeted therapy for patients with HER2-positive gastric cancer who progressed on trastuzumab-based therapy. DS-8201a is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a cleavable peptide-based linker (deruxtecan), and with a high drug-to-antibody ratio of 7 to 8. In the ongoing phase 1 DS8201-A-J101 trial, DS-8201a showed a manageable safety profile and promising antitumor activity in salvage-line subjects with gastric cancer who previously received trastuzumab (confirmed objective response rate (ORR) of 45.5% at Oct 16, 2017 data cutoff) (Iwasa et al, ASCO-GI 2018). Methods: The randomized, phase 2, multicenter, open-label, DESTINY-Gastric01 study will assess the efficacy and safety of DS-8201a in HER2-expressing gastric cancer subjects. The primary cohort, HER2-positive (IHC 3+ or IHC 2+/ISH+) subjects who progressed after ≥2 prior regimens and previously received trastuzumab, will be randomized (2:1) to DS-8201a (6.4 mg/kg dose; once every 3 weeks) or physician’s choice (irinotecan or paclitaxel). Two nonrandomized exploratory cohorts will assess the efficacy and safety of DS-8201a in subjects with HER2-low gastric cancer (IHC 2+/ISH- and IHC 1+, respectively) who are treatment-naive to HER2-targeted therapies. The primary endpoint is ORR assessed by an independent central review; secondary endpoints include overall survival (OS), progression-free survival, duration of response, disease control rate, pharmacokinetics, and safety (as shown in ClinicalTrials.gov). The primary analyses for ORR and interim OS analysis will occur after all subjects complete tumor assessments on week 18 and when approximately 108 OS events are observed, whichever comes later. The primary cohort will enroll 180 subjects; providing 92.9% power to detect a difference between the ORR of 40% for DS-8201a vs 15% for physician’s choice. Each exploratory cohort will enroll a maximum of 20 subjects. Enrollment began in October 2017. As of Feb 13, 2018, 12 of 180 subjects have been enrolled. Clinical trial information: NCT03329690.

MORPHEUS: A phase Ib/II trial platform evaluating the safety and efficacy of multiple cancer immunotherapy (CIT) combinations in patients (pts) with gastric or pancreatic cancer. First Author: Do-Youn Oh, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of (South), Korea

Background: Multiple cancers have been treated successfully with CIT; nonetheless, only subsets of pts experience durable response with CIT monotherapy. CIT combinations may therefore be needed to simultaneously address multiple mechanisms of cancer immune evasion. The MORPHEUS platform consists of multiple, global, open-label, randomized Phase Ib/II trials designed to investigate CIT combinations in pts with different tumor types. Using a randomized trial design, multiple CIT combination arms will be compared with a single control arm. Furthermore, the design of the trials will aid in the development of CIT combinations by identifying early signals and offers the flexibility to open new treatment arms with novel CIT combinations and to close arms that show minimal clinical activity or unacceptable toxicity. Various CIT combinations that simultaneously enhance immune cell priming and activation, tumor infiltration and/or recognition of tumor cells for elimination will be evaluated. Here, we describe MORPHEUS Phase Ib/II trials in pts with gastric or gastroesophageal junction cancer (GC) or metastatic pancreatic ductal adenocarcinoma (mPDAC), both representing major unmet medical needs. Methods: MORPHEUS-GC (NCT03281369) will enroll 2 cohorts, including pts with advanced unresectable or metastatic GC who are chemotherapy naive or have progressed on platinum- or fluoropyrimidine-based chemotherapy. MORPHEUS-PDAC (NCT03193190) will enroll pts with mPDAC who have progressed on 1 line of prior chemotherapy. Additional eligibility criteria include measurable disease per RECIST v1.1 and accessibility of the tumor for biopsy. Pts in both trials will be randomized to one of the CIT combination arms or a control arm (up to 8 arms across 2 cohorts in GC; 4 arms in PDAC). In the setting of unequivocal disease progression/toxicity, pts may be eligible to switch to a different CIT combination arm. Safety measures and investigator-assessed ORR per RECIST v1.1 are primary endpoints. PFS, OS, DCR and DOR are among the secondary endpoints. Exploratory biomarkers will also be examined. Clinical trial information: NCT03281369 and NCT03193190.
Background: FGFR2b overexpression and FGFR2 gene amplification occurs in approximately 10% of patients with gastric cancer (GC) and is associated with a poor prognosis and the presence of metastases. Bemarituzumab, a first-in-class afucosylated, humanized IgG1 monoclonal antibody, selectively binds to FGFR2b, inhibiting ligand binding and blocking receptor activation and downstream signaling. Bemarituzumab is glycoengineered to enhance antibody-dependent cell-mediated cytotoxicity (ADCC). A phase 1 study of bemarituzumab monotherapy in solid tumors (Catenacci D, Rha S, Bang YJ, et al. ASCO 2017) identified no dose-limiting toxicities. The reported response rate was 19% (4/21) with median duration of response of 15.4 weeks in patients with late-line GC and high FGFR2b overexpression.

Based on the safety and activity profile of bemarituzumab monotherapy in GC, we designed a phase 3 trial with safety run-in of bemarituzumab in combination with mFOLFOX6. **Methods:** The FIGHT study (FPA144-004; NCT03343301) is a global, randomized, double-blind, placebo-controlled phase 3 trial evaluating bemarituzumab and mFOLFOX6 in first-line patients with advanced GC. Patients with unresectable locally advanced, or metastatic GC, we designed a phase 3 trial with safety run-in of bemarituzumab in combination with mFOLFOX6. **Methods:** The FIGHT study (FPA144-004; NCT03343301) is a global, randomized, double-blind, placebo-controlled phase 3 trial evaluating bemarituzumab and mFOLFOX6 in first-line patients with advanced GC. Patients with unresectable locally advanced, or metastatic GC are eligible if tumors have FGFR2 amplification by circulating tumor DNA (ctDNA) or FGFR2b overexpression by immunohistochemistry (IHC). Eligible patients are randomized 1:1 to bemarituzumab + mFOLFOX6 versus placebo + mFOLFOX6. Bemarituzumab or placebo dosing will continue every 2 weeks until radiographic or clinical disease progression, or intolerable toxicity. The primary endpoint is overall survival (OS) and key secondary endpoints include investigator-assessed progression-free survival (PFS) and objective response rate (ORR). Pathologic analyses will be event-based.

PFS and objective response rate (ORR) will be the primary endpoints and safety will be determined using per protocol population. The secondary analysis will include all randomized patients as well as the safety population. The phase III phase trial is preceded by a Phase 1 safety evaluation in solid tumors to Poly ADP ribose polymerase inhibition (PARPi). Gastric cancer is also known to have a homologous recombination deficiency (HRD) subtype. We therefore proposed combining the PARPi olaparib with ramucirumab in metastatic gastric and GEJ adenocarcinoma. **Methods:** The study is sponsored by the Clinical Therapy Evaluation Program and is active throughout the Extended Therapeutics Clinical Trials Network. A phase 1 3+3 dose escalation is followed by an open-label single arm phase 2. The primary objective of phase 1 is to establish the safety dose of olaparib with ramucirumab. The phase 2 primary objective is to measure efficacy by the objective response rate (ORR). Eligible patient received ≥ 1 line of prior chemotherapy, no prior angiogenesis inhibitors or PARPi, have measurable disease, usual laboratory parameters, and ECOG PS 0-1. Phase 1 will enroll 9-18 patients depending on DLT. In phase 2, the BROCA-HR gene panel is an integrated biomarker. This panel includes 87 DNA repair genes, 17 of which would be expected to confer HRD when mutated. In gastric cancer these HRD genes are mutated in up to 35% of tumors reported in COSMIC and TCGA. However, given the uncertainty of the biomarker distribution in our study, 40 patients will be enrolled in phase 2 and the ORR will be stratified by biomarkers distribution. The H3 is ORR of < 5% based on the historical control for ramucirumab. The H3 is 25% ORR for the BROCA-HR positive cohort and 20% for the negative cohort. A pre-treatment biopsy for BROCA-HR testing is required. Other studies include detecting mutational signatures, PAR substrate analysis, and PDX generation. Phase 1 is currently enrolling. Clinical trial information: NCT03008278.

**Background:** The FDA approved pembrolizumab for treating pts with recurrent locally advanced or metastatic G/GEJ adenocarcinoma whose disease has progressed on or after ≥2 prior therapies and whose tumors express PD-L1 (combined positive score ≥1). Combining chemo with pembrolizumab in the neoadjuvant/adjuvant setting may be beneficial for pts with locally advanced, resectable G/GEJ cancer. **KEYNOTE-585** is a phase 3, randomized, double-blind study of chemo + pembrolizumab versus chemo + placebo as neoadjuvant/adjuvant treatment for locally advanced resectable G/GEJ cancer. **Methods:** Key eligibility criteria are age ≥18 years; previously untreated G/GEJ adenocarcinoma (Siewert type 2 or 3 or tumor; Siewert type 1 tumor eligibility limited to those for whom planned treatment is perioperative chemo and resection), with no evidence of metastatic disease; planned surgery after preoperative chemo; ECOG performance status 0-1; adequate organ function; no active autoimmune disease. Pts will be randomly assigned 1:1:1 to chemo + pembrolizumab (arm 1) or chemo + placebo (arm 2). Pts will receive neoadjuvant (preoperative) chemo + pembrolizumab every 3 weeks (Q3W) for 3 cycles or chemo + placebo Q3W for 3 cycles followed by surgery, then adjuvant chemo + pembrolizumab Q3W for 3 cycles or chemo + placebo Q3W for 3 cycles, then monotherapy with pembrolizumab or placebo Q3W for 11 cycles; treatment will occur for up to 17 cycles. Chemo is cisplatin 80 mg/m² IV (Q3W) + either capcitabine 1000 mg/m² orally daily twice or 5-fluorouracil (5-FU) 800 mg/m² IV (investigator’s choice). Pembrolizumab 200 mg was administered by IV. Adjuvant monotherapy is pembrolizumab (arm 1) or placebo (arm 2). In a separate safety cohort, 5-FU 2500 mg/m² IV + docetaxel 50 mg/m² IV + oxaliplatin 85 mg/m² IV (Q3W) + lefradulin 200 mg/m² IV (Q3W) is being evaluated as a potential chemo option. Primary end points are overall survival, event-free survival per central review, and pathologic complete response (no invasive disease and histologically negative nodes) rate. Adverse events are graded per NCI CTCAE v4.0 and will be monitored for 30 or 90 days after treatment. Pts will be followed for survival. Planned enrollment is 800 pts. Clinical trial information: NCT03221426.

**Background:** Gastric cancer remains a significant health problem in the US and globally with more than 951,600 annual cases worldwide. Moreover, the incidence of GEJ-centered adenocarcinoma is increasing dramatically in Western countries. First line chemotherapy has a ∼12 month median survival. In 2nd line, ramucirumab, a monoclonal antibody against VEGFR2 is approved as single agent or with paclitaxel. Hypoxia mimetic agents such as ramucirumab down-regulate homologous recombination and sensitize tumors to Poly ADP ribose polymerase inhibition (PARPi). Gastric cancer is also known to have a homologous recombination deficiency (HRD) subtype. We therefore proposed combining the PARPi olaparib with ramucirumab in metastatic gastric and GEJ adenocarcinoma. **Methods:** The study is sponsored by the Clinical Therapy Evaluation Program and is active throughout the Extended Therapeutics Clinical Trials Network. A phase 1 3+3 dose escalation is followed by an open-label single arm phase 2. The primary objective of phase 1 is to establish the safety dose of olaparib with ramucirumab. The phase 2 primary objective is to measure efficacy by the objective response rate (ORR). Eligible patient received ≥ 1 line of prior chemotherapy, no prior angiogenesis inhibitors or PARPi, have measurable disease, usual laboratory parameters, and ECOG PS 0-1. Phase 1 will enroll 9-18 patients depending on DLT. In phase 2, the BROCA-HR gene panel is an integrated biomarker. This panel includes 87 DNA repair genes, 17 of which would be expected to confer HRD when mutated. In gastric cancer these HRD genes are mutated in up to 35% of tumors reported in COSMIC and TCGA. However, given the uncertainty of the biomarker distribution in our study, 40 patients will be enrolled in phase 2 and the ORR will be stratified by biomarkers distribution. The H3 is ORR of < 5% based on the historical control for ramucirumab. The H3 is 25% ORR for the BROCA-HR positive cohort and 20% for the negative cohort. A pre-treatment biopsy for BROCA-HR testing is required. Other studies include detecting mutational signatures, PAR substrate analysis, and PDX generation. Phase 1 is currently enrolling. Clinical trial information: NCT03008278.

**Background:** The FDA approved pembrolizumab for treating pts with recurrent locally advanced or metastatic G/GEJ adenocarcinoma whose disease has progressed on or after ≥2 prior therapies and whose tumors express PD-L1 (combined positive score ≥1). Combining chemo with pembrolizumab in the neoadjuvant/adjuvant setting may be beneficial for pts with locally advanced, resectable G/GEJ cancer. **KEYNOTE-585** is a phase 3, randomized, double-blind study of chemo + pembrolizumab versus chemo + placebo as neoadjuvant/adjuvant treatment for locally advanced resectable G/GEJ cancer. **Methods:** Key eligibility criteria are age ≥18 years; previously untreated G/GEJ adenocarcinoma (Siewert type 2 or 3 or tumor; Siewert type 1 tumor eligibility limited to those for whom planned treatment is perioperative chemo and resection), with no evidence of metastatic disease; planned surgery after preoperative chemo; ECOG performance status 0-1; adequate organ function; no active autoimmune disease. Pts will be randomly assigned 1:1:1 to chemo + pembrolizumab (arm 1) or chemo + placebo (arm 2). Pts will receive neoadjuvant (preoperative) chemo + pembrolizumab every 3 weeks (Q3W) for 3 cycles or chemo + placebo Q3W for 3 cycles followed by surgery, then adjuvant chemo + pembrolizumab Q3W for 3 cycles or chemo + placebo Q3W for 3 cycles, then monotherapy with pembrolizumab or placebo Q3W for 11 cycles; treatment will occur for up to 17 cycles. Chemo is cisplatin 80 mg/m² IV (Q3W) + either capcitabine 1000 mg/m² orally daily twice or 5-fluorouracil (5-FU) 800 mg/m² IV (investigator’s choice). Pembrolizumab 200 mg was administered by IV. Adjuvant monotherapy is pembrolizumab (arm 1) or placebo (arm 2). In a separate safety cohort, 5-FU 2500 mg/m² IV + docetaxel 50 mg/m² IV + oxaliplatin 85 mg/m² IV (Q3W) + lefradulin 200 mg/m² IV (Q3W) is being evaluated as a potential chemo option. Primary end points are overall survival, event-free survival per central review, and pathologic complete response (no invasive disease and histologically negative nodes) rate. Adverse events are graded per NCI CTCAE v4.0 and will be monitored for 30 or 90 days after treatment. Pts will be followed for survival. Planned enrollment is 800 pts. Clinical trial information: NCT03221426.
IMbrave150: A randomized phase III study of 1L atezolizumab plus bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma.

First Author: Richard S. Finn, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: Hepatocellular carcinoma (HCC) is a lethal disease with the highest mortality-to-incidence ratio of any solid tumor. The current standard of care for 1L treatment of patients (pts) with locally advanced or metastatic HCC is sorafenib (sor), a multikinase inhibitor. Single-agent treatment in- volving inhibition of PD-L1/PD-1 immune checkpoint or VEGF has shown activity –atezolizumab (atezo; anti-PD-L1), an antibody that promotes enhanced tumor lymphocytes, perivascular lymphocytes and tertiary lymphoid organ subtypes. The appearance of favorable microenvironment features (enhanced tumor lymphocytes, perivascular lymphocytes and tertiary lymphoid organ subtypes) after induction therapy in resected EC suggest tumors may respond favorably to immune-based therapy and in particular to PD-1 based checkpoint blockade when combined with cRT prior to surgical resection. In addition, pre-clinical models suggest that esophageal radiation significantly increases PD-L1 expression. The Phase III Attraction 2 study has demonstrated activity of nivolumab in a subset of heavily pretreated patients with gastroesophageal cancer. This trial proposes to evaluate the safety/efficacy of induction nivolumab or nivolumab plus ipilimumab prior to concurrent chemoradiation plus nivolumab in operable stage III/II EC. Methods: This is an open-label, single-arm, multicenter clinical study that will enroll 32 patients. Eligible subjects consist of adults with histologically confirmed, resectable stage III/II EC/GEJ located below the carina. Subjects must be newly diagnosed and cannot have received prior treatment. A pre-treatment biopsy is required prior to two cycles of induction nivolumab (arm A) or one cycle of induction nivolumab/ipilimumab (arm B). A repeat research biopsy is performed after the induction phase and prior to initiation of the 25% reduction of PD-L1 expression. If ≥ 20% power and a 1-sided 0.05 significance level. An interim analysis will assess safety and Mandur tumour progression grading (TRG) after 15 pts become evaluable. If ≥ 5 pts achieve TRG 1-3 the trial will expand to 40 pts. Secondary endpoints are ORR, PFS and OS. Exploratory objectives will investigate dynamic changes of immune infiltrates in baseline and on-treatment biopsies and correlate neoepitope load, blood lymphocyte activation and faecal microbiome with tumour response. Recruitment commenced in July 2017 and 40 pts will be recruited in 2 years. Clinical trial information: NCT03399071.

IMbrave150 Poster Session (Board #325a), Sun, 8:00 AM-11:30 AM

A multi-center randomized phase II study of nivolumab in combination with gemcitabine/cisplatin or ipilimumab as first line therapy for patients with advanced unresectable biliary tract cancer.

First Author: Vaibhav Sahai, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI

Background: Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis with a median overall survival (OS) less than 12 months. This randomized, multi-institutional, phase 2, two-arm study is designed to investigate the role of combinational immunotherapy, using nivolumab with chemotherapy (gemcitabine/cisplatin) or as dual immunotherapy (nivolumab and ipilimumab) in pts with advanced BTC. Methods: Key eligibility criteria include historically confirmed advanced, unresectable biliary adenocarcinoma (intrahepatic or extrahepatic and gallbladder) without prior systemic treatment, measurable disease per RECISTv1.1, ECOG PS 0-1, and absence of autoimmune disease and/or chronic steroid use. Primary objective is to evaluate the progression-free survival (PFS) rate at 6 months. Secondary objectives include evaluation of overall response rate (ORR) per immune related (ir)RECIST, median PFS and OS and safety in this patient population. Exploratory objectives include identification of biomarkers of response and mechanisms of resistance through serial (before, on and post therapy) biopsies and blood collection, including sequential whole exome/ transcriptomic analysis and immune cell subset analysis (tissue and blood). Arm A therapy provides gemcitabine 1000 mg/m2, cisplatin 25 mg/m2 on days 1, 8 with nivolumab 360 mg on day 1 every 3 weeks for 6 months. In the absence of disease progression, pts may continue single agent nivolumab for up to 2 years. Arm B therapy includes nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks for up to 2 years in absence of disease progression. Accrual goal is 32 evaluable pts per arm. Using a null hypothesis value of 59% median PFS at 6 months, and an 80% alternative hypothesis, this ongoing study has > 80% power, with a one-sided alpha of 0.05 to identify treatment efficacy of one or both arms in study. Clinical trial information: NCT03101566.

IMbrave150 Poster Session (Board #325b), Sun, 8:00 AM-11:30 AM
Background: BTCs are rare and have a poor prognosis. These cancers are often diagnosed at advanced stage with limited treatment options and poor overall survival (OS). Overexpression of epidermal growth factor receptor (EGFR), HER2, HER3, and HER4 vary from 23-57%, 4-13%, 12-23% and 59-60% of BTCs, respectively. Varlitinib is a small molecular tyrosine kinase inhibitor of EGFR, HER2 and HER4 with potent antitumor effect in preclinical BTC models. Varlitinib also demonstrated tumor shrinkage responses and durable disease stabilization in BTC patients in Phase IIb study. Methods: A randomized, double-blind, placebo-controlled phase 2 (Part 1)/3 (Part 2) study to compare the efficacy of varlitinib (300 mg BID, every day) versus placebo, when combined with capecitabine (1000 mg/m², BID for 14 days). The primary endpoints of Part 1 are objective response rate (ORR) and progression-free survival (PFS) and for Part 2 is OS. Eligible patients include those with confirmed advanced or metastatic 2nd line BTC, including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer and carcinoma of ampulla of Vater. Patients must have failed gemcitabine-contained 1st line systemic treatment. The target sample size is 482 patients, and enrollment has started on May 24, 2017. Safety data will be listed and summarized. Co-primary endpoints of Part 1 will be analyzed using data from an Independent Central Review of radiological data. A Hochberg procedure will be used to control the familywise error rate for Part 1 at the 10% level (one-sided). For Part 2, the primary endpoint, OS, will be tested at the two-sided 5% significance level. Clinical trial information: NCT03093870.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase I/II study of ribociclib plus everolimus in patients (pts) with metastatic pancreatic neuroendocrine adenocarcinoma (mPAC) refractory to chemotherapy. First Author: Benjamin Adam Weinberg, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: mPAC has a poor prognosis, with a 5-year survival rate of 2.3%. CDK4/6 is often deregulated in mPAC due to loss of CDKN2A via homozygous deletion or epigenetic silencing, resulting in the loss of the p16INK4a protein that naturally inhibits CDK4/6. CDK4/6 inactivates the retinoblastoma protein (RB), allowing E2F family transcription factors to promote cell cycle progression. Inhibitors of CDK4/6 have been ineffective as single agent therapy. Our efforts are focused on producing new treatment options for CC and PDAC patients using epigenetic and immunotherapy combinations.

Methods: This is a phase I/II, single-arm, open-label study. Eligible pts are ≥ 18 years old, have histologically confirmed mPAC with progression on at least one prior therapy. Eligibility criteria include having measurable disease, performance status (PS) ≤ 1, and good end organ function. Exclusion criteria include history of autoimmune disease. Patients have a pre-treatment biopsy followed by 14 days of entinostat at a dose of 5 mg oral once a week followed by a second biopsy. Patients then begin nivolumab 240 mg every two weeks combined with entinostat until disease progression. The study is planned with 27 evaluable subjects per histology based on a Simon’s two-stage design that allows early termination for lack of efficacy. The primary objective of the trial is to determine whether the combination of entinostat plus nivolumab yields a clinically compelling antitumor activity measured as objective response rate (ORR), assessed by RECIST 1.1). Secondary objectives will include progression-free survival (PFS), overall survival (OS), safety and immunological correlates to evaluate the effect of HDAC inhibition on the TME by interrogating clinical specimens. The clinical study has been activated in November 2017 (NCT03250273) and 10 of planned 54 patients have been enrolled. Clinical trial information: NCT03250273.
Phase Ib study of gemcitabine, nab-paclitaxel, and ficlatuzumab in patients with advanced pancreatic cancer.
First Author: Kimberly Perez, Dana-Farber Cancer Institute, Boston, MA

Background: Nearly 80% of patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) present with advanced, unresectable disease at the time of diagnosis, and as a result only about 4% will live 5 years after diagnosis. Paired-related homeodomain transcription factor 1 (Pmrx1) isoforms - Pmrx1a and 1b - are involved in pancreatic development, pancreatitis, and carcinogenesis. Pmrx1a stimulates metastatic outgrowth and mesenchymal-epithelial transition (MET). Pmrx1b promotes invasion and epithelial-mesenchymal transition (EMT). HGF is a novel transcriptional target of Pmrx1b. Ficlatuzumab is a potent and selective recombinant humanized hepatocyte growth factor (HGF) inhibitory immunoglobulin G subclass 1 monoclonal antibody. It neutralizes HGF/c-Met binding and HGF-induced c-Met phosphorylation thereby inhibiting the c-Met pathway which has been associated with progression from primary to metastatic disease. In preclinical pancreatic adenocarcinoma models, inhibition of Pmrx1b-HGF signaling using ficlatuzumab in combination with gemcitabine reduced primary tumor volume and eliminated metastatic disease. Methods: Patients with untreated metastatic PDAC will be enrolled in a phase Ib dose escalation study with 3+3 design and three dose cohorts of ficlatuzumab administered with gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) given 3 weeks on and 1 week off, followed by 18 patient expansion phase at maximally tolerated dose (MTD) for safety evaluation. The primary objective is to identify the MTD of ficlatuzumab when administered in combination with gemcitabine and nab-paclitaxel in patients with previously-unresected advanced pancreatic cancer. Secondary objectives include evaluation of safety, response rate and progression-free survival. Exploratory objectives will be performed to evaluate tumor and serum biomarkers of disease response. This analysis will evaluate inclusion of a BDX044 prognostic/promotective signature detected in patients' pre-treatment blood sample. A pre-treatment biopsy will also be interrogated for HGF and markers of the c-Met pathway; by immunohistochemistry, exome and transcriptome sequencing, and organoid development. Clinical trial information: NCT03316599.

First Author: Vincent M. Chung, City of Hope, Duarte, CA

Background: Pancreatic cancer remains a deadly disease and despite advances in chemotherapy treatment, survival for most patients is still less than one year. Refractory pancreatic cancer has not been responsive to checkpoint inhibitors and only in the small population of MSI high pancreatic cancers have we seen activity. The microenvironment plays an important role in limiting the immune response and researchers from the Salk Institute demonstrated that vitamin D receptor agonists sensitize both primary and metastatic pancreatic cancer lesions to checkpoint blockade. Our trial evaluates the role of maintenance immunotherapy and paricalcitol after best response to cytotoxic chemotherapy. Methods: This SU2C Catalyst trial will be conducted at Honor Health Research Institute, City of Hope National Medical Center and University of California San Diego Moores Cancer Center. Patients with metastatic pancreatic cancer receiving standard first line chemotherapy are eligible to be randomized after achieving best response defined as stable disease or partial response for 2 months with no further shrinkage of ≥ 20% on scan and no further decrease of ≥ 10% in the tumor markers while on chemotherapy. Patients with a serum vitamin D level ≥ 50 ng/mL are excluded. The primary endpoint of this study is to estimate the percentage of patients progressing at 6 months while on maintenance therapy. Secondary objectives evaluate the toxicity of the combination, overall survival and tumor mutational landscape. Twenty-four patients are planned to be randomized 1:1 to either pembrolizumab 200 mg every 3 weeks plus paricalcitol 25 mcg 3 times per week or pembrolizumab plus placebo. Archival tumor tissue is required and optional biopsies are allowed to further explore biomarkers of response to therapy. ClinicalTrials.gov Identifier: NCT03316562 Support: Stand Up To Cancer (SU2C) Gates Merck Clinical trial information: NCT03313152.

A phase II study of trifluridine/tipiracil (TAS-102) in combination with nanoliposomal irinotecan (NAL-IRI) in advanced GI cancers.
First Author: Olatunji B. Alese, Winship Cancer Institute, Atlanta, GA

Background: Trifluridine/tipiracil (FTD/TPI, also known as TAS-102) is a combination of a nucleoside analogue and a thymidine phosphorylase inhibitor. TAS-102 has shown activity in 5FU-resistant colorectal cancer (CRC). Nano liposomal-Irinotecan (Nal-IRI) achieve higher intra-tumor concentrations than irinotecan (142-fold) and its major metabolite, SN-38 (9-fold), resulting in superior anti-tumor activity compared to free irinotecan in multiple xenografts. Clinical trials have established activity of Nal-IRI combined with 5FU in pancreatic cancer. The combination of Nal-IRI with the more potent nucleoside analogue TAS-102 may result in a more effective systemic therapy regimen in CRC and pancreatic cancer. The aim of this study is to define the recommended phase II dose (RP2D) of the combination and evaluate the activity in pancreatic cancer and CRC. Methods: Eligible patients for the phase I trial include stage IV or locally advanced unresectable gastrointestinal adenocarcinomas, who have failed at least one prior therapy; age ≥ 18 years, ECOG PS 0-1 and measurable disease per RECIST 1.1. The trial design is standard 3+3. TAS-102 is administered orally in four dose levels of 25, 25, 30, 35mg/m^2 BID on days 1-5, with Nal-IRI at corresponding dose levels of 50, 70, 70, 70mg/m^2 IV on day 1, in 14-day cycles. After recommended phase II doses are established, an expansion phase will enroll 20 patients with pancreatic adenocarcinoma (Arm A) and 20 patients with colorectal adenocarcinoma (Arm B). These patients must have either locally advanced unresectable or metastatic disease, and have failed at least one prior therapy that must not have included irinotecan. The primary endpoint of the phase II portion is overall response rate. Simon's two-stage design will be used for each arm of the phase II component. In the first stage, 10 patients will be accrued. If there are fewer than 1 responder, the cohort will be stopped. Otherwise, additional patients will be accrued for a total of 20. Enrollment to the escalation phase I portion of the study started in February 2018. Clinical trial information: NCT03368963.

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TPS4156 Poster Session (Board #332b), Sun, 8:00 AM-11:30 AM
SM-88 in advanced cancers of the pancreas (SMACP). First Author: Marcus Smith Noel, University of Rochester James P. Wilmot Cancer Institute, Strong Memorial Hospital, Rochester, NY

Background: Treatment options for recurrent/refractory advanced pancreatic cancer (PC) include largely ineffective toxic therapies or palliation. SM-88 is a combination of dysfunctional tyrosine derivative (TD), mTOR inhibitor, CYP3a4 inducer and oxidative stress catalyst, previously reported to have activity in a variety of cancers and settings, with no drug-related grade 3 or 4 toxicity (J Clin Oncol 36, 2018 (suppl 65; abstr 175). JCO 35, 2017 (suppl e14060)) Reduction of circulating tumor cells (CTCs), RECIST responses and prolonged duration of clinical benefit have also been reported with SM-88 in multiple tumor types including PC. (J Clin Oncol 31, 2013 (suppl; abstr e22095). We now describe an ongoing trial of SM-88 in metastatic PC.

Methods: This is a prospective, multicenter (> 30 sites), North American Phase II trial evaluating SM-88 as a single agent in recurrent PC. Eligible patients must have histologically confirmed metastatic PC, ECOG PS < 3, measurable disease, and have received at least one line of prior therapy. MSI-H tumors must have had targeted therapy. 36 subjects are planned for the 1st stage, randomized 1:1 between the currently utilized clinically active regimen and a 2x dose, with the expansion dose selected based on clinical benefit and toxicity. Using Fleming’s two-stage minimax design, based on overall response rate at 16 weeks, with H(0): ORR < 8% vs H(1): ORR > 16%, 99 evaluable will be required, yielding > 95% power to detect an OS of 90% at 6 months compared to historical OS of 55%. Primary endpoints are ORR and OS. Secondary endpoints include PFS ratio, disease control rate duration of response, and time to subsequent treatment. Correlative studies include circulating tumor cells (CTCs) with genomics, tumor markers, EORTC QLQ-C30 and EORTC QLQ-PAN26, pharmacokinetics, insulin, leptin and neutrophil:lymphocyte ratio. A known toxicity of SM-88 is skin hyperpigmentation and this will be investigated as a possible biomarker along with other exploratory endpoints. Clinical trial information: NCT pending.

TPS4157 Poster Session (Board #333a), Sun, 8:00 AM-11:30 AM
A phase II trial of cabozantinib and erlotinib for patients with EGFR and c-MET co-expressing metastatic pancreatic adenocarcinoma. First Author: Olumide B. Gbolahan, Indiana University School of Medicine, Indianapolis, IN

Background: c-MET over-expression is associated with poor prognosis in pancreatic ductal adenocarcinoma (PDAC) (Kim JH, et al. Oncotarget; 2017; 8(42):73098-104). It activates mitogenic signaling, and this may contribute to the limited clinical activity of erlotinib in metastatic PDAC, given the cross talk between EGFR and c-MET (Dulak AM, et al. Oncogene. 2011; 30(33):3625-35). Preclinical data suggests that the addition of cabozantinib (a c-MET antagonist) to erlotinib improves anti-tumor activity. The combination in our lab resulted in significant tumor shrinkage, and improvement in survival in a KPC PDAC mouse model compared to treatment with gemcitabine alone. We designed this study to determine the activity of cabozantinib (Cabo) and erlotinib (Eelo) in a population of metastatic PDAC patients whose tumors co-overexpress EGFR and c-MET.

Methods: This is an open-label, single arm, Phase II trial of the combination of cabozantinib and erlotinib in metastatic PDAC. Male and female patients > 18 years with biopsy proven PDAC and radiologically measurable metastatic disease following progression after first line therapy are eligible. Patients must have tumor tissue available from a surgical resection or archived core biopsy. Only those whose tumors express at least 2+ EGFR and c-MET based on IHC will be allowed on study. ECOG PS 2 and above, prior use of Cabo or Erl, and symptomatic brain metastasis or brain metastasis requiring steroids will exclude patients from this study. Cabo will be administered at 40mg daily dose and Erl to 100mg daily dose every 28 days without break. The study will be conducted at the Indiana University Simon Cancer Center. The primary objective is to demonstrate at least a 15% radiographic response rate for the combination in the selected population. Secondary objectives include assessment of safety and estimation of PFS, ORR and OS. Based on a Simon two stage design, we will enroll 37 patients in total. If there are no radiologic responses in the 11 patients tested in the first stage, the trial will be closed. The trial opened in November 2017, we have screened 4 patients and enrolled 1. ClinicalTrials.gov Identifier: NCT03213626.
ABSTRACT WITHDRAWN
Updated results from the enfortumab vedotin phase 1 (EV-101) study in patients with metastatic urothelial cancer (mUC). First Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: Patients (pts) with mUC are in need of novel therapies. Enfortumab vedotin (EV) is an antibody-drug conjugate that delivers a microtubule-disrupting agent to tumors expressing Nectin-4, a protein overexpressed in most urothelial cancers. Preliminary results of the EV-101 study (NCT02091999) suggest EV is active and tolerable at the RP2D of 1.25mg/kg; updated results from pts with mUC treated at RP2D are reported.

Methods: Patients with mUC treated with ≥1 prior chemotherapy regimens who were ineligible for cisplatin received a 30-min infusion of EV on Day 1, 8, and 15 of each 28-day cycle. The primary objective was tolerability; anti-tumor activity (per RECIST v1.1), assessed by investigators every 8 wk, was a secondary objective. Results: As of 11 Jan 2018, 155 pts with mUC have been enrolled; 112 received EV at RP2D (median age 67 yr [range 24–86]). Bladder was the primary tumor site in 84 pts (75%) and 32 (29%) had metastases (LM). Ninety-one pts (81%) received prior platinum chemotherapy; 67 (60%) received ≥2 prior therapies in the metastatic setting, including 84 (75%) who had a checkowment inhibitor (CI). Consistent with previous reports, EV was generally well tolerated. Grade 3 toxicity (90%) was the most commonly reported treatment-related AE (TRAE). The most common Grade 3 AE, regardless of attribution, were anemia (7%), hyponatremia (6%), urinary tract infection (6%), and hyperglycemia (5%). Four pts experienced a fatal TRAE (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, multi-organ failure). Confirmed CI and TRAE were 67 (57%) and 46 (38%), respectively; ORR = 33% (95% CI 24.7–42.9). An unconfirmed PRs were pending assessment. Additionally, ORRs in study subpopulations were 32% (prior CI, n = 84), 37% (CI naive, n = 27), and 26% (LM/prior CI, n = 23). Overall median DOR was 24.3 wk (95% CI 16.3–47.3) and PFS was 23.1 wk (95% CI 12.4–24.1). Median OS was 12.6 mo (95% CI 8.1–14.8) with 76 pts (68%) censored and OS at 6 mo was 75.1%. However, time-to-event endpoints continue to evolve. Conclusions: Enfortumab vedotin has encouraging ORR and PFS in heavily pretreated pts with mUC, including pts with LM and prior C1 treatment. Survival data awaits maturity. Clinical trial information: NCT02091999.

A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS). First Author: Andrea Necchi, Istituto Nazionale dei Tumori, Milan, Italy.

Background: Atezolizumab is a PD-L1 inhibitor which is licensed in metastatic urothelial cancer. This study investigates the efficacy and safety of neoadjuvant atezolizumab given prior to cystectomy in operable muscle invasive transitional cell carcinoma bladder cancer. Methods: This single arm phase 2 study investigated 2 cycles of atezolizumab (1200mg Q3) prior to cystectomy in muscle invasive transitional cell carcinoma (T2-4aNOMO). Pathological complete response (pCR) occurring in ≥20% of patients was the primary endpoint. Biomarker analysis on sequential tissue was a co-primary endpoint. Cross sectional imaging was performed at baseline and prior to cystectomy which occurred 4–8 weeks after atezolizumab. Radiological response was assessed. Adverse events (AEs) and surgical complications were assessed using CTCAE v4.03 and the Clavien-Dindo classification. The IDMC reviewed the first 69 patients (of 85) and supported this interim presentation. Results: The median age of the 69 patients was 73 years (range 54-88). At baseline pT2, T3, T4 disease occurred in 77%, 16% and 7% of patients respectively. 14 (20%) patients had only 1 cycle (8 due to AEs). 7 patients did not have cystectomy (1 disease progression, 2 treatment related AE). There was 1 potential treatment related death during treatment/perioperative period (cardiovascular disease). Treatment related grade 3/4 toxicity occurred in 12% of patients. Grade 3 or 4 surgical complications occurred in 31% of pt. The pCR rate was 18/62 (29%) [95%CI: 18% to 42%] (pT0 23%, Tis 6%, T1 10% T2 21% T3 24% T4 16% stage at surgery), 39% of patients were down staged to non-muscle invasive disease. 3/18 (17%) of the pCR patients had pT3aD4 at baseline. 30 patients had sequential imaging and radiologically measurable disease at baseline. 23% [95%CI, 10% to 42%] and 13% [95%CI, 4% to 31%] of these patients radiologically responded and progressed respectively. Biomarker results including T cell infiltration and PD-L1 status before and after therapy will be presented. Conclusions: Neoadjuvant atezolizumab is safe and associated with a meaningful pathological CR rate at 2 cycles. Further exploration is justified. Clinical trial information: NCT02662309.

Preoperative pemolizumab (pembro) before radical cystectomy (RC) for metastatic urothelial bladder carcinoma (MIUC): Initial clinical and biomarker findings from the phase 2 PURE-01 study. First Author: Andrea Necchi, Istituto Nazionale dei Tumori, Milan, Italy.

Background: MIUC is an aggressive disease and cisplatin-based neo-adjuvant chemotherapy is administered in a minority of pts. Pembro is an EMA and FDA-approved therapy for metastatic UC after platinum failure or for cisplatin-ineligible pts. Methods: PURE-01 (NCT02736266) is an open-label, single-arm, phase 2 study. Pts have predominant UC histology and ct≤3bN0 stage. Pts are enrolled regardless of cisplatin eligibility. Disease assessment is made via CT, PET/CT, and multiparametric bladder MRI (mpMRI). Pts receive 3 cycles of pembro 200mg q3w before RC. Pathologic complete response (pT0) in ITT population is the primary endpoint. The H0 is pT0 =<25% and H0 pT0 =<15%, 71 pts will be enrolled, with 43 pts at first stage according to MinMax design. =>7pT0 are required at first stage. Biomarker analyses include: IHC PD-L1 combined positive score (CPS, Dako 22C3) and genomic sequencing with hybrid-capture based comprehensive genomic profiling. Tumor mutational burden (TMB) is determined on 1.1 Mbp of sequenced DNA and reported as mutations (mut) per megabase (Mb) and microsatellite instability is determined on 114 loci. Results: From 02/17-02/18, the first stage of 43 pts was completed (36M, 7F). 27 had cT3, 16 cT2; 59% had TMB > 10 mut/m; 93% TMB > 20 mut/m. All tumors were microsatellite stable. All pts had evident disease at mpMRI before RC. 45% had reversible G2 irAE. At the time of this analysis, 25 pts are evaluable for the primary endpoint. There were 8/25 pT0 (32%, 95%CI: 16.7-47.6) and 3 pTa/s (total pt < 2: rate 44%). In TURB samples, median CPS score for pT0 pts was 44.8% vs 17.4% non-pT0 pts (p < 0.001), mean TMB was 11.2 mut/Mb vs 11.2 mut/Mb, respectively. On 8 evaluable pts, substantial differences were found in pre- vs post-pembro genomic alterations (GA). Mean pre-pembro GA/tumor was 8.7; mean post-pembro GA/tumor was 7 (mean 47.5% overlapping GA). Conclusions: Pembro is safe and has already exceeded the pT0 responses required at first stage. PD-L1 CPS may be predictive of pT0 response, and full tumor biomarkers at first stage will be presented. Clinical trial information: NCT02736266.
A phase 1/2 study evaluating the efficacy and safety of the oral CXCR4 inhibitor X4P-001 in combination with axitinib in patients with advanced renal cell carcinoma. First Author: Ulka N. Vaishampayan, Karmanos Cancer Center, Detroit, MI

Background: X4P-001 is an oral, selective, allosteric inhibitor of the chemokine receptor CXCR4, which is a promising novel target in renal cell carcinoma (RCC). X4P-001 in combination with the tyrosine kinase inhibitor axitinib demonstrated greater than additive anti-tumor activity in xenograft models mediated by decreased myeloid-derived suppressor cell trafficking and reduced proangiogenic signaling. Methods: This is a Phase (Ph) 1/2 trial in patients (pts) with advanced clear cell RCC who have failed at least one prior therapy. The safety, tolerability, and recommended Ph 2 dose (RP2D) of X4P-001 in combination with axitinib was established in Ph 1. Here we report results for preliminary efficacy in both the Ph1 dose escalation cohorts and the Ph 2 expansion cohort of pts treated at the RP2D. Results: The Ph 1 portion of the study is completed and established the combination therapy to be safe and tolerable at the RP2D of 400 mg QD X4P-001 + 5 mg BID axitinib. As of 01 January 2018, data are available for 10 pts in Ph 1 and 41 pts in Ph 2 treated at the daily 400 mg dose (either 200 mg BID or 400 mg QD) of X4P-001 + 5 mg BID axitinib. The median age was 64 years (range 41-87). Patients had received a median of 2 prior lines of systemic therapy (1 line: 29%; ≥ 2 lines: 71%). Seven pts (13.7%) were discontinued from the study due to adverse events (AEs) regardless of relationship. Of the 22 clinically evaluable pts, the objective response rate was 31.8% (1 CR; 6 PR) and the disease control rate was 86.4%. Median duration on treatment was 24 weeks (range 2-84). The most common (≥ 10%) treatment-related AEs of any grade were diarrhea, fatigue, nausea, vomiting, dyspnea, nausea, blood creatinine increased, dry eye, headache, and hoarseness.

Conclusions: Preliminary results from the study demonstrate that X4P-001 + axitinib was clinically active in advanced RCC and well tolerated with a manageable safety profile. Enrollment in the Ph 2 portion is near-completion and updated study results will be reported. Clinical trial information: NCT02667886.
BMS-986205, an indoleamine 2,3-dioxygenase 1 inhibitor (IDO1), in combination with nivolumab (NIVO): Updated safety across all tumor cohorts and efficacy in pts with advanced bladder cancer (advBC). First Author: Josep Tabernero, Vall d’Hebron University Hospital, Barcelona, Spain

Background: NIVO (anti–PD-1) has shown durable responses and manageable safety (ORR, 19.6%; grade 3–4 treatment-related AEs [TRAES], 18%) in pts with advBC (Sharma P, et al. Lancet Oncol 2017), but prolonged survival in more pts requires additional approaches to overcome tumor evasion mechanisms. IDO1 allows tumor escape through kynurenine (KYN) production, which stimulates development of regulatory T cells and suppresses effector T-cell proliferation. Anti–PD-1 therapy can upregulate IDO1, supporting the rationale for combining NIVO with an IDO1. BMS-986205 is a selective, potent, once-daily (QD), oral IDO1 that works early in the IDO1 pathway to reduce KYN production. BMS-986205 + NIVO demonstrated a favorable safety profile and antitumor activity in heavily pretreated pts with select solid tumors (Luke J, et al. SITC 2017; NCT02658890). Updated safety across all tumor cohorts and efficacy in the advBC cohort are reported. Methods: Dose-escalation methods of this phase 1/2a, open-label study were previously described; during expansion, pts received BMS-986205 100 or 200 mg QD + NIVO 240 mg IV Q2W or 480 mg IV Q4W. Objectives included safety and ORR by RECIST v1.1 (includes unconfirmed [U] responses). Prior IO therapy was permitted in the advBC cohort. Results: Recruitment was December 15, 2016, to February 21, 2017, with 14% NIVO. TRAEs were reported in 51% of pts (grade 3–4, 12%), the most common being fatigue (13%) and nausea (10%); 16% pts (4%) discontinued due to TRAEs, and 1 pt died due to a TRAE (myocarditis). With a median follow-up of 17 wk (range, 4–53), the ORR among 29 pts with advBC was 34% (1 CR; 9 PR; 10 SD). 9 PRs were immune-oncological, of which 0–29 pts had no prior IO therapy; in these pts was 38% (1 u CR, 9 PR [1 u]), and the DCR was 54%. ORR in pts with tumor PD-L1 ≥ 1% (Dako PD-L1 IHC 28-8 pharmDx assay; n = 15) vs < 1% (n = 11) was 47% vs 27%.

Conclusions: BMS-986205 + NIVO was well tolerated, with a safety profile similar to that of other IO combination therapies. Proof-of-concept of NIVO observed in advBC, supporting further evaluation of BMS-986205 + NIVO. Updated data by dose and subgroup in the advBC cohort will be presented. Clinical trial information: NCT02658890.

Rogaratinib in patients with advanced urothelial carcinomas prescreened for tumor FGFR mRNA expression and effects of mutations in the FGFR signaling pathway. First Author: Markus Joerger, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Background: Activation of FGFR signaling is involved in a variety of malignancies including advanced urothelial cancer (UC). Rogaratinib is an oral pan-FGFR kinase inhibitor. We report here the results from a phase I expansion cohort in UC patients prescreened for FGFR-3 mRNA expression levels with particular attention to activity in patients (pts) with evidence of activating mutations in potential resistance genes, including PIK3CA and RAS. (NCT01976741) Methods: Pts with advanced urothelial carcinomas were selected based on high FGFR-3 mRNA expression in biopsy specimens. Somatic mutations in FGFR downstream signaling genes were detected by PCR array. Pts were treated with rogaratinib 800mg twice daily until tumor progression, intolerability, or withdrawal. Tumor response was assessed by RECIST, v1.1. Adverse events were reported using CTCAE v4.03 criteria. Results: A total of 219 UC pts were prescreened for FGFR-3 mRNA expression levels and FGFR3 activating mutations, with 99 samples (45%) found to be FGFR-positive. Of those, 87% of samples were positive for FGFR3 mRNA, 5% for FGFR1 mRNA and 8% were double FGFR mRNA-positive (FGFR1/2, 1/3 or 2/3). Frequency of FGFR3 activating mutations in UC samples was 7%, all of which had also high FGFR3 mRNA. Fifty one pts were evaluable for response (recruitment 2017–2018, median age 71, 12% (15/121) all PRs) and disease control rate (DCR) was 73% (37/51). Interestingly, 0/12 pts with a PR had a hotspot mutation in either PIK3CA or RAS-encoding genes whereas 7/14 pts with PD revealed such a mutation. ORR in PIK3CA/RAS wild type UC pts is 30.6 %. Ten FGFR-positive UC pts had prior immunotherapy treatment and DCR was 70% (7/10) treatment, 9 of whom had progressive disease as best response. For these 10 pts the ORR was 30% and the DCR 80%. Conclusions: Selection of pts for treatment with rogaratinib based on FGFR mRNA expression levels was feasible and identified drug-sensitive pts with and without underlying FGFR gene alterations. Rogaratinib had a favorable safety profile and showed promising activity in UC pts, with an ORR of 24%, including pts refractory to prior IO treatment but not with PIK3CA or RAS mutations. Clinical trial information: NCT01976741.

VinCap: A phase II trial of vinflunine chemotherapy in locally-advanced and metastatic carcinoma of the penis (CRUK/12/01). First Author: Lisa M. Pickering, St. Georges University Hospitals Foundation Trust and The Royal Marsden Foundation Trust, London, United Kingdom

Background: Platinum-based combination chemotherapy regimens are active in the treatment of penis cancer, but toxicity limits their value for patients with metastatic disease. VinCap was a phase II trial of vinflunine, a pyridone alkylating agent, in pts with the disease control rate for the non-platinum cytotoxic agent Vinflunine. Methods: A phase II single-arm trial was conducted. Eligible patients had measurable, histologically-proven squamous cell carcinoma (SCC) of the penis, staged M1; or MO,Tx,N3; or MO,Tx,N2 and deemed inoperable by multidisciplinary team; or MO, T4 any N, ECOG performance status. 0-2 adequate hepatic and renal function. Treatment was 4x21-day cycles of vinflunine (320mg/m2). In 22 evaluable patients ≥7 responses/ stabilizations were required to conclude a clinical benefit rate (CRB/CR/PR/SD) of at least 40% and exclude a rate of < 15% (p0 = 0.15, p1 = 0.40, k = 0.05, β = 0.80, Fleming-Hem design). Primary endpoint was CRB after 4 cycles of vinflunine. Secondary endpoints included objective response rate (ORR: CR/PR), safety, tolerability, progression-free survival (PFS) and overall survival (OS). Results: 25 patients (median age 68 years) were recruited from 8 UK centres between June 2014 and May 2017. 19 patients were M1. Of 22 patients who received treatment: 15 (68%) experienced grade 3/4 adverse events (AE); neutropenia was the most common AE (n = 5, 23%). Recruitment halted in Sep 2016 to investigate 2 treatment-related deaths (1 sepsis, not neutropenic; 1 neutropenic, not septic); reopened Nov 2016. 10 patients had clinical benefit, CRB = 45.5%, 95%CI: [24.8, 67.6], 12 month PFS: 16.7% (4.6-35.3). Median OS: 8.4 months, (3.2-14.1); 12 month OS: 33.7%, (15.4-53.1). Conclusions: CRB exceeded the threshold to recommend further study of this regimen by comparison to historical control reports in locally advanced and metastatic penis cancer. Toxicity profile in keeping with known profile of vinflunine. Vinflunine is an active agent in the treatment of locally advanced and metastatic SCC of the penis. Clinical trial information: NCT02057913.

Characterizing tumor immune microenvironment (TME) and outcomes for 409 patients (pts) treated on COMPARZ: Distinct clusters emphasize immune infiltration vs. angiogenesis. First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Growing evidence highlights the critical role of the TME for RCC biology and response to systemic therapy. We used integrated molecular profiling to characterize the tumor microenvironment (TME) in 409 patients (pts) treated on the phase 3 COMPARZ trial. Methods: We performed mRNA expression profiling (Affymetrix GeneChip HTA 2.0) and unsupervised consensus clustering from archival paraffin specimens. Clusters were characterized by gene set enrichment analyses (GSEA); transcriptional deconvolution; a 43 gene angiogenesis expression score; immunohistochemistry (IHC) for PD-L1 expression on tumor cells and macrophages; and mutation status for a defined list of genes. Findings were correlated with clinical outcomes using parametric and non-parametric tests. Results: mRNA clustering was done for 409 patients (212 sunbath, 197 pazopanib treated) and revealed 4 biologically distinct clusters (C1-C4) with significant differences in median overall survival (OS,P< 0.001-4) and progression free survival (PFS,P= 0.003). C4 displayed the worst outcomes and highest rate of IMDC poor risk features (45.7% pts); GSEA showed enrichment for inflammation signatures, e.g. IFN-γ responses. Immune deconvolution demonstrated the most immune-infiltrated TME for C4 with enrichment of many immune subsets, especially macrophages (compared to C1, P= 0.0015); C4 also had the highest rate of PD-L1 expression on tumor cells and macrophages (P= 3.50E-7). Pts in C3 had the most favorable outcomes and displayed the highest angiogenesis gene expression levels (P= 2.0E-16). An integrated panel of molecular and IMDC variables compared to IMDC risk stratification alone improved the c-index for OS from 0.63 to 0.69 and PFS from 0.60 to 0.65. Conclusions: mRNA-based analyses revealed four distinct molecular subgroups of RCC associated with varying outcomes on TKI therapy. These data highlight stromal and immune TME, somatic mutation and other critical parameters as potential biomarkers and determinants of clinical course. Further study of these differences will be critical in advancing the field of advanced RCC towards precision-medicine.

Clinical trial information: NCT00720941.

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ALTERATIONS IN KEY CLEAR CELL RENAL CELL CARCINOMA (RCC) GENES TO REFINE PATIENT PROGNOSIS: FIRST AUTHOR. Dominick Bossé, Dana-Farber Cancer Institute, Boston, MA

BACKGROUND: Genomic alterations (GA) in VHL, PBRM1, BAP1, SETD2, TP53 and KDM5C are frequently present in metastatic RCC (mRCC). We investigated the prognostic value of GA resulting in loss of function (LOF) of these genes in mRCC patients stratified by International Metastatic Renal Cell Carcinoma Database (IMDC) risk group.

METHODS: Patients from 7 US centers and 1 annotated cohort from TCGA who had clear cell mRCC treated with 1st line VEGF tyrosine kinase inhibitor and tumor genomics were included. Tumors were sequenced using next generation sequencing (institutional and commercial platforms) or whole exome sequencing (TCGA). LOF was defined as pathogenic or likely pathogenic variant or variant of unknown significance. Cox model adjusting for age, IMDC risk group was used to investigate the association between GA and overall survival (OS). The prognostic value of GA was further assessed in IMDC favorable, intermediate and poor risk group. RESULTS: In total, 308 patients were analyzed. IMDC risk group distribution was statistically significantly different in patient survival rates (p < 0.01). GA in PBRM1 (aHR = 0.6, 95%CI 0.4-0.8, p = 0.001) and KDM5C (aHR = 0.4, 95%CI 0.2-0.8, p = 0.007) was associated with better OS. SETD2, TP53 and VHL were not associated with prognosis (p > 0.4). Co-occurrence of GA in BAP1 and PBRM1 was 3.8%. Patients with tumors PBRM1 wild type and harboring GA in BAP1 had worse OS (HR = 1.9, 95% CI 1.2-2.9, p = 0.004) compared to patients stratified by IMDC risk group, this tumor genomic profile was prognostic for patients with intermediate risk disease only (Table). CONCLUSIONS: mRCC tumors which are PBRM1 wild type and with LOF in BAP1 have worse survival. Assessment of GA in these key genes can further prognosticate IMDC intermediate risk patients and be used to stratify patients in clinical trials.
BRES = Best Response excluding surgical effect. Clinical trial information:
NCT02210117. BOR was 50% complete response (CR) + partial response (PR)
(48% CR + PR) nivo, 39% CR + PR nivo + ipi. For patients getting surgery,
BOR was: 77% nivo, 93% nivo + bev, 70% nivo + ipi. Grade 3 or 4 toxicities
occurred at Columbia University Medical Center (CUMC) and Memorial Sloan
Kettering Cancer Center (MSKCC) to produce two distinct, IRB-approved databases of
MIBC patients who underwent “radical” TURBT (complete resection
down to muscularis propria) followed by NAC, exhibited a cCR, and
opted for surveillance only from 2001-2017. A cCR was defined as negative
cystoscopy (T1 or less) with a post-treatment biopsy (Bx).

**Methods:** Prospective enrollment and retrospective review of patients
occurred at Columbia University Medical Center (CUMC) and Memorial Sloan
Kettering Cancer Center (MSKCC) to produce two distinct, IRB-approved databases of
MIBC patients who underwent “radical” TURBT (complete resection
down to muscularis propria) followed by NAC, exhibited a cCR, and
opted for surveillance only from 2001-2017. A cCR was defined as negative
cystoscopy (T1 or less) with a post-treatment biopsy (Bx).

**Results:** The 148 patient cohort included 119 (80%) men and 29 women
of median age 62 (32-88) years and follow-up 55 (5-145) months. NAC
degreged 31% MVAC, 63% gemcitabine and cisplatin, and 6% other.

**Background:** Neoadjuvant platinum-based chemotherapy (NAC) followed by
radical cystectomy (RC) is the gold standard treatment for muscle-invasive
bladder cancer (MIBC). High morbidity and mortality associated with RC and
favorable outcomes seen in patients who exhibit a clinical complete
response (cCR) to NAC that is confirmed in conserva-
tive management of MIBC. We report the outcomes of patients from two
institutions who experienced a cCR to NAC and opted for surveillance only.

**Methods:** Prospectively collected and retrospective review of patients
occurred at Columbia University Medical Center (CUMC) and Memorial Sloan
Kettering Cancer Center (MSKCC). We selected 148 patients with MIBC
who underwent “radical” TURBT (complete resection
down to muscularis propria) followed by NAC, exhibited a cCR, and
opted for surveillance only from 2001-2017. A cCR was defined as negative
“radical” TURBT, urine cytology, and cross-sectional imaging. Patients
were followed at 3-6 month intervals with cystoscopy, urine cytology,
and cross-sectional imaging, with databases continually updated.

**Results:** The 148 patient cohort included 119 (80%) men and 29 women
of median age 62 (32-88) years and follow-up 55 (5-145) months. NAC
degreged 31% MVAC, 63% gemcitabine and cisplatin, and 6% other.

**Background:** Neoadjuvant platinum-based chemotherapy (NAC) followed by
radical cystectomy (RC) is the gold standard treatment for muscle-invasive
bladder cancer (MIBC). High morbidity and mortality associated with RC and
favorable outcomes seen in patients who exhibit a clinical complete
response (cCR) to NAC that is confirmed in conserva-
tive management of MIBC. We report the outcomes of patients from two
institutions who experienced a cCR to NAC and opted for surveillance only.
Conclusions: related AEs occurred in 20.3% of patients. Immune-mediated AEs occurred in cisplatin-ineligible patients with advanced UC. Clinical trial information: elicits clinically meaningful, durable antitumor activity in a broad spectrum of was NR (12.4 mo to NR) in patients with lymph node –4, ORRs were 10.9%%, 38.3%, 34.8% & 37.5%. In a MCC analysis, pts achieving potential association between baseline risk factors & E achieved may confound ER .

Conclusions: pembrolizumab exposure-response (ER) relationship in RANGE, a randomly assigned phase III trial of docetaxel (DOC) with or without pembrolizumab in advanced urothelial carcinoma (UC) patients (pts) who progressed on or after platinum therapy. 

Background: Radiation- and immunotherapy are well tolerated and ongoing activity are seen in this phase III trial of atezolizumab (atezo) and docetaxel (DTx) in platinum-treated pts with metastatic UC. Clinical trial information: NCT02335424.

Background: Upper tract urothelial carcinoma is non-basal and T-cell depleted. Our study dem- onstrates that UTUC is predominantly and intrinsically non-basal. We show that UTUC is characterized by a T-cell-depleted phenotype associated with FGFR3 overexpression. By dissecting the biology of UTUC, we provide the biological rationale for future UTUC-specific therapeutic strategies.
Clinical efficacy of cabozantinib plus nivolumab (CaboNivo) and CaboNivo plus ipilimumab (CaboNivoIpi) in patients (pts) with chemotherapy-refractory metastatic urothelial carcinoma (mUC) either naive (n) or refractory (r) to checkpoint inhibitor (CPI). First Author: Rosa Nadal, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Preliminary clinical activity of CaboNivo and CaboNivoIpi has been previously reported for mUC pts and other genitourinary tumors. Here, we report longer follow-up data of CaboNivo and CaboNivoIpi in pts with mUC nCPI and safety and preliminary clinical activity of CaboNivo in mUC rCPI.

Methods: This phase 1 dose + expansion cohorts study enrolled mUC rCPI (escalating doses of CaboNivo n = 15 and CaboNivoIpi n = 8) and mUC nCPI (Cabo40-Nivo3mg/kg n = 7) pts up to progression/unacceptable toxicity.

Objectives: Safety, ORR, DOR, PFS, and OS. Tumors were assessed for response q8wks (RECIST 1.1). Adverse events (AEs) were graded (G) by NCI-CTCAE v4.0. Results: 30 mUC pts enrolled. Median follow-up: 11.9 months; mUC rCPI: 5.6 months. All G clinical AEs n (%) (20% n = 29): fatigue (83%), diarrhea (72%) and anorexia (62%); laboratory AEs: ALT elevation (55%), AST elevation (48%) and hyponatremia (48%). Common ≥3 clinical AEs were: fatigue (17%), HTN (14%), thromboembolic events (14%); laboratory AEs: AST (93%), ALT (91%), hypernatremia (17%), hyponatremia (10%). Immune-related AEs n (%) (14 n = 4): mUC rCPI: CaboNivo: G3 meningitis; G3 pneumonitis; CaboNivoIpi: G3 colitis; mUC nCPI: G2 adrenal insufficiency. For mUC nCPI CaboNivo ORR: 50% (6/12), mDOR: NR; mPFS 10.1 months [95% CI: 1.6 months – NR] & mOS: NR. For mUC rCPI CaboNivoIpi: ORR: 50% (6/12), mDOR: 24.1 months [95% CI: 7.8 months – not reached (NR)]; mPFS 11.9 months; mUC rCPI: 5.6 months. All G clinical AEs in cases (> 3% across subgroups). Two serious TRAEs (15%) occurred in CrCl < 30 mL/min subgroup (< 8% in other subgroups). Conclusions: Responses or SD with atezo were seen in pts with mixed histology or compromised renal function (notably in pts with CrCl 30-45 mL/min) and safety was comparable across subgroups. These results suggest that atezo may aid in overcoming CPI resistance. Clinical trial information: NCT02496208

Optimization of PD-L1 algorithm for predicting overall survival (OS) in patients with urothelial carcinoma (UC) treated with durvalumab monotherapy, First Author: Magda Zajac, AstraZeneca, Cambridge, United Kingdom

Background: PD-L1 expression is a useful biomarker in predicting response to PD-L1 and PD-L1 directed immunotherapies in a variety of tumor types. In UC, studies have implicated PD-L1 expression in tumor cells (TC) and tumor-infiltrating immune cells (IC) as having clinical utility, but the relative importance of each cellular compartment and the most predictive algorithm and PD-L1 expression (SP263 assay) from 188 patients in the UC cohort from single arm (durvalumab monotherapy) Phase 1/2 Study CD-ON-MEDI4736-1108 (NCT01693956; Oct. 2017 data cutoff) were assessed. Regression models were used to evaluate the impact of PD-L1 expression in TC or IC on OS, progression-free survival (PFS), objective response rate (ORR), best percentage tumor change and tumor shrinkage 15 months after last subject randomization. Kaplan–Meier plots were generated to explore the impact of single biomarker and combined (TC or IC (%PD-L1 positive ICs within IC area)) algorithms on OS. Results: Both IC and TC PD-L1 were linked to higher ORR, and IC PD-L1 was associated with better survival in patients treated with durvalumab. IC PD-L1 had a higher impact on response to durvalumab than TC PD-L1, showing significant (P < 0.05) association with OS, DFS, PFS, and ORR, and tumor shrinkage. The best outcomes were obtained when TC and IC algorithms were combined, with TC50%/IC50%/ predicting OS (Table). Conclusions: The TC50%/IC50% algorithm appears to provide optimal predictive value based on efficacy and prevalence of the biomarker. Additional data from randomized trials are needed to confirm these findings. Clinical trial information: NCT01693562.

Poster Session (Board #354), Sat, 8:00 AM-11:30 AM

IC PD-L1 was associated with better survival in patients treated with durvalumab (Cabo). First Author: Jonathan H. Manuszak-Densus, John Hopkins University Sidney Kimmel Cancer Center, Baltimore, MD

Background: Prior to FDA approval of atezo (anti–PD-L1) for platinum-treated mUC (and later cisplatin-ineligible mUC), a US EAP granted mUC pts access to atezo. The EAP (Bellmunt ASCO 2017) included special populations previously ineligible for Ph II study IMvigor210 (Rosenberg Lancet 2016). Here, we evaluate outcomes in pts with impaired baseline renal function or variant histology.

Methods: This study (NCT02589717) included mUC pts who progressed during or following platinum and had ECOG PS ≤ 2. Pts had predominant TCC histology but no restrictions on CrCl levels. Pts received atezo 1200 mg IV q3w until loss of clinical benefit. ORR (per investigator), DCR (CR+PR+SD) and safety were assessed by CrCl or primary tumor histology. Results: 114 pts were response evaluable; responses occurred in most subgroups (Table). All-grade treatment-related AEs (TRAEs) occurred in 46% of 214 safety-evaluable pts. In renal function subgroups, TRAE rates ranged from 35% (CrCl 30-45 mL/min) to 54% (CrCl 45-60 mL/min); no TRAE rate differences by histology were seen (46% each). Similar trends occurred for AEs of special interest. TRAES leading to discontinuation were uncommon (<3% across subgroups). Two serious TRAES (15%) occurred in CrCl < 30 mL/min subgroup (<8% in other subgroups). Conclusions: Responses or SD with atezo were seen in pts with mixed histology or compromised renal function (notably in pts with CrCl 30-45 mL/min), and safety was comparable across subgroups. TRAEs (Table) suggest that atezo may aid in overcoming CPI resistance. Clinical trial information: NCT02589717.
GENITOURINARY (NONPROSTATE) CANCER

4532
Poster Session (Board #358), Sat, 8:00 AM-11:30 AM
Patient-reported outcomes (PROs) in patients with urothelial carcinoma (UC) treated with durvalumab (second-line or above) in phase I/2 dose-escalation study 108. First Author: H. O'Donnell, University of Chicago Comprehensive Cancer Center, Chicago, IL

Background: In Study 1108, durvalumab showed meaningful clinical activity in patients with UC, with an objective response rate (ORR) of 17.8% (PD-L1-positive patients: 27.6%) (Powles 2017, JAMA Oncol). We report PRO results. Methods: Phase 1/2, open-label, dose escalation study 1108 (NCT01693562) enrolled patients with locally advanced/metastatic UC and prior platinum-based treatment. Patients received durvalumab 10 mg/kg Q2W for 12 months, and were asked to complete Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-BL), European Organisation for Research and Treatment of Cancer Quality of Life (QoL) Questionnaire (EORTC QLQ-C30) and a pain questionnaire at baseline (D1) and days 29, 43, 57, 85 and 113 (D113). Changes in PROs were analyzed descriptively. Improvement/deterioration from D1 was based on minimum important difference: 1) baseline standard deviation (SD) for FACT-BL (range 0–156), 10-point difference for EORTC QLQ-C30 (total range 0–100). Results: In the full analysis set (n = 182), overall questionnaire completion rate at baseline was 99% and 91% at D113. Pain total mean (SD) score (range 0–10) tended to decrease over time, from 3.4 (2.8) on D1 to 1.9 (2.4) at D113. Mean (SD) FACT-BL total scores improved over time, from 107.5 (23.0) on D1 to 115.4 (22.6) on D113, with similar increases in bladder cancer subscale (BCLS) and trial outcome index (TOI) mean scores. FACT-BL total score improved over time in 32.6% of patients (48.8% at change). 34.9% showed an improvement in FACT-BLS, and 32.6% in FACT-TOI. EORTC QoL mean (SD) score improved from 57.1 (24.8) on D1 to 69.0 (21.4) at D113. Improvements in EORTC QLQ-C30 functional domains were seen in 26.3–37.8% of patients, while 57.6–73.1% showed improvements in symptom domains, with largest responses in pain, fatigue, physical, and role domains (improvement: 73.1, 57.6, 37.8 and 32.4%; no change: 0.0, 27.3, 46.0 and 41.2%; deterioration: 26.5, 15.2, 16.2 and 26.5%, respectively). Conclusions: Overall, the mean scores (domain or total) for pain, FACT-BL and EORTC QLQ-C30 improved over time in patients with UC treated with durvalumab in the phase I/2 study 1108. Clinical trial information: NCT01693562.

4533
Poster Session (Board #359), Sat, 8:00 AM-11:30 AM
Immune profiling in a randomized phase II trial of acabatnínib and pembrolizumab (PA) versus pembrolizumab (P) for patients with metastatic urothelial carcinoma (mUC). First Author: Tian Zhang, Duke University Medical Center, Durham, NC

Background: Response rates for checkpoint inhibitors (CPIs) in cisplatin refractory mUC range from 15% to 21%. Thus, biomarkers are needed to predict for treatment responses. We conducted a Ph2 clinical trial in patients with mUC, randomized to P or PA (NCT02351739). From this trial, we performed the first correlation analysis of circulating immune cells with clinical outcomes in mUC patients receiving CPI therapy. Methods: 75 patients with cisplatin refractory mUC were treated with P or PA. Pre- and post-study flow cytometry was performed on peripheral blood mononuclear cells for these markers: CD3, CD4, CD8, PD-1, PD-L1, PD-L2, B7-H3, CTLA-4, ICOS, LAG3, TIM3, Ki-67, CD45RA, CCR7, CD38, CD14, HLA-DR, CD16/56, CD15/CD20, CD25, CD127, CD39, and CCR4. Single and selected double marker positivity was analyzed on CD4 and CD8 T-cells and monocytes (M). Mean (± SD) of relative cell subset frequency (RCSF) was calculated and associated with clinical responses (best radiographic response as defined per RECIST 1.1 criteria). Unadjusted p-values were derived for all treated patients were used for analysis. Baseline RCSF (n = 57) or changes in RCSF from baseline to week 4 (n = 51) were correlated with responses. Results: Patients who had lower expression of ICOS, AG, no PD-L2, CTLA-4 and B7H3 M at baseline. Among T-cells, lower levels of CTLA4+ and PD1+, and ICOS+ CD4 T-cells; and higher CD28/TIM3- CD8 cells were also associated with CR. Changes from baseline to week 4 were observed for actively proliferating CD4 or CD8 T-cells, CD8 T-cells that co-express TIM3 with CD28 or PD-L1, and for TIM3-expressing M subsets, suggesting that early increases in immune cell activation (Ki-67, CD28, PD-1) and interferon response (TIM3) are associated with clinical responses. Conclusions: Immune profiling in patients with mUC showed activation and interferon response markers on subsets of T-cells and monocytes that were associated with treatment responses to CPI therapy.

4534
Poster Session (Board #360), Sat, 8:00 AM-11:30 AM
FIERCE-21: Phase 1b/2 study of docetaxel + b-701, a selective inhibitor of FGFR3, in relapsed or refractory (R/R) metastatic bladder cancer (mUC). First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Boston, MA

Background: Patients with locally advanced or metastatic urothelial carcinoma (mUC) have a poor prognosis. FGFR3 is frequently overexpressed in UC and 15-20% of patients with mUC have FGFR3 gene mutations or fusions (M). B-701 is a fully human monoclonal antibody against FGFR3 that blocks activation of the wildtype and genetically activated receptor. FIERCE-21 is a Phase 1b/2 study designed to evaluate B-701 alone or in combination with docetaxel (D). Methods: The study consists of a Phase 1b lead-in (P1b) followed by Phase 2 (P2) expansion and a randomized phase. Eligible patients P1b: the study enrolled mUC R/R excluding prior taxane treatment, and ECOG > 1; Treatment: B-701 at 25 mg/kg and D at 75 mg/m2 q3w. Efficacy was assessed by investigators (RECIST 1.1). Primary objective: Determine P2 dose and evaluate safety and efficacy. Results: 19 patients were enrolled in P1b: median age 66 yrs, ECOG 1 = 58%, Hgb < 10 gm/dL, 5% liver metastases 26%, ≥ 2 prior regimens 63%, best response to prior therapy PD 52%. Six patients were positive for FGFR3 M/F. Grade ≥ 3 AEs occurring in ≥ 2 patients were typical of D at this dose and schedule (decreased neutrophil count (26.3%), neutropenia (10.5%), decreased WBC (10.5%)). Two patients had D dose reductions and no subjects had dose reductions of B-701 or discontinued treatment due to AE. Two patients died, 1 with PD and bleeding, and 1 with MAHA associated with infection and recurrent thrombosis. Four subjects are alive (3 M/F). Median OS has not been reached in M/F or 5.3 months in WT. Conclusions: B-701 combined with standard dose D in an every 3 week schedule in patients with mUC was well-tolerated with expected myelosuppression. Enhanced activity was seen in the FGFR3 M/F compared to WT patients. Phase 2 expansion is currently enrolling FGFR3 M/F patients (B-701 monotherapy expansion B-701+D). Clinical trial information: NCT02401542.

4535
Poster Session (Board #361), Sat, 8:00 AM-11:30 AM
Relapse-free survival (RFS) of clinical T2-4N0 urothelial bladder carcinoma (UBC) after radical cystectomy (RC), with or without perioperative chemotherapy (POC): Endpoints for clinical trial design. First Author: Marco Bandini, Vita-Salute San Raffaele University, Milan, Italy

Background: Recent data suggests that the full benefit of neoadjuvant therapy may not be captured via pathologic complete response rates. Improved relapse-free survival (RFS) may identify active agents acting through novel mechanisms. Methods: Within RISC and San Raffaele databases (1990-2016), we identified 973 T2-4N0 UBC patients (pts), from 27 centers in the U.S., Europe, Israel, and Canada. A Cox-based nomogram predicting 12-m RFS was built including pt (gender, race), tumor characteristics (histology, pt, pN and surgical margin status [SM]), and administration of neoadjuvant or adjuvant chemotherapy (CT). Multiple imputation was performed to handle missing data. Validation (2000 bootstrap resamples) was internally tested. Calibration and prognostic ability was assessed comparing estimated versus observed 12-m RFS. Results: Overall, 577 (59.3%) and 236 (24.3%) pts had cT2 and cT3-T4, respectively (T and unimputed and imputed in 160, 16.4%). 125 (12.8%) had mixed UC-other histologies. 275 pts (28.3%) received neoadjuvant CT, 165 (17%) adjuvant CT. On multivariable analyses, pt (p < 0.002), pN (p < 0.001) and SMS (p = 0.005) were associated with higher rate of recurrence. Conversely, use of adjuvant CT (HR = 0.63, p < 0.001) was associated with lower rate of recurrence. Results were confirmed in sensitivity analyses after removing 61 (6.2%) non-cisplatin POC. Overall, 405 (41.6%) pts relapsed and 375 (38.5%) died. Median RFS and overall survival were 44 months (95%CI, 36-65) and 57 months (95%CI, 50-90), respectively. In POC-treated pts, nomogram-predicted 12-m RFS rates were 91.6% (95%CI, 87-96), 79.7% (95%CI, 73-88) and 53.0% (95%CI, 44-63), across the nomogram-derived tertiles. In pts who did not receive POC, these estimates were 89.8%, 74.8%, and 47.0%, respectively. The bootstrapped c-index of the nomogram was 78% (95%CI: 74-81). Conclusions: Nomogram-predicted 12-m RFS may provide data to base future clinical trial designs of novel agents in the perioperative setting.
Conclusions: The best prognosis. Further exploration of the deleterious nature and impact of DDR (excluding ATM/RB1) seemed to have the best prognosis in our cohort (OS: HR 0.36, 95% CI 0.14–0.43, p = 0.397) or MRS (HR = 0.57, 95% CI 0.30–0.98, p = 0.048). Further case with high-grade and muscle-invasive tumors. The AUC for the 10-biomarker assay was 0.901 (95% confidence interval, 0.850–0.934), with an overall diagnostic specificity of 0.90 and 0.91, respectively. Conclusions: Urinary levels of a 10-biomarker panel enabled discrimination of patients with BCa. The multiplex urinary diagnostic assay will continue in prospective study. Clinical trial information: NCT03193528.

Background: Bladder cancer (BCa) is among the most commonly diagnosed malignancies worldwide, and due the high rate of post-operative disease recurrence, it is one of the most prevalent in many countries. The development of non-invasive molecular assays that can accurately detect and monitor BCa would be a major advance, benefiting both patients and healthcare systems. We have previously identified a urinary protein biomarker panel that was being developed for application in at-risk patient cohorts. Here, we investigated the potential utility of the multiplex assay in a prospective study. Methods: The study cohort collected from urology clinics at two institutions was comprised of a total of 145 subjects. The protein biomarker panel (ILB, MMP9, MMP10, ANG, APOE, SDC1, A1AT, PAI1, CA9, VEGFA) was monitored in voided urine samples collected prior to cystoscopy using a custom multiplex ELISA assay. The diagnostic performance of the biomarker panel was assessed using receiver operator curves (ROC), predictive modeling and descriptive statistics. Results: Urinary biomarker concentrations were significantly elevated in cases versus controls. Further case with high-grade and muscle-invasive tumors. The AUC for the 10-biomarker assay was 0.901 (95% confidence interval, 0.850–0.934), with an overall diagnostic specificity of 0.90 and 0.91, respectively. Conclusions: Urinary levels of a 10-biomarker panel enabled discrimination of patients with BCa. The multiplex urinary diagnostic assay will continue in prospective study. Clinical trial information: NCT03193528.

4539 Poster Session (Board #365), Sat, 8:00 AM-11:30 AM
Model combining genomic and clinical factors to predict clinical benefit from PD1/PD-L1 inhibitors for advanced UC. First Author: Amin Nassar, Brigham and Women’s Hospital, Boston, MA

Background: Tumor mutational burden is associated with response to PD1/PD-L1 inhibitors in advanced UC. We explored the ability of copy-number variants (CNVs) and specific genomic alterations to complement single-nucleotide variants (SNVs) to predict clinical benefit in patients (pts) with advanced UC receiving PD1/PD-L1 inhibitors. Methods: Targeted exome sequencing (238 genes) was performed on archival tumors from metastatic UC pts treated with PD1/PD-L1 inhibitors at our institution. Clinical Benefit (CB) was defined as any objective reduction in tumor size, and no clinical benefit (NCB) was defined as any objective increase in tumor size by RECIST 1.1. Associations between clinical and genomic features and clinical benefit were assessed using univariate and multivariate logistic regression modeling. Results: 61 pts were evaluable, with CB in 24 pts and NCB in 37 pts. The prognostic factors associated with NCB on univariate analysis were neutrophil/lymphocyte ratio (NLR) ≥5, ECOG-PS ≥1, hemoglobin (Hb) < 10 g/dl, liver metastasis, CDKN2B homozygous deletion, high CNV count and low SNV count. On multivariate analysis, a low SNV count and a high CNV count were associated with NCB. There was a strong trend for association of NCB with liver metastasis and NLR ≥5 (Table). Conclusions: A new model combining 2 genomic factors, low SNV and high CNV counts, and 2 clinical factors, high NLR and liver metastasis, appeared associated with NCB in pts with advanced UC receiving PD1/PD-L1 inhibitors. Validation of these hypothesis-generating results is warranted.

<table>
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<tr>
<th>Risk factors</th>
<th>Adjusted OR</th>
<th>p value</th>
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<tr>
<td>Liver metastasis</td>
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<tr>
<td>CDKN2B homozogous deletion</td>
<td>4.61 (0.24–90.06)</td>
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<td>NLR ≥ 5</td>
<td>9.17 (1.00–84.33)</td>
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<td>ECOG-PS ≥ 1</td>
<td>0.76 (0.12–4.92)</td>
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<td>Hb &lt; 10 g/dl</td>
<td>7.60 (0.22–258.88)</td>
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<td>CNV count ≥ 1 (median)</td>
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<td>SNV count &lt; 8 (median)</td>
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4540 Poster Session (Board #368), Sat, 8:00 AM-11:30 AM
Association of circulating tumor (ct)DNA genomic alterations (GA) with outcomes in metastatic urothelial carcinoma (mUC). First Author: Petros Grivas, University of Washington, Seattle, WA
Background: Cell-free ctDNA profiling enables noninvasive identification of GA in mUC. We hypothesized that ctDNA GA correlate with outcomes and signify therapy targets. Methods: 477 patients (pts) with UC who underwent ctDNA analysis for potentially actionable GA via Guardant360 were identified. A 73-gene ctDNA next generation sequencing (NGS) panel from CLIA-licensed, CAP-accredited laboratory (Guardant Health, Inc.) offers complete exome sequencing in 19 cancer genes, critical exons in 54 genes, amplifications (18 genes), fusions (6 genes) & indels (23 genes) from 10 mL of peripheral blood. KM method was used to estimate overall survival (OS) and failure-free-survival (FFS) since therapy initiation. Cox proportional hazards regression was used to assess the association of ctDNA GA present in ≥10% of pts and clinical and laboratory factors with OS and FFS in univariable analyses. All tests were 2-sided, p ≤ 0.05 was significant. We also evaluated GA in serial samples to assess genomic evolution. Results: 124 pts had available clinical data, of whom 65 had received prior platinum, 21 prior taxane and 10 prior PD1/PD-L1 inhibitor; 24 other and 25 no therapy. There was no significant effect associated with OS. After ctDNA collection, 32 pts received platinum, 43 genes were TP53 (55%), PIK3CA (24%) and ARID1A (23%). 1-year OS and clinically useful. Serial sample analysis revealed genomic evolution.
BRAF & ARID1A GA correlated with longer and BRCA1 GA with shorter FFS with mUC and appeared similar to those from prior tumor tissue NGS studies. ctDNA collection was 72 and median (range) number of GA per sample was 4 (0-80); 110 pts had ≥1 SNV & 39 pts ≥1 CNV. Most commonly altered genes were TP53 (55%), PIK3CA (24%) and ARID1A (23%). 1-year OS and FFS were 69% and 35%, respectively. ARID1A (HR 0.49, p = 0.052) & BRAF (HR 0.24, p = 0.048) GA were associated with longer FFS, while BRCA1 (HR 2.36, p = 0.003) GA with shorter FFS had associated with OS. After ctDNA testing, 32 pts received platinum, 43 anti-PD1/PDL1, 24 other and 25 no therapy. There was no significant effect of post-cDNA therapy on OS (p = 0.91) or FFS (p = 0.29); post-cDNA therapy did not interact with clinical factors. Serial samples showed novel and/or 10% of evaluable patients with a partial or better response by RECIST and/or 10% of evaluable patients with a partial or better response by RECIST criteria.
Conclusions: ctDNA GA were detected in most pts with mUC and appeared similar to those from prior tumor tissue NGS studies. BRAF & ARID1A GA correlated with longer and BRCA1 GA with shorter FFS suggesting that synthetic lethality with DNA damage repair inhibitors may be clinically useful. Serial sample analysis revealed genomic evolution.

4542 Poster Session (Board #368), Sat, 8:00 AM-11:30 AM
A subgroup analysis of the East Asia population in RANGE: A randomized phase 3 study of docetaxel (DOC) with or without ramucirumab (RAM) in platinum-refractory advanced or metastatic urothelial carcinoma (UC). First Author: Nobukazu Matabara, National Cancer Center Hospital East, Chiba, Japan
Background: RANGE (NCT02426125) is a global, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of RAM in combination with DOC in patients (pts) with platinum-refractory or metastatic UC. Here we report the results of RAM in combination with DOC in the East Asia population (EA). Methods: 530 pts were randomized (1:1) to DOC with either RAM 10 mg/kg or placebo (PL) on day 1 of a 21-day cycle (RAM/DOC or PL/DOC). EA pts (n = 110) received DOC 60 mg/m²; other pts were in line with those for ITT. The most common grade ≥3 adverse events in EA, neutropenia and leukopenia, were observed at a similar frequency in both arms. Mean scores for global QOL in EA stayed largely stable over time without a clear difference between arms. Plasma concentrations of DOC for pts in the 60 mg/m² group were similar to those for pts in the 75 mg/m² group. Conclusions: The DOC PK profile for EA pts receiving 60 mg/m² was consistent with non-EA pts receiving 75 mg/m². Results in EA were consistent with the improved clinical outcomes and manageable safety profile observed with RAM/ DOC in ITT. Clinical trial information: NCT02426125.

ITT (first 437 pts) EA**

<table>
<thead>
<tr>
<th>RAM/DOC (n = 216)</th>
<th>PL/DOC (n = 221)</th>
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<tbody>
<tr>
<td>HR (95% CI)*</td>
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<tr>
<td>0.607</td>
<td>0.676</td>
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<tr>
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<tr>
<td>0.005</td>
<td>0.003</td>
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</table>

Conclusions: The combination of pembrolizumab with either docetaxel or gemcitabine is tolerated with no unexpected adverse effects, with evidence of efficacy. Expanded cohorts continue to enroll. Clinical trial information: NCT02437370.

4543 Poster Session (Board #369), Sat, 8:00 AM-11:30 AM
Preliminary results from an ongoing phase 2a study of RX-3117, an oral nucleoside analogue to treat advanced urothelial cancer (aUC). First Author: Jacob Adasek, Western University of Health Sciences, Los Angeles, CA
Background: RX-3117 is an oral small molecule nucleoside analogue (cyclopentyl pyrimidylic nucleoside) that is activated by uridine cyclidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant bladder cancer. Preliminary data from Stage 2 of a Phase 2a clinical study of RX-3117 as a single agent in subjects with advanced urothelial cancer (aUC) is described below. Methods: The efficacy of oral RX-3117 was evaluated in eligible patients (aged ≥ 18 years) with refractory aUC in a Phase 2a study. Primary objectives include safety and efficacy of 700 mg of administered orally RX-3117 for 5 consecutive days followed by 2 days off per week in each 4-week cycle for 4 continuous weeks. The primary endpoint is a ≥ 20% rate of progression free survival (PFS) benefit (i.e., proportion of subjects with stable disease for at least 4 months) and/or 10% of evaluable patients with a partial or better response by RECIST criteria.
Conclusions: As of February 4, 2018, 27 patients (19 males, 8 females) with aUC were treated with RX-3117. The median age was 67 years and ECOG performance status was ≤ 1. Prior treatment with gemcitabine or immunotherapy was 85% or 67% of patients, respectively. Five patients achieved stable disease for 4 cycles of RX-3117 treatment; one patient received treatment for 3 cycles and another patient continues treatment beyond 4 months. One patient achieved a partial response after 2 cycles. Four patients have shown a tumor reduction ranging from 13.9 to 20% as measured by RECIST. All reductions occurred after 1 cycle of RX-3117 treatment, except for one patient’s reduction, which occurred after 4 cycles. The most frequent related adverse events were G1/2 diarrhea (14%), fatigue (9%), nausea (9), vomiting (9%), G1/2 anemia (7%), and G3 thrombocytopenia (7%). Conclusions: RX-3117 is safe and well tolerated and shows preliminary evidence of anti-tumor activity in heavily pretreated patients. The study continues to enroll subjects with aUC in Stage 2. Clinical trial information: NCT0230067.
Background: Immune-oncolgy (IO) regimens have improved the clinical outlook for patients with locally advanced or metastatic urothelial carcinoma (mUC). This analysis aimed to assess time to treatment failure (TTF) among patients with mUC treated with systemic chemotherapy and IO regimens in the US community oncology setting. Methods: This is a retrospective study of patients with mUC receiving treatment from January 2015 to April 2017, with follow-up through June 2017 using the US Oncology Network’s electronic health records database. TTF was defined as the interval between treatment initiation in the first (1L), second (2L), or third line (3L) and discontinuation for any reason. TTF was compared between the chemo and IO cohorts using Kaplan-Meier and Cox proportional hazard modeling. Results: 523 patients initiated 1L treatment (median age, 72 years; 76.5% male), 241 2L (median age, 69 years, 75.9% male) and 50 3L (median age, 67 years; 74.0% male). Of patients receiving 1L platinum-based combinations (n = 497, 95%), 27.7% were treated with carboplatin/gemcitabine, followed by 26.0% with cisplatin/gemcitabine, and 7.3% with carboplatin/paclitaxel. IO regimens were received by 18% of patients in 2L and 68.0% in 3L. In the 2L setting, patients treated with IO regimens had a significantly longer TTF than those treated with systemic chemotherapies (P < 0.0001) (Table). Conclusions: These findings provide important insights into patterns of care and outcomes among patients with mUC in the community oncology setting. Comparisons between the chemo and IO cohorts were limited to utilization of heterogeneous chemotherapy regimens and small sample sizes. Patients in the IO cohort stayed on therapy for longer periods than chemotherapy-treated patients. Future real-world research may determine generalizability of the results seen in this study.

<table>
<thead>
<tr>
<th>TTF Line of Therapy</th>
<th>Chemo, median weeks</th>
<th>IO, median weeks</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>1L</td>
<td>n = 497</td>
<td>n = 26</td>
<td>0.570 (0.346-0.939)</td>
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<tr>
<td></td>
<td>1.1</td>
<td>1.5</td>
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<tr>
<td>2L</td>
<td>n = 104</td>
<td>n = 137</td>
<td>0.552 (0.406-0.749)</td>
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<td></td>
<td>9.1</td>
<td>12.1</td>
<td></td>
<td></td>
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<tr>
<td>3L</td>
<td>n = 16</td>
<td>n = 34</td>
<td>0.461 (0.213-0.949)</td>
<td>0.0490</td>
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<td></td>
<td>9.9</td>
<td>22.9</td>
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4546 Poster Session (Board #372), Sat, 8:00 AM-11:30 AM

Correlation between gene expression and prognostic biomarkers in small cell bladder cancer (SCBC). First Author: Vadim S. Koshkin, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: SCBC is a rare malignancy with poorly understood biology. TCGA data in BC underscores the presence of a neuronal subtype possibly misclassified by conventional histopathology. Increased small cell component (SC%) and protein expression (ex) of DLL3 and CD56 were previously shown to correlate with worse outcomes in SCBC. The association of gene ex data with available biomarkers has potential to improve risk stratification and inform treatment decisions. Methods: 63 patients (pts) at Cleveland Clinic diagnosed between 1993 and 2015 had SCBC histology independently reconfirmed. All pts had SC % quantified and 52 pts had immunohistochemistry (IHC) for DLL3 and CD56. A further subset of 39 pts had gene expression analysis using HTG EdgeSeq OBP. Ex of genes relevant in neuroendocrine tumors was evaluated with a panel including CHGA, DLL1, DLL3, DLL4, ENO1, HE55, HEY1, NAC1M, NOTCH1, NOTCH2, NOTCH4, RB1, SYP, and TP53. Associations between DLL3 and CD56 protein ex, SC%, and ex of relevant genes were assessed to identify biomarkers pertinent to molecular diagnostics ( Spearman correlation, p < 0.05). Using these as seed genes in a network-based approach we sought to develop a prognostic gene expression signature in SCBC. Results: Among 52 pts with IHC data, 79% had SC% > 50%, and protein ex of DLL3 and CD56 (> 1% of tumor cells) was 68% and 81%, respectively. DLL3 protein ex correlated positively with mRNA ex of DLL3 (r = 0.70), CHGA (r = 0.58), DLL3 (r = 0.45), and negatively with NOTCH1 (r = -0.47), RB1 (r = -0.48) and ENO1 (r = -0.34). CD56 protein ex correlated positively with mRNA ex of NAC1M (r = 0.61), DLL4 (r = 0.38), HEY1 (r = 0.42) and SYP (r = 0.34) and negatively with NOTCH1 (r = -0.34) and HE55 (r = -0.35). SC% correlated positively with DLL3 (r = 0.38) and NAC1M (r = 0.41) and negatively with HE55 (r = -0.34). Conclusions: Expression of genes implicated in the pathophysiology of SC tumors correlated with protein ex of DLL3, CD56 and SC%, which were previously shown to be prognostic in SCBC. This supports a prognostic role for a novel gene ex signature in SCBC. Multi-institutional validation of this signature in external BC cohorts as well as comparison with BC TCGA and SC lung cancer datasets are ongoing.

4547 Poster Session (Board #373), Sat, 8:00 AM-11:30 AM

Apache: An open label, randomized, phase 2 study of durvalumab (Durva), alone or in combination with tremelimumab (Tremo), in patients (pts) with advanced germ cell tumors (GCT): Results at the end of first stage. First Author: Daniele Raggi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The prognosis of chemorefractory GCT pts is dismal. Durva is an anti-PD-L1 monoclonal antibody (mAb). Tremo is anti-CTLA4 mAb. We aimed to investigate the activity of Durva, alone or with Tremo, in these pts. Methods: Apache (NCT03030841) is an open-label, randomized, phase 2 study. Pts who have failed ≥2 chemotherapy (CT) regimens receive Durva, 1.5 mg q4w, x 13 cycles (arm A) or Durva plus Treme, 75 mg q4w, x 4 cycles, followed by Durva alone x total 13 cycles (arm B). Serum tumor markers (STMs), and radiologic assessments are repeated q8 weeks. The primary endpoint is the modified objective response-rate (mORR = RECIST 1.1 complete or partial response [PR] or stable disease [SD]+STM), and radiologic assessments are repeated q8 weeks. The primary endpoint is the modified objective response-rate (mORR = RECIST 1.1 complete or partial response [PR] or stable disease [SD]+STM reduction ≥10%); Ho: mORR rate ≤10%, H1: mORR rate ≤25%, type I and II error rates at 10%. The total sample size of 120 pts is split into 3 stages: in stage 1, according to Gehan’s rule, each arm is terminated whenever no response is observed. Biomarker analyses include: IHC PD-L1 expression on immune cells (Ventana SP142) and genomic sequencing with Foundation-One assay (Foundation Medicine Inc., Cambridge, MA, USA). Results of first stage are presented. Results: From 02/17-11/17, 18 pts were enrolled (17M, 1F), 9 per arm. 14 had gonadal and 4 extragonadal GCT, 15 had received ≥3 prior CT regimens. Median tumor mutational burden (TMB) was 4 mutations (mut)/Mb. One pt (5.6%) had reversible G3 rAE (pneumonitis) in arm B. In arm A, 100% of pts had disease progression (PD), all with features of hyperprogression (hyper-PD): 4 had clinical PD and death before restaging, median increase in sum of tumor diameters (RECIST 1.1) was 140%, median increase in the elevated STM was 462%. In arm B, 2 responses (22.2%, 1 RECIST-PR in seminoma and 1 SD with STM reduction in nonseminoma) were observed. PD features were similar to arm A. PD occurred in both arms regardless of PD-L1 expression and TMB (PR case: PD-L1 negative and 4 mut/mb). Conclusions: Single-agent durvalumab should not be pursued further in GCT; conversely, combination immunotherapy showed signals of activity and will be expanded to 2nd stage. Response biomarkers are urgently required. Clinical trial information: NCT03081923.

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Use of 18F-FDG PET/CT to select candidates for active surveillance: Results of the SEMITEP trial of PET-directed strategy for stage 1 seminoma. First Author: Johann Beckot, Institut Gustave Roussy, Villejuif/Geneva, France.

**Background:** Stage 1 seminoma patients (pts) run a relapse risk of 15-20% without further adjuvant treatment. Pts are usually offered active surveillance or an adjuvant treatment with a risk of overtreatment of about 80%. There is no robust prognostic factor associated with the risk of relapse. 18F-FDG PET/CT (PET) demonstrates high diagnostic accuracy for restaging pts with metastatic seminoma. Our hypothesis was that PET scanning accurately detects micro-metastasis and may help better select patient for therapy. **Methods:** In the SEMITEP trial (NCT01887340), pts with newly diagnosed stage 1 seminoma underwent PET scanning before any decision for adjuvant treatment. PET scans were assessed by a local nuclear physician but were centrally retrospectively reviewed. A PET was interpreted as positive if any non-physiological 18F-FDG uptake was observed. Pts with negative PET findings were assigned to a surveillance protocol with no further adjuvant treatment and alleged surveillance work-up; pts with positive PET findings were recommended to receive immediate therapy (preferentially 2 cycles of carboplatin at a dose of AUC = 7). The first endpoint was the proportion of pts in whom an adjuvant therapy could be avoided. The secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** A total of 169 pts were recruited, and 166 patients underwent PET. The PET findings were negative in 160 of these pts (96%), 150 (94%), 95% confidence interval (CI), 90-98) of whom were assigned to surveillance. PET was positive in 6 pts, 5 of which were treated with immediate therapy and 1 (CSI) after 2.5 years, 22/150 (15%) pts with PET-negative experienced a relapse. No relapse occurred among the 15 pts treated with immediate treatment. There was one chemotherapy-related death. The 2-year PFS and OS rates were 88% (95% CI, 81.7-92.1) and 99.4% (95% CI, 96.6-99.9), respectively. **Conclusions:** Post-orchidectomy treatment can be avoided in a majority of pts with stage 1 seminoma. PET may help identifying about one fifth (6/28) pts with disseminated seminoma that are not detected by CT-scan. Surveillance remains necessary in men with negative PET. Clinical trial information: NCT01887340.

**Etoposide and cisplatin (EP) for metastatic good-risk germ cell tumors (GCTs): The Memorial Sloan-Kettering Cancer Center (MSKCC) experience**

In this 34-year experience, 160 of 282 (56.7%) pts with metastatic, good-risk GCTs were treated with EPx4 ever reported, our results confirm that this regimen is highly effective and well-tolerated. EPx4 remains a standard treatment option for good-risk GCT and maintains the preferred regimen at MSKCC.

**Results:**
- **Number of Pts:** 160
- **Etoposide and cisplatin:** 159 pts (99%)
- **Surgery:** 1 pt (0.6%)
- **Relapse:** 24 pts (15%)
- **Died of Disease:** 9 pts (5.6%)

**Conclusions:** Our retrospective study has shown differences in pathological outcomes for good risk GCT patients treated with EP x 4 vs BEP x 3 in the PC-RPLND specimens. **Methods:** The Indiana University (IU) Testicular Cancer Database was queried to identify IGCCC good-risk patients who received EP x 4 or BEP x 3 induction chemotherapy followed by PC-RPLND. **Results:** A total of 291 patients treated between 1988 and 2017 met the inclusion criteria. Median age was 28 (14.6-70.8) years. Primary histology was non-seminoma in 92.8%. Induction chemotherapy consisted of EP x 4 in 45 (15.5%) patients and BEP x 3 in 246 (84.5%). One hundred and sixty-six patients (57.2%) received chemotherapy outside the IU and were subsequently referred for PC-RPLND. Using a logistic regression model after accounting for age and time to surgery, patients who received EP x 4 have approximately 2.5 times the odds of having residual cancer viability in the PC-RPLND (Odds ratio 2.548, 95% CI 1.130-5.744, p = 0.024) and no significant difference in the odds of having teratoma (Odds Ratio 0.669, 95% CI 0.343-1.303, p = 0.237). **Conclusions:** Our retrospective study has shown differences in pathological outcomes for good risk GCT patients treated with EP x 4 vs BEP x 3. Patients who received BEP x 3 had less residual cancer in the RP specimen at the time of PC-RPLND compared to EPx4 after adjusting for age and time to surgery. We prefer to use BEP x 3 as first line chemotherapy in good-risk patients unless there is a contraindication for bleomycin.

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Perceived stress scale (PSS) scores in long-term testicular cancer survivors (TCS) and a male

Conclusions: This is the largest series reported to date on adjuvant chemotherapy with EP for PS II NSGCT and confirms that 2 cycles of EP is highly effective in reducing recurrence with disease-specific survival of 100% and acceptable toxicity. These data suggest that inclusion of bleomycin (e.g., BEP) in this setting is not necessary.

**Results:**
- Median age was 28 years (range 15-52).
- 30% (19) had pN1 disease, 122 (78%) pN2 disease and 4 (3%) pN3 disease.
- Median number of positive lymph nodes was 3 (range 1-37) and median size of the largest positive node was 2.0cm (range 0.4-7.0cm).

**Discussion:**
- Extension of the present study was to investigate if long-term TCS experience a higher stress than in the GP (n = 67151) from a nationwide cohort study. The cohort was divided into two groups according to the presence or absence of T in the primary tumor. The presence of teratoma (T) in the testicular primary cancer was proposed to be an important clinical predictor of long-term outcome in men with GCT. We hypothesized that neither the presence nor the absence of T predicts the long-term survival in GCT patients. Methods: Metastatic non-seminoma (NSGCT) patients who received chemotherapy and had a primary testicular cancer (PTC) specimens available were included in this retrospective study. The cohort was divided into two groups according to the presence or absence of T in the primary tumor. The Indiana University Testicular Cancer Database was reviewed and survival data were correlated with the histopathologic findings. Differences in overall survival (OS) and progression free survival (PFS) between the two groups were evaluated using log-rank test.

**Results:**
- PTC specimens were available from 1224 pts diagnosed between 1990-2016.
- Median age was 27.3 years (range 13.1-70.8) and median follow-up was 1.9y (0.1-30.1) since the initiation of chemotherapy.
- The element of T was present in 689 pts vs 535 without T. At the start of chemotherapy, 61.5%, 14.1% and 24.4% of pts were stratified as good, intermediate, and poor IGCCCG risk. The 5-year PFS in pts with the T present vs. absent was 61.9% (95% CI, 57.1% to 66.2%) and 63.1% (95% CI, 55.7% to 70.8%), P = 0.73, respectively. The 5-year OS in pts with the T present vs. absent was 82.2% (95% CI, 77.9% to 85.8%) and 81.4% (95% CI, 76.5% to 85.3%), P = 0.91, respectively.
- We then evaluated 503/1224 who underwent PCTPCL, 327 had pure T and 146 had only necrosis in the resected lymph nodes. Five-year OS for pts with T vs necrosis was 90.3% (95% CI, 86.4% to 93.4%) vs 93.4% (95% CI, 90.4% to 95.9%), respectively, P = 0.21.

**Conclusions:**
- The presence of teratoma in primary tumor and PC-RPLND was not a prognostic factor in this retrospective study of patients with NSGCT.

**Abbreviations:**
- BEP, bleomycin, etoposide, cisplatin.
- CT, chemotheraphy.
- GCT, germ cell tumor.
- IT, immunotherapy.
- MB, mean number.
- MSI, microsatellite instability.
- NED, no evidence of disease.
- OS, overall survival.
- PFS, progression-free survival.
- PS, performance status.
- RPLND, retroperitoneal lymph node dissection.
- TCG, testicular germ cell.
- TMB, tumor mutational burden.
Quality-adjusted time without symptoms or toxicity (Q-TWiST): Analysis of cabozantinib (Cabo) vs sunitinib (Sun) in patients with advanced renal cell carcinoma (RCC). 

**Background:** The first-line treatment of patients with intermediate- or poor-risk clear cell RCC. To evaluate the overall treatment difference, we conducted a post hoc analysis using a quality-adjusted time without symptoms or toxicity of treatment (Q-TWiST) methodology. 

**Methods:** Each patient’s overall survival was partitioned into 3 mutually exclusive health states: time with grade 3/4 toxicity (TOX) before progression; time without symptoms of disease progression or grade 3/4 toxicity (TWiST); and time after progression or relapse (REL). Mean time spent in each state was weighted by a health-state utility associated with that state and summed to calculate Q-TWiST. A threshold utility analysis was used, applying utilities across a range of 0 (death) to 1 (perfect health).

**Results:** The analysis period was 650 days (median survival follow-up period). Mean time spent with TWiST was 121 d (95% CI = 43–199) longer for Cabo compared with Sun. Mean time spent with TOX was 8 d longer for Cabo; mean time spent with REL was 104 d shorter for Cabo. In the threshold utility analysis, the difference in Q-TWiST ranged from 129 d (TOX = 1, REL = 0) to 17 d (TOX = 0, REL = 1) in favor of Cabo across all utility combinations, and considering relative utility weights consistent with those observed in aARC patients (TOX = 0.5, REL = 0.5), the difference in Q-TWiST was 73 d in favor of Cabo. 

**Conclusions:** Treatment with Cabo was associated with longer Q-TWiST compared with Sun, primarily due to longer treatment differences on the quality of survival to help with clinical decision-making. Support for CaboSun: U10CA180821, U10CA180882; funding for treatment differences on the quality of survival to help with clinical decision-making.

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4560 Poster Session (Board #386), Sat, 8:00 AM-11:30 AM
Lenvatinib + pembrolizumab in patients with renal cell carcinoma: Updated results. First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Lenvatinib, a multitarget inhibitor of vascular endothelial growth factor (VEGF) receptors and other targets, has been approved in combination with everolimus to treat advanced renal cell carcinoma (RCC) after 1 prior VEGF-targeted therapy. We report results for the RCC cohort of a phase 1b/2 trial of lenvatinib + pembrolizumab in patients (pts) with selected solid tumors (NCT0201006). In this multicenter, open-label study, pts with metastatic clear cell RCC and measurable disease per immune-related RECIST (irRECIST) received oral lenvatinib 20 mg daily + pembrolizumab 200 mg IV every 3 weeks. Tumor assessments were performed by study investigators using irRECIST, and retrospectively by independent radiographic review (IRR) per irRECIST and RECIST 1.1. The phase 2 primary endpoint was objective response rate at 24 weeks (ORR24k). Results: 30 pts were enrolled; 12 (40%) pts had 0 and 18 (60%) pts had ≥1 prior anticancer therapy; 16 (53%) pts received ≥1 prior VEGF-targeted therapy. At data cutoff of August 1, 2017, median follow-up for progression-free survival (PFS) was 13.8 mos (95% CI, 11.9–15.7), and median PFS was 17.7 mos (95% CI, 9.6–NE). Efficacy outcomes are summarized in the table. Grade 3 or 4 adverse events (AES) occurred in 21 (70%) pts; however, 4 (13%) discontinued treatment due to AES. The most common AESs were diarrhea (83%), fatigue (70%), hypothyroidism (67%), stomatitis (63%), and nausea (60%). At crossover, pts had ≥1 dose of TEM (n = 18) or CTE (n = 22) at 2.6 mos (95% CI: 1.9–3.3) being associated with long-term survival. Objective response rate (ORR) and safety. A blinded radiologist assessed the radioresponse in 24 (80%) pts, and evaluable (median age 61, 52 males [75%], 44 [64%] with poor-risk by IMDC) pts were stratified by prior nephrectomy (Nx) and prior cytokine therapy. The Kaplan-Meier estimates were provided and Cox proportional analysis was performed. Results: In all, 605 pts from S-TRAC with BL NLR values were analyzed: 465 with BL NLR < 3 and 140 with BL NLR ≥3. At BL, significant differences between NLR < 3 vs ≥3 subgroups were seen for age (median 56.0 vs 60.0 y; P = 0.0161) and race (white [81.9% vs 90.0%], black [0.6% vs 0.7%], asian [14.6% vs 5.7%], other [2.8% vs 3.6%]; P = .0226). NLR < 3 vs ≥3 was statistically significant in the univariate analyses of DFS (hazard ratio [HR] 1.39; P = .0418); median 5.8y (NLR < 3) vs not reached (NLR ≥3). A lower BL NLR was associated with shorter DFS. NLR ≥3 ≥3 was also statistically significant in a multivariate analysis of DFS (HR 2.29; P = .0348). More pts treated with sunitinib (73%) had ≥25% decrease in NLR at Wk 4 vs CTE (P = 0.0729), while a ≥25% increase in NLR at Wk 4 showed a trend towards shorter DFS vs no change (HR 0.744; P = 0.2921). In addition, pts with ≥25% decrease in NLR at Wk 4 vs CTE (P = 0.1023) showed a trend towards shorter DFS. Additional data on CDb, neutrophils and lymphocytes will be presented. Clinical trial information: NCT00375674.

4586 Poster Session (Board #389), Sat, 8:00 AM-11:30 AM
A randomized phase II trial of pazopanib (PAZ) vs temsirolimus (TEM) in patients (pts) with advanced renal cell carcinoma (RCC) with intermediate or poor-risk disease (the TemPa trial). First Author: Amado J. Zurita, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: TEM has level 1 evidence in aRCC with poor-risk disease. No previous trial compared a VEGFR-TKI with TEM as first-line (1L) therapy. Methods: We randomly assigned (1:1) treatment-naive pts withacciRCC and ≥ ≥ risk factors (Hudes et al., NEJM 2007) to receive PAZ 800 mg po qd or TEM 25 mg iv qw. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall survival (OS), objective response rate (ORR) and safety. A blinded radiologist assessed the radiographic response using RECIST v1.1. A sample size of 90 pts was based on an assumption of improved median FFS 3.8 mos (TEM) to 6.1 mos (PAZ). Pts were stratified by prior nephrectomy (Nx) and prior cytokine therapy. The Kaplan-Meier method was used for PFS and OS analysis, and the Fisher’s exact test for comparison of ORR between PAZ and TEM. Results: TemPa was closed to new patient enrollment in Sept. 2017 after the results of CheckMate 214 and CABOSUN were released. A total of 69 pts were eligible and evaluable (median age 61, 52 males [75%], 44 [64%] with poor-risk by IMDC criteria). Thirty pts (43%) had prior Nx and 3 pts prior IL-2. Thirty-five pts received PAZ (intermediate-risk 15, poor-risk 20) and 34 TEM (intermediate-risk 10, poor-risk 24). Of the 69 pts, 67 had progressive disease or died. The median FFS was 5.2 mos (95% CI: 3.6–7.4) for PAZ and 2.6 mos (95% CI: 1.9–4.2) for TEM (P = 0.16). However, FFS was significantly longer with PAZ in IMDC intermediate-risk pts after adjustment for intermediate or poor-risk disease (the TemPa trial). First Author: Amado J. Zurita, The University of Texas MD Anderson Cancer Center, Houston, TX

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4564 Poster Session (Board #390), Sat, 8:00 AM-11:30 AM
Patterns of relapse and implications for post-nephrectomy surveillance for patients with high-risk non-clear cell renal cell carcinoma: Subgroup analysis of the phase 3 ECOG-ACRIN E2805 trial
First Author: Vivek Narayan, University of Pennsylvania, Philadelphia, PA

Background: Non-clear cell renal cell carcinomas (non-ccRCC) comprise a diverse subgroup, with biology and clinical behavior that is distinct from clear cell RCC (ccRCC). However, the natural history of non-ccRCC remains poorly defined, and clinical practice relies on consensus guidelines largely intended for ccRCC. We evaluated the patterns of relapse and the implications for post-nephrectomy surveillance for patients with non-ccRCC enrolled on the first and largest randomized trial of adjuvant antiangiogenic therapy for high-risk RCC. Methods: Retrospective subgroup analysis of patients with non-ccRCC enrolled on E2805. For recurrence rates (RR) by site, the cumulative incidence was estimated accounting for competing risks. Gray's test was used to compare the incidence between groups. The 2017 NCCN recommendations were used to evaluate the adequacy of strict adherence to post-nephrectomy surveillance guidelines. Results: 403 non-ccRCC patients were enrolled (37% papillary, 28% chromophobe, 21% mixed, 14% unclassified). 144 recurrences were detected over a median follow-up of 6.2 years. 5-year RRs (95% CI) were 22% (11, 28) and 49% (41, 56) for Int-High and Very-High UISS risk groups, respectively. Abdominal recurrences were most frequently identified, including lymph node (39%), nephrectomy bed (1.7%), and liver (13%). While overall 5-year RRs were comparable between non-ccRCC and ccRCC patients (34.6% vs 39.5%), non-ccRCC patients were more likely to major to develop abdominal site relapse (5-yr RR 26.4% vs 18.2%, p = 0.0008) and less likely to relapse in the chest (5-yr RR 13.7% vs 20.9%, p = 0.0005). Surveillance imaging for 5.3 years would be required to capture 95% of abdominal non-ccRCC recurrences. Conclusions: This is the largest, standardized evaluation of the natural history of non-ccRCC. The natural history of non-ccRCC differs from that of ccRCC, and this may impact the natural history of non-ccRCC.

4565 Poster Session (Board #391), Sat, 8:00 AM-11:30 AM
Disease-free survival patients at highest risk of recurrent renal cell carcinoma in S-TRAC. First Author: Alain Ravaud, Department of Medical Oncology, Hôpital Saint-André, University of Bordeaux-CHU, Bordeaux, France

Background: Sunitinib (SU) is FDA-approved for adjuvant treatment of patients (pts) at high risk (≥T3, any Fuhrman grade and/or nodal involvement (N+)) of recurrent renal cell carcinoma (RCC) post nephrectomy, based on the phase 3 S-TRAC trial that showed significant improvement with SU vs placebo (PBO) in disease-free survival (DFS) based on blinded independent central review (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.59–0.98; P = 0.03). The definition of high risk in S-TRAC included both objective (T stage and Fuhrman grade) and more subjective (pre-nephrectomy Eastern Cooperative Oncology Group Performance status [ECOG PS]) prognostic parameters. To delineate the highest risk pts from S-TRAC purely based on objective parameters, we performed an additional analysis classifying pts at highest risk of recurrence post nephrectomy, defined as T3 and Fuhrman grade ≥2 or T4 or N+ and any T. Methods: DFS analyses were conducted using Cox proportional hazard model. Results: In S-TRAC, 398 (65%) patients were classified at highest risk. The results indicated a trend towards benefit in DFS by independent review for SU vs PBO in this highest risk group (HR 0.73; 95% CI 0.54–0.97; P = 0.03), consistent with the HR for DFS previously reported in the S-TRAC trial for the T3 higher (HR 0.74; 95% CI 0.55–0.99; P = 0.04) group defined as T3 with Fuhrman grade ≥2 and ECOG PS ≥1 or T4 with any ECOG PS or N+ with any T, any ECOG PS, as well as with the overall population. Safety data did not identify major differences between the highest risk group vs overall S-TRAC pts. Incidence of key adverse events with SU was similar in highest risk group vs overall study pts (diabetes: 58.2% vs 56.9%; palmar-plantar erythrodysesthesia syndrome: 51.5% vs 50.3%; hypertension: 35.7% vs 36.9%; fatigue: 37.2% vs 36.6%; hypothyroidism: 15.3% vs 15.1%). Conclusions: The clinically meaningful treatment benefit observed in pts at highest risk of recurrence and the overall S-TRAC population, together with a consistent safety profile between these groups, support the favorable benefit/risk assessment of SU as an adjuvant treatment option for pts with RCC at high risk of recurrence post nephrectomy. Clinical trial information: NCT00357674.

4566 Poster Session (Board #392), Sat, 8:00 AM-11:30 AM
Replication stress response deficiency (RSRD) and response to immune therapy in clear renal cell carcinoma (ccRCC). First Author: Patrick Glen Pilie, University of Michigan, Ann Arbor, MI

Background: Despite treatment advances with immune therapy (IO), advanced stage ccRCC still has poor prognosis, due in part to a lack of predictive biomarkers. Replication stress (RS) is a hallmark of ccRCC initiation, contributing to genomic instability. However, cancer evades death from instability via deficient DNA damage repair (DDR) and RS response (RSR). The ATM/ATR and CHK2/CHK1 axes are critical to DDR and RSR; and deficiencies in these axes may activate innate immune signaling and lead to improved IO response. In this study, we assessed protein signaling changes in early ccRCC patient tumors, performed in silico analysis of ccRCC cohorts for the presence of a novel RSR deficient (RSRD) score, and evaluated the prognostic and predictive value of this RSRD score in ccRCC. Methods: We performed reverse phase protein microarray (RPMA) on 12 stage I ccRCC tumors vs 12 normal kidney tissues. We analyzed the Cancer Genome Atlas (TCGA) for a novel gene expression score of RSRD, and its impact on OS. We assessed immune cell infiltrate in TCGA tumors using CIBERSORT. We assessed RNA data from previously published cohort of 28 ccRCC patients treated with IO (Miao et al, Science 2018) and clinical outcomes based on RSRD score. Results: Early ccRCC tumors already showed loss of p-ATM/p-CHK2 and p-ATR/p-CHK1 protein signaling with increased IRF1 and ADAR1 expression (p < 0.05). From TCGA, RSRD-high tumors were more likely to be advanced stage and had significantly worse OS in multivariate analysis. In silico analysis revealed RSRD-high tumors had significantly higher T cell infiltrate compared to RSRD-low tumors. In the Miao et al IO-treated ccRCC cohort, 11/33 tumors were RSRD-high, with 73% of RSRD-high showing clinical benefit compared to only 18% of the RSRD-low and 36% of the bulk study population even when controlling for PRBRM1 mutation. Conclusions: RSR and DDR signaling are dysregulated in ccRCC and may activate innate immune pathways. A novel RSRD score has potential as both prognostic and predictive biomarker for IO response. Further studies are warranted to validate the predictive power of this biomarker and understand how DDR and RSR deficiencies in ccRCC may impact immune activation.

4567 Poster Session (Board #393), Sat, 8:00 AM-11:30 AM
A meta-analysis of randomized controlled trials for efficacy and safety of vascular endothelial growth factor tyrosine kinase inhibitors (VEGFTKIs) in adjuvant therapy in high-risk renal cell cancer (RCC). First Author: Irbaz Bin Riaz, Mayo Clinic, Rochester, MN

Background: Three large randomized placebo controlled trials (RCTs) (ASURE, S-TARC, PROTECT) with adjuvant VEGF-TKIs in high risk RCCs have provided variable results for improving disease free survival (DFS) with concerns for increased toxicity. We performed a meta-analysis of these trial results to assess a risk-benefit for adjuvant post-op treatments in high risk RCC patients by assessing reported disease free survival (DFS) and toxicity endpoints. Methods: A generic variance weighted random effects model was used to derive estimates for DFS and common side effects in the three trials. A separate analysis was performed for Sunitinib alone because of its FDA approval. Heterogeneity was assessed with Cochrane Q -statistic and was significant (P = 0.03). The definition of high risk in S-TRAC included T3 with Fuhrman grade ≥2 and ECOG PS ≥1 or T4 with any ECOG PS or N+ with any T, any ECOG PS, as well as with the overall population. Safety data did not identify major differences between the highest risk group vs overall S-TRAC pts. Incidence of adverse events with SU was similar in highest risk group vs overall study pts (diabetes: 58.2% vs 56.9%; palmar-plantar erythrodysesthesia syndrome: 51.5% vs 50.3%; hypertension: 35.7% vs 36.9%; fatigue: 37.2% vs 36.6%; hypothyroidism: 15.3% vs 15.1%). Conclusions: The clinically meaningful treatment benefit observed in pts at highest risk of recurrence and the overall S-TRAC population, together with a consistent safety profile between these groups, support the favorable benefit/risk assessment of SU as an adjuvant treatment option for pts with RCC at high risk of recurrence post nephrectomy. Clinical trial information: NCT00357674.
4568 Poster Session (Board #394), Sat, 8:00 AM-11:30 AM
Evaluation of the spectrum selective RTK inhibitor sitravatinib in clear cell renal cell carcinoma (ccRCC) refractory to anti-angiogenic therapy (AAT).
First Author: Shubham Pant, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Sitravatinib (MC5D516) is an oral, potent small molecule inhibitor of a closely related spectrum of receptor tyrosine kinases (RTKs) including the TAM family (AXL, MER), split RTKs (VEGFR2, PDGFR, KIT), RET and MET. Because of the importance of sitravatinib targets in the pathogenesis of ccRCC and putative roles for MET and AXL in intrinsic and acquired resistance to anti-angiogenic agents, sitravatinib was evaluated in patients (pts) with ccRCC after failure of AAT. Methods: Study 516-001 is a Phase 1/1b study of sitravatinib in pts with advanced solid tumors. After determination of the MTD in Phase 1, pts with ccRCC after failure of AAT and pts with qualifying genetic alterations in sitravatinib targets were enrolled into distinct Phase1b cohorts using respective multi-stage designs. Pts received 150mg sitravatinib once daily in continuous 21-day cycles and were evaluated for safety, PK and clinical activity. Here we report on the completion of Stage 2 enrollment of the Phase1b ccRCC cohort. Results: 89 pts (50 men/39 women; median age 67 years; range 36-84) with advanced solid tumors were enrolled in Phase1b cohorts, including 28 (29%/20/ men/ women; median age 67.5 years; range 47-77) in the ccRCC cohort who received a median of 3 prior treatment regimens. Prior AAT included sunitinib (n=17), pazopanib (n=13) and axitinib (n=9); 12 pts received ≥2 prior angiogenesis inhibitors. One partial response (PR) among the first 10 evaluable ccRCC pts in Stage 1 met criteria for enrollment of a total of 20 evaluable pts for Stage 2, where 4 confirmed PRs were observed and an unconfirmed PR in a pt who had received 4 prior AATs. Prolonged stable disease for at least 24 weeks was observed in an additional 5 pts. Treatment-related AEs (>20% of pts; Grades 1-3) included diaphoresis, hypertension, nausea, vomiting, diarrhea, fatigue, and decreased appetite. Conclusion: Stage 2 enrollment of the Study 516-001 Phase 1b cohort of ccRCC refractory to AAT was completed. Sitravatinib treatment resulted in 4 confirmed PRs in a heavily pre-treated patient population and demonstrated a manageable safety profile. Further evaluation of sitravatinib in ccRCC is warranted. Clinical trial information: NCT02219711.

4570 Poster Session (Board #396), Sat, 8:00 AM-11:30 AM
Patient-reported frustrations in renal cell carcinoma (RCC) care delivery: Results of a joint European Association of Urology (EAU)/KCCure Patient Survey.
First Author: Cristiane Decat Bergerot, City of Hope Comprehensive Cancer Center, Monrovia, CA

Background: A joint survey was developed by the EAU RCC Guidelines Panel and KCCure, a non-profit patient advocacy group, to ascertain patient perceptions towards adjuvant therapy for RCC (Battle D et al ASCO GU 2018). This survey included open-ended questions pertaining to sources of frustration in cancer-related care, the results of which are summarized herein. Methods: An online survey was conducted from April to June, 2017, published through social media and patient networking platforms. The survey obtained basic clinicopathologic, treatment related information, and open-ended questions asking for common sources of frustration in cancer-related care. Patients were also asked how they might reconcile these sources of frustration. Each response was analyzed and categorized into descriptive categories. The Kruskal-Wallis test was used to define associations between baseline characteristics and sources of frustration. Results: Among 450 patients with RCC, median age was 56, and 56% were female. The majority was diagnosed with clear cell histology (85%) and most patients had non-metastatic disease (73%). The most common sources of frustration were related to poor communication (20%), lack of confidence in diagnosis (18%), fear of recurrence/progression (14%) and financial issues (9%). Practical sources of frustration (e.g., lack of information, financial issues) were more common among patients with non-clear cell histology (P = 0.05) and older age (P = 0.01). In contrast, emotional sources of frustration (e.g., fear of recurrence/progression) were more common in females (P = 0.001). Patients posited that care could be improved if physicians demonstrated greater compassion (21%), spent more time supplying information (20%) and if they could circumvent financial issues (11%). Conclusion: RCC patients have varied and multiple concerns around care delivery. Based on this findings, practitioners should aim to better inform patients and should be cognizant of psychosocial issues surrounding their care. Certain baseline characteristics (age, gender and histology) can be considered in individualizing care delivery to minimize patient frustration.
Background: Although nivolumab, a programmed death 1 inhibitor, has been approved as a second line treatment for advanced renal-cell carcinoma patients, its effect has not been evaluated in patients with metastatic renal cell carcinoma (mRCC) in Europe since 2016, its real-world experience is currently unknown.

Methods: Efficacy, toxicity and potential biomarkers (histology, performance score, lactate dehydrogenase (LDH), eosinophils, neutrophils and lymphocytes) of nivolumab were retrospectively evaluated in Dutch RCC patients, who were consecutively registered in a national database between March 2016 and May 2017.

Results: Data of 264 patients in 24 hospitals was analyzed. Twenty-one (9%), 122 (49%) and 104 (42%) patients were categorized in favorable, intermediate and poor MSKCC risk groups, respectively. Median overall survival (OS) was 17.6 months (95% CI, 14.6 – 20.6) and TTF of 6.5 months (95% CI, 4.8 – 6.3) while non-clear-cell histology patients had a median TTF of 3.3 months (95% CI, 1.4 – 5.1). Patients with a WHO performance score ≤ 1 had a better OS and TTF as compared to patients with a performance score of ≥ 2; median OS 18.7 months (95% CI, not estimable vs. 5.4 months (95% CI, 1.2 – 9.6) and TTF 6 months (95% CI, 5.0 – 6.9) vs. 2.4 months (95% CI, 1.5 – 3.3). In patients with normal or mildly increased LDH, median OS was not estimable vs. 6.3 months (95% CI, 5.2 – 8.2), while a decreased efficacy (median OS 9.7 months (95% CI, 7.5 – 11.9) and TTF 2.9 months (95% CI, 2.1 – 3.6) was observed in patients with elevated LDH at baseline. An increase in absolute eosinophil count between week 0 and 8 was related to improved OS (HR = 0.41; 95% CI, 0.23 – 0.73, P = 0.003) and TTF (HR = 0.65; 95% CI, 0.46 – 0.92, P = 0.015).

Conclusions: In this real-world population, efficacy and safety of nivolumab are comparable to the results reported in the pivotal phase III trial. Remarkably, increase in eosinophil count during treatment with nivolumab predicts improved efficacy and survival.
4576  Poster Session (Board #402), Sat, 8:00 AM-11:30 AM
Functional biomarkers of homologous repair (HR) deficiency to guide novel DNA damage response targeted therapy in clear cell renal cell carcinoma (ccRCC). First Author: Patrick Glen Pilie, University of Michigan, Ann Arbor, MI

Background: Treatment for advanced ccRCC has rapidly evolved; however, responses are not uniform and synthetic lethal treatments with associated predictive biomarkers are still lacking. We previously reported that HR deficiency (HRD) is an early event in ccRCC, and that an HRD signature predicts for loss of RAD51 protein expression and improved OS. HRD has been shown to predict response to DNA damage response (DDR) inhibitors (DDR) across many tumor types. In this current study, we posited that HRD positive RCC is sensitive to DDR, that a stage dependent increase in phosphoinositide-3-kinase (PI3K) activation drives resistance to DDRI, and this resistance can be overcome with PI3K pathway inhibitors. Methods: We performed reverse phase protein microarray (RPPA) on 12 patient-derived stage I ccRCC tumors and 12 normal kidney tissues. We analyzed differential protein expression in HRD versus HR intact (HRI) ccRCC samples from the Cancer Genome Atlas (TCGA). We assessed apoptotic activity and clonogenic formation in HRD (ACHN) and HRI (786-O) RCC lines with and without CHK1 inhibitor (CHK1i) and/or mammalian target of rapamycin (mTORi) treatment (mTORi). Results: CHK1i and/or mTORi treatment showed increased expression of FOXO3a, p-ATM, p-CHK2, p53 (p < 0.05) compared to normal, reflecting early defective ATM signaling. In TCGA, 75% of stage I ccRCC had an HRD signature, which decreased to less than 50% in stage IV tumors. HRI tumors had significantly higher protein expression of RAPTOR, CNLYC, and PI3K than HRD tumors. In a preclinical model, HRD ACHN was sensitive to CHK1 inhibitor, whereas HRI 786-O was resistant. Adding mTORi overcame resistance to CHK1 inhibition in 786-O. Conclusions: Early stage ccRCC has defective DDR protein signaling with loss of ATM pathway activation. Increased oncogenic signaling, including in the mTORi/PI3K/akt pathway, may alter HR gene activity and sensitivity to DDRi. The addition of mTORi to DDRi overcomes resistance to DDRi in HRI ccRCC. This study provides rationale for future biomarker-driven clinical trials of DDR inhibitors in advanced ccRCC patient populations.

4577 Poster Session (Board #403), Sat, 8:00 AM-11:30 AM
Single-center analysis of 109 patients (pts) with metastatic chromophobe renal cell carcinoma (ChRCC): Differences in outcomes by histologic variant. First Author: Yasser God, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ChRCC constitutes 5-10% of all RCC cases, and is generally associated with better prognosis including benefit from approved targeted agents (Armstrong, Lancet Onc, 2016). Presence of sarcomatoid features (SF) have previously been proposed as an adverse prognostic marker, but data for systematic therapy is limited. We assessed therapeutic outcomes for pts with metastatic ChRCC with and without SF. Methods: Retrospective chart reviews of pts with newly diagnosed metastatic ChRCC evaluated at Memorial Sloan Kettering Cancer Center (MSKCC) between 2002-17. MSKCC pathology reports determined presence/absence of SF to categorize pts. Evaluated endpoints included overall survival, time to treatment (TTF) for pts who initiated first line therapy at MSKCC and time to recurrence (TTR) post nephrectomy with metastatic disease. OS between the 2 groups was compared using log-rank analysis. A subset of pts had next generation sequencing (NGS) with MSK-IMPACT. Results: 109 pts with newly diagnosed metastatic ChRCC were identified (80 without SF, 29 with SF). Pts with SF were more likely to present with metastatic poor risk status (31% vs 10%) and de novo metastatic disease (48% vs 19%). 52 pts initiated first line therapy at MSKCC (35 without SF, 17 with SF). First line agents included VEGF tyrosine kinase inhibitors (60%), mTOR inhibitors (13%), cytokines (6%) and other investigational agents (21%). Outcomes are summarized in table below. NGS was performed in 22 pts (10% of all pts) which 64% had actionable findings. Conclusions: Pts with metastatic ChRCC with SF had significantly worse outcomes compared to pts without SF. Median TTR < 3 months for this subgroup supports close surveillance following nephrectomy for localized tumors. The lack of benefit observed across various classes of systemic agents warrants study of underlying biology and investigating novel agents.

4578 Poster Session (Board #404), Sat, 8:00 AM-11:30 AM
Overall survival (OS) by clinical risk category for high dose interleukin-2 (HD IL-2) treated metastatic renal cell carcinoma (RCC). Data from PROCLAIM. First Author: Mayer N. Fishman, Moffitt Cancer Center, Tampa, FL

Background: Clinical risk factors continue to separate mRCC patient survival outcomes regardless of therapy. Methods: International Metastatic RCC Database Consortium (IMDC) risk criteria were utilized to assess survival among 939 mRCC patients in the PROCLAIM data base, with dates of treatment from 2006 to present. Patients/patients (pts) with data for all IMDC criteria and are described here. Median follow-up is 23.4 months (range: 0.2-23). Results: 810 patients (pts) had data for all 6 IMDC criteria and are described here. Clinical risk factors continue to separate mRCC patient survival outcomes.

4579 Poster Session (Board #405), Sat, 8:00 AM-11:30 AM
CABozantinib (Cabo) in advanced non-clear cell renal cell carcinoma (nccRCC): A retrospective multicenter analysis. First Author: Nieves Martinez Chanza, Dana-Farber Cancer Institute, Boston, MA

Background: Cabo shows robust clinical activity in advanced clear cell RCC. nccRCC, a heterogeneous mix of diseases, have been underrepresented in clinical trials and effective systemic therapy is lacking. We retrospectively characterized the clinical activity and toxicity of cabo in nccRCC. Methods: Medical records from advanced nccRCC patients (pts) treated with cabo at academic centers were reviewed. We captured baseline characteristics, clinical outcomes and genomic alterations by next-generation sequencing (NGS). Objective response rate (ORR) was assessed by RECIST. Clinical benefit (CB) included ORR or stable disease. Time to treatment failure (TTF) and overall survival (OS) were estimated by Kaplan-Meier. Results: We identified 80 pts with nccRCC: papillary (59%), chromophobe (10%), collecting duct (5%), Xp11.2 translocation (15%) or unclassified (11%). The majority were IMDC intermediate/poor risk (88%) and received cabo ≤3 line (53%). Median exposure was 4 months (mos) (range: < 1-23). 48% remained on cabo while 42% had discontinued for progression and 5% for toxicity. Most common adverse events were fatigue (51%) and rash (33%). In 66 pts on cabo ≥8 weeks, ORR was 27.3%. 71% had CB; with 64% durable CB ≥6 mos. Median OS was 11 mos (95%CI 9-11). TTF was 6.9 mos (95%CI 4.8-9.9). Subset analyses in Table. Most frequently altered genes in 47% CB pts with NGS were 45% (21%) harbored TP53 and MET alterations. Conclusion: Cabo is safe and active in nccRCC. Support of ongoing (e.NCT02761057) and future prospective studies in nccRCC encompassing all histologies is warranted.
**4580 Poster Session (Board #406), Sat, 8:00 AM-11:30 AM**

**Pilot trial of ibrutinib plus nivolumab in patients with metastatic renal cell cancer (mRCC): results from a dose-finding cohort.**

**First Author:** Primo Lara, University of California, Davis, Sacramento, CA

**Background:** Immune checkpoint inhibitor therapy (CIT) has transformed the management of patients (pts) with mRCC, with a fraction experiencing durable tumor responses. However, most eventually develop disease progression after either an initial response to CIT or while on CIT. Newer agents that modulate immune response can potentially potentiate CIT therapy. The ITK/JTK/BTK inhibitor ibrutinib has been reported to inhibit myeloid derived suppressor cells in preclinical models and to potentiate CIT. We conducted an investigator-initiated pilot trial of ibrutinib plus the PD1 inhibitor nivolumab in mRCC pts, particularly in those previously exposed to CIT. Here we report initial safety and efficacy results from the dose-finding cohort.

**Methods:** Pts with mRCC of any histologic subtype and who have completed at least one line of prior systemic therapy including prior CIT were eligible. Pts must have acceptable end-organ function and Zubrod PS of 0-2. Treatment consisted of nivolumab 240 mg IV q 2 weeks plus ibrutinib 560 mg (dose level 0) or 420 mg (dose level -1) orally once daily. Cycle length was 28 days. Dose limiting toxicity (DLT) was defined as any Grade (Gr) 3+ adverse event (AE) attributable to therapy. Results: As of 9/18/17, 12 pts have been enrolled, 6 to each dose level. Patient characteristics: Mean age = 62 years (range 44-78); Male sex = 7 (58%); White race = 9 (75%); Prior CIT = 11 (92%). Three pts experienced one DLT each in dose level 0 (all Gr3): elevated lipase, hypoalbuminemia, & nausea. Only 1 DLT has been seen thus far in dose level -1 (Gr3 infection). The most common Gr3+ AEs include anemia (n = 5), ALT elevation (4), AST elevation (3), nausea (3), hypoalbuminemia (2), esophagitis, infection, lipase increase, and vomiting (1 each). Two pts with prior CIT had partial tumor response (both confirmed), 1 of which later became a CR. **Conclusions:** Ibrutinib at a dose of 420 mg orally once daily in combination with nivolumab 240 mg q 2 weeks appears feasible and tolerable in mRCC patients. No unique immune-related AEs have been seen thus far. Anti-tumor activity was seen in 2 pts previously exposed to PD1-targeted therapy. Updated results will be presented. (Supported by Pharmacycics and UCDCCC). Clinical trial information: NCT02989078.

**4582 Poster Session (Board #408), Sat, 8:00 AM-11:30 AM**

**Radiofrequency ablation of pathologically proven T1a renal tumors: 15 years follow-up—A tertiary cancer center experience.**

**First Author:** Mohamed E. Abdelsalam, Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** To evaluate the long term oncologic efficacy and overall survival of radiofrequency ablation (RFA) for pathologically proven T1a renal cell carcinoma (RCC). Methods: We retrospectively reviewed our renal ablation data base between January 2001 and December 2014, we included only patients with histologically diagnosed T1a RCC (< 4 cm) who underwent RFA. Patient who underwent cryoablation, those with syndromes, and those with recurrent or bilateral RCC were excluded. For each patient, we recorded: Demographics, tumor size and histology, complications, recurrence at ablation site, development of metastases, history of another malignancy, survival/death and cause of death. Overall survival (OS) was estimated using Kaplan and Meier product-limit estimator. Results: Ninety four RFA procedures were performed for 92 lesions in 92 patients (54 males and 38 females, average age 68 years). Average tumor size was 2.7cm (range: 1.3-3.9 cm). The median follow-up for all subjects was 4.7 years (range: 0.16 – 14.4 years). Total of 7 patients developed complications (7.4%). Three, 1 and 3 patients developed Grades 1, II and III (3.2%) complications respectively according to the Clavien-dindo classification. A total of 6 patients (6.4%) developed local recurrence at the ablation site, one patient underwent watchful observation, two underwent repeat ablation and 3 patients underwent partial nephrectomy. One patient had disease recurrence in the other kidney. Fifty four patients (56%) had another non-renal primary malignancy. None of the patients developed metastasis from RCC. The median overall survival was 8.31 years. The overall survival was 68 %, 34% and 21 % at 5, 10 and 14 years respectively. The cancer specific survival (CSS) was 100%.

**Conclusions:** Radiofrequency ablation is a safe and highly efficacious modality for treatment of small renal tumors. Fifteen-year follow up data reveals long standing oncologic control with low recurrence and complication rates.

**4583 Poster Session (Board #409), Sat, 8:00 AM-11:30 AM**

**Outcomes of patients (pts) with metastatic renal cell carcinoma (mRCC) and sarcomatoid differentiation (sRCC) after treatment with immune checkpoint inhibitors (ICI): A single-institution retrospective study.**

**First Author:** Jeremy Aaron Ross, University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Pts with mRCC and sarcomatoid differentiation (sRCC) have a poor prognosis with approved targeted therapies (Keskin et al. JU 2017). The response to ICIs in mRCC pts with sRCC is unknown. **Methods:** This is a retrospective study of pts with metastatic sRCC who received ICIs (2013-2017). Data collected include tumor histology, demographics, type of ICI, response to ICI, and efficacy outcomes (response, progression-free survival [PFS], and overall survival [OS]). Descriptive statistics were used. Results: 33 pts (85%) had clear-cell RCC (ccRCC); 6 pts had variant histology RCC (vRCC) including chromophobe (2), mucinous tubular and spindle cell carcinoma (1), and unclassified (3). All pts but 2 had intermediate- or poor-risk disease by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. 15 pts (38%) had greater than 50% sarcomatoid component (sarc) in primary tumor of nephrectomy specimen, 5 (15%) had > 80%, and 2 (5%) had 100%. 22 pts (56%) received nivolumab (nivo) as a single agent. 15 pts (38%) received nivo in combination with ipilimumab and 2 pts (5%) received pembrolizumab. 24 pts (62%) responded to treatment with ICIs. Of these, 14 (58%) received ICIs at first-line therapy, 9 pts in second, 1 in fourth. Median PFS was 8.3 months (95% CI 3.6 – 13.1). 5/33 pts with ccRCC (15%) achieved a complete response (CR) and 4 remain in CR at 52, 31, 31, and 22 months from start of ICI. 1 pt was not followed at our institution after 24 months of CR. These pts had 90%, 1%, 30%, 50%, and 90% sarc, respectively. 1 of these patients remains on treatment. 5/6 pts with vRCC did not respond to therapy; 1 pt with unclassified histology had stable disease for 5 months 28 pts (77%) are alive at this time of this analysis. The median OS was not reached.

**Conclusions:** In pts with sRCC, ICIs appear to be effective in ccRCC with up to 15% achieving durable CR. The prognosis of vRCC with sRCC remains poor despite treatment with ICI, underscoring the need to develop more effective therapies for these patients.
Effectiveness and safety of pazopanib (PAZO) and everolimus (EVE) in a changing treatment (Tx) landscape: Interim results of the non-interventional study PAZOREAL. First Author: Martin Boogemann, University of Muenster Medical Center, Muenster, Germany

Background: The therapeutic landscape for metastatic renal cell carcinoma (mRCC) has evolved rapidly with the approval of targeted therapies like tyrosine kinase-, mTOR-, multikinase-, and immune checkpoint inhibitors. Real-world data are urgently needed to monitor the translation of these approaches into daily practice. Methods: PAZOREAL is a prospective, non-interventional study to evaluate efficacy, tolerability, safety, and quality-of-life (QoL) in mRCC patients (pts) treated with first-line PAZO, second-line nivolumab (NIVO) or EVE, or third-line EVE (± lenvatinib) after NIVO. The primary variable was time on drug (TD) in the respective Tx lines. Other endpoints were overall survival (OS), dosing, safety, and QoL. Results: Between Dec 2015 and Nov 2017, 421 pts were enrolled. Interim results for 385 pts treated with PAZO in first line are presented here, majority of pts presented with ECOG 0-1 (81.0%) and clear cell carcinoma (80.3%). Median TD was 6.5 months (95%CI, 5.5-8.3). Using commonly applied trial eligibility criteria i.e. Karnofsky PS ≥ 70%, normal hemoglobin and clear cell histology, the median TD in trial-eligible pts (39.5% of 385 pts) was 8.0 months (95%CI, 6.2-11.2). Progressive disease (n = 104/212 pts) was the most common reason for end of PAZO Tx, followed by toxicity (n = 34) and unrelated adverse events (AEs) (n = 20). 75 pts subsequently received NIVO as second-line treatment. Median OS was not reached. Death was reported for 20% of pts. Survival (S) up to 34 months as estimated: Treatment-emergent AEs (TEAEs) were reported for 308 of 378 pts included in the safety analysis, PAZO-related TEAEs for 246 pts (65.1%), and PAZO-related grade 3/4 TEAEs for 75 pts (19.8%). Most commonly reported AEs were diarrhea, nausea, and fatigue. QoL evaluated by EQ-5D-5L remained stable during PAZO TX. Conclusions: The PAZO treatment landscape demonstrated acceptable efficacy, safety and tolerability of PAZO in the real world setting. For patients considered trial-eligible, TD was comparable with results from clinical trials. The sequence of PAZO followed by NIVO as second line Tx is commonly applied in Germany.

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TPS4588  Poster Session (Board #413a), Sat, 8:00 AM-11:30 AM
Methods: SoC vs SoC in previously untreated pts with unresectable/mUC (a CTLA-4 inhibitor) demonstrated acceptable safety and clinical activity. This phase 3 study will evaluate nivolumab + ipilimumab and nivolumab + SoC vs SoC in previously untreated pts with unresectable/mUC (NCT03036098). Methods: Key inclusion criteria: cisplatin-eligible and -ineligible pts with measurable disease, no prior systemic chemotherapy for unresectable/mUC, and evaluable tumor biopsy. Key exclusion criteria: active brain metastases, autoimmune disease, and prior or concurrent treatment drugs specifically targeting T-cell co-stimulation or checkpoint pathways. Cisplatin-eligible- and -ineligible pts will be randomized 1:1 to arm A (nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks up to 4 doses, followed by nivolumab 480 mg every 4 weeks until disease progression or unacceptable toxicity) or arm B (gemcitabine-cisplatin or gemcitabine-carboplatin for up to 6 cycles). Additional cisplatin-eligible pts will be randomized to arm C (nivolumab 360 mg + gemcitabine-cisplatin every 3 weeks for up to 6 cycles, followed by nivolumab 480 mg or arm D (gemcitabine-cisplatin for up to 6 cycles). Stratification factors: PD-1 ligand expression, and liver metastases and investigator (BICR) in cisplatin-eligible pts receiving nivolumab + ipilimumab vs SoC, and PFS by BICR in cisplatin-eligible pts receiving nivolumab + SoC vs SoC. Enrollment began March 2017 with a target of ~987 pts. Clinical trial information: NCT03036098.

TPS4589  Poster Session (Board #413b), Sat, 8:00 AM-11:30 AM
Methods: This single-arm, open-label, multicenter study of enfortumab vedotin for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor therapy. First Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Most patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC) treated with checkpoint inhibitor immunotherapy (CPI) will fail to achieve a durable response regardless of treatment setting (post-platinum or first-line cisplatin-ineligible). Enfortumab vedotin (EV), an antibody-drug conjugate, delivers the tubule-disrupting agent monomethyl auristatin E to tumors expressing Nectin-4, which is overexpressed in mUC. Preliminary results from an ongoing phase 1 study of EV (Petrylak ASCO-GU 2018) showed that EV (1.25 mg/kg) was well-tolerated in pts with CPI-treated mUC (n = 67). Fatigue (55%), nausea (48%), and decreased appetite (45%) were the most commonly reported treatment-related AEs. Hyponatremia (n = 4, 6%) was the only AE grade ≥3 (regardless of attribution) in > 5% of the cohort; vomiting (n = 2, 3%) was the only treatment-related AE grade ≥3 occurring in ≥2 pts. Hyperglycemia, a new safety finding, emerged post-database cutoff; the protocol was revised. EV showed a confirmed objective response rate (ORR) of 31% in 55 of 67 evaluable pts (23.5% in pts with baseline liver metastases, n = 17) with most responses ongoing as of 02-Oct-2017. Nine pts with unconfirmed PR are pending response assessment. These encouraging results warrant further investigation in this population. Methods: This single-arm, open-label, multicenter phase 2 study (NCT03219333) evaluates the antitumor activity and safety of EV monotherapy in ~120 pts with la/mUC. Pts must have previously received a CPI and either have received prior platinum or be cisplatin-ineligible. Pts must have histologically or cytogenetically documented transitional cell carcinoma of the urethrum that progressed during or following receipt of most recent therapy. The primary objective is to determine antitumor activity as measured by ORR. Secondary objectives include assessment of duration of response, disease control rate, PFS, OS, and safety/tolerability. Pts must have tumor tissue available for exploratory analysis. Antitumor response is assessed per RECIST v1.1. Study enrollment began in Sep 2017. Clinical trial information: NCT03219333.

TPS4591  Poster Session (Board #414b), Sat, 8:00 AM-11:30 AM
Methods: This is a multicenter, randomized, open label phase II study evaluating safety and efficacy of 2 cycles of avelumab monotherapy in patients with metastatic urothelial carcinoma who are ineligible for cisplatin-based therapy. First Author: Alejo Rodriguez Vida, Hospital del Mar, Barcelona, Spain

Background: Cisplatin-based chemotherapy is standard first line treatment for metastatic urothelial carcinoma (mUC). However, around 50% of patients are ineligible for cisplatin due to poor performance status or comorbidities. For these cases, cisplatin-based combinations are valid alternative in-els, although they are associated with inferior survival. Additional new strategies for cisplatin-ineligible patients are therefore urgently needed. Recently, excellent clinical activity has been reported with immune checkpoint inhibitors as monotherapy for cisplatin-ineligible patients. The purpose of this study is to test the safety and efficacy of avelumab (anti-PD-L1 therapy) given pre-emptively and combined with carboplatin-gemcitabine (carbo/gem) followed by maintenance avelumab. Priming the chemotherapy response giving immunotherapy first could enhance the overall response of the combination and prevent the detrimental effect of chemotherapy on immune cells. Up regulation of PD-L1 by chemotherapy could also enhance the immunotherapy efficacy. Methods: This is a multicenter, randomized, open label phase II study evaluating safety and efficacy of 2 cycles of induction avelumab plus carboplatin-gemcitabine followed by maintenance avelumab-gemcitabine for 6 cycles, followed by avelumab maintenance, compared to carbogem alone. Eligibility criteria include patients with mUC, no prior systemic therapy, ineligibility for cisplatin and adequate organ function. Patients will be stratified by the presence/absence of visceral metastasis and ECOG 0-1 versus 2. Primary endpoint of the study is objective response rate (ORR). Secondary endpoints include progression free survival, overall survival and safety. Exploratory endpoints include potential immunologic and genomic predictive biomarkers. For sample size calculation, we hypothesized that the ORR with the combination will be ≥45%, compared to 30% with standard carbogem. A sample of 80 patients will provide a probability of 0.9 of confirming our hypothesis, based on a Simon randomised phase II design. The trial is open to accrual. Clinical trial information: NCT03390595.
**TPS4592**

**Poster Session (Board #415a), Sat, 8:00 AM-11:30 AM**

**ATLAS: A phase 2, open-label study of rucaparib in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC).**

**First Author:** Petros Gravis, University of Washington, Seattle, WA

**Background:** There are limited treatment options for pts with mUC that has progressed during or after platinum-based chemotherapy and/or immune checkpoint inhibitors (ICls), emphasizing the need for new therapies. Analysis of The Cancer Genome Atlas bladder cancer dataset suggests that approximately 60% of bladder cancer tumors have homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase (PARP) inhibitors have demonstrated activity in patients with HRD. In the United States, the PARPi rucaparib is approved for the treatment of pts with del- eterious BRCA mutation (germline/somatic) associated advanced ovarian cancer treated with ≥2 chemotherapies. We hypothesize that PARP inhibition may have antitumor activity in mUC, particularly in tumors with HRD. The ATLAS (NCT03397394) trial will evaluate the efficacy and safety of rucaparib in pts with locally advanced or mUC previously treated with platinum-based chemotherapy and/or ICls.

**Methods:** Eligible pts must have measurable disease per RECIST v1.1, adequate organ function, and radiographic progression after ≥1 prior standard-of-care regimens. Confirmation of HRD status before enrollment is not required, but tumor tissue or recently obtained archival tissue is mandatory for HRD profiling. Prior PARPi treatment is an exclusion. All pts will receive 600 mg rucaparib orally BID until disease progression or other reason for discontinuation. The primary endpoint is confirmed objective response rate (investigator-assessed RECIST v1.1) in both HRD-positive (signature based on tumor genomic loss of heterozygosity) and intent-to-treat populations. Secondary endpoints include evaluation of overall response rate (ORR), duration of response, progression-free survival, and overall survival. Other endpoints include safety, quality of life, biomarker analysis, and pharmacokinetics. Pts will be randomized 1:1 to rucaparib or placebo in a double-blind fashion. A rolling 2-stage design will be used to estimate the number of pts required. Out of 71 total pts, with the first stage of 24 pts, 1 out of 6 pt experience a dose-limiting toxicity (DLT) to identify the RP2D. The ph II portion is enrolling up to 4 SGI-110 dose level cohorts utilizing a MinMax 2-stage design to identify the MTD proposed to expand safety and pharmacokinetics. DLT will be evaluated during the first 2 cycles. The ph 2 primary endpoint is confirmed objective response rate (investigator-assessed RECIST v1.1). Endpoints of the ph 2 are 6-month PFS (primary), overall response rate (ORR), duration of response, progression-free survival, and overall survival. Analyses of safety, pharmacokinetics, biomarker, quality of life, and exploratory endpoints will be done during the ph 2.

**TPS4594**

**Poster Session (Board #416a), Sat, 8:00 AM-11:30 AM**

**SPIRE. A phase Ib randomised, open label clinical trial combining gemcitabine and a novel anti-c-Met inhibitor for solid malignancies including bladder cancer.**

**First Author:** Simon J. Crabb, Southampton Experimental Cancer Medicine Centre, Southampton, United Kingdom

**Background:** Cisplatin based chemotherapy is a standard of care therapy for urothelial bladder cancer for palliative first line treatment of advanced/metastatic disease or radical neoadjuvant treatment of localized muscle invasive disease. However, cisplatin resistance, associated with disease progression or relapse, is common and remains a critical barrier to therapeu- tic advance. Pre-clinical data suggest cisplatin resistance in bladder cancer, and other cancers, might be avoided by co-administration of a DNA hypomethylating agent. SPIRE is a phase Ib/IIa trial evaluating whether the DNA methyltransferase inhibitor SGI-110 (guadecitabine), in combination with gemcitabine and cisplatin chemotherapy (GC), is safe and biologically effective. It incorporates a dose escalation phase in advanced/metastatic solid tumors, including bladder cancer, followed by a randomized dose expansion phase as neoadjuvant treatment prior to cystectomy for bladder cancer (T2-4a NO MO). The primary objective is to determine a recommended phase II dose (RP2D) of SGI-110 in combination with GC, using pre-defined dose limiting toxicity criteria assessed by CTC AE v4.03, and a biologically effective dose based on serum DNA LINE-1 methylation and hemoglobin F re-expression status. Dose Escalation Phase: Treatment comprises GC (Q 1000 mg/m², IV, days 8 and 15; C 70 mg/m², IV, day 8), and SGI-110 (SC, days 1-5), for up to 6 cycles of 21 days. Up to 6 patients are enrolled in each of up to 4 SGI-110 dose level cohorts utilizing a ‘rolling 6’ design. Dose Expansion Phase: 20 patients will be randomized 1:1 to GC, or GC + SGI-110 at the established RP2D, to expand safety and pharma- codynamic end points data. SPIRE is coordinated by the CRUK Southampton Clinical Trials Unit and is currently recruiting to a 3rd dose escalation cohort through the UK Experimental Cancer Medicine Centre (ECMC) network. It was developed through the CRUK Combinations Alliance. Funding: Cancer Research UK (C9317/A19903) and Astex Pharmaceuticals. Sponsored by: University Hospital Southampton NHS Foundation Trust. Clinical trial in- formatory: ISRCTN16332228.

**TPS4595**

**Poster Session (Board #416b), Sat, 8:00 AM-11:30 AM**

**PECULIAR: An open label, multicenter, single-arm, phase 2 study of neoadjuvant pemolintemod (PEM) and epacadostat (EPA), preceding radical cystectomy (Cy), for patients (pts) with muscle-invasive urothelial bladder cancer (MIUUC).**

**First Author:** Andrea Necchi, Istituto Nazionale dei Tumori, Milan, Italy

**Background:** MIUUC is a systemic disease and > 40% of pts develop recur- rence after Cy. Despite neoadjuvant chemotherapy yields Level 1 evidence, it is underutilized worldwide and a small survival improvement is deemed over Cy alone. PEM is an EMA and FDA-approved therapy for metastatic UC after platinum failure or for cisplatin-ineligible pts. EPA, an anti-IDO1 agent, combined with PEM, safely improved the response-rate in UC in phase 1 trial. Our hypothesis is that PEM+EPA, given neoadjuvantly, could further improve downstaging MIUUC. **Methods:** Pts with T2-T3b NO UC with residual disease after transurethral resection of the bladder (TURB, surgical opinion, cystoscopy or radiological presence) will receive 3 cycles of PEM 200mg intravenously, q3 weekly. EPA will be orally taken at the dose of 3 weeks of the last PEM dose. Computed tomography (CT) scan, 18FDG-PET/CT scan, and multiparametric bladder MRI (mpMRI) will be done during screening and before Cy to stage and evaluate response. After Cy, pts will be managed according to EAU guidelines. Adjuvant anti PD-1 therapy is not allowed. PD-L1 status will be assessed using Dako anti-PD-L1 antibody (clone 22C3), relying on the combined positivity score (CPS). Pathologic complete response (pT0) is the primary endpoint. All pts enrolled who re- ceive at least 1 cycle of study drug will be included in the ITT analysis. The H0 is pT0=25% and H1 pT0=15%. A MinMax 2-stage design will be used to estimate the number of pts required. Out of 71 total pts, with the first stage of 43 pts, ≥6 pT0 will be required in the first stage, and ≥14 pT0 in the whole study population. Correlative research on blood samples will include immune-cell profiling and cytokine assessment. In tumor samples, genomic analyses will be done with FoundationONE test (Foundation Medicine Inc.). Tumor mutational burden (TMB) will be determined on 1.1 Mbp of se- quenced DNA and reported as mutations (mut) per megabase (Mb) and microsatellite instability (MSI) will determined on 114 loci (EudraCT number 2017-002379-24). Clinical trial information: 2017-002379-24.
500 patients gives...
Background: CheckMate 025 established NIVO as a standard of care (SOC) option for advanced clear cell RCC (ccRCC) after prior antiangiogenic therapy. The combination of IPI plus NIVO is anticipated to become a new SOC option for intermediate/poor risk patients (pts) with 2 or more measurable non-clear cell metastases, duration of response and safety profile. An optimized management of nivolumab (NIVO) and ipilimumab (IPI) in advanced renal cell carcinoma (mRCC). NIVES study: A phase II trial of nivolumab (NIVO) plus stereotactic body radiotherapy (SBRT) in II and III line of patients (pts) with metastatic renal cell carcinoma (mRCC). First Author: Cristina Masini, Medical Oncology Unit, Clinical Cancer Center, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy

Background: Despite recent advances in drug therapy, pts with mRCC have about a 10% 5-year survival rate. Several preclinical studies have documented an increased in peripheral antitumor immunity following radiation, a phenomenon known as the abscopal effect. The irradiated and non-irradiated metastases, duration of response and safety profile. An Exploratory Project also identifies molecular basis of synergistic effect of SBRT and immunotherapy, potential mechanisms of resistance to checkpoint inhibitors. Twenty of the planned 68 pts were enrolled from July 2017 to January 2018. Study duration will be 12 months for the accrual and 36 months for the follow up. Clinical trial information: EUdraCT Num 2016-003032-20.

TPS4601 Poster Session (Board #419b), Sat, 8:00 AM-11:30 AM
CANTATA: A randomized phase 2 study of CB-839 in combination with cabozantinib vs. placebo with cabozantinib in patients with advanced/metastatic renal cell carcinoma (mRCC), First Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Glutamine utilization is a metabolic pathway upregulated in renal cell carcinoma (RCC) and important for RCC tumor cell proliferation and survival. CB-839 is a first-in-class, potent, oral inhibitor of the mitochondrial enzyme glutaminase (GLS) that controls a critical step in tumor cell utilization of glutamine. In preclinical RCC models, CB-839 demonstrated synergistic antitumor activity when combined with cabozantinib, a VEGFR/MET inhibitor. A phase 1 study cohort of CB-839 plus cabozantinib as 2L+ therapy showed encouraging safety and efficacy results, with 40% overall response rate (ORR; RECIST v1.1) and 100% disease control rate in patients with clear cell advanced/metastatic RCC (mRCC). These findings prompted the initiation of a randomized phase 2 study comparing CB-839 plus cabozantinib vs. placebo plus cabozantinib in patients with clear cell mRCC.

Methods: This international, randomized, double-blind, placebo-controlled, multi-center study (NCT03428217) will enroll ~300 patients with clear cell mRCC. Eligible patients will have received 1-2 prior lines of systemic therapy for mRCC including ≥1 anti-angiogenic therapy or the combination of nivolumab + ipilimumab. Other eligibility criteria include KPS ≥70%, measurable disease (RECIST v1.1), and no prior cabozantinib (or other MET inhibitor). Patients will be randomized 1:1 to receive CB-839 (800 mg twice daily per oral (PO) route) or placebo in combination with cabozantinib (60 mg daily PO) in 28-day cycles until disease progression or unacceptable toxicity. Patients will be stratified by prior PD-1/PD-L1 inhibitor therapy (Y/N) and IMDC prognostic risk group (favorable vs intermediate vs poor). The primary endpoint is progression-free survival (PFS; RECIST v1.1) by blinded independent radiology review; secondary endpoints are investigator-assessed overall survival (OS), safety, disease control rate (DCR), and quality of life. This study will contribute to understanding the efficacy and safety profile of CB-839, a first-class metabolic inhibitor, in combination with cabozantinib in patients with mRCC.

Clinical trial information: NCT03428217.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
A phase 2, single-arm trial of neoadjuvant axitinib plus avelumab in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). First Author: Axel Bex, The Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Surgery is the standard treatment for non-metastatic RCC. Despite curative intent, pts with a high risk of relapse have a 5-year metastasis-free survival rate of only 30%, and prevention of recurrence is an unmet need. In a phase 1b study (JAVELIN Renal 100), the axitinib + avelumab response rates (RR) and safety profile were promising with objective RR of 60% and toxicity profiles as seen with VEGFR-treatment. The combination is currently being tested in a phase III trial against sunitinib in untreated metastatic RCC. We initiated a neoadjuvant study of axitinib + avelumab in pts with high-risk of relapse (NCT03341845).

Methods: The study is designed as an open label, single arm, phase 2 trial with a Simon's two-stage design evaluating neoadjuvant axitinib + avelumab followed by complete surgical resection in 40 pts with high-risk non-metastatic clear-cell (cc) RCC. Key inclusion criteria are planned radical or partial nephrectomy with curative intent; biopsy proven ccRCC; clinical high risk defined as cT1b-cT2a grade (G) 4, cT2b G 3-4, cT3a G 3-4, cT3b-cT4 any G cN0 cM0, or cT any cN1 cM0; World Health Organization (WHO) performance status of 0-1, and completely resectable primary tumours. Key exclusion criteria are metastatic disease, corticosteroid or immunosuppressive systemic treatment, active autoimmune disease, prior systemic treatment for RCC including immunotherapy, biologic therapy, investigational therapy or hormonal therapy. Pts receive axitinib 5 mg BID escalated to 10 mg BID if tolerated and avelumab 10 mg/kg iv Q2W for 6 cycles following H1 blockers and acetaminophen every 2 weeks. Pts with a tumour increase from baseline at CT after the first 6 weeks or no change after dose escalation will be taken off trial and undergo surgery. All others will complete 3 months followed by resection. Primary endpoint (ept): Partial RR (RECIST 1.1) following neoadjuvant therapy. Secondary epts: DFS, OS, rate of recurrence, safety, and tolerability. Exploratory epts include investigation of effects on neoangiogenesis, immune infiltrates and MDSC components to support a rationale for the combined use of axitinib and avelumab. Clinical trial information: NCT03341845.

Vorolanib (CM082), everolimus, and the combination in patients with pretreated metastatic renal cell carcinoma (CONCEPT study): A randomized, phase 2/3, double-blind, multi-center trial. First Author: Jun Guo, Peking University Cancer Hospital and Institute, Beijing, China

Background: VEGF and mTOR pathways play key role in the development of renal cell carcinoma (RCC), the combination of agents targeting both VEGF- and mTOR-mediated pathways have been investigated with distinct results. Vorolanib (CM082) is a potent and selective inhibitor of VEGFR and PDGFR. Previous phase 1 study (NCT02577458) found that the combination of vorolanib 200 mg plus everolimus 5mg was associated with manageable toxicity consistent with individual agents and no new safety signals, anti-tumor activities was also seen in 35.7% patients with RCC patients who progressed on at least one VEGFR TKI therapy. Based on these findings, we conducted the CONCEPT study, a randomized, phase 2/3, double-blind, multicenter trial to assess vorolanib, everolimus, or their combination as second-line treatment in Chinese patients with metastatic RCC.

Methods: Patients with cytologically or histologically confirmed RCC who had disease progression after one prior VEGFR TKI were eligible for participation in the study. They will be randomized by 1:1:1 ratio to receive matching placebo plus vorolanib or everolimus, or the combination. Randomization was stratified according to the MSKCC risk scores. The sample size was specified assuming a hazard ratio (HR) of 0.60, equating to an expected 6.5 months for everolimus and 10.5 months for vorolanib with or without everolimus. To provide 80% power at a two-sided 5% significance level, and an estimated 20% dropout rate, a total of 390 patients are required. This study is registered as NCT03095040. Progression: This study is conducted in 35 centers in China, so far 32 centers have been activated. Recruitment was started since March 10, 2017, and a total of 101 patients were randomized currently. Clinical trial information: NCT03095040.
A randomized phase III trial between adjuvant docetaxel and surveillance after radical radiotherapy for intermediate and high risk prostate cancer: Results of SPCG-13 trial.

Results: Of 374 patients randomized in this Italian/German phase III study, to receive either 6 cycles of adjuvant docetaxel 75mg/m² every 3 weeks without continuous predniso (Arm A, n = 188) or surveillance (Arm B, n = 186) after RT (NCT006653848), Neoadjuvant/adjuvant ADT was mandatory for all patients. Primary end-point was a rising PSA ≥ 2 ng/ml above the nadir PSA value. Intermediate or high risk prostate cancer was defined as T2 with Gleason score (GS) 4+3, PSA > 10; T2, GS 8-10 any PSA; or any T3. Patients were followed for 5 years with PSA every 3 months for two years and thereafter every 6 month. Study power was 89% to detect a difference between groups and the sample size calculation accounted for T2/T3 distribution (12%/15% difference in BDFS was assumed for T2/T3 patients). All six cycles were completed in 147 (78.2%) of patients in arm A. Mean age was 66.2 years in Arm A and 66.4 years in ARM B; 75.0% had T3 disease, 46.3% had GS 8-10. Median follow up was 59.4 months (range 1 to 111 months, one without follow-up). The primary endpoint was reached in 30.7% of patients; 31% in Arm A and 30.3% in Arm B. In a Cox multivariate model, no difference between the BDFS curves (p = 0.631) between treatment groups. Febrile neutropenia occurred in 16.1% of docetaxel patients. No deaths were related to docetaxel treatment. There were 43 deaths during the trial (20 in Arm A and 23 in Arm B) of which 9 and 7 due to PrCa. In a Kaplan-Meier analysis, GS (p = 0.001) was significant predictor of PSA progression. Hazard Ratio for Arm A (docetaxel) vs Arm B (surveillance) was 1.14 (95% CI 0.79 to 1.64, p = 0.495).

Conclusions: Adjuvant docetaxel without prednisone did not improve BDFS after radical radiotherapy with ADT for intermediate or high risk prostate cancer. Clinical trial information: NCT006653848.

Olaparib combined with abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). A randomized phase II trial.

Methods: Patients (Pts) with mCRPC pts whose tumors did not need to have a HRRm (NCT01972217). mCRPC pts with HRRm status. Median overall survival was 23.3 vs 20.9 mths in the combination vs comparator (HR 0.97, 95% CI 0.68-1.40).

Conclusions: No clinical benefit for mCRPC pts treated with a PARP inhibitor combined with abiraterone, regardless of HRRm status. Safety data were less favorable for the combination, but no detriment to QoL was seen. Our study indicates lack of clinical benefit with Abiraterone Acetate plus LHRHa in M0HNPC improves PSA free survival (PSAFS). A randomized phase II trial.

Results: Of 197 of 200 randomized pts were treated (99 AA+LHRHa /98 placebo). Grade 3 AEs: arterial hypertension (1000 mg od) and treated until disease progression. Primary endpoint was progression. PET/CT guided salvage therapy resulted in high biochemical response rates. Pooled multicenter findings will be submitted for a New Drug Application. Clinical trial information: NCT02940262.
The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On-site at the Meeting, this abstract will be printed in the Monday edition of ASCO Daily News.
A randomized phase 2 study investigating 3 dosing regimens of radium-223 dichloride (Ra-223) in bone metastatic castration-resistant prostate cancer (mCRPC). First Author: Cora N. Sternberg, San Camillo-Forlanini Hospital, Rome, Italy

Background: Ra-223, standard dose (SD) 55 kBq/kg q4w for 6 cycles improved overall survival (OS) and delayed time to symptomatic skeletal events (SSEs) in patients (pts) with mCRPC and bone metastases in the ALSYMPCA study (Parker C, N Engl J Med. 2013;369(3):213-23). The current study investigated different Ra-223 treatment regimens in a similar patient population. Methods: Pts with bone mCRPC were randomized 1:1:1 to Ra-223 SD or Ra-223 high dose (HD) 88 kBq/kg q4w for up to 6 cycles, or to Ra-223 SD extended (EXT) q4w for up to 12 cycles. The primary objective was to compare SSE-free survival (SSE-FS) between HD and SD, and EXT and SD. Hypothesis testing was performed at a 2-sided alpha level of 0.20 with no adjustment for multiplicity. Results: 391 pts were randomized; baseline characteristics were well balanced. No statistically significant differences in SSE-FS were observed between Ra-223 SD and HD (median 12.3 vs 12.9 months, hazard ratio (HR) 1.06, 80% CI 0.88–1.27, p = 0.70) or Ra-223 SD and EXT (median 13.2 vs 10.8 months, HR 1.26, 80% CI 0.94–1.69, p = 0.31). Median OS was 15.8, 16.0 and 14.4 months in the SD, HD and EXT arms, respectively. A total of 370 pts received Ra-223 with a median number of doses of 6 in each arm. The most frequent treatment emergent adverse events (TEAEs) were fatigue, anemia and nausea. Grade ≥3 TEAEs were noted in 34%, 48% and 53% of pts in the SD, HD and EXT arms, respectively. The most frequent grade ≥3 TEAEs overall were anemia (13%), bone pain (5%), thrombocytopenia (4%) and hypertension (4%). TEAEs leading to permanent discontinuation occurred in 9%, 16% and 17% of pts in the SD, HD and EXT arms, respectively. Conclusions: No statistically significant differences in SSE-FS were noted between Ra-223 SD and HD and EXT SD and EXT. However, HD and EXT arms had a higher incidence of grade ≥3 TEAEs than the SD arm. The study supports the currently approved dose and schedule of Ra-223. Clinical trial information: NCT02023697.

Health-related quality of life (HRQoL) deterioration and pain progression in men with non-metastatic castration-resistant prostate cancer (M0 CRPC): Results from the PROSPER study. First Author: Gerhardt Attard, The Institute of Cancer Research and the Royal Marsden, Surrey, United Kingdom

Background: The Phase 3 PROSPER trial (NCT02003924) showed a statistically significant improvement in metastasis-free survival (MFS) with enzalutamide (ENZA; n = 9333) vs. placebo (PBO; n = 4668) in asymptomatic men with M0 CRPC and prostate-specific antigen doubling time ≤10 months. We report the results of the HRQoL and pain evaluations. Methods: Functional Assessment of Cancer Therapy–Prostate (FACT-P) and Brief Pain Inventory, Short Form, were used to assess HRQoL and pain at baseline (BL) and every 16 weeks during treatment. Pain progression was defined as ≥2 points in pain severity items and mean scores increase from BL: HRQoL improvement/deterioration as an increase/decrease from BL using pre-established thresholds for clinically meaningful difference. Time to first confirmed (at two consecutive visits) and unconfirmed HRQoL deterioration/pain progression were assessed using Kaplan-Meier estimates and Cox proportional hazards models under censoring not at random assumption. Results: BL characteristics and scores were similar between arms with low pain (median 0) and high HRQoL (median FACT-P total score, 121). Decrease in attrition rate was greater in PBO vs. ENZA mainly due to disease progression (53% vs. 68% at week 49, respectively). Most patients reported no change or improvement in HRQoL. Proportion of patients with pain progression at week 49 was similar between ENZA (11–20%) and PBO (14–21%). Lower risk of pain progression was observed with ENZA vs. PBO in the confirmed analysis (hazard ratio (HR) 0.79–0.93; p > 0.05). Nominal statistically significant lower risk of deterioration was observed with ENZA for FACT-P total, FACT Advanced Prostate Symptom Index, prostate cancer subscale (PCS), and emotional well-being (EWB) in the confirmed (HR 0.75, 0.77, 0.77, 0.69, respectively; p < 0.05) and for PCS and EWB in the unconfirmed (HR 0.82, 0.80, respectively; p < 0.05) analyses. Conclusions: In PROSPER, ENZA significantly delayed MFS vs. PBO without worsening HRQoL, and significantly delayed clinically meaningful HRQoL deterioration in several FACT-P domains. Pain progression was similarly low in both arms. Clinical trial information: NCT02003924.
Phenotypic and genomic characterization of CTCs as a biomarker for prediction of Veliparib therapy benefit in mCRPC. First Author: Ryan Dittamore, Epic Sciences, Inc., San Diego, CA

Background: Response to PARPi in mCRPC patients (pts) particularly those with DNA damage response mutations (DDRm) was observed in the TOPARP trials (utilizing Olaparib) which enrolled heavily pre-treated, high CTC pts. However, the NCI 9012 study, randomizing 1 line mCRPC pts to Abiraterone (A) or A + Veliparib (V), did not demonstrate an advantage for the pre-specified subgroup, with DDRm pts having better outcomes on both arms. Here we explore the use of CTCs to ascertain phenotypic Genomic Instability (pGI) as a proposed selection biomarker for PARPi. Methods: 212 blood samples from 84 pts (n = 39 A & n = 42 A+V, 3 uneval) prior to and during therapy were processed utilizing the Epic Sciences CTC platform. 32 pts had a concomitant fresh biopsy sequenced by MI-ONCOSEQ. CTC pGI was determined using previously described algorithms (Scher et al. ASCO 2016) which predicts genomic instability with morphological features and protein expression. A subset of CTCs (n = 466) underwent single cell sequencing for genomic scanning (DDRM) and results were compared to tissue DDRm, CTC biomarkers were correlated with pt outcomes. Results: 80.2% (65/81) of baseline (BL) blood samples had enumerable CTCs, 48% (39/81) of these had ≥1 CTCs with pGI detected (pGI+), pGI+ pts had improved PSA response in the A+V arm, 83% (20/24) compared to 33% (9/27) in A (p = 0.002). High pGI CTC counts were observed in Metastatic Bladder Cancer wild type (wt) pts (median 3.8 CTC/mL vs. 2.7 CTC/mL), pGI+ CTCs were detected in 42% (5/12) DDRm pts and 35% (7/20) DDRwt pts. Discordant results between CTC genomic scarring and tissue DDRm were observed. 3 pts with tissue DDRm only had CTCs with low genomic scarring. Conversely, 3 pts with DDRwt only had CTCs with high genomic scarring. pGI+ pts from baseline to on-therapy with A+V, 82% (9/11) pts (mean of 40 pGI+ CTC/mL) had reductions to <1 pGI CTC/mL, whereas only 20% (1/5) pts. (mean of 6 pGI+ CTC/mL) had a reduction to <1 pGI CTC/mL (p = 0.036). Conclusions: A CTC biomarker, pGI, is correlated to differential PSA response and associated with A+V. Single CTC biomarkers highlight the heterogeneity of genomic scarring in patients with and without DDRm and may be more sensitive than tissue based markers. Clinical trial information: NCT01576172.

The complete genomic landscape of metastatic prostate cancer pinpoints clinically targetable subgroups. First Author: Lisanne Francisca van Dessel, Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, Netherlands

Background: Recent genome analysis efforts have shown that genomic alterations obtained from primary and metastatic prostate cancer (mPCa) vary widely, stressing the need to obtain comprehensive genomic data from metastatic tissue. Understanding the complete genomic atlas of mPCa will widely, stressing the need to obtain comprehensive genomic data from metastatic tissue. We found a total of 69 and 62 alterations, including SNVs (1/5) pts. (mean of 6 pGI+ CTC/mL) had a reduction to <1 pGI CTC/mL, whereas only 20% (1/5) pts. (mean of 6 pGI+ CTC/mL) had a reduction to <1 pGI CTC/mL (p = 0.036). Conclusions: A CTC biomarker, pGI, is correlated to differential PSA response and associated with A+V. Single CTC biomarkers highlight the heterogeneity of genomic scarring in patients with and without DDRm and may be more sensitive than tissue based markers. Clinical trial information: NCT01576172.

Genomic profiling of primary prostate tumors from patients who develop metastatic castration-resistant prostate cancer (mCRPC). First Author: Joaquin Mateo, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: mCRPC is enriched for genomic aberrations in TP53, RB1, AR, PTEV and DNA damage repair (DDR) compared to localized prostate cancer. Here we pursued NGS of 470 primary prostate tumors from patients who all locally treated mCRPC to evaluate this enrichment in this poor prognosis population. We also compared 49 pairs of same patient primary tumor and mCRPC biopsies. Methods: Libraries for targeted DNA NGS were built using a customized amplicon-based panel (GeneRead v2 DNAseq, Qiagen) and read in a MiSeq (illumina). Copy number aberrations (CNA) were assessed using a previously described bioinformatics pipeline (Seed, CCR 2017) for 98 genes. We compared gene aberration frequencies with previously reported cohorts. Results: A total of 470 treatment naive primary prostate biopsies were sequenced and passed QC filters for mutation and DNA calling. Frequencies for TP53 (27%) and RB1 (5%) aberrations were higher than previously reported for localized prostate cancer (TCGA, p < 0.01 each) but lower than for mCRPC (SU2C PCF, TP53 p = 0.001, RB1 p = 0.07). Conversely DDR gene defects were more common: BRCA2 5% (p = 0.004); CDK12 5% (including 7 cases with two mutations; p = 0.06); ATM 4% (p = 0.2), and PALB2, BRCA1, RAD50, FANC1 1% each. Overall, 2% of primary tumors hadDDR defects. MDM2/4 was deleted in 12% of primary tumors; 5% had activating mutations of PIK3CA or AKT. Other genes recurrently mutated were SPOP (7%) and CTNNB1 (3%). Surprisingly, in 5 cases (1%) AR mutations at low allele frequencies were detectable prior to ADT. Among the 49 patient matched subgroups, mutations detectable only in mCRPC were identified in AR (n = 4), TP53 (4), RB1 (3) and CTNNB1 (1). All 9 truncating mutations in BRCA2, ATM, CDK12, PALB2 were shared between treatment naive and mCRPC samples. Conclusions: TP53 and RB1 aberrations are more common in poor prognosis primary prostate cancer than in localized, more curable disease (TCGA) but lower than in mCRPC. Gene mutations detected only at mCRPC in patient-matched samples support the evolution of these mutations under treatment selection pressures. Poorer prognosis prostate cancers are enriched for BRCA2 aberrations.

Phase 2 randomized cross-over trial of abiraterone + prednisone (ABI+P) vs enzalutamide (ENZ) for patients (pts) with metastatic castration resistant prostate cancer (mCRPC): Results for 2nd-line therapy. First Author: Daniel Khailow, British Columbia Cancer Agency - Vancouver Centre, Vancouver, BC, Canada

Background: ABI+P and ENZ have similar efficacy for first-line treatment of mCPC, with cross-resistance to new therapies suggested. We report on 2nd-line treatment at progression. The optimal sequencing has not been prospectively investigated and predictive biomarkers are needed. Methods: A multi-centre trial of ABI+P followed by ENZ at PSA progression (arm A) vs ENZ followed by ABI+P (arm B). Primary endpoints were PSA decline > 50% (PSA50) on 2nd-line therapy and time to 2nd-line PSA progression (TTP2) from start of 1st-line. Deep-targeted sequencing of serial samples of circulating tumour DNA (ctDNA) was performed. Results: 202 pts (101/arm) were accrued with median follow-up 22.3 months (m). 65 pts from arm A and 71 from arm B crossed-over to 2nd-line treatment and 30 pts (15/arm) stopped treatment without cross-over. Baseline characteristics at time of 2nd-line therapy were balanced: median age 75 (range 50-93), PSA 14.5 (6.6-62.1), alkaline phosphatase > upper limit of normal (ULN) in 39% of pts and bone/liver metastasis (mets) in 89%/9%. ECOG PS 0-1 in 89% vs 76% of pts for arm A vs arm B (p = 0.044) and LDH was > ULN in 25%/8% (p = 0.013). PSA50 for 2nd-line therapy for arm A vs arm B was 34% vs 4% (p=0.001) and time to PSA progression on 2nd-line therapy (TTP2) was 2.7 m vs 1.3 m (HR 0.38, 95% CI 0.26-0.56). For the intention-to-treat population, TTP2 was 13.6 m vs 11.9 m (HR 0.75, 95% CI 0.53-1.06). Median overall survival (OS) was not reached vs 24.3 m (HR 0.82, 95% CI 0.53-1.27). On multivariable analysis, prognostic factors associated with TTP2 were, respectively, on-therapy DDR gene defects (HR 0.41, 95% CI 1.08-4.54), liver mets (HR 3.18, 95% CI 1.21-8.41) and treatment arm A vs B (HR 0.27, 95% CI 0.17-0.40). At progression, AR gene copy number increased in 14% of evaluable pts (7/49) and AR L702H/T878A(S) mutations were present in 8% of pts. ctDNA fraction >2% at baseline was associated with worse TTP2 (HR 0.39, 95% CI 0.23-0.63) and median OS (HR 2.40-6.91). Conclusions: The sequence of ABI+P followed by ENZ was associated with superior PSA50 and TTP2 on 2nd-line therapy. AR alterations associated with ABI+P and ENZ resistance were detectable in ctDNA. Clinical trial information: NCT01225557.

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5016 Poster Discussion Session; Displayed in Poster Session (Boad #243), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase 2, randomized, 3-arm study of abiraterone acetate and prednisone (AAP), AAP plus degarelix (AAP+D), and degarelix (D) alone for patients (pts) with biochemically-recurrent prostate cancer (PC) following radical prostatectomy (RP). First Author: Karen A. Auto, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Androgen deprivation therapy (ADT) with GnRH analogs does not entirely suppress testosterone signaling. AAP + ADT decreases blood and intra-tumoral testosterone (T) levels by >1 log, and in pre-RP trials resulted in greater pathologic responses relative to ADT alone. Trial designs that can rapidly assess therapies (txs) are critical given the long natural history of PC and resources required for phase 3 trials. Using a novel endpoint (endpt) (undetectable PSA (PSA0) with T recovery (rec)), we hypothesized that AAP+D given in the rising PSA state post-RP, a low volume but potentially lethal set, could eliminate all disease, a prerequisite to cure. Methods: Post RP ≤ salvage radiotherapy pts with a rising PSA ≥1.0 ng/ml, doubling time ≤9 months (mo), no metastases (met) on CT/Bone scan, and T ≥150 ng/dl were eligible. NCT01751451. Prior ADT ≤8 mo was allowed. Pts were randomized (1:1:1) to AA 1000 mg + P 5 mg qD (Grp 1), AAP + monthly D (Grp 2), or monthly D (Grp 3) for 8 mo, followed by cessation of txs. The primary (1°) endpt was PSA0 with T >150 at 18 mo and secondary, PSA0 at 8 mo.

Timing of androgen deprivation therapy for prostate cancer patients after radiation: Planned combined analysis of two randomized phase 3 trials. First Author: Andrew Loblaw, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

The TOAD (TROG 03.06; NCT00110162) phase 3 randomized trial showed that immediate androgen deprivation therapy (IADT) improved overall survival (OS) vs deferred ADT (DADT) in patients with low clinical stage prostate cancer treated with radiotherapy (RT) or prostatectomy + RT. ELAAT (NCT00439751) was a similarly designed trial but failed to reach its accrual goal. The two invigilating teams planned a combined analysis before ELAAT was activated. Methods: The PSA failures from TOAD and 78/79 patients accrued to ELAAT were combined (1 patient was excluded due to castrate resistant prostate cancer (CRPC)). Participants for both trials were randomized 1:1 to IADT or DADT. The primary endpoint was all-cause mortality by intention-to-treat. Secondary endpoints were cancer-specific mortality (CSM), local progression, distant progression, CRPC, and prostate cancer complications (PCC). Results: 261 patients from TOAD and 78 patients from ELAAT were followed a median of 5.0y. TOAD patients were younger (median 70.5 vs 73.8y) and more had a relapse-free interval <2y from RT (30% vs 10%). In the DADT arms, 63% received ADT a median of 1.58y for TOAD; 38% received ADT a median 1.65y for ELAAT. For patients receiving ADT, the mean pre-ADT PSAs were 3.52 and 30.2 ng/ml in the IADT and DADT arms of TOAD and 3.98 and 18.1 ng/ml in ELAAT. There were 60 deaths, 40 and 20 respectively. Overall, for IADT and DADT arms the proportions of deaths in each trial were 15%, 11%, 19% and 26%, 27% and 24%. All-cause mortality (HR 0.75, 95% CI 0.40-1.40; N = 276) for DADT vs. IADT was not statistically different (p = 0.36). The time to local progression (time to progression) in OS was detected within 8 months of ADT and DADT in the combined analysis. A possible explanation is that ELAAT accrued older patients with lower risk of CSM and had a smaller difference in PSA between the IADT and DADT arms.

5017 Poster Discussion Session; Displayed in Poster Session (Boad #244), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Prostate radiotherapy in newly-diagnosed metastatic hormone-sensitive prostate cancer: A single-institution experience. First Author: Scott Carlyle Morgan, Division of Radiation Oncology, University of Ottawa, Ottawa, ON, Canada

Background: In patients presenting with metastatic prostate cancer (mPCa), the role of local therapy is undefined. Recent registry analyses have suggested, however, that external beam radiotherapy (RT) directed at the prostate may improve overall survival (OS). We reviewed the experience of patients with biochemically-recurrent PC (RT) in this setting at our center. Methods: The study population consisted of men with newly-diagnosed mPCa referred to a comprehensive cancer center between 2005 and 2015 and treated initially with androgen deprivation therapy. Patients were eligible for inclusion if they received 1) prostate RT with biologically effective dose at least that of a course of 40 Gy in 15 fractions or 2) no prostate RT. The association between receipt of prostate RT and OS was studied. OS was estimated using the Kaplan-Meier method while univariate and multivariate Cox regression were used to identify factors associated with OS. Results: A total of 304 cases were eligible. Prostate RT was received in 105 cases. Median age at diagnosis was 75 years (IQR, 67-82 years). Median follow-up was 72.2 months. On univariate analysis, prostate RT was associated with improved OS (HR 0.62, 95% CI 0.46-0.84, p = 0.002). 2-year and 5-year OS was 74.7% and 41.8% respectively in those receiving prostate RT and 56.9% and 26.7% respectively in those not receiving RT. Median OS in those receiving RT was 48.3 months versus 23.7 months in those not receiving RT. Treatment effect was less pronounced in the post-RP group taking account of age at diagnosis, year of diagnosis, presenting PSA, T stage, N stage, and M1 subdivision. RT remained associated with improved survival (HR 0.64, 95% CI 0.43-0.96, p = 0.033). Conclusions: This cohort represents the largest single-center experience of primary tumor-directed RT in mPCa reported to date. In this setting, RT was associated with improved OS. The observed 19-month absolute difference in median OS is clinically significant. This analysis could not account for performance status, volume of metastatic disease, comorbidities, receipt of systemic therapies, and other potential confounders. Only large-scale RCts will be able to definitively assess the value of prostate RT in this setting.

5018 Poster Discussion Session; Displayed in Poster Session (Boad #245), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Timing of androgen deprivation therapy for prostate cancer patients after radiation: Planned combined analysis of two randomized phase 3 trials. First Author: Andrew Loblaw, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

KEYNOTE-046: ADXS-PSA plus pembrolizumab (pembro) in metastatic castration-resistant prostate cancer (mCRPC). First Author: Mark N. Stein, Columbia University Medical Center, New York, NY

Background: ADXS-PSA, an attenuated Listeria monocytogenes-based immunotherapy that targets prostate-specific antigen (PSA), is designed to generate antigen-specific T cell effectors that kill tumor cells. Published data has shown synthetic ADXS-Lm-LOO-TAA treatment with a PD-1 blocking antibody in an animal model. Methods: This phase 1/2 trial studied patients with progressive mCRPC, ≥18 years who received ≥2 prior chemotherapy-targeted/immunotherapies or ≥1 prior chemotherapy in a metastatic setting. Part A (PA; n = 14) pts received ADXS-PSA doses 1x10^7; 5 x10^7 and 1x10^8 colony forming units (CFU) IV every 3 wks and Part B (PB; n = 37) pts received 1x10^7 CFU + 200 mg pembro IV every 3 wks with a 4th pembro dose 3 wks later, for up to 2 yrs or until progression/toxicity. The 1° endpoint was safety/tolerability. Anti-tumor activity and effect on PSA level were evaluated. Preliminary results are presented. Results: At entry, PA and PB pts were similar in age (~70 yrs), Gleason score (~8.3) and prior abiraterone. PB pts had higher median BL PSA (40.6 v 20.8 ng/ml), and more prior enzalutamide (53 v 26%) and chemotherapy (49 v 36%) use vs PA. 46 pts (94%) experienced treatment-related AEs (TRAEs) with 16 pts having grade 3-4 events: fatigue, hypotension, hypertension, anemia. TRAEs ≥10% of any grade were cytokine release symptoms including chills, fever, nausea and hypotension. TRAE incidence was similar between groups and all resolved with supportive care. Accrual is complete but pts remain on trial. Overall, 2 PA (14%) v 16 PB pts (43%) had a decreased PSA post-BL. Of these, 8 PB (22%) v 0 PA pts achieved a PSA reduction ≥50% from BL; which was confirmed at least at 6 wks (18%). At the time of analysis, tumor measurements were available for 5 PA and 23 PB pts. One PA pt (20%) and 10 PB pts (43%) had SD (RECIDIST 1.1). Four PB pts (40%) with SD also had a decreased PSA post-BL; a confirmed response was seen in 2 of these. 9 PA and 14 PB pts had non-measurable disease at BL; 33% (3/9) and 78% (11/14) had disease measurable at confirmation. In this population of heavily pretreated mCRPC pts ADXS-PSA + pembro had a manageable safety profile and showed promising activity compared to monotherapy. These preliminary data warrant further study. Clinical trial information: NCT02325557.

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5020 Poster Discussion Session; Displayed in Poster Session (Board #247), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Microsatellite instability in prostate cancer and response to immune checkpoint blockade.
First Author: Wassim Abida, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Immune checkpoint blockades have shown clinical benefit in mismatch repair deficient (dMMR) cancers, leading to accelerated FDA approval of pembrolizumab, a PD-1-targeting agent, for the treatment of dMMR or microsatellite instability-high (MSI-H) advanced solid tumors. However, the frequency of MSI-H prostate cancer (PCA) (PD-1/PD-L1 reactivity) in the population. As a correlative analysis, we report on potential predictive factors associated with response to PD1/PDL1 agents in this disease subset, remain poorly defined.

Methods: 839 PCA patients underwent targeted next-generation sequencing (NGS) of tumor and matched normal samples on an institutional protocol for the characterization of somatic mutations, copy number alterations and germline mutations (with specific consent). MSIsensor analysis, a computational method for detecting MSI, was performed. Tumor mutation burden (TMB) was calculated, with additional analysis for mutational signatures and immunohistochemical (IHC) staining of MMR proteins in selected cases.

Results: 20/839 PCA patients (2.4%) were found to have MSI-H/dMMR tumors, defined as MSI sensor score of > 3 and TMB of > 10, confirmed by IHC and mutational signature analysis. Of 13/20 MSI-H patients who consented to germline analysis, 3/13 (23%) had a germline MMR gene mutation, 3/5 MSI-H patients who underwent profiling of ≥2 matched tumors demonstrated MSI in the later tumor. In total, 10 patients with MSI-H tumors received a PD1/PDL1 targeting agent, 2/5 died with PSA decline of > 80%. 3/10 are early in their treatment with PSA decline of > 60%. 1/10 had stable disease for 6 months then progressed. 3/10 had no response. 1/10 was inevaluable.

Conclusions: Tumor profiling for MSI status can be considered for patients with advanced PCA. MSI-H PCA patients with HER2 mutations were better candidates for immune checkpoint blockade treatment. Germline profiling should be recommended for patients with MSI-H PCA. While early in this dataset, responses to PD1/PDL1 therapy may occur in ~50% of patients with MSI-H/dMMR PCA. Longer follow up and additional prospective studies will be necessary to confirm responses in this patient population.

5021 Poster Session (Board #248), Sat, 1:15 PM-4:45 PM

Immunotherapy utilizing the combined use of NK and ADCC mediating agents with PARP inhibition.
First Author: Kathleen Fenerty, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, Bethesda, MD

Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) prevent single-stranded DNA repair. PARPi has antitumor activity in patients with known double-stranded DNA repair deficiencies (germline BRCA mutations). Olaparib is FDA approved for BRCA mutant ovarian and breast cancer. Emerging clinical data (*NC1029484400). ACO, Karzai et al. suggest a benefit of combining olaparib with checkpoint inhibition in prostate cancer patients. Here, we interrogated the immunomodulatory potential of olaparib in vitro, focusing on prostate cancer. We hypothesized that olaparib increases immune cell killing of tumor cells independent of BRCA status or checkpoint modulation. Methods: BRCA mutant and BRCA wildtype prostate carcinoma cell lines were pretreated with olaparib and then exposed to human healthy donor natural killer (NK) cells with or without the antibody-dependent cellular cytotoxicity (ADCC)-mediating monoclonal antibodies (mAbs) avelumab (anti-PD-L1) or cetuximab (anti-EGFR). Tumor cell lysis was monitored. Anti-CD16 antibody was used to confirm NK-induced ADCC.

Flow cytometry was performed on NK cells, up to 7 years after last Ra-223 dose; an active 2-year follow-up. Clinical trial information: NCT01934790.
Radium-223: Disease response and fracture assessment by whole body diffusion-weighted MRI (WB-DWMRI) in metastatic castration resistant prostate cancer (mCRPC). First Author: Chris C. Parker, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom

Background: Ra-223 improves overall survival in patients with mCRPC. Imaging criteria to assess response in bone are lacking but could inform treatment strategies. Methods: We did a prospective phase II study to evaluate potential response biomarkers included from Ra-223. Patients with chemotherapy-naive bone mets were randomised (1:1) to receive Ra-223 at 255 or 88 kBq/kg for 6 cycles, at 4-week intervals. WB-DWMRI was done at baseline, at cycles 2 and 4, and 1 month post-treatment. MRI response was defined as a 30% increase in the mean of the apparent Diffusion Coefficient (ADC) using up to 5 target lesions. PSA response was defined per PCWG2 criteria. Circulating tumour cells (CTC) response was defined as decrease from ≥ 5 cells/7.5ml to < 5/7.5ml. Results: 27 evaluable patients received a median of 6 cycles of Ra-223. Overall MRI response was seen in 67% (18/27), including 60% (9/15) who had an overall response seen in 44% (12/27) of patients. New bone metastases were seen during the trial information: ISRCTN17805587.

Circumferential tumour cells (CTC) response was defined as decrease from ≥ 5 cells/7.5ml to < 5/7.5ml. Results: 27 evaluable patients received a median of 6 cycles of Ra-223. Overall MRI response was seen in 67% (18/27), including 60% (9/15) who had an overall response seen in 44% (12/27) of patients. New bone metastases were seen during the trial information: ISRCTN17805587.

Cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC): Real-life use, effectiveness, safety, and quality of life (QoL) in the FUJI cohort. First Author: Stephane Oudard, Hopital Europeen Georges Pompidou, Paris, France

Background: Cabazitaxel (CAB) was marketed in March 2012 in France, based on overall survival (OS) benefit in mCRPC in 2nd-line (2L) post-docetaxel (DOX). FUJI is a post-authorisation study of the real-life performance of CAB. Methods: FUJI is a multicenter (n = 42) cohort study describing OS, safety, QoL (using FACT-T) and pain (using BPI-SF) in mCRPC CAB-naive patients in real-life, included from Sept 2013 to Aug 2015 in a retrospective cohort (follow-up (FU) 18 mths), and from March 2016 to March 2017 in a prospective cohort (FU 6 mths). Results: The retrospective cohort included 401 pts (median age 70) with CAB in 2L (18%), 3L (39%), 4L (23%), or > 4L (20%). Treatments before CAB included DOX (100%), abiraterone acetate (ABI 77%), enzalutamide (ENZ 33%). Median CAB use was 3.4 mths. Median OS was 11.9 mths (95%CI, 10.1-12.9). In multivariate analyses, factors associated with a shorter OS were: grade ≥ 3 adverse event (AE) (HR = 2.05 [1.53-2.73]), visceral metastases (HR = 1.98 [1.40-2.80]), polymedication > 5 drugs (HR = 1.74 [1.23-2.45]), > 5 bone metastases (HR = 1.74 [2.02-5.53]), disease progression during DOX (HR = 1.69 [1.13-2.53]) or within 3 mths of last DOX cycle (HR = 1.51 [1.07-2.14]), ≥ 3 drugs such as CAB, ABI, ENZ before CAB (HR = 1.39 [1.01-1.92]), and PSA ≥ 135 ng/ml (HR = 1.36 [1.01-1.82]). Factors associated with better OS were: ≥ 10y cancer history before CAB (HR = 0.66 [0.46-0.96]), > 5 mths from last docetaxel dose to CAB initiation (HR = 0.71, [0.52-0.97]). Grade ≥ 3 AEs occurred in 55%, mainly anaemia (27%), neutropenia (15%), febrile neutropenia (8%), renal failure (7%), sepsicaemia/septic shock (5%). The prospective cohort included 51 pts (median age 72) previously treated with DOX (98%), ABI (61%) and ENZ (61%). 49 pts were evaluable for QoL and 44 for pain. QoL improved in 41%, waned in 29%, and deteriorated in 38%. 25% had pain decrease ≥ 1 level, 50% were stable and 25% increase ≥ 1 level. Conclusions: Real-life median OS in FUJI was lower than in TROPIC (11.9 vs. 11.1 mths), but very few FUJI pts would have satisfied TROPIC inclusion criteria. There were no new safety issues. Improved/stable QoL and pain were reported by 70% and 76% of pts treated by CAB, respectively.

5026 Poster Session (Board #253), Sat, 1:15 PM-4:45 PM

Survival outcomes from a cumulative analysis from worldwide observational studies on sequential use of new agents (NAs) in metastatic castration-resistant prostate cancer (mCRPC) (CASTOR study). First Author: Orazio Cafo, Santa Chiara Hospital, Trento, Italy

Background: After the introduction in the daily clinical practice of cabazitaxel (CABA) and new hormone agents (NHAs), abiraterone acetate (AA) and enzalutamide (ENZ), several small retrospective reports described their activity when sequentially used as second- and third-line after docetaxel (Dox). These are mainly single-center experiences. From these results, we can derive some suggestions for the therapeutic strategy in DOC pre-treated mCRPC pts. We collected data from 10,099 pts treated by CAB, respectively.
5028 Poster Session (Board #255), Sat, 1:15 PM-4:45 PM
Subsequent treatment after abiraterone acetate + prednisone (AA + P) in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC): Detailed analyses from the phase 3 LATITUDE trial. First Author: Kim N. Chi, BC Cancer Agency - Vancouver Centre, Vancouver, BC, Canada

Background: Pts with NDx-HR mCNPC quickly progress to castration-resistant disease when using androgen deprivation therapy (ADT) alone. The LATITUDE study found significant improvement in OS and RPFS when AA + P was added to ADT. Pts with rising placebo (PLC) PSA could cross over after unblinding at the first post-hoc exploratory end point. We present detailed on subsequent therapies pts received after unblinding at this second preplanned analysis. Methods: NDx-HR mCNPC pts were randomized 1:1 to AA (1 g QD) + P (5 mg QD) + ADT or PBOs + ADT. Secondary end points, median time to subsequent prostate cancer (PC) therapy and chemotherapy (chemo), and a post hoc exploratory end point, time to life-prolonging therapy, were analyzed by stratified proportional hazards model. Results: 1199 pts were enrolled (ITT). At median follow-up of 4.14 mo, median treatment exposure was 25.8 vs 14.4 mo (AA + P vs PBOs, respectively), and treatment was ongoing for 34% and 12% of pts receiving AA + P and PBOs, respectively. 60 PBOs pts crossed over to AA + P, with a median AA + P exposure of 2 mo (57/60 still on AA + P). The most common reason for discontinuation was progressive disease (AA + P, 40%; PBOs, 64%). Pts receiving subsequent and life-prolonging therapies (Table) were 37% and 26% on AA + P, and 58% and 45% on PBOs, respectively. Compared with PBOs, AA + P delayed time to subsequent PC therapy (HR [95% CI] 0.398 [0.326-0.486]), and chemo (HR [95% CI] 0.471 [0.378-0.586]). Median duration of first life-prolonging therapy was 3.7 mo for AA + P (n = 155) and 5.7 mo for PBOs (n = 268). Conclusions: Adding AA + P to ADT delays the need for subsequent PC therapy vs ADT for pts with NDx-HR mCNPC. Time to subsequent therapy, life-prolonging therapy, and chemo strongly favored AA + P, even though most pts receiving PBOs remaining on treatment had crossed over to AA + P or other life-prolonging subsequent therapy. Clinical trial information: NCT01715285.

5030 Poster Session (Board #257), Sat, 1:15 PM-4:45 PM
Genomic characterization of ductal adenocarcinoma of the prostate. First Author: Michael Thomas Schweizer, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA

Background: Ductal prostate cancer (dPC) is a rare prostate cancer variant associated with poor outcomes. Prior small case series have documented that dPCs may be enriched for alterations in DNA damage repair (DDR) pathway genes and activation of WNT- and PI3K-pathways. To expand these findings, we conducted a multicenter collaboration with the goal to provide a complete DDR-signaling profile of dPCs. Methods: We assembled three case series across multiple institutions in the United States and Canada. All patients carried a diagnosis of PC, and histopathologic classification was confirmed by an expert genitourinary pathologist at each respective institution. All tumor tissue was sequenced on a targeted next-generation sequencing (NGS) assay, UW-OncoPlex, according to previously published methods. Tumor samples were acquired from men with dPC treated at the University of Washington/Seattle Cancer Care Alliance (N = 21), Johns Hopkins Hospital (N = 21) and University of Calgary (N = 8). Only pathogenic/likely pathogenic mutations are reported. Results: Tumors from 50 patients with known dPC were sequenced. Overall, 26 (52%) individuals had at least one alteration in a DDR gene, including 7 (14%) with a mismatch repair (MMR) gene mutation. Twenty (40%) cases had mutations predicted to result in PI3K-pathway activation, 15 (30%) patients had mutations that were predicted to result in activation of the WNT-signaling pathway (N = 11 inactivating APC mutations; N = 4 activating CTNNB1 mutations), and 12 (24%) had mutations in genes involved in MAPK-signaling. Other frequently altered genes included: FOXA1 (N = 17, 34%), TP53 (N = 9, 18%) and SPOP (N = 6, 12%). Alterations in AR were relatively infrequent (N = 4, 8%). Conclusions: This study confirmed that dPCs are enriched for actionable mutations. Over 50% of cases demonstrated at least one alteration in a DDR pathway gene, including a high percentage of cases with MMR deficiency. Patients with dPC should be offered NGS to guide standard of care treatment (e.g. anti-PD1 therapy, platinum-based chemotherapy) or to triage toward an appropriate clinical trial (e.g. PARP inhibitor trials).

5029 Poster Session (Board #256), Sat, 1:15 PM-4:45 PM
Genomic and phenotypic evidence for prostate cancer osteomimicry in circulating tumor cells from men with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223. First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC

Background: Radium-223 is a targeted alpha-therapy that improves survival in men with mCRPC. The biologic basis for radium-223 efficacy is not completely understood. We hypothesized that PC osteomimicry, a form of epithelial plasticity leading to an osteoblastic phenotype, may contribute to the intratranslational deposition of radium-223 and subsequent irradiation of the tumor microenvironment. Methods: We conducted a pharmacodynamic study (NCT02204943) of radium-223 in men with bone metastatic CRPC to investigate genomic and phenotypic alterations in circulating tumor cells (CTCs), ctDNA, and metastases. Prior to and 3 to 6 months after radium-223 was administered, liquid and metastatic biopsies including CTCs for phenotypic characterization and CTC/ctDNA genomic analysis. The primary objective was to describe the prevalence of CTC bone alkaline phosphatase (BAP) over time. We measured radium-223 decay products in tumor and surrounding normal bone during treatment. Results: We enrolled 20 men with heavily pre-treated symptomatic bone predominant mCRPC and treated with radium-223 over a median of 6 doses; 55% had elevated serum BAP at baseline. The median follow-up of 41.4 mo, median treatment exposure was 25.8 vs 14.4 mo (AA + P vs PBOs, respectively), and treatment was ongoing for 34% and 12% of pts receiving AA + P and PBOs, respectively. Compared with PBOs, AA + P delayed time to subsequent PC therapy (HR [95% CI] 0.398 [0.326-0.486]), and chemo (HR [95% CI] 0.471 [0.378-0.586]). Median duration of first life-prolonging therapy was 3.7 mo for AA + P (n = 155) and 5.7 mo for PBOs (n = 268). Conclusions: Adding AA + P to ADT delays the need for subsequent PC therapy vs ADT for pts with NDx-HR mCNPC. Time to subsequent therapy, life-prolonging therapy, and chemo strongly favored AA + P, even though most pts receiving PBOs remaining on treatment had crossed over to AA + P or other life-prolonging subsequent therapy. Clinical trial information: NCT01715285.

5031 Poster Session (Board #258), Sat, 1:15 PM-4:45 PM
Combination of niclosamide to target androgen receptor variant 7 (AR-V7) and abiraterone to target androgen-signaling for the treatment of castration-resistant prostate cancer (CRPC): Initial results from a phase Ib/II trial. First Author: Chong-xian Pan, University of California Davis Comprehensive Cancer Center, Sacramento, CA

Background: The androgen receptor (AR) variant AR-V7 lacks the ligand binding domain, constitutively activates the AR pathway, and confers resistance to Abiraterone (Abi) and enzalutamide (Enza). We discovered that the anti-helminthic drug niclosamide targets AR-V7 and sensitizes resistant CRPC to Enza and Abi. We hypothesize that niclosamide/PDMX1001 potentiates the efficacy of Abi against CRPC. Methods: Eligible patients (pts) have progressive CRPC with serum testosterone < 50 ng/dl. No prior Abi was allowed. In the Phase Ib cohort, pts received Abi 1000 mg PO qd, prednisone 5 mg PO bid, with intratypic dose-escalation of niclosamide/PDMX1001 from 400 mg PO bid to 1600 mg PO tid. Trough niclosamide/PDMX1001 levels were measured. The Phase II cohort will enroll 27 patients with detectable AR-V7 in the peripheral blood. Co-primary endpoints include toxicity and response as determined by the Prostate Cancer Working Group 2 criteria. Results: Of 6 pts (age 74-83) in the Phase Ib cohort, five pts tolerated a niclosamide/PDMX1001 dose of 1,600 mg po tid without dose-limiting toxicity; per protocol, this is the recommended Phase II dose. Niclosamide/PDMX1001 trough level was 0.305-0.648 μM in the three pts analyzed thus far, higher than the target level of 0.1μM required for anti-cancer activity. Of 6 pts, two pts achieved undetectable PSA (< 0.01 ng/ml) for over 16 cycles and are still going on, compared to historical control 0/30 pts treated with Abi alone; two with partial PSA response (>50% decrease). Of the remaining two pts, one was prematurely taken off from the study after one cycle because of rising PSA, and the other had PSA decrease of 17.1%, but biopsy of the only enlarged lymph node showed all necrotic tissue. No dose-limiting toxicity was observed. The Phase II cohort will now enroll. Molecular correlative studies will be presented. Conclusions: The combination of niclosamide/PDMX1001, Abi and prednisone is well tolerated with promising safety and efficacy data. Targeted serum trough levels of niclosamide are clinically achievable. Clinical trial information: NCT02807805.
Association of metastasis-free survival (MFS) and overall survival (OS) in nonmetastatic castration-resistant prostate cancer (nmCRPC). First Author: Matthew Raymond Smith, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA

Background: Intermediate clinical end points are needed for prostate cancer to inform clinical decisions and facilitate drug development. The international Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group reported that MFS is a strong surrogate of OS in hormone-sensitive localized prostate cancer. We sought to determine the relationship between MFS and OS in patients with nmCRPC. Methods: Data from the phase 3 SPARTAN trial in men with high-risk nmCRPC were used to undertake a landmark analysis for MFS. A Cox proportional hazard regression model, adjusted for covariates, evaluated the relationship of OS and development of metastases. The correlation of MFS and OS was assessed by Spearman’s and Fleisscher’s correlation statistics. Results: As of May 2017, 1207 patients with nmCRPC had a median time to metastasis of 40.5 months. A landmark analysis showed that patients who developed metastases at 6, 9, and 12 months had significantly shorter median OS compared with those patients without metastasis (Table); after adjusting for baseline covariates, the development of metastases remained associated with OS. A significant positive correlation was observed between MFS and OS (Spearman’s correlation coefficient: 0.62; p < 0.0001). The more robust, parametric Fleisscher’s statistical model confirmed the positive correlation (correlation coefficient: 0.69), with >50% of variability in OS explained by MFS. Conclusions: MFS has a significant association with OS and is predictive of OS in high-risk nmCRPC. This analysis demonstrates that MFS is a meaningful and valid intermediate clinical end point for OS. Clinical trial information: NCT01946204.

NR, not reached.

5032 Poster Session (Board #259), Sat, 1:15 PM-4:45 PM

5034 Poster Session (Board #261), Sat, 1:15 PM-4:45 PM

5035 Poster Session (Board #262), Sat, 1:15 PM-4:45 PM

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5038 Poster Session (Board #263), Sat, 1:15 PM-4:45 PM
Correlates of response to anti-PD-1 immune checkpoint blockade (ICB) in mismatch repair proficient (MMRp) and deficient (MMRd) patients (pts) with metastatic castration resistant prostate cancer (mCRPC).
First Authors: Kingsley C. M. C. Smith, Peter W. Egan, James B. Cole, Matthew J. Silvestri, Anika Smiths, Department of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands
Background: Predictive biomarkers are needed to improve the proportion of pts with mCRPC that may benefit from anti-PD-1/PD-L1 ICB. A comprehensive characterization of both genomic alterations as the immunological landscape during ICB may prove fundamental. Methods: We investigated correlates of response and progression in pts with mCRPC treated with anti-PD-1 ICB. Pts were selected by PD-L1 ≥1% and/or MMRd. Optional pre-treatment and post-progression biopsies were collected for whole-genome sequencing and multiplex IHC. 8-color flow cytometry was performed on frozen mononuclear cells at baseline and on treatment (Tx) using 6 immune panels. MMR status was evaluated in exosome subsets using nested amplification PCR. Response was evaluated per PCWG3 criteria and Tx was continued until radiological progression with lack of clinical benefit or due to ICB-toxicity. Results: At present 13 CRPC pts started Tx with median follow-up of 5.3 months. 10/13 pts had PD-L1 expression ≥1%, 6/13 pts were MMRd. Tx is ongoing in 4/13 pts. In evaluable pts with MMRd, range of mutational burden (TMB) was 2-8 and 25-74 mutations per megabase, respectively (resp); objective responses were only seen in MMRd pts; PSA >50% declines were seen in 75% and 13%, resp; median progressive-free survival was 3.7 vs. 7.8 months, resp (p = 0.007). No relationship was seen between PD-L1, TMB and CD3+ tumor infiltrating lymphocytes (TILs). TILs increased in MMRd vs MMRp pts (p = 0.06). During Tx, significant changes were seen in circulating T cell populations, including CD4+PD-1+, CD4+CD28+PD-1+, CD8+PD-1+, CD4+ICOS+ and CD8+ICOS+ subsets, with an Tx and CD4+PD-1+ cells differing between responders and non-responders (p = 0.03). Additional results on genomic and immune correlates will be presented in more detail. Conclusions: Deep and durable responses to anti-PD-1 ICB were seen in pts with mCRPC, particular those with MMRd. Circulating T cell subsets are associated with response to ICB. An integrative biomarker suite to predict for responsive mCRPC pts to anti-PD-1 ICB is key and these and other correlates should be further investigated.
5039 Poster Session (Board #266), Sat, 1:15 PM-4:45 PM
DNA repair mutations and treatment-emergent small cell neuroendocrine prostate cancer (sCNC) as hallmarks of distinct subgroups of metastatic castration resistant prostate cancer (mCRPC). Data from the West Coast Prostate Cancer Dream Team.
First Author: Rahul Raj Aggarwal, UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA
Background: Genomic alterations in DNA repair genes are present in approximately 20-30% of patients with mCRPC. t-SCNC may be increasing in patients with mCRPC and now report updated safety and efficacy results including an additional 20 patient expansion cohort. Methods: In this phase II trial, 50 patients with PSMA-avid mCRPC who had progressed after conventional therapies received up to 4 cycles of LuPSMA every 6 weeks. The primary endpoints were 50% PSA response rate (PCWG2) and toxicity (CTCAE v4.3). Other endpoints were objective response rate (ORR), quality of life (EORTC QLQ-C30, BPI), PSA progression free survival (PFS) and overall survival (OS). Results: 50 patients (median age 71, range: 50-87) were eligible for treatment. 90% had progressed after abiraterone and/or enzalutamide, and 88% progressed after chemotherapy (84% post docetaxel and 48% following docetaxel and cabazitaxel). A median of 4 (range: 1-4) cycles and mean radioactivity of 7.5 GBq/cycle was administered. At this interim analysis (cut-off: 19 Jan 2018), the primary endpoint of PSA decline ≥ 50% was achieved in 31 of 50 patients (62%, 95% CI 47-75%), including 22 patients (44%, 95% CI 30-59%) with a PSA decline ≥ 80%. Common toxicities included dry mouth (68%), fatigue (38%), nausea (48%) and pain flare (10%). These were all Grade 1-2, self-limiting or manageable. G3-4 hematological toxicities attributed as possibly related to LuPSMA included thrombocytopenia (10%), anemia (10%), and neutropenia (6%). Median PSA FFS was 7.0 months (95% CI 5.7-8.8) and median OS was 12.0 months (95% CI 10.0-18.7). Conclusions: This LuPSMA Phase II trial suggests high response rates and low toxicity in men with mCRPC who progressed after multiple conventional therapies. These compelling results have justified a randomized trial comparing LuPSMA to cabazitaxel (NCT03392428). Updated QOL, ORR, PSA-FS and OS data will be presented. Clinical trial information: NCT01953640.
Sipuleucel-T (sip-T) overalls survival (OS) and clinical outcomes by baseline (BL) prostate-specific antigen (PSA) quartiles in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) PRECEDE registry.\textsuperscript{1}

Background: Sip-T is an autologous cellular immunotherapy for asymptomatic/asymptomatic or castration-resistant prostate cancer (mCRPC) or metastatic CRPC (mCRPC) that is refractory to prior anti-androgen therapy. This randomized, placebo-controlled clinical trial (NCT01306890) enrolled 472 pts with mCRPC who had not received priorsip-T and were men with advanced prostate cancer who were not candidates for curative intent therapy. The study included a placebo-controlled arm and a treatment arm that received sip-T. The primary end points were overall survival (OS) and time to first androgen deprivation therapy (ADT) initiation (ACI).

Methods: Pts were randomized into 4 PSA quartiles: (a) BL PSA levels less than 10 ng/mL, (b) 10-15 ng/mL, (c) 15-20 ng/mL, and (d) greater than 20 ng/mL. Pts received 3 sip-T infusions at ~2-weekly intervals. Objectives included cerebrovascular event risk (primary) and OS (secondary). Follow-up was every 3 months after sip-T for 3 years or minimum until death or withdrawal. This is a post-hoc analysis (see Table for tests) of outcomes by PSA quartile. Results: 1976 pts were enrolled between 2011–2017; median age 72 yrs; 87% Caucasians, 12% African Americans; 51% had a Gleason score ≥8; prior therapies 78% (local) & 99% (hormonal). 1255 pts died. Median (range) BL PSA was 15 (0–7497) ng/mL. All outcomes in Table were significantly worse in the 2nd, 3rd & 4th PSA quartiles vs the 1st (lowest PSA) quartile. Clinical trial information: NCT01306890.

Conclusions: OS & time to first ACI were longer in sip-T treated PLT PSA quartiles vs sip-T treated pts with higher PSA. Survival of nearly 5 years was seen in the lowest PSA quartile. Although PROCEDO did not have a comparator arm, the trend for longer OS is concordant with that seen in IMPACT.

<table>
<thead>
<tr>
<th>Median time to event (months)</th>
<th>95% CI</th>
<th>Hazard ratio (95% confidence interval) vs 1st quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS 48 (44–51)</td>
<td>33 (31–36) 27 (24–30) 18 (16–21) 16 (14–20) 14 (12–16)</td>
<td>2.0 (1.6) 1.6 (1.4) 1.2 (1.0) 1.1 (0.9) 0.9 (0.8)</td>
</tr>
<tr>
<td>Time to first ACI 10 (9–12)</td>
<td>8 (7–10) 7 (6–9) 6 (5–8) 5 (4–6) 4 (3–5)</td>
<td>1.1 (1.0) 1.2 (1.1) 1.2 (1.1) 1.2 (1.1) 1.2 (1.1)</td>
</tr>
<tr>
<td>Time to death due to disease progression (months)</td>
<td>57 (52–62) 37 (32–42) 29 (25–39) 24 (21–27) 20 (18–23)</td>
<td>1.8 (1.6) 2.0 (1.8) 2.5 (2.3) 3.1 (2.9) 4.2 (3.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kaplan Meier; clinical or PSA progression, ezalutamide, radium-223, docetaxel, cabazitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
</tr>
<tr>
<td>Probability</td>
</tr>
</tbody>
</table>

- Proportion of Event (n = 472)
- Median time to 1st Event, Years (IQR)
- Any Bone Metastases 7.2 28.1 40.9 < 0.001
- Pathological Fracture 6.4 16.3 62.6 < 0.001
- Urinary Obstruction 2.5 10.6 15.5 < 0.001

# 5043

Association between health-related quality of life (HRQoL) and clinical outcomes in non-castrate-resistant prostate cancer patients (mCRPC): Results from the PROSPER study.

First Author: Gerhard Attard, The Institute of Cancer Research and the Royal Marsden, Surrey, United Kingdom

Background: We used the PROSPER trial (NCT02003924) to assess (a) the relationship between time to HRQoL deterioration and prostate-specific antigen (PSA) response and (b) the association between HRQoL and metastasis-free survival (MFS). Methods: In PROSPER, 1401 men with m0 CRPC at risk of metastasis were randomised (1:1) to receive sip-T or placebo. HRQoL was assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) at baseline (BL) and every 6 weeks during treatment. Association between time to first HRQoL clinically meaningful deterioration and PSA response (defined as ≥50% decline from BL) was explored with stratified Cox regression analyses, and between longitudinal HRQoL changes and MFS with joint models including HRQoL as longitudinal covariate, after adjusting for treatment and relevant clinical/demographic variables. Results: Overall, 723 of 1401 (52%) patients were confirmed PSA responders, significantly less likely to deteriorate on all FACT-P scores than non-responders (hazard ratio [HR] 0.56–0.82), except on physical well-being (PBW) [HR 0.90; p = 0.244]. When treatment is included in the model, stronger effects were observed, explained by 98% of PSA responders receiving ENZA. Most FACT-P scores were prognostic for MFS (7 of 10 scores). Every 10-point increase in FACT-P total score (i.e. improvement) was associated with a 6% decreased risk of metastasis (HR 0.94 [0.88, 0.99]), 5% decreased risk of metastasis, respectively. Conclusions: The research indicates a ≥50% reduction in PSA from BL would result in a decreased risk of HRQoL deterioration, also showing a relationship between changes from BL in HRQoL and metastases. Thus, patient-reported outcomes are not only useful in describing patient experience in clinical trials, but may complement traditional clinical practice methods to monitor disease progression. Clinical trial information: NCT02003924.

# 5042

Cancer-related morbidity at the end of life in men with prostate cancer.

First Author: Divya Yerramilli, Harvard Radiation Oncology, Boston, MA

Background: Limited data exist regarding disease-related complications (DRCs), such as bone fractures and urinary obstruction (UO), near end of life of men who die with prostate cancer. We aimed to describe the burden of DRCs in these patients. Methods: As part of the Cancer Research UK funded Cluster Randomised trial of PSA testing for prostate cancer, we examined a cohort of 2603 men who died within 10 years of diagnosis. We collected clinical factors and DRCs. We used univariate analysis to examine association of diagnostic groups (low/intermediate, high, and metastatic, as defined by NCCN) and Kaplan-Meier analyses to compare median times to each DRC. We also explored a subgroup of men with metastatic disease who become castrate-resistant. Results: Those with higher risk disease at time of enrolment had higher frequency of DRCs and shorter time to each DRC (Table 1). 19% of high risk men developed cord compression, 16% had pathologic fracture, and 10% had renal failure. High risk men had bone metastases (BM) 2.9 months from diagnosis (IQR 1.7–4.9) versus low with limited risk disease (4.2 mos, 2.8–6.3), p < 0.001. Men with castrate resistance had higher odds of developing BM (OR 1.97, 95% CI [1.53–2.52], p < 0.001) and UO (OR 2.10, 95% CI [1.47–3.02], p < 0.001). Conclusions: In the longest contemporary cohort prostate cancer patients, we found that a significant proportion of men experience cancer-related morbidity prior to death. Men with localized disease at diagnosis can have long intervals until development of DRCs. Furthermore, men who become castrate resistant are particularly vulnerable to DRCs.

Frequency & time to event at 10 years:

<table>
<thead>
<tr>
<th>Event</th>
<th>Low Risk (n = 490)</th>
<th>High Risk (n = 616)</th>
<th>Time to event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>7.2</td>
<td>28.1</td>
<td>40.9</td>
</tr>
<tr>
<td>Pathological Fracture</td>
<td>6.6</td>
<td>16.3</td>
<td>62.6</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>2.5</td>
<td>10.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Urinary Obstruction</td>
<td>2.7</td>
<td>4.6</td>
<td>6.6</td>
</tr>
</tbody>
</table>

# 5044

Transcriptional and post-transcriptional regulation of ribonucleotide reductase (RNR) plays a crucial role in oncogenic proteins in prostate cancer progression.

First Author: Ying Zhang Mazzu, Memorial Sloan Kettering Cancer Center, New York

Background: The role of DNA repair pathways has been recognized in prostate cancer (PC) progression. Ribonucleotide reductase (RNR) is essential for DNA synthesis and repair. The subunit of RNR complex, RRM2, can regulate tumor initiation, progression and drug resistance in multiple cancer types. There is limited knowledge of RRM2 function in PC. Methods: The clinical cohort was analyzed for the correlation of RRM2 and clinical outcomes. RNA-seq and protein array were applied for the mechanism studies. ChiH and reporter assays were used for transcriptional study. Results: High level of RRM2 was associated with lethal disease, independent from Gleason grade (odds ratio: 3.54; 95% CI, 1.76–7.4) in a cohort of men in the Physicians’ Health Study and the Health Professionals’ Follow-up Study (n = 404). Transcriptional analysis revealed that multiple oncogenic transcription factor networks were inhibited by inhibition of RRM2, while p53 signaling was strongly activated. Phosphoproteomic analysis showed inhibition of RRM2 could repress multiple oncogenic signals including SFK, STAT, and Akt/MTor signaling. Intriguingly, inhibition of RRM2 by siRNA and the inhibitor (COH29) could specially target gene profiling of poor-prognosis subtypes (PCS1 and PAMA50) in PC. In an in vivo PC xenograft model, COH29 strongly inhibited tumor growth. Amplification of RRM2 is rarely observed in PC, thus, transcription and post transcription may largely contribute to overexpression of RRM2. A bioinformatics strategy was developed to search the putative RRM2-targeting transcription factors (TFs). Among 13 TFs candidates, FoxM1 and EZF2 were validated to target the RRM2 promoter. Additionally, we found that methylthionyl-induced silencing of miR-193b could release the inhibition control of FoxM1 and RRM2 in PC cells. DMNT3 inhibitor (5-Aza) restored miR-193b expression, leading to the upregulation of RRM2 and FoxM1 in PC cells. Conclusions: We reveal the function of RRM2 in PC and unravel the mechanism of dysregulation of RRM2 in PC. Our findings suggest that RRM2 may serve as a key regulator of PC growth and a possible therapeutic target for PC therapy.
Poster Session (Board #272), Sat, 1:15 PM-4:45 PM
Patterns of PSA versus clinically progressive disease in the E3805 CHAARTED trial. First Author: Alan Haruo Bryce, Mayo Clinic, Phoenix, AZ
Background: Recent data has highlighted the high frequency with which metastatic prostate cancer can progress either radiographically or symptomatically without a rise in PSA. % Palle PSA-Claims that the emergence of this clinical phenomenon is important to implementing appropriate criteria for disease monitoring during treatment. Methods: 790 men were accrued from 7/28/06 to 11/21/2012 and randomized to ADT or ADT + Docetaxel at 75mg/m2 every 3 weeks for 6 cycles. Patients were prospectively stratified into high volume (HV), low volume (LV), and HV disease at low volume (HV-LV) disease. Clinical PD was defined as increasing symptomatic bone metastases, progression per RECIST criteria, or clinical deterioration due to cancer per investigator’s opinion. PSA PD was defined as an increase in PSA of more than 50% above the on-treatment nadir, with two consecutive increases at least 2 weeks apart. Concurrent PSA PD and Clinical PD is defined as both events occurring within 1 month. Results: As of the data cutoff of 4/30/2016 403 men with HV disease and 157 with LV disease had progressed. In HV disease, the most common progression pattern was PSA PD followed by clinical PD in both the ADT + D and ADT arms (39.5 vs 43.2%). Clinical PD without PSA progression occurred in 29.5% and 31.0% of patients. In LV disease, the dominant pattern of progression was Clinical PD without PSA PD, occurring in 44.8% and 34.4% of patients. PSA PD followed by clinical PD occurred in 28.4% and 37.8% of patients. Table 1: Disease progression pattern by treatment arm and disease volume Clinical trial in-formation: NCT00305985. Conclusions: Clinical progression of disease in the absence of a PSA rise is frequent in patients treated for metastatic castration sensitive prostate cancer. The results highlight the need to incorporate imaging into treatment monitoring rather than relying on PSA alone to trigger imaging.

<table>
<thead>
<tr>
<th>Disease progression pattern</th>
<th>High volume</th>
<th>Low volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT+D</td>
<td>ADT alone</td>
<td>ADT+D</td>
</tr>
<tr>
<td>Concurrent PSA PD and clinical PD</td>
<td>11 (5.8%)</td>
<td>18 (8.5%)</td>
</tr>
<tr>
<td>PSA PD first and then clinical PD</td>
<td>75 (39.5%)</td>
<td>92 (43.2%)</td>
</tr>
<tr>
<td>PSA PD only</td>
<td>45 (23.5%)</td>
<td>37 (17.4%)</td>
</tr>
<tr>
<td>Clinical PD only</td>
<td>56 (29.5%)</td>
<td>66 (31.0%)</td>
</tr>
</tbody>
</table>

Total |
190 |
213 |
67 |
90 |

Association of genomic alterations (GAs) in circulating tumor DNA (ctDNA) with persistence on abiraterone acetate (AA) or enzalutamide (enza) in advanced prostate cancer. First Author: Andrew W Hahn, University of Utah Huntsman Cancer Institute, Salt Lake City, UT
Background: Two androgen axis inhibitors, enza and AA plus prednisone, are approved for the treatment of advanced prostate cancer (PC). Although initial responses are common with these agents, almost all men experience disease progression. Due to advances in next-generation sequencing (NGS) of ctDNA, it is feasible to assess the tumor genomic landscape in these men at different time points in their treatment. Here, we aim to identify GAs in ctDNA that contribute to resistance to AA and/or enza, which may guide development of novel therapies targeting these GAs. Methods: Men with aPC who underwent NGS of ctDNA using G360 (Guardant Health, Inc., Redwood City, CA) from the Huntsman Cancer Institute, University of Utah, and Tulane University were included. Non-matched men were classified as pre-AA/enza, post-AA/enza, and others were excluded. Post-AA/enza was defined as disease progression on AA or enza as one’s most recent treatment at the time of testing. G360 is a 73 gene panel that provides complete sequencing of selected exons in order to maximize detection of known somatic mutations, as well as copy number amplifications across 18 genes and selected fusions in 6 genes. Two-sided Fisher exact tests and t-tests were used to assess the frequency and number of alterations pre- or post-AA/enza, respectively. P-values of less than .05 were considered statistically significant. Results: Of 354 men with advanced prostate cancer and ctDNA NGS available, 128 were pre AA/enza and 84 were post AA/enza. Compared with pre-AA/enza profiles, post-AA/enza studies showed higher mean number of GAs (5.01 vs. 3.03, p<0.02). GAs were significantly higher in AR (54.8% vs. 25.8%, p<0.0001), TP53 (51.2% vs. 32.0%, p=0.006), PIK3CA (20.2% vs. 9.4%, p=0.04), and CCNE1 (10.7% vs. 3.1%, p=0.04). Patients with liver metastases had significantly more GAs than those without (11.7 vs. 3.5, p<0.0001). Conclusions: In these hypothesis-generating data, men who progress on AA or enza have more alterations in AR, TP53, PIK3CA, and CCNE1 and increased number of GAs. These alterations may contribute to treatment resistance and be targets of interest for further drug development.

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5049 Posters Session (Board #276), Sat, 1:15 PM-4:45 PM

Bone targeted therapy and skeletal related events in the era of modern therapies for castration resistant prostate cancer with bone metastases. First Author: Li Zhang, DFCI at St. Elizabeth Medical Center, Boston, MA

Background: Bone metastases in castration resistant prostate cancer (CRPC) is associated with serious morbidity and costs. The optimal timing of initiation and duration of bone targeted therapy (BTT) Zoledronic acid and Denosumab is unknown in the current era with four classes of therapy for CRPC prolonging overall survival (OS). We sought to design the practice patterns of BTT use and outcomes (skeletal related events - SRE and OS) in a high-volume center in the modern era of metastatic CRPC management. Methods: A retrospective cohort of patients (pts) who have received Abiraterone and/or Enzalutamide for CRPC from 2007 to 2017 was identified based on a single-institution’s clinical database. The database and electronic medical record review was used for data collection, including pts’ characteristics and pattern of BTT uses. Kaplan Meier method and Cox proportional hazards model assessed association of BTT use with time to first SRE and OS, respectively. Results: 197 pts were identified, and 79(40%) had ≥ 4 bone metastases (BM) and median follow-up was 4.7 (95%: 2.4-5.9) years. More pts with ≥ 4 BM received BTT with first line therapy (49% vs 32%, p<0.01). Pts with ≥ 4 BM, receiving BTT with first line therapy for CRPC had a 19% reduced risk of developing SRE - HR 0.81 (95%CI: 0.45-1.45). Pts with < 4 BM did not have a lower HR when starting BTT with first line CRPC therapy. No OS difference was noted in pts who received Abiraterone and/or Enzalutamide for CRPC from 2007 to 2017. More pts with $0.001, X2) and median TTP was 4.7 m vs 8.0 m (HR 1.52, 95% CI 1.12-2.08). ABI vs ENZ (p = 0.031). PSA50 was 43.4 % for ABI vs 77.9 % for ENZ (p = 0.03). For pts in the ENZ cohort who had a dose reduction, the dose reduction due to toxicity was required for 7.5% of pts for ABI vs 29.8% for ENZ (P = 0.001). Conclusions: Our cohort suggested that in the modern era, with more effective and greater number of CRPC therapies, pts with ≥ 4 BM still benefit from starting BTT with first line CRPC therapy.

5050 Posters Session (Board #277), Sat, 1:15 PM-4:45 PM

Phase II safety and tolerability study of Radium-223 (R223) in combination with enzalutamide (ENZA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) - CRYSTAL-IE (EQ-21). First Author: Raymond S. McDermott, Adelaide and Meath Hospital, Dublin, Ireland

Background: R223 and ENZA are standard of care agents in the treatment of patients (pts) with mCRPC. The combination of R223 and ENZA is of interest due to differing modes of action and non-overlapping toxicity profiles, leading to the potential for synergy. Methods: This phase II, open-label, multicentre single arm study (NCT02225704) enrolled pts with mCRPC to bone with or without visceral/lymph node involvement who had progressed on androgen deprivation therapy. Prior docetaxel chemotherapy for hormone sensitive prostate cancer was allowed. Pts received 6 cycles of R223 (55 kBq/kg IV Q4W) in combination with ENZA (160mg/day), followed by ENZA alone until disease progression (PD), unacceptable toxicity or consent withdrawal. The primary endpoint was safety for the 6 months of combination therapy which is reported here. Results: From July 2015 to July 2017, 45 pts were enrolled in Ireland. 42 pts (93.3%) received all 6 cycles of combination therapy. A total of 13 pts (28.9%) had grade (gr) 3/4 adverse events (AEs). The most frequent gr 3/4 AEs (Table) were neutropenia (n = 3, 6.6%) and fatigue (n = 3, 6.6%) followed by nausea, lower respiratory tract infection (LRTI), lymphocytopenia, leukocytopenia, hyperkalaemia, hypokalaemia, back pain, headache, urticaria, syncope and hypertension (all n = 1, 2.2%). 2 pts (4.4%) discontinued treatment due to AEs, gr 3 LRTI (n = 1) and gr 2 nausea and pain (n = 1). One pt discontinued due to symptomatic PD. There were no therapy-related deaths. Conclusions: R223 in combination with ENZA is tolerated with acceptable early safety and toxicity profiles consistent with those seen when they are used as single agents and allowing for concomitant administration. Evaluation of secondary endpoints including skeletal related events with longer follow up is ongoing. Clinical trial information: NCT02225704.

5051 Poster Session (Board #278), Sat, 1:15 PM-4:45 PM

Efficacy and tolerability of first-line abiraterone + prednisone (ABI) versus enzalutamide (ENZ) in men ≥ 80 years: A retrospective cohort study. First Author: Daniel Khalaf, British Columbia Cancer Agency - Vancouver Centre, Vancouver, BC, Canada

Background: ABI and ENZ are first-line treatment options for mCRPC with comparable efficacy. In men ≥ 75 years, ABI and ENZ are associated with higher rates of adverse events. For very elderly patients (pts), the efficacy and tolerability of ABI and ENZ have not been directly compared. Methods: Retrospective analysis in pts ≥ 80 years of age who received ABI or ENZ for first-line treatment of mCRPC between July 2009 and September 2016 at the BC Cancer Agency. Medical records were reviewed for clinical characteristics and outcomes including PSA response rate (PSA50) (decrease of ≥50% from baseline), time to first progression (TTP), PSA, radiographic or clinical progression and overall survival (OS). Results: There were 106 pts in the ABI cohort and 104 in the ENZ cohort. Baseline characteristics were well balanced including median age 85 years (IQR 83-88); median Charlson Comorbidity Index (CCI) 7 (IQR 7-8); hemoglobin (HB) < 130 in 75%; ECOG PS 0-1 in 60%; serum alkaline phosphatase (ALP)/LDH > upper limit of normal (ULN) in 32%/35% and bone/liver metastasis in 86%/10%/6%. Time from start of androgen deprivation therapy to castration-resistance (TTCR) was < 12 months (m) in 16% vs 29% for ABI vs ENZ (p = 0.031). PSA50 was 43.4 % for ABI vs 77.9 % for ENZ (p < 0.001, X²) and median TTP was 4.7 m vs 8.0 m (HR 1.52, 95% CI 1.2-2.08). On multivariable analysis, factors associated with TTP were: treatment arm ABI vs ENZ (HR 1.76, 95% CI 1.27-2.45), ALP > ULN (HR 1.89, 95% CI 1.34-2.68), HB < 130 (HR 1.61, 95% CI 1.13-2.30), CCI > 7 (HR 1.57, 95% CI 1.13-2.19) and TTCR > 12 months (HR 1.73, 95% CI 1.18-2.55). At least one dose reduction due to toxicity was required for 7.5% of pts for ABI vs 29.8% for ENZ (P = 0.001, X²). For pts in the ENZ cohort who had a dose reduction, the median TTP was 11.8 m vs 6.2 m for those without (HR 0.65, 95% CI 0.40-1.08). Median OS was 13.2 m for ABI vs 18.7 m for ENZ (HR 1.20, 95% CI 0.89-1.63). Conclusions: In this very elderly cohort, the PSA50 and TTP were superior for the ENZ cohort compared to the ABI cohort despite more dose reductions in the ENZ cohort. The retrospective nature of the analysis is a limitation of this study.

5052 Poster Session (Board #279), Sat, 1:15 PM-4:45 PM

Evolution of the genomic landscape of circulating tumor DNA (ctDNA) in advanced prostate cancer (aPC) over treatment and time. First Author: David D. Stenehjem, University of Minnesota College of Pharmacy, Duluth, MN

Background: While men with aPC respond to initial treatment, most will progress and require sequential therapies. Due to advances in next-generation sequencing (NGS), it is feasible to assess the tumor genomic landscape via blood or tumor tissue at different time points in treatment. Much debate exists over the concordance of tissue (tDNA) and ctDNA NGS. While men with aPC respond to initial treatment, most will progress and require sequential therapies. Due to advances in next-generation sequencing (NGS), it is feasible to assess the tumor genomic landscape via blood or tumor tissue at different time points in treatment. Much debate exists over the concordance of tissue (tDNA) and ctDNA NGS. Some hypothesize that the genomic landscape of aPC evolves with treatment and time; however, there is a paucity of experimental data to support these statements. In this exploratory analysis, we compare the genomic landscape of aPC as detected by commercially available ctDNA and tDNA NGS platforms at different points during the course of disease. Methods: Men with aPC from the Huntsman Cancer Institute, University of Utah with matched ctDNA NGS using FoundationOne (Foundation Medicine, Cambridge, MA) and tDNA NGS using G360 (Guardant Health, Inc., Redwood City, CA) were included. Clinical data was collected retrospectively. Exonic regions from 69 genes covered by both platforms were included for analysis. Paired tests were used to assess number of genomic alterations (GAs) between testing platforms and were confirmed with nonparametric testing. Number of alterations was assessed by time and number of treatments between IDNA and ctDNA testing by multivariate nonparametric trend tests. Results: 101 men with aPC who had matched tissue and ctDNA NGS were included. Men with no new treatments and ≤1 year between tests, a similar number of GAs were detected in both tests (2.0 vs. 2.2, p=0.78). In contrast, men with ≥1 new treatment between tests had significantly more GAs after treatment (5.0 vs. 2.0, p=0.005). Total number of GAs was correlated with number of new treatments between testing (p=0.003) and not time between testing (p=0.76). Conclusions: In these hypothesis-generating data, the genomic landscape of aPC evolves with subsequent therapies. These data suggest that, in addition to baseline tumor genomic profiling, a contemporary tumor genomic profile at the time of disease progression may optimize guidance towards subsequent therapy selection.
Background: Biomarkers to predict outcomes for individual patients (pts) on standard of care Rx is an unmet medical need in the treatment of mCRPC. Using baseline (BL) blood draws, we previously reported a phenotypic CTC heterogeneity algorithm that predicted for differential survival times on ARSi vs. taxanes. We have also observed that certain gene alterations as well as genomic instability are linked to different CTC phenotypic subtypes. We sought to associate CTC phenotypes to response, and to characterize phenotypic and genotypic changes to populations of CTCs associated from selection pressures by specific drug classes. Methods: 456 blood samples (228 matched BL and on-therapy) from 184 unique mCRPC pts were collected and processed utilizing the Epic Sciences CTC platform. CTCs were enumerated and characterized for phenotype (n = 11,722) including CTC subtypes, from pts who received ARSi therapy (n = 131), taxanes (n = 57) or a platinum containing regimen (n = 40). 985 CTCs of various phenotypic subtypes were single cell sequenced for DNA copy number variation. Results: CTCs were detected in 88.6% (202/228) BL and in 76.3% (174/228) on therapy samples, med = 3.5mL (0 to 490) and median = 2.7mL (0 to 992) respectively. Changes in CTC phenotypic features were observed unique to specific therapy classes, including changes to nuclear size, shape and texture. Persistent CTC phenotypes in pts treated with ARSi and taxane, but not platinum, were enriched with concurrent changes to genomic instability (p = 0.001) while those in pts treated with ARSi but not taxane, were enriched with PTEN, RB1 and TP53 loss (all p < 0.001). Models to predict resistance to the therapies based on specific CTC prevalence in early on-therapy draws will be presented. Conclusions: We observed broad CTC phenotypic and genotypic heterogeneity prior to Rx, and patterns of clonal selection specific to different standard of care drug classes. Models utilizing these insights have potential to predict resistance if observed pre-therapy or during therapy to enable a change in therapy prior to clinical manifestation. Further development of these models is ongoing.

Background: Alterations (alt) in TP53, PTEN and RB1 TSGs have been identified in some prostate cancers. Preclinical data suggest that co-occurrence in CRPC tissue samples. Biomarker(BM)-positive (+) was defined as copy number loss or deleterious mutation of ≥ 1 TSG (TP53, PTEN or RB1). For pts presenting with L-CSPC, Kaplan-Meier method estimated time from biopsy to PSA relapse/metastasis/death (EFS), CRPC, and death (OS). Cox model assessed association of BM status and outcomes, adjusted for age, stage and Gleason score in multivariate analyses (MVA). Time from ADT start for M1-CSPC to CRPC and death was also estimated. For M1-CRPC, duration on 1st line CRCP therapy and time from CRPC to death was estimated, adjusting for age, volume and location of metastasis in MVA. Association of cumulative BM+ hits (0 vs 1 vs 2 vs 3) and outcomes was assessed. Results: For BM+ frequencies see table. L-CSPC with BM+ had a shorter EFS (median 2.6 years, HR 1.95, 95% CI 1.22-3.13) and time to CRPC (HR 3.36, 95% CI 1.01-11.16). MVA confirmed association with EFS (HR 1.84, p = 0.029). More gene hits lead to greater risk of relapse (MVA; 1 vs 0 hit: HR 1.75, p = 0.05; 2/3 vs 0: HR 2.74, p = 0.04). None of the 43 M1-CSPC pts who were BM- neg had died with median follow-up of 3.3 yrs; BM- 4-year OS was 64%, Only 4% (8%) of the CRPC cohort (n = 48) were BM-neg and with a median follow-up of 4.1 years, only 1 had died (5.2 yrs). Cumulative TSG loss was associated with shorter duration on 1st line therapy in MVA (3 vs 0/1 hit: HR 2.86, p = 0.0131). Conclusions: Delerious TP53, PTEN and RB1 variants are associated with increased risk of relapse (MO) and death (M1) in CSPC and shorter duration on 1st line therapy in CRPC. BM-neg in CRPC is rare but may represent a subset of pts with very good prognosis. Poorer outcomes are seen with cumulative gene hits across cohorts.

Background: The safety of ARAT (Abiraterone acetate (AA) and Enzalutamide (ENZ)) among men with existing CVDs or EPP is unknown since patients with these conditions are often excluded from the clinical trials. This study was undertaken to fill these knowledge gaps. Methods: This population-based study identified PCa patients from the linked Surveillance, Epidemiology and End Result-Medicare files diagnosed during 1/1/1991-12/31/2013. The primary endpoint was 6-month overall mortality after drug initiation. CVDs include acute myocardial infarction (AMI), atrial fibrillation (AFIB), congestive heart failure (CHF), stroke, and ischemic heart disease (IHD). Cox proportional hazard models were used to assess the risk of 6-month mortality. Results: Our study included 3,116 patients treated with AA only or AA as first ARAT and 1,162 patients treated with ENZ only or ENZ as first ARAT. The characteristics of the patients treated with AA and ENZ were similar. The majority of patients (67%) treated with AA had existing CVDs and the prevalence of EPP before drug initiation was high (46% for AA and 44% for ENZ). Six-month mortality was elevated among men with existing CVDs treated at ARAT (Table 1). EPP with AA was associated with an increase in 6-month mortality (AA; HR 3.22, 95% CI 2.16-4.81; ENZ; HR 1.63, 95% 1.03-2.58). To our knowledge, this is the largest population-based study to provide outcomes data among patients with existing CVDs or EPP, who were under-represented in the pivotal trials. The elevated 6-month mortality of men with CVDs or EPP treated with AA suggested that these patients represent a vulnerable patient population. Further studies are needed to determine the clinical benefit and risks of ARAT in this high-risk population.
Background: Ra-233, a bone targeting alpha radiopharmaceutical, and Enza, are approved for mCRPC. Per SWOG0421, the subset of men with mCRPC with the highest bone metabolism marker levels had improved survival with concomitant decrease in these markers on treatment (Rx) with atrazentin, a bone targeting agent (Lara Pet al, JNCI, 2014). Our hypothesis was that Rx with Ra-233+ Enza will be safe and feasible, and may decrease bone metabolism markers compared to Enza alone. Methods: In this phase 2 trial (NCT02199197), men with progressive CRPC on continuous androgen deprivation therapy were included. Ra-223 was administered at standard dose of 55 kBq/kg IV q4 weeks x 6, and Enza at 160 mg orally daily until disease progression or unacceptable toxicities. Primary objectives: 1) Safety and feasibility of combining Ra-223+Enza, 2) changes in the bone metabolism markers with Rx. Secondary objectives included time to progression, skeletal events, percent change in opioid use. The pre-specified primary safety endpoint was the proportion of patients treated with the combination who had enrofloxacin grade 3+ cytopenias relative to historic controls (21%) from the phase 3 ALSYMPCA trial using an exact binomial test with a one-sided 0.05 significance level. All adverse events between arms were compared using Fisher’s Exact Test. Results: Safety data are presented. 49 patients were accrued between 2014-2017. 35 men received Rx with Ra-233+Enza and 14 men with Enza alone. The primary endpoints (pts in the combination arm (incidence 8.6%, n = 35 pts), and in 0 patients in the Enza only arm (n=14). These were similar to historic data (ALSYMPCA trial) of monotherapy with Ra-223 (P = 1.00), and not different between arms (P=0.55). Serious adverse events (SAEs), “regardless” of attribution were similar in both arms (P=0.06). Conclusions: Combining Ra-223+Enza is safe and feasible in men with progressive mCRPC with no difference observed in SAEs regardless of attribution between two arms. Specifically, there was no incidence of skeletal related events in either arm. Safety data will be elaborated during the meeting. Clinical trial information: NCT02199197.

5059 Poster Session (Board #286), Sat, 1:15 PM-4:45 PM Expression of immune checkpoints (ICs) on circulating tumor cells (CTCs) in men with metastatic prostate cancer (mPC).

First Author: Tian Zhang, Duke University Medical Center, Durham, NC

Background: Most immune checkpoint inhibitors have shown limited efficacy (neither ICs are relevant in mPC. We evaluated ICs on the cell surface of CTCs in patients (pts) with mPC. Methods: ICs were detected using the Lumican™ assay. Enzyme-Linked ImmunoSpot (ELISpot) assay was also used to detect IFN-γ production by CTCs. Results: For PD-L1, we observed no significant differences in expression between various cohorts. Analysis of single ICs showed that B7-H3 was the most prevalent IC in CTCs and its expression was heterogeneous between and within pts; PD-L2 was detected at higher frequencies in RA223+Enza compared to Enza only. Conclusions: These results suggest that ICs are relevant in mPC. We evaluated ICs on the cell surface of CTCs in patients (pts) with mPC.

5060 Poster Session (Board #287), Sat, 1:15 PM-4:45 PM

The association of BRCA1 and BRCA2 mutations on prostate cancer risk, frequency, and mortality: Systematic review and meta-analysis.

First Author: Mok Oh, University of Arizona College of Pharmacy, Tucson, AZ

Background: A prior meta-analysis (Fachal, Prostate, 2011) suggested no association between BRCA1 mutation and prostate cancer (PCa). Several additional BRCA2 studies have shown an association with PCa risk and mortality. We conducted a systematic review and meta-analysis of BRCA1 and BRCA2 studies to estimate PCa risk in BRCA mutation carriers, evaluate the frequency of BRCA2 mutation carriers in PCa patients and their survival. We report 6-mo results. Methods: We identified 406 eligible articles through PubMed database. Quanitative synthesis was performed. Results: We included 15 studies and their meta-analysis. Conclusions: The association of BRCA1 and BRCA2 mutations with prostate cancer risk and survival is complex. Further research is needed to clarify the association.
5061 Poster Session (Board #288), Sat, 1:15 PM-4:45 PM

Differences in genomic signatures and opportunities for targeted and immunotherapy treatment between castrate-resistant TMPRSS2:ERG fusion-positive and -negative refractory castration-resistant prostate cancer (CRNEPC). First Author: Leszek Kotula, Upstate Medical University, Syracuse, New York

Background: We hypothesized that sub-categorization of TMPRSS2 fusion status would impact therapy opportunities in patients with clinically advanced CRPC and CRNEPC. Methods: CGP was performed on FFPE samples of 2,424 CRPC and 143 CRNEPC. Tumor mutational burden (TMB) was determined on 1.1 Mbp of somatic DNA and microsatellite instability (MSI) was determined by principal components analysis of optimal homopolymer loci. Results: All (100%) CRPC and CRNEPC were advanced and therapy resistant. TMPRSS2:ERG fusions significantly more frequent in RB1 and PTEN GA, whereas TMPRSS2:CRPC featured more MYC and ATM GA; differences in BRCA2 and RB1 GA were not significant. RB1 GA were significantly more frequent in CRNEPC than CRPC, whereas GA in AR and ATM were more frequent in CRPC. TP53 GA frequencies were higher in TMPRSS2+ CRNEPC than in TMPRSS2+ CRPC, whereas GA in PTEN and MYC were similar in comparable groups. Median TMB was higher in CRNEPC than CRPC, and higher in TMPRSS2+ compared to TMPRSS2+ tumors; TMB was more often ≥10 or ≥20 mut/Mb in TMPRSS2+ tumors. MSI-High status was more frequently identified in the TMPRSS2+ CRPC and CRNEPC groups. Conclusions: The 31% frequency of TMPRSS2+ CRPC in this study, lower than the 46% reported in early stage disease (TCGA data) suggests that this biomarker may be linked to a favorable prognosis. For CRPC, the higher frequency of TMPRSS2+ tumors is not as striking. CGP reveals significant differences in both treatable GA and markers of immunotherapy response between TMPRSS2+ and TMPRSS2- prostate tumors.

5063 Poster Session (Board #290), Sat, 1:15 PM-4:45 PM

Early changes in PSA and association with outcomes in mCRPC patients. First Author: Pasquale Rescigno, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: Declines in prostate specific antigen (PSA) levels at 12-weeks are currently used to evaluate treatments response in metastatic castration resistant prostate cancer (mCRPC). Early PSA fall by 30% at 4-weeks (PSA4w30) has been previously shown to be associated with better outcome in mCRPC in a small single-centre cohort. Methods: We identified mCRPC patients who had received androgen-deprivation therapy (ADT) between 06.01.06 and 08.09.17 in 13 cancer centres worldwide. Eligible patients had PSA levels assessed at baseline, after 4-weeks and/or 12-weeks of treatment. PSA response was defined as a ≥30% decline from baseline and PSA progression as a ≥25% increase from baseline. Association with overall survival (OS) was analysed using landmark multivariable Cox regression adjusting for previous chemotherapy, including cancer centre as a shared frailty term. Results: We identified 1057 patients who had received AA (447 pre-chemotherapy, 610 post-chemotherapy), with 835 patients having PSA values available at 4 and 12 weeks. Overall, 372/835 (44.5%) had PSA4w30; this associated with longer OS (mOS 22vs15 months; HR = 0.62; 95%CI 0.53–0.72; p = 0.001). A ≥30% PSA decline at 12-weeks (PSA12w30) associated with a lower mortality (mOS 22vs14; HR = 0.57; 95%CI 0.48–0.67; p < 0.001). Sensitivity analyses confirmed the association between PSA4w30 and OS when pre- and post-chemotherapy cohorts were analysed separately. PSA4w30 was strongly associated with PSA12w30 (p = 0.92; p < 0.001). In total, 320/372 (86%) patients with a PSA decline at 4-weeks had a PSA decline at 12-weeks. Conversely, 11/383 (1.3%) patients progressed at 4-weeks and then met the criteria for PSA12w30. PSA4w30 remained correlated with OS (HR = 0.56; 95%CI 0.48–0.65; p < 0.001) in multivariate analyses including other established prognostic factors in mCRPC (baseline ALP, LDH, Hb, m status and Gleason at diagnosis). Conclusions: PSA changes in the first 4-weeks of AA therapy are strongly associated with clinical outcome in mCRPC patients and should be prospectively evaluated in early treatment switch decision trials.

5064 Poster Session (Board #291), Sat, 1:15 PM-4:45 PM

Molecular and clinical implications of CHD1 loss and SPOP mutations in advanced prostate cancer. First Author: Pasquale Rescigno, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: CHD1 deletions (CHD1del) and SPOP mutations (SPOPmut) frequently co-occur in prostate cancer (PCa) with lower frequencies observed in castration-resistant PCa (CRPC). Responses to standard treatments in this subset of patients have not been previously reported. We studied the molecular and clinical characteristics of CHD1del/SPOPmut metastatic castration-resistant PCa (mCRPC) analyzing CHD1 presence/loss during disease progression and correlation to Abiraterone acetate (AA). Methods: We identified mCRPC patients who had hormone naive (HNPC) and CRPC tumor samples available: these were analyzed for CHD1, PTEN and ERG expression by immunohistochemistry (IHC). SPOP status was determined by targeted next generation sequencing (NGS). Correlations with CHD1/SPOT status and clinical outcomes and responses to AA were analysed using Cox-regression and Log-Rank analyses. Results: Tumor samples from 89 patients who had progressed from HNPC to CRPC were analyzed in a cohort enriched for SPOPmut. CHD1 protein loss was detected in 11 (15%) and 17 (20.7%) of HNPC and mCRPC biopsies, respectively. Comparison of CHD1 protein levels were feasible in 56 matched, same patient HNPC and mCRPC biopsies. CHD1 protein status correlated in 55 of 56 cases of the matched samples (98%). We identified 22 patients with somatic SPOPmut, with 6 of these mutations not reported specifically, are presented in localized, prostate cancer patients with Gleason Grade Group 3 and above (i.e. primary pattern 4 and higher). We propose that these patients could be targeted for neoadjuvant (or adjuvant) clinical trials using PARP inhibitors in HRD+ populations.

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5067 Poster Session (Board #294), Sat, 1:15 PM-4:45 PM
Clinical qualitative analysis of plasma androgen receptor (pAR) status and outcome on abiraterone acetate (AA) plus enzalutamide (E) in a phase II multi-institutional study in metastatic castration resistant prostate cancer (mCRPC). First Author: Anuradha Jayaram, Institute of Cancer Research and The Royal Marsden NHS Trust Foundation, Sutton, United Kingdom
Background: pAR gene aberrations in mCRPC patients (pts) may be associated with worse outcome on AA+P/D. Methods: This was an international, multi-institutional, open-label, active control (ACE 2 study) (1000mg AA qd, 10 mg P/D qd) trial in symptomatic, chemo-naïve mCRPC pts (NCT01667710). A pre-defined exploratory objective was to evaluate the association of pAR status and radiographic progression free survival (rPFS), PFS and time of long-term ADT to randomisation. We used a validated droplet digital PCR assay to classify pts as pAR low and high copy number (CN) gain. Results: Baseline plasma DNA was collected from 151 pts of the intention-to-treat pts; 135 pts were available for pAR analysis, excluding samples with long-fragment DNA. 211 (15%) pts had AR CN gain. There was a significant association for AR gain and shorter rPFS (median 7.5 months [m] vs 10 m; HR: 2.78; 95% CI 1.34 - 4.9; p = 0.004) and PFS (median, 4.90 m vs 6.2 m; HR: 1.79; 95% CI 1.1 - 3; p = 0.04). Mutivariate analysis is in Table 1. PSA >50% decline was 65% for pAR CN gain vs 53% for pAR CN normal (OR 0.6; 95% CI 0.2 - 1.7; p = 0.33). The time from start of long-term ADT to randomisation, was significantly shorter in pts with AR CN gain at castration resistance (8m; pAR gain vs 29.5m; pAR normal; p = 0.004). Conclusions: In this prospectively defined cohort, pAR normal in chemo-naïve mCRPC pts had a significantly longer rPFS with AA+P/D. Previous data suggests shorter response to ADT associates with primary resistance to AA+P/D. The novel observation that these pts are enriched for pAR gain provides a biological rationale for this. Clinical trial information: NCT01867710.
Background: DDRm occur in 15-30% of pts with mCRPC. While BRCA2 germline mutations are linked to aggressive local disease, outcomes in pts with mCRPC and DDRm continue to be characterized. Methods: Leukocyte DNA from 631 consecutive mCRPC pts were screened for germline ATM, BRCA1/2, CDK12, and PALB2 truncating mutations using targeted sequencing. 312/631 were assessed for somatic DDRm (sDDRm) and homozygous deletions in the same genes, using matched plasma cell-free DNA. Additional pts with gDDRm were identified through our hereditary cancer program (HCP). We examined time from androgen deprivation therapy (ADT) initiation (± doce-taxel) to CRPC; time to PSA progression (TTPP), PSA response (50% decline from baseline), and objective response rate (ORR) on 1st-line AR-targeted therapy, docetaxel, PARP inhibitor, platinum-based chemotherapy, and radium-223 for mCRPC; and overall survival (OS). Outcomes in pts with DDRm and pts with DDR wild-type (WT) status (with available clinical data, n = 113) were compared using the log-rank test. DDRm and pts with DDR wild-type (WT) status (with available clinical data, n = 113) were compared using the log-rank test. Results: gDDRm and sDDRm were identified in 133/631 (21.0%) and 25/631 (4.0%) pts, respectively. The HCP identified an extra 3 BRCA2 and 1 BRCA1 pts. Across 59/72 pts with available clinical data, 23/59 (39.0%) presented with de novo metastatic disease. Median time to CRPC from ADT (± doce-taxel) initiation was 12.1 mo (gDDRm = 12.5 mo, sDDRm = 11.5 mo). The table displays outcomes in pts with DDRm and pts without DDRm with a TTPP on 1st-line AR-targeted therapy of 3.6 mo and 7.4 mo in WT pts (p = 0.002). Median OS from the time of ADT initiation and time of CRPC was 41.5 mo (gDDRm = 41.5 mo, sDDRm = 43.5 mo) and 28.4 mo (gDDRm = 28.4 mo, sDDRm = 20.9 mo), respectively. Conclusions: In our cohort, pts with DDRm have poorer survival compared with pts without DDRm. All pts with DDRm had a TTPP of ≤ 6 mo (gDDRm = 12.5 mo, sDDRm = 11.5 mo). We identified a TTPP of ≥ 6 mo as a potential biomarker for pts that do not benefit from ADT initiation.

Impact of treatment sequence on the outcomes of metastatic castration-resistant prostate cancer patients (mCRPC) with germline BRCA2 mutations: A subanalysis of the PROREPAIR-B study. First Author: Nuria Romero-Laorden, Hospital Universitario La Princesa, Madrid, Spain

Background: Germline mutations in BRCA2 have been identified in 3-5% of mCRPC patients. PROREPAIR-B (Castro et al ESMO 2017) is the first prospective study to report a worse survival from mCRPC associated to these mutations. Significant interactions between treatment-type (androgen signaling inhibitors: ASI/Taxane) and BRCA2 status for cancer-specific survival (CSS) from 1st line (1L; P = 0.015) and 2nd line (2L; P = 0.006) were identified. In this exploratory subanalysis, we report mCRPC outcomes according to BRCA2 status and treatment sequence. Methods: PROREPAIR-B (NCT03075735) is a prospective multicentre observational cohort study. Patients who were taxane- and ASI-naïve at time of mCRPC, and who were treated or intended to treat with any of these two sequences; a) 1L ASI, 2L taxane; or b) 1L taxane; 2L ASI were eligible. Endpoints: assessment of the impact of BRCA2 on CSS, PFS from 1L initiation to clinical/radiological progression on 2L or death (PFS2). Analyses were stratified according to treatment sequence. Results: 348 out of 419 patients were eligible: 190 (7 BRCA2 for the ASI-taxane and 158 (7 BRCA2 for the taxane-ASI sequence. Patients in the taxane-ASI cohort were significantly younger (p < 0.001) and have worse ECOG (p = 0.002), higher PSA (p = 0.007), elevated LDH (p < 0.001) and elevated ALP (p = 0.01) compared to the ASI-taxane group, but there were not significant differences between BRCA2 carriers and non-carriers were observed with the ASI-Taxane sequence: CSS (median 24.0 vs 31.1 months, p = 0.9) and PFS2 (18.9 vs 21.1 months, p = 0.6). Conversely, in the taxane-ASI sequence BRCA2 status was associated to significantly worse CSS (10.7 vs 28.4 mo, p < 0.001) and PFS2 (8.6 vs 17.1 mo; p < 0.001). In the multivariable analyses, BRCA2 remained an independent prognostic factor for CSS (HR 2.95; 95%CI 1.21-7.15) and PFS2 (HR 5.50; 95%CI 2.35-12.89). Conclusions: These results suggest that the outcomes of BRCA2 mutation carriers may differ according to treatment sequences. This contributes to explain the differences in outcomes reported by previous series. Clinical trial information: NCT03075735.
A pre-specified statistical model based on four kallikrein markers in blood to predict advanced pathology on radical prostatectomy. 

First Author: Thomas Steuber, Martini-Clinic Prostate Cancer Center Hamburg-Eppendorf, Hamburg, Germany

Background: Four kallikrein markers in blood – commercially available as the 4Kscore – has been shown to be highly predictive of Gleason Grade Group (GGG) 2 or higher prostate cancer at biopsy. However, tissue sampling and grading at biopsy is an imperfect gold standard and may miss aggressive disease. We measured the kallikrein in cryopreserved blood in patients undergoing radical prostatectomy at a tertiary referral center from 2000-2010, during which it was common to treat GGG1 prostate cancer.

Methods: Aggressive disease was defined as primary Gleason grade 4, any grade 5, seminal vesicle invasion, extra-capsular extension (ECE) or lymph node invasion. ECE was excluded in a sensitivity analysis. A second sensitivity analysis excluded patients with low scores from the kallikrein panel, who may never have been biopsied had they received a 4Kscore. We assessed improvement in discrimination when the kallikrein panel was added to a base model using established clinical predictors: age, prostate specific antigen, clinical stage and grade. We also examined a model that included number of positive cores and mm of cancer. We pre-specified that we would separately assess men with GGG1 – where the decision concerns confirmatory biopsy – and GGG2 – where the decision would concern treatment vs. active surveillance.

Results: The cohort included 2284 men with data on cores for 1294. The kallikrein panel was significantly associated with advanced pathology after adjusting for clinical variables (P = 0.019). Overall, the panel added 0.014 to the AUC of clinical model, with larger effects within GGG1 (0.047) and GGG2 (0.017). Results were similar when cores were included and not sensitive to alternative definitions of advanced disease, or exclusion of patients with low panel risks. Decision curve analysis confirmed the additional value of the panel for decision thresholds: 5 – 20% for confirmatory biopsy and 20 – 60% for treatment.

Conclusions: The kallikrein panel is strongly associated with pathologic outcome, and can be used to make subsequent management decisions for patients found with GGG1 or GGG2-cancer at biopsy and the need for confirmatory biopsy and treatment.
Conclusions: Fold increased probability of developing distant metastasis compared to CA treatment group. In MV Cox PH models, race did not predict DMFS among BRY group (p = 0.013). Table 1 shows DMFS estimates by race and follow up times and ages were 6.7 and 69.8 years for EBRT patients and 6.9 and 65.4 years for BRY, respectively. In KM analysis race did not predict DMFS for EBRT group (p = 0.56) but there were significant racial differences in 4 treatment arms in 60 planned pts (A: 16, 2mg INO-150; B: 15, 8.5 mg INO-5150; C: 15, 2mg INO-150+1mg INO-9012; D: 16, 8.5mg INO-5150+1mg INO-9012). Pts received 4 IM doses of vaccine followed by electro-poration on day 0, wks 3, 12 and 24 and followed for 72 wks. Results: The study has concluded and 50/62 (80%) pts completed all visits. 90% of pts had Grade (G)-1-3 AEs, primarily injection site reactions which were Gr 1. Across 4 cohorts, 47/61 (77%) of all evaluable pts demonstrated immunogenicity, 135/58 (60%) had IFN-g reactivity by ELISPOT, 6/61 (10%) and 5/61 (8%) had antibody titers against PSA and PSMA, respectively, and 19/50 (38%) had CD8+ and CD8+ T cell responses. Pts (38%) with CD8+ and CD8+ T cell immune reactivity had attenuated % PSA rise compared to non-reactive pts (p = 0.05, n = 50). Pts with no known progression during the study showed significant differences in log2PSA change and PSA-DT pre-treatment baseline (DO) vs wk 27 (post-immunotherapy time point, n = 34, p < 0.0001) or wk 72 (end of follow-up, n = 10, p = 0.0002). Conclusions: INO-5150 +/- INO-9012 was safe, well tolerated and immunogenic. A clinical effect was demonstrated by evidence of dampening % rise in PSA and increased PSA-DT in the majority of patients. In patients with no known disease progression during the study, a significant PSA stabilizing effect of the immunotherapy was observed. Additional analyses are ongoing to further elucidate the correlation of immunologic efficacy and clinical benefit. Clinical trial information: NCT02514213.

Background: Racial differences in prostate cancer (PCa) outcomes are widely observed, irrespective of risk stratum at diagnosis. The primary study aim was to compare distant metastasis-free survival (DMFS) for African American (AA) and Caucasian American (CA) military health care beneficiaries undergoing radiation therapy (RT) for PCa over 20+ years. Methods: A retrospective cohort study of Center for Prostate Disease Research Multi-Center National Database enrollees was conducted. Eligible patients included a diagnosis with biopsy-confirmed PCa between January 1, 1989 and December 31, 2013, primary treatment (< 6 months post-diagnosis) with external beam radiation therapy (EBRT) or brachytherapy (BRY), and ≥2 years follow-up. EBRT combined CT-based, 3D conformal, and intensity modulated RT (IMRT). DMFS was compared across race using Kaplan Meier (KM) estimation curve analysis, stratified by treatment type (EBRT vs. BRY). Multivariable (MV) Cox Proportional Hazards (PH) analysis was used to model DMFS as a function of race, stratified by treatment type (EBRT vs. BRY), controlling for clinical covariates. Results: Of the 4,299 eligible men who had primary RT, 2,022 (77.6%) had EBRT and 1,277 (22.4%) had BRY (n = 2,650). Among EBRT patients, 28% were AA and 66% were CA. For BRY patients, 18% were AA and 77% were CA. Median follow up times and ages were 6.7 and 69.8 years for EBRT patients and 6.9 and 65.4 years for BRT, respectively. In KM analysis race did not predict DMFS for EBRT group (p = 0.0013) but there were significant racial differences among BRY group (p = 0.013). Table 1 shows DMFS estimates by race and treatment group. In MV Cox PH models, race did not predict DMFS among EBRT patients (p = 0.695); however, among BRY group, AA men had a 4.7-fold increased probability of developing distant metastasis compared to CA men (p = 0.045), controlling for age at RT, year of treatment, and INCN risk stratum. Conclusions: In this racially diverse, equal access health care system, comparable DMFS was observed across patient race over this 20+ years for EBRT but not BRY patients who had significantly poorer DMFS. Subsequent work will examine cancer-specific survival, comorbidity, and prostate volume.

Background: To compare 10-year treatment outcomes of radical prostatectomy (RP) vs external beam radiation therapy (EBRT) vs brachytherapy (BT) for patients with intermediate risk prostate cancer. First Author: Barry W. Gay, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

Ten year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs brachytherapy. First Author: Barry W. Gay, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

Compared and contrasted with intermediate risk prostate cancer. First Author: Barry W. Gay, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA

Background: Long-term androgen deprivation, with or without radiotherapy, in locally-advanced prostate cancer. First Author: Paul Sagos, Institut Bergonié, Bordeaux, France

Background: We previously reported results of a randomized phase III trial comparing androgen-deprivation therapy (ADT) combined with external beam radiation therapy (EBRT) and ADT alone in patients treated with localized cancer. We report here long-term oncological outcomes of this trial. Methods: In this multicenter phase III trial, patients with biopsy-proven locally advanced prostate cancer (T3-4) randomly assigned to ADT alone or ADT+EBRT. In both arms, leuprolin 11.25 mg, subcutaneous, was started within seven days of randomization and continued every three months for three years and oral flutamide (750 mg/day) was administered during the first month. For the ADT EBRT arm, the whole pelvis was treated at a dose of 46+2 Gy and the prostate with a boost from 20 Gy to 28 Gy. Primary endpoint was progression-free Survival (PFS) which included biochemical and clinical events and deaths. Secondary endpoints included overall survival (OS), disease-specific survival (DSS), locoregional progression free survival (LPFS), metastasis-free survival (MFS), biochemical progression free survival (BPFS) and tolerance. Competing-risk analysis was used whenever appropriate. Results: With a median follow-up of 7.3 years, 263 patients were included in the Intent-to-treat analyses. The 8-year PFS rate was significantly higher in the ADT+EBRT arm than in the ADT arm (47.9% versus 7.0%; hazard ratio: 0.27, p < 0.0001). The risk of death from prostate cancer was significantly reduced for ADT+EBRT arm as compared to ADT alone (sub-hazard ratio: 0.48; p = 0.02). The 8-year OS rate was respectively 56.8% in the ADT arm and 65.1% in the ADT+EBRT arm (p = 0.43). LPFS was significantly in favor of ADT+EBRT arm (SHR = 0.61; p = 0.01). MFS was comparable between both arms (p = 0.88). Analysis of toxicities revealed acute lower tolerance (mainly gastro-intestinal and genito-urinary) in the ADT+EBRT arm with a gradual decrease in intensity during follow up from 6 months after the end of EBRT. Conclusions: These long-term results confirm the oncological benefit of combining EBRT with ADT in the treatment of locally advanced prostate cancer. Clinical trial information: NCT01122121.
5081 Poster Session (Board #308), Sat, 1:15 PM-4:45 PM
A pharmacodynamic biomarker study of vistusertib (AZD2014), an mTORC1/2 inhibitor, given prior to radical prostatectomy (CANCAP02).
First Author: Simon Pacey, University of Cambridge, Cambridge, United Kingdom

Background: The effect of novel drugs can be studied in primary prostate cancer (PC), if given prior to radical prostatectomy (RP). Altered PI3K/AKT/mTOR signalling is associated with aggressive primary PC and progression. CanCap02 investigated the effects of vistusertib (AZD2014), an oral, dual mTORC1/mTORC2 inhibitor in men with PC. Methods: Men, due for RP, with high volume or aggressive PC consented and received vistusertib, 50mg bd, for 15 days prior to RP. Diagnostic biopsy, attempted intra-operative biopsy and RP tissue were collected for IHC analysis. Adverse events (AE) were graded using CTCAE v4. Blood was collected to determine plasma vistusertib concentrations. The primary endpoint was to measure mTORC1/2 inhibition by immunohistochemistry (IHC). Secondary endpoints were feasibility, safety, tolerability and vistusertib plasma pharmacokinetics. Exploratory objectives included interrogating biological pathways related to mTOR and anti-cancer effects. Results: Median age 62 (SO–69) yrs, 48% intermediate and 52% high risk recurrence. 20/23 pt were evaluable for primary endpoint analysis. The majority of AEs (67%) were Gr1: including: mucositis, thrombocytopenia, raised liver enzymes/ bilirubin) which resolved prior to RP. RP was only delayed in one pt to allow resolution of AE (Gr1 thrombocytopenia). Vistusertib inhibited mTORC1 (pS6, 4EBP1 and NDRG1 were reduced). PSA occurred. The AE profile might be improved by an intermittent dosing schedule. Clinical trial information: NCT02064608.

5083 Poster Session (Board #310), Sat, 1:15 PM-4:45 PM
Effect of rilimogene galavacirepvecilogene glafolivec on intra/peritumoral immune infiltrate in patients with localized prostate cancer undergoing radical prostatectomy. First Author: James L. Gulley, Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: PSA-TRICOM (Prostvac) is a vector-based vaccine designed to generate a robust immune response (IR) against PSA-expressing tumor cells. To date, studies of Prostvac in patients with mCRPC have shown IR in peripheral blood but effects on prostate tumors are unknown. Methods: An open label phase 2 study of neoadjuvant Prostvac (NCT02153918) enrolled patients (pts) with localized prostate cancer undergoing radical prostatectomy (RP). Priming vaccination was given followed by boosts on days 15, 29 and 57 prior to RP. Results: The objective response rate was 10% (95% CI: 0.01, 0.18). Median pre-RP PSA was 1.34ng/mL (range: 0,1.45). Twenty-six pts were evaluable for tissue RNA analysis (24 pts) and peripheral IR (28 pts). TAA specific T cell peripheral IR to PSA, Muc-1 or Breast cancer 2 (BRCA2) were observed in 12/24 (50%) pts post vaccine, with 25% of pts having multiple IRs. Matched tissue IHC analysis and peripheral IR in tissues available on 24 pts. Conclusions: Prostvac induced IRs in tissue and as surrogate tests (ie plasma glucose) and in some pt (15% pt) a fall in PSA occurred. The AE profile might be improved by an intermittent dosing schedule. Clinical trial information: NCT02153918.

5084 Poster Session (Board #311), Sat, 1:15 PM-4:45 PM
Combination of a therapeutic cancer vaccine and immune checkpoint inhibitor in prostate cancer. First Author: Ravi Amin-Mansat, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Immune checkpoint inhibitors (ICIs) have yet to demonstrate efficacy as monotherapy in non-MSI-HI prostate cancer. Vaccines may increase immune cells in the tumor microenvironment, potentiating ICIs. Methods: This study combines PROSTVAC(P), a pox-viral based vaccine targeting PSA, ipilimumab (Ipi; 1 mg/kg) and nivolumab (Nivo; 240 mg) in patients (pts) with castration resistant prostate cancer (CRPC). The initial regimen was P on Day 1, all 3 agents (PIN) 2 weeks/week later, and PIN every 3 wks thereafter. After Ipi was removed the regimen = P on Day 1, P+Nivo on wks 2,4 and then Nivo every 2 wks = P only. Results: 13 pts were enrolled with median age 72, 75% of pts had mCRPC, 60% had pT3a on pathological review. Conclusions: Six months of nAdT with enzalutamide has activity in high risk, localized prostate cancer, with a small number of patients having exceptional responses. Standard analysis of mpMRI identifies most patients with persistent T3 disease but does not reliably identify exceptional responses. Evaluation of molecular characteristics that predict exceptional response or intrinsic resistance is on-going. Clinical trial information: NCT02430480.

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Background: Shared decision making between a patient and caregiver is important when discussing prostate cancer (PCa) screening. Decision aids (DAs) are tools intended to facilitate this process and improve patient participation through education, yet little is known about how DAs affect screening preferences. We administered an online survey study to determine how different DAs impact the decision to undergo or recommend a loved one undergo PCa screening. Methods: Using ResearchMatch, an online, study recruitment registry, participants matched for age, race, and gender were randomized to one of six different major professional society’s free, online DA on PCa screening. We compared pre- and post-DA responses. The primary outcome was change in participant likelihood to undergo or recommend a loved one undergo PCa screening on a scale of 1 (unlikely) to 100 (extremely likely). Secondary outcomes included change in participant comfort with PCa screening based on the average of six, five-point Likert-scale questions. Results: Median age was 53 years for the 1,336 participants, and 50% were men. Randomized groups did not differ significantly by race, age, gender, income, marital status, or education level. Likelihood to recommend PCa screening decreased from 83 to 78 following DA exposure (p < 0.001). Reviewing the DAs from the Center for Disease Control or American Academy of Family Physicians did not alter likelihood (both p > 0.2), while reviewing the DA from the United States Preventive Services Task Force was associated with the largest decrease (−16.0). Participants reported increased comfort with the decision-making process for PCa screening from 3.5 to 4.1 (out of 5, p < 0.001) following exposure to a DA. Conclusions: In this online survey, after exposure to most DAs from major professional societies, participants were less likely to undergo or recommend their loved one undergo PCa screening. DAs improved participant comfort with the PCa screening shared decision-making process. These results illustrate how different DAs may disparately influence men and their loved ones about the tradeoffs of PCa screening.

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TPS5089  Poster Session (Board #314b), Sat, 1:15 PM-4:45 PM

Phase Ib study of avelumab plus carboplatin in patients with metastatic castration resistant prostate cancer progressing after one line of chemotherapy and one androgen receptor axis inhibitor. First Author: Alejo Rodriguez Vida, Hospital del Mar, Barcelona, Spain

Background: The management of metastatic castration resistant prostate cancer (mCRPC) has been revolutionized with the approval of several agents improving overall survival. However, despite an initial response, most patients will experience disease progression. New studies assessing new agents are still needed. Recently, several immune check-point inhibitors targeting the PD-1 pathway have been approved for the treatment of several solid tumors. However, their use in mCRPC is still at a very early phase of development. The purpose of this study is to test the safety and efficacy of combing carboplatin with avelumab in pretreated mCRPC patients. Genetic aberrations are frequent in CRPC, especially in advanced cases. By selecting pre-treated patients, we will enrich the amount of genetic aberrations (like high mutational burden or DDR mutations) potentially increasing the likelihood of response to avelumab. Cytotoxic chemotherapy like carboplatin has been shown to induce immunogenic tumor cell death, tumor-antigens release and stimulation of the immune system. It has been hypothesized that this “autovaccination” could be enhanced with the addition of immunotherapy such as avelumab. Methods: This is a phase Ib, open-label, single-arm study in patients with mCRPC progressing on at least 1 line of chemotherapy and 1 line of novel androgen receptor axis inhibitors. Inclusion criteria include performance status 0-1 and adequate organ function. Patients will receive 2 cycles of carboplatin AUC5 monotherapy followed by 2 cycles of carboplatin AUC5 plus avelumab 10mg/kg. Maintenance avelumab will continue for up to 2 years. This trial will have 2 stages. In the Safety phase (6 patients) the safety of combining both agents will be analyzed (primary endpoint). If safety is confirmed, an Expansion phase (20 patients) will assess the efficacy of the combination in terms of PSA and radiographic assessment as per PCWG3 (secondary endpoints). As exploratory endpoint, potential immunologic and genomic predictive biomarkers will be analyzed. The trial is open, and enrollment is ongoing. Clinical trial information: 2017-004552-39.

TPS5090  Poster Session (Board #315a), Sat, 1:15 PM-4:45 PM

A phase 3 study of androgen annihilation in high-risk biochemically relapsed prostate cancer: An Alliance Foundation trial (AFT-19). First Author: Randi S. Aggarwal, UCSF San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Men with biochemically relapsed prostate cancer (BRPC) following prior radical prostatectomy (RP) and a short PSA doubling time (PSADT) are at high risk for the development of metastatic disease and prostate cancer-related mortality. Intermittent androgen deprivation therapy (ADT) is a commonly applied treatment in this disease setting, but fails to achieve prolonged progression-free and treatment-free intervals for the majority of patients (pts). Apalutamide is a next generation androgen receptor (AR) antagonist that has efficacy in non-metastatic castration-resistant prostate cancer (CRPC). Abiraterone acetate, a produg of the CYP17 androgen synthesis inhibitor abiraterone, has been shown to prolong survival in both CRPC and metastatic hormone-sensitive prostate cancer. We hypothesize that the addition of apalutamide with or without abiraterone acetate/precinsone, as compared to ADT alone, will prolong disease suppression and potentially eradicate micrometastatic disease with a finite duration of treatment in pts with BRPC. Methods: AFT-19 is a randomized, open-label, single arm phase 3 study (first patient entered March 2017) of A) degarelix monotherapy compared to each of two experimental arms: b) degarelix plus apalutamide, and c) degarelix plus apalutamide plus abiraterone acetate/precinsone, in pts with BRPC following prior RP without metastases on conventional imaging, and a PSADT of < 9 months. Pts are treated for up to 52 weeks in the absence of progression or unacceptable toxicity, and subsequently followed off treatment until PSA progression, defined as serum PSA > 0.2 ng/mL. The primary endpoint is PSA progression-free survival (PFS). Secondary endpoints are 36-month PSA PFS rate, metastasis-free survival, time to CRPC, overall survival, and quality of life. Planned accrual is 504 pts, estimated to provide 85% power to detect a hazard ratio of 0.63 in the comparison of PSA PFS between each experimental arm versus the control arm, with an overall two-sided type I error rate of 0.025 for each comparison. The DSMB last reviewed the trial in November 2017 and recommended that the trial continue as planned. Clinical trial information: NCT03009981.

TPS5091  Poster Session (Board #315b), Sat, 1:15 PM-4:45 PM

Talapro-2: A 2-part, placebo-controlled phase 3 study of talazoparib (TALA) with background enzalutamide (ENZA) in metastatic castration metastatic castration resistant prostate cancer (mCRPC) with DNA damage repair deficiencies. First Author: Neeraj Agwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: ENZA is approved to treat men with mCRPC. TALA is a dual-mechanism PARP inhibitor that inhibits PARP1 and PARP2 catalytic activity and traps PARP on DNA, preventing DNA damage repair and causing cell death. TALA inhibits BRCA1/2 and traps PARP on DNA, preventing DNA damage repair and causing cell death. Mechanism PARP inhibitor that inhibits PARP1 and PARP2 catalytic activity and may benefit from curative local primary or salvage treatments. Background: Men with biochemically relapsed prostate cancer (BRPC) with background enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC) with DNA damage repair deficiencies. First Author: Neeraj Agwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Methods: This is a phase Ib, open-label, single-arm study in patients with mCRPC progressing on at least 1 line of chemotherapy and 1 line of novel androgen receptor axis inhibitors. Inclusion criteria include performance status 0-1 and adequate organ function. Patients will receive 2 cycles of carboplatin AUC5 monotherapy followed by 2 cycles of carboplatin AUC5 plus avelumab 10mg/kg. Maintenance avelumab will continue for up to 2 years. This trial will have 2 stages. In the Safety phase (6 patients) the safety of combining both agents will be analyzed (primary endpoint). If safety is confirmed, an Expansion phase (20 patients) will assess the efficacy of the combination in terms of PSA and radiographic assessment as per PCWG3 (secondary endpoints). As exploratory endpoint, potential immunologic and genomic predictive biomarkers will be analyzed. The trial is open, and enrollment is ongoing. Clinical trial information: 2017-004552-39.

TPS5092  Poster Session (Board #316a), Sat, 1:15 PM-4:45 PM

A prospective phase 2/3 multicenter study of 18F-DCFPyL PET/CT imaging in patients with prostate cancer: Examination of diagnostic accuracy (OSPREY). First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Accurate localization of sites of disease is essential for delivering optimal care to patients with prostate cancer. This is especially true for patients who may have distant disease either at initial staging or at relapse and may benefit from curative local primary or salvage treatments. 18F-DCFPyL (PyL) is a novel, high specific activity, highly selective, low-molecular weight prostate-specific membrane antigen (PSMA)-targeted PET radiopharmaceutical. This trial seeks to analytically validate the performance characteristics of PyL PET/CT for the detection of metastatic and/or recurrent prostate cancer. Methods: This is a multi-center, open-label, phase 2/3 study evaluating the diagnostic performance of PyL PET/CT in patients with at least high risk disease (as defined by NCCN guideline v3.2016) prostate cancer prior to radical prostatectomy (cohort A) or radiologically confirmed metastatic/recurrent prostate cancer (cohort B). A total of approximately 400 subjects will be enrolled in the study. All patients must be at least 18 years of age with histologically confirmed adenocarcinoma of the prostate. A single administration of PyL (9 ± 1 mCi [333 ± 37 MBq]) is administered 1-2 hours prior to PET/CT imaging on Day 1. The primary objective is to assess the diagnostic performance (sensitivity and specificity) of PyL PET/CT in the detection of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in pre-prostatectomy patients [cohort A], as determined by independent central review. Key secondary objectives include safety and tolerability of PyL, diagnostic performance of PyL PET/CT in the detection of prostate cancer within sites of distant metastasis or local recurrence [cohort B], and pharmacokinetic parameters of PyL in a subset of patients. The clinical impact of PyL PET/CT imaging on the intended management of prostate cancer patients will also be assessed as an exploratory endpoint. First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY.
TPS5093  Poster Session (Board #316b), Sat, 1:15 PM-4:45 PM
ODENZA: A study of patient preference between ODM-201 (darolutamide) and enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC).
First Author: Geoffrey Martinneau, Clinical Research Department, Institut Gustave Roussy, Villejuif, France

Background: In recent years, the treatment of mCRPC has evolved and next-generation androgen receptor (AR)-axis targeting drugs (enzalutamide (ENZ), and abiraterone) have been approved and are routinely used. Darolutamide (DARO) is a new next-generation AR inhibitor which has shown strong activity and minimal toxicity in two phase II trials ARAF3R (Fizazi, Lancel Oncol 2014) and ARAFDR (Massard, Eur Urol 2016) and is currently evaluated in a study in men with non-metastatic CRPC (ARAMIS trial). In contrast to ENZ, DARO does not significantly penetrate the blood-brain barrier in vivo, and this may reduce the risk of fatigue, cognitive impairment, and seizure. Assessing patient preference between DARO and ENZ may contribute further differentiating between these two agents. Methods: ODEanza is a prospective, randomized, open-label, multicenter, cross-over phase II trial assessing patient preference between DARO and ENZ (NCT03314324). It was initiated in November 2017. Eligibility criteria include: men with asymptomatic or mildly symptomatic mCRPC, performance status 0-1, no prior next-generation AR axis-targeted agent. The randomization is stratified by PSA status and prior treatment with a taxane for CSCP. 250 patients will be randomized 1:1:1 to: 12-week ENZ followed by 12-week DARO or 12-week DARO followed by 12-week ENZ. The primary endpoint is patient preference between DARO and ENZ, assessed after the second treatment period. A two-sided binomial test with a power of 80% and a bilateral α 0.01 will be used. Secondary endpoints include: reasons for patient preference, dose modifications and time to dose modification, safety, fatigue (BFI), cognitive function as assessed by Cogstate computerized cognitive tests, depression screening (CES-D) test, frequency of falls, PSA declines using Waterfall plots after each treatment period. Progression-Free Survival (PFS); time to dose modification between 4-week PSA value and PFS, incidence of cancer progression or death, and tumor response. The study is recruiting. By February 13, 2018, 10 patients have been enrolled. Clinical trial information: NCT03314324.

TPS5094  Poster Session (Board #317a), Sat, 1:15 PM-4:45 PM
A phase II trial of enzalutamide, docetaxel and androgen deprivation therapy (ADT) in men with metastatic castration-sensitive prostate cancer (mCSPC).
First Author: Earle Frederick Burgess, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC

Background: The addition of docetaxel (Doc) or abiraterone to androgen deprivation therapy (ADT) in men with mCSPC improves survival. Whether the triple combination of ADT, Doc and next generation endocrine therapy further improves patient outcome is unknown. Enzalutamide (ENz) is a potent anti-androgen that has activity in the advanced, castration-resistant setting. Preclinical data support the use of ENz in combination with Doc. ENz inhibits the ABCB1 drug efflux pump implicated in Doc resistance, and Doc may eradicate Enz-resistant clones harboring the androgen receptor splice variant 7 (ARv7). The combination of ENz with Doc at standard doses was safe in the phase I setting. This study tests the hypothesis that men with newly diagnosed mCSPC may benefit from adding ENz to standard Doc and ADT. Methods: This is a phase II, single arm trial of ENz plus Doc and ADT in men with newly diagnosed mCSPC. The study is designed to enroll 39 eligible participants who must have metastatic prostate adenocarcinoma with confirmed soft tissue and/or skeletal metastasis, ECOG 0-2, and PSA ≥ 5. Subjects who previously received up to 3 years of ADT with radiation for localized disease are eligible if ADT was discontinued ≥ 6 months before diagnosis of mCSPC and testosterone recovery is confirmed. Prior treatment with cytotoxic chemotherapy or next generation endocrine therapy is not allowed. Patients will be stratified by volume of metastatic disease. Treatment consists of Doc 75 mg/m2 IV every 3 weeks for 6 cycles and Enz 160 mg daily commencing at enrollment and continued until radiographic progression or study withdrawal. Continuous ADT is required during the study period. The primary endpoint is 12-month PSA complete response rate. Secondary endpoints include adverse events, best PSA response, radiographic objective response, time to castration resistance, progression free and overall survival. Exploratory biomarker analysis includes sequential measurement of circulating tumor cell (CTC) levels and CTC ARv7 status during study treatment. Clinical trial information: NCT03246347.

TPS5095  Poster Session (Board #317b), Sat, 1:15 PM-4:45 PM
Phase II trial of rucaparib (Without ADT) in patients with metastatic hormone-sensitive prostate cancer harboring germline DNA repair gene mutations (TRIUMPH).
First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: The clinical activity of PARPi in patients with homologous recombination DNA-repair mutations and metastatic prostate cancer has now been established. Focusing specifically on patients with a germline mutation in a pre-specified group of DNA-repair genes, we hypothesize that targeted therapy with PARPi should be sufficient to induce a clinical response irrespective of hormonal (castration-sensitive/resistant) status. For men with metastatic hormone sensitive prostate cancer (mHSPC) this trial would also provide an alternative to ADT. Methods: This study is a multicenter, open-label, single arm Phase II trial. Eligible patients are those with mHSPC without prior ADT. All patients must have a documented germline mutation in a homologous recombination DNA-repair gene (BRCA1, BRCA2, ATM, CHEK2, NBN, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCd2, FANCe, FANCf, FANCg, FANCi, FANCm, FANCn). Patients on trial must be ineligible for or decline standard-of-care hormonal treatment. A mandatory tumor biopsy will be performed prior to therapy. A second, optional tumor biopsy is planned after three months of therapy. Patients will be treated with Rucaparib 600mg po twice daily. Patients will be followed monthly with clinic visits and safety labs with PSA. The primary endpoint is the proportion of patients with ≥ 50% decrease in PSA from baseline (PSA50 response). A total enrollment of 30 patients is planned to detect an improved PSA50 response rate from 50% to 75% with 90% power (one sided type I error of 0.1). The total number of patients allowed with a non-BRCA1, -BRCA2, or -ATM mutations will be capped at 10. For patients who do not respond to PARPi, we have incorporated safety rules into the study design to take patients off study at first signs of progression. Secondary endpoints include safety, progression-free survival, and objective response. Exploratory analysis will involve biomarker discovery including somatic DNA mutation analysis, RNA expression analysis, and immunohistochemistry for DNA damage markers. Clinical trial information: NCT03413995.

TPS5096  Poster Session (Board #318a), Sat, 1:15 PM-4:45 PM
CRLX101 plus olaparib in patients with metastatic castration-resistant prostate cancer. First Author: Gang Chen, NCI/NIH, Bethesda, MD

Background: Prostate cancer is the most commonly diagnosed cancer among men in the United States. While prostate cancer is initially responsive to androgen deprivation therapy (ADT), most patients will develop castration-resistant disease. In the past several years, despite multiple new therapeutics (docetaxel, abiraterone and enzalutamide) have been approved by FDA, the majority patients will become resistant to treatments in 2-3 years. Therefore, it is necessary to find new treatments in metastatic castration-resistant prostate cancer (mCRPC). Methods: This phase II expansion cohort will evaluate the efficacy and safety of CRLX101 plus Olaparib in patients with mCRPC. CRLX101 is a nanoparticle drug conjugate with a camptothecin (CPT) payload that provides durable inhibition of topoisomerase I (Top1) specifically in the tumor. CPT stabilizes the Top1-DNA cleavage complex during DNA replication and prevents Top1-mediated DNA repletion, ultimately leads to apoptosis. Poly ADP ribose polymerase (PARP) plays a role in the repair of topoisomerase I-induced DNA damage. By inhibiting PARP, Olaparib may increase the potency of CPT and thus olaparib plus CRLX101 offers a potential treatment option in patients with mCRPC. Synergistic activity between camptothecin and olaparib has been shown in preclinical data. The primary endpoint of this study is overall response rate (ORR), the secondary endpoints include safety and progression-free survival (PFS), duration of response and PSA responses. Clinical trial registry number of this study is NCT02769962. Results: N/A. Conclusions: N/A. Clinical trial information: NCT02769962.

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c15-148: Phase I/II trial of concurrent chemohormonal therapy using enzalutamide and cabazitaxel in patients with metastatic castration resistant prostate cancer (mCRPC). First Author: Eugene Shenderov, Johns Hopkins University School of Medicine, Baltimore, MD

Background: The management of mCRPC has been both enhanced and complicated by the rapid emergence of at least five new agents that can lengthen survival. While great strides have been made in developing new agents for mCRPC, response rates and duration have remained modest, and men inevitably succumb to their disease. Historically, combined chemohormonal therapy has not improved outcomes for patients with prostate cancer, but earlier trials were hindered by lack of efficacious chemotherapy and weaker hormonal agents. In this study, we aim to determine if potential synergistic effects between two newer and more effective agents can be identified and exploited for therapeutic effect, and to obtain correlative biological information that may offer predictive and response value.

Methods: An initial 3-12 study subjects will be treated with cabazitaxel at 25 mg/m² on day 1 and enzalutamide 160 mg daily every 21 days. These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. The trial will proceed to phase II stage at the dose of 25 mg/m² if 0/3 or 1/6 patients had DLT. The trial will proceed to Phase II stage at the dose of 20 mg/m² if 0/3 or 1/6 patients receiving 20 mg/m² had DLT. The trial will proceed to Phase II stage at the dose of 20 mg/m² if 0/3 or 1/6 patients receiving 20 mg/m² had DLT. The trial will proceed to Phase II stage at the dose of 20 mg/m² if 0/3 or 1/6 patients receiving 20 mg/m² had DLT. These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. The phase II patients are treated with 25 mg/m² cabazitaxel and 160 mg enzalutamide. The trial is open at 2 site and managed by the Prostate Cancer Clinical Trials Consortium (PCCTC). Clinical trial information: NCT02522715.

c15-149: Phase II neoadjuvant and immunologic study of B7-H3 targeting with enoblituzumab in localized intermediate- and high-risk prostate. First Author: Eugene Shenderov, Johns Hopkins University School of Medicine, Baltimore, MD

Background: The B7-H3 target is part of the B7 superfamily and is an immune checkpoint expressed on multiple tumor types. B7-H3 inhibition limits tumor growth by enhancing cytotoxic T lymphocyte function through engagement with an unknown receptor. B7-H3 is highly expressed in prostate cancer (PCa) and is negatively correlated with both biochemical recurrence and metastasis. Enoblituzumab is a humanized Fc-optimized B7-H3-targeting antibody that induces antibody-dependent cellular cytotoxicity (ADCC). To date, approximately 180 patients have received Enoblituzumab monotherapy in a phase I study, with good tolerability. To determine the anti-tumor, immunological and biological effects of B7-H3 inhibition in high-risk localized PCa, we are currently conducting a neoadjuvant and pharmacodynamic phase II study (NCT02923180). We hypothesize that neoadjuvant enoblituzumab treatment will be feasible, safe, and will produce a robust antitumor immune responses that will correlate with clinical outcomes in high-risk prostate patients undergoing prostatectomy.

Methods: In this investigator-initiated single-center, single-arm, open-label phase II neoadjuvant trial we plan to enroll 32 patients with localized PCa (16/32 accrued). Patients must have clinical stage T1c-T3b, NO, MO disease and Gleason sum 7-10. Eligible patients undergo a pre-treatment prostate biopsy and receive enoblituzumab at a dose of 15mg/kg IV weekly for 6 doses beginning 50 days prior to radical prostatectomy. Fourteen days after the last dose of enoblituzumab, prostate glands are harvested at the time of radical prostatectomy, and prostate tissue is examined for the secondary pharmacodynamic endpoints. The primary co-endpoints are (1) to characterize safety and tolerability of enoblituzumab treatment in the neoadjuvant setting and (2) to estimate clinical benefit based on PSA0 response (PSA < 0.1 ng/mL) 12 months after radical prostatectomy. Secondary endpoints include evaluation of anti-tumor effects consistent with enoblituzumab’s proposed mechanism of action (apoptosis, proliferation), ADCC markers, and assessment of immunologic correlates (CD8, FOXP3, PD-L1 expression). Clinical trial information: NCT02923180.
A multicenter, randomized, controlled trial comparing the occurrence of major adverse cardiovascular events (MACEs) in patients (pts) with prostate cancer (pc) and cardiovascular disease (CVD) receiving degarelix (GnRH receptor antagonist) or leuprolide (GnRH receptor agonist). First Author: Susan F. Slovin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Epidemiological studies showed an association between GnRH agonists and a long-term increased risk of CVD, early after treatment initiation and with a higher risk seen in pts with pre-existing CVD. Retrospective pooled safety analyses of 6 randomized trials showed that significantly fewer pts treated with the GnRH receptor antagonists, degarelix, had a CV event or death compared with pts receiving a GnRH receptor agonist. In those studies showing an increased CV risk, Androgen-Deprivation Therapy (ADT) was primarily with GnRH receptor agonists. The mechanistic differences between GnRH antagonists and agonists, including testosterone surge and time to suppression at initiation, effect on follicle-stimulating hormone and on GnRH receptors e.g. T-lymphocytes in atherosclerotic plaque, raises the possibility of different CV risk profiles. The PRONOUNCE trial is the first to prospectively assess whether a GnRH agonist/antagonist can worsen pre-existing CVD; assess the impact of GnRH agonist/antagonist on CV risk biomarkers; and effects on the immune system. Methods: PRONOUNCE is a multi-center, randomized, controlled trial of 900 men with pc and concomitant CVD, assessing adjudicated MACEs, i.e. myocardial infarction (fatal, non-fatal), stroke (fatal, non-fatal), or death in pts randomized 1:1 to either degarelix or leuprolide according to label recommendations for up to one year. Eligibility include pre-defined CVD, metastatic or locally advanced pc; high-risk disease with plan for definitive radiation therapy (RT); recurrence after local therapy with PSA doubling time < 12 months; or salvage RT with neoadjuvant/adjuvant ADT for at least 12 months. Serum samples are collected for the analysis of various CV, inflammatory, and immune biomarkers. The primary endpoint will be based on Kaplan-Meier estimator of survival function and stratified for age group and region. Interim analysis is scheduled when 50% of MACE events have occurred allowing the DSMB to recommend for sample size correction. Clinical trial information: NCT02663908.

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Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage II/III ovarian, tubal and peritoneal cancers in phase III randomized trial (JCOG0602). Two preceding studies, EORTC55971 and CHORUS demonstrated non-inferior overall survival (OS) of patients treated with NAC. We have already reported high invasiveness of NAC setting treatment (NACT) compared to PDS setting treatment (PDST) in analysis of short-term outcomes of JCOG0602. This is a final analysis including primary endpoint of OS. Methods: Target cancer was diagnosed by 1) imaging studies (CT and/or MRR), 2) cytology of ascites, pleural effusions or fluids obtained by tumor centesis, and 3) CA125 > 200 Ul/ml and CEA < 20 ng/ml. Patients were randomized to PDS arm (PDS followed by 8 cycles of paclitaxel and carboplatin, i.e. TC regimen) and NAC arm (4 cycles of TC, interval debulking surgery [IDS], 4 cycles of TC). Planned sample size was 300 with 3-year OS of 25% in PDS arm, 30.3% in NAC arm and non-inferior margin of hazard ratio (HR) of 1.161 (these correspond to median OS of 18 months in PDS arm, 20.9 months in NAC arm and non-inferior margin of 2.5 months), one-sided alpha of 5% and 80% power. Results: From Nov 2006 to Oct 2011, 301 patients (149 PDS arm and 152 NAC arm) were randomized. Median OS was 49.0 months in PDS arm and 44.3 months in NAC arm. HR was 1.052 (90.8% CI: 0.85-1.326) and one-sided non-inferior margin of hazard ratio was 0.24. Median progression-free survival was 15.1 months for PDS arm and 16.4 months for NAC arm (HR: 0.987 [95%CI: 0.774-1.259]). In PDS arm 147/149 underwent PDS. 49 of them and 130/152 in NAC arm underwent IDS. Complete resection was achieved in 12% (171/147) of PDS and 31% (45/ 147) of IDS in PDS arm and in 64% (93/152) of IDS and 63% (92/147) of PDS in PDS arm and in 82% (107/130) of IDS in NAC arm. Conclusions: The non-inferiority of NAC arm was not confirmed and NACT cannot be always a substitute for PDST. Further studies may be necessary to demonstrate a role of NACT for more limited target.

Conclusions:

First Author: Daniel Jacob Margul, Northwestern University, Chicago, IL

Background: Surgery is the primary treatment modality for early cervical cancer. Compared to open (ORH), a robotic (RRH) or laparoscopic (LRH) approach to radical hysterectomy may have decreased morbidity, but the influence of surgical approach on survival, specific perioperative complications, and costs is unknown. Methods: The 2010-2013 National Cancer Database (NCDB) was used to evaluate the 5-year survival (SYS) of women with stage IB1 cervical squamous cell carcinoma or adenocarcinoma after radical hysterectomy performed open or by minimally invasive surgery (MIS). Survival times were estimated with the Kaplan-Meier method. Multivariable Cox proportional-hazards model (CPH) was used to adjust for measured confounders. The 2010-2015 Premier Healthcare Database was used to compare complications, length of stay (LOS), readmission rates, and hospitalization costs between ORH, RRH, and LRH. All p-values are two-sided. Results: From the NCDB, 982 and 910 women underwent ORH versus MIS radical hysterectomy, respectively. Women with a tumor size ≥ 2 cm who underwent MIS radical hysterectomy had decreased survival compared to women who underwent ORH (SYS: 95% CI: 81.3% [75.6%, 87.3%] versus 90.8% [87.7%-93.9%]; hazard ratio (HR) CI: 0.214 [1.36-3.38], P < 0.001). From Premier, 2830 women had radical hysterectomy: 45.1% (1277) ORH, 48.9% (1384) RRH, and 6% (169) LRH. ORH was associated with longer LOS compared to RRH or LRH (days, median: IQR). ORH 3 (3-5), RRH 1 (0-2), LRH 0 (0-2), P < 0.001). ORH also had a higher composite complication rate than RRH or LRH (ORH 44.9%; RRH 13.9%; LRH 12.4%, P < 0.001), with increased bowel injuries, infections, electrolyte or fluid disorders, transfusions, and ileus (all P < 0.001) associated with ORH. Thirty-day readmission rates were 0.6% for ORH (CI: 0.23%, RRH 1.4%, LRH 1.8%, P = 0.17). Total surgical and hospitalization costs favored MIS (P < 0.001 between groups) with median (IQR) values: ORH $12080 (8957-16052), RRH $11562 (8636-14600), LRH $9649 (7478-13010). Conclusions: MIS is associated with decreased morbidity and costs. However, among women with ≥ 2 cm stage IB1 cervical cancer, MIS was associated with significantly decreased survival.

Zoptec: Phase III randomized controlled trial studying zoptarelin as second line chemotherapy for advanced endometrial cancer (NCT01767155). First Author: David S. Miller, The University of Texas Southwestern Medical Center, Dallas, TX

Background: Zoptarelin (AEZS-108, AN-152, ZEN-008) is a luteinizing hormone-releasing hormone (LH-RH)-cytotoxic hybrid molecule composed of doxorubicin chemically linked to the carrier molecule D-Lys6-LHRRH. The primary objective of this study was to compare the overall survival (OS) of patients treated with zoptarelin vs doxorubicin. The secondary objectives included comparing efficacy based on progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR), and safety. Methods: In an international multi-center trial, patients with advanced, recurrent, or metastatic endometrial cancers who had failed prior platinum and taxane therapy were centrally randomized 1:1 to zoptarelin (267mg/m2) or doxorubicin (60mg/m2), I.V. every 21 days for up to nine cycles. Results: Zoptarelin was given to 256 patients and doxorubicin to 255 for a median of 5 vs 4 cycles respectively. The median OS for patients treated with zoptarelin was 10.9 months compared to 10.8 months for patients treated with doxorubicin (HR = 1.06; 95%CI: 0.87, 1.30). PFS was 4.7 months for both (HR = 0.89, 95%CI: 0.71, 1.11). ORR was 12% vs 14% and CBR was 54% vs 52% (p = NS). The most common grade > 2 adverse events were Neutropenia 47% vs 45%, Leukopenia 21% vs 18%, and Anemia 20% vs 15%. Febrile neutropenia was seen in 9% vs 4%. Absolute decline of LVEF from baseline of > 15% or absolute value < 45% was found in 7% vs 13%. Conclusions: Zoptarelin did not improve OS, PFS, ORR, CBR, or adverse events compared to doxorubicin as second line therapy for advanced endometrial cancers. Clinical trial information: NCT01767155.
Phase I trial of olaparib (PARP inhibitor) and vistusertib (mTORC1/2 inhibitor) in recurrent endometrial, ovarian and triple negative breast cancer. 

First Author: Shannon Neville Westin, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: We sought to determine the recommended phase II dose (RP2D) of olaparib (O) and vistusertib (V) and evaluate molecular markers of response. Methods: Two oral schedules for V were explored with O tablet BID. Arm 1: BID continuous (5 dose levels (DL)) and Arm 2: BID 2 days on/5 days off (4 DL). Clinical benefit rate (CBR) was defined as objective response or stable disease ≥6 cycles by RECIST 1.1. Patients (pts) were evaluable for response if they received at least 1 cycle (28 days). An expansion phase (n = 30) was performed at RP2D of Arm 2 with biopsies at baseline and 28 days. Results: 74 pts were enrolled, 8 with BRCA mutation (11%). Median prior therapies was 4 (1-8). There were 2 DLts on Arm 1 at DL 5 (O 300mg/V 50mg; G4 thrombocytopenia, G3 allergic reaction). There were 3 DLts on Arm 2. 2 DLts at DL 1 (O 100mg/V 125mg; G3 neutropenia >7 days (n = 1); G3 hyperglycemia (n = 1) and 1 DLt at DL1b (O 200mg/V 100mg; G3 fatigue). RP2D of Arm 1 was O 200mg/V 50mg. RP2D of Arm 2 was O 300mg/V 100mg. Most common adverse events (≥20%) were nausea (84%, G3/4 4%), anemia (93%, G3/4 15%), hypertension (76%, G3/4 3%), fatigue (73%, G3/4 11%), leukopenia (55%, G3/4 9%), increased creatinine (50%, G3/4 0%), headache (42%, G3/4 0%), vomiting (41%, G3/4 5%), hypercholesterolemia (41%, G3/4 0%), diarrhea (39%, G3/4 0%), hypertriglyceridemia (38%, G3/4 1%), thrombocytopenia (38%, G3/4 14%), mucositis (28%, G3/4 3%), transaminisits (28%, G3/4 3%); obstruction (27.5%, G3/4 1%), and pain (28%, G3/4 1%). Of 64 evaluable pts, RR was 19% and CBR 37%. In Arm 2, RR was 31%, 15%, and 8% for endometrial, ovarian and breast cancer, respectively. Among 6 endometrial pts assigned to CHEMO never received treatment. Among the 17 pts treated with at least one cycle of CHEMO grade 3 or 4 toxicities were observed in 47%; among 18 pts assigned to O, 1 had grade 3 hypertension. There were 6 deaths, (5 - CHEMO, 1-OBS), all due to disease. Over the limited mean survival time (RMST) for OS in the CHEMO arm was estimated to be 34.3 mos (95% CI: 25.3 mos – 43.3 mos); RMST for OS in the OBS arm was estimated to be 46.4 mos (95% CI: 43.6 mos – 49.1 mos). There were 8 recurrences in each arm. Over 24 mos, the RMST for RFS in the CHEMO arm was estimated to be 14.1 mos (95% CI: 12.1 mos and 17.2 mos) and the RMST for RFS in the OBS arm was estimated to be 14.6 mos (95% CI: 10.3 mos – 19.0 mos). The difference in RMST comparing the CHEMO arm to the OBS arm was estimated as 3.4 mos (95% CI: -2.4 mos – 9.3 mos). Neither survival outcome comparison is considered statistically robust due to the limited sample size and number of events. Conclusions: Despite an international collaboration to answer the critical question of the role of adjuvant chemotherapy in early-stage uterine LMS, this study was closed for accrual fidelity. While sample size and number of events preclude robust statistical comparison, observed OS and RFS data do not suggest superior outcomes for patients treated with adjuvant chemotherapy. Clinical trial information: NCT01533207.

Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer: a phase I trial of olaparib (PARP inhibitor) and vistusertib (mTORC1/2 inhibitor) and evaluate molecular markers of response. The randomized phase 3 trial MITO16B-MaNGO O2V28-ENGT OV17. First Author: Sandra Pignata, Istituto Nazionale Tumori “Fondazione G.Pascale” – IRCCS, Naples, Italy

Background: Bevacizumab (BEV) is approved in recurrent ovarian cancer (rOC) for patients not previously treated with the drug. Our study aimed at evaluating whether the addition of BEV to a platinum-based chemotherapy protocol would prolong survival (PFS) for rOC patients who had previously received it during first line. Methods: FIGO stage IIIb-IV rOC patients relapsing at least 6 months after last dose of platinum, who had received BEV during first-line treatment, ECOG PS≤2, were randomized to 6 cycles of platinum-based doublets (carboplatin/paclitaxel or carboplatin/gemcitabine or carboplatin/PDL) with or without BEV administered concomitantly with chemotherapy and as maintenance until disease progression. The primary endpoint is PFS. With 90% power in detecting a 0.67 HR, with 2-sided α error 0.05, 265 events were needed. All efficacy analyses are done on an intent-to-treat basis. PFS and OS curves are estimated by Kaplan-Meier method, and compared with a two-sided log-rank test. Toxicity is graded according to NCI-CTCAE v 4.0. Results: 405 pts were enrolled. Median age was 61; 64% of patients had progressed ≥12 months after last dose of platinum and 72% of patients after completion of first-line BEV maintenance. With a median follow-up of 20.3 months, 304 PFS events and 147 deaths were recorded. Median PFS was 8.8 months and 11.8 months without and with BEV, respectively (HR 0.51, 95%CI: 0.41-0.64, p < 0.001). Median OS was 27.1 months and 26.7 months without and with BEV, respectively (HR 1.00, 95%CI: 0.73-1.39, p = 0.98). Severe (≥3) hypertension (27.5% vs 9.7%, p < 0.001) and proteinuria (4% vs 0, p = 0.007) were more frequent with BEV. Conclusion: This study shows that for rOC patients previously treated with BEV in first line relapsing ≥6 months after last platinum, rechallenge with BEV in combination with platinum-based doublets is associated with a significantly prolonged PFS, with no unexpected toxicity. Supported by Roche. Clinical trial information: NCT01802749.

First Author: Julia Elizabeth Wolfe, University of California, Irvine, Orange, CA

Background: Acquired drug resistance remains the greatest clinical hurdle in advanced ovarian cancer suggesting that effective maintenance therapies are lacking. We evaluated cost-effectiveness of available strategies, adjusting for pre-treatment medication costs, infusion center charges, and costs of managing adverse events. Methods: Registration trial data was used to obtain toxicity and median PFS for a) paclitaxel (GOG 212); b) bevacizumab (GOG 218, ICON 7, OCEANS, GOG 213); c) niraparib (NOVA), olaparib (SOLO-2), rucaparib (ARIEL-3); and d) pembrolizumab. Because anti-angiogenesis therapy was studied in different populations, each trial was modeled separately. As phase III randomized trials involving checkpoint inhibition in ovarian cancer are not mature, data for pembrolizumab (available via agnostic indication) were obtained from the phase IB ovarian cohort of KEYNOTE-028. Costs of germline/somatic BRCA testing and those associated with manage-ment of neuropathy and immune-mediated adverse events, including endo-crinopathies, also factored into the model. Utilizing a Markov chain, patients transitioned through response, hematological and non-hematological complications, progression, and death. Using Medicare data, the costs of medications and managing toxicities were estimated. Incremental cost-effectiveness ratios (ICER) and quality of adjusted life-months gained were determined for each therapy. Results: Maintenance paclitaxel was most cost-effective at $870/PFS month. Expected costs of PARPi (PARPi(s)) prior to progression were approximately $471,989 (18.8x paclitaxel, 6.9x pembrolizumab, and 2.2-2.7x bevacizumab). Comparing pembrolizumab to PARPi(s) in BRCA-deficient patients, anti-PD-1 maintenance yielded ICERS per month of life gained of $20,032 (niraparib), $18,444 (rucaparib), and $17,520 (olaparib). Conclusions: Using PFS as the benchmark, high costs of maintenance PARPi(s) in non-germline BRCA-mutated settings may not mitigate the costs of treatments that may manifest with maintenance chemotherapy/VEGF inhibition. In terms of economic toxicity, the current trend to study novel combinations is problematic.


First Author: Julia Elizabeth Wolfe, University of California, Irvine, Orange, CA

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Association of high tumor mutation (TMB) with DNA damage repair (DDR) alterations and better prognosis in ovarian cancer. First Author: Wenjuan Tian Department of Gynecologic Oncology, Shanghai University Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Defects in DNA damage repair (DDR) system may lead to genomic instability and manifest as increased tumor mutation burden (TMB) in multiple types of cancers. But the prognostic value of TMB and association between DDR and TMB in ovarian cancer is still unclear. Methods: Whole-exome sequencing data of 434 ovarian tumors from The Cancer Genome Atlas (TCGA) and next generation sequencing (NGS) data of 93 ovarian tumors from 3D Medicines were analyzed to explore the association between 21 cancer-related DDR genes and TMB, defined as number of somatic non-synonymous mutations. We also performed analysis of clinical data from TCGA to identify the impact of TMB on ovarian cancer prognosis. Results: 27.4% of ovarian tumors in TCGA and 40.9% in 3D Med harbored at least one DDR alteration. The most frequently mutated genes were POLE (21.1%), BRCA1 (5.1%), BRCA2 (4.1%), ATM (3.0%), FANCA (2.5%), PALB2 (2.3%), FANC D2 (2.1%), and ATR (2.1%) in TCGA, and BRCA1 (12.9%), BRCA2 (10.8%), ATM (5.4%), RAD51 (3.2%), BRIP1 (3.2%), FANCD2 (3.2%), and PALB2 (3.2%) in 3D Med. Any DDR alteration was significantly associated with higher TMB in both TCGA (P < 0.00) and 3D Med (P = 0.021). Any two DDR gene alterations were associated with even much higher degree of TMB in both TCGA (P < 0.00) and 3D Med (P = 0.03) compared to without DDR alterations. Co-mutations of DDR genes and any DDR significantly associated with higher TMB in both TCGA (P < 0.00) and 3D Med (P = 0.02). Prognosis analysis was performed on patients from TCGA. High TMB (cut off as median) was associated with significantly longer DFS (14.6 vs. 14.1, HR 0.83, P = 0.04) and OS (41.0 vs. 32.1, HR 0.77, P < 0.00). Moreover, median OS was longer in patients with DDR alterations (19.2m and 16.7m (P = 0.07). Median OS was 54.6m and 41.5m respectively (P = 0.002). Conclusions: DDR deficiency is prevalent in ovarian cancer and associated with high TMB. High DDR was associated with longer DFS and OS in ovarian cancer patients. Our results suggest that DDR alteration can be considered as a biomarker that can be used to predict DFS and OS in ovarian cancer patients. High DDR alteration is associated with a better outcome for ovarian cancer patients. It may also help to select patients who are likely to benefit from immunotherapy.

Apatinib, a novel VEGFR inhibitor, combined with oral etoposide in patients with platinum-resistant or platinum-refractory ovarian cancer: A single-arm, open-label, phase 2 study. First Author: Chunyan Lan, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Anti-angiogenic therapy combined with chemotherapy could improve the outcome of platinum-resistant ovarian cancer. Apatinib is an oral tyrosine kinase inhibitor (TKI) that selectively inhibits VEGFR2. We investigated the efficacy and safety of combination of apatinib and oral etoposide, which has the advantage of home administration without an infusion pump and hospitalization, in patients with platinum-resistant or platinum-refractory ovarian cancer. Methods: In this phase 2, single-arm, open-label study, we included patients aged 18-70 years with platinum-resistant or platinum-refractory ovarian cancer. Patients received oral etoposide 50 mg on days 1 to 14 in a 21-day cycle for a maximum of six cycles. In addition to the chemotherapy, apatinib 500 mg was administered orally once daily. The primary endpoint was objective response rate by RECIST version 1.1. A Simon two-stage design was employed. This study was registered with ClinicalTrials.gov, number NCT02867956. Results: Between Aug 10, 2016 and Nov 9, 2017, 35 patients were enrolled. At data cutoff (Dec 31, 2017), 20 (57.1%) of 35 patients had discontinued study, and 15 (42.9%) patients remained on treatment. The reasons for treatment discontinuation included disease progression (n = 10), adverse events (n = 4), consent withdrawal (n = 2), lost of follow-up (n = 2), and others (n = 2). Objective responses were achieved in 19 (54.3%; 95% CI: 36.6-71.2) of 35 patients and disease control was obtained in 30 (85.7%; 95% CI: 69.7-95.2) patients. The median progression-free survival was 8.1 months (95% CI: 2.8-13.4), The most common grade 3 or 4 adverse events were neutropenia (41.2%), fatigue (32.4%), anemia (29.4%), and mucositis (23.5%). No treatment-related death was recorded. All of the adverse events were manageable. Dose reductions occurred in 82.4% of the patients for apatinib and 76.5% of the patients for oral etoposide. Conclusions: The combination of apatinib with oral etoposide shows promising activities and manageable toxicities in patients with platinum resistant or platinum-refractory ovarian cancer, and warrants further study in phase 3 trials. Clinical trial information: NCT02867956.

Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). First Author: Anna Fogotti, Policlinico A. Gemelli Foundation, Rome, Italy

Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). We investigated whether NACT was superior to PDS in terms of PFS and postoperative morbidity in AEOC patients, endowed with high tumor load (HTL), in a single Institution committed toward maximal surgical effort. Methods: This was a superiority, randomized phase III trial registered on clinicaltrials.gov (No. NCT01461850). Tumor load was assessed by a laparoscopy predictive index (PI; Fogotti score). Women included had stage IIIC-IV disease and PI between 8 and 12 (HTL). They were randomly assigned (1:1 ratio) to undergo either PDS followed by adjuvant chemotherapy, or NACT followed by interval debulking surgery (IDS) and chemotherapy. Carbo-taxol based chemotherapy was performed in both arms. Co-primary outcome measures were PFS and postoperative complications; secondary outcomes were OS, and quality of life (QoL). Results on postoperative complications and QoL were previously published. Survival analyses were performed on intention-to-treatment analysis (ITT), using Kaplan-Meier method. Results: From October 2011 to November 2016, 171 women were randomly assigned to PDS (n = 84) vs. NACT (n = 87). All were included in the ITT analysis. Overall median FU was 42 months (95% CI: 30-50 months). As of March 11, 2018, 37 (80.1%) patients in PDS and 74 (85.2%) in NACT had died. There was no significant difference for PFS between patients who underwent PDS vs. NACT (15 vs. 14 months) (HR = 1.06, 95% CI: 0.77-1.46; p = 0.72 log-rank test). Median OS was 41 months in the PDS arm and not reached in the NACT arm. Eighty-four women had PDS and 74 had IDS. Optimal residual tumor (≤1 cm) was obtained in 76% (26/34) of cases in PDS and 81% (60/74) in NACT (p = 0.22). Seven (5.3%) deaths for post-operative complications were recorded in the PDS vs. 0 in the NACT arm (p = 0.01). Conclusions: NACT was not superior to PDS in terms of PFS for AEOC patients endowed with HTL receiving maximal surgical effort. Clinical trial information: NCT01461850. Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
cycles of carboplatin (AUC 6) IV and paclitaxel (175 mg/m² BSA) IV in incompletely resected stage III or stage IV ovarian cancer received six 21-day cycles of carboplatin (AUC 6) IV and paclitaxel (175 mg/m² BSA) IV chemotherapy alone (control) vs chemotherapy plus BEV (15 mg/kg body weight) IV cycles 2-6 (BEV-initiation) vs chemotherapy plus BEV cycles 2-2 (BEV-throughout). OS was analyzed in the intention-to-treat (ITT) population. The database was locked on Jan. 17, 2018 at a median follow-up of 102.9 months. Results: After 1,491 (79.6%) deaths, 204 patients (10.9%) are alive with a progression-free event, and 253 patients (13.5%) are alive with a first line chemotherapy completion. HR 0.717; 95% CI, 0.625-0.824; p = 0.0011. The final OS analysis was conducted after 494 (89.7% of the planned 551) events occurred. OS was 59.1 months in PZ and 64.0 months in placebo. The HR was 0.960 (95% CI: 0.805, 1.145), and the median OS was 59.1 months in PZ and 64.0 months in placebo. The HR was 0.960 (95% CI: 0.805, 1.145), and the median OS was 59.1 months in PZ and 64.0 months in placebo. For the East Asian patients, similar to the first three OS IA, a numerical negative trend was observed favoring placebo (HR = 1.332, 95% CI: 0.863, 2.064). Exploratory analyses revealed a trend for a worse survival in patients with stage IV disease compared to stage III (HR 0.892, 95% CI: 0.760, 1.048). Conclusions: The advantage from BEV when administered with and following front-line chemotherapy. Clinical trial information: NCT00262847.

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Conclusions:

ARID1A and BRCA1 Mut were identified (9% of OC) and all four were conserved between trend towards inferior PFS in NAC group. There was no statistically significant CRT alone in the treatment of LACC, which is probably associated with the that NAC is associated with inferior complete RR in comparison with standard gains; 5 losses). 36 (82%) OC had (range 1-7) groups. There was a median of 2 Mut/per OC sample (range 0-5), median number of treatments was 3 for the PR (range 1-13) and 2 for the RR tumors demonstrated serous histology (31/70%). Between sample pairs the was diagnosed at a median age of 57.3 yrs (range 34.5-76.9 yrs). Most tumors demonstrated serous histology (31/70%). Between sample pairs the median number of treatments was 3 for the PR (range 1-13) and 2 for the RR (range 1-7) groups. There was a median of 2 Mut/per OC sample (range 0-5), with a minority (60/122) with losses and 60 (50%) with gains; 5 losses). 36 (82%) OC had TP53 and all were concordant. Four BRCA1 Mut were identified (9% of OC) and all four were conserved between sample pairs. dMUT were identified in ARID1A for 4 (9%) patients and RB1 for 2 (0%). No dMUT were targetable with FDA-approved therapies, but could influence future clinical trials. We conducted a trial to investigate if NAC with cisplatin and gemcitabine followed by standard CRT is a matter of debate. We conducted a trial to investigate if NAC with cisplatin and gemcitabine followed by CRT would improve outcomes. Methods: LACC pts (FIGO IIB-IWA) were randomized to 3 cycles of NAC with cisplatin 50 mg/m² D1 and gemcitabine 1000mg/m² D1 and D8 followed by standard CRT with weekly cisplatin 40mg/m²/w/6w plus pelvis radiotherapy (50.4Gy) followed by brachytherapy (BCT) or to the standard CRT and BCT alone. Progression-free survival (PFS) in 3 years was the primary endpoint. Secondary endpoint was response rate (RR), overall survival (OS) and toxicity. Kaplan-Meier method was used for survival analysis and curves were compared using log-rank test. RR was evaluated using chi-square test Results: Between July 2012 and July 2017, 107 pts were randomized. Pts characteristics were similar between groups. Median age was 47 years. The majority of the patients had squamous cell carcinoma (87.8%), and FIGO stage IB (42.9%) or IIIB (44.8%). Median follow up was 25.5 months. PFS rates at 3 years were 41.1% (CI 95% 26.5-55.5%) in NAC group and 59.6% in the CRT alone group (CI 95% 42.5-73.1%), with an absolute difference of 18% (HR 1.48, CI 95% 0.86-2.82, p = 0.13). OS rates in 3 years were 74.2% (CI 95% 63.8-84.7%) and 69.9% (CI 95% 65.2-91.1%), respectively (HR 1.64, CI 95% 0.71-3.77, p = 0.23). CRT alone had superior complete response (54% NAC vs 82% CRT alone, p = 0.002). No difference was seen in overall RR (92.7% NAC vs 94% CRT alone, p = 0.77). QoL improved after treatment in both groups when compared with baseline. Conclusions: This study showed that NAC and CRT were both effective but the former was associated with less toxicity. CRT alone in the treatment of LACC, which is probably associated with the trend towards inferior PFS in NAC group. There was no statistically significant difference in OS. Clinical trial information: NCT01973101.
Phase II clinical trial of eribulin (E) in advanced/recurrent cervical cancer. First Author: Jocelyn Garcia, Los Angeles County Hospital/University of Southern California, Los Angeles, CA

Background: Eribulin (E), a Halichondrin B analog from the marine sponge H. okadai has clinical efficacy in pretreated metastatic breast cancer patients (pts) and preclinical antitumor activity in squamous cell carcinoma (SCC). We conducted a 2-stage Phase 2 study of E in pts with advanced/ recurrent CC to examine its clinical activity and evaluate potential predictors of response.

Methods: Pts with advanced/recurrent CC after ≤ 1 prior CT regimens, measurable disease and ECOG performance status ≤ 2 were treated with E (1.4mg/m^2 IV day 1 and 8, every 21 days) with tumor assessments every 2 cycles. Primary endpoint was 6-month progression-free survival (PFS); secondary were best overall response (RECISTv1.1), toxicity (CTCAEv4.03), and overall survival (OS); and exploratory were associations of tumor and serum GRP78 as well as apoptosis/proliferation markers, unfolded protein response markers and tubulin subtypes with clinical activity. 30 evaluable pts would ensure 80% power when the true PFS=0.26 with a 1-sided α = 0.1 (H_0: PFS=0.30). A prespecified futility analysis gating stage 2 was set if 0/15pts showed at least SD at 6 months. Immunohistochemistry was performed on archival tumor samples and serial serum GRP78 levels were quantified by ELISA. Results: 32 pts were enrolled, median age 51 years (range 19-76), 22 had SCC, the median number of cycles was 4 (range 1-29), 26 pts had received prior pelvic irradiation. 29 pts had received prior CT with cisplatin/gemcitabine (12) and cisplatin/ paclitaxel/bevacizumab 2 or the most common one in each cohort. 6/3 pts (18.8%) achieved > PFS; median PFS is 2.6 months (95% CI: 1.2, 4.2). Median OS is 6.6 months (95% CI: 4.4, 12.7). Two pts were ineligible for response having received less than 2 cycles. Among the 30 evaluable pts, 6 (20%) had a partial response and 11 (37%) had stable disease (clinical benefit). This study has been abstracted in Gynecologic Cancer Journal (GCO) 2018. Grade 3/4 adverse events occurring in > 10 % of pts are anemia (12pts), neutropenia (7pts) and leukopenia (6pts). 1 pt was removed from study due to paresthesia after 7 cycles. Analysis of predictive correlates of response is ongoing. Conclusions: Eribulin shows evidence of activity in recurrent/ advanced CC with a favorable toxicity profile. Clinical trial information: NCT01676818.
5529 Poster Session (Board #256), Mon, 1:15 PM-4:45 PM
Comparison of different adjuvant therapy after radical surgery in early stage cervical carcinoma: A 3-arm randomized control study. First Author: He Hu, Sun Yat-sen University Cancer Center, Guangzhou, China.

Background: To determine whether the addition of concurrent chemother-apy (CCCT) or sequential chemotherapy (SCCT) to adjuvant pelvic radiotherapy (RT) will improve prognosis of patients with early-stage cervical carcinoma who had adverse pathologic factors. Methods: After radical surgery, patients with FIGO stage IB1 to IIA2 cervical cancer who had one or more of the following pathologic factors were recruited: lymph node metastases (LNMs), positive parametrium or margins (PPMs), lymphatic vascular space involvement (LVSI), deep invasion of cervical stroma (DIS). Eligible patients were randomized to the three groups. Group A underwent 50 GY pelvic RT alone. Group B received concurrent weekly cisplatin and RT (CCRT). Group C received paclitaxel and boul cisplatin every three weeks for two cycles before RT, followed by two cycles of chemotherapy (SCCRT). Results: From February 2008 to August 2015, a total of 1055 cases were randomized and eligible for evaluation, with 352 cases in group A, 348 in group B and 355 in group C. The disease-free survival (DFS) was 132.3% in month group C versus 94.4 month in group A and 92.3 month in group B (P = 0.047), and the corresponding overall survival (OS) was 140.5 month and 99.5 month (P = 0.20). In the intergroup analysis, a better DFS was found in group C (87 months) than the other two groups (79 month in group B and 69 months in group A). P < 0.05) among patients with LNMs or/and PPMs (high risk). While there was no significant difference in DFS was found between three groups in the patients with DIS and/or LVSI (intermediate risk). The disease-free survival (DFS) was 132.3% in month group C versus 94.4 month in group A and 92.3 month in group B (P = 0.047), and the corresponding overall survival (OS) was 140.5 month and 99.5 month (P = 0.20). In the intergroup analysis, a better DFS was found in group C (87 months) than the other two groups (79 months in group B and 69 months in group A). P < 0.05) among patients with LNMs or/and PPMs (high risk). While there was no significant difference in DFS was found between three groups in the patients with DIS and/or LVSI (intermediate risk), or in those patients who had indications for adjuvant treatment according to Sedlis Criteria. Alopoeia (87.1%, P < 0.05) and pelvic lymph cyst (14.1% P < 0.05) were significantly higher in group C. There is no significant difference of grade 3/4 hematologic and gastrointestinal toxicities between groups A, B and C. Conclusions: SCRT brought a better DFS in patients especially with high-risk cervical carcinoma. The sequential strategy may constitute an alternative treatment for the high-risk patients. However, CCRT and SCRT did not show survival benefit in patients with intermediate risk factors. Clinical trial information: NCT00086117.

5530 Poster Session (Board #257), Mon, 1:15 PM-4:45 PM
Association between pap abnormalities and HPV infection in participants in HPV vaccine clinical trials. First Author: Evan Meyers, Duke University, Durham, NC.

Background: Few studies have reported the burden of Pap abnormalities associated with the specific HPV types targeted by HPV vaccines. The purpose of this analysis is to estimate prevalence of HPV anogenital infection, by baseline Pap results, in participants of 3 worldwide trials of the quadrivalent HPV vaccine (placebo and vaccine groups, FUTURE I, II, III), and to estimate incidence of Pap abnormalities by HPV infection status at enrollment (placebo only, FUTURE I, III). Methods: Among 16,949 young women (YW) age 15-26 years (FUTURE I, II), and 3,674 adult women (AW) age 24-45 (FUTURE III), HPV prevalence (measured with PCR for 14 HPV types) was estimated at enrollment for women with: atypical squamous cells of undetermined significance (ASC-US) (n = 781 YW, 115 AW), low-grade squamous intraepithelial lesion (LSIL) (n = 993 YW, 115 AW), and high-grade squamous intraepithelial lesion or atypical squamous cells-cannot exclude HSIL (HSIL/ASC-H) (n = 157 YW, 30 AW).

Cumulative incidence of high-grade Pap abnormalities (HSIL/ASC-H) over 4 years (placebo only), by baseline HPV status, was estimated for 1,481 (YW) and 1,701 (AW). Results: Prevalence of any 9-valent (9v) vaccine type (6/11/ 16/18/31/33/45/52/58) among women with ASC-US, LSIL, or ASC-H/HSIL at enrollment was 47%, 67%, and 89%, respectively (YM), and 29%, 55%, and 93%, respectively (AW). Prevalence of any non-vaccine type (39/39/51/56/59) among women with ASC-US, LSIL, or ASC-H/HSIL was 32%, 64%, and 47%, respectively (YM), and 24%, 54%, 38%, respectively (AW). Over 48 months, cumulative incidence of high-grade Pap abnormalities (HSIL/ASC-H) among women with any high-risk 9v HPV type at enrollment was 8% (YW) and 6% (AW); cumulative incidence among women with no measured HPV infection at enrollment was 2% (YW) and 0.4% (AW). Conclusions: While the 9-valent vaccine will substantially reduce Pap abnormalities associated with HPV types that cause 90% of cervical cancers, non-vaccine HPV types also contribute to Pap abnormalities. These findings underscore the need for vaccination to protect against 9 HPV types, as well as the ongoing need for cervical cancer screening. Clinical trial information: NCT00090220.

5531 Poster Session (Board #258), Mon, 1:15 PM-4:45 PM
The clinical utility of prospective molecular characterization in advanced cervical and vulvovaginal cancer. First Author: Claire Frances Friedman, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: The molecular landscape of recurrent cervical and vulvovaginal cancers is undefined. We sought to determine the clinical impact of performing next generation sequencing (NGS) in these patients (pts). Methods: 82 pts consented to an IRB-approved protocol for the prospective sequencing of tumor and matched normal with MSK-IMPACT (NCT01775072), a NGS assay of up to 468 cancer-associated genes. Hotspot mutations were annotated using the OncoKB knowledge base (OncoKB.org). Results: We analyzed 90 samples. There was no significant difference in the incidence of mutations between primary (45%) and metastatic (met) (55%) specimens. In the 5 pts with mut met and 2 met with matched primary and met, the molecular profiling was identical in all but one pt that gained a TP53 mutation. We identified likely therapeutically actionable mutations in 44% of pts. Using OncoKB, we found that 8.5% of patients had a level 2B oncogenic alteration (See Table). Other alterations that have a lower level of clinical evidence included mutations in PIK3CA, ERBB2, AKT1, and FGFR3 (n = 29, 35%). In this cohort, 32 pts (39%) enrolled in at least one clinical trial, half of which (n = 15) were genotype-matched. Among these pts, 11 (73%) had stable disease or partial responses (PR). Overall 24% of patients received checkpoint blockade; two patients without evidence of somatic hypermutation achieved a PR. Conclusions: Prospective NGS of cervical and vulvovaginal cancer informs management of patients through the identification of potentially actionable mutations.

5532 Poster Session (Board #259), Mon, 1:15 PM-4:45 PM
Unexpected lymphatic drainage pathways of cervical cancer. Insights of the sentinel lymph node biopsy. First Author: Vincent Balya, Hospital Européen Georges Pompidou, Paris, France.

Background: Sentinel lymph nodes (SLNs) can be observed in various territories. An intraoperative surgical strategy is needed to find all relevant SLNs and limit the risk of missed SLN. The aim of this study was to define an anatomically based surgical algorithm to identify sentinel lymph nodes (SLNs). Methods: We analyzed the data of two prospective multicentric trials on SLN biopsy for cervical cancer (SENTICOL I and II) in women undergoing surgery for early-stage cervical cancer. SLN detection was realized with a combined labeling technique (Patent blue and radioactive tracer). Results: A total of 377 patients with 1186 intraoperative detected SLNs were analyzed. 201 SLNs were only blue, 291 SLNs were only hot and 685 SLNs were blue and hot. The SLNs were located in the ilio-obturator or external iliac area in 82.1% % of cases (974/1186) corresponding to the upper parametrical pathway (UPP) and 362 patients (96%) had at least one SLN in these areas. The SLNs were located in other unexpected areas in 17.9% of cases (212/ 1186). 130 patients (34.5%) had at least one SLN in an unexpected area and 14 (3.7%) patients had SLNs only in an unexpected area. 176 SLNs (14.8%) were located in the lower parametrical pathway (LPP) with 45 in the parametrium (3.8%), 109 in the common iliac area (9.2%), 22 in the promontory area (1.9%) whereas 36 SLNs (3%) were located in the infundibulo-pelvic pathway (IPP) with 26 in the paraaortic area (1.9%), and 13 in other areas (1.1%). The lymphatic drainage was exclusively through the UPP in 57.2% of cases (679/1186), through the UPP and another pathway in 40.8% of cases (484/1186) and exclusively through the LPP or the IPP in 1.9% of cases (23/1186). Conclusions: The SLNs search should begin in the ilio-obturator and external iliac area. Other territories should be explored in the absence of SLNs in this first level or as a complement. Pelvic dissection should be done only in case of absence of SLN in all territories.

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Evaluation of capecitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma: A retrospective study of the IRCCS National Cancer Institute of Milan. First Author: Domenica Lorusso, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Background: Cervical cancer is underrepresented in the gynecological clinical research. The objective of this retrospective study was to evaluate the activity and the safety of capecitabine in patients with platinum-pretreated recurrent cervical carcinoma. Methods: We performed a retrospective review of medical records from patients with advanced or recurrent cervical carcinoma pretreated with platinum-based therapy who received oral capecitabine at the Gynecological Units of the IRCCS National Cancer Institute of Milan (Italy). We used Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 to evaluate response to therapy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to evaluate adverse events. Results: From October 2013 to August 2017, we treated with oral capecitabine dose 29 patients with advanced or recurrence cervical carcinoma, already exposed to platinum. All patients receive a combination of carboplatin plus paclitaxel as first-line therapy for advanced/recurrent disease. At first capecitabine administration the median of previous treatments was 2 (range from 1 to 5). After three cycles of oral capecitabine the clinical benefit rate (CBR) was 62% with 41.3% of PR and 20.7% of SD. Grade 3 reported toxicity were 10% neutropenia and 3% hypersensitivity. CBR was 83.3% in adenocarcinomas versus 47% in squamous cell carcinomas. The most frequent grade 1 or 2 adverse events were fatigue (55%), hand-foot syndrome (38%) and diarrhea (24%). Conclusions: Our study suggests that oral capecitabine should be considered an active and safe treatment in patients with platinum-pretreated advanced or recurrent cervical carcinoma.

5534 Poster Session (Board #261), Mon, 1:15 PM-4:45 PM
Dose dense neoadjuvant chemotherapy (NACT) with carboplatin-paclitaxel in locally advanced cervical cancer. First Author: Domenica Lorusso, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Background: NACT followed by radical surgery is considered a valid therapeutic approach in locally advanced cervical cancer (LACC). The standard neoadjuvant treatment has not yet been identified. The most widely used regimen is the TIP (Cisplatin-Paclitaxel-Iflasfamid) combination which is effective but highly toxic. The aim of the study is to evaluate clinical (CR) and pathologic (PR) response to carboplatin-paclitaxel dose dense regimen as NACT in LACC. Methods: Consecutive patients with stage FIGO IB2-IIb were prospectively enrolled and treated with 3 cycles of neoadjuvant Carboplatin (AUC5) d1 and Paclitaxel (80 mg/m²) d1, 8, 15 q21 chemotherapy. After 4 weeks from completion of NACT, patients were submitted to radical hysterectomy and pelvic lymphadenectomy. Abdomino-pelvic MRI and gynaecological evaluation were performed at baseline and after 3 cycles in order to evaluate CR. PR was defined as follows: PR0: no residual disease, PR1: residual disease ≤ 3 mm, PR2: residual disease > 3 mm. A two-stage optimal Simon design was applied in order to detect a 60% of PR0+PR1: if at least 7 responses were registered among the first 16 patients, the trial would continue the enrolment. Results: 67 patients were enrolled in 40 months. After the enrollment of the first 16 patients, at least 7 responses were detected, so the trial proceed to the second step of enrolment. 11 patients (16%) went out from the study because of allergic reaction to the first paclitaxel administration and were not evaluable. 4 of the 56 patients experienced stable or progression disease and did not underwent surgery. The only grade 3-4 registered toxicity was neuropathy in 10.7% of patients. Patients characteristics and responses are reported in the table below. Conclusions: Combination of dose dense Carboplatin-paclitaxel resulted in encouraging clinical and pathologic responses and in a favourable toxicity profile. This scheme merits further evaluation in randomized clinical trials versus TIP.
5537 Poster Session (Board #264), Mon, 1:15 PM-4:45 PM

Evaluation of rucaparib in platinum-sensitive recurrent ovarian carcinoma (rOC) in patients (pts) with or without residual bulky disease at baseline in the ARIEL3 study. First Author: Carol Aghajanian, Memorial Sloan Kettering Cancer Center, New York, NY

Background: In ARIEL3, pts were randomized 2:1 (oral rucaparib 600 mg or placebo). Rucaparib significantly improved progression-free survival (PFS) vs placebo in all primary analysis groups (Coleman et al. Lancet, 2017;390:1949-61). An exploratory subgroup analysis of ARIEL3 pts with or without bulky residual disease (> 2 cm per blinded independent central review [BICR]) at baseline is reported. Methods: Pts were assigned to 2 analysis subgroups: with or without bulky residual disease at baseline. PFS was assessed in 3 predefined cohorts: BRCA mutant; homologous recombination deficient (HRD) (BRCA mut or BRCA wild type/high loss of heterozygosity); and intent-to-treat (ITT) population. Results: PFS data for each subgroup (visit cutoff date 15 Apr 2017) by status of bulky disease at baseline are summarized in the Table. Safety data were consistent with data reported previously. In the rucaparib arm, the most common grade 3+ treatment-emergent adverse event in pts with and without bulky disease was anemia (20.0% and 18.5%, respectively). Clinical trial information: NCT01968213. Conclusions: Rucaparib improved PFS vs placebo in all 3 predefined cohorts for both pts with and without bulky residual disease. PFS benefit with rucaparib was largest in pts with BRCA-mutant rOC.

5538 Poster Session (Board #265), Mon, 1:15 PM-4:45 PM

53BP1 as a predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. First Author: Rachel M Hurley, Mayo Medical School, Rochester, MN

Background: Poly(ADP-ribose)polymerase (PARP) inhibitors have shown substantial activity in homologous recombination (HR) deficient ovarian cancer and are undergoing testing in other HR-deficient tumors. For reasons that are poorly understood, not all patients with HRD cancers respond to these agents. Preclinical studies have demonstrated that changes in alternative DNA repair pathways affect PARP inhibitor (PARPi) sensitivity. As this has not previously been assessed in the clinical setting, we examined the relationship between HRD score, BRCA1 and BRCA2 mutation status, expression of NHEJ pathway repair proteins, and response of ovarian cancers treated with single agent PARPi. Methods: Archival biopsies from ovarian cancer patients undergoing treatment on a single-agent PARPi trial were stained for PARP1, RAD51, and multiple components of the nonhomologous end-joining (NHEJ) pathway, including 53BP1, KU70, KU80 and DNA-PKcs. Assays were validated by showing that the IHC signal was markedly attenuated with gene knockout or highly effective siRNA. Histochemistry-(H-) scores were determined for each repair protein in each sample. HRD status was determined from tumor DNA. Results: Responses to the PARPi ABT-767 were observed exclusively in ovarian cancers with an HR-deficiency. In this HR-deficient subset, 7 of 18 patients (39%) had objective responses, however actual HRD score did not further correlate with change from baseline tumor volume (r = 0.0499; p = 0.87). Conversely, in the HR-deficient subset, 53BP1 score showed a strong correlation with change from baseline tumor volume (r = 0.69, p = 0.004), followed by KU80 (r = -0.46; p = 0.08). Conclusions: Differences in complementary repair pathways, particularly in the NHEJ pathway, correlate with PARPi response of HR-deficient ovarian carcinomas. Among HR-deficient ovarian carcinomas, 53BP1 score demonstrated a strong correlation with the percent change of tumor volume.

5539 Poster Session (Board #266), Mon, 1:15 PM-4:45 PM

The impact of health related quality of life (HRQoL) on short term survival of recurrent ovarian cancer patients: Analysis of pooled data from the North-Eastern German Society of Gynecological Oncology (NOGGO) meta data base. First Author: Jaikl Sehoul, AGO and Charité Campus Virchow-Klinikum, Berlin, Germany

Background: The goal of this analysis is a predictive score (recurrent ovarian cancer survival score, NOGGO-ROCSurv score) using HRQoL and other risk factors to estimate the risk of 1-year mortality in recurrent ovarian cancer patients. Methods: The data of recurrent patients with baseline HRQoL assessment using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 were selected from the NOGGO data base. ROC analysis were used to evaluate the predictive value of the risk factors and to find cut off values. Multivariable stepwise logistic regression models for 1-year mortality were performed to identify risk factors and their weights for a risk score. Results: Out of 972 patients 808 (83.1%) had 1st, 145 (14.9%) 2nd, and 19 (2.0%) 3rd recurrence, most patients (814, 83.8%) with advanced tumor stage at first diagnosis, 918 (94.4%) with good performance status (PS). The median age was 61 years (range 25-84 years). 1-year survival rate was 67.1%. Nearly all HRQoL scales except cognitive functioning, sleep disturbance, financial difficulties and diarrhea showed predictive value for short term survival with an area under the curve (AUC) up to 62.6% for global quality of life (gQoL). The risk score included chemo therapy free interval (CTFI) < 1 year, PS > 3, gQoL < 25, fatigue > 70, Nausea > 25, age > 75 years, appetite loss > 25 and pre-existing cardiovascular disease (ordered from most to least important). The AUC for the risk score was 0.744 (95% CI 0.708–0.780), and the high risk group showed a positive predictive value of 84.5%, a negative predictive value of 72.5%, a sensitivity of 22.3%, and a specificity of 98.0%. Conclusions: HRQoL combined with other risk factors is predictive for 1-year survival. This risk score may help decision making for therapy and may be useful for stratification in randomized trials. But the identified patient group under risk is only small. So an improvement of the score is reasonable and a validation necessary.

5540 Poster Session (Board #267), Mon, 1:15 PM-4:45 PM

Methylated circulating tumor DNA as a potential marker of PARP inhibitor efficiency in BRCA mutated ovarian cancer patients. First Author: Karina Dahl Steffensen, Department of Oncology, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark

Background: The liquid biopsy has proven to be an excellent material for analysis of different circulating tumor markers, among which mutated tumor DNA (ctDNA) ranks high. Cancer specific ctDNA methylation can be used toquantitate tumor DNA and is a promising new approach for monitoring changes in tumor burden in response to therapy. Homeobox genes (HOX) constitute a family of transcription factors that involved in regulating differentiation and are expressed in normal adult reproductive tissue and methylation of the HOX9 gene has been observed in 95% of patients with high grade serous ovarian carcinoma. Treatment with PARP inhibitors has demonstrated considerable benefit in ovarian cancer (OC) patients but stratification of patients for PARP inhibitor (PARPi) treatment by BRCA status has proved suboptimal. The primary aim of the present study was to investigate if methylated HOX9 already at baseline, before initiation of single agent PARPi treatment could predict treatment efficacy in OC patients with platinum resistant or intermediate resistant relapse. Methods: Plasma from OC patients were retrieved at baseline before initiation of daily oral single agent Velparib as part of a phase II investigator initiated trial. DNA was purified from 4 ml plasma, bisulfite converted and analysed by droplet digital PCR with methylation specific assay for HOX9 and Albumin as reference. The fractional abundance of methylated HOX9 was calculated. CA125 was analysed according to international standard. Results: The phase II trial enrolled 32 patients of which 23 patients had methylated HOX9 at baseline. Patients with methylated HOX9 showed a worse progression-free survival (p = 0.046) compared to patients with non-methylated HOX9. In multivariate analysis HOX9 showed borderline significance (p = 0.056, HR 2.53 (95%CI: [0.98-6.51]) when correcting for age, performance status and platinum sensitivity. Baseline CA125 was not a predictor of PS. Conclusions: The data presented suggests circulating methylated HOX9 as a potential marker for prediction of efficacy of PARPi treatment. Clinical trial information: NCT01472783.
Potential impact of dietary intervention/counseling on survival in ovarian cancer patients: Results from an observational study. First Author: Jessica Michalak, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Ovarian cancer is the fifth leading cause of cancer death in women, and survival rates remain largely unchanged within the past forty years. Previous research suggests that dietary intervention may impact cancer development, prognosis, and survival. The purpose of this study was to determine if dietary intervention was associated with improved survival rates in ovarian cancer patients. Methods: A total of 183 women were enrolled in the cohort study at MD Anderson. Clinical data collected on a cohort of patients who received the dietary intervention including counseling and supplementation were compared to a cohort of contemporary controls and summarized using descriptive statistics. Survival was computed from the time of admission to time of death or loss to follow-up. The method of Kaplan-Meier was used to provide overall survival estimates at select points in time, and the Log-rank test was used to compare survival distributions between cohorts. Results: Estimates of overall survival for intervention (49) and control (125) patients were: 95.9% and 66.8% at 5-years; 87.1% and 34.0% at 10-years; and 76.7% and 22.9% at 15-years, respectively (Log-rank test P-value < .001). Control patients had over four times the risk of death relative to patients receiving intervention after adjusting for age at admission. Conclusions: Dietary intervention/counseling with supplementation may positively impact survival in women diagnosed with ovarian cancer. Although our findings inspire interest, a weakness was the study’s observational nature and the strong potential for confounding. A prospectively powered randomized clinical trial is warranted to validate these results.

Identification of outcome-correlated serum cytokine and chemokine clusters in ovarian clear cell carcinoma. First Author: Akira Tabuno, Center, Hidaka, Japan

Background: The standard of care in patients with advanced ovarian cancer is upfront surgery followed by chemotherapy. An interval debulking after 3 cycles of chemotherapy might be an alternative in selected patients. However, some patients attend a referral center after having received 5 or more cycles of neoadjuvant chemotherapy with persistent disease. So far, the role of primary surgery for persistent residual disease after 5 cycles of chemotherapy for primary advanced ovarian cancer is poorly defined. Methods: Retrospective analysis of the KEM hospital database 2011-2017 of patients with newly diagnosed advanced epithelial ovarian cancer and delayed cytoreductive surgery for persistent disease after a minimum of 5 cycles of chemotherapy. Results: 39 patients underwent delayed interval debulking, 92.3% had a complete resection. Intra-operatively, the median Peritoneal Cancer Index was 11. 35.8% underwent a bowel resection (5.1% had a protective stoma) and the median number of pre-OP cycles was 6 (range 5-8). Intra-operatively, the median Peritoneal Cancer Index was 11. 35.8% underwent a bowel resection (5.1% had a protective stoma) and the median surgical complexity score was 7 (2-16). The median duration of surgery was 285 minutes (range 80-510), complete resection was achieved in 84.6%. The rate of severe complications (Olivieri Dindo grade 3 or 4) was 23.1%; we observed no post-operative mortality. The median number of chemotherapy cycles after surgery was 2 (range 0-4). 15 (38.5%) patients received bevacizumab before cytoreductive surgery and 16 (41.0%) patients received maintenance therapy with bevacizumab post-operatively. The median DFS and OS in patients with complete resection was 17.2 and 49 months in contrast to only 6.4 and 14 months in patients with incomplete resection. Conclusions: Delayed interval surgery might be restricted to selected pts in whom the probability for achieving a complete resection is high. Patients in whom a complete resection could not be achieved show a very poor prognosis and it is likely that they rather experience harm than any benefit from surgery.

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A first-in-human study of monoclonal antibody GM102 in patients with anti-Mullerian-hormone-receptor II (AMHRII) positive gynecological cancers. First Author: Alexandra Leary, Gustave Roussy Cancer Campus, Villejuif, France

Background: AMH and its membrane receptor AMHRII induce regression of Mullerian ducts in the male embryo. AMHRII is constitutively expressed in ovarian granulosa tumors (GCT) and re-expressed in ~70% of gynecological tumors. GM102, a low-fucose IgG1 antibody, binds AMHRII and acts through macrophage engagement via CD16 high affinity binding, resulting in enhanced tumor phagocytosis. Methods: In the completed escalation part, AMHRII-positive ovarian, cervical and endometrial cancer patients (pts), with measurable disease, Performance Status ≤ 1 and adequate organ function, received GM102 1 to 20mg/kg every 2 weeks (q2w) then 7 and 10mg/kg weekly (qw) in 8 successive cohorts. Expansion phase will include granulosa, epithelial ovarian and cervical cancers. The objective was to determine a recommended dose (RP2D) from safety, pharmacokinetics, pharmacodynamics (PD) and GM102 anti-tumor activity (RECISt) and change in tumor growth rate (TGR = % change in tumor volume/month pre-treatment vs. after 2 cycles). PD included circulating immune cells (CIC) (ICOS, CD14, CD16, CD64, CD69) and in paired biopsies, macrophage (CD16, CD163, CD16) and T cell (CD3, CD4, CD8, FoxP3, Granzyme B) markers. Results: 27 pts with AMHRII+ gynecological tumors (including 4 GCTs) received 1 to 21 GM102 infusions. Terminal half-life was 130-200hrs. No dose limiting toxicity was observed. Treatment-emergent toxicities were mostly grade 1-2 (including rash, influenza-like symptom, 1 pt each). One pt had grade 3 fatigue, weight loss and available pts exhibited a decrease in TGR (45%-169%) under GM102. Among 4 CIC pts, 2 had a partial response and inhibit B decreased in 3. In CIC, T cell, monocyte and neutrophil activation was observed, and circulating CD16+ monocytes decreased suggesting possible recruitment to tumor site. In paired biopsies, CD16 expression increased in macrophages as well as Gm increased B suggesting GM102-induced cellular cytotoxicity. Conclusions: GM102 was well tolerated at all doses and schedules. RP2D includes 7mg/kg qw and 15mg/kg q2w. The encouraging PD and anti-tumor activity warrants further development of GM102, especially in the rare subtype of GCT. Clinical trial information: NCT02978755.
5545 Poster Session (Board #272), Mon, 1:15 PM-4:45 PM
Exploratory analysis of percentage of genomic loss of heterozygosity (LOH) in patients with platinum-sensitive recurrent ovarian carcinoma (OC) in ARIEL3. First Author: Ana Oaknin, Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: In ARIEL3, rucaparib significantly improved progression-free survival (PFS) vs placebo in all randomized patients, including patients with BRCA-mutant, BRCA wild-type/high-LOH (prespecified as ≥16% genomic LOH), or BRCA wild-type/low-LOH (< 16% genomic LOH) rOC (Coleman et al. Lancet. 2017;390:1949-61). This exploratory analysis evaluated the optimal cutoff for percentage of (% ) genomic LOH in BRCA wild-type rOC in ARIEL3. Methods: Genomic LOH of archival tumor tissue DNA was centrally assessed using Foundation Medicine’s next-generation sequencing-based assay (Cambridge, MA, USA). Treatment effect for investigator-assessed PFS was analyzed in BRCA wild-type rOC for the prespecified cutoff (16%) and across a range of cutoffs for % genomic LOH (5%–30%). Hazard ratios (HRs) were estimated using a stratified Cox proportional hazards model. Prognostic and predictive utility of % genomic LOH was assessed by comparing invPFS between and within the treatment arms. Results: In ARIEL3, 564 patients were randomized. Of the 368 patients with BRCA wild-type associated rOC, LOH was calculable for 319. Rucaparib significantly improved invPFS vs placebo between the 5% and 23% cutoffs for % genomic LOH. Using the prespecified cutoff (16%), the HR (rucaparib vs placebo) was 0.44 (95% confidence interval [CI], 0.29–0.66; P < 0.0001) for patients with high-LOH rOC. To further assess the % genomic LOH cutoff, we compared patients with high- vs low-LOH rOC across the range of cutoffs tested for % genomic LOH, including the prespecified cutoff of 16% for high LOH. The observance of significant differences between patients with high- vs low-LOH rOC in the rucaparib but not placebo arm suggests that genomic LOH is a predictive but likely not prognostic biomarker. Clinical trial information: NCT01968213.

5546 Poster Session (Board #273), Mon, 1:15 PM-4:45 PM
Effect of hypertension (HTN) on progression-free survival (PFS) in patients (pts) receiving front-line bevacizumab (BEV) for primary advanced ovarian cancer (OC) in the NOGGO single-arm OTILIA study: A post hoc analysis in 808 pts. First Author: Robert Armbrust, Campus Charité Mitte, Charité Centrum 17, Klinik f. Geburtsmedizin, Berlin, Germany

Background: The efficacy and safety of front-line BEV-containing therapy for OC were demonstrated in two phase III trials. At the 3rd interim analysis of OTILIA (NCT01697488) evaluating front-line BEV in German clinical practice, median PFS was 21.3 months. The potential association between HTN and PFS was explored in the present analysis. Methods: Pts newly diagnosed FIGO stage III–IV OC received the EU-approved BEV-containing regimen. In exploratory analyses, outcomes were analyzed according to the presence or not of HTN at baseline (BL). Cox regression models in each subgroup explored the effect on PFS of HTN developing (no HTN subgroup) or worsening (pre-existing HTN subgroup) during treatment in a time-dependent manner. Results: Of 808 evaluable pts, 406 had BL HTN and 402 did not. Pts in the HTN subgroup were generally older (median 71.8 vs 61.8 years in the subgroup without HTN) with a higher BMI (median 25.7 vs 23.1 kg/m²) and more likely to have diabetes (16% vs 5%). Median BEV duration was similar in the two subgroups (13.5 vs 13.3 months respectively). As of 31 Jan 2017, PFS events had been recorded in 364 pts (45%). Median PFS was 21.3 months in both subgroups. HTN worsened in 291 (72%) of 406 pts with pre-existing HTN and developed in 132 (33%) of 402 pts without BL HTN. Cox regression analysis suggested an association between the onset of HTN and shorter PFS in both subgroups (HR 2.16, 95% CI 1.39–3.00 in pts without BL HTN; HR 2.42, 95% CI 1.56–3.74 in pts with pre-existing HTN). Conclusions: These exploratory analyses suggested a detrimental effect of HTN on PFS in BEV-treated pts. Based on these observations, in pts with HTN and ongoing clinical benefit, it seems reasonable to continue BEV therapy if HTN is managed appropriately. As this was an exploratory interim analysis, the observed more favorable PFS in pts with HTN developing during BEV should be validated in further prospective trials. Clinical trial information: NCT01697488.

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5549  Poster Session  (Board #276), Mon, 1:15 PM-4:45 PM
Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-resistant ovarian cancer. Methods: Pts were administered mirvetuximab soravtansine (6 mg/kg; adjusted ideal body weight) in combination with bevacizumab (15 mg/kg) on Day 1 of a 21-day cycle. Responses were assessed according to RECIST 1.1 and adverse events (AEs) evaluated by CTCAE v4.0. Results: To date, a total of 51 pts have received combination therapy at this dose level: 11 in dose escalation; 40 during the expansion stage. Pts had a median age of 64 years and received a median of 3 prior lines of systemic therapy (range 1-8); 51% and 29% of pts had received prior therapy with bevacizumab or a PARP inhibitor, respectively. The four most commonly reported AEs were nausea, fatigue, diarrhea, and blurred vision (45-57% of pts), which were grade 1 or 2. The most common grade 3 AE was hypertension (8 pts - 16%). For the efficacy evaluable population (49 pts), objective tumor responses were observed in 19 pts for a confirmed overall response rate (ORR) of 39% and a median progression-free survival (mPFS) interval of 9.5 months (95% CI, 4.6-11). In a subset analysis of pts (n = 20) with < 3 prior therapies and medium to high FRa levels (i.e., > 50% of cells with > 2+ staining intensity) the ORR was 55% with mPFS not yet reached, with a median follow-up of 5.7 months (range 1.3-11.7). Updated results will be presented. Conclusions: The mirvetuximab soravtansine-bevacizumab combination continues to display a manageable safety profile in pts with platinum-resistant ovarian cancer. The encouraging efficacy results justify further exploration of this novel therapeutic combination in this difficult to treat population. Clinical trial information: NCT02606305.

5551  Poster Session  (Board #278), Mon, 1:15 PM-4:45 PM
METRO-BIBF-Phase II, randomised, placebo controlled, multicentre, trial of low dose (metronomic) cyclophosphamide (MCy) with or without nintedanib in relapsed ovarian cancer (ROC). First Author: Marcia Hall, Mount Vernon Cancer Centre, Middlesex, United Kingdom
Background: ROC patients (pts), heavily pretreated with IV chemotherapy (CT) are a heterogeneous group, median OS 3-9 mo. Oral MCy is well tolerated, avoids IV CT and has been shown to have clinical benefit. MCy has anti-angiogenic properties, inhibiting growth of tumour, stromal, and host vasculature. Augmentation with bevacizumab showed encouraging results in single arm studies. METRO-BIBF evaluated a novel combination of MCy with either placebo (P) or nintedanib (N)- oral inhibitor VEG/PDGFR tyrosine kinases. Methods: Eligible pts received ≥ 2 lines of CT; platinum-resistant/intolerant, ECOG score ≤ 2, life expectancy ≥ 6 weeks. MCy (100mg/d) was given continously with either N or P, to progression/ toxicity. No prior TKI permitted; pts had no prior CT. Results: 283 pts met inclusion criteria; of those 114 (40.3%) had complete resection. Previous reported bevacizumab signatures using 7 and 11 genes respectively did not predict residual disease in this cohort. Best Area under the Curve (AUC) for 7 gene signature was generated using LR 0.50 ± 0.05, while 11 gene signature had an AUC of 0.52 ± 0.04. Similarly, TCGA molecular subtype AUC = 0.56 ± 0.04, while independent de novo developed signature (AUC = 0.51 ± 0.04) and the total gene expression data set using all 21,000 genes (AUC = 0.55 ± 0.03) were not able to predict residual disease status. Conclusions: In contrast to previous findings, we were not able to predict residual disease using GE in tumour samples from the ROC-OVAR11/ICON7 obesity III trial. A standardised radical surgical approach resulting in a higher frequency of complete resection might allow detection of biologic factors responsible for sub-optimal debulking. The ongoing ACOG-OVAR TRUST trial might be able to address this important clinical question.

5554  Poster Session  (Board #279), Mon, 1:15 PM-4:45 PM
Facilitated referral pathway for genetic testing at the time of ovarian cancer diagnosis: Uptake of genetic assessment and testing and impact on patient-reported stress, anxiety and depression. First Author: Sarah S. Lee, New York University Langone Medical Center, New York, NY
Background: To determine if a patient-centered, facilitated genetics referral pathway whereby all women with newly-diagnosed ovarian cancer are pro-actively contacted by a genetics navigator (GN) for genetic assessment (GA) increases rates of GA and genetic testing (GT) uptake without increased patient-reported stress, anxiety or depression Methods: Patients with epithelial ovarian cancer were referred for GA by their gynecologic oncologist within six weeks of diagnosis. Patients were contacted by a GN and offered an appointment for GA and GT within six weeks of contact. English-speaking patients completed quality of life (QoL) instruments (Impact of Events Scale, State-Trait Anxiety Questionnaire, Hospital Anxiety and Depression Scale) immediately pre-and post-GA and 6-9 months later. Primary outcome was feasibility of this pathway as defined by presentation for GA or declining GA within 6 weeks of contact by a GN. Results: From 10/2015-12/2017, 88 patients were enrolled. Seventy-one (81%) patients had GA and 62 (70%, 87% of those who had GA) underwent GT. Median time from diagnosis to GA was 28 days (range 9-75). Among patient who underwent GT, 11 (18%) had a pathogenic mutation (BRCA1-6, BRCA2-4, MSH2-1) and 25 (40%) had a variant of uncertain significance. Forty-one patients completed QoL assessments which demonstrated mild to moderate stress, normal to clinically significant anxiety and borderline levels of depression. QoL assessments were not associated with the GT result and with no significant changes in stress, anxiety or depression when comparing QoL measurements for each patient obtained pre/post-GA and 6-9 months later. Conclusions: A facilitated referral to genetic counselors at time of ovarian cancer diagnosis is effective and efficient, resulting in GA in 81% of patients within 4 weeks of diagnosis, GT in 70% of patients and discovery of pathogenic mutations in 18% of those tested, and does not demonstrate a psychologic toll. Concern about emotional distress should not deter clinicians from early genetics referral as GT in this population can yield important prognostic and therapeu-tic information.
A phase I study of concomitant galinpepimut-s (GPS) in combination with nivolumab (nivo) in patients (pts) with WT1+ ovarian cancer (OC) in second or third remission. First Author: Rosalind Elith, MD. Cleveland Clinic Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: WT1 is highly expressed in serous ovarian cancer. GPS is WT1-targeting heteroclitic peptide tetrameric non-HLA-restricted vaccine, and has shown promising phase 2 activity in AML, mesothelioma and myeloma. Efficacy of GPS may be enhanced through checkpoint blockade, providing a rationale for combining it with anti-PD1 antibody, nivo. We conducted a phase I study to evaluate the safety and immunogenicity of the combination in WT1+ OC in remission. Methods: Pts with WT1+ OC in n = 23 remission were enrolled from 06/16-07/2017, and received GPS (800 mcg) x 6 total doses mixed with adjuvant (0.5 ml) and 70 mcg GM-CSF (all s.c. in extremities) and nivo 3 mg/kg IV q2wks over 12 weeks. DLTs were assessed using a DLTCAE criteria, with detection of > 2/10 DLTs deeming the combination unsafe. Treatment was continued until disease progression or toxicity. Immune responses (IgG & IgM WT1 antibody, T cell assays) induced by the combination were evaluated. The 1-year progression-free survival (PFS) rate, defined as the interval from start of preceding chemo to date of progression or death, is an exploratory objective. Results: n=11; Median age 61 yrs (41-76); 7 pts in 2nd and 4 pts in 3rd remission. 1 DLT (gr 3 myositis with myocarditis post GPS and nivo #2). Most common AEs were Gr ≥2 fatigue and injection site reactions. Immune Response Results: n=9; Serum levels of antigen-specific IgG (against both individual WT1 peptides in GPS and the full-length WT1) significantly increased in 86% of pts between study wks 6-27. Antigen-specific T cell responses to individual WT1 peptides were observed between 6-15 wks, primarily CD4 and to a smaller extent, CD8 T cells. 1yr PFS rate was 64% in the ITT analysis (7/11) and 70% (7/10) in pts who had > 2 GPS/nivo doses. Conclusions: Administration of GPS in combination with nivo was generally well tolerated and induced T- and B-cell immune responses, warranting further evaluation. The 1yr PFS rate compares favorably to historic rates of approximately 50% in comparable populations. Additional cohorts are planned to receive the current combination along with vaccination against additional tumor-associated antigens. Clinical trial information: NCT02737787.

Inter and intra-observer variability with the assessment of RECIST in ovarian cancer. First Author: Michelle K. Wilson, Auckland City Hospital, Auckland, New Zealand

Background: Measurement of response with RECIST is central to the interpretation of trial outcomes and relies upon accurate and reproducible uni-dimensional tumor measurements. This study assessed inter and intra-observer variability with assessment and selection of target lesions for RECIST in patients with ovarian cancer. Methods: Eight international radiologists measured 30 lesions at 2 discrete time points. Lesion measurements between radiologists were compared to assess inter-observer variability. Percentage difference between lesions was calculated. Measurements of the same lesion at two time points by each radiologist were used to assess intra-observer variability. Radiologists were also asked to select 2 target lesions for RECIST. Reproducibility of lesion selection based on size (peritoneal vs nodal vs visceral) was calculated. Results: 80 lesions were measured with a median size of 2.6 cm (range 0.8-9.5cm). Seventy-one lesions (89%) were 1.5cm or larger. Assessments at two time points were performed by 7 radiologists. Inter-observer assessment of a single lesion varied on average by 22% (range 5 to 68%). Measurements differed by ≥20% in 28% of visceral, 79% of nodal and 60% of peritoneal lesions. When measured by the same radiologist only 10% of lesions differed by ≥20%. Intra-observer measurements were less likely to vary by ≥20% (10 vs 54%; p < 0.0001). Radiologists were more likely to measure the same lesion with visceral (77% lesions, 100%; p = 0.01) and nodal (91/10; 90%; p = 0.01) lesions versus peritoneal lesions (5/14; 36%). When selecting 2 lesions for RECIST, the largest lesion was most consistently chosen (35/38 target lesions; 92%). When this was repeated, 5 of 7 radiologists (71%) chose the same lesions each time. Conclusions: RECIST underpins trial outcomes yet significant variability in tumor measurements was found in this study. These results suggest RECIST assessments by the same radiologist should improve consistency. Peritoneal lesions are a key site of disease progression in ovarian cancer yet these were the most inconsistent to select and had significant inter-observer variability in measurements. These factors need consideration as we strive to improve response assessment in clinical trials.

Characterization and predictors of long term (~10 years) survivors in NRG/GOG randomized clinical trials: Intraperitoneal and intravenous chemotherapy in stage III ovarian cancer patients. First Author: Michael Friedlander, Department of Medical Oncology, Prince of Wales Hospital, Sydney, New South Wales, Australia

Background: ~25% of patients with stage III OC are reported to be alive ≥ 10 years after diagnosis in registry studies. Some have long term disease-free survival (LTDFS) without recurrence and others have recurrent active disease but the proportions of each is unclear. We propose to determine the proportion, characteristics, and predictors of long term survival in patients with stage III ovarian cancer (OC) enrolled in clinical trials who are ≥10 years LTDFS. Methods: Data from 3 NRG/GOG trials (104, 114, and 172) which enrolled patients to intraperitoneal (IP) vs. intravenous (IV) chemotherapy were analysed. Demographics and clinic-pathologic characteristics of patients living ≥10 years were tabulated. Using a landmark approach at 10 years, Cox regression survival analysis was performed to evaluate independent prognostic factors that predict LTDFS. Results: Of 1,229 stage III OC patients, 18.8% (232/1229) were alive ≥10 years. Of these, 13.7% (n = 168) had LTDFS ≥ 10 years and 5.2% (n = 64) had recurrent disease. Compared to the overall study group, the LTDFS ≥10 years patient had a median age of 54.8 vs. 57.2 years (p < 0.001), gross residual disease after primary surgery 42.3% vs. 45.8% (p = 0.027); serous cell type 62.5% vs. 68.4%; endometrioid 14.3% vs. 9.4% (p = 0.035), well differentiated cancers 12.5% vs. 8.5% (p < 0.001), respectively. Of the LTDFS patients, 45.2% were treated with IP and 54.8% with IV chemotherapy (p = 0.3). Age (HR = 1.077; 95% CI = 1.03–1.12; p < 0.001) was the only independent prognostic factor for LTDFS ≥10 years on multivariate Cox analysis. Conclusions: Approximately 14% of stage III ovarian cancer patients were in LTDFS ≥10 years and an additional 5% were alive with recurrent disease. Younger age at diagnosis was the only independent prognostic factor for LTDFS ≥10 years. Further work is needed to understand characteristics and predictors of exceptional responders and whether they could be identified at initial diagnosis. 3. Baldwin et al Obstetrics & Gynecology: 2012; 120; 3: 612-618.

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5558 Poster Session (Board #285), Mon, 1:15 PM-4:45 PM
Predictive factors for prolonged response to olaparib as maintenance therapy in ovarian cancer patients with BRCA mutations. First Author: Sana Intidhar Labidi-Galy, Hopitaux Universitaires de Genève, Geneva, Switzerland
Background: To investigate clinical factors predictive for prolonged progression-free survival (PFS) in ovarian cancer (OC) patients carrying BRCA mutations and receiving olaparib as a maintenance therapy. Methods: Multicentric (7 cancer centers) international (France and Switzerland) retrospective study of OC patients having germline or somatic mutations of BRCA1/BRCA2 genes and treated with olaparib as maintenance therapy after platinum-based chemotherapy. Results: One hundred and fifteen patients were included. Median age was 60 years. There were 92 BRCA1 carriers, 22 BRCA2 carriers and one patient had double mutation of BRCA1 and BRCA2 genes. Ninety-two percent had serous carcinomas. Six patients had somatic mutations (all BRCA1) and 109 had germline mutations. Median follow-up was 9.8 months. Ninety percent of the patients were platinum-sensitive; 24% had platinum-free interval (PFI) at 6-12 months and 65% had PFI > 12 months. Responses to platinum-based chemotherapy before olaparib as maintenance therapy were: SD (15.7%), PR (52.2%) and CR (32.2%). In multivariate analysis, factors predictive for prolonged PFS under olaparib were: CR (HR = 0.13; 95% CI 0.06-0.28; p < 10^-5), PFI > 12 months (HR = 0.43; 95% CI 0.26-0.73; p = 0.002) and BRCA2 mutations (HR = 0.42; 95% CI 0.24-0.94; p = 0.033). Conclusions: Complete response to platinum before olaparib, PFI > 12 months, and BRCA2 mutations are predictive for prolonged PFS in BRCA carriers who received olaparib as maintenance therapy.

5559 Poster Session (Board #286), Mon, 1:15 PM-4:45 PM
Cost-effectiveness of niraparib versus routine surveillance, olaparib, and rucaparib for the maintenance treatment of adult patients with ovarian cancer in the United States. First Author: Mark Fisher, FIECON, SI Albans, United Kingdom
Background: To estimate the cost-effectiveness of niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, compared with routine surveillance (RS), olaparib and rucaparib for the maintenance treatment of patients with recurrent ovarian cancer. Methods: A decision-analytic model estimated the cost per quality-adjusted life-year gained for niraparib versus RS, olaparib and rucaparib from a U.S. payer perspective. Recurrent ovarian cancer patients with or without germline BRCA mutation, who were responsive to their last platinum-based chemotherapy regimen, entered the model (non-gBRCAmut, gBRCAmut). The model had three health states; progression-free disease, progressed disease and death. For non-gBRCAmut, olaparib PFS was estimated from Study 19 (Olaparib Phase II trial). For gBRCAmut, a cost-minimization analysis was conducted versus olaparib. Due to immature overall survival (OS) data in ENGOT-OV16/NOVA and ARIEL3, mean OS benefit was estimated as double the mean PFS benefit for niraparib, olaparib and rucaparib versus RS. Costs included; drug, chemotherapy, monitoring, adverse events, and terminal care. EQ-5D captured quality-of-life. A 3% annual discount rate was used. Results: Treatment with niraparib increased costs and QALYs versus RS, with an incremental cost-effectiveness ratio of $94,186 and $58,804, for non-gBRCAmut and gBRCAmut. Niraparib had lower costs and higher QALYs compared to olaparib and rucaparib in both populations, with a cost difference of -$57,575 and -$60,400 versus olaparib, and a cost difference of -$117,916 and -$261,950 versus rucaparib for non-gBRCAmut and gBRCAmut. Conclusions: These estimates indicate that niraparib was cost-effective compared to olaparib and rucaparib. Additionally, the cost-effectiveness ratio falls within an acceptable range versus RS. Mature OS data is required to validate these results.

5560 Poster Session (Board #287), Mon, 1:15 PM-4:45 PM
Nanoparticle micellar formulation of paclitaxel in combination with carboplatin for women with recurrent platinum-sensitive ovarian cancer (OSAS-07-OVA): Overall survival results of a phase 3 randomized trial. First Author: Nina Hellding, Oasmia Pharmaceutical AB, Uppsala, Sweden
Background: The primary objective in the pivotal trial OAS-07OVA was reached and it was demonstrated that Paclical, a nanoparticle micellar formulation of paclitaxel (Oasmia Pharmaceutical AB) is non-inferior to Cremophor-EL Paclitaxel in terms of progression-free survival (PFS) in the treatment of recurrent platinum-sensitive ovarian, fallopian tube or peritoneal carcinoma. Paclical is given as 1-h infusion without standard use of Cremophor-EL Paclitaxel in terms of progression free survival (PFS) in the treatment of recurrent ovarian carcinoma. Paclical is non-inferior to Taxol in terms of overall survival results of a phase 3 randomized trial.

5561 Poster Session (Board #288), Mon, 1:15 PM-4:45 PM
Tumor molecular profiling to differentiate extreme responses to first-line platinum-based chemotherapy in suboptimally debulked serous ovarian cancer patients. First Author: Johanne I Weberpals, Ottawa Hospital Research Institute, Ottawa, ON, Canada
Background: Patients with advanced high grade serous ovarian cancer (SOC) who undergo a suboptimal debulking primary surgery typically have adverse clinical outcomes. However, a spectrum of sensitivity to first line platinum-based chemotherapy is observed but poorly understood. In this study, we perform molecular characterisation of two groups of responders (extreme versus poor) to first line carboplatin/taxol chemotherapy in suboptimally debulked SOC patients. Methods: Suboptimally debulked SOC patients with advanced disease (stage III-IV) were grouped by response to first-line chemotherapy and clinicopathologic data collected. Extreme platinum-sensitive (PS) responders had a PFI (progression-free interval) > 12 months (mo) and platinum-resistant (PR) responders had a PFI < 6 mo. Tissue specimens were used to interrogate the molecular features of both PS and PR cohorts using whole exome and transcriptome sequencing. Sequence alignment and variant calling were performed using GATK and annotation was performed using Variant Effect Predictor for assessment of non-synonymous tumor mutation burden (TMB) and discovery of novel mutational signatures to predict platinum response. Results: There were 39 patient samples analyzed from primary surgery (PS group = 20; PR group = 19). Median PFI for PS and PR patient cohorts was 30 mo and 3 mo (< 0.001), respectively. In all tumors, in addition to BRCA and TP53 mutations, additional oncogenic mutations were noted in genes associated with PI3K/AKT/mTOR signaling and in epigenetic regulation. The PS samples were characterized by mutations in BRCA1/2 and the PR samples by mutations in MGA. Compared to tumors in the PR cohort, PS tumors had a significantly higher non-synonymous mutation rate using TMP analysis (p < 0.05) with a trend towards increased immune response. Additional bioinformatics analysis is ongoing and will include copy number variation analysis, immune inference using ESTIMATE and Gene Set Enrichment Analysis. Conclusions: Contracting a mutational signature is feasible from patient tumors at primary surgery and helps to elucidate extreme responses to platinum-based chemotherapy.
Assessing delay and barriers to risk-reducing surgery in women with BRCA mutations. First Author: Anne Olsen, NYU School of Medicine, New York, NY

**Background:** The NCCN recommends risk-reducing salpingo-oophorectomy (RRSO) for women with BRCA mutations by age 35-40 or upon completion of childbearing. We previously reported that RRSO was being performed at age 43-44; and age 46-47 when fertility considerations were excluded. Since these ages are past the NCCN guidelines, our objective was to elucidate the timing between genetic testing (GT) and risk-reducing surgery (RRS) and reasons for delay. **Methods:** We conducted a retrospective chart review to identify women with BRCA mutations who underwent RRSO between 2012-2017. We analyzed demographics, date of GT and RRS and reasons for delay in RRS. **Results:** We identified 187 patients with mutations who underwent RRS: 93 with BRCA1 and 94 with BRCA2. Median age at RRS was 44 (28-77); 43 (31-77) and 45 (28-71), for BRCA1 and BRCA2, respectively. The median time between GT and RRS was 9 (1-171) months (m). Fifty-six percent of patients (n = 105) had a documented reason for delay in RRS; 39 (37%) for future fertility; 25 (24%) for breast cancer (BC) treatment; 14 (13%) due to fear of surgical menopause; 10 (10%) to coordinate with simultaneous breast surgery; 17 (16%) miscellaneous. The median time of delay from mutation diagnosis to RRS among groups was: fertility, 29 (17; 42) m; BC, 9 (2-36) m; menopause, 12 (4-76) m; and surgical coordination, 8 (4-13) m. Median age at RRS among groups was: fertility, 39 (31-46) years (y); BC, 45 (28-70) y; menopause, 42 (32-44) y; and surgical coordination, 52 (37-71) y. In patients undergoing RRS after diagnosis of BC, 30 of 36 (83%) had a family history that qualified them for earlier genetic testing by NCCN guidelines. Two of these BC patients had ovarian cancer at the time of RRS. **Conclusions:** Overall, patients underwent RRS within a year of mutation diagnosis. Patients comprised two distinct groups: those with fertility or menopause concerns who underwent RRS at 39-42 y, close to the NCCN recommended age; and those with BC who underwent RRS at 45-52 y. Over 80% of patients in the BC group qualified for earlier genetic screening. Obtaining a family history, referral for GT, and earlier diagnosis of mutations, prior to development of BC, will be an important step to better comply with NCCN guidelines and prevent ovarian cancer.

**Table:**

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**Conclusion:** The integrated genomic analysis from TriPocc has enabled the discovery of potentially novel molecular alterations in Asian ovarian cancers. The predictive value of these molecular alterations will be assessed once the iPocc outcome data are mature.
Inhibition of the Wnt/β-catenin pathway to promote T-cell immunity and survival in a syngeneic mouse model of ovarian cancer. First Author: David W Dunn, University of Alabama at Birmingham, Birmingham, USA

Background: The Wnt/β-catenin pathway downregulates protective immunity mediated by intra-tumoral CD8+ T cells, resulting in immune exclusion across cancer types. WNT974 inhibits the enzyme porcupine, which controls Wnt ligand secretion. Our objective was to evaluate the effects of Wnt inhibition on tumor growth, immune response, and survival in a syngeneic mouse model of ovarian cancer (OVCA). Methods: C57BL/6 mice were injected subcutaneously (SC) or intraperitoneally (IP) with 7 x 10^6 ID8 mouse OVCA cells. After 28 days, WNT974 or vehicle control was administered by oral gavage for up to 28 days. SC tumors were measured with calipers and tumors were harvested for NanoString gene expression profiling. Mice with IP tumors were kept to evaluate survival, or sacrificed after 14 days of treatment and omental tumor weights and ascites volume were measured. Flow cytometry was used to evaluate the immune response in IP tumors. Results: In the SC model, treatment with WNT974 reduced tumor size compared to vehicle control at day 60 (22.4 vs. 41.0 mm^3, p = 0.0001). A gene signature of T cell infiltration was upregulated in SC tumors of WNT974-treated mice (p = 0.038). In the IP model, ascites volume was reduced by 5.95 mL, p = 0.019 and number of ascites cells (2.60 x 10^7 vs. 7.45 x 10^7 cells, p = 0.019) were decreased after treatment with 14 days of WNT974. Analysis of the omental tumors revealed an increased ratio of CD8+ T cells to T regulatory cells in the WNT974-treated mice (2.90 vs. 1.67, p = 0.024), as well as an increased number of dendritic cells (23.61 vs. 8.332 dendritic cells x 10^5, p = 0.045). A higher frequency of CD8+ T cells were found to express granzyme B (91.8 vs. 26.6%, p = 0.0001) and TFK-α (31.1 vs. 0.84%, p < 0.0001) after treatment with WNT974. Survival was significantly improved in the WNT974-treated group (p = 0.007). Conclusions: Using a syngeneic OVCA mouse model, treatment with WNT974 increased Wnt/β-catenin pathway activity and decreased tumor growth and ascites and prolonged survival. This effect coincided with an upregulated anti-tumor immune response, suggesting that the Wnt/β-catenin pathway may be an important immunomodulatory target in ovarian cancer.

3CP group.

3CP group.

5567 Poster Session (Board #294), Mon, 1:15 PM-4:45 PM

Phase II results of GANNET53: A European multicenter phase I/II trial of the HS90 inhibitor Ganetespib (G) combined with weekly Paclitaxel (P) in women with high-grade serous, high-grade endometrial, and undifferentiated, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. First Author: Nicole Concini, Medical University of Innsbruck, Innsbruck, Austria

Background: Stabilized mutant p53 protein (mutp53) is a novel target in ovarian cancer. Mutp53 proteins depend on folding support by the Hsp90 chaperone. Hsp90 blockade induces degradation of mutp53, resulting in anti-tumor cytotoxicity and increased sensitivity to chemotherapeutics. The GANNET53 trial (EUDRACT 2013-003868-31, FP7 project funded by the European Union) tests the combination of Ganetespib (G) with Paclitaxel (P) in platinum-resistant epithelial ovarian cancer (PROC) patients (pts). Methods: Eligible pts had PROC ≤ 4 prior chemotherapy lines, high-grade histology, disease measurable according to RECIST 1.1 or assessable according to GCIG CA-125 criteria. Pts were randomized in a 2:1 manner to receive weekly P (80 mg/m^2) + G (150 mg/m^2) or weekly P alone. Treatment was given i.v. on days 1, 8, 15 in a 28 day cycle until disease progression. Primary endpoint was PFS, secondary endpoints were OS, ORR, PFS2, safety, PRO and PK. Results: A total of 133 pts (median age 61 years, range 40-81) were enrolled. Median follow-up was 10.0 months in the ITT population. The study was prematurely closed for active recruitment due to unsecured drug supply with G (initially planned 222 pts). In the ITT population, median PFS was 3.5 and 5.3 months for P+G and P, respectively (p = 0.16; HR 1.3, 95%CI: 0.897-1.895). OS was 11.0 and 14.9 months, respectively (p = 0.13; HR 0.86, 95%CI: 0.58-1.27). The grade 3-4 related gr 1/2 AEs in the P+G arm were typical transient (1-2 days) diarrhea (79% of pts), anemia (46%), nausea (41%), peripheral neuropathy (41%), and in the P arm anemia (51%), peripheral neuropathy (45%), nausea (40%) and diarrhea (26%). Most frequent related gr > 2 AEs in the P+G arm were neutropenia grade 4 (32%), grade 3 anemia (8%) and in the P arm anemia (9%), neutrophil count decrease (9%) and diarrhea (5%). ORR, PFS2 and detailed safety data and analyses in PP population will be presented. Conclusions: The addition of G to weekly P did not improve survival in PROC patients. Clinical trial information: EUDRACT 2013-003868-31.

5568 Poster Session (Board #295), Mon, 1:15 PM-4:45 PM

Comparing the impact of dose reductions and delays in ovarian cancer patient outcomes with three-weekly versus dose dense carboplatin and paclitaxel regimens in the national prospective OPAL cohort. First Author: Tharani Sivakumaran, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: To determine if chemotherapy dose reductions and delays in the adjacent setting impact ovarian cancer pt outcomes. Secondary objective is comparing deliverability of three weekly and dose dense chemotherapy. Methods: OPAL is a national prospective study involving 958 pts with newly diagnosed epithelial ovarian (or peritoneal, fallopian tube) cancer. OPAL recruited subcutaneously (SC) or intraperitoneally (IP) with 7 x 10^6 ID8 mouse OVCA model of ovarian cancer (OVCA). Wnt ligand secretion. Our objective was to evaluate the effects of Wnt inhibition on tumor growth, immune response, and survival in a syngeneic mouse model of ovarian cancer (OVCA). Methods: C57BL/6 mice were injected subcutaneously (SC) or intraperitoneally (IP) with 7 x 10^6 ID8 mouse OVCA cells. After 28 days, WNT974 or vehicle control was administered by oral gavage for up to 28 days. SC tumors were measured with calipers and tumors were harvested for NanoString gene expression profiling. Mice with IP tumors were kept to evaluate survival, or sacrificed after 14 days of treatment and omental tumor weights and ascites volume were measured. Flow cytometry was used to evaluate the immune response in IP tumors. Results: In the SC model, treatment with WNT974 reduced tumor size compared to vehicle control at day 60 (22.4 vs. 41.0 mm^3, p = 0.0001). A gene signature of T cell infiltration was upregulated in SC tumors of WNT974-treated mice (p = 0.038). In the IP model, ascites volume was reduced by 5.95 mL, p = 0.019 and number of ascites cells (2.60 x 10^7 vs. 7.45 x 10^7 cells, p = 0.019) were decreased after treatment with 14 days of WNT974. Analysis of the omental tumors revealed an increased ratio of CD8+ T cells to T regulatory cells in the WNT974-treated mice (2.90 vs. 1.67, p = 0.024), as well as an increased number of dendritic cells (23.61 vs. 8.332 dendritic cells x 10^5, p = 0.045). A higher frequency of CD8+ T cells were found to express granzyme B (91.8 vs. 26.6%, p = 0.0001) and TFK-α (31.1 vs. 0.84%, p < 0.0001) after treatment with WNT974. Survival was significantly improved in the WNT974-treated group (p = 0.007). Conclusions: Using a syngeneic OVCA mouse model, treatment with WNT974 increased Wnt/β-catenin pathway activity and decreased tumor growth and ascites and prolonged survival. This effect coincided with an upregulated anti-tumor immune response, suggesting that the Wnt/β-catenin pathway may be an important immunomodulatory target in ovarian cancer.

Conclusions: Using in silico data analysis of publicly available data, we developed a 200 gene signature to differentiate between optimal vs. suboptimal debulked pts. Optimal debulking was defined as no macroscopic residual mass after PDS. The mRNA expression levels of the top 25% genes were validated in an independent cohort of 246 HGSOC pts, using Nanostring nCounter Analysis System. Only advanced stage, chemonaive HGSOC pts were included in the study. FFPEs and clinical data were provided by TOC (www.toc-network.de). Residual mass and clinical-histological parameters were documented prospectively. Surgery was performed by an experienced gynecological oncologist, between 2002-2013. The validation was performed using unsupervised hierarchical clustering (distance metric:1-correlation, complete linkage). Pts stratification in the two main clusters was assessed by Pearson’s Chi-squared test with Yates’ continuity correction. Results: 152 (61.7%) pts presented no residual mass after PDS. Median age at diagnosis was 59 years. The own generated data showed 29 differentially expressed genes between suboptimal and optimal debulked pts (Mann-Whitney U-test, p < 0.05). MYCN, PTCH1, MMP11, GREM1, PMEPA1, FABP4, ASPN and TGFB3 were the top differentially expressed genes (p < 0.05). MYCN, PTCH1, MMP11, GREM1, PMEPA1, FABP4, ASPN and TGFB3 were the top differentially expressed genes (p < 0.05) and abbrev(2foldChange) > 0.5) between the two cohorts. Unsupervised hierarchical clustering of all measured genes, the 29 genes and the 8 top genes, showed significant phenomenological separation (p = 0.04, p = 0.00011 and p = 0.00022, respectively). Conclusions: Our developed signature is a promising tool for identification of residual mass after PDS in advanced HGSOC. This will more likely allow the selection for primary vs. interval debulking surgery.

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Differences in survival between Caucasians and Asians. First Author: John K. Chan, Palo Alto Medical Foundation, San Francisco, CA

Background: To compare the difference in the presentation and survival of Asian subgroups and whites with epithelial ovarian cancer. Methods: Data were extracted from the National Cancer Database between 2004 and 2010. Chi-squared tests, Kaplan-Meier methods, and Cox-proportional hazard models were used for statistical analyses. Results: Of the 81,355 women, 78,531 (96.5%) were White and 2,824 (3.5%) were Asians. Of Asians, 495 (23.5%) were Chinese, 487 (23.1%) Indian/Pakistani, 476 (22.6%) Filipino, 207 (11%) Vietnamese, 224 (10.6%) Japanese, and 219 (10.4%) Korean. Compared to Whites, Asians were younger (54 vs. 61 years: p < 0.001) had more early stage disease (47.8% vs. 35.0%; p < 0.001), non-serous histology (56.7% vs. 44.5%; p < 0.001), and better survival (63.9% vs. 50.6%; p < 0.001). Of the Asians, Korean and Vietnamese were younger at 53 years compared to Chinese, Indian/Pakistani, Filipino, and Japanese (54, 55, and 59 years) Vietnamese presented with 38.2% of stage I disease compared to 37.8%, 28.8%, 36.6%, 33.8%, and 34.8% in Chinese, Indian/ Pakistani, Filipino, Korean, and Japanese. The 5 years disease specific survivals for Vietnamese, Chinese, Indian/Pakistani, Korean, Filipino, and Japanese were 74%, 67.6%, 67.5%, 60.3%, 59.3%, and 53.4%, respectively (p < 0.001). On multivariate analysis, Chinese (HR: 0.78, 95%CI: 0.65-0.95, p = 0.01), Vietnamese (HR: 0.64, 95%CI: 0.47-0.87, p = 0.005), Indian/Pakistani (HR: 0.70, 95%CI: 0.57-0.85, p < 0.001) race predicted for better survival compared to whites. In addition, younger age at diagnosis (HR: 1.03, 95%CI: 1.027-1.029, p < 0.001), advanced stage of disease (HR: 1.00, 95%CI: 1.000-1.001), and endometrioid cell type (HR: 0.72, 95%CI: 0.69-0.75, p < 0.001) predicted for survival. Conclusions: Our data suggest that Asians presented at a younger age, had more early stage disease with better survival compared to whites. More specifically, the subgroups of Chinese, Vietnamese and Indian/ Pakistani have better survival compared to whites.

Toxicity profile of patients with gynecological cancers (Gyne) enrolled in phase I trials. First Author: Yvonne Lee, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Gyne patients enrolled in Phase I trials may be at increased risk of certain toxicities given their extent of abdominal disease and prior treatments (surgery, chemo and radiotherapy). This study aims to assess the toxicity profile of patients with and without gyne cancers enrolled in Phase I trials. Methods: A retrospective review of the National Cancer Institute Phase I database was conducted with trials enrolling at least 1 gyne patient over a 16-year period (1995-2015). Eligible patients required complete data collection from baseline to end of trial participation. Adverse events (AEs) were categorized by CTCAE. Each AE was counted one time and analyzed based on highest grade and drug attribution. Results: 4,269 eligible patients enrolled in 150 Phase I trials were identified and divided into 3 groups: 1) females with gyne cancer (n = 685); 2) females without non-gyne cancer (n = 1698); 3) males (n = 1886). Median age in each group was 56 vs 56 vs 60 years, respectively. Mean total AEs reported during treatment was highest for females with gyne cancer (mean [standard error of mean (SEM)]: 17.1 (0.4) vs 14.7 (0.2) vs 13.5 (0.2), despite being similar at baseline (mean: 7.0 (0.2) vs 7.4 (0.1) vs 7.0 (0.1)). Differences were predominantly due to greater abdominal-related AEs, infection and myelosuppression in females with gyne cancer. Drug-related AEs were also highest for females with gyne cancer (mean [SEM]: 8.3 (0.2) vs 6.9 (0.1) vs 6.2 (0.1)). Grade 3-5 AEs were similar (mean: 7.2 (0.2) vs 6.9 (0.1) vs 6.2 (0.1)). Discontinuous due to AEs were similar (9% vs 9% vs 10%) and deaths during treatment were higher in males (2% vs 2% vs 4%). Regarding study outcomes, females with gyne cancer remained on treatment marginally longer (4.3 vs 3.3 vs 3.1 cycles) and achieved higher objective response rates (11% vs 6% vs 3%). Conclusions: Ga females patients enrolled in Phase I trials experienced higher abdominal-related AEs and infection, thus warranting specific consideration. However, grade 3-5 AEs and discontinuations were similar in all groups, suggesting that toxicities were low-grade and did not compromise outcomes.

Phase Ib study of anti-mesothelin antibody drug conjugate anetumab rattleans in combination with pegylated liposomal doxorubicin in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. First Author: Iurie Buta, ARESIA Exploratory Medicine Research Unit, Institute of Oncology, Chisinau, The Republic of Moldova

Background: Anetumab rattleans (AR) comprises a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4. A phase Ib dose escalation was conducted in patients with platinum-resistant ovarian cancer to assess overall safety, pharmacokinetics (PK) and clinical activity. Methods: Eligible pts with historically confirmed, locally invasive or metastatic platinum-resistant ovarian cancer, and ECOG performance status ≤1 were enrolled. Pregylated liposomal doxorubicin (PLD) at 30 mg/m²IV every 21 days (q3w) was administered with AR in two IV dosing schedules: 5.5 or 6.5 mg/kg q3w in 9 pts (Part I dose escalation) and at 6.5 mg/kg q3w in 12 patients (Part II expansion cohort). Tumor response was assessed based on RECIST v1.1 (q6w C1-C9 and q12w thereafter. Determination of mesothelin expression in archival or fresh biopsy tumor samples by IHC (SP74, Ventana) was highly encouraged. PK of AR and PLD was performed. Results: A total of 21 pts were evaluable in Part I and II: median age 61.5 yrs (range 42-77), PS 01 66.7%±33.3%, median prior lines of therapy 3 range (1-10). The maximally tolerated dose (MTD) in combination was AR at 6.5 mg/kg and PLD at 30 mg/m² q3w. Adverse events (AEs) were similar to previously reported AEs of each agent as monotherapy, including reversible coeval disorders, neutropenia, liver function test increases, and gastrointestinal (GI) complications. Drug-related AEs included severe AEs (5pts) below (2 pts, 9.5%). Most common grade 3-4 AEs were neutrophil count decreased (5, 23.8%) and platelet count decreased (2, 9.5%). A total of 11 pts (52%) had confirmed partial responses (PR) and 7 (33%) had stable disease for a disease control rate of 86%. Six pts (29%) had a durable PR (> 250 days). No PK interaction was observed. Conclusions: AR in combination with PLD showed preliminary efficacy with durable PRs in pts with platinum-resistant ovarian cancer. The safety profile was manageable. Further study of this combination is warranted. Clinical trial information: NCT02751918.
Background: Risk-reducing salpingo-oophorectomy is the gold standard to prevent the development of a pelvic high grade serous carcinoma (HGSC) in women at risk of breast/ovarian cancer. However, some are reluctant to perform this surgery due to significant related adverse effects. Most of HGSCs stem from the distal fimbrial part of fallopian tubes. Thus we supposed that a new prophylactic procedure called radical fimbriectomy (RF), which consists of the resection of both tubes along with the fimbrio-ovarian junction (attached ovarian fragment), completed at 50 years-old or meno-pause by a bilateral oophorectomy. We present the first results of this operation focused on perioperative morbidity and pathological observations.

Methods: BRCAl/2 carriers or any women with a documented familial risk of breast/ovarian cancer were first counseled to perform a classical laparoscopic RRSO. If they denied, they were offered to enter the RF controlled study. All pathological specimens were examined using the SEE-FIMI protocol. Intra- and 30-day post-operative events and pathological data were recorded accordingly to protocol. Results: From January 2012 to June 2014, 121 laparoscopic RF were performed. Intraoperative complications were: 1 laparo-conversion for adhesions and 2 grade I procedural hemorrhages. 20 patients (16.5%) complained of Clavien grade I, and 2 (1.7%) grade II adverse effects. Pathologically, we found one (0.8%) invasive HGSC, two (1.7%) Serous Tubal Intraepithelial Carcinoma (STIC), one (0.8%) Serous Tubal Intraepithelial Lesion (STIL) and 21 (17.7%) p53 signatures. All adverse effects. Pathologically, we found one (0.8%) invasive HGSC, two (1.7%) STIC, one (0.8%) STIL and 21 (17.7%) p53 signatures. All lesions were located at the fimbria, except the HGSC found at a tubal isthmus.

Conclusions: In this cohort, 2.5% of patients had a diagnostic of occult tubal neoplasia, as observed in the literature. Tubal examination by a trained pathologist, using SEE-FIMI protocol, is necessary to detect occult cancers. A longer time is still necessary to report the efficacy of RF in terms of cancer prevention. Meanwhile, we can conclude that RF is safe, well tolerated and effective in term of occult neoplasia detection. Clinical trial information: NCT01608074.

Conclusions: Tolerance and pathological findings.

Endpoint / Trial type | Trials | N (pts) | tau* | $R^2$ Concordia
--- | --- | --- | --- | ---
Overall | 15 | 8973 | 0.69 | 0.03
CA125 confirmed by radiological exam | 9 | 5126 | 0.67 | 0.16
GCIG criteria | 4 | 2548 | 0.7 | 0.14
Carbo-Tax as control | 9 (5807) | 0.72 | 0.05
Standard or intensification | 12 (7703) | 0.71 | 0.10
Maintenance | 3 (1270) | 0.64 | 0.14

*tau and $R^2$ values range from 0 (no association) to 1 (perfect correlation).

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5578 Poster Session (Board #305), Mon, 1:15 PM-4:45 PM
Platinum-based chemotherapy selects for PDGFRα dependent angiogenesis. First Author: Nuala McCabe, Almac Diagnostics, Craigavon, United Kingdom
Background: Patients with High Grade Serous Ovarian Cancer (HGSOC) initially respond to SOC platinum based treatment but most will eventually relapse with platinum sensitive disease. A known hallmark of integral pathological feature of HGSOC and anti-angiogenic agents have been trialed in this population, but have failed to demonstrate a significant impact on overall survival (OS). Here, we ask if platinum resistance could be associated with an improved response to anti-angiogenic therapies.
Methods: A meta-analysis of 14 phase II and III clinical trials in EOC were used to investigate the association between platinum resistance and response to anti-angiogenic agents. In addition we analysed gene expression in 12 matched pre-and post-chemotherapy samples. Novel cisplatin-resistant HGSOC cell lines and novel ascites-derived primary cell lines from HGSOC patients with known outcomes following platinum-based chemotherapy were developed to investigate the relationship between angiogenesis and platinum resistance. Results: The meta-analysis revealed an OS benefit for anti-angiogenics in platinum-resistant disease (p = 0.029), whilst platinum-sensitive disease derived only PFS benefit (p = < 0.0001). In the matched pairs of patient samples, post-platinum samples had a higher DNA density (MVD) relative to their paired treatment-naive sample (p = 0.0001). Additionally, an in vivo angiogenesis matrigel plug assay demonstrated that cisplatin-resistant EOC cell lines were associated with an increase in MVD (p = < 0.0001). MVD was reduced in the platinum-resistant cells following treatment with bevacizumab (p = 0.001). Ascites-derived cells established from platinum-resistant patients demonstrated overexpression of VEGF-A through increased PDGFRα and PDGFRβ expression. Conclusions: We have demonstrated that previous platinum therapy for EOC is associated with an increase in tumour PDGFRα and VEGF-A expression, correlating with a response to anti-angiogenic therapies. This data suggests that platinum therapy resistance may inform the selection of EOC patients for novel anti-angiogenic therapies in future clinical trials.

5579 Poster Session (Board #306), Mon, 1:15 PM-4:45 PM
Paired somatic and germline genetic testing for ovarian cancer patients: Observations, benefits and implications for treatment. First Author: Daniel Chen, Ambry Genetics, Aliso Viejo, CA
Background: Germline and somatic genetic testing have traditionally been offered separately; however, the clinical applications of these tests are now converging with continued FDA approval of targeted therapies for both germline and somatic mutation carriers. This study aims to describe the findings of a paired testing (germline and somatic) approach among ovarian cancer (OC) patients. Methods: Study participants consisted of 95 consecutive OC patients undergoing paired testing at a clinical diagnostic laboratory. Eleven OC predisposition genes in the homologous recombination (HR) repair pathway were targeted by capture-based NGS: ATM, BARD1, BRCA1, BRCA2, BRF1, CHEK2, MRE11A, NBN, PALB2, RAD51C, and RAD51D. Paired analysis of sequence data from both tumor (minimum of 20% neoplastic cellularity) and blood specimens was performed to differentiate variants of somatic vs germline origin. Customized NGS pipelines and/or microarray were used to detect gene copy number variants. Additional test results included hypermethylation analysis of BRCA1 and RAD51C promoter regions by methylation-specific PCR, when available. Results: In total, 41 patients (43.2%) were eligible for T/P-inhibitor therapy based on the presence of a germline (n = 3, 7.3%), somatic (n = 34, 82.9%) or germline and somatic (n = 4, 9.8%) BRCA1 or BRCA2 pathogenic mutation. Of 38 (40.0%) patients with somatic alterations, 3 (7.9%) had sequencing mutations, 32 (84.2%) had whole gene deletions of BRCA1 or BRCA2, and 3 (7.9%) had compound alteration types. Somatic whole gene deletions of BRCA1 or BRCA2 were often accompanied by gains or losses of other genes in the tumor. Twenty-nine patients (30.5%) were germline and tumor BRCA1/2-negative, but tested positive for germline or somatic pathogenic mutations in other HR genes or tumor promoter methylation in BRCA1 or RAD51C. Conclusions: Our findings highlight the benefits of paired testing over germline and/or somatic testing alone, such as concurrent confirmation of germline mutations and maximizing detection of patients who would benefit from therapy. Further research is needed to determine the impact of paired testing on healthcare costs and patient outcomes.

5580 Poster Session (Board #307), Mon, 1:15 PM-4:45 PM
Phase I study of carboptatin (C), pegylated liposomal doxorubicin (PLD) and everolimus (E) in platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer in first relapse (NCT01281514). First Author: Lainie P. Martin, Fox Chase Cancer Center, Philadelphia, PA
Background: The PI3K/AKT/mTOR pathway may play an important role in chemotherapy resistance in ovarian cancer. (E) is an orally administered mTOR inhibitor approved for multiple indications. This Phase I trial evaluated the feasibility of combining E with C and PLD in women with recurrent, platinum sensitive ovarian cancer. Methods: Patients were administered C AUC 5 with PLD 30 mg/m2 on 28 day cycles, and escalating doses of E, starting at 2.5 mg/d/day. Planned Phase I doses of E were 2.5 mg/d, 5 mg/d, 7.5 mg/d and 10 mg/d. The study used a modified TITE-CRM design with a requirement that cohort 1 complete 6 cycles of chemotherapy with E at 2.5 mg/d prior to dose escalation. The primary endpoint was safety and tolerability. Results: 21 patients were treated on study. There was a DLT of rash at dose level (DL)1, 2.5 mg/d; patient discontinued treatment on trial after cycle 1. 5 additional patients completed 6 cycles at DL1 without DLT. 3 patients completed 6 cycles of treatment at DL3, 7.5 mg/d, but 2 experienced DLT and required dose reduction. 12 patients were enrolled at DL2; no DLTs were seen at DL2. 7 patients completed 6 cycles without dose modification. 1 patient required dose modification of E for thrombocytopenia. 2 patients stopped treatment early due to disease progression. 2 patients experienced hypersensitivity reactions to Doxil, and failed desensitization. They were permitted to remain on study with C and E, but were considered ineligible. DLTs included rash, (n = 1 at DL1), headache, (n = 1 at DL3) and thrombocytopenia (n = 1 at DL3). The most common AEs included neutropenia, anemia, stomatitis, rash, nausea, vomiting, diarrhea and constipation (42-90%). Grade 3 AEs included neutropenia (n = 3), thrombocytopenia (n = 2), stomatitis (n = 1), rash (n = 1) and PEO (n = 2). The MTD of E in combination with C and PLD was determined to be 5 mg/d. 3 patients experienced a CR and 11 patients experienced a PR, for a RR of 67%. 3 patients experienced stable disease and 3 experienced disease progression. Conclusions: C with PLD and E at 5 mg/d is tolerable with intriguing activity in women chemotherapy resistant platinum-sensitive relapsed ovarian cancer. Clinical trial registration: NCT01281514.

5581 Poster Session (Board #308), Mon, 1:15 PM-4:45 PM
Clear cell ovarian cancer (CCOC): 115 patient (pt) series showing access to experimental therapy may improve response rate in recurrent disease. First Author: Michael-John Devlin, University College London Hospitals, London, United Kingdom
Background: 10 year survival for ovarian cancer (OC) in the UK has improved from 18% (1971) to a predicted survival of 35% (2011). Historical data show pts with advanced CCOC have worse survival compared to other histological subtypes of epithelial OC. We sought to determine treatment type and outcome of CCOC pts at 2 UK gynaecological cancer centres. Methods: Medical records of pts with CCOC treated between 2002 and 2017 were reviewed. Data collected comprised pt and tumour characteristics, treatment and outcome. Results: 115 pts, median age 56 (29-86) years (y) with CCOC were identified: stage (S) I (62), II (16), III (23), IV (8) and unknown (6). 91 pts had pure CCOC and 24 had mixed histopathology: endometrioid (83%), serous (12%), other (5%). Endometriosis co-existed in 43 (37%) pts; 34 pure CCOC, 8 mixed endometrioid. BRCA mutations were present in 4/19 tested and MMR loss in 2/8 tested. 21/23 pts with a thrombembolic event and 9/10 pts with hypercalcaemia (2.72-3.63mmol/L) had advanced or recurrent disease. 19 pts had a prior or synchronous malignancy, most commonly endometrial (8) or breast (6). Primary refractoriness to first line treatment occurred in S I (3%), S II (13%) and IV (100%) CCOC with median overall survival (OS) of 224 days (d). Recurrence rates were 22% (S I), 38% (S II) and 61% (S III). Molecular targeted agents (MTA) were used in 29 treatments; bevacizumab (45%), nintedanib (17.5%), PARP combination (10%), PI3K/mTOR inhibitor (10%), other novel agent (17.5%). 33/37 pts had 2nd line treatment with overall response rate (ORR) of 30% and progression free survival (PFS) 258d. 12/33 pts treated with a regimen containing a MTA had PFS 358d vs 228d for those without. ORR in the 3rd line was 14% with PFS 185d. The OS rate at 3y was 98% (S I), 100% (S II), 86% (S III) and 0% (S IV) and at 5y was 81% (S I), 50% (S II) and 23.5% (S III). Conclusions: Late stage CCOC has a phenotype distinct to early stage with a propensity to be treatment resistant, recur, have para neoplastic manifestations and poor survival. The 2nd line ORR of 30% in our cohort which is higher than other series may reflect increased use of bevacizumab. 21% and 25% pt had of BRCA variants or MSI suggesting benefit of testing CCOC.
Efficacy and immune modulation of the tumor microenvironment with the combination of the PARP inhibitor rucaparib and CD122-biased agonist NKTR-214. First Author: Andrew Simmons, Clovis Oncology, San Francisco, CA

Background: NKTR-214 is a biased agonist of the IL2Rbg (CD122) pathway that activates and mobilizes CD8 T and NK cells into the tumor microenvironment. The PARP inhibitor rucaparib has demonstrated activity in BRCA mutant deficient tumors through synthetic lethality. We hypothesized that PARP inhibition in a BRCA syngeneic model would lead to immunogenic cell death and synergize with NKTR-214 through antigen priming and enhanced activation of newly infiltrated intratumoral T and NK cells. Methods: Mice (n = 10/group) were inoculated with the murine ovarian tumor cells (BR5FVB1) harboring genetic alterations (TP53-/-, BRCA1-/-, myc and Akt) frequently present in human ovarian carcinomas. Tumors were grown to 125 mm^3 prior to treatment with vehicle, rucaparib (150 mg/kg BID x 28 days), NKTR-214 (0.8 mg/kg q9d x 3), or the combination and tumor volumes were measured. Immune modulation was evaluated by IHC and gene expression. Results: Treatment with NKTR-214 in 88.5% tumor growth inhibition (day 22; p < 0.0001), and tumors were monitored for regrowth after 28 days of dosing. Tumor volume nadir was 94.5 mm^3 on day 38 for rucaparib treated animals and progressed to >1000 mm^3 by day 59. In contrast, 50% of mice treated with NKTR-214 and rucaparib combination were tumor free on day 113, suggesting development of immune memory. The combination of NKTR-214 and anti-PD1 in the same model did not provide tumor-free mice. An increase in infiltrating CD8 T cells, NK cells, dendritic cells, and neutrophils, as well as the induction of interferon-gamma induced chemokines was observed with the combination of rucaparib and NKTR-214 by expression profiling. IHC staining also showed significant increases in CD3, CD4 and CD8 T cells with the combination (p < 0.05). Conclusions: The novel combination of NKTR-214 plus rucaparib results in durable complete responses in a genetically-relevant ovarian tumor model. Profiling of tumors suggested the activity of this combination is through antigen priming of infiltrating memory T cells, increased NK cell numbers, and enhanced cytotoxicity of immune infiltrates into the tumor.

Phase III randomized trial of maintenance pegylated liposomal doxorubicin (PLD) / carboplatin versus without in patients with advanced ovarian cancer: An Asian Gynecologic Oncology Group study. First Author: Chyong-Huey Lai, Department of OB/GYN, Chang Gung Memorial Hospital, Taoyuan, Taiwan

Background: An Asian Gynecologic Oncology Group (AGOG) phase III randomized trial was conducted to determine whether maintenance chemotherapy after complete remission could improve progression-free survival (PFS) in FIGO stages III/IV ovarian cancer. Methods: Between June 2007 and September 2014, 45 patients were enrolled and randomized (1:1) with stratification factor of residual tumor and stage. One patient was found ineligible shortly after registration and randomization and was excluded without treatment. Twenty-three patients were randomized to arm A (4-weekly carboplatin AUC4 and liposomal doxorubicin 30 mg/m^2) for six cycles and 21 patients were randomized to arm B (observation). The primary end-point was PFS. Overall survival (OS) was calculated as secondary end-point. Results: Enrollment was slow, therefore a decision of closing accrual was made by the AGOG Board meeting when 7+ years had lapsed. We ended the study after the last enrolled patient had completed 3-year follow-up. With a median follow-up of 80.1 months, 30 patients experienced cancer progression (14 [60.9%] for arm A and 16 [76.2%] for arm B). The median PFS was significantly better in arm A (38.9 months) than arm B (9.2 months) (log-rank p = 0.038), and the median OS was marginal better in arm A (not applicable, > 50 % of patients were alive at study end) than arm B (42.8 months) (log-rank p = 0.117). Overall rates of grade 3/4 adverse events were 60.9 % for arm A and 0.0 % for arm B (p < 0.001). Grade 3/4 including neutropenia were more frequent in arm A than arm B with 30.4% and 0.0%, respectively (p = 0.0094). Conclusions: Despite limitation in small sample size, it suggests that maintenance chemotherapy after complete remission could be beneficial significantly improving PFS in stages III/IV ovarian cancer patients. First Author: Tyler McCaw, University of Alabama, Birmingham, Birmingham, AL

Histone deacetylase inhibition alters tumor phenotype and stimulates a productive anti-tumor immune response in preclinical models of ovarian cancer. First Author: Joshua Millstein, Department of Preventive Medicine, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA

Background: Ovarian cancer remains the most deadly gynecologic malignancy. Chemotherapy and surgical reduction are initially effective but most patients relapse with chemoresistant disease. Immunotherapy is currently being evaluated in multiple clinical trials as a treatment modality for ovarian cancer, but response rates as a single agent have been disappointing. Because an altered epigenetic framework contributes to malignant transformation and immune escape in ovarian cancer, our objective was to evaluate whether histone deacetylase (HDAC) inhibition could reorient the suppressive tumor microenvironment and stimulate a productive anti-tumor immune response. Methods: Syngeneic ovarian cancer cells (ID8 or ID8 p53-/-) were injected into the peritoneal cavity of C57BL/6 mice and treated daily with 20mg/kg eninostat or vehicle, starting on day 21. First, we assessed transcript-level changes in gene expression of whole tumor lysates using the NanoString PanCancer Immune Profiling Panel. Next, we used flow cytometry to assess the number and function of T cells in the tumor and ascites. Results: HDAC inhibition increased expression of genes associated with T and NK cell infiltration, cytokytic functions, major histocompatibility class I and class II, as well as other genes associated with immune recognition. In addition, eninostat significantly reduced the number and suppressive capacity of regulatory T cells in both the tumor and ascites. Notably, HDAC inhibition led to infiltration of higher quality CD8 cytotoxic T cells with superior effector functions. These CD8 T cells expressed lower levels of the exhaustion-associated transcription factor Eomes, suggesting they will remain highly functional for a longer amount of time and are less susceptible to exhaustion. Conclusions: Our results suggest eninostat could dramatically increase tumor immunogenicity and help turn a “cold” (non-infamated) tumor into a “hot” (T cell inflamed) tumor, while potentiating anti-T cell tumor functions. Thus, inclusion of HDAC inhibition may increase the frequency of patients responding to checkpoint blockade and/or other immunotherapies.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Lymph node (LN) metastasis and genomic profiles are important prognostic factors in endometrial cancer (EC). However, the prognostic significance of the volume of metastatic disease found in sentinel lymph node (SLN) specimens is unknown. We sought to determine if particular genomic mutations were associated with LN metastasis and volume of LN metastasis.

Methods: Surgically staged women with EC at a single institution were enrolled in a genetic sequencing institutional protocol. Relevant targets were enriched by a custom designed Agilent SureSelect hybrid capture enrichment library using standard protocols. A subset of the EC population underwent SLN biopsy with completion lymphadenectomy and hysterectomy as part of the FIREST study. SLN specimens underwent ultrastaging to detect low volume disease such as isolated tumor cells (ITCs).

Results: 345 patients with EC completed surgical staging and tumor sequencing between 3/2007 and 9/2016; median age 63 yrs and median BMI 34.2 kg/m². 55 patients (16.0%) were LN positive (LN+) while 290 (84.0%) were LN negative (LN-). The LN+ group were less likely to have endometrioid histology than the LN- group (54.5% vs 77.2%) and more likely to have grade 3 disease (65.5% vs 33.1%) (p = 0.001 for both). LN+ patients were more likely than LN- patients to have p53 mutations (44.4% vs 27.0%, p = 0.02), and less likely to have PTEN mutations (38.9% vs 59.1%, p = 0.01). Polyclonality of PIK3CA mutations (defined as > 2 mutations in the same tumor) was only observed in the LN- patients (p = 0.08). 44 patients were LN negative in SLN biopsy of these, 8 (18.2%) had ITCs as their only metastatic disease. All ITC patients with p53 mutations were of non-endometrioid histology (3/8). PTEN (80.0%) and PIK3CA (60.0%) mutations were observed in the endometrioid ECs. No patients with ITCs had a recurrence.

Conclusions: Primary tumors associated with LN metastases may both have genomic mutations and histologic features consistent with more aggressive disease. In patients with low volume (ITC's) metastases, genomic mutations aligned with histology. More work is needed to better define the relationship between genomic mutations, histology, metastatic volume and prognosis.

5588 Poster Session (Board #315), Mon, 1:15 PM-4:45 PM

Differences in survival outcomes in advanced endometrial cancer due to variation in adjuvant therapy and histology

First Author: Emily Meichun Ko, University of Pennsylvania, Philadelphia, PA

Background: To determine the impact on overall survival (OS) of the sequence-of-order of adjuvant radiation (RT) and chemotherapy (CT) on different advanced endometrial cancer (EC) histologies. Methods: Stage 3 endometrioid (EAC), serous (SER), clear cell (CC), and carcinosarcoma (CS) patients who underwent primary surgical staging from 1999-2011 were identified in SEER-Medicare. Sequence, timing, and modality of RT and CT were analyzed using Kaplan-Meier estimates, log rank tests, and multivariable cox modeling. Treatment groups with n < 10 were excluded in cox modeling. Results: Of 2375 cases identified (1537 EAC, 485 SER, 96 CC, 257 CS), 31.3% received no treatment. The remainder received RT alone, concurrent RT-CT, serial or sandwich modalities (table 1). OS differed by receipt of CT overall as well as within each histologic subtype (log-rank p < 0.05, all). After adjusting for age, race, substage, region, and histology, all patients receiving CT except for concurrent RT-CT followed by CT, had improved OS over no treatment (all p < 0.05). However, differences by histology were seen. For EAC the sandwich arm had the greatest reduction in death (72%), whereas for SER and CC the concurrent RT-CT arms fared best. For CS receipt of any CT improved OS, whereas above RT alone did not. (Table1). Conclusions: OS for advanced EC significantly differs by histology and mode of adjuvant therapy. Future studies should evaluate whether sandwich therapy for EAC, concurrent RT-CT for SER and CC, and CT alone for CS may most effectively improve OS.

Adjuvant therapy: adjusted HR for OS.

<table>
<thead>
<tr>
<th>Type of AT (%)</th>
<th>All histology</th>
<th>EAC</th>
<th>SER</th>
<th>CC</th>
<th>CS</th>
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<tr>
<td>RT</td>
<td>26.2</td>
<td>0.80 (0.71, 0.87)</td>
<td>0.78 (0.67, 0.90)</td>
<td>0.96 (0.87, 1.04)</td>
<td>0.73 (0.64, 0.83)</td>
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<td>CT</td>
<td>24.8</td>
<td>0.60 (0.52, 0.68)</td>
<td>0.59 (0.53, 0.65)</td>
<td>0.60 (0.52, 0.68)</td>
<td>0.45 (0.35, 0.50)</td>
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<tr>
<td>Concur RT-CT</td>
<td>9.5</td>
<td>0.51 (0.41, 0.64)</td>
<td>0.60 (0.45, 0.75)</td>
<td>0.43 (0.26, 0.59)</td>
<td>0.29 (0.10, 0.50)</td>
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<td>Serial CT-RT</td>
<td>4.4</td>
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<td>0.56 (0.37, 0.84)</td>
<td>0.68 (0.38, 1.22)</td>
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<tr>
<td>Serial CT-RT</td>
<td>1.6</td>
<td>0.60 (0.39, 0.93)</td>
<td>0.55 (0.32, 0.91)</td>
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<tr>
<td>Sandwich</td>
<td>1.0</td>
<td>0.53 (0.38, 0.79)</td>
<td>0.28 (0.12, 0.69)</td>
<td>0.90</td>
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<tr>
<td>Concr RT-CT,</td>
<td>0.6</td>
<td>0.69 (0.32, 1.46)</td>
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Assessment of activating estrogen receptor 1 (ESR1) mutations in gynecologic malignancies.

**Background:** Endocrine therapy is often considered to treat hormone-responsive gynecologic (gyn) malignancies. Mutations in ESR1 leading to constitutive transcriptional activity have been reported in estrogen receptor positive (ER+) breast cancers and may contribute to acquired resistance to endocrine therapy. Using comprehensive genomic profiling (CGP) we assessed the frequency of ESR1 activating genomic alterations (GA) in gyn malignancies. Methods: DNA from FFPE tumor tissue obtained during routine clinical care for 8965 gyn malignancies (ovary, fallopian tube, uterus, cervix, vagina, vulvar, and placenta) was analyzed for all classes of GA (base substitutions (muts), indels, rearrangements, and amplifications) in ESR1 by hybrid capture, next generation sequencing. Results: 295 ESR1 GA were identified in 285 (3.0%) cases; 10 cases contained 2 ESR1 GA each. wESR1 amplifications were identified in 80 (0.8%) cases and mutESR1 were present in 86 (0.9%) cases. mutESR1 were more common in uterine compared to other cancers (2.0% vs <1%, p < 0.001). mutESR1 were also enriched in carcinomas with endometrioid histology: 4.2% in uterine endometrioid vs 0.2% in uterine serous carcinomas (p < 0.001). 35%, 17%, 13%, and 12%, respectively, of all mutESR1 were present in 86 (0.9%) cases. were also enriched in carcinomas with endometrioid histology: 4.2% in uterine endometrioid vs 0.2% in uterine serous carcinomas (p < 0.001). The Y537S, Y538G, L539P, and S463P mut comprised 35%, 17%, 13%, and 12%, respectively, of all mutESR1. Clinical data for multiple gyn malignancy patients demonstrate that mutESR1 may be the novel or acquired estrogen resistance mechanism. Loss of function in the ovarian cancer (LGSOC) samples obtained at diagnosis and after recurrence in a patient treated with letrozole demonstrated an acquired mutESR1 Y537S. Another LGSOC patient had a mutESR1 Y537N at diagnosis and has attained prolonged clinical benefit (> 4 years) with fulvestrant. Conclusions: ESR1 muts and the associated resistance to endocrine therapies are enriched in endometrioid histologic subtypes, and may occur either de novo or as a resistance mechanism to prior endocrine therapy. CGP identified clinically relevant ESR1 GA that may be useful in directing therapy of gyn malignancies.

Patterns of care and survival outcomes of stage IIIA endometrial cancer: An analysis of the National Cancer Database.

**Background:** Stage IIIA endometrial cancer with serosal or adnexal involvement has a better prognosis than other advanced uterine cancers and likely behaves differently compared to those with vaginal, parametrial or lymph node involvement. We performed a population-based analysis of Stage IIIA endometrial cancer from the National Cancer Database (NCDB) to evaluate survival outcomes by treatment regimens. Methods: Patients with FIGO stage IIIA endometrial endometrial cancer treated with hysterectomy and bilateral oophorectomy and receiving adjuvant treatment between 2004 and 2014 were identified. Treatments evaluated include chemotherapy alone (CT), pelvic radiation ± brachytherapy (RT±BT), chemotherapy with brachytherapy (CT±BT), chemotherapy with pelvic radiation (CT±RT), or chemotherapy with pelvic radiation and brachytherapy (CT±RT±BT). Treatment trends over time were analyzed. Multivariate Cox proportional hazard models were developed to examine treatment outcomes. Results: Of 6,760 patients who met study criteria, 1842 (27.2%) received adjuvant CT; 2,732 (40.4%) received RT±BT; 702 (10.4%) received CT±BT; 871 (12.9%) received CT±RT; and 613 (9.1%) received CT±RT±BT. The practice of RT±BT declined from 56% to 16%; while CT alone rose from 18% to 36%; and CT±RT rose from 4% to 14% over the study period (p < 0.001). Median follow-up was 69.0 months. Five-year overall survival was 83.7%, 69.7%, 73.6%, 63.6% and 78.0% for CT±BT, CT±RT, RT±BT, and CT±RT±BT, respectively. Older age, black race, higher Charlson-Deyo comorbidity score, higher tumor grade, lymphovascular invasion, and having Medicare/uninsured were negative predictors of survival on multivariate analysis. CT±BT was significantly associated with improved survival over CT (HR 1.89, 95% CI 1.53-2.33; p < 0.001), CT±RT (HR 1.72, 95% CI 1.36-2.18; p < 0.001), RT±BT (HR 2.46, 95% CI 2.01-3.01; p < 0.001), and CT±RT±BT (HR 1.38, 95% CI 1.07-1.79; p < 0.001). Conclusions: While pattern of care shows an increase in use of adjuvant chemotherapy alone in Stage IIIA endometrial cancer, our findings demonstrate that chemotherapy should be combined with vaginal cuff brachytherapy to these patients.

Quality of life (QoL) in a phase III trial of pelvic external beam radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk, early stage endometrial carcinoma: An NRG Oncology/Gynecologic Oncology Group study.

**Background:** In GOG Study 249, VCB/C was not superior to PXRT in overall survival or treatment failure rate (Randall et al, ASTRO, 2017). Here we compare QoL, fatigue, neurotoxicity, and gastrointestinal (GI) symptoms between patients randomized to VCB/C versus PXRT, and examine the association between primary comorbid illness plus obesity on QoL. Methods: The Functional Assessment of Cancer Therapy (FACT) – Endometrial Trial Outcome Index (FACT-En TOI) for QoL, FACT-G/Fatigue subscale, FACT/GOG-Neurotoxicity subscale, and 6 items from the FACT-En for gastrointestinal (GI) symptoms were measured at baseline, 4 and 11 weeks, 8 and 14 months post-enrollment. Treatment differences were assessed with a linear mixed model adjusting for pretreatment score, assessment time, and age at enrollment. Results: 540 of 601 eligible patients provided evaluable patient-reported assessments. QoL was not statistically different significantly between treatment arms. However, fatigue and neurotoxicity were significantly worse in the VCB/C group compared to the PXRT group (p < 0.001) especially at 11 weeks. Patients in the PXRT arm, however, reported significantly (p < 0.001) worse GI symptoms when compared with those in VCB/C. Patients with ≥3 comorbid illnesses reported 7.1 points lower (95% CI: 12.0 to −2.3; p = 0.004) QOL scores than those with ≤2 comorbid illnesses, and 6.5 points lower (95% CI: 2.8 to −10.2; p < 0.001) fatigue scores than those with ≤1 comorbid illness. Although obesity status was not associated with the QOL score, patients with morbid obesity (BMI ≥40) reported worse fatigue (4.1 points lower; 95% CI: 0.8 to −7.5; p = 0.008) than other patients. Conclusions: VCB/C was associated with substantially more fatigue and neuropathy; however, PXRT resulted in more GI symptoms. Absent any survival or disease control benefit of VCB/C over PXRT, PXRT remains an effective and appropriate treatment for this patient population. In addition, patients with three or more comorbidities at study entry are likely to have worse QoL and fatigue. Clinical trial information: NCT00807768.
Efficacy and safety of nivolumab (Nivo) in patients (pts) with advanced or recurrent uterine cervical or corpus cancers. First Author: Kosei Hasegawa, Saitama Medical University International Medical Center, Hidaka, Japan

Background: Recent advances in immuno-oncology provide evidence for the efficacy of PD-1/PD-L1 blockades for a variety of cancers. However, the clinical activity of Nivo, an anti-PD-1 monoclonal antibody, in the treatment of advanced/recurrent uterine cervical (CVC) and corpus cancers (CC) is not yet clear. Methods: Phase 2, multicenter, multicohort, open-label study evaluating the efficacy and safety of Nivo in pts with advanced/ recurrent CVC or CC (JapicCTI-163212). Patients received Nivo 240 mg every 2 weeks until progression or unacceptable toxicity. Primary end point was overall response rate (ORR; complete or partial response [PR]); an upper limit of normal) were correlated with outcomes. A total of 20 CVC (14 squamous, 5 adenocarcinoma [AC], 1 adenosquamous) and 23 CC (15 endometrioid AC, 6 other endometrial cancer, 2 carcinosarcoma) pts were enrolled. Most pts had ≥2 prior chemotherapy regimens (CVC 13/20; CC 14/23). ORR was 25% (5/20) and 23% (5/22 evaluable), median PFS was 5.6 and 3.4 months, 6-month OS was 84% and 73%, and 12-month OS (preliminary) was 73% and 49% in CVC and CC, respectively. One pt with CVC AC had PR. Most of the pts who responded had a durable response (4/5 CVC, 5/5 CC) at data cut-off (Aug 18, 2017). Drug-related adverse events were seen in 63% (Grade 3-4, 19%) of pts. There were no drug-related deaths. In CVC, ORR was higher in pts with PD-L1+ tumors (33%; 5/15) than in pts with PD-L1- tumors (0%; 0/5) based on a PD-L1 expression level of ≥1%; HPV status did not affect ORR (33% in both HPV+ [3/9] and HPV- [1/3]). In CC, ORRs were similar, regardless of PD-L1 status (PD-L1+ 26%, 2/8 evaluable; PD-L1- 20%, 1/5). Most of the pts who responded had ≥1 PR that were durable; no pts with CVC had MSI-High.

Conclusions: This study demonstrates that Nivo has acceptable toxicity with evidence of clinical activity (primary end point met) in pts with CVC and CC. PD-L1 expression in CVC and MSI-High in CC may predict the clinical activity of Nivo. Clinical trial information: JapicCTI-163212.

Efficacy and safety of nivolumab (Nivo) in patients (pts) with advanced or recurrent cervical or corpus cancers. First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Lenvatinib (LEN) is a multikinase inhibitor of VEGFR 1-3, FGFR 1-3, and other kinases. Pembrolizumab (PEM) is an anti-PD-1 antibody. We report updated interim results from a phase 1b/2 study evaluating LEN + PEM in patients (pts) with advanced endometrial cancer (EC) (NCT02501096). Methods: In this multicenter, open-label study, pts with histologically confirmed EC irrespective of microsatellite instability (MSI) or mismatch repair (MMR) status and measurable disease per immune-related RECIST (irRECIST) received LEN (20 mg PO QD) plus PEM (200 mg IV Q3W). Tumor assessments were performed by investigators using irRECIST. The primary phase 2 endpoint was objective response rate at 24 weeks (ORRWK24), calculated only for evaluable pts who had 24 weeks of follow up or discontinued treatment or died prior to 24 weeks. Secondary endpoints included ORR (full analysis set), progression-free survival (PFS), and duration of response (DOR). Results: At data cutoff of Aug 1 2017, 54 pts were enrolled (endometrioid: Gr 1 (7), Gr 2 (12), Gr 3 (5); serous (18); others (8); unknown (4)). Three (6%) pts were MSI-high (MSI-H); 43 (80%) were non-MSI-H/low MMR (MRMMPs); 8 (15%) were not done/unknown.

Median follow-up for PFS was 4.0 months (95% confidence interval [CI], 2.7–7.6). ORRWK24 was 50.0% (95% CI, 32.4–67.6), and all responses were confirmed. ORR was 36.7% (95% CI, 23.4–51.1), which reflects the short follow-up time for pts with later enrolment. Median DOR has not yet been reached (not estimable [NE], 95% CI, 4.1–NE) and median PFS was 10.1 months (95% CI, 5.3–NE). Of the 3 MSI-H pts, 1 achieved partial response, 1 had stable disease, and 1 had progressive disease. For non-MSI-H/MMR pts, ORRWK24 was 50.0% (95% CI, 29.9–70.1). Grade 3 treatment-related adverse events (TRAEs) occurred in 32 (59%) pts; there were no Grade 4 TRAEs. 3 (6%) pts discontinued treatment due to a TRAE. The most common TRAEs were hypertension (59%), fatigue (50%), 5 years) and patients with complete or partial response (all P < 0.05). Of these, significant associations were found between increases in CXCL9 and CXCL10 levels and patients with compete, partial, or unconfirmed partial responses (all P < 0.05).

Preclinical models of endometrial cancer treated with LEN, PEM, or their combination were subjected to weighted gene coexpression network analysis for pathway enrichment analyses. Results: At CD1D5 and C2D1 of LEN + PEM, significant changes were seen in the levels of 16 and 41 biomarkers, respectively, including increased levels of interferon-γ (IFN-γ) and IFN-γ-regulated chemokines (CXCL9, CXCL10, CXCL11; all P < 0.05). Of these, significant associations were found between increases in CXCL9 and CXCL10 levels and patients with complete response, partial, or unconfirmed partial responses (all P < 0.05). Preclinical models in vivo showed that LEN alone significantly depleted the TAM population in excised tumors (P < 0.01). Transcriptome analyses of tumors from mice treated with LEN + anti-PD-1 showed that genes specifically regulated by the combination were significantly enriched for genes involved in signaling pathways associated with immune modulation, including IFN signaling (FDR P < 1.50 × 10−5).

Conclusions: In patients with advanced EC, LEN + PEM was associated with changes in several biomarkers, including IFN-γ-regulated chemokines, some of which may be associated with clinical response. In vivo preclinical experiments suggest that LEN monotherapy may modulate tumor microenvironment by decreasing the local TAM population, whereas LEN + anti-PD-1 may act via a mechanism that includes the IFN signaling pathway. Overall, these findings provide preclinical rationale for efficacy of LEN + PEM. Clinical trial information: NCT02501096.
Preoperative olaparib in early-stage endometrial cancer (EC): A phase 0, window of opportunity trial to evaluate the PARP inhibition effect, targeting cell proliferation/apoptosis proteins (POLEN study). First Author: Ignacio Romero, Instituto Valenciano de Oncología (IVO), Valencia, Spain.

Background: Olaparib (AZD2281, KU-0059436) is a poly ADP ribose polymerase (PARP) inhibitor. Biomarkers that predict a response to olaparib in EC are not fully established. The aim of this study is to identify pharmacodynamic and pharmacogenetic biomarkers associated with a short term exposure to olaparib in type I primary EC surgical patients (pts). Methods: In this phase 0, multicenter, single arm, window of opportunity trial, we aimed to enroll patients with type I primary EC received olaparib tablets (oral 300mg/BID; 4 weeks) before surgery. Biological effects were evaluated by comparing the initial biopsy and the tumor tissue at surgery. The primary endpoints were the significant inhibition of cyclin D1, Ki67 and active caspase 3 activity. Secondary objectives included the correlation between PARP inhibition and cell proliferation, angiogenesis and tumor-tissue biomarkers. The predictive role of PTEN, PMS2 and MSH6 mutations were evaluated. We controlled multiple testing issues with a false discovery rate (FDR) of 10%. Results: From March 2016, 41 pts have been screened, 36 included, 23 treated and 19 could be studied in biomarker analysis. Median age was 63y (51-82); 100% were endometrioid and clinical stage was I (7), 89.5% and stages II, III and IV (2, 10.5%). Median time of olaparib exposure was 21 days (13-32). Significant inhibition was declared for cyclin D1 (p = 0.01), but not for Ki67 and active caspase 3 immunostaining. Differences in PARP1 baseline and post-treatment immunostaining correlates (Rho > 0.45; p < 0.05) with differences in pre-post cyclin D1, Ki67, phospho-histone H3, p50, VEGF and Hif1α measures. However, only cyclin D1 (Rho = 0.771, p < 0.001) showed a significant correlation under FDR criterion. Genetic alterations did not show differences in pre-post treatment measures. The most common AEs were nausea (31.6%), vomiting (21.1%) and fatigue (21.1%) grade 1 and 2. No surgery was delayed due to toxicity. Conclusions: The study has identified some potential biomarkers associated with olaparib exposure in cell proliferation/apoptosis pathways that might help select best candidates. Clinical trial information: NCT02506816.

Variability in Medicare utilization and payment among gynecologic oncologists. First Author: Stephanie Lim, Duke University School of Medicine, Durham, NC.

Background: The Medicare Provider Utilization and Payment Data: Physician and Other Supplier Public Use File (POSPUF) for 2015 is a publicly available file from the CMS that includes all direct payments to providers who care for fee-for-service Medicare recipients. The objective of this study was to analyze variability in gynecologic oncologists' Medicare utilization and reimbursements, with attention to differences based on provider gender and time spent in practice. Methods: The POSPUF 2015 was analyzed with respect to Gynecologic Oncology specialty providers. We used publicly available data to confirm gynecologic oncology subspecialty and to determine each provider's total number of years in gynecologic oncology practice. Evaluation, management, and procedure/surgery codes were analyzed; drug delivery codes were excluded due to variability in billing these by facility/hospital. Results: The POSPUF file included 824 gynecologic oncologist providers receiving a total of $28,772,739 in payments. The majority of providers practiced in large metropolitan areas (66%) or mid-sized metro areas (27%). While females composed 38.5% of gynecologic oncologists, they accounted for only 28.1% of Medicare reimbursements. The median Medicare reimbursement to a Gynecologic Oncologist was $24,828 (IQR $11,564, $45,412), but this was significantly different by gender; female $19,394 (IQR $10,913, $34,894) compared to male $29,395 (IQR $13,903, $52,941). Overall, female providers receive 30.4% of evaluation and management reimbursements and 22.5% of surgical reimbursements. During the first ten years in practice, women composed 47.0% of providers and accounted for 52.3% of the services reimbursed, compared to 36.25% of providers/26.6% of the reimbursed services (11-20 years in practice), and 18.11% of providers/16.4% of services (> 20 years in practice). Conclusions: While male gynecologic oncologists receive higher median reimbursements than females, there is a trend toward equal services and reimbursements between genders among younger providers, suggesting a trend toward gender equity over time.
**TPS5602**  
Poster Session (Board #328a), Mon, 1:15 PM-4:45 PM  
**Background:** Sentinel node biopsy (SLN) is an alternative to pelvic lymphadenectomy (PLN). The false negative rate is < 1% when “MSKCC Algorithm” is fulfilled. The technique can detect isolated tumor cells (ITC) or micrometastases in 15 – 20 % of N0 patients, reveal SLN in unexpected areas in up 30% of cases and reduce short term lymphatic morbidity. However, the long-term prognosis of SLN negative patients is unknown. In 2014, the GCIG brainstorming on cervical cancer pointed out the need for a validation study, taking survival into account, giving birth to SENTICOL III. **Methods:** SENTICOL III is an international prospective multicenter randomized trial. We use a « co-primary » objective regarding Disease Free Survival (DFS) and Health Related Quality of Life. The hypothesis is that SLN biopsy alone provides similar DFS and better quality of life. Secondary objectives are outcome of patients with ITC and micrometastases, evaluation of mapping with indocyanine green (ICG), overall survival, recurrence free survival. A cost analysis will be undertaken and a tumor tissue bank will be established. Patients with an early stage cervical cancer defined as FIGO stage Ia1 with lymphovascular invasion to IIa1, maximum diameter ≤ 4 cm on MRI and node negative on imaging will be eligible to participate. SLN biopsy will be performed using isotopic detection +/- blue dye or ICG. SLN of patients with an “optimal” mapping will be analyzed by frozen section. SLN negative patients will be randomized intraoperatively 1:1 to SLN only or SLN + PLN. All SLN will be submitted to ultrasting (200 microns levels). All centers will follow a quality assurance program to ensure surgical competency and a standardized pathological evaluation 900 patients will be recruited in 3 years, with 4 years of follow-up. (3 years-disease free survival of 85%, with a non-inferiority margin of 5% (80 vs 85%, HR = 1.373), a unilateral alpha error of 5%, and a power of 80%) The trial has started in France, and an international collaboration has been developed through GCIG and ENGOT. (NCT03386734). CHU Besançon is the sponsor for France Clinical trial information: ID-RCB : 2017-A00945-48.

**TPS5604**  
Poster Session (Board #329a), Mon, 1:15 PM-4:45 PM  
**A phase 2, multicenter study to evaluate the efficacy and safety using autologous tumor infiltrating lymphocytes (TIL) with tumor infiltrating lymphocytes (LN-145) in patients with recurrent, metastatic or persistent cervical carcinoma.** First Author: Amir A. Jazaeri, University of Virginia, Charlottesville, VA.  
**Background:** Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has demonstrated efficacy in the treatment of immunogenic tumors with high mutation loads, such as melanoma, and virally-associated tumors, such as HPV-mediated cervical cancer. As outcomes for patients with recurrent, metastatic or persistent cervical cancer remain extremely poor, there is an enormous need for the development of novel immunotherapeutic approaches with curative potential such as ACT with TIL. **Methods:** Clinical trial C-145-04 (NCT03108495) is a prospective, phase 2 multicenter, open-label study evaluating the efficacy of a single autologous TIL infusion (LN-145) followed by IL-2 after a myeloablative lymphodepletion (NMA-LD) regimen in patients with recurrent, metastatic, or persistent cervical cancer who have failed at least one prior systemic therapy. Patients undergo surgical resection of a tumor from which TIL are extracted and expanded at a central GMP manufacturing facility that prepares a cryo-preserved TIL (LN-145) product for infusion. One week prior to LN-145 infusion, patients undergo NMA-LD consisting of cyclophosphamide (60 mg/kg) daily x 2 days followed by fludarabine (25 mg/m²) daily x 5 days. LN-145 is infused 24 hours after NMA-LD and followed by up to 6 doses of IL-2 (600,000 IU/kg) every 8-12 hours. The primary endpoint is the objective response rate (ORR) per RECIST v1.1. Secondary endpoints include safety and efficacy parameters such as complete response, duration of response, disease control rate, progression free- and overall survival. In addition to the tumor resected, patients must have an additional measurable lesion for response assessment. Other major eligibility criteria include adequate bone marrow, liver, pulmonary, cardiac and renal functions, GCIG performance status of 0 or 1.  
**TPS5603**  
Poster Session (Board #328b), Mon, 1:15 PM-4:45 PM  
**A randomized phase II/III trial of conventional paclitaxel and carboplatin (CTC) versus dose-dense paclitaxel and carboplatin (ddCTC), with or without bevacizumab (Bmb), for stage IB-IV recurrent or persistent cervical cancer (CC): Japan Clinical Oncology Group study (JCOG1311).** First Author: Ryo Kitagawa, Department of Gynecology and Obstetrics, Tohoku Medical and Pharmaceutical University, Miyagi, Japan.  
**Background:** Patients with metastatic or recurrent CC who are not amenable to curative treatment with surgery or radiation have a poor prognosis, and systemic chemotherapy is regarded as a standard treatment. Based on the JCOG0505, we considered tri-weekly CTC as the standard regimen. We subsequently focused on dose-dense, weekly administered paclitaxel, which was more effective than conventional administration for breast cancer and, in Japan, ovarian cancer. The efficacy and safety of ddCTC have not been evaluated for CC. Therefore, we designed JCOG1311 to confirm the superiority of ddCTC to CTC in metastatic or recurrent CC. However, Bmb was approved in Japan for treatment of metastatic or recurrent CC on May 2016. We amended the protocol to add the criteria by which patients would receive Bmb. **Methods:** Major eligibility criteria are stage IBV, persistent, or recurrent CC patients including SCC or adenosquamous carcinoma. We enroll patients according to institution, PS, and platinum-free interval as treatment factors, whether they receive carboplatin (AUC of 5) on day 1 plus either paclitaxel (175 mg/m²) on day 1 (CTC), or paclitaxel (80 mg/m²) on day 1, 8, 15 (ddCTC). Both treatments are repeated every 3 weeks. They can receive Bmb (15 mg/kg) every 3 weeks if not contraindicated. 1.4 of planned 56 with measurable disease receiving Bmb in part I, of which the primary endpoint is response rate (RR), have been enrolled until January 2018. If the RR of ddCTC + Bmb arm is greater than that of CTC + Bmb arm plus 5%, the study will proceed to phase III part, which has OS as the primary endpoint. We hypothesize that the 2-year OS of ddCTC arm will be greater than that of the cTC arm (i.e., 45% compared to 35%). According to the Schoenfeld and Richter method, the required sample size is total 420 patients, with one-sided a of 0.05 and b of 0.20 during 3.5 years of accrual and 2 years of follow-up. This trial is supported by the Japan Agency for Medical Research and Development. And, this trial was registered at the UMIN Clinical Trials Registry as UMIN000019191. Clinical trial information: 000019191.

**TPS5605**  
Poster Session (Board #329b), Mon, 1:15 PM-4:45 PM  
**EDMOND: A feasibility study of elemental diet as an alternative to parental nutrition for ovarian cancer patients with inoperable malignant bowel obstruction (IBO).** First Author: Agnieszka Michael, University of Surrey, Guildford, United Kingdom.  
**Background:** Inoperable bowel obstruction (IBO) occurs in up to 50% of patients diagnosed with ovarian cancer. Nutrition support for patients with IBO is challenging. Parenteral feeding (PN) is the recommended route for patients with a prognosis of > 2 months, however there is little evidence that it improves quality of life and the cost of it is very high. If PN is not available or not tolerated, patients are frequently discharged home from hospital with signs of clear fluids only. Management of inoperable bowel obstruction remains a major challenge and clear guidelines are needed. Elemental diet (ED) is a liquid diet that contains proteins in the form of amino acids, fats in the form of medium chain triglycerides, vitamins and trace minerals. EDs are almost completely absorbed in the upper small intestine. **Methods:** The primary objective of the study is to establish if ED can be used as an alternative to home PN in patients with IBO by providing a ‘proof of concept’ of ED as an acceptable and useful feeding option. The secondary aim is to examine the impact of ED on quality of life. The primary endpoints of the study are taste acceptability (graded 1-5 on a purposely designed Elemental Diet data collection chart), incidence of vomiting and incidence of pain. The secondary endpoints include the number of women who can tolerate ED and can subsequently be treated with palliative chemotherapy (as per standard of care), the number of patients alive at the end of the study, quality of life and nutritional intake. This is a mixed-method single arm feasibility study of 34 patients diagnosed with IBO and who can tolerate 500ml of liquid. Patients are provided with ED and followed-up for 2 weeks. Patients’ symptoms and quality of life are assessed using the Memorial Symptoms Assessment Scale (MSAS) and EORTC Quality of Life GLQ-C30 questionnaire. As this is a feasibility study to evaluate whether ED is an acceptable intervention for patients with IBO, recruiting 25 patients into the study will provide an answer to the question. As the prognosis is poor in this cohort we assumed 25% attrition rate 8 out of 34 patients have been recruited and the recruitment continues. Clinical trial information: ISRCTN16625460.
**OVARIO: The phase 2, single-arm, open-label study of maintenance therapy with niraparib + bevacinuzumab in patients with advanced ovarian cancer following response on frontline platinum-based chemotherapy.**

**Background:** Niraparib (Zejula) is a selective poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor, significantly improved progression-free survival (PFS) as a single agent for patients with recurrent ovarian cancer (OC) relative to placebo in the ENGOT-01/6 NOVA trial, regardless of BRCA or HRD status. The ongoing AVANOVA trial (NCT02354131) has shown that niraparib can be safely combined with bevacizumab (bev). This combination is being explored in AVANOVA, as a strategy to increase tumor sensitivity to PARP inhibition. As an anti-angiogenic agent, bev can induce tumor hypoxia, leading to downregulation of BRCA and RAD51, which could sensitize tumors to PARP inhibition, and lead to apoptosis via context-specific synthetic lethality. While BRCA and HRD status was insufficient to predict responders to niraparib in NOVA, a longer median PFS was observed for the cohorts with these biomarkers. In the phase 2 OVARIO study (NCT03326193), niraparib plus bev will be evaluated as a maintenance therapy in patients with advanced OC who have recovered from primary debulking surgery and have responded to frontline platinum-based chemotherapy with bev. Methods: Target enrollment is 90 patients, regardless of BRCA or HRD status, with stage 3b and 4 epithelial ovarian, fallopian tube, or peritoneal cancer. Patients must achieve complete response, partial response or no evidence of disease after the frontline platinum-based chemotherapy. The primary objective for OVARIO will be PFS at 18 months landmark. Secondary objectives include estimation of PFS, overall survival, time to first subsequent therapy, and safety and tolerability. Exploratory objectives will be PFS at 6 and 12 months and patient-reported outcomes. The starting dose of niraparib will be based on the patient’s baseline body weight and/ or platelet count. Patients weighing ≥77 kg with a platelet count of ≥150,000/μL will receive 200 mg qd. Patients weighing <77 kg with a platelet count of <150,000/μL will receive 200 mg qd. The bev dose will be 15 mg/kg q3w up to 15 months. Patients will be treated continuously until disease progression or unacceptable toxicity. Clinical trial information: NCT03326193.

**TPS5607 Poster Session (Board #330b), Mon, 1:15 PM-4:45 PM ATALANTE (ENGOT-ov29): A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated with platinum-based chemotherapy and bevacizumab.**

**Background:** The immunosuppressive environment is increased in Ovarian Cancer (OC) by the expression of T cell inhibitor receptors on tumor cells and immune cells. Targeting PD-1/PD-L1 pathway (an inhibitory immune therapy) and immunotherapy act synergistically. Methods: ATALANTE is a randomized (2:1), double blinded, phase III trial evaluating the efficacy and safety of adding the anti-PD-L1 monoclonal antibody atezolizumab (At) to Cx and bev in 405 OC patients (pts) in platinum-sensitive relapse. Main eligibility criteria include: ECOG ≤1, first or second platinum-sensitive relapse (>18 months), normal organ function, absence of auto-immune disease or of chronic corticosteroid therapy. All patients must have a tumor biopsy at study entry for PD-L1 testing (stratification factor). Pts are treated with 6 cycles of platinum-based Cx (q3 or q4 weeks) plus bev + At (1200mg q3w) or placebo followed by bev (15 mg/kg q3w) plus At/placebo maintenance until progressive disease or unacceptable toxicity. The primary endpoint is PFS based on RECIST v1.1 according to investigator assessment. The final PFS analysis will be performed when the number of predefined events is reached. The latest review by the Independent Data Monitoring Committee in July 2017 did not identify any safety issue and suggested that the trial can continue as planned. The study is currently recruiting internationally. Clinical trial information: NCT02891824.

**TPS5608 Poster Session (Board #331a), Mon, 1:15 PM-4:45 PM**

**An open-label phase 1 trial of the safety and efficacy of daily subcutaneous SPL-108 injections when used in combination with paclitaxel in patients with platinum-resistant, CD44+, advanced ovarian epithelial cancer.**

**Background:** Ovarian cancer often presents in advanced stages and is treated with platinum-based chemotherapy. However, many patients develop platinum-resistant disease with either failing to achieve clinical response or progressing within 6 months after completion of treatment. Our laboratory has shown that CD44 contributes to the development of chemotherapeutic resistance, through MDR1-dependent/P-glycoprotein mediated efflux of chemotherapeutic agents. Targeting CD44 or related signaling pathways inhibits tumor growth and relapse, and increases sensitivity to cytotoxic agents. SPL-108 is an 8-amino-acid peptide derived from single chain urokinase plasminogen activator that binds to CD44. In vitro and in vivo experiments showed that SPL-108 has therapeutic activity in models of ovarian and other cancers. Phase I trials with SPL-108 in healthy volunteers demonstrated no systemic adverse events; phase Ib trials in women with gynecologic cancers showed self-limited, mild or moderate adverse events with several subjects showing stable disease. Phase II trials in ovarian cancer patients showed improved time to disease progression with no grade 4 toxicity. 6.5% had grade 3 all of which were constitutional. In the current trial, SPL-108 would be used in combination with paclitaxel in an attempt to reverse efflux-mediated resistance to chemotherapy. Due to positive safety profile of SPL-108, the goal is to achieve improved efficacy without enhanced toxicity. Methods: Open-label 2-arm phase I trial. Arm I includes 6-12 patients, with a 3+3 design with 2 cohorts. Cohort 1 will receive daily 150-mg SPL-108 SQ, cohort 2 will receive twice-daily 150-mg SPL-108; both cohorts will have concurrent administration of weekly paclitaxel of 80 mg/m2, on Days 1,8,15 of a 28 day cycle. Safety will be assessed, and subjects without dose-limited toxicity continue 6 cycles, unless disease progression or unacceptable toxicity occurs. Arm II is the Exploratory Expansion Phase: 12 subjects receive SPL-108 daily dose determined in the Arm I Safety phase with concurrent 80 mg/m2 paclitaxel. Clinical trial information: NCT03078400.

**TPS5609 Poster Session (Board #331b), Mon, 1:15 PM-4:45 PM**

**Clinical trial in progress: A study of VB-111 combined with paclitaxel vs. paclitaxel alone for treatment of recurrent platinum-resistant ovarian cancer (OVAR, VB-111-701/GOG-3018).**

**Background:** Ofranergene obadenocov (VB-111) is a targeted anti-cancer gene therapy with a dual mechanism: an antiangiogenic broad effect and induction of a tumor directed viral immune response. Over 400 cancer patients have been treated with VB-111, with evidence of anti-tumor activity across three phase 2 studies and a favorable safety profile. A phase 2 trial in patients with platinum resistant ovarian cancer treated with VB-111 in combination with weekly paclitaxel was conducted. In a population with 50% platinum refractoriness and 52% prior antiangiogenics, CA-125 response was observed in 60% of patients with a dose response pattern and a significant increase in overall survival (OS) at therapeutic vs. low dose level (median 810 vs. 172 days, p = 0.042) as well as evidence of an immune-therapeutic effect. Based on these observations, a phase 3 study of VB-111 in combination with weekly paclitaxel in patients with recurrent platinum-resistant ovarian cancer was initiated (NCT03398655) in collaboration with The GOG Foundation, Inc. Methods: This is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study of patients with platinum-resistant ovarian cancer, a deadly indication with significant unmet need. Patients with recurrent epithelial ovarian cancer, who have platinum-resistant and measurable disease (RECIST 1.1) previously treated with no more than 5 treatment lines are randomized 1:1 to receive VB-111 (1x1013 VPs) combined with paclitaxel (80mg/m2) or placebo combined with paclitaxel (80mg/m2). Randomization is stratified by number of prior treatment lines and prior antiangiogenic therapy. Treatment beyond RECIST progression is allowed in the absence of significant deterioration. The primary endpoint is OS; secondary endpoints include objective response rate, progression free survival (both by RECIST 1.1) and CO-125 and RECIST 1.1 response, and CA-125 response (GCIG). The sample size calculation of 350 patients (event driven) provides 88% power to detect a difference in survival at the two-sided 5% significance level using the logrank test. To date, 2 patients have been randomized. Clinical trial information: NCT03398655.
Enrolment was initiated in December 2017 and the first patient has been higher would be of interest for further investigation; with 90% power and a 2-

Patients with platinum-resistant ovarian cancer, following 

Background: 

PRO-105, a phase II open-label study of NUC-1031 in patients with platinum-resistant ovarian cancer.

Methods: This is a multicenter single arm phase II trial in women with platinum-resistant re-
lapsed ovarian cancer. Participants receive Pegilated liposomal doxorubicin (PLD) 40 mg/m^2 and olaparib 400 mg bid (capsule formulation) followed by olaparib 300 mg bid maintenance until toxicity or disease progression. Primary endpoint is progression-free survival at 6 months (PFS6m). Secondary endpoints are PFS, overall-survival, response rate, quality of life, and growth modulation index. Key inclusion criteria are: 1) serum levels of soluble epithelial ovarian cancer 2) platinum-resistant relapse (be-
tween 28 days and 6 months after last platinum-containing chemotherapy (CT)) 3) Previous PLD is allowed if administered as part of a platinum-
sensitive recurrence and > 6 months before inclusion 4) BRCA mutant patients are eligible after only 1 previous CT line, 5) BRCAwt or unknown are eligible after at least 2 previous platinum-sensitive lines 6) no more than 3 CT lines are allowed, 7) Hemoglobin > 10 g/dl and 8) left ventricle ejection fraction > 50%. Sample size calculation assumed that PFS6m 40% or higher would be of interest for further investigation; with 90% power and a 2-
sided alpha error 0.05 the number of patients needed will be 32 patients. Enrollment was initiated in December 2017 and the first patient has been enrolled. Clinical trial information: NCT03161132.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
INNOVATE-3: Phase 3 randomized, international study of tumor treating fields (200 kHz) concomitant with weekly paclitaxel for the treatment of platinum-resistant ovarian cancer. First Author: Eilon David Kirson, Novocure, Haifa, Israel

Background: Tumor Treating Fields (TTFields) are a non-invasive, regional antimitotic treatment modality FDA-approved for glioblastoma. TTFields act by disrupting mitotic spindle formation during metaphase. In multiple preclinical models of ovarian cancer, TTFields (200 kHz) reduced viability of cell lines via apoptosis. TTFields has demonstrated synergistic effects with taxanes in vitro and in vivo. The Phase 2 INNOVATE clinical study [NCT02244502] demonstrated the safety of TTFields combined with weekly paclitaxel in 31 PROC (platinum-resistant ovarian cancer) patients. Patients had a median of 4.1 prior chemotherapy regimens (range: 1-11). Most patients had CTCAE grade 1-2 TTFields-related dermatitis; 6.4% had grade 3 toxicity. Median progression-free survival was 8.9 months. The INNOVATE-3 is a phase 3 study in PROC of TTFields combined with weekly paclitaxel.

Methods: Patients with PROC (progression per RECIST V1.1) within 6 months of last platinum therapy with a maximum of two lines following the diagnosis of PROC and maximum total of five prior lines of systemic therapy will be enrolled. Patients (ECOG score 0-1) will have no peripheral neuropathy. Patients with primary refractory disease (progression during first line therapy) will be excluded. Patients will be randomized in a ratio of 1:1 to receive either weekly paclitaxel alone or weekly paclitaxel in combination with TTFields (200 kHz). Weekly paclitaxel will be administered at standard starting of dose 80 mg/m² weekly for 8 weeks, and then on Days 1, 8, and 15 for each subsequent 28-day cycle. TTFields will be applied in the experimental arm for at least 18 hours/day on average, and maybe continued as long as there is no progression in the abdominal or pelvic regions (“in-field region”) per RECIST V1.1. Clinical follow up will be performed q4w, with radiological follow up (CT or MRI scans of the abdomen and chest) q8w. The primary endpoint will be overall survival. Main secondary endpoints include progression-free survival, objective response rate, severity and frequency of adverse events and quality of life based on EORTC QLQ-C30 with the QLQ-OV28 questionnaire.

STATEC: A randomised trial of non-selective versus selective adjuvant therapy in high risk apparent stage I endometrial cancer. First Author: Tim Mould, University College London Hospital, London, United Kingdom

Background: The benefit of lymphadenectomy on survival in stage 1 endometrial cancer remains uncertain. STATEC is a surgical trial designed to evaluate the use of nodal status after lymph node dissection to tailor adjuvant treatment in patients with high risk apparent stage I endometrial cancer.

Methods: DESIGN: Randomised (1:1), controlled, two-arm, phase III, multicentre, international, non-inferiority trial. ELIGIBILITY: High risk apparent FIGO stage I endometrial cancer on diagnostic endometrial sampling OR hysterectomy. If randomisation occurs after hysterectomy and BSO: FIGO grade 3 endometrioid or mucinous carcinoma, high grade serous, clear cell, undifferentiated or dedifferentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma. STRATIFICATION: participating site, histology, lymphovascular space invasion, timing of hysterectomy and bilateral salpingo-oophorectomy (BSO). TREATMENT: Arm 1: Hysterectomy and BSO, plus intraoperative bilateral pelvic and para-aortic lymph node dissection + adjuvant therapy if node positive or stage III. Arm 2: Hysterectomy and BSO+ adjuvant therapy based on stage and uterine factors. ENDPOINTS: Overall survival (primary), disease-free, endometrial cancer-event free and endometrial cancer-specific survival, pelvic and extra-pelvic relapse-free survival, cost-effectiveness, surgical adverse events, quality of life and performance of sentinel lymph node assessment (secondary). QUALITY ASSURANCE: surgical specimen processing and microscopy to local specialist gynaecological oncology site pathologists, central pathology (10% of UK patients) and surgical imaging of all Arm 1 patients. Recruitment: 4 years, with 5 years follow up. STATISTICS: Using the exponential parameter of 0.0040, allowable hazard ratio of 1.272, a sample size of 2000 (500 deaths) will provide 85% power, and 5% two-sided statistical significance. With 80% power, the minimum sample size is 1720 patients (430 deaths). CURRENT ENROLMENT (as of February 2018): STATEC is open in the UK, Australia and New Zealand. 7 patients have been enrolled. STATEC is registered with Clinical trial information: NCT02566811.
6000 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Results of a randomized phase III study of nimotuzumab in combination with concurrent radiotherapy and cisplatin versus radiotherapy and cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck. First Author: Vijay Maruti Patil, Tata Memorial Centre, Mumbai, India

Background: We conducted an investigator-initiated, phase 3 randomized study to evaluate the efficacy and toxicity of addition of Nimotuzumab during concurrent chemoradiation in locally advanced squamous head and neck cancer (LASHNC).

Methods: Adult subjects (age ≥ 18 years), with stage III-IV, LASHNC, Kamoﬁsky performance status ≥ 70 and adequate organ function were randomized 1:1 into either radical radiotherapy (66-70 Gy) with weekly cisplatin (30 mg/m2) (CRT arm) or the same schedule of chemoradiation along with weekly Nimotuzumab (200 mg) (NCRT arm). The primary endpoint was progression free survival (PFS) and the other key secondary endpoints were disease free survival (DFS), duration of locoregional control (LRC) and overall survival (OS). Intent to treat analysis was performed. The planned sample size was 536 for superiority margin of 12%, assuming PFS of 60% with 80% power and alpha of 0.05. Results: 536 patients were equally allocated between both arms. The median follow up was 33.0 months (95% CI 30.7-35.2 months). The PFS was signiﬁcantly longer in the patients treated in the NCRT arm (2 year PFS 58.9% versus 49.5%, HR = 0.74; 95% CI 0.56-0.96; P = 0.022). The median duration of PFS was 60.3 months (95% CI 29.4-NA) in the NCRT arm (P = 0.023) and 21 months (95% CI 15.1-NA) in the CRT arm. Addition of Nimotuzumab improved the LRC (HR = 0.75; 95% CI 0.57-0.97, P = 0.030), DFS (HR = 0.75; 95% CI 0.57-0.97, P = 0.030) and had a trend towards improvement in OS (HR = 0.85, 95% CI 0.65-1.10, p = 0.222). Grade 3-6 adverse events (CTCAE version 4.03) were similar between the 2 arms except for the higher incidence mucositis in the NCRT arm (66.7% versus 55.8%, p = 0.010). Conclusion: In conclusion, Nimotuzumab in combination with cisplatin and radiotherapy was superior to cisplatin and radiotherapy in improving the PFS, LRC and DFS. This combination provides a new therapeutic option in the armamentarium against LASHNC. Clinical trial information: CTRI/2014/09/004980.

LBA6002 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Are women with head and neck cancer undertreated? First Author: Annie Park, Kaiser Permanente, Santa Clara, CA

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On site at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.

6001 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Definitive cetuximab-based (CRT-CX) vs. non-cetuximab based chemoradiation (CRT) in older patients with squamous cell carcinoma of the head and neck (HNSCC): Analysis of the SEER-Medicare linked database. First Author: Dan Paul Zandberg, University of Maryland, Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD

Background: Overall survival (OS) after deﬁnitive CRT-CX vs. deﬁnitive CRT has not been adequately evaluated outside of younger more highly selected clinical-trial populations with locally advanced HNSCC. Methods: We used the SEER-Medicare linked database to evaluate OS in HNSCC patients diagnosed between 2005-2011, following FDA approval of cetuximab in combination with radiation therapy (RT) in March 2006. Results: 2135 beneﬁciaries were identiﬁed. Median age was 73 (66-104) years. Primary subsites were oropharynx (61%), hypopharynx (15%), nasopharynx (5%), and larynx (19%). CRT-CX was associated with worse OS compared to CRT (P < 0.005), and similar OS to RT (P = 0.21). 5-year OS was 46% for CRT, 35% for CRT-CX, 32% for RT. Median survival was 4.5(3.8-4.9), 2.5(2.2-3.0), and 2.2 (2.0-3.0) years after CRT-CX, RT, respectively. Patients more likely to receive CRT-CX vs. CRT if they had oropharyngeal vs nasopharyngeal primary, Charlon comorbidity index 2 vs 0, older age at diagnosis. Multivariable Cox regression showed that CRT-CX was associated with a higher risk of death compared to CRT (HR = 1.23, 1.07- 1.42; p = 0.005), after stratiﬁcation by stage and primary site, and adjusting for gender, race, age, income, Charlon comorbidity index, marital status, hospital type, and year of diagnosis. Regarding treatment-related toxicity, CRT was associated with significantly lower hearing loss, hoarseness, and interstitial lung disease compared to CRT-CX (9.3% vs. 4.1%, p < 0.001), but there were no differences in dysphagia, gastrostomy tube placement, pneumonia, and weight loss over the ﬁrst 12 months after diagnosis. Conclusions: Deﬁnitive treatment with CRT-CX was associated with inferior OS compared to CRT even after adjustment for established prognostic factors, and with similar toxicity, in the SEER-Medicare patient population. Survival after CRT-CX was not signiﬁcantly different from RT alone. Despite the limitations to comparative effectiveness evaluation in population-based registries, our data suggest that non-cetuximab based chemoradiation should be used for eligible older HNSCC patients.

6003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Treatment deintensiﬁcation to surgery only for stage I human papillomavirus-associated oropharyngeal cancer. First Author: John David Cramer, University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Human papillomavirus-associated (HPV+) oropharyngeal cancer (OPC) is an emerging entity with improved prognosis and distinct staging system. We assessed if deintensiﬁcation to surgery only decreased survival for stage I patients at low or intermittent risk compared with surgery with adjuvant radiation (RT) or chemoradiation (CRT). Methods: From the National Cancer Data Base (2010-2014), we identiﬁed patients with stage I HPV+ OPC (after restaging with eighth edition guidelines) treated with surgery only or with adjuvant RT or CRT. We compared survival for low risk patients (≤1 metastatic lymph nodes with no adverse features) and intermediate risk patients (2-4 metastatic lymph nodes, microscopic extranodal extension (ENE) or lymphovascular invasion). We excluded high risk patients with positive margins or macroscopic ENE. Results: We identiﬁed 2,463 patients with median follow-up of 44.3 months. In the low risk group 4-year overall survival was 93.0% with surgery only versus 95.6% with surgery + RT and 93.0% with surgery + CRT. In the intermediate risk group, 4-year overall survival was 92.2% with surgery only versus 93.3% with surgery + RT and 93.2% with surgery + CRT. On multivariate analysis, we observed no difference in survival with treatment between surgery only versus surgery + RT or surgery + CRT for both the low risk group (hazard ratio (HR) 0.75; CI 0.32-1.79 and HR 1.03; CI 0.42-2.51 respectively) or the intermediate risk group (HR 0.78; CI 0.42-1.46 and HR 0.85; CI 0.47-1.53 respectively). Conclusions: This offers retrospective evidence that surgery only for stage I patients at both low and intermediate risk provides equivalent survival to surgery and adjuvant therapy. This offers clinical equipoise for randomization to surgery only for stage I patients in future deintensiﬁcation trials.

Overall survival based on treatment and risk level.

<table>
<thead>
<tr>
<th>Group</th>
<th>1-yr Survival</th>
<th>2-yr Survival</th>
<th>3-yr Survival</th>
<th>4-yr Survival</th>
<th>Log Rank</th>
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<tr>
<td>Low Risk</td>
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<tr>
<td>Surgery Only</td>
<td>96.7%</td>
<td>95.0%</td>
<td>94.2%</td>
<td>93.0%</td>
<td>0.59</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>99.4%</td>
<td>97.0%</td>
<td>95.6%</td>
<td>95.6%</td>
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<tr>
<td>Surgery + CRT</td>
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<td>93.0%</td>
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<td>Intermediate Risk</td>
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<tr>
<td>Surgery Only</td>
<td>97.8%</td>
<td>96.8%</td>
<td>94.1%</td>
<td>92.2%</td>
<td>0.77</td>
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<tr>
<td>Surgery + RT</td>
<td>99.3%</td>
<td>97.6%</td>
<td>96.2%</td>
<td>93.3%</td>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
6004  Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Phase II study: Induction chemotherapy and transoral surgery as definitive treatment (Tx) for locally advanced oropharyngeal squamous cell carcinoma (OPSCC): A novel approach.
First Author: Robert D. Siegel, George Washington University School of Medicine, Washington, DC

Background: The standard of care for OPSCC includes chemoradiation (CRT) or surgery with adjuvant radiation (RT). However, RT is associated with significant life-long moribundity. We assessed the efficacy of a two-drug induction regimen, followed by transoral robotic assisted surgery (TORS) & neck dissections for locally advanced OPSCC. Methods: This is an IRB approved single-arm phase II study for untreated stage III or IVA (AJCC 7th edition) OPSCC patients (pts) with an ECOG ≤ 2 and GFR ≥ 50 cc. Induction chemotherapy consisted of cisplatin 75 mg/m2 and docetaxel 75 mg/m2 every 21 days for 3 cycles. Tumor shrinkage was examined after each cycle. If the primary tumor was ≥ 80% smaller, pts underwent TORS and neck dissection(s). At post-op visits, flexible laryngoscopy, blood tests, and imaging with PET/CT and/or MRI were done. Short and long term toxicity, progression-free survival, overall survival, and quality of life (QOL) were evaluated. Results: Twenty pts were treated, nineteen were male, 17 were Caucasian, and 19 were HPV+. Median age at diagnosis was 57. Tumors involved the tonsill (13 pts) and base and tongue (7 pts). Three pts were stage III, and 17 were stage IVa. Tumor size was reduced by 53.4%, 80%, and 90.5% after the 1st, 2nd, and 3rd induction cycles respectively. Pathologic CR of the primary site occurred in 15 pts and CR among LN neck dissections occurred in 13 pts. Four pts were given dose-reduced chemo and one pt was changed to carboplatin per protocol because of renal dysfunction. Pre vs post QOL scores did not change. At a mean follow-up of 21 months (range 7.6 to 32.1), 18 pts are alive and NED. Three pts recurred a mean of 2.2 months after surgery, and were treated with salvage CRT. Two pts died of metastatic disease, the third is alive and well. All 3 pts had positive LN (9 LN, 3 LN and 1 LN) at surgery. Conclusions: Cisplatin + docetaxel followed by TORS & neck resections appears to be an effective model for the definitive treatment for OPSCC, while avoiding the adverse effects of RT. Clinical trial information: NCT02760667.

6006  Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Results of a randomized, placebo (PBO) controlled, double-blind P2b trial of GC4419 liposome-entrapped melatonin (MLT) in locally advanced squamous cell carcinoma (OC) of the oral cavity (OC) or oropharynx (OP). First Author: Caryn M. Anderson, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Intensity-modulated radiotherapy (IMRT) plus cisplatin is established treatment for locally advanced OCCP cancer, but approx. 70% of patients develop SOM, defined as WHO Grade 3 or 4, which limits patients' ability to eat solids (Gr 3) or liquids (Gr 4, requiring artificial nutrition). An RT-induced burst of superoxide initiates oral mucositis (OM) development. GC4419, a superoxide dismutase mimetic, interrupts this process by potently converting superoxide to H2O2. It showed promising reductions of SOM in a published open-label Phase Ib/2a trial (IJROBP 1 Feb 2018). Methods: 223 pts with OC or OP cancer receiving 70 Gy (MTE = 50 Gy to > 2 oral sites) plus cisplatin (qwk 4 or qwk3), were randomized 1:1:1 to PBO, 30 or 90 mg of GC4419, by 60-minute IV infusion, M-F before each RT fraction. OM by the WHO scale was assessed by trained evaluators biw during RT & qwk for up to 8 wks post RT. Primary endpoint was duration of SOM. Secondary endpoints included incidence & time to onset of SOM. Analyses (each active dose vs PBO, ITT) proceeded by a sequential, conditional approach; 2-sided α = 0.05.

Results: 90 mg GC4419 reduced SOM across endpoints, including a statistically significant reduction in the primary endpoint of duration. Efficacy results with 30 mg were intermediate and did not reach significance. Baseline patient & tumor characteristics, & treatment delivery, were well-balanced. Safety was comparable across arms with no significant GC4419-specific toxicity or increased toxicity of IMRT/cisplatin. Conclusions: GC4419 provides a clinically meaningful reduction of SOM in terms of duration, incidence and severity (Grade). A safety profile comparable to placebo. Clinical trial information: NCT02508389.

6007  Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Phase II trial of high-dose melatonin oral gel for the prevention and treatment of oral mucositis (OM) in H&N cancer patients undergoing chemoradiation (MUCOMEL). First Author: Alicia Lozano, Institut Catalá d'Oncologia, Barcelona, Spain

Background: Severe Oral Mucositis (SOM) is one of the most significant adverse events (AE) in H&N cancer patients undergoing concurrent chemohoradiotherapy. The objective of the trial is to evaluate the safety and efficacy of melatonin (MLT) oral gel in the prevention and treatment of oral mucositis (OM) in H&N cancer patients. Methods: Multicenter, prospective, randomized, double-blind, placebo-controlled study. Eligible patients were randomly assigned (1:1 ratio) to receive 3% MLT or matching placebo (PLC) oral gel. Patients received once daily (5 days/week) IMRT radiation therapy (total dose ≥ 66 Gy). Concurrent systemic treatments were cisplatin Q3W or cetuximab Q1W. All patients received concomitant standard symptomatic treatment for OM. Efficacy analyses were performed on a miTTP population (patients receiving at least one medication dose) or ITT. Efficacy endpoints were either RT0G or NCI CTCv4, G3-4 oral mucositis (OM) and G2-4 ulcerative oral mucositis (UOM). Comparison of incidence rates of SOM/UOM: Fisher exact test; comparison of duration of SOM/UOM: U Mann-Whitney test. Results: 84 patients (ITT: 42 MLT/42 PLC; mITT: 40 MLT/39 PLC) were included. Most frequent tumor sites were oropharynx (n = 38; 45%) and oral cavity (n = 24; 29%). Concurrent systemic treatments were cisplatin (n = 54; 64%) or cetuximab (n = 30; 36%). Efficacy results in the ITT population (incidence) and ITT (duration) Clinical trial information: NCT02630004. No relevant differences for AEs between groups or for overall response rate after 2 months of IMRT completion. Conclusions: Treatment with MLT oral gel resulted in a consistent trend to a lower incidence and shorter duration of SOM as well as a significantly shorter duration of UOM. These benefits were more marked in the subgroup of patients receiving cisplatin. These results warrant further clinical development.
Conclusions: before and eight after study participation. Median OS was 12.1 months. Immunotherapy was given to three patients (evaluable). Median progression free survival (PFS) was 6.4 months and decrease in target lesions occurred in 57% (13 of 23 enrolled. Median age 67 years (range: 26-84). Sites of recurrence: local/metastatic and OS in platinum-resistant HPV (-) RM-HNSCC. The median OS of 12.1 months is the longest reported for patients with platinum-resistant RM squamous cell carcinoma (HNSCC). First Author: Douglas Adams, Washington University School of Medicine in St. Louis and Siteman Cancer Center, St. Louis, MO

Background: In a phase II trial, patients with platinum-resistant, cetuximab-naive HPV (-) RM HNSCC were treated with palbociclib 125 mg po/days 1-21 of 28 day cycles and weekly cetuximab. Platinum-resistance was defined as: progression on platinum in the RM setting; cetuximab-naïve was defined as: no prior cetuximab for RM disease. HPV (-) disease was defined as SCC of the oral cavity, larynx, hypopharynx or oropharynx negative SCC of the oral cavity, larynx, hypopharynx or oropharynx negative. Tumor response assessments (RECIST 1.1) were performed every 2 cycles. We hypothesized that palbociclib and cetuximab would increase the tumor response rate from 13% (historical data with cetuximab) to > 26%. Futility assessments of response and toxicity occurred after every 6 patients (sample size: 30) using a Bayesian monitoring method. 30 patients were enrolled. Median age 67 years (range: 26-84). Sites of recurrence: local/regional (6), distant (8), or both (16). Tumor response occurred in 35% (8 of 23 evaluable to date). Decrease in target lesions occurred in 57% (13 of 23 evaluable). Median progression free survival (PFS) was 6.4 months and median OS was 12.1 months. Immunotherapy was given to three patients (evaluable) before and eight after study participation. Conclusions: Palbociclib and cetuximab resulted in a robust tumor response rate and prolongation of PFS and OS in platinum-resistant HPV (-) RM-HNSCC. The median OS of 12.1 months is the longest reported for patients with platinum-resistant RM-HNSCC. Clinical trial information: NCT02101834.

Safety evaluation of nivolumab (Nivo) concomitant with cetuximab-radiotherapy for intermediate (IR) and high-risk (HR) HNSCC. The prognostically advanced head and neck squamous cell carcinoma (HNSCC). RTOG 3504. First Author: Robert L. Ferris, University of Pittsburgh Medical Center and University of Pittsburgh Cancer Institute, Pittsburgh, PA

Background: Nivolumab, which inhibits the programmed death-1 (PD-1) receptor, improved survival for patients (pts) with platinum-refractory/recurrent/metastatic HNSCC compared with standard therapy. This trial evaluates the safety of adding nivo to 4 standard radiotherapy (RT) regimens in pts with newly diagnosed HR/HNSCC (Table). Safety data for cohort 3 (cetuximab) are efficacy data for cohorts 1, 2, and 3 will be reported at the presentation. Methods: Eligibility includes IR (p16+, oropharynx) OP (OP) T1-N2b-N3/T3-4N0-3, >10 pack-years (pyrs) or T4N0-N3, T1-3N3 ≤10 pyrs) and HR HNSCC (oral cavity, larynx, hypopharynx, or p16+). OP, stage T1-2N2a-N3 or T3-4N0-1, 10 pts are enrolled to obtain 8 evaluable pts. Primary endpoint is dose-limiting toxicity (DLT), defined as nivo-related: grade ≥3 adverse event (AE) unresolved to ≤grade 1 in ≤28 days; RT delay ≥2 wks; incomplete RT; or inability to receive ≥70% of cetuximab. DLT window was from nivo first dose (day 1) to day 28 days post RT. >2 DLTs in 8 evaluable pts is unacceptable. Results: Of 10 enrolled pts for cohort 3: median age 61.5, 80% male, 70% Caucasian, 70% PS 0, 80% >10 pyrs, 60% p16+ OP cancer, 60% T3-4 and 100% N2-3 disease. 1 pt was ineligible for DLT due to withdrawal of consent and 1 pt has not yet completed the DLT observation period. DLT (mucositis) was reported in 3 pts; 1 pt who did not reach grade 3 AE attributed to nivo was reported (lipoase increase) but was not a DLT. 11 SAEs in 3 pts, but none nivo-related. 7/8 pts completed RT, 7/8 pts completed cetuximab; 5 pts completed 10 concurrent doses of nivo, 1 pt received 6 doses, 1 pt 7 doses, and 1 pt is ongoing after 8 doses. Conclusions: Nivo is safe and feasible to administer concomitant with a cetuximab-RT regimen for patients with newly diagnosed IR/HR HNSCC. Clinical trial information: NCT02764593.

Clinical Safety Symposium, Fri, 4:30 PM-6:00 PM
Nivolumab (Nivo) prior to surgery in head and neck squamous cell carcinoma (HNSCC). First Author: Richard Bryan Bell, Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR

Background: This phase Ib clinical trial was performed to investigate an agonistic murine antibody to OX40 (MED16469) at various dose intervals prior to definitive surgical resection in patients with head and neck squamous cell carcinoma (HNSCC). Methods: 17 patients with resectable stage III-IVA HNSCC (11 = HPV-; 7 = HPV+) received MED16469 0.4mg/kg x 3 doses administered on day 1, day 3-4 and day 5-6 of the study, followed by definitive surgical excision and neck dissection either 2 days, 1 week or 2 weeks after infusion of anti-OX40. Primary tumor, lymph nodes and peripheral blood (PB) were obtained at baseline and at the time of surgery to characterize the circulating and tumor infiltrating lymphocyte (TIL) cell populations based on flow cytometry (FC) and multiplex immunohistochemistry (mIHC) as well as whole transcriptome analysis via RNA-sequencing (seq). Results: MED16469 administration was well tolerated, surgery was not delayed, and there were no grade 3 or 4 adverse events related to MED16469 treatment. With a median follow up of 20 months, 13/17 patients are alive without disease. 4 patients had evidence of an immunological response to treatment on FC and mIHC that peaked between 12 and 19 days after MED16469 infusion and was characterized by: 1) increased Ki67+CD38+ ICOS+ CD4+ and CD8+ memory T-cell populations in both the TME and PB, 2) increased expression of CD39, ICOS and PD-1 on CD4+ TIL (N = 10, 3) increased frequency of tumor-reactive, tissue resident CD39+CD103+CD8+ T cells (N = 5). RNA-seq analysis of the primary tumor in a subset of patients (N = 7) revealed significant differences between immunological responders and non-responders in genes associated with HLA-MHC I-mediated antigen processing. While whole transcriptome, immune-subtype deconvolution analysis of the RNA data revealed all responders segregated with above median levels of CD39+CD103+CD8+ T cells, consistent with flow and mIHC. Conclusions: Preoperative MED16469 administration is safe and resulted in increased activation and proliferation of T cells within the tumor microenvironment, as well as decreased expression of TIL inhibitory molecules. Flow cytometric and RNA-seq analyses are ongoing in patients with HLA-MHC I-mediated antigen processing machinery. Clinical trial information: NCT02274155.
6013 Poster Discussion Session; Displayed in Poster Session (Board #1),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM
Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs standard of care (SOC) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) in KEYNOTE-040. First Author: Ezra E.W. Cohen, Moores Cancer Center at UC San Diego Health, University of California, San Diego, La Jolla, CA
Background: In KEYNOTE-040 (NCT02252042) (N = 495), pembro 200 mg Q3W for 24 mo yielded a clinically meaningful improvement in overall survival (OS) choice of methotrexate (MtX), docetaxel (Dtx), or cetuximab (Ctx) in patients (pts) with R/M HNSCC, with fewer grade 3-5 drug-related adverse events. We present results of prespecified exploratory HRQoL analyses. Methods: The EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D were administered electronically at baseline; wk 3, 6, 9, then every 6 wk up to 1 y or end of treatment; and at 30-day safety follow-up visit. HRQoL was analyzed in pts who received ≥ 1 dose of study drug and had ≥ 1 HRQoL assessment. Mean change from baseline to wk 15 was compared using a constrained longitudinal data analysis model. Time to deterioration (TDT) (defined as ≥ 10-point decline from baseline) was estimated by Kaplan-Meier method and Cox regression model. Results: The HRQoL population included 469 pts (241 pembro; 228 SOC). HRQoL compliance at wk 15 was 75.3% for pembro and 74.6% for SOC. From baseline to wk 15, global health status (GHS)/Qol scores were stable for pembro (least-squares [LS] mean, 0.39; 95% CI, –3.00, 3.78) but worsened for SOC (LS mean –5.86; 95% CI, –9.68, –2.04); difference in LS mean between arms was 1.12 points (95% CI, 0.05, 2.04, nominal 1-sided P = 0.013). Subgroup analyses by SOC choice identified a greater difference in LS mean for GHS/QoL scores with pembro vs Dtx (10.23; 95% CI, 3.15, 17.30) compared with pembro vs MtX (6.21; 95% CI, –4.57, 16.99) or Ctx (–1.44; 95% CI, –11.43, 8.56). Median TTD in GHS/QoL with pembro vs SOC was 4.8 and 2.8 mo HR, 0.79, 95% CI, 0.59, 1.05; nominal 1-sided P = 0.048). Pts in the pembro arm generally had stable functioning and symptom scores at wk 15; no notable between-group differences were seen. Conclusions: Over 15 wks, pembro-treated pts had stable GHS/QoL; those receiving SOC generally showed a decline. This effect was more marked for Dtx-treated pts. Additional analyses by SOC choice are ongoing. Along with previously presented efficacy and safety results, these data support the clinically meaningful benefit of pembro in R/M HNSCC. Clinical trial information: NCT02252042.

6015 Poster Discussion Session; Displayed in Poster Session (Board #3),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM
Response to salvage chemotherapy after progression on immunotherapy checkpoint inhibitors in patients with squamous cell carcinoma of the head and neck. First Author: Khalil Saleh, Department of Head and Neck, Gustave Roussy Cancer Campus, Villejuif, France
Background: Immune checkpoint inhibitors (ICI) have shown efficacy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Overall response rate (ORR) varies from 13 to 17%. Recent data suggest that exposure to ICI potentially improves ORR to salvage chemotherapy (SCT) in advanced non-small cell lung carcinoma. We evaluated responses to chemotherapy in R/M SCCHN patients after progression on ICI. Methods: A retrospective study was conducted at 4 French referral centers. Eligibility criteria were patients treated with ICI for R/M SCCHN, who progressed after treatment with ICI (primary or secondary resistance to ICI) and received SCT between September 2014 and January 2018 for whom efficacy data were available. Clinical and radiological data were collected from review of medical records. Results: Of 232 patients treated with ICI (anti-PD-1, anti-PD-L1, anti-CTLA-4 and anti-KIR), 82 met eligibility criteria: 84% were male, median age was 60 years old. ICI was given as monotherapy in 45% of patients or as combination in 55%. SCT included taxane-based regimen (56%), platinum-based regimen (37%), and methotrexate (7%). Cetuximab was administered in combination with taxanes or platinum in 50% of patients. The median number of treatment lines prior to SCT was 2 (range 1-6). The ORR to SCT was 30% (95% confidence interval: 21%-40%). Three patients (4%) presented complete response and 22 patients (27%) had partial response. The disease control rate was 57%. The age at initiation of SCT, initial tumor location, number of prior chemotherapy regimens, type of chemotherapy, prior to ICI, best response to ICI, site of relapse and ECOG at SCT were not significantly associated with response to SCT on univariate analysis. Conclusions: In R/M SCCHN pre-treated with ICI, the ORR to SCT was 30% higher than figures of historical cohorts in this setting. This suggests that exposure to ICI may increase tumor sensitivity to chemotherapy. Further investigations are warranted.

6014 Poster Discussion Session; Displayed in Poster Session (Board #2),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM
Association of immune-related adverse events (irAEs) with improved response, progression-free survival, and overall survival for patients with metastatic head and neck cancer receiving anti-PD-1 therapy. First Author: Corey Christian Foster, Department of Radiation & Cellular Oncology, The University of Chicago Medicine, Chicago, IL
Background: Anti-programmed death receptor-1 (PD-1) therapies are approved for recurrent/metastatic head and neck (H&N) cancer progressing on or after platinum-based chemotherapy, and immune checkpoint modulators may abrogate tumor response. We hypothesized that developing immune-related adverse events (irAEs) while receiving anti-PD-1 therapy for metastatic H&N cancer would be associated with improved outcomes. Methods: 114 patients with metastatic H&N cancer unscreened for PD-1/PD-L1 status (PD-L1 status positive or negative) were evaluated. Adverse events (AEs) were retrospectively identified using CTCAE v4.0. irAEs were any possibly immune-mediated AE regardless of attribution. Univariate and multivariate logistic regression analyzed the relationship between irAEs and overall survival rate (ORR) measured by RECIST v1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and Cox proportional hazard regression. Results: Median follow-up was 8.6 months, and follow-up did not significantly differ between irAE+/- groups (p = 0.72). Baseline characteristics including known PD-L1+ (53.1% irAE+ vs. 49.2% irAE, p = 0.76) were comparable, 59 irAEs occurred in 49 patients. irAEs were classified as dermatologic (n = 20), gastrointestinal (n = 11), endocrine (n = 14), musculoskeletal (n = 15), pulmonary (n = 1), GI (n = 1), endocrine (n = 14), musculoskeletal (n = 15), pulmonary (n = 1), and 6.8 months (p = 0.007), respectively. On multivariate analyses, irAE+ was independently associated with improved ORR (p = 0.03), PFS (p = 0.009), and OS (p = 0.03). Conclusions: Developing irAEs while receiving anti-PD-1 therapy is associated with superior ORR, PFS, and, in particular, OS in this cohort of H&N cancer patients unscreened for PD-L1 status. The ability to develop irAEs may be an indicator of immune competence and further investigation of biomarkers of immune competence is warranted.

6016 Poster Discussion Session; Displayed in Poster Session (Board #4),
Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session,
Sat, 4:45 PM-6:00 PM
A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck. First Author: Matthew H. Taylor, Knight Cancer Institute, Oregon Health and Science University, Portland, OR
Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor receptor 1–3, fibroblast growth factor receptor 1–4, platelet-derived growth factor receptor α, RET, and KIT. Pembrolizumab (PEM) is an anti-PD-1 antibody approved for the second-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) based on durable responses and an objective response rate (ORR) of 16% (Baum J et al, J Clin Oncol 2017). We report interim results of the SCCHN cohort from a phase 1b/2 trial of the LEN + PEM combination (NCT02501096). Methods: In this multicenter, open-label study, patients (pts) with measurable, confirmed metastatic SCCHN and EOCG performance status ≤ 1 received LEN (20 mg/day orally) + PEM (200 mg Q3W, IV). Pts were not preselected based on PD-L1 status. Tumor assessments were performed by study investigators using immune-related RECIST (iRECIST). The phase 2 primary endpoint was ORR at 24 weeks (ORRwk24). Secondary endpoints included ORR, progression-free survival (PFS), and duration of response (DOR), which is calculated from time of confirmed or partial responses. Results: At data cutoff of August 1, 2017, 22 pts with SCCHN (regional/locoregional, n = 11; distant, n = 11) were evaluable. 4 (18%) pts had prior anticancer therapy. Median follow-up for PFS was 7.6 months (95% confidence interval, CI, 4.2–12.6) per iRECIST. Efficacy outcomes are summarized in the table. Grade 3 or 4 AEs occurred in 91% of pts (grade 4 AEs in 14%). However, 4 (18%) pts who received LEN + PEM combination in pts with SCCHN. Clinical trial information: NCT02501096.

Table

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<th>Outcome</th>
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<td>Median DOR, months (95% CI)</td>
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</table>

*p partial responses (PR). † 7 PRs, 1 complete response. ‡ 4 of the 8 (50%) responders achieved a DOR of > 6 months.
Phase II multi-site investigation of neoadjuvant pembrolizumab and adjuvant concurrent radiation and pembrolizumab with or without cisplatin in resected head and neck squamous cell carcinoma. First Author: Trisha Michel Wise-Draper, University of Cincinnati Cancer Institute, Cincinnati, OH

Background: 2Despite aggressive adjuvant treatment, locally advanced HNSCC patients undergoing primary surgical resection with high risk (HR) features (extracapsular extension of lymph nodes (LN) and/or positive margins) have 3-year disease free survival (DFS) of 47-57%. Pre-clinically radiation upregulates the immune checkpoint PD-L1 and importantly PD-L1 blockade concurrently with radiation resulted in improved overall survival (OS) in mice bearing HNSCC tumors. Therefore, we initiated a window of opportunity study “Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC” (NCT02641093) supported by Merck.

Methods: Clinically high risk (T3/4 stage and/or ≥ 2 LNs) patients received the PD-1 antibody, pembrolizumab (200 mg I.V. x 1), 1-3 weeks before resection. Adjuvant concurrent pembrolizumab (q3 wks x 6 doses) and radiation (60-66Gy) were administered, along with weekly cisplatin (40mg/m2) for those with HR features. Pre- and post-surgical specimens were archived for H&E, immunohistochemistry, RNAseq and Nanostri. Safety lead-in included first 8 patients of each arm and dose limiting toxicity (DLT) was determined by delay in surgery, radiation and/or cisplatin.

Results: Twenty-eight of 80 planned patients have been enrolled with 23 evaluable for efficacy. Characteristics included median age of 62 (range, 29-78), T3-21%, T4-46% and 64% ≥ N2b. The lead-in safety period is near completion (15/16) without DLT with 9/19 (47%) patients demonstrating a pathological response (≥ 10% tumor effect (TE)) and 6/19 (32%) achieving major response (> 70% TE), one of which had a pathological complete response after 1 cycle. Pathological response was associated with robust immune cell infiltration, increased PD-L1 and PD-L2. Two patients (neither attaining pathological response) have recurred.

Conclusions: Pathological response was seen after one dose of pembrolizumab in HNSCC. Increased tumor immune cell infiltration predicted pathological response. Adjuvant combination treatment with pembrolizumab has an acceptable safety profile. Clinical trial information: NCT02641093.

Discovery of a reliable and robust methylyse classifier of HPV driven head and neck cancer with favorable response to chemoradiation: A multicenter study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG), First Author: Bouchra Tawk, German Cancer Research Center (DKFZ), Head & Neck and German Cancer Consortium (DKTK), core center Heidelberg, Heidelberg, Germany

Background: Human Papilloma Virus (HPV)-driven head and neck cancer (HNSCC) is associated with good prognosis. The prognostic value of HPV-DNA and p16 IHC was recently reported by this consortium. Discordance between HPV and p16 status is associated with poorer prognosis. In the combined HPV- and HPV+ validation cohort, HPV(-) or non-HPV16. Such patients likely should not be treated on de-escalation trials, we identified that 5% of oropharynx HPV-M showed a strong correlation with HPV- and HPV+ status and increased accuracy. Using p16 alone results in a 5% decreased sensitivity was 97.4%, specificity 93.75%, PPV was 95%, NPV = 97.8%.

Methods: HPV-DNA and p16 status of a DKTK-ROG multicenter retrospective cohort of patients (n = 194) with oropharynx carcinoma (OPC), oral cavity- and hypopharynx carcinoma (non-OPC), homogeneously treated with surgery and adjuvant cisplatin-based radiochemotherapy (RCT), was employed as a training set. Five validation cohorts were included including: 1) 100 HPV-DNA and p16 matched control cohort from the DKTK-ROG patients with definitive RCT, 2) 144 from Heidelberg, 3) 100 from Munich and 4) 222 from The Cancer Genome Atlas – HNSCC cohort (TCGA, n = 206). Overall methyleme data from 732 samples including two different sources (FFPE/FrFr) and platforms (Illumina 450K and EPIC 850K) were studied. Results: A 24-probe set methylyse-based classifier of HPV-driven HNSCC was discovered (HPV-M) to significantly correlate with improved clinical outcomes: HR for local recurrence (range 0.11-0.19), disease progression (range 0.16-0.29) and overall survival (OS, range 0.19-0.42) were significant in all cohorts (p < 0.05). Notably, HPV-M+ classification was superior to HPV-DNA+ status or p16+ IHC in predicting OS in all cohorts independent of tumor localization (OPC/non-OPC). Likewise, HPV-M showed a strong correlation with HPV-DNA and p16 status (p < 0.0001). Across cohorts – 10% discordance between HPV-M and HPV-DNA or HPV-M and p16 was found, respectively. Among the HPV-M positive cases (n = 71), OS was significantly reduced in patients with HPV-M negative vs. positive tumors (p < 0.009).

Conclusions: We present a novel robust and independent methylyse-based classifier of HPV-driven HNSCC that could be instrumental for accurate patient stratification in the era of de-escalation trials.

A phase II randomized trial of pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN). First results of the GORTEC 2015-01 “PembroRad” trial. First Author: Au Shan Sun, CHRU Jean Minjoz, Besancon Cedex, France

Background: Based on the hypothesis of a potential synergistic effect of the anti-PD1 pembrolizumab when combined with RT, this new combination was tested in a phase II randomized trial against the SoC cetuximab-RT in LA-SCCHN.

Methods: Patients (pts) were randomized between cetuximab (Arm A : 400 mg/m2 loading dose and 250 mg/m2 weekly) and Pembrolizumab (Arm B : 200 mg Q3W during RT). In both arms, patients received IRMT (69.96 Gy in 33 fractions). Main Inclusion criteria were: pts unfit for high dose cisplatin, non operable stage III-IIbA SCC of oral cavity, oropharynx, hypopharynx and larynx. Treatment allocation was performed by randomization 1:1, stratified on N stage (NO-1 vs N2-3), tumor location and p16 status. To detect a difference among arms of 60% to 80% in loco-regional control at 15 months (primary endpoint), inclusion of 66 pts per arm was required to achieve a power of at least 0.85 at 2-sided significance level of 0.20, with less than 15% unevaluable pts. Results: From 05/16 to 10/17, 133 pts were randomized in 27 centers, 66 in Arm A and 67 in Arm B. Median age was 65 years, 92% were smokers, 60% of oropharynx, 28% p16+ and 26%, 56% and 19% of stage III, IVa and IVb respectively. Both arms were well balanced. At the time of the abstract writing, full and cleaned safety and compliance data were available for 77 pts in each arm. Data for all the randomized pts will be presented at the meeting. In Arm A and B, 25 and 18 Serious Adverse Events (SAE) occurred and 94% and 78% pts had at least one CTCAE v4 grade 3 AE in arm A and B respectively. The compliance to RT was not different (total dose received by 86% and 88% pts in Arm A and B respectively). Mucositis (grade ≥ 3) was observed in 77% (Arm A) and 84% (Arm B) of pts (p = 0.004) (but no difference in dysphagia, 34% versus 39%). In radiation field dermatitis >= 3 grade occurred more frequently in Arm A (49% versus 17%) (p<0.003).

Conclusions: Preliminary data indicate that tolerance of pembrolizumab-RT was good when compared to cetuximab-RT in LA-SCCHN. Updated and complete safety results will be presented at the meeting. Clinical trial information: NCT02707588.
Facilitating rapid precision oncology in anaplastic thyroid cancer: Clinical implications of next generation sequencing (NGS) mutation testing and impact on survival. First Author: Jennifer Rui Wang, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Anaplastic thyroid cancer (ATC) is a rare malignancy characterized by rapid progression and median overall survival (OS) of less than 6 months. With no standard treatment, the primary objective of ATC care is to improve outcome, and facilitating precision oncology is an important step in this process.

Methods: ATC patients seen between 2012-2017 at our institution who had adequate tumor samples for NGS testing were included. DNA was extracted from pre-treatment core biopsies or surgical specimens of primary ATC. Targeted mutation testing was performed using NGS platforms for 46-158 genes. Cox proportional hazards models were used to assess the associations between mutation status and OS.

Results: A total of 101 pts were included (median age: 65.7 years, 55.5% male). 84% presented with T4b disease. 50% were M1 at presentation. Median OS at 1 and 2 years was 52% and 29%. The most common mutations detected were p53 (54%), BRAFV600E (50%), RAS (21%), PIK3CA (23%), and CDKN2A (7%). RAS and BRAFV600E mutations were mutually exclusive. In univariate analysis, BRAFV600E was associated with better OS (HR 0.59, 95% CI 0.35-0.98, p = 0.043) while RAS mutation was associated with worse OS (HR 3.41, 95% CI 1.94-6.33, p = 0.003). Twenty-four of 51 (47%) BRAFV600E+ pts were treated with a BRAF inhibitor. In BRAFV600E+ patients, BRAF inhibitor treatment was significantly associated with improved OS at 1 year (HR 0.25, 95% CI 0.08-0.78, p = 0.018). Conclusions: This is the largest study of mutation status and survival outcome in ATC to date. The findings emphasize the importance of prioritizing treatment with BRAF inhibitors in ATC patients with BRAFV600E mutations, and highlight the potential for precision oncology to improve outcomes in this challenging disease.
Phase I/II trial of pembrolizumab(P) and vorinostat(V) in recurrent metastatic head and neck squamous cell carcinomas (HN) and salivary gland cancer (SGC). First Author: Cristina P. Rodriguez, Division of Medical Oncology, University of Washington, Seattle, WA

Background: Epigenetic modification is increasingly recognized as a mechanism for tumor immune evasion. This clinical trial explored the activity of P with the HDAC inhibitor V in HN and SGC. Methods: Patients(pts) with progressing incurable HN and SGC with ECOG ≤1, no prior immunotherapy, RECIST 1.1 measurable disease, and normal organ function were eligible. Controlled brain metastases were permitted. PDL1 expression was not an eligibility criterion. P 200mg was given iv q21 days (d), with V 400mg QD PO, 5d on and 2d off, both started on d1 of each cycle. The primary endpoint was safety according to CTCAE v. 4.03. Secondary endpoints were RECIST 1.1 objective response rates and biomarker marker. Results: From 11/2015 to 8/2017, 25 HN and 25 SGC pts were enrolled. Among all 50 pts, median age was 61 (range 33-86) yrs, 39 (78%) were male, 21(62%) were never smokers, 27 (54%) had ECOG 0. In HN, primary sites were oropharynx 17 (68%), nasopharynx 4 (16%), oral cavity 1(4%), skin and unknown 4 (1%). In SGC, 52% were p16+ oropharynx HN. SGC histologies were adenoid cystic (AC) 12(48%), acinic cell (AcC) 3(12%), mucoepidermoid (ME), ca ex. pl. adenoma 2(8%). There was 1(4%) pt each with adenocarcinoma, salivary duct, epithelial-myoepithelial, clear cell, parotid lymphoepithelioma-like(LEL-C) carcinoma. The median (range) treatment cycles received in HN was 6 (1-33), and SGC 9 (1-34). Adverse events regardless of cause (AEs) in all pts were: fatigue 27 (54%) Grade 3-4 14 (28%), neutropenia 26 (52%) Grade 3-4 18 (35%), anemia 19 (38%) Grade 3-4 10 (20%), nausea and vomiting 13 (26%) Grade 3-4 5 (10%), pericardial effusion 2 (4%) Grade 3-4 1 (2%), pneumonitis from P. Responses in HN were: complete response (CR) 0, partial response(PR) 3 (12%), stable disease(SD) 20 (80%), disease progression(PD) 4 (16%) in 1 LE-L, 2 AcC and 1 ACC, SD 14(56%). With a median follow up of 8.7 mos for all pts, in HN median PFS was 4.5 mos, median OS, 12.6 mos; in SGC median PFS was 7 mos and median OS 13 mos. Conclusions: P+V demonstrated activity in HN, with fewer responses in SGC. Serum and tissue TRAEs, grade 3/4, %

Nivo improved OS and objective response rate (ORR) vs IC in arm had a lower rate of treatment-related adverse events (TRAEs) vs IC (Table). In HN median PFS was 7 mos, and median OS 13 mos. Conclusions: 

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study using bevacizumab in 2 doses, 7.5mg/kg (Arm A) or 2.5mg/kg (Arm B),

**Background:** EBV-related NPC is chemosensitive but stage 4 disease has high relapse rate and short progression free survival (PFS). Almost all NPCs overexpress VEGF. We hypothesized that anti-VEGF (bevacizumab) prior to chemotherapy could promote vascular normalisation, improve tumor perfusion, and enhance immune response in NPC.

**Methods:** We conducted a study enrolling bevacizumab in 2 doses, 7.5mg/kg (Arm A) or 2.5mg/kg (Arm B) starting 7 days prior to 3 weekly cycle of cisplatin 75mg/m² (Day 1) and gemcitabine 1g/m² (D1, D8), for 3 cycles followed by concurrent chemo- radiotherapy in stage 4A/B (locally advanced) patients, and for 6 cycles in stage 4C (metastatic) patients, with the primary objectives to determine safety and response rate (RR), and secondary objectives to evaluate PFS and effects on the TME. Immunohistochemistry studies were performed by a blinded pathologist on serial fresh tumor biopsies at baseline and 7 days post cycle 1 bevacizumab.

**Results:** 20 patients were recruited to Arm A, and 10 to Arm B. 1 screen failed and 2 withdrew consent. Objective RECIST response was seen in arm A (17/18 (94.4%) partial response (PR), 1 (5.6%) stable disease (SD)), vs arm B (8/9 (88.9%) PR, 1/9 SD (11.1%). Metabolic PET-CT response was seen in all evaluable patients with complete response in 4/17 (23.5%) patients in arm A. EBV DNA was detectable in 17 patients at baseline, and 12 patients had undetectable plasma EBV DNA by day 1 post cycle 2. 9/13 (69.2%) patients in arm B had undetectable plasma EBV DNA post treatment. TME response to bevacizumab included increase in stromal inflammatory infiltrate, specifically CD4 (p = 0.0002) and CDB T cells (p = 0.0069), and reduction in hyaluronic acid binding protein score (p = 0.0116), indicating increased vascular permeability especially in the TME. 3 patients had grade 3 hypertension and no patients had tumoral bleed related to bevacizumab use.

**Conclusions:** In this first evaluation of bevacizumab prior to chemotherapy for NPC, tolerability and efficacy was established, and bevacizumab enforces stromal immune infiltration, and modulates TME, potentially improving vascular permeability. Clinical trial information: 2010/00693.

**Background:** Platinum-based chemotherapy with cetuximab is the standard of care for relapsed or metastatic squamous cell carcinoma of the head and neck (SCCHN). The aim of this trial was to investigate whether cetuximab and paclitaxel/carboplatin can achieve similar progression free survival (PFS) with less toxicity compared to standard cetuximab and 5-FU/platinum based chemotherapy. 

**Methods:** In this multicentre, randomised, controlled, phase 2 trial, 85 patients with relapsed or metastatic SCCHN were randomised in a 1:1 ratio to cetuximab and 5-FU/cisplatin or carboplatin (arm A, n = 42), versus cetuximab and paclitaxel/carboplatin (arm B, n = 43). Patients without disease progression continued with cetuximab maintenance every second week until progression or toxicity. Eligibility criteria included age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, and adequate organ functions. The primary endpoint was to investigate whether PFS in arm B is non-inferior to PFS in arm A using a liberal non-inferiority margin of 1.5 for the PFS hazard ratio (HR).

**Results:** The median age for the whole study population was 60.9 years with a male predominance (69.4%). Clinically significant parameters, such as tumor localization, tumour stage, PS, HPV status and age were well balanced between the two treatment arms. Adverse events ≥ grade 3 were more frequent in arm A than in arm B (60% vs 40%, p = 0.034). Median PFS in arm A was 4.37 months (95% CI: 2.9-5.9 m) and 6.5 months (95% CI: 4.8-8.2 m) in arm B. 

**Conclusions:** Cetuximab and paclitaxel/carboplatin can achieve similar progression free survival (PFS) with less toxicity compared to standard cetuximab and 5-FU/platinum based chemotherapy.
6035 Poster Session (Board #23), Sat, 1:15 PM-4:45 PM
Saline alone vs saline plus manniol hydration for the prevention of acute cisplatin nephrotoxicity: A randomized trial. First Author: Bradley Beeler, USAF, Fort Sam Houston, TX

Background: Cisplatin is a widely used chemotherapeutic in treating malignancies. One of the common side effects of cisplatin is kidney injury, or nephrotoxicity. This can be a reason for discontinuation of treatment. The majority of the cisplatin is excreted by urination. Mannitol is a diuretic, causing increased amount of urination, thereby enhancing excretion of cisplatin. Multiple studies have indirectly looked into the effect of mannitol in preventing kidney damage in patients receiving cisplatin. However, there are limited prospective data that evaluate the effect of mannitol in preventing cisplatin-induced nephrotoxicity. In this study, we determine the effects of pre-hydration with mannitol on reducing the risk of cisplatin-induced nephrotoxicity, as opposed to traditional saline pre-hydration in patients receiving cisplatin.

Methods: 48 patients eligible to receive IV cisplatin therapy at a dose of ≥ 50mg/m² were identified and randomized to receive 1 L saline alone (A) or saline plus mannitol (B) before and after chemotherapy. Serum creatinine and BUN were drawn on days 1, 5, and 14. Results: Renal function as measured by BUN/Cr ratio, GFR, creatinine, proteinuria and BUN were similar at baseline (BL), day 1, day 5, and day 14. Cisplatin caused acute decline in renal function as determined by serum Cr, BUN to serum Cr ratio and GFR, however, the addition of mannitol to NS pre-hydration did not change the outcome. The decline in renal function is limited to grade 1 and most patients recover.

Conclusions: Mannitol does not prevent acute nephrotoxicity in patients receiving cisplatin. The addition of mannitol to NS pre-hydration does not improve adequate hydration in patients treated with cisplatin.

6036 Poster Session (Board #24), Sat, 1:15 PM-4:45 PM
Safety and preliminary efficacy of talimogene laherparepvec (T-VEC) in combination (combo) with pembrolizumab (Pembro) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M HNSCC): A multicenter, phase 1b study (MASTERKEY-232). First Author: Kevin J. Harrington, The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, Surrey, United Kingdom

Background: We evaluated the safety and efficacy of the combo of T-VEC, the first FDA-approved oncolytic immunotherapy that enhances systemic antitumor immune responses, and Pembro, an immune checkpoint inhibitor against programmed death receptor-1 (PD-1), in pts with R/M HNSCC. Methods: Pts were eligible for enrollment if they had histologically confirmed R/M HNSCC unsuitable for curative resection or radiotherapy, and platinum-refractory and injectable disease. T-VEC was injected intratumorally at a dose of up to 8.0 mL of 10⁶ PFU/mL on day 1. After 3 weeks, subsequent doses of up to 8.0 mL of 10⁶ PFU/mL were administered every 3 weeks (Q3W). Pembro was administered intravenously at a dose of 200 mg Q3W. The primary objective was to evaluate safety, as assessed by the incidence of dose limiting toxicity (DLT). Key secondary objectives were objective response rate (ORR), best overall response per immune-related RECIST, and long-term safety. Results: 36 pts were enrolled and treated: 28 (78%) had confirmed PD-L1-positive status, 18 (50%) were HPV-positive and 13 (36.1%) were HPV-negative, with 18 (50%) unknown. One (6.3%) DLT, fatal arterial hemorrhage, was observed among 16 DLT- evaluable pts. Overall, 24/36 (66.7%) pts had grade 3 or higher treatment-emergent adverse events (TEAEs): 9 (13.9%) and 3 (8.3%) pts had TEAEs related to T-VEC and Pembro; 2 (5.6%) and 1 (2.8%) pts had TEAEs not related to treatment due to T-VEC- and Pembro-related TEAEs, respectively. The most common TEAEs were pyrexia (36.1%), dyspnea (33.3%), and fatigue (25.0%). 24/36 (66.7%) pts had serious AEs. 7 deaths were reported during the study, 1 of which was related to T-VEC (the DLT pt) and none to Pembro. The ORR was 16.7% (6/36 pts; 95% CI, 6.4–33.8%). Pembro combined with T-VEC increased disease control rate (objective response/stable disease) was 38.9% (14/36 pts; 11 PD-L1-positive; 95% CI, 23.1–56.5). Conclusions: The combo demonstrated a manageable safety profile. Preliminary ORR showed activity in R/M HNSCC. Further follow-up is ongoing for PFS/OS. Clinical trial information: NCT02626000.

6037 Poster Session (Board #25), Sat, 1:15 PM-4:45 PM
An open-label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with two chemotherapeutic agents for second-line R/M HNSCC treatment. This is the first trial to combine pembrolizumab with cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Results of the interim safety analysis. First Author: Assuntina Gesualda Sacco, University of California San Diego Moores Cancer Center, La Jolla, CA

Background: Pembrolizumab (a humanized monoclonal antibody blocking programmed death receptor-1), and cetuximab (a chimeric monoclonal antibody inhibiting epidermal growth factor) are both FDA-approved as single agents for second-line R/M HNSCC treatment. This is the first trial to combine pembrolizumab with cetuximab to evaluate anti-tumor synergy. As this specific drug combination has not been previously tested, an interim safety analysis was conducted completed per protocol. Methods: Patients (pts) with R/M HNSCC were treated with pembrolizumab at a fixed dose of 200mg IV on day 1 and cetuximab 400mg/m² loading dose followed by 250mg/m² weekly (21-day cycle). The first 10 pts who enrolled and completed at least 1 cycle of therapy were included in the safety analysis. A mandatory study hold and Data Safety Monitoring Committee (DSMC) review were required if at least 4 of the 10 pts developed any grade 3 (G3) or higher hematoxicologic toxicity. Results: Of the 10 patients included in the analysis, median age 58y (range 47-79y), M: F 5:5. 8 pts had mucosal (6 oral cavity, 1 oropharynx, 1 larynx) and 2 had cutaneous HNSCC primaries. 65 adverse events (AEs) were reported in 9 pts; G1: 39, G2: 15, G3: 11. Of the 11 G3 AEs, only 1 was treatment-related (see Table). There were no treatment-related deaths or dose-limiting toxicities (DLTs). 3 pts discontinued treatment, none of which were due to toxicity (2 had disease progression, 1 withdrew from study). DSMC reviewed the safety data and permitted resumption of trial accrual. Of 7 evaluable pts, 4 partial responses were identified and randomized to receive 1 L saline alone (A) or saline plus mannitol (B) before and after chemotherapy. Serum creatinine and BUN were drawn on days 1, 5, and 14. Results: Renal function as measured by BUN/Cr ratio, GFR, creatinine, proteinuria and BUN were similar at baseline (BL), day 1, day 5, and day 14. Cisplatin caused acute decline in renal function as determined by serum Cr, BUN to serum Cr ratio and GFR, however, the addition of mannitol to NS pre-hydration did not change the outcome. The decline in renal function is limited to grade 1 and most patients recover.

Conclusions: Mannitol does not prevent acute nephrotoxicity in patients receiving cisplatin. The addition of mannitol to NS pre-hydration does not improve adequate hydration in patients treated with cisplatin.

6038 Poster Session (Board #26), Sat, 1:15 PM-4:45 PM
Association of a baseline neutrophil-to-lymphocyte ratio (NLR) with progression-free and overall survival in head and neck cancer patients receiving anti-PD-1 therapy. First Author: Corey Christian Foster, Department of Radiation & Cellular Oncology, The University of Chicago Medicine, Chicago, IL

Background: An elevated neutrophil-to-lymphocyte ratio (NLR) is associated with tumor-induced inflammation and poor prognosis in a variety of treatment settings. Moreover, tumor-derived myeloid growth factors (Seiwert et al: ASCO 2017) could elevate the NLR and suppress cytotoxic T-cell activity and anti-PD-1 efficacy. We hypothesized that high baseline NLR will associate with poor outcomes in patients with metastatic head and neck (H&N) cancer receiving anti-PD-1 therapy. Methods: 114 patients with metastatic H&N cancer unselected for PD-ligand 1 (PD-L1) status received anti-PD-1 therapy. Baseline NLRs were divided into quartiles with high NLRs being the highest quartile (≥ 8.77). Univariate logistic regression analyzed the relationship between NLR and overall response rate (ORR) by RECIST v1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and Cox proportional hazard regression. Results: Median follow-up was 8.6 months. Baseline characteristics including known PD-L1 positivity (n = 15/29 high NLR vs. n = 38/78 low NLR, p = 0.15) were comparable between groups. ORR was 22.3% with a trend towards lower ORR for the high NLR group (odds ratio: 0.42, 95% confidence interval [CI]: 0.11–1.57, p = 0.20). Median PFS was 1.7 months (95% CI: 1.0–3.6) for high NLR patients and 3.6 months (95% CI: 2.6–5.6) for low NLR patients (p = 0.02). Notably, median OS was 4.1 months (95% CI: 2.1–5.5) in the high NLR group and 12.5 months (95% CI: 9.0–17.2) in the low NLR group (p = 0.007). NLR more strongly associated with outcome than PD-L1+, which was not associated with PFS (p = 0.67) or OS (p = 0.53). On multivariate analyses, a high baseline NLR remained independently associated with reduced PFS (p = 0.04) and OS (p = 0.01). Conclusions: A high baseline NLR showed a strong inverse relationship with OS and PFS in patients receiving anti-PD-1 therapy for metastatic H&N cancer regardless of PD-L1 expression. Future investigation of NLR as a clinically-useful bio-marker, NLR kinetics over time, and a mechanistic understanding of tumor-driven factors influencing NLR and anti-PD-1 efficacy are warranted.
Background: Patients with recurrent HNSCC (rHNSCC) have limited therapeutic options and poor prognosis. We report promising results of a Phase 2a trial of photoinmunotherapy (PIT) for the treatment of rHNSCC using a novel targeted light activated drug RM-1929; a conjugate of the EGFR-directed monoclonal antibody cetuximab with the phthalocyanine dye, IRDye 700DX.

Methods: A multi-institutional, open label Phase 2a study of HNSCC patients who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy was conducted to evaluate the safety and efficacy of RM-1929. For each treatment, non-thermal red light was applied to the tumors 24 hours after intravenous infusion of RM1929. Light was applied by surface illumination for superficial disease or interstitial illumination via intratumoral placement of fiber optic diffusers for deep tumors. Therapeutic response was calculated using CT RECIST 1.1 determined by an independent blinded radiologist.

Results: Thirty rHNSCC patients were enrolled in this Phase 2a trial. Safety data are currently available from 30 subjects, outcome data from 28 subjects. There were no dose-limiting toxicities or skin photosensitivity reactions observed. SAEs reported to be possibly related to study treatment, included treatment site pain, tumor hemorrhage, and swelling. Objective response rate was 28% (8/28), complete response was 14% (4/28). Median progression free survival for 28 evaluable patients was 17.3 days (5.7 months). Median overall survival for the entire 30 patient cohort was 278 days (9.1 months). Conclusions: Photoinmunotherapy with RM1929 in patients with rHNSCC is safe and well tolerated. CT RECIST 1.1 PFS, ORR and CR wereevaluated. There were no dose-limiting toxicities or skin photosensitivity reactions observed. SAEs reported to be possibly related to study treatment, included treatment site pain, tumor hemorrhage, and swelling. Objective response rate was 28% (8/28), complete response was 14% (4/28). Median progression free survival for 28 evaluable patients was 17.3 days (5.7 months). Median overall survival for the entire 30 patient cohort was 278 days (9.1 months).

6041 Poster Session (Board #29), Sat, 1:15 PM-4:45 PM
CAPTN: A nomogram for predicting survival and guiding therapy for patients with de novo metastatic head and neck squamous cell carcinoma
Author: Jared R. Robbins, Medical College of Wisconsin, Milwaukee, WI
Background: Determining prognosis for de novo metastatic head and neck squamous cell carcinoma (mHNSCC) is difficult with limited data to direct clinical management. Recommendations for aggressive treatment must be measured since the duration and toxicity of treatment may exceed the projected lifespan. For this reason, tools to predict survival are needed to guide decisions like the appropriateness of radiation, standard versus experimental therapy, or supportive care alone. Purpose/Objective: To develop and evaluate a model for predicting survival for patients with de novo mHNSCC. Methods: We identified 8,441 patients diagnosed with de novo mHNSCC (oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, and paranasal sinuses) in the National Cancer Database from 2004-2013. Test and validation cohorts were randomly generated. Univariate and multivariate Cox regression models were used to identify factors associated with overall survival. A simple scoring system based on clinically-relevant factors was used to generate the CAPTN nomogram (see table).

Results: For all patients, the median OS was 9.5 months. In 1-year OS of 43%. In both the test and validation cohorts, the CAPTN accurately predicted outcomes between each group by pairwise comparison (all p < 0.001, see table). A CAPTN score of 0 correlated to the best prognosis while higher score represented step-wise worse prognosis. Conclusions: Patients with de novo mHNSCC have heterogeneous outcomes, but the CAPTN score can accurately discriminate survival. Although further validation in other cohorts is needed, the CAPTN is useful clinically for tailoring treatment intensity to prognosis and may be pertinent to clinical trial design as a stratification factor.

6042 Poster Session (Board #30), Sat, 1:15 PM-4:45 PM
Absolute lymphocyte count (ALC) during and after chemoradiation (CRT) for squamous cell carcinoma of the head and neck (SCCHN): Effect of the regimen and potential therapeutic implications
Author: Marit Ugle, NorthShore University HealthSystem, Evanston, IL
Background: Radiation (RT) or (CRT) is a component of treatment (tx) for locally advanced (LA) SCCHN. ALC and lymphocyte subsets are known to decrease as a result of RT for SCCHN. The changes in and variables affecting ALC during or after RT/CRT are not well described. Methods: We retrospectively reviewed the ALC of 298 consecutive patients (pts) treated with IMRT based therapy for SCCHN from 7/2003-7/2015. ALC was categorized using a prespecified algorithm at day 0 of RT, weeks (wk) 1,2,3,4,5,6,7,8,9, months (mo) 3, 6, 12 and years (yr) 2,3,4,5. Chemotherapy (CT) was categorized as induction (IC) yes/no and CRT as one of 4 categories. We performed ALC and lymphocyte subset analysis using 90% confidence intervals.

Results: ALC nadir for the entire group occurred at week 9 at a mean level of 0.4 (CTCAE 4.03 grade 3, normal range 1.0 - 4.0 10^3/uL) for CRT patients and 0.76 for RT only patients (p = 0.016). At yr 1, ALC ranged from 0.83-1.04 (p = 0.2) amongst 4 groups. By year 5, ALC had only recovered to 69% of baseline with no significant differences between groups. The use of IC did not affect nadir ALC. Pts receiving bilateral neck RT vs. unilateral had significantly lower mean ALC nadirs from wk 3-9 (wk 9: 0.38 vs. 0.88 p < 0.001) but not after 3 mo. ALC nadir had no effect on relapse or survival parameters. 19 pts had documented cases of shingles (VZV) occurring at a median time of 10 mo. There was no effect on nadir ALC by p16 status for oropharynx pts. Conclusions: Pts undergoing RT or CRT for SCCHN have a quick and severe nadir ALC which never recovers to normal. CRT compared with RT decreased the severity of the nadir but not the recovery. IC does not impact ALC, but bilateral neck RT leads to a deeper nadir than unilateral. ALC nadir does not affect survival. VZV could be a related adverse event as it follows CRT in at least 6% of patients at a median of 10 mo. The severe and sustained ALC nadir may also have important effects on the timing of the use of checkpoint inhibitor therapy during RT or CRT.
The use of exosome and immune profiling to analyze a phase 2 study on the addition of patritumab or placebo to cetuximab and a platinum agent for recurrent or metastatic head and neck cancer (HNSCC) patients. First Author: Tony Ng, King’s College London, London, United Kingdom

**Background:** The use of patritumab (Daichi Sanyo), an internalizing anti
HER3 monoclonal antibody, in combination with cetuximab and cisplatin was investigated in a cohort of patients with R/M HNSCC in a Phase II trial (NCT02633800). We investigated the EGRF-HER3 dimer (an established marker of cetuximab resistance within a previous study) in the circulating exosomes from patients enrolled in this trial. The objective was to identify potential immune monitoring parameters. **Methods:** We extracted exosomes from patient serum at 2 timepoints: pretreatment (c1) and pre-cycle 2 (c2, day 1). Exosomes were stained with fluorescently labelled antibodies for fluorescence lifetime imaging microscopy (FLIM) to assess EGRF-HER3 dimerization by FRET. Serum exosomal miRs were analyzed using ddPCR. Fluorescence lifetime imaging microscopy (FLIM) to assess EGFR-HER3 dimerization by FRET. Serum exosomal miRs were analyzed using ddPCR.

**Results:** Contributions to risk.

**Conclusion:** Multivariate risk scores/signatures were derived that predicted either: progression free survival (PFS), with parameters including c1 MDSC, and c2 CD27-lgd-double-negative exhausted memory B cells; or RECIST response, with parameters including suppressive transitional cells (c1 - c2 difference predicting response), and exosomal EGRF-HER3 dimer (c1 - c2 difference negatively predicting response).

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6044 Poster Session (Board #32), Sat, 1:15 PM-4:45 PM

Cisplatin dose intensity (CDDP-D) in human papillomavirus-positive (HPV+) localized oropharyngeal carcinoma (OPC) treated with chemoradiotherapy (CRT). First Author: Marc O'Brien, Princess Margaret Cancer Centre; Toronto, ON, Canada

**Background:** CDDP-D ≤ 200 mg/m² has been shown to have a detrimental impact on overall survival (OS) in HPV negative disease with a similar trend in T4/ N3 HPV+ patients (pts). We evaluated the impact of CDDP-D on OS in a larger cohort of HPV+ OPC, staged using 8th Ed. AJCC/UICC TNM staging criteria (TNM8- S). **Methods:** We performed a retrospective single institution analysis of HPV+ OPC pts treated with CRT (IMRT) between 2005-2015. HPV status was tested by 316 invasive treatment stratification and longitudinal monitoring markers. Since antibody-directed cytotoxicity is involved as a mechanism of action for these therapies, exosomal microRNAs (miR21 and miR142), which promote the expansion of functional myeloid-derived suppressor cells (MDSC), as well as other suppressive adaptive and innate immune cell components are postulated as potential immune monitoring parameters. **Methods:** We extracted exosomes from patient serum at 2 timepoints: pretreatment (c1) and pre-cycle 2 (c2, day 1). Exosomes were stained with fluorescently labelled antibodies for fluorescence lifetime imaging microscopy (FLIM) to assess EGRF-HER3 dimerization by FRET. Serum exosomal miRs were analyzed using ddPCR. We performed a retrospective single institution analysis of HPV+ OPC pts treated with CRT (IMRT) between 2005-2015. HPV status was tested by 316 invasive treatment stratification and longitudinal monitoring markers. Since antibody-directed cytotoxicity is involved as a mechanism of action for these therapies, exosomal microRNAs (miR21 and miR142), which promote the expansion of functional myeloid-derived suppressor cells (MDSC), as well as other suppressive adaptive and innate immune cell components are postulated as potential immune monitoring parameters. **Methods:** We extracted exosomes from patient serum at 2 timepoints: pretreatment (c1) and pre-cycle 2 (c2, day 1). Exosomes were stained with fluorescently labelled antibodies for fluorescence lifetime imaging microscopy (FLIM) to assess EGRF-HER3 dimerization by FRET. Serum exosomal miRs were analyzed using ddPCR. Fluorescence lifetime imaging microscopy (FLIM) to assess EGFR-HER3 dimerization by FRET. Serum exosomal miRs were analyzed using ddPCR.

**Results:** Contributions to risk.

**Conclusion:** Multivariate risk scores/signatures were derived that predicted either: progression free survival (PFS), with parameters including c1 MDSC, and c2 CD27-lgd-double-negative exhausted memory B cells; or RECIST response, with parameters including suppressive transitional cells (c1 - c2 difference predicting response), and exosomal EGRF-HER3 dimer (c1 - c2 difference negatively predicting response).

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6045 Poster Session (Board #33), Sat, 1:15 PM-4:45 PM

Randomized phase 2 trial of patritumab (P) or placebo (PBO) + cetuximab (C) + carboplatin (Cis) or carboplatin (C) + radiation (CRT) + patritumab (P) + radiation (CRT) in R/M squamous cell carcinoma of the head and neck (SCC). First Author: Kevin J. Harrington, Royal Marsden Hospital/Institute of Cancer Research, London, United Kingdom

**Background:** P, a fully human monoclonal antibody can block HER3 activation. HER3 activation is a resistance mechanism to C, induced by the ligand heregulin (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR+Por PBO for R/M SCCN. (HRG). This randomized phase 2 study in Europe evaluated...
Development and validation of a combined metabolic and immune prognostic profile and immune status. Both facets could impact on response to standard and chemotherapies. As part of our ongoing studies, we identified metabolic and immune signatures to define patient subgroups that are likely to benefit from personalized treatment approaches. Methods: We developed an integrative genomic immune metabolic signature (MIGS) using a large cohort of patients with head and neck cancer (HNC) treated in 14 centers. The MIGS was constructed using machine learning methods to identify a classifier of metabolic and immune profiles that distinguishes patients with good outcomes from those with poor outcomes. Results: A total of 1,800 patients were included in the study. The MIGS classifier distinguished patients with good outcomes from those with poor outcomes with a significant P-value of 0.033. Conclusions: Our findings suggest that a combined metabolic and immune signature can be used to predict clinical outcomes in HNC patients. Future studies are needed to validate this classifier in independent cohorts and to further investigate the mechanisms underlying the relationship between metabolic and immune profiles and clinical outcomes.

Cisplatin-induced ototoxicity in head and neck squamous cell carcinoma (HNSCC) patients treated with chemoradiation. The role of WFS1 and ABC2 heritable variants. First Author: Mary Mahler, Western University, London, ON, Canada

Background: Ototoxicity is a common adverse drug reaction associated with cisplatin therapy and with radiation to the HN region. We evaluated the differential effect on hearing impairment in HNSCC patients by candidate polymorphisms of genes associated with either hearing loss or cisplatin function. Methods: In this observational study of locally-advanced HNSCC patients treated with cisplatin chemoradiation, hearing impairment attributed to treatment was defined as ≥ grade 2 audiometric change from baseline to post-treatment, evaluated within 18 months of completing therapy. Patients were genotyped for 30 polymorphisms using Sequenom. Logistic regression evaluated associations between genetic variants and ototoxicity. Cox regression assessed relationships between genetic variants and locoregional control (LRC), distant control (DC), and overall survival (OS). Results: Of 246 patients who had audiometric testing pre- and post-chemoradiation, 79% were male; 76%, oropharyngeal cancers; 11%, oral cavity cancers; 8%, laryngeal cancer; 91%, stage IV; 58% had hearing loss. Two polymorphisms had significant associations with hearing loss post treatment: WFS1 rs62283056 and ABC2 rs3740066. In an additive inheritance model, individuals with WFS1 variants had a significantly decreased risk of ototoxicity (P = 0.012; adjusted odds ratio (aOR) = 0.56; 95% CI, 0.4-0.9, per increase in one minor allele), while the minor allele of ABC2 was associated with greater risk of ototoxicity (P = 0.016; aOR = 1.68; 95% CI, 1.1-2.6). In contrast, the same genetic variants were not associated with LRC, DC, DFS or OS in a larger cohort of 642 HNSCC patients. Conclusions: WFS1 genetic variant is associated with differential hearing loss in LA-HNSCC patients. An ABC2 variant, involved in removal of cisplatin from cells, is associated with increased cisplatin-induced ototoxicity. The same genetic variants were not associated with any efficacy outcomes. This information could be useful in the development of predictive models for cisplatin-induced ototoxicity.
Cardiovascular disease risks among head and neck cancer survivors in a large, population-based cohort study. First Author: Mei Wei, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Over 63,000 Americans develop head and neck cancer (HNC) yearly. The 5-year survival rate for HNC patients is 40-90%. HNC shares risk factors to cardiovascular disease (CVD), such as age > 60 years, male sex, low fruit and vegetable intake, tobacco and alcohol use. Our study was to investigate cardiovascular complications and risk factors for CVD among HNC survivors. Methods: A total of 1,901 HNC patients diagnosed between 1997 and 2012, and 7,796 age and sex matched individuals from the general population were identified. CVD diagnoses were identified in electronic medical records; statewide ambulatory surgery and inpatient visit databases linked to the Utah Population Database. Multivariable Cox proportional hazard models were used to calculate hazard ratios (HR) for cardiovascular outcomes at 0-2 years, 2-5 years and 5+ years after HNC diagnosis. Results: Within the first 2 years after cancer diagnosis, HNC survivors had higher risks of developing CVD than matched comparison individuals, such as heart valve disease (HR 3.33, 95% 2.60-4.28), cardiomyopathy (HR 3.21, 95% 2.04-5.03), systolic heart failure (HR 3.90, 95% 3.10-4.89), conduction disorders (HR 5.73, 95% 4.02-9.16), acute myocardial infarction (HR 3.11, 95% 2.08-4.65), coronary atherosclerosis (HR 3.42, 95% 2.90-4.03) and cardiac dysrhythmias (HR 4.26, 95% 3.68-4.93). The risks persisted even 5 years after cancer diagnosis. More baseline comorbidities (HR 1.27, 95% 1.01-1.58), late stage of disease (HR 2.20, 95% 1.64-2.96), age > 65 years, (HR 3.55), 1-5 years old (HR 1.27), radiation therapy (HR 1.33, 95% 1.07-1.65) and chemotherapy (HR 1.72, 95% 1.39-2.13) were associated with increased CVD baseline. Baseline comorbidities such as diabetes (HR 3.68, 95% 2.82-4.80), hypertension (HR 2.90, 95% 1.60-2.52) and cigarette smoking (HR 3.97, 95% 2.86-5.65) were associated with increased CVD risk. Conclusions: Compared to the general population, HNC survivors have higher risk of developing CVD. Older age, late stage of cancer, comorbidities, radiation therapy and chemotherapy were risk factors. Close CVD monitoring and preventive treatments should be considered in this population.

Comprehensive proteomic and genomic profiling to identify therapeutic targets in adenoid cystic carcinoma. First Author: Sheena P. Thyparambil, NanOtics, LLC, Rockville, MD

Background: Adenoid cystic carcinoma (ACC) is a rare cancer of secretory glands accounting for 10% of salivary gland cancers and 1% of head and neck cancers. ACC rarely responds to chemotherapy or targeted therapy and there is no standard therapy for advanced ACC. Comprehensive molecular profiling of ACC tumors could identify targets of FDA-approved or investigational therapies. Methods: ACC specimens (n = 24) were analyzed with the GPS Cancer test, which includes whole genome sequencing, RNA-seq, and mass spectrometry-based targeted proteomic analysis. Tumor areas of FFPE tissue sections were marked by a pathologist, microdissected and solubilized for mass spectrometric quantitation of 30 clinically relevant proteins. A subset of tumors was further analyzed by global proteomics and compared with results from squamous cell carcinoma of the head and neck (SCCHN). RNA-seq results from ACC tumors was compared with that of various solid tumor types using the k-nearest neighbors algorithm. Results: Targeted proteomic analysis of chemopredictive proteins suggested that 17% of patients were likely to respond to irinotecan, while 33% were likely to be resistant to taxane. The vast majority of patients (96%) did not express any target proteins of FDA-approved targeted therapies. Global proteomic analysis with unsupervised hierarchical clustering of 4,002 proteins from 8 ACC specimens and 6 SCCHN specimens revealed a clear separation between the two groups. In genomic analysis, tumor mutational burden was lower in ACC than in SCCHN (1.53 vs 3.53 per MB). In ACC, MYB-NFIB fusion and missense mutations involved in transcriptional regulation (ZNF43, ZNF519 and ZNF429) were frequent. Expression of CDK6 protein and CDK6 mRNA (transcripts per million) were 4-fold and 3-fold higher in ACC than in SCCHN, respectively. None of the ACC tumors exhibited RB1 deficiency. Among solid tumors, breast cancer was closest to ACC based on mRNA expression. Conclusions: Proteogenomic analysis identified CDK6 overexpression at both protein and mRNA levels in ACC. The combination of CDK6 overexpression and RB1 deficiency suggests that ACC patients may benefit from CDK6 targeted therapy.
Prognostic role of pretreatment plasma EBV DNA on stage III nasopharyngeal carcinoma staged by AJCC/UICC 8th edition TNM staging classification. Prognostic role of pretreatment plasma EBV DNA on stage III nasopharyngeal carcinoma (NPC) was launched in 2018. We previously proposed new stage groups which incorporated pretreatment plasma EBV DNA and T-, N-classifications into recursive partitioning analysis. Stage III disease remains heterogeneous with different combinations of T and N-classifications. We investigated if pretreatment plasma EBV DNA can stratify stage III into high-risk vs. low-risk groups (NCT02476669). Methods: 518 patients with non-metastatic NPC confirmed by PET-CT and MRI scans were prospectively recruited from 2010 to 2016. They all had plasma EBV DNA measured at baseline, and then 8 weeks and 6 months following IMRT with/without concurrent -/- adjunct chemotherapy. They were treated based on 7th edition TNM but were re-staged by 8th edition TNM for subsequent analysis. Covariates including age, sex, ACE-27, pretreatment LDH and plasma EBV DNA were analyzed by Cox regression for prognostic factors of progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS). Results: 234 (45.2%) patients had stage III disease (see Table). 0.01). Interestingly, patients whose PCT harbored more than one TP53 mutations or its frequency more than 5% have more tendency to relapse (P < 0.01). Conclusions: Tumor-specific mutations can be detected in cfDNA from nasopharyngeal carcinoma. The relationship between nutritional immune competence and has been associated with poor outcomes with antimicrobial and oncologic therapies. The relationship between nutritional status and outcomes with anti-PD-1 checkpoint blockade has not been reported, and we examined this association in patients with metastatic head and neck (H&N) cancer. Methods: 114 patients with metastatic H&N cancer unslected for PD-ligand 1 (PD-L1) status received anti-PD-1 therapy. Low baseline serum albumin concentration was < 4.0 g/dL. Univariate logistic regression analysis the relationship between albumin and overall response rate (ORR) measured by RECIST v1.1, and the association with body mass index (BMI) was performed with Chi-square analysis. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and Cox proportional hazard regression. Results: Median follow-up was 8.6 months. Baseline characteristics including known PD-L1+ (n = 27/48 high albumin vs. n = 27/60 low albumin, p = 0.38) were comparable between groups. ORR was 22.3%. Albumin status not associated with ORR (p = 0.41) but was associated with BMI (p = 0.04). There was a trend towards lower median PFS for the low albumin group (2.4 months, 95% confidence interval (CI): 1.9-3.7) compared to the high albumin group (4.6 months, 95% CI: 2.6-7.5) (p = 0.1). OS was significantly reduced for the low albumin group (median: 5.4 months, 95% CI: 3.6-9.5) compared to the high albumin group (median: 12.5 months, 95% CI: 9.1-17.3) (p<0.003). On multivariate analysis, albumin was the strongest independent predictor of poor OS (p = 0.01). Conclusions: Poor nutritional status as measured by low baseline serum albumin concentration is associated with worse outcomes in patients with metastatic H&N cancer receiving anti-PD-1 therapy and is a potential measure of immune competency. Investigation of clinical measures of immune competency including albumin as a marker of nutritional status in larger patient cohorts is warranted.
Gene expression signature after one dose of neoadjuvant pembrolizumab associated with tumor response in head and neck squamous cell carcinoma (HNSCC). First Author: Eunjung Kim, University of Cincinnati Medical Center, Cincinnati, OH

Background: Immune checkpoint inhibitors have been shown to induce durable tumor response in a subset of recurrent and/or metastatic HNSCC. Higher expression of PD-L1, INF-γ, and composite signatures such as “T cell-inflamed” profiles have been reported as biomarkers of response. However, prospective study of gene expression profiles after a single dose of Pembrolizumab compared to pre-treatment biopsy have not been reported. As part of a study “Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC” (NCT02641093), we have investigated gene expression changes associated with Pembrolizumab pathological response in HNSCC. Methods: Total RNA was extracted from 11 paired samples of pre- and post- Pembrolizumab treatment and between five responders and six non-responders. Response was defined as more than 10% of pathologic treatment effect. Results: Higher expression of PD-L1, PD-L2, and INF-γ in pre-treatment samples were associated with tumor response after one dose of Pembrolizumab (Welch’s t-test, p = 0.015, 0.021, 0.006). Existence of T cells, B cells, NK cells, macrophages, neutrophils in pre-treatment samples were not predictive with response. However, decreased numbers of PD-L1+ macrophages, T and B lymphocytes were increased in post-treatment samples of responders, implying that these were recruited effectors. There was no such difference in NK cells and neutrophils. INF-γ induced genes including CXCL9, OASL, IFI35, and IDO1 showed higher expression in responders (Welch’s t-test p = 0.005, 0.007, 0.011). Conclusions: Inflamed tumor microenvironment, evidenced by increased INF-γ irrespective of lymphocyte infiltration is associated with pathological response after a single dose of Pembrolizumab in HNSCC.

Immune profiling of head and neck squamous cell carcinoma (HNSCC) by a multiplex immunofluorescence (mIF) panel using multispectral microscopy.

First Author: Janis De La Iglesia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: Treatments based on immune checkpoint inhibition have shown great promise in HNSCC. Comprehensive evaluation of lymphoid-inflamed tumor-immune microenvironment may contribute to the identification of a subgroup of patients that may have a favorable outcome using immunotherapy. Methods: HNSCCs were analyzed by a mIF panel (CD3, CD8, FOXP3, PD-1, PD-L1, pancytokeratin AE1/AE3, and DAPI) using multispectral microscopy and image analysis. Three regions of tumor core, tumor margin and adjacent stroma were chosen for measurement. The mIF results were correlated with clinical parameters. Results: Sixty-eight HNSCC patients were stained and numbers of positive cells from all 7 markers could be obtained. In the subset of 9 tumors with known p16 status (4 positive, 5 negative), numbers of PD-L1+ cells were marginally significantly higher in p16- tumors cores (p < 0.1) compared to p16+ tumor cores while numbers of CD3+ and CD8+ cells were higher in stroma of p16- tumors compared to p16+ tumors (p < 0.01 and p = 0.02, respectively). Regardless of p16 status, numbers of CD3+ and CD8+ cells in the tumor cores were marginally significantly higher in never smokers (N = 12) (both p < 0.1) and numbers of CD8+ cells within 25 micron from the tumor cells were again higher in never smokers (p = 0.048) compared to former (N = 14) and current smokers (N = 42). Patients with tumors harboring high numbers of CD8+ cells within 25 micron of the tumor cells showed a trend towards longer survival times (p = 0.16). Conclusions: This is the first study to examine the distribution of immune cells in tumor core, the invasive margin, and adjacent stroma and the proximity between immune and tumor cells. Our data suggest that p16- tumors may be more immunosuppressed by increased expression of PD-L1 while CD8+ cells are unable to infiltrate the tumor mostly residing in the stroma. In addition, never smokers may have more active immune response by having closer proximity of CD8+ cells to tumor cells compared to never and former smokers. Complete data from a total of 176 patients will be presented at the meeting.

First author: Eejung Kim, University of Cincinnati Medical Center, Cincinnati, OH

Poster Session (Board #47), Sat, 1:15 PM-4:45 PM

Poster Session (Board #48), Sat, 1:15 PM-4:45 PM

Second primary thyroid cancer following index head and neck cancer. First Author: Katherine M. Polednik, Saint Louis University School of Medicine, Saint Louis, MO

Background: Thyroid cancer incidence has increased in the last three decades, and studies have shown that radiation treatment for index cancers may play a role in its development. We examined the rate of second primary thyroid cancer (SPTC) following index head and neck cancer (HNC) and determined whether radiation treatment among HNC survivors increased risk of developing SPTC. Methods: Patients with index HNC diagnosed from 1975-2014 in the Surveillance, Epidemiology, and End Results (SEER) database were included. We calculated incidence rate for SPTC per 100,000 person-years. A multivariable competing risk proportional hazards model tested risk of developing a SPTC following an index HNC. Covariates included age, county-level poverty percentage, year of diagnosis, anatomic site, stage, grade, surgery, radiation, chemotherapy, race, marital status, and sex. Two sensitivity analyses using proportional hazards models were also performed: (1) comparing patients who received both radiation and chemotherapy to those who did not receive both; and (2) restricting the main model to patients who received radiation. Results: There were 229 SPTC cases out of 127,563 HNC patients (0.2%). The rate of SPTCs was 26.1 per 100,000 person-years. In the main model, for every increasing year of age at diagnosis, patients were 3% less likely to develop an SPTC (adjusted hazard ratio (aHR) = 0.97, 95% confidence interval (CI): 0.96, 0.98). Compared with non-Hispanic white patients, non-Hispanic Asian/Pacific Islander/Native American/Alaskan Native patients were 66% more likely to develop a SPTC (aHR = 1.66, 95% CI: 1.10, 2.50). Males were 27% less likely to develop an SPTC than females (aHR = 0.73, 95% CI: 0.55, 0.96). Radiation (aHR = 0.92, 95% CI: 0.68, 1.25), surgery (aHR = 0.79, 95% CI: 0.56, 1.11), and chemotherapy (aHR = 1.13, 95% CI: 0.76, 1.69) were not significantly associated with developing a SPTC. The sensitivity models also did not find an association between treatment and risk of SPTC. Conclusions: Rate of developing SPTC following index HNC was very low, and previous exposure to radiation did not significantly increase our risk study population. More studies are needed to understand the increasing incidence of thyroid cancer across the United States.

Number of nodal metastases associated with overall survival in HPV-negative head and neck cancer. First Author: Doug Farquhar, University of North Carolina, Chapel Hill, NC

Background: The 8th edition AJCC staging guidelines for HNSCC incorporated the number of positive nodal metastases into the pathologic staging criteria for HPV-positive oropharyngeal HNSCC. However, the number of positive nodes is not used for pathologic staging of HPV-negative HNSCC and may have prognostic significance. In this study, we evaluated whether the number of nodal metastases and other surgical pathology characteristics, including extracapsular extension (ECE), positive surgical margins (PSM), and perineural invasion (PNI), were associated with overall survival (OS) in HPV-negative HNSCC. Methods: Patients were identified from the Carolina Head and Neck Cancer Study (CHANCE). All HPV-negative patients without distance metastasis (MO) who received surgical treatment for their primary tumor were included. The number of positive nodes on surgical pathology was divided into 0, 1-4, and >4 nodes. T and N stage were based on 8th edition AJCC guidelines. Hazard ratios (HR) were calculated by Cox proportional hazard models. Results: We identified 212 HPV-negative HNSCC patients who received primary surgery with neck dissections; (81 had no positive nodes, 90 had 1-3 positive nodes, and 41 had >4 nodes). Number of positive nodes, LVI, and ECE were all associated with 5-year OS in univariate models. In a multivariate model that controlled for T and N staging, the number of positive nodes remained significantly associated with OS (HR = 1.8, 95% CI: 1.0-3.3 for 1 node; HR 5.7 for 4 nodes. T and N stage were based on 8th edition AJCC guidelines. Hazard ratios (HR) were calculated by Cox proportional hazard models. Results: We identified 212 HPV-negative HNSCC patients who received primary surgery with neck dissections; (81 had no positive nodes, 90 had 1-3 positive nodes, and 41 had >4 nodes). Number of positive nodes, LVI, and ECE were all associated with 5-year OS in univariate models. In a multivariate model that controlled for T and N staging, the number of positive nodes remained significantly associated with OS (HR = 1.8, 95% CI: 1.0-3.3 for 1 node; HR 5.7 for 4 nodes. ECE, PSM, and LVI were not independently predictive of OS in adjusted models. Conclusions: In this population of HPV-negative HNSCC patients, the number of positive nodes had a stronger association with 5-year OS than staging based on nodal size and laterality found in AJCC 8. No other pathologic variables were associated with survival after adjusting T and N for stage. Further research is necessary to determine whether the number of positive nodes should replace other criteria in future prognostic staging systems.
6063 Poster Session (Board #51), Sat, 1:15 PM-4:45 PM
Using mobile and sensor technology to identify early dehydration risk in head and neck cancer patients undergoing radiation treatment: Impact on symptoms and quality of life
First Author: K. Peterson, The University of Texas MD Anderson Cancer Center, Houston, TX
Background: Assessment and intervention with mobile and sensor technology may improve early detection and mitigation of treatment-related phenomena, impact quality of life (QOL), reduce complications, and lower health care costs. The CYCORE (Cyberinfrastructure for COmparative effectiveness Research) system utilizes sensor and mobile technology to remotely assess daily weight, blood pressure (BP)/pulse, and patient-reported outcomes in head and neck cancer (HNC) patients undergoing radiation treatment (RT). Clinicians reviewed data daily to identify early risk of dehydration and support early intervention to improve symptom management. We compared longitudinal symptom data in patients randomized to use CYCORE during RT versus those randomized to usual care. Methods: Methods: HNC patients (n = 357) completed the 28-item MD Anderson Symptom Inventory (MDASI) at RT initiation (baseline), completion of RT (6-7 weeks post-baseline), and 6-8 weeks post-RT completion. Symptom severity and interference were rated on 0-10 scales; lower scores indicated better outcomes. Repeated measures ANOVA evaluated time point and group differences in MDASI scores. Results: Mean age was 60 years (range 25-86); 21% were female, 85% were White, and 54% completed college. Baseline MDASI mean scores were similar in patients randomized to CYCORE (n = 169) or usual care (n = 188). Mean scores on the severity of general and HNC-specific symptoms were lower in the CYCORE versus usual care group at completion of RT (2.92 vs. 3.4, p = .003; 1.69 vs. 1.96, p = .009), and at 6-8 weeks post-RT completion (1.69 vs. 1.96; p = .003; 1.78 vs. 2.11, p = .009). Mean scores on symptom interference in daily life were similar in both groups across time. Conclusions: HNC patients randomized to the CYCORE group during RT self-reported lower severity of general and HNC-specific symptoms compared to usual care. Mobile technology can enable monitoring of patients’ symptoms and related outcomes during critical periods of outpatient cancer treatment, can provide timely information to facilitate rapid clinical decision making about care, and may ultimately result in better QOL and health outcomes. Clinical trial information: NCT02253238.

6064 Poster Session (Board #52), Sat, 1:15 PM-4:45 PM
Minimally-invasive dual testing for active HPV E6,E7 and PD-L1 expression in HNSCC. First Author: Haitham Mirghani, Gustave Roussy Cancer Campus, Villejuif, France
Background: Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) have better prognosis when HPV associated or with a positive PD-L1 status. The often invasive nature of testing as well as the turnaround time for results are impactful on the doctor-patient relationship as available testing influences levels of care. This assay was performed with minimally invasive swabs of lesions from HNSCC patients. Non-subjective and quantitative results for E6,E7 mRNA overexpression as well as PD-L1 expression in these tumors were obtained by a three color flow cytometry assay. Methods: Swabs from patients with oropharynx lesions at the Institut Gustave Roussy were fixed with a proprietary solution (IncellMAX, IncellDx) and sent for processing. Received samples were stained through a 35 uM filter, underwent ISH with E6, E7 mRNA probes (HPV OncoTect, IncellDx), stained with a PD-L1 Antibody (28-8), and stained with a cell cycle dye to verify cells. Stained samples were analyzed by flow cytometry. Institut Gustave Roussy provided FFPE lesion biopsy tissue collected from the same area of swab collection. Slides from FFPE lesion biopsy tissue were processed with p16 IHC. Positive p16 results were confirmed by HPV gDNA ISH (Inform HPV III, Ventana). Slides were also processed by Biofire Reference Laboratories for PD-L1 expression by IHC (PD-L1 IHC 28-8 pharmDx, Agilent). Results: Oral pharynx swabs samples from 40 unique patients with HNSCC were tested by flow cytometry for E6,E7 and PD-L1 overexpression. Results were compared to p16 positive and PD-L1 positive results from the tumor biopsy. Initial analysis of 30 samples show concordance of 73.3% between E6,E7 over expression by flow cytometry and p16 by IHC. (Additional data to be presented at the conference, currently pending PD-L1 IHC results). Conclusions: Providing quantification of HPV E6, E7 mRNA and PD-L1 expression through a minimally invasive method presents a profound ability for clinicians to decide treatment options for patients. Ease of sampling coupled with the ability to both multiplex targets and scale-up the assay provides great possibility in treatment in disease.

6065 Poster Session (Board #53), Sat, 1:15 PM-4:45 PM
A double-blind, randomized pilot study of NS-21 in the prevention of radiation dermatitis in patients with head and neck cancer. First Author: Chen-Hsi Hsieh, National Yang-Ming University, Taipei, Taiwan
Background: The purpose of this single-institution pilot study was to evaluate the feasibility and safety of NS-21, a natural citruso-free ingredient, on skin-related toxicity in patients with head and neck cancer (HNC) undergoing concurrent chemoradiation (CCRT) or radiotherapy (RT). Methods: Between July 2015 and November 2017, 29 HNC patients underwent RT or CCRT were double-blind, randomly allocated to application of either NS-21 (14 patients) or placebo (aloe vera gel, 15 patients) to the irradiated fields in neck three times per day from the first day of RT to the 2 weeks after RT is completed or to the development of severe skin toxicity. The skin moisture and dermatitis in the left and right irradiated-area of neck were recorded separately. The area in the level I-II-III-Va was named as upper neck and the area in the level IV-Va was named as lower neck. The RT dose to the low- and intermediate-risk area was 46 Gy and 60 Gy, respectively. The maximum grade of radiation used the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The relative humidity of skin was monitored by digital hygrometer. Results: The number of neck fields received radiation dose larger than 46 Gy (Neck_{46Gy}) was 80 and 82 in the study and placebo group, respectively. The occurrence of acute grade 3 or higher dermatitis in Neck_{46Gy} was significantly lower in the NS-21 group than in the placebo group (5.0% vs. 20.3%; p = 0.024). The median time of grade 3 or higher dermatitis occurred was 6 and 7 weeks for the control and NS-21 group, respectively (p < 0.001). From beginning of RT to 2 weeks after the completion of RT, Neck_{46Gy} (p < 0.001) and applying NS-21 (p = 0.014) were independent factors for the incidence of grade 3 dermatitis. There was a trend of skin moisture protection by using NS-21 in HNC patients under RT or CCRT (p = 0.052). Moreover, Neck_{46Gy} (p < 0.001) and dermatitis grading (p = 0.006) were independent factors associated with the skin moisture. Conclusions: For HNC patients, applying NS-21 from the first day of RT or CCRT and through the treatment course that can decrease the incidence of acute grade 3 or higher dermatitis in the neck effectively and preserve skin moisture in the neck potentially. Clinical trial information: FEMH 104048F.

6066 Poster Session (Board #54), Sat, 1:15 PM-4:45 PM
Safety and effectiveness of transoral surgery for superficial head and neck cancer. First Author: Chikotshika Katada, Kitasato University, Kanagawa, Japan
Background: The national registration survey of transoral surgery (TOS) for superficial head and neck cancer (SHNC) was performed to retrospectively examine safety and effectiveness. Methods: From April 2001 through July 2012, a total of 599 patients with SHNC (954 lesions) who underwent TOS as initial treatment were enrolled in 27 hospitals in Japan. Of these patients, we studied 899 lesions (665 initially treated lesions and 234 metachronous multiple cancers) in 568 patients who were given a central pathological diagnosis of initially treated squamous-cell carcinoma. The study variables were clinicopathological findings, the incidences of adverse events, and treatment outcomes. Results: The median age was 66 years, and 534 (94%) of the patients were men. A total of 202 lesions (22.4%) were located in the oropharynx, 660 (73.3%) in the hypopharynx, 23 (2.6%) in the larynx, 12 (1.3%) in the oral cavity, 2 (0.2%) in other sites. The surgical procedures were endoscopic mucosal resection in 374 lesions (41.6%), endoscopic submucosal dissection in 359 (39.9%), endoscopic laryngopharyngeal surgery in 48 (5.3%), transoral videoendoscopic surgery in 40 (4.4%), direct mucosectomy in 28 (3.1%), laser microsurgery in 20 (2.2%), and others in 28 (3.1%). The median clinical tumor diameter was 12 mm. The histopathological findings of the 869 lesions treated by TOS were well differentiated squamous-cell carcinoma in 333 lesions (38.3%). The median treatment time of 777 sessions of TOS was 49 minutes. Adverse events occurred in 89 patients (11.5%). Life-threatening complications occurred in 10 patients (1.3%), but there was no treatment-related death. Tracheotomy was performed in 72 patients (9.3%). Local recurrence was found in 53 lesions (5.9%), nodal recurrence in 26 patients (4.6%), and distant recurrence in 3 patients (0.5%). The median follow-up period was 46.1 months. At 3 years, the overall survival rate, the relapse-free survival rate and the cause-specific survival rate were 88.1%, 84.4% and 99.6%, respectively. Conclusions: TOS for SHNC is a safe and effective, minimally invasive treatment option. Clinical trial information: UMIN000008270.
Neck dissection rate in node positive human papillomavirus associated oropharyngeal carcinoma following chemoradiotherapy. First Author: Sandro Porceddu, Princess Alexandra Hospital, University of Queensland, Brisbane, Brisbane, Australia

**Background:** With results of chemio-radiotherapy de-escalation trials for Human Papillomavirus (HPV)-associated oropharyngeal carcinoma (OPC) pending, any reduction in toxicity may be offset by the increased need for post-therapy neck dissection (PT-ND) for suspected residual nodal disease. We report the rate of PT-ND and overall regional failure rate following standard radiotherapy (RT) with or without chemotherapy (chemo)RT in node positive HPV-associated OPC. Secondary objectives include estimated 5-year regional failure free survival (FFS), loco-regional FFS, distant metastatic FFS and overall survival (OS).

**Methods:** Patients treated between Jan 2005-Jan 2016 on a pre-defined (chemo)RT protocol and 12-week restaging PET/CT (treatment package) with a minimum of 18 months follow up (FU) were analysed. Patients receiving concurrent chemo were prescribed high-dose cisplatin and 70Gy/7 weeks to gross disease. Those ineligible for cisplatin received weekly cetuximab. PT-ND was performed if residual nodal disease was suspected on the restaging scan with complete response at the primary site and no evidence of distant disease. Median follow up was 60 months, with 302 (88%) alive at the close-out date. Median age was 59 (range, 21-89) yrs. The predominant AJCC/UICC 7th Edition (Ed) I & N-stage were T2 (37.3%) & N2b (44.9%), respectively. The 8th Ed group staging were; Stage I-49%, Stage II-28% & Stage III-23%. Median RT dose was 70.5Gy (range, 66-70Gy) and 336 (95.6%) received systemic therapy. At the completion of the treatment package 4.6% (16pts) underwent a ND. 10 pts (62.5%) were pathologically positive. The overall regional failure rate was 6.4%. The estimated 5-year regional FFS was 93% (95% CI: 90.2-95.9), loco-regional FFS 90.6% (95% CI: 87.3-94.0) and distant metastatic FFS 86.9% (95% CI: 83.1-90.8) and overall survival (OS). The overall regional failure rate of 6.4% was similar to that seen previously with standard radiotherapy (RT) with or without chemotherapy (chemo)RT in node positive HPV-associated OPC. Secondary objectives include estimated 5-year regional failure free survival (FFS), loco-regional FFS, distant metastatic FFS and overall survival (OS).

**Conclusions:** Following the treatment package the ND rate was low and regional failure uncommon. These findings serve as a benchmark to assess the benefit of de-escalation trials, which may be offset by an increased need for PT-ND.

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Preliminary toxicity data from the combination of pembrolizumab and definitive dose radiotherapy for locally advanced head and neck cancer with contraindication to cisplatin therapy. First Author: Jared Weiss, University of North Carolina Hospitals, Chapel Hill, NC

**Background:** Bolus cisplatin in combination with radiation is a standard of care for the treatment of locally advanced SCCHN, but contraindications such as hearing loss, tinnitus, inadequate renal function or neuropathy are common. Pembrolizumab is a PD1 inhibitor with FDA approval for the treatment of platinum refractory recurrent SCCHN. **Methods:** This is a phase II study (NCT02609503) for patients with locally advanced SCCHN who are not optimal candidates for the standard therapy of cisplatin and radiation. The primary endpoint is PFS. Patients are treated with 3 cycles of pembrolizumab concurrent with radiation followed by 3 adjuvant cycles. Planned accrual is 29 subjects and 1100 pts have been accrued. Because of rapid advance in studies combining PD1-axis agents with radiotherapy, we report early toxicity data on the first 12 patients who have completed six cycles of pembrolizumab and at least 30 days of followup from last pembrolizumab dose. **Results:** All patients completed 70 Gy radiation. 11 patients completed 6 cycles of pembrolizumab and 1 patient completed 5 (discontinued due to PD, not toxicity). The most common primary reason for cisplatin ineligibility was abnormal hearing (4) followed by tinnitus (3), nephropathy (2), neuropathy (2) and diabetes with poor control (1). The most common toxicities were mucositis and lymphopenia. Pneumonitis and auto-immune toxicity were absent. All toxicities that occurred more than once and listed as possible, probable or definitely related to pembrolizumab and radiation are listed in the table. PEG tubes were placed in 3 patients. **Conclusions:** Early data suggest low toxicity and high feasibility of pembrolizumab combined with radiotherapy. Clinical trial information: NCT02609503.

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A randomised, double-blind, placebo-controlled phase IIa trial of AMG319 given orally as neoadjuvant therapy in patients with human papillomavirus (HPV) positive and negative oropharyngeal and nasopharynx SCC. (HNSCC). First Author: Christian H.H Ottenheimer, Cancer Research UK, Southampton, United Kingdom

**Background:** AMG319 is a PI3Kδ inhibitor. Preclinically, target inhibition abrogates Treg mediated immunosuppression, augmenting CD8+ T-cell anti-tumour activity. This study aims to quantify the immunological effects of AMG319 on the tumour microenvironment in HNSCC patients (pts). **Methods:** The trial is a neoadjuvant window study of 94 pts, randomised 2:1 to AMG319/placebo for 20-29 days. Eligible pts have operable HNSCC, ECOG 0/1, adequate organ function and no active autoimmune disease. Primary endpoints are changes in tumour-infiltrating immune cell density, safety and toxicity. Changes in circulating immune markers, pAKT and change in tumour volume (pre-dosing vs immediately pre-surgery) are also assessed. Steady state plasma concentrations of AMG319 are determined at days 8, 15 and 22. Humoral and cellular immune responses to a tetanus vaccine are employed to confirm non-tumour immuneocompetence.

**Results:** Blinded clinical and laboratory data have been reviewed for 22 pts with fixed incidence data and 26 pts with fixed incidence data. Data from 10 pts have been presented. AEs resolved with withdrawal of AMG319 in 9 pts; 8 pts received less than 80% of the intended dose. pAKT levels on both day 1 and day 8 were reduced by 68% (p = 0.005) and 58% (p = 0.001) respectively. All pts except one completed the study. Two pts were withdrawn due to toxicity (37% and 43%). T-cell responses were observed in 40% of pts. A 2-fold increase was seen in anti-tetanus antibody response in 5/10 pts analysed. One patient experiencing immune-like toxicity with a T1 oral cavity squamous cell carcinoma achieved a complete pathologic response. **Conclusions:** The percentage inhibition demonstrated in the pAKT assay and observed in HNSCC is similar in magnitude to that seen previously with AMG319 in patients with advanced B cell malignancies, thereby supporting target inhibition. Cutaneous and GI toxicities are consistent with Treg depletion suggesting that efficacy and toxicity may be mechanistically interrelated. The trial is ongoing to further explore AMG319 solid tumour dosing regimens. Clinical trial information: NCT02540928.

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Impact of patient symptoms and caregiver tasks on psychological distress in caregivers for head and neck cancer (HNC). First Author: Emily Castellanos, Vanderbilt University Medical Center, Nashville, TN

**Background:** Caregiver support for HNC patients affects clinical outcomes including survival. Psychological distress in caregivers may impair the quality of support they provide. The impact of patient symptom burden and caregiver tasks on psychological distress in caregiver psychological distress is unknown. **Methods:** Patient symptom burden was assessed with the Vanderbilt Head and Neck Symptom Survey 2.0 (VHNSS 2.0; 10 domains, 3 single items). Caregiver task burden was assessed with the Caregiver Task Inventory (CTI; 11 domains), and quantified as task number and task difficulty/desire. Psychological distress was measured with the Profile of Mood States short form (POMS-SF). Two-step clustering analysis was used to independently generate clusters of caregiver distress, caregiver task burden, and patient symptom burden. Chi-Square and logistic regressions were used to test for associations of the resultant clusters of task burden and patient symptoms with caregiver distress. **Results:** 89 HNC patient-caregiver dyads were included. Patients were mostly male (77%) and Caucasian (88%). Mean time since diagnosis was 3.7 months (IQR 2–7); 90% received combined modality therapy. Caregivers were mostly Caucasian (92%), female (85%) and spouses (80%). We found two caregiver clusters of psychological distress (40% mod-high, 60% low), and two clusters of caregiver task scores (40% mod-high, 60% low). Similarly, two clusters of patient symptom burden were found: 51% mod-high, 49% low. Caregivers with mod-high task scores were more likely than low to report mod-high levels of psychological distress (71% vs. 24%, p < 0.001). Patients with mod-high symptom burden were more likely than low to have caregivers with mod-high psychological distress (55% vs. 23%, p = 0.005). No effect modification of patient symptom burden on the association between caregiver task and caregiver psychological distress was seen (p > 0.05). **Conclusions:** Psychological distress in HNC caregivers is correlated more strongly with caregiver task scores than patient symptoms. Further work to define the caregiver and task characteristics that lead to psychological distress should inform future interventions to support caregivers and patients.
A phase I study of the PI3K inhibitor buparlisib (B) with concurrent chemoradiotherapy (CRT) in patients with high risk locally advanced squamous cell carcinoma of the head and neck (LASCHC). First Author: Jochien H. Lorch, Dana-Farber Cancer Institute, Boston, MA

Background: Prognosis in smokers with LASCHCN remains poor. Activating mutations of PI3K are linked to poor outcome and PI3K activation in response to RT is implicated in resistance to CRT. Methods: In this phase I study, the oral pan-PI3K inhibitor B combined with CRT was tested in pts with stage III/IV LASCHCN and ≥ 10 pack-year history of tobacco use treated with curative intent. Pts received B during a 2-week run-in phase and during CRT consisting of 70Gy/35fx of radiotherapy plus weekly cisplatin. Results: Twenty-three pts (19 m, 4 f) were enrolled. Four had stage III, 19 (83%) had stage IV disease. 18 were former smokers, 5 smoked currently. Primary tumor locations: Oral cavity (6, 26%), oropharynx (11, 48%), larynx (3, 13%), other (3, 13%). HPV was pos in 14 cases. Among 7 pts enrolled on dose level 1 (DL1) (B 40mg daily, CDDP 30mg/m2/IMRT), 1 pt experienced 3 DLTs were observed in 4 cases (gr 3 neutropenia, LFT abn, mucositis, rash). Ten additional pts were enrolled at the RP2D (DL1). Additional gr 3 AEs included anorexia, anemia, dysphagia and confusion. One pt experienced grade 4 hyperamylasemia. With a median follow-up of 12 months (range 3-24), 2 pts (29%) had recurrence, one of whom died. Five pts had a response to buparlisib alone during the run-in phase assessed clinically or radiographically. To date, targeted NexGen sequencing was available in 8 pts. 4/5 cases with response to B alone had secondary or concurrent mutations in FANC/D2/EP300; FANCA/FGFR3; FANCI/FLT1 and PI3CA/PTC300. The patient who died had PTC3CA/STL11 mutations. Conclusions: B was tolerable in combination with CRT and appears to have promising activity. Genetic analysis is ongoing and may be helpful to identify patients suitable for this approach. Clinical trial information: NCT02113878.

Cisplatin (CIS) versus cetuximab (CET) with definitive concurrent radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC): An analysis of veteran's health data. First Author: Joshua Bauml, University of Pennsylvania, Philadelphia, PA

Background: The addition of CIS or CET to RT improves outcomes compared to RT alone in the non-operative management of HNSCC, but limited data exist on the comparative effectiveness and safety of these approaches. We compared outcomes of pts treated with RT plus CIS or CET using population-based Veterans Health Administration (VHA) data. Methods: We identified stage III-Ivb HNSCC patients (pts) treated non-surgically with RT and CIS or CET from 2002 to 2014 in the VHA. Pts were analyzed by the drug used in their first cycle (CIS or CET; intent-to-treat). Variables including primary cancer site, age, stage, smoking/alcohol use, and Charlson Comorbidity Index were used to generate propensity scores (PS) for the use of CET. We compared overall survival (OS) by treatment group using Cox regression models, matching for PS. We determined the risk of toxicities using PS-matched logistic regression. Results: A total of 3,986 pts were included in the analysis with a median follow-up of 3 years (yrs). 81% received CIS (19.9% low dose - 30-50 mg/m2). CIS pts were younger (p < 0.001) and had fewer comorbidities (p < 0.001). In an unadjusted analysis, CIS was associated with inferior OS (p < 0.001). This remained significant after matching for PS (HR 1.66, 95% CI 1.48-1.86, p < 0.001), corresponding to a median OS of 1.8 vs 4.2 yrs. CIS was associated with inferior survival across all primary subsites, CET was associated with inferior survival vs low dose CIS, after PS matching (See Table). Matching for PS, CET was associated with a lower rate of neutropenia, renal failure and hearing loss than CIS (all p < 0.001). Conclusions: CET yields inferior OS compared to CIS with RT for non-operative management of Stage III-Ivb HNSCC. Based on this registry study, CIS should remain the preferred partner for RT in this setting.

6072 Poster Session (Board #60), Sat, 1:15 PM-4:45 PM
The prognostic impact of level I lymph node involvement in oropharyngeal squamous cell carcinoma. First Author: Roy Xiao, Cleveland Clinic Lerner College of Medicine, Cleveland Heights, OH

Background: Current staging for oropharyngeal squamous cell carcinoma (OPSCC) may not capture the implications of regional lymph node involvement (LNI). We investigated the impact of level I LNI on survival for patients with OPSCC. Methods: We used the National Cancer Database for a cohort study of patients with OPSCC who underwent surgical resection from 2010-2014. The primary outcome was level I LNI, modeled by multivariable logistic regression. Overall survival (OS) for OS was modeled by Cox proportional hazards regression. Results: Among 7,231 patients with OPSCC, 1,061 (14.7%) had level I LNI. Most patients had pT1 (3,412, 47.2%) or pT2 (2,860, 39.6%) tumors with pN2 (5,482, 7.58%) lymph node stage by AJCC 7th Edition. Independent predictors of level I LNI included higher pT stage (pT3 vs. pT1, OR 1.82, 95% CI 1.38-2.31; pT4 vs. pT1, OR 2.92, 95% CI 2.28-3.76) and higher number of positive regional lymph nodes (OR 1.06, 95% CI 1.05-1.08). Among included patients, 5,543 had known survival status. Level I LNI was a significant predictor of inferior OS (HR 1.83, 95% CI 1.56-2.15) after adjusting for covariates. Subset analysis by pT and pN stage revealed level I LNI to be a consistent predictor of mortality across all stages for patients with confirmed HPV status, level I LNI significantly predicted OS among HPV(+) patients (N = 888, HR 1.99, 95% CI 1.43-2.74) but not among HPV(-) patients (N = 2,339, HR 1.38, 95% CI 0.89-2.05). Level I LNI remained a significant predictor of OS within additional analyses subset by age, sex and race. Number of positive lymph nodes, number of primary sites, and adjuvant treatments. Conclusions: Level I lymph node involvement in OPSCC is a significant and independent predictor of mortality. Patients with HPV(-) OPSCC and level I LNI may warrant intensified therapies.

Adjusted hazard ratio of mortality for level I nodule involvement subset by pT/pN.

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<th>Stage:</th>
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*Statistically significant, p < 0.05

Conclusions: For the first time, MET is shown to be safe and tolerable in combination with CRT with an impressive impact on survival in LAHNSCC pts. This warrants further investigation in a phase II trial, with the established MTD of 2500 mg as the recommended dose. Clinical trial information: NCT02325401.

6074 Poster Session (Board #62), Sat, 1:15 PM-4:45 PM
A phase I dose-finding study of metformin in combination with concurrent cisplatin and radiation for patients with locally advanced head and neck squamous cell carcinoma. First Author: Shuchu Gulati, University of Cincinnati Medical Center, Cincinnati, OH

Background: Up to 60% of HNSCC present as locally advanced disease (LHNSCC). Although prognosis has improved significantly, 3 year PFS and OS remain at 62%, and 73% respectively (RTOG 0222) despite definitive cisplatin (Cis) based chemo-radiation (CRT), underscoring the need for improved therapeutic strategies. Metformin (MET) is hypothesized to suppress tumor cell growth by inhibiting mTOR pathway inhibition, which mediates the phosphoinositol 3-kinase/Akt signaling pathway (frequently deregulated in HNSCC). Retrospective studies suggest that MET improves survival in HNSCC patients (pts). Therefore, we conducted a phase I open-label dose-escalation study combining MET with CRT in LHNSCC (NCT02325401). Methods: Previously untreated LHNSCC (Stage III/IV) pts were enrolled to receive escalating doses of MET with a 7-14 day lead-in prior to CRT based on modified toxicity probability interval design. Starting dose of MET was 2000mg daily in addition to cisplatin (50mg/m2/days 1, 22 and 43) and standard radiation (70Gy) (Table 1). Adverse events were categorized per CTCAE v4.03. Results: 20 pts were enrolled, (2 replaced due to withdrawal of consent during lead-in period). Most common grade ≥ 2 toxicities were nausea (25%), vomiting (25%), diarrhea (20%), and AKI (15%). Dose limiting toxicity (DLT) included Grade 3 diarrhea (cohort 3) and AKI (cohort 2). MTD was established at 2500mg daily in combination with CRT. Median age was 55 (46-65); majority pts were male (95%), Caucasian (95%), tobacco users (70%), and HPV positive (70%). After a median follow up of 18 months (range 1-26), 1-year PFS, and OS remain at 94%, 1 death was reported (suicide, unrelated, occurred ≥ 8 weeks after stopping MET). Pharmacokinetic data showed that Cis did not affect MET steady state. Conclusions: For the first time, MET is shown to be safe and tolerable in combination with CRT with an impressive impact on survival in LHNSCC pts. This warrants further investigation in a phase II trial, with the established MTD of 2500 mg as the recommended dose. Clinical trial information: NCT02325401.
Suboptimal regimens in sequential treatment (ST) with ICT (induction chemotherapy) followed by CCRT (concomitant chemotherapy) in "real life" patients with locally advanced head and neck squamous cell carcinoma (LAPLSCC) and prognosis. First Author: Carmen Orte, Hospital de Barbastro, Huesca, Spain

Background: ST is a treatment modality widely used in LAPLSCC. Although ICT with TPF (docetaxel-Cisplatin-5FU) and CCRT with 3-weekly Cisplatin have been proved as the most active regimens, unfit patients (n) often cannot receive them. There are few data about efficacy of modified ST regimens in unsellected population. From 15/06 to 2013, data from 2153 patients treated in our institution with ST were retrospectively reviewed. Patient and treatment-related prognostic factors (PFs) were collected. Both uni and multivariate proportional hazards were used to determine associations with overall survival (OS) and DFS (disease-free survival). Local Ethical Committee approval was obtained. Results: 337 consecutive patients were treated with ST with ICT and CCRT. Median age: 57 years. Male:92%. Stage: III: 133 (40.1%), 202 IV (59.9%). Median follow-up: 38.9 (0-222 m). Median OS: 48.3 m (95%CI 36-60). Median DFS: 105.3 m (95%CI 90-120). Analyzed tumor-related PFs: location, stage, differentiation. Patient-related PFs: age, blood cells ratios (NLR, nNLR, LMN), ACE-72 comorbidity index, Hemoglobin, albumin. Treatment-related PFs: ICT type , CCRT type, ICT response. In Multivariate analysis (MA) several PFs independently correlated with OS and DFS (Table 1). Use of TPF as ICT was independently linked to better OS and DFS. Use of 3-weekly Cisplatin as CCRT was associated with OS and DFS (Table 1). Use of TPF as ICT was independently linked to better OS and DFS. Use of 3-weekly Cisplatin as CCRT was associated with better OS and DFS. Conclusions: In unsellected LAPLSCC patients treated with ST selection of proved efficacious therapies affects outcome, independently of other tumor and patient-related PFs. Suboptimal regimens work worse. In unfit patients other alternatives should be considered.

### Outcome measure vs independent Prognostic factors (MA) vs-p value HR (95%CI)

| OS | Stage (IV vs III) | 0.007 | 1.70(1.15-2.49) |
| -- | Post-ICT Hemoglobin (< 10 vs > 10 g/dl) | 0.001 | 2.83(1.55-5.14) |
| -- | ICT response (Non CR vs CR) | 0.009 | 1.71(1.14-2.56) |
| -- | ICT (Non TPF vs other) | 0.027 | 1.58(1.05-2.38) |
| -- | CCR (Non CCRT vs CCRT) | 0.006 | 1.63(1.15-2.32) |
| -- | LMR (< 3.1 vs > 3.1) | 0.013 | 1.71(1.11-2.61) |
| DFS | ICT (non TPF vs TPF) | 0.035 | 1.01(0.64-1.31) |

**6077** Poster Session (Board #65), Sat, 1:15 PM-4:45 PM

Long-term outcomes for re-irradiation of recurrent head-and-neck cancers: Results of acute and long-term toxicity. First Author: Nima Aghdam, Georgetown University Medical Center, Washington, DC

Background: Long-term toxicity is a concern in patients undergoing head and neck re-irradiation. Durable local control is achieved in majority of patients in combination with chemotherapy and surgery. Here, we report the incidence and predictors of severe toxicity. Methods: From 2002 to 2016, 133 lesions in 123 patients received SBRT to the oropharynx (n = 21), hypopharynx (n = 8), nasopharynx (n = 9), parapharyngeal sinus (n = 7), neck (n = 39), and other sites (n = 49). 92 lesions in 88 patients were treated definitively, and 41 lesions were treated with palliative intent. 36.5% underwent complete macroscopic resection before SBRT. Seventy-eight patients received chemosensitization. The median initial radiation dose was 70.4 Gy, and the median re-irradiation SBRT dose was 20 Gy (21-42.5 Gy) in 2.5 fractions. Mean planning volume was 147.1 cm³ (64-654 cm³). Locoregional control (LRC) and overall survival (OS) were calculated using the Kaplan Meier method. $\chi^2$ test was utilized for differences in rates of acute and late toxicity. Severe toxicity was defined based on the RTOG Common Toxicity Criteria (version 4.0). Results: Median follow-up was 31 months. Of 133 lesions, 81 were treated definitively (61%) and 52 were treated with palliative intent (39%). 38.9% of patients had severe acute toxicity (n = 212) and 12.6% had severe late toxicity (n = 21). 45.6% of patients received chemosensitization. The median initial radiation dose was 70.4 Gy, and the median re-irradiation SBRT dose was 20 Gy (21-42.5 Gy) in 2.5 fractions. Median planning volume was 75 cm³ (6-645 cm³). Locoregional control (LRC) and overall survival (OS) were calculated using the Kaplan Meier method. $\chi^2$ test was utilized for differences in rates of acute and late toxicity. Severe toxicity was defined based on the RTOG Common Toxicity Criteria (version 4.0). Results were interpreted using the Ion Reporter Software. Results: A total of 21 patients had sufficient tumor content in FFPE samples that passed QC testing. Eight (38%) matched sets of PTs and LNs displayed the same mutational profile. LNs from four patients (19%) showed loss of mutations across known cancer-related genes. Conclusions: Safety of re-irradiation is achievable in majority of patients with severe toxicity. Further prospective studies are needed to define the impact of concurrent chemosensitization on toxicity.
Post-treatment evaluation of head and neck cancer patients in the era of advanced imaging and value-based care. First Author: Thomas Hirsch, Medical College of Wisconsin, Milwaukee, WI

Background: Current guidelines recommend imaging (CT and/or PET) to evaluate treatment response and detect residual disease after nonsurgical management of head and neck cancers squamous cell cancers (HNSCC). To objectively evaluate the utility of these diagnostic tests, we reviewed our institutional cohort to better understand the value of these interventions compared to routine history and physical examination (PE). Methods: After IRB approval, we retrospectively reviewed an institutional cohort of 160 HNC patients who underwent definitive radiation +/- chemotherapy from 2003-2014. All patients had post-treatment history, PE, and imaging data, including a 4-month PET scan. The sensitivity, specificity, negative-predictive and positive-predictive values were calculated, along with Kaplan-Meier survival analyses for each symptom, PE, and imaging finding. Results: PE and symptoms had higher specificity than imaging but had lower sensitivity (see table). While imaging had good sensitivity and NPV, excess false positives led to poor specificity and PPV. When PE and symptoms were evaluated together, performance was similar to CT and PET. On KM analysis, all PE/ symptom factors and PET response correlated with outcome, whereas CT did not. There were no early interventions resulting from baseline CT scans. Conclusions: In an era of value-based care, a renewed emphasis on patient symptoms and PE findings may allow for improved resource utilization and cost of care. These are strong predictors of residual disease in the immediate post-treatment setting, suggesting a need to reevaluate current imaging paradigms, particularly the utility of post-treatment CT scans.

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<th>Post-Treatment CT</th>
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8082 Poster Session (#70), Sat, 1:15 PM-4:45 PM
An open-label, randomized phase III trial of gemcitabine and carboplatin (GC) followed by Epstein-Barr virus-specific autologous cytotoxic T lymphocytes (EBV-CTLs) versus GC as frontline therapy for patients (pts) with advanced nasopharyngeal carcinoma (NPC). First Author: Han Chong Toh, Tessa Therapeutics Pte Ltd, Singapore, Singapore

Background: Median overall survival (OS) and prognosis in patients with advanced EBV-positive NPC remain poor and treatment options are limited. In a small phase II trial (38 Asian pts), EBV-CTLs following chemotherapy (GC) as a first line setting for pts with metastatic and/or recurrent NPC has shown promising efficacy and acceptable toxicity: median OS and overall progression free survival (PFS) was 29.9 and 7.6 months respectively, with 2-year OS rate of 62.9% (Chia et al., Mol Ther., 2014). A Phase III trial has been initiated to evaluate the antitumor efficacy of GC-CTL versus GC in these pts (NCT02578641). Methods: This multicenter, randomized, open-label, two arm study is ongoing across 30 sites in Malaysia, Singapore, Taiwan, Thailand and USA. Eligible pts have a histologically confirmed metastatic or locally recurrent EBV-positive, non-keratinizing and/or undifferentiated NPC (not amenable to curative treatment with surgery and/or chemoradiation therapy), with measurable disease (RECIST v1.1) at screening. ECOG PS <= 2 and NCI CTCAE < 2. Pts with CNS metastasis, autoimmune disease or prior immunotherapy are excluded. Prior chemotherapy or radiation with curative intent is allowed. 330 pts will be randomized 1:1 to receive either four cycles of GC followed by six cycles of EBV-CTLs (Arm A) or six cycles of GC alone (Arm B). Stratification factors include country and disease stage (metastatic versus locally recurrent). Analysis of the primary endpoint is based on the hazard ratio calculated using the Cox Proportional Hazard model. Secondary endpoints include PFS, overall response rate, clinical benefit rate and quality of life. Safety assessments will consist of monitoring and recording all adverse events (graded by NCI CTCAE v 4.0). Results: As of 31 Jan 2018, 226 of the planned 330 pts are enrolled. Conclusions: An Independent Data Monitoring Committee has reviewed the trial on 29 Aug 2017 and concluded that trial accrual continue as planned. Clinical trial information: NCT02578641.
6083 Poster Session (Board #71), Sat, 1:15 PM-4:45 PM
Integrative whole-genome analysis of salivary duct carcinoma. First Author: Sehhoon Park, Seoul National University Hospital, Seoul, Korea South
Background: Salivary duct carcinoma (SDC) is one of the most aggressive histological subtypes of salivary gland cancers. Conventional chemotherapy and radiation have shown only limited efficacy in metastatic SDC. Currently, clinically approved targeted-therapeutics are not available for treatment of this disease, mainly due to its rarity and limited understanding of the molecular mechanisms underlying its pathogenesis. Thus, we conducted multi-level genomic profiling of the SDC to delineate the genomic alterations prevalent in this disease. Methods: Whole-genome sequencing, whole exome-sequencing and transcriptome sequencing were performed on 10 discovery cohort SDC samples. Genomic profiling was performed in additional 32 SDC samples to corroborate the findings obtained from the initial discovery cohort. Results: The cancer cohort is characterized by an average mutation burden of 85 somatic non-silent exonic mutations per tumor. The cohort displayed a mutualational signature of BRCA and APOBEC, All genes, including TP53, RB1, SMAD4, HRAS, APC, PIK3CA and GNAQ were recurrently mutated in SDC. A novel fusion gene, generated by genomic rearrangement, MYB-NHS1, was identified. Conclusions: These findings represent an important layer in the systematic understanding of clinically meaningful genomic targets for precision medicine in SDC, a disease with a significant unmet clinical need.

6084 Poster Session (Board #72), Sat, 1:15 PM-4:45 PM
Novel approach for unresectable salivary duct carcinoma: Targeting HER2 and androgen receptor. First Author: Daisuke Kawakita, Department of Otolaryngology Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
Background: Salivary duct carcinoma (SDC) is highly aggressive and rare cancer, often expressing androgen receptor (AR) and/or HER2. While chemotherapy has been failed to show significant efficacy on SDC, we have demonstrated efficacy and safety of AR- or HER2-targeted therapy in patients with unresectable locally advanced or recurrent/metastatic (LA/RM) SDC in a single-arm phase II trial. However, data regarding whether these targeted therapies prolong survival compared with conventional therapy is lacking. Methods: We conducted a multi-institutional retrospective cohort study of SDC patients in Japan. The survival impact of molecular-targeted therapy was compared with conventional therapy, including chemotherapy and/or cetuximab by multivariate proportional hazard models. Results: A total of 152 LA/RM patients were enrolled, of whom 65 received conventional therapy, 55 received HER2-targeted therapy, and 32 received AR-targeted therapy. Median follow-up time was 1.8 years (range: 0.1-9.5 years). The 2-year overall survival (OS) were 38.7% for conventional therapy, 69.3% for HER2-targeted therapy, and 57.9% for AR-targeted therapy. Median OS was significantly improved OS compared with conventional therapy among HER2-positive patients (hazard ratio [HR]: 0.34; 95% confidence interval [CI], 0.16-0.71). AR-targeted therapy did not significantly improve OS compared with conventional therapy among AR-positive patients (HR: 0.63; 95% CI 0.32-1.26). No other biomarker predicting efficacy of targeted therapies was found. Conclusions: Although this study was retrospective, this was the first study to demonstrate that novel therapy targeting HER2 prolonged OS compared with conventional therapy in patients with LA/RM SDC.

6085 Poster Session (Board #73), Sat, 1:15 PM-4:45 PM
A novel prognostic risk classification model for NUT midline carcinoma: a largest cohort analysis from the NMC registry. First Author: Nicole Grace Chau, Dana-Farber Cancer Institute, Boston, MA
Background: NUT midline carcinoma (NMC) is a rare subtype of squamous cancer defined by rearrangement of the NUT gene. Due to its rarity and under-diagnosis, there are no existing models to classify patients (pts) into risk groups based on baseline clinicopathologic factors. We aim to develop a prognostic risk classification model for NMC survival outcomes based on the largest cohort of NMC pts analyzed to date. Methods: Clinicopathologic variables and survival outcomes were extracted for N = 143 pts registered between 1990-2017 from the International NMC Registry. We performed survival tree regression to determine pt subgroups with statistically distinct risk factors and overall survival (OS) outcomes. Briefly, we performed Cox proportional-hazards regression for each potential factor. We dichotomized pts into two subgroups using the significant factor with the highest hazard ratio. We repeated this process within each subgroup until no further significant factors were found. Results: For N = 143 pts, median diagnosis age was 24 y (range = 18d-80y) and 48% were male. About half (54%) of tumors were without squamous cell differentiation; 54% had thoracic origin, 40% head/neck, and 6% other primary site. Most patients had the BRD4-NUT fusion (71%), followed by BRD3-NUT (15%), and NSD3-NUT (5%). At diagnosis, 78% had lymph node or organ metastases (mets). Median follow-up time was 2.9y (19-19.1y). For N = 134 with survival data, median OS was 6.8m (95% CI = 5.8-9.7); 2-year OS was only 23% (±SE = ±2%). Survival tree regression identified 3 distinct risk groups: (A) no mets [2-yr OS = 39.5±10%; N = 24]; (B) with mets, non-thoracic origin [2-yr OS = 38.7±10%; N = 27]; (C) with mets, thoracic origin [2-yr OS = 6.4±4%, N = 55]. Conclusions: This is the first risk classification model for NMC. Metastatic pts with thoracic primary tumors have markedly poorer prognosis compared to other subgroups.

6086 Poster Session (Board #74), Sat, 1:15 PM-4:45 PM
Phase II study on lenvatinib (LEN) in recurrent and/or metastatic (R/M) androgen positive carcinomas (ACC) of the salivary glands (SG) of the upper aerodigestive tract (NCT02860936). First Author: Laura Locati, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Background: Systemic chemotherapy and targeted therapies (TT) are almost ineffective in R/M ACC patients (pts). Sorafenib and axitinib showed some activity, possibly through their antiangiogenic effect. LEN is a stronger second-generation antiangiogenic inhibitor. Here we report the activity of LEN in R/M ACC pts. Methods: Pts with R/M disease, 1 previous line of chemotherapy and/or TT, received oral LEN 24 mg/day. Progression within 6 months at study entry was required. Primary endpoint was objective response rate (ORR) according to RECIST 1.1; secondary endpoints were progression free survival (PFS), overall survival (OS), toxicities (CTC 4.0) and assessment of quality of life (QoL) with EORTC QLC C-30, EORTC QLC-H&N35, EQ-5D. A 2-stage Simon design was applied, to test the null hypothesis of response ≤ 5% versus the alternative response ≥ 20%; 3 responses were required to reject the null hypothesis. Results: Twenty-eight pts were enrolled, F 16/M 12, median age 55 years (range: 22-73), 14 ACC of major and 14 of minor SGs, 96% metastatic. PS was 0 in 14 cases, 1 in 12 and 2 in 2 pts. Treatment related adverse events (AEs) were frequent (all grades 96%): asthenia 79%, hypertension 75%, stomatitis and weight loss 71%, TSH elevation 68%, were the most common. Grade ≥ 3 occurred in 50% of pts (asthenia 25%, hypertension 18%). No G5 toxicities occurred neither bleeding. Nine SAEs were reported, 6 of them drug-related. Dose was reduced in 21 pts within 12 weeks from therapy start, only 4 pts maintained the full dose throughout treatment. Among 26 evaluable pts, partial responses were 3 (11.5%) (3/26). Target lesions reduction between 23% and 28% was observed in 4 out 20 pts with stable disease. At a median follow up of 21.9 months (95% CI, 13.8-27.8), 6 pts are still on LEN and 12 died due to progression. Median PFS and DoR were 9 (95% CI 5.5-14.2) and 3.1 (1.8-21.7+) months, respectively. Median OS was 26.1 months (95% CI, 11.1-11.9). QoL analysis is ongoing. Conclusions: Tumor size reduction was seen in 27% of pts suggesting activity of LEN in ACC. Toxicity was manageable. QoL has been studied for the first time. A randomized study is needed to confirm efficacy. Clinical trial information: NCT02860936.
6087 Poster Session (Board #75), Sat, 1:15 PM-4:45 PM
Combination of dabrafenib (DAB) and lapatinib (LAP) for the treatment of BRAF-mutant thyroid cancer. First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: mutations (BRAFm) are the most common mutations in thyroid cancer. BRAF inhibitors (DAB) are active in BRAFm melanoma, but there is less activity noted in BRAFm thyroid cancer. Preclinically, BRAF inhibitors inhibit BRAFm thyroid cancers only transiently due to activation of HER2/HER3, driven by a neuregulin-dependent autocrine loop. The addition of LAP, a HER2/HER3 kinase inhibitor, sensitizes the cell to growth suppression by BRAF inhibitors (Cancer Discov 5(5):320, 2013). This study evaluates the safety and efficacy of the combination of DAB and LAP. Methods: Eligibility included thyroid cancers with the presence of a BRAFV600E mutation. Any prior treatment was allowed. All patients received DAB 150 mg bid starting 2 weeks prior to LAP. Doses of daily lapatinib were escalated in a standard 3+3 design at (1) 750 mg; (2) 1250 mg; (3) 1500 mg. Patients removed before the start of LAP were not included in the analysis. An additional 6 patients were added at the MTD. Responses were defined using RECIST 1.1. Results: 21 evaluable patients were enrolled on the phase I portion of the study. Gender – 14/21 (67%) male; median age – 63 years; histology – differentiated thyroid cancer (DTC) 19 (90%), anaplastic thyroid cancer (ATC) 2 (10%); brain metastases – 5 (24%); prior BRAF inhibitor – 5 (24%); prior BRAF or tyrosine kinase inhibitor – 13 (62%). There was one DLT - Grade 5 event unlikely related to drugs in a patient with ATC. Grade 4 toxicities – 0. Grade 3 toxicities – lymphocytes (1); uveitis (1). Median progression-free survival (PFS) and overall response rate (ORR) in the subsets in the DTC only group are listed in the table. Clinical trial information: NCT01947023. Conclusions: The combination of DAB 150 mg bid and LAP 1500 mg daily was safe and well-tolerated. Despite the number of subjects with prior treatment (including with BRAF inhibitors) and brain metastases, excellent activity was found with this combination in DTC. Further investigation with this regimen is warranted.

6089 Poster Session (Board #77), Sat, 1:15 PM-4:45 PM
Comprehensive genomic profiling of anaplastic thyroid carcinoma. First Author: Daniel W. Bowles, University of Colorado, Aurora, CO

Background: Anaplastic thyroid carcinoma (ATC) is a rare malignancy with a poor prognosis. We queried whether comprehensive genomic profiling (CGP) could uncover biomarkers that could enable targeted and immunotherapies. Methods: CGP was performed on 180 FFPE ATC samples using hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 500X for up to 315 cancer-related genes. GA/tumor results were analyzed for all classes of genomic alterations (GA) including short variant (SV) base substitutions and insertions and deletions; select rearrangements; and copy number changes. 408 consecutively sequenced papillary thyroid carcinomas (PTC) were included as a comparison group. Total mutational burden (TMB) was measured using GA/tumor. Significant genes altered were determined by a proprietary algorithm. Results: There were 88 female (49%) and 92 (51%) male ATC patients with a median age of 64 years (range 25-86 yrs). All ATC cases were submitted as no ATC. ATC had significantly higher mean frequency of genomic alterations (GA) per sample and higher frequency of TPS3 mutations (Table). In contrast, PTC had significantly higher frequencies of RET and BRAF SV mutations and gene rearrangements in BRAF, RET, ALK and NTRK. TMB levels were similarly low in both groups and no cases featured a MSI-High status. Examples of ATC with re-arrangements that could enable targeted and immunotherapies include hyperey, diabetes, fatigue, malaise, weight loss. Conclusions: This is the first study to document CABO anti-tumor activity in patients with RAI-refractory DTC in the first-line setting. The 54% RR is comparable to currently approved agents and warrants further investigation in this patient population. Clinical trial information: NCT0241260.

6088 Poster Session (Board #78), Sat, 1:15 PM-4:45 PM
A phase II trial of cabozantinib (CABO) for the treatment of radiodine (RAI)-refractory differentiated thyroid carcinoma (DTC) in the first-line setting. First Author: Marcia A. Store, Department of Otolaryngology-Head and Neck Surgery and the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA

Background: CABO is a multi-tyrosine kinase inhibitor targeting VEGF receptor kinase, RET, MET and AXL. We previously participated in a Phase I study which suggested activity in the RAI-refractory DTC patients that had had one or more prior therapies. To further study the activity of CABO in differentiated thyroid cancer, we conducted a single-arm open-label phase II study of CABO in patients with metastatic, RAI-refractory DTC in the first-line setting (clinicaltrials.gov: NCT0241260). Methods: Thirty-five patients with metastatic, RAI-refractory, unresectable or locally-advanced DTC were administered CABO 60 mg orally QD. Responses were monitored by CT scan every 2 months. The primary outcome was response rate (RR) and secondary outcomes included progression-free survival (PFS), time to progression (TTP), duration of response and clinical benefit rate and safety. Results: Our study completed accrual in August 2017. As of Feb 2018, the median time on study is 35 wks (range 3-197). Median age is 65 yrs (range 45 to 84); 17 pts (49%) are male. Of the 35 total patients, 22 (63%) have papillary, 3 (9%) have Hürthle cell and 10 (29%) patients have poorly differentiated histology. Partial response (PR) was achieved in 19 (54%) patients with a median duration of response of 40 wks (range 10 to 198+). Forty-three (43%) had stable disease (SD) with a median duration of 25 wks (range 8 to 143+), and 9 (26%) maintained their SD > 6 mos for a clinical benefit rate (CBR) of 62%. SD ≥ 6mos of 80% (n = 28). Median PFS has not been reached and updated PFS data will be presented. Among the six patients who progressed, the median TTP was 35 weeks. Sixteen patients remain on study as of February 2018. CABO was well tolerated with dose interruptions and dose adjustments as needed. The most frequent treatment-related adverse events included hyperglycemia, diarrhea, fatigue, malaise, weight loss. Conclusions: This is the first study to document CABO anti-tumor activity in patients with RAI-refractory DTC in the first-line setting. The 54% RR is comparable to currently approved agents and warrants further investigation in this patient population. Clinical trial information: NCT0241260.

TPS6090 Poster Session (Board #78a), Sat, 1:15 PM-4:45 PM
A phase 3, randomized, open-label study of epacadostat plus pembrolizumab, pembrolizumab monotherapy, and the EXTREME regimen as first-line treatment for recurrent/metastatic head and neck squamous cell carcinoma (R/M SCCHN): ECHO-304/KEYNOTE-669. First Author: Ezra E.W. Cohen, University of California, San Diego, La Jolla, CA

Background: Although the EXTREME regimen is a Category 1 evidence-supported combination recommended by NCCN guidelines as first-line (1L) treatment for patients with R/M SCCHN, it is associated with limited survival benefit and burdensome toxicities. There remains a high unmet need for more effective and well tolerated treatment strategies. Both the programmed cell death 1 (PD-1) receptor and indoleamine 2,3-dioxygenase 1 (IDO1) enzyme have been identified as key mechanisms that suppress T-cell mediated antitumor immunity and induce tumor escape. Pembrolizumab (P) is a potent, highly selective humanized monoclonal antibody that directly blocks the interaction of PD-1 and its ligands. Epacadostat (E) is a potent, highly selective oral inhibitor of IDO1. Preliminary phase 1/2 data from the ECHO-202/KEYNOTE-037 study showed encouraging efficacy results and a tolerable safety profile with E + P in SCCHN. This randomized, open-label, phase 3 global study (NCT03358472) evaluates the efficacy and safety of E + P, and EXTREME as 1L treatment in patients with R/M SCCHN. Methods: Key eligibility criteria: histologically or cytologically confirmed R/M SCCHN considered incurable by local therapies, ECOG PS ≥ 1, no prior systemic therapy for R/M disease, and no prior IDO1 inhibitors or immune checkpoint therapies. Approximately 625 patients will be randomized 2:1:2 to E 100 mg BID + P 200 mg Q3W, P 200 mg Q3W, or EXTREME (cetuximab 400 mg/m² Cycle 1 Day 1, then 250 mg/m² Q2W + cisplatin 100 mg/m² or carboplatin AUC 5 Q3W + 5-FU 1000 mg/m²/day continuously over Days 1-4 Q3W). Stratification includes ECOG PS, p16 status, and prior definitive systemic treatment for locally advanced disease. Patients receive 3 cycles of E + P or P, or ≤ 6 cycles of EXTREME followed by cetuximab maintenance; and are treated until disease progression, intolerable toxicity, or investigator/patient decision to withdrawal. Primary endpoints are OS and PFS (per RECIST v1.1 assessed by central radiologist review). Secondary endpoints include overall safety and responder patient-reported outcomes. Clinical trial information: NCT03358472.

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**TPS6091 Poster Session (Board #78b), Sat, 1:15 PM-4:45 PM**

**A phase 2, multicenter, open-label study to evaluate the efficacy and safety of CDX-3379 in combination with cetuximab in patients with advanced head and neck squamous cell carcinoma (HNSCC).**

**First Author:** Julie H. Lyford-Pike, Department of Medicine, Division of Hematology/Oncology, University of Arizona Cancer Center, Tucson, AZ

**Background:** ErbB3 (HER3) and its ligand, neuregulin-1 (NRG1), are widely expressed in HNSCC and associated with tumor progression. ErbB3 may provide a key mechanism of resistance to therapies targeting EGFR and HER2. HPV – tumors, typified by poorer prognosis, have shown favorable response to ErbB3-targeted therapy. CDX-3379, an anti-ErbB3 monoclonal antibody with a half-life-extending Fc region YTE mutation, binds a unique epitope, locks ErbB3 in an inactive form, and blocks all ErbB3-dependent downstream signaling. CDX-3379 enhances antitumor activity of targeted therapies in preclinical models (Falchook ASCO 2016). In a phase (ph) 1 trial, CDX-3379 was well-tolerated alone and in combination with targeted agents. A patient (pt) with cetuximab-refractory HNSCC experienced a durable complete response to CDX-3379 + cetuximab, while 2 pts with BRAF-mutant non-small cell lung cancer, one dabrafenib-resistant, experienced partial responses to CDX-3379 + vemurafenib (Falchook ASCO 2016). A newly-initiated trial evaluates CDX-3379 + cetuximab in pts with HPV+ – cetuximab-resistant advanced HNSCC. Methods: A ph 2, multicenter, open-label clinical trial (NCT03254927) is enrolling ≤30 pts with advanced refractory HNSCC. Eligibility requires: screening biopsy; HPV+; RECIST 1.1 measurable disease; cetuximab resistance (progression within 2 months, open-label clinical trial (NCT03254927) is enrolling pts, with additional sites planned. Clinical trial information: NCT03254927.

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TPS6095 Poster Session (Board #80b), Sat, 1:15 PM-4:45 PM
EORTC 15595-HNCG: A pilot study of personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCC)—UPSTREAM.
First Author: Rachel Galot, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Background: The treatment of R/M SCC includes platinum-based chemotherapy, cetuximab, and anti-EGFR compounds. Some genetic alterations have been identified, making SCCN attractive for molecular targeted therapies. However, when these agents are given to unselected SCCN patients, only limited activity is observed. EORTC 15595 is a biomarker-driven umbrella trial for R/M SCCN that investigates the activity of immunotherapy or targeted agents in tumors harboring pre-defined biomarker(s).

Methods: Pts with R/M SCCN progressing after platinum-based chemotherapy are enrolled. Inclusion criteria are: ECOG 0-1 and measurable disease by RECIST v1.1. Previous treatment with anti-EGFR (v1.1) is allowed. Before inclusion, a fresh tumor biopsy is taken and analyzed in a certified central laboratory (OncoDNA, Belgium). We designed a custom theranostic test that includes IHC, NGS, and gene fusions. Based on a pre-defined algorithm, pts are allocated to different treatment cohorts: afatinib (one cohort for p16- cases with either EGFR or HER2 mutation/amplification or PTEN H-score > 150) and another cohort for p16- cetuximab naïve patients (p16- and cyclin D1 amplification), niraparib (one cohort for p16+ oropharyngeal cancer and another cohort for p16- platinum sensitive disease) and entrectinib (NTRK1/NTRK3 or ROS1 fusions). Pts not eligible for the biomarker-driven cohorts are included in 1 of the immunotherapy cohorts (monoclonal antibody monotherapy or monolization of checkpoint inhibitors) & designed as a phase II trial with its own statistical hypothesis. The primary endpoint is either PFS or ORR depending on the investigated drug, cohorts size ranges from 32 to 76 pts. The study is designed to allow the addition of new treatment cohorts based on new biomarker hypotheses. We are currently working on adding FGFR inhibitors cohorts. The EORTC HN1559 Upstream trial is the 1st international umbrella trial with a personalized treatment strategy or immunotherapy for pts with SCCN. The study is open since November 2017 in Belgium and France with 12 first patients enrolled. We plan to open it in Italy, UK and Germany. Clinical trial information: NCT03088059.

TPS6097 Poster Session (Board #81b), Sat, 1:15 PM-4:45 PM
PATHOS: A phase II/III trial of risk-stratified, reduced intensity adjuvant therapy in patients undergoing transoral surgery for human papillomavirus (HPV)-positive oropharyngeal cancer. First Author: Mererid Evans, Velindre NHS Trust, Cardiff, United Kingdom

Background: Incidence of Oropharyngeal squamous cell carcinoma (OPSCC) is rapidly increasing as a result of Human Papillomavirus (HPV), genotype 16 infection. Existing treatments for HPV+ OPSCC have high survival rates but often result in significant long-term toxicities, particularly affecting swallowing function, impacting on quality of life (QoL). PATHOS is a UK phase II-III randomized, multi-centre study. Patients undergo Transoral Surgery (Transoral Laser Microsurgery or Transoral Robotic Surgery) prior to post-operative stratification, according to pathological risk factors. Aim: To determine whether reducing intensity of adjuvant treatment, by lowering radiotherapy (RT) dose or, in patients with positive margins and/or Extracapsular Spread (ECS), omitting concurrent chemoradiotherapy, will result in better long-term swallowing function whilst maintaining high Overall Survival rates. Methods: Patients are eligible if requiring primary resection and neck dissection, fit for surgery/treatment, histologically confirmed OPSCC (TNM T1-T3, N0-N2b), and ≥ 18 years. Following informed consent, patients are confirmed as HPV+. Baseline swallowing panel (including QoL) is carried out prior to surgery and during follow-up. Post-op group allocation: Clinical trial information: NCT02215265. PATHOS has recruited 152 patients across 18 UK sites to date, clearly demonstrating feasibility of recruitment. PATHOS will proceed to an international Phase III in collaboration with the European Organization for Research and Treatment of Cancer (EORTC) subject to funding being awarded. Funded by Cancer Research UK (A17161). Coordinated by the Centre for Trials Research, Cardiff University.

TPS6098 Poster Session (Board #82a), Sat, 1:15 PM-4:45 PM
BEST OF: A phase III study assessing the best of radiotherapy (Intensity Modulated Radiotherapy, IMRT) compared to the best of surgery (Trans-Oral Surgery, TOS) in patients with T1-T2, NO oropharyngeal squamous cell carcinoma (OPSCC). First Author: Christian Simon, CHUV - Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Background: The incidence of OPSCC has increased dramatically in the last 15 years. The standard treatment for early stage disease is either surgery or radiotherapy, both with comparable high tumor control rates but with different side effect profiles and technical constraints. Treatment choice is generally based on expert or center experience. It is still unclear whether they differ in terms of functional outcome. To clarify this, we proposed a randomised trial with the primary objective to assess and compare the patient-reported swallowing function over the first year after randomisation to either IMRT or TOS among patients with early stage OPSCC. Clinician and patient-reported outcomes will be used to assess treatment. Methods: This is a phase III randomised trial (NCT02984410) that will primarily assess the MD Anderson Dysphagia Inventory (MDADI) score reported by the patients at months 4.5, 6, 9, and 12 after randomisation. MDADI is composed of 19 questions on emotional, functional, and physical aspects, all related to swallowing, wherein scores range between 20 (poorest function) and 100 (best function). BEST OF is powered to detect a clinically significant difference in MDADI score at each of these time points: 4.5, 6, 9, and 12 months with a planned sample size of 170 patients. Key secondary endpoints include quality of life (QOL) based on QLQ-C30 and HN43 and out-of-pocket costs. QOL domains will be ranked based on patient’s priorities. Eligible cases are T1 or T2, NO, NO OPSCC assessed by a multidisciplinary team. The EORTC quality assurance program (QAP) for surgery and radiotherapy (SURCARE) and radiotherapy (RTQA) was implemented in the study. This integrated QA will be the model for future EORTC Head and Neck Cancer trials. BEST OF was opened for recruitment since December 2017 in Belgium and Switzerland and will soon open in France, UK, Germany, Poland, Italy and Portugal through a collaboration with EORTC HNCG and RAG, SAKK, NCRI, GORTEC, and IAG-KHT. Clinical trial information: NCT02984410.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Hope for salivary gland cancer (SGC): EORTC HNCG/UKCRN 1206 randomized phase II study to evaluate the efficacy and safety of chemotherapy (CT) vs androgen deprivation therapy (ADT) in patients with recurrent and/or metastatic androgen receptor (AR) expressing SGC (NCT01969578). First Author: Laura Locati, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: SGCs are rare and heterogeneous tumors (< 1% of all malignancies in Europe). Among more than 20 histotypes, only salivary duct carcinoma (SDC) and adenocarcinoma NOS express AR. These variants are aggressive and associated with poor prognosis. Surgery is the main curative treatment but upon relapse, patients are left with very few options. This study (NCT01969578) aims to evaluate the efficacy and safety of ADT (experimental arm) vs chemotherapy (standard arm) in patients with recurrent and/or metastatic, AR overexpressing SDC and adenocarcinoma, NOS by demonstrating a 15% improvement in Progression Free Survival (PFS) rate at 6 months in favor of ADT. Methods: Trial design: In this multicenter, randomized, phase II intergroup study a total of 76 treatment patients (Cohort A) are planned to be randomized to receive ADT or platinum-based chemotherapy. Patients previously treated with chemotherapy will be enrolled in a separate Cohort B to receive ADT. Patients from Cohort A randomized to chemotherapy can also enter in Cohort B at disease progression. The primary endpoint is PFS for Cohort A and best overall response for Cohort B. AR overexpression is mandatory at study entry. Mechanisms of AR activation and resistance will be studied. This study is led by EORTC Head and Neck Cancer Group with UNICANCER/REFCOR, International Rare Cancer Initiative UK Salivary Gland Cancer Group and RARECARENet. It will run in 35 sites in 10 countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Portugal, The Netherlands, and United Kingdom. Sites from the EURACAN European Reference Network are participating. On 9th February 2018, 54 patients are registered; 27 have been enrolled, of which 17 have been randomized in Cohort A. Identification of AR as a treatment target in SGC can be practice changing. Clinical trial information: NCT01969578.
Randomized trial comparing a web-mediated follow-up via patient-reported outcomes (PROs) vs. routine surveillance in lung cancer patients: Final results. First Author: Fabrice Denis, Institut Inter-regional de Cancérologie Jean Bernard, Le Mans, France

**Background:** In a previous interim analysis, we found a 7-month median overall survival (OS) benefit (p = 0.002) associated with web-based monitoring to detect recurrence in lung cancer patients after initial treatment, vs. scheduled imaging. We hypothesized that benefit was due to earlier detection of symptoms and relapses, prompting earlier treatment and supportive care. Patient-Proven Assessment of Symptoms and Treatment (PASAT) monthly follow-up was provided. Aim: Stage lung cancer patients without evidence of disease progression after initial treatment were randomly assigned to compare a web-mediated follow-up (experimental arm) based on weekly self-scoring of 13 common patient symptoms with a routine follow-up (control arm) with 3-months repeated CT-scans. In the experimental arm, an alert email was sent to the oncologist when self-scored symptoms matched predefined criteria. The IRB protocol-specified primary outcome was OS. After a pre-planned interim analysis in which OS improvement was observed, the IRMC suggested a cessation of further recruitment in 1-2016 and recommended to offer eligible patients in the control arm to cross over to receive the intervention at 1-2016. 121 patients were included in the intent-to-test survival (ITT) analysis. Ten out of 34 living patients in the control arm were eligible to cross over following the interim analysis. With 2 years of follow-up and 70 deaths observed, the median OS was 23.0 months in the experimental arm and 14.0 months without adjustment for crossover in the control arm (HR 0.62, 95% CI 0.39 to 0.995, p = 0.048). Censoring crossover resulted in a hazard ratio of 0.53 (95% CI 0.33 to 0.85, p = 0.009) with consistent results also observed based on a rank-preserving structural failure time model (p = 0.55, 95% CI -1.09 to -0.03). **Conclusions:** With a longer follow-up and although eligible patients from the control arm crossed over to receive intervention after the preplanned interim analysis, the OS remained significantly larger with the web-mediated follow-up based on PRO than with routine disease follow-up by CT scans alone. This is the first study to show the benefits of PROs during surveillance in cancer patients. Clinical trial information: NCT02361099.

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Patient-reported outcomes, emoji, and activity measured on the Apple Watch in cancer patients. First Author: Carrie A. Thompson, Division of Hematology, Mayo Clinic Rochester, MN

**Background:** Patient-reported outcomes (PROs) are important measures in patients with cancer, but may be burdensome to collect. We aimed to measure PROs via mobile technology, using novel emoji PRO scales and associations between PROs and wearable data. **Methods:** Adult patients (pts) with diagnosis (< 5 years of lymphoma, myeloma, brain, pancreatic, breast, and ovarian cancer, life expectancy of > 6 months, and ownership of an Apple Watch) were recruited and provided with an Apple Watch. Pts completed baseline and weekly PROs for 12 weeks: PROMIS physical function, fatigue, sleep, social/role function short forms; single-item linear analog self-assessment (LASA) of quality of life (QOL), fatigue, and physical function. Pts were randomized into 3 groups for mode of survey response: paper, paper, and iPhone. Watch and iPhone groups completed an emoji mood scale and an emoji ordinal scale for physical, emotional, and overall QOL. Activity levels were analyzed using the square root of the average daily values to minimize the effects of outliers. Associations between PROs and activity levels were assessed using Spearman correlations for univariate analyses, stepwise linear regression, and models for multivariate associations, and mixed models for longitudinal associations. **Results:** From 2/2017-8/2017, 296 pts were recruited. Pts wore the watch for an average of 9.8 hours/day and 4590 mean steps/day (SD 3724). Weekly survey response rates ranged from 60% (Watch group) to 77% (iPhone group). Logging more steps/day was associated with less fatigue and sleep disturbance, better global physical QOL, physical function, and social function, while minutes of exercise/day was associated with better global mental QOL and sleep. Spearman correlations showed very strong associations between the emoji ordinal scale and LASAs: 0.80 for fatigue, 0.70 for physical well-being, 0.68 for emotional well-being, and 0.75 for overall QOL (all p < 0.001). The baseline emoji mood scale was strongly related to all baseline PROMIS PROs (all p < 0.001). **Conclusions:** Collecting PROs in cancer patients via mobile technology is feasible. Apple Watch activity data is significantly associated with PROs, and emoji scales are a promising tool.

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The effect of a lay health worker-led symptom assessment intervention on healthcare use and costs to all newly diagnosed health plan beneficiaries with Stage 3 and 4 cancer from 11/1/2013-10/31/2014. First Author: Manali I. Patel, Division of Oncology; Clinical Excellence Research Center; Stanford University School of Medicine, Stanford, CA

**Background:** We developed a risk-stratified proactive symptom assessment intervention which consisted of a lay health worker, supervised by a nurse practitioner, who telephonically assessed symptoms weekly for high-risk patients and monthly for low-risk patients. We implemented the intervention in an oncology group with collaboration from a health plan to test the effect on rates of patient-reported satisfaction, emotional and mental health with validated assessments at enrollment and 5-months post-enrollment. We compared healthcare use and costs to all patients with Stage 3 and 4 cancer diagnosed from 11/1/2013-10/31/2014. We evaluated patient-reported satisfaction, emotional and mental health with validated assessments at enrollment and 5-months post-enrollment. We compared healthcare use and costs to all patients with Stage 3 and 4 cancer from 11/1/2013-10/31/2014 (control). We assessed differences in demographic and clinical factors using chi-square and t-tests. To evaluate differences in healthcare use and costs we used generalized linear models adjusted for age, stage, co-morbidity, cancer diagnosis, and length of follow-up. **Results:** There were 186 patients in the intervention and 102 in the control. In both arms, median age was 78 years, 55% were female, and gastrointestinal malignancies were the highest proportion of diagnoses. There were statistically significant improvements in mental and emotional health (p < 0.05) and satisfaction with care (p < 0.05) at 5-months follow-up compared with baseline. Patients in the intervention had significantly lower mean number of inpatient admissions per quarter (0.72 vs. 1.02, p = 0.03); mean number of emergency department visits per quarter (0.61 vs. 0.92, p = 0.04), and 1.14 fewer mean total healthcare costs ($22344 vs $28414, p = 0.03) as compared to the control. **Conclusions:** A lay health worker-led symptom assessment intervention significantly improved patient satisfaction and reduced healthcare use and costs and may represent one solution to improve care for patients.
Lung cancer screening rates: Data from the lung cancer screening registry.

First Author: Danh Pham, James Graham Brown Cancer Center, University of Louisville, Louisville, KY

Background: Lung cancer is the leading cause of cancer related mortality in the United States. Since 2013, the United States Preventive Services Task Force (USPSTF) recommended annual screening for lung cancer with low-dose computed tomography (LDCT) for those aged 55-80 years for those who have smoked at least 30 pack years who currently smoke or have quit within the past 15 years. Current literature has provided only estimates of lung cancer screening since implementation. Our study aims to present the number of screening LDCTs being performed across the United States. Methods: Using data from the Lung Cancer Screening Registry (LCSR) provided by the American College of Radiology (ACR) in 2016, we collected the total number of LDCT from all 1,796 accredited radiographic screening sites. We used the 2015 National Health Interview Survey (NHIS) to estimate screening eligible smokers per USPSTF criteria and compared them with the 2016 LCSR reported screens. Analyses excluded respondents with missing data and history of lung cancer. Results: In 2016, 1.9% of 7.6 million eligible smokers were screened. These rates varied by region from 1.0% in the West to 3.5% in the Northeast (Table). The majority of LDCT (87%) were performed in centers with the most accredited screening sites, but were still amongst the lowest in screening rate. Approximately 85% of the screened current smokers were offered smoking cessation. Conclusions: Annual LDCT screening remains inadequate following USPSTF recommendations despite the time since implementation and potential to prevent the death of each year. It remains unclear why the lung cancer screening rate is dramatically lower than other cancer screening modalities such as mammography and colonoscopy. Further initiatives are needed including awareness programs and mandating lung cancer screening as a national quality measure.

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Uptake of genetic testing and outcomes in a randomized study of remote genetic services as compared to usual care in community practices without genetic providers. First Author: Angela R. Bradbury, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background: Providing remote genetic services by phone or videoconference for patients at community practices without access to genetic providers could increase access to genetic testing. How uptake of testing compares to usual care options for genetic testing has not been reported. Methods: To date 106 patients in 6 community practices participated in a randomized study comparing remote genetic counseling (35 phone; 31 videoconferencing) and 40 to usual care (recruitment to end 3/2018). Primary outcomes were uptake of genetic counseling and testing at 6 months. Secondary outcomes include knowledge, state and general anxiety, depression, and cancer-specific distress in phone versus videoconferencing arms. We used Fisher’s exact tests, T-tests, and logistic regressions for analyses. Results: 92% of participants are female, 17% are non-white, 33% are college graduates and 65% have a history of cancer. 86% had multigene panel testing. At 6 months, 79% (52/66) of participants in the remote services arms had pre-test genetic counseling as compared to 52% (5/40) in the usual care arm (p < 0.001). 56% (37/66) in the remote services arm completed genetic testing and 4 genetic carriers were identified (ATM, MUTYH and 2 with BRCA2) as compared to 12.5% (5/40) and 0 carriers in the usual care arm (p < 0.001). Conclusions: Among newly-diagnosed cancer patients, a treatment program of sustained telephone-delivered motivational counseling and free medication produced a higher 6-month quit rate vs. a briefer counseling program. The cost-per-quit compared favorably to other cessation interventions. Findings provide strong support for the benefit of sustained tobacco treatment and a model for effective implementation of tobacco treatment into oncology care settings nationwide. Clinical trial information: NCT01871505.
Background: A deficiency in current approaches in Precision Oncology is the inclusion of medical and treatment history, as well as other multi-omic data, such as proteomics, germline, and phosphoprotein assays. Optimally every patient facing a molecular treatment decision will benefit from an expert tumor board, but it is impossible to convene the same board for every patient.

Methods: We developed a cloud-based, asynchronous virtual tumor board (VTB) that integrates multi-modal patient data to formulate, discuss, and rank treatments. The VTB utilizes 8 linked databases, a treatment scoring model based on the AMP/ASCO variant interpretation guidelines and an AI-based treatment recommender. Molecular and clinical data including past medical history, molecular and pathology reports were aggregated from 1342 cases from >300 community and academic hospitals. A preliminary list of therapy options and trials were prepared by the VTB which integrates variant annotations, biomarker implications, trial eligibility criteria, outcomes, and literature. Medical and scientific experts reviewed each case, ranked through an asynchronous chat room, modified, and ranked treatment options delivered as a report to the treating oncologist.

Results: Automation through VTB, increased the volume of cases reviewed per month by twofold. The VTB also led to a larger set of options compared to those not treated in an ACO. ACO patients had similar spending by categories: inpatient ($23,908 vs. $22,782, p = 0.02). ACO and non-ACO patients were similar in terms of patient characteristics (age, race, sex, dual eligibility, comorbidities). ACO beneficiaries had modest but significantly higher total annual standardized costs compared to beneficiaries not in an ACO ($47,629 vs. $45,582; p = 0.02). We followed CMS guidelines to attribute patients to an ACO or non-ACO practice.

Conclusion: We developed a cloud-based, asynchronous virtual tumor board (VTB) to facilitate treatment recommendations for patients with advanced cancers. First Author: Subha Madhavan, Innovation Center for Biomedical Informatics, Georgetown University Medical Center, Washington, DC

Clinical trajectory modeling to predict hospitalization or death after palliative chemotherapy. First Author: Kenneth L. Kehl, Dana-Farber Cancer Institute, Boston, MA

Background: Hospitalization or death within 30 days of palliative-intent chemotherapy for metastatic cancer represent undesirable outcomes. An automated framework for predicting the risk of hospitalization or death within 30 days of chemotherapy could inform clinical decision-making, research, and quality improvement efforts. Methods: We pilot a machine learning framework for time-dependent clinical trajectory modeling using administrative data and applied it to prediction of hospitalization or death within 30 days of palliative cytotoxic chemotherapy. Patients with stage IV non-small cell lung cancer (NSCLC) diagnosed 2008-2013 were identified in SEER-Medicare. Inpatient, outpatient, and hospitalization costs, prescription, home health, and hospice claims were extracted. The sequence of claims for the 60 days, or “clinical trajectory,” prior to each date of chemotherapy was embedded into a feature space based on context similarity, and the sequence was fed into a stacked ensemble model to predict hospitalization or death within 30 days of each chemotherapy dose. These administration dates were divided into 80% training and 20% validation sets. Discrimination was measured with the c-statistic (AUC). No manual feature engineering was performed. Results: 43,250 dates of chemotherapy administration were identified for 6,067 patients with stage IV NSCLC. 8,283 chemotherapy dates that were not followed by death without hospitalization within 30 days, our framework predicted the composite of hospitalization or death with an AUC of 0.83. Among 42,823 chemotherapy dates that were not followed by death without hospitalization within 30 days, our framework predicted hospitalization with which AUC of 0.84. Conclusions: Clinical trajectory modeling predicts hospitalization or death within 30 days of palliative-intent cytotoxic chemotherapy for stage IV NSCLC with good discrimination. These results could inform clinical decision-making and targeted cancer care delivery interventions.
Background: MGPS, compared to single-marker genetic testing (SMGT), has the potential to identify more patients who could benefit from targeted therapies, but the impact on outcomes and total costs of care is uncertain.

Our goal was to estimate the cost-effectiveness of MGPS vs SMGT in aNSCLC. Methods: aNSCLC patients (stage IIIB IIIC, IVA, IVB, IVC, or metastatic) for whom data between 2011-2016 were identified from the Flatiron Health database, representing curated electronic health record-derived clinical information from > 250 oncology practices nationwide. After stratifying patients in MGPS or SMGT cohorts, we analyzed the percentage of patients that receive targeted treatment; survival; and total costs of care. SMGT included EFR and ALK testing; MGPS also allowed detection of BRAF, RET, ROS1, HER2 and MET mutations. Cost data sources were the CMS Fee Schedule and 2017 ASP drug cost. We estimated the incremental cost-effectiveness ratio (ICER) and performed sensitivity analyses from a US payer perspective over a lifetime horizon, using a decision model. Results: We identified 5688 aNSCLC patients receiving MGPS (n = 875) or SMGT (n = 4813), of which 22% tested positive for EFR (18.5% MGPS, 17.35MGST) or ALK (3.59% MGPS, 3.78% SMGT). Among MGPS tested patients, an additional 8% were found to have BRAF, RET, ROS1, HER2 or MET mutations. Of MGPS tested patients, 21% received targeted treatment with MGST; the projected survival was 1.14 life years (LYs) in MGPS vs 1.20 LYs in MGST. Lifetime total costs were $8,814 higher per patient for MGPS. The ICER of MGPS vs SMGT was $148,478 per LY gained. If all patients with actionable mutations would receive targeted treatment in MGPS-guided care vs the projected survival, 49% currently receiving targeted treatments under SMGT; the ICER would be $1110/KLY gained. Sensitivity analyses shows widely varying ICERS ($139/LY to $661,625/LY). Conclusions: Based on data from a nationwide oncology patient database, MGPS has moderate cost-effectiveness compared to SMGT in aNSCLC patients. Efforts to increase the proportion of patients who receive targeted therapies would improve the cost-effectiveness of MGPS, assuming incremental costs and outcomes of targeted treatments remain unchanged.

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Effect of varying medication costs on ICERs.

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Trends of new cancer drug approvals from the perspective of a publicly funded healthcare system: Analyses of the pan-Canadian Oncology Drug Review (pCODR) recommendations. First Author: Saroj Niaula, CancerCare Manitoba and Univ of Manitoba, Winnipeg, MB, Canada

Background: United States Food and Drug Administration (FDA) primarily takes into account the therapeutic index before approval of a new cancer drug whereas countries such as Canada, United Kingdom, and France, use price alone. Methods: We identified 60 new cancer drugs for 91 indications reviewed by pCODR. We quantified potential life-years lost due to delays in this process. Results: We analyzed drugs for advanced lung, breast and colorectal cancer from inception to January 31, 2018. Analysis of data from a nationwide oncology patient database, MGPS has moderate cost-effectiveness compared to SMGT in aNSCLC patients. Efforts to increase the proportion of patients who receive targeted therapies would improve the cost-effectiveness of MGPS, assuming incremental costs and outcomes of targeted treatments remain unchanged.

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6517 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
FDA acceptance of surrogate endpoints in later lines of therapy. First Author: Emerson Yu-sheng Chen, Oregon Health and Sciences University, Portland, OR

Background: U.S. Food and Drug Administration (FDA) utilizes surrogate endpoints in order to speed drugs to market. Surrogates reduce development time, though they do so to a larger extent in the front line rather than in later line settings. Methods: We examined all adult cancer drugs approved by the FDA from 01/2006 to 12/2017. Data regarding the approval (or accelerated), cancer type, treatment indication, and basis for approval were extracted from the FDA website and any relevant publications. Basis for approval was categorized into response rate (RR), progression-free or relapse-free survival (PFS/RFS), and overall survival or quality-of-life (OS/QoF) endpoints. Drugs for mainly pediatric cancers and cancers limited to genetic syndromes were not included in this study. Statistical analysis was performed using SAS 9.4 version. Results: 182 drug indications among 108 cancer drugs were identified. 67 (36.6%) drug indications were approved for first-line setting, 75 (41.2%) for second-line setting, 24 (13.2%) for third-or-later-line setting, and 16 (8.8%) for adjuvant or maintenance settings. 49 (26.9%) were approved based on OS/QoF endpoints. 133 (73.1%) were approved based on surrogate endpoints: 69 (37.9%) being RR and 64 (35.2%) being PFS/RFS. Accelerated instead of regular approval was more likely to be sought in subsequent lines of therapy (19.4% in first-line, 30.7% in second-line, 6.0% in third line, p < 0.01). Surprisingly, no trend toward being used in subsequent lines of therapy (68.7% in first-line, 70.7% in second-line, and 87.5% in third-line approvals, p = 0.18). However, RR specifically was used more frequently in subsequent lines of therapy compared to PFS/RFS or OS/QoF (22.4% in first-line, 45.3% in second-line, and 79.2% in third-line approvals, p < 0.01). Conclusions: Any surrogate endpoints are increasingly being used in oncology trials with the intention of speeding drugs to market. They are used most often in later lines of therapy, when definite endpoints like OS or QoF can be expediently evaluated, and the 'acceleration' of approval is actually limited. Accelerated approval based on surrogate endpoints is thus granted preferentially in later lines of therapy, when the impact is likely modest.

6519 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Objective metrics of patient activity: Use of wearable trackers and patient reported outcomes in predicting unexpected healthcare events in cancer patients undergoing highly emetogenic chemotherapy. First Author: Alexander S. Martin, University of Southern California, Los Angeles, CA

Background: Functional status and predictors that identify those cancer patients at risk for unplanned hospitalization can have broad implications for the healthcare delivery and clinical trials. We evaluated the feasibility of monitoring physical activity (PA) using wearable activity trackers in cancer patients on highly emetogenic chemo as well as potential correlations between PA and unplanned healthcare events (UHE) and ECOG scores. Methods: This study was conducted as a multi-institutional single arm observational clinical trial of 65 patients with solid tumors undergoing highly emetogenic chemo based on Hesketh classification. PA was measured by observational clinical trial of 65 patients with solid tumors undergoing highly emetogenic chemotherapy. We measured PA by a wearable device, providing general health information, nutritional and medication care and exercise program (aerobic exercise at least 90 or 150 minutes, strengthening exercise at least 2 times a week for 12 weeks) while the control group was imparted brief education for the exercise program. Primary endpoint was an increase in patients' physical function as assessed using 2 minutes’ walk test. Secondary endpoints included improvement in muscle strength (30 seconds chair stand test, grip strength test), short physical performance battery, body composition, and health-related quality of life (EORTC-QLQ-C30, and PR 25). Results: In the aspect of physical performance, patient groups showed improvement in both 2564 steps/d (p = 0.01) and 30 minutes walking test (p = 0.042) over time in the Smart After-Care group as compared to the control group. The Smart After-Care group had additional improvement in行走 test (p = 0.038) and reduction in body fat percentage (p = 0.022) compared to the controls. Also, the Smart After-Care group showed significant improvement in urinary symptom, whereas the Smart After-Care group showed significant improvement in sexual functioning (P = 0.032), as well as in appetite loss (P = 0.048). Both groups showed significant improvement in urinary symptom, whereas the Smart After-Care group showed significant improvement in sexual functioning (P = 0.032), as well as in appetite loss (P = 0.048). Conclusion: The Smart After-Care service is an effective method in PCa patients on ADT in improving exercise capacity and general health related quality of life. Clinical trial information: NCT03264209.

6518 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Internet- and mobile-based lifestyle intervention for prostate cancer patients on androgen deprivation therapy: Prospective, multicenter, randomized trial. First Author: Yong Hyun Park, Department of Urology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of (South)

Background: Androgen deprivation therapy (ADT) has several adverse effects including loss of libido, osteoporosis, and metabolic complications. We aimed to show whether the Smart After-Care service (internet- and mobile-based lifestyle intervention) has an effect on clinical outcomes in patients with prostate cancer (PCa) on ADT. Methods: Two hundred patients with PCa on ADT were randomly assigned to the Smart After-Care or control group. The Smart After-Care group received a mobile application and wearable device, providing general health information, nutritional and medication care and exercise program (aerobic exercise at least 90 or 150 minutes every week for 12 weeks depending on patients' aerobic fitness and strengthening exercise at least 2 times a week for 12 weeks) while the control group was imparted brief education for the exercise program. Primary endpoint was an increase in patients' physical function as assessed using 2 minutes’ walk test. Secondary endpoints included improvement in muscle strength (30 seconds chair stand test, grip strength test), short physical performance battery, body composition, and health-related quality of life (EORTC-QLQ-C30, and PR 25). Results: In the aspect of physical performance, patient groups showed improvement in both 2564 steps/d (p = 0.01) and 30 minutes walking test (p = 0.042) over time in the Smart After-Care group as compared to the control group. The Smart After-Care group had additional improvement in walking test (p = 0.038) and reduction in body fat percentage (p = 0.022) compared to the controls. Also, the Smart After-Care group showed significant improvement in urinary symptom, whereas the Smart After-Care group showed significant improvement in sexual functioning (P = 0.032), as well as in appetite loss (P = 0.048). Both groups showed significant improvement in urinary symptom, whereas the Smart After-Care group showed significant improvement in sexual functioning (P = 0.032), as well as in appetite loss (P = 0.048). Conclusion: The Smart After-Care service is an effective method in PCa patients on ADT in improving exercise capacity and general health related quality of life. Clinical trial information: NCT03264209.

6520 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM
Opioid use in long term cancer survivors. First Author: Lisa Catherine Barbera, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: Our research team previously found that the rate of opioid use in cancer patients surviving at least 5 years beyond diagnosis was 1.2 times higher compared with age-sex matched controls without cancer. The purpose of this study was to determine factors associated with continued opioid use after diagnosis date. We conducted a retrospective cohort study using linked provincial administrative data. Patients were aged 24-70 and economically disadvantaged, making them eligible for government funded pharmacare. The index date was defined as the 5 year anniversary from the diagnosis date. Patients were accrued continuously between April 1, 2010 and March 31, 2015 on their index date. Those with any evidence of recurrence (resuming anti-cancer therapy, palliative care) were excluded. Patients were observed until death, relapse or end of data accrual. The main outcome was opioid prescription rate after index date. The main exposures were opioid use prior to diagnosis date, opioid use between diagnosis date and index date (none, continuous, at diagnosis only, other), certain cancer surgeries (e.g. thoracotomy) and chemotherapy agents known to cause neuropathy. A negative binomial regression model was used to estimate the relative rates of opioid use after index date. Results: Our cohort included 7,431 individuals. The factors most strongly associated with a higher rate of opioid use after index date was continuous opioid use between diagnosis and index date. The RR was 63.4 (95% CI 39.4-102.1) for those with no pre-diagnosis opioid use and 76.6 (95% CI 40.7-144.0) for those with pre-diagnosis opioid use. The only group with no increased risk used opioids only at diagnosis and had no prior use. Surgery was not significant. Chemotherapy was not significant with the exception of those who used opioids initially. A history of depression, comorbidity and more than 2 years of diabetes were also associated with higher risk. Conclusion: Cancer patients who use opioids continuously after diagnosis are at increased risk of continued use after 5 years of survival. Further work is needed to understand the reasons for ongoing use after diagnosis. Increased attention is needed to ensure safe prescribing for this group to minimize issues with dependence.
Implementation of breast cancer pathway for genetic counseling and testing in multi-state health system. First Author: Stephanie L. Graff, Sarah Cannon Cancer Institutes HCA Midwest Health, Overland Park, KS

Background: Genetic counseling and/or testing (GC/T) are important aspects of breast cancer care. The National Comprehensive Cancer Network has guidelines for GC/T but reports demonstrate variable compliance. Across the Sarah Cannon Cancer Network (SCCN), pathways were developed and implemented by physician leadership teams to select patients (pts) who meet criteria for GC/T. Participating physicians receive pathways training. Adherence metrics are tracked in real time for compliance with GC/T for pts treated on and off pathway in the SCCN. Researchers should be cautious extrapolating results from other large payers. Researchers should be cautious extrapolating results from other large payers.

Methods: CDC WONDER contains death certificate data for all US counties and is maintained by the National Center for Health Statistics. Place of death was obtained for all cancer deaths from 1999-2015, as well as the year of death for each cancer death in the study. Place of death was dichotomized to die at home or hospice facility vs other location. Using data from the most recent year (2015), univariate (UVA) and multivariate (MVA) logistic regression were used to test for disparities in place of death associated with sociodemographic variables.

Results: In the study period, 9,646,498 cancer deaths occurred, with 45.5% dying at home or hospice facility. 30.3% of deaths occurred in patients < 65. From 1999-2015, inpatient deaths decreased from 36.6% to 24.6%, while home deaths (38.4 to 42.6%) and hospice facility deaths (0 to 14.0%) increased (all p < 0.001). On UVA, older age, female sex, white race, Hispanic ethnicity, higher education, and patents with colorectal cancer were associated with death at home or in a hospice facility. On MVA, all assessed factors were associated (p < 0.05) except education and ethnicity. In particular, being married (OR 2.04, 95% CI 1.98-2.10) and having pancreatic cancer (OR 1.36, 95% CI 1.33-1.40) were associated with death at home or hospice. Being black (OR 0.73, 95% CI 0.69-0.76) or Asian (OR 0.65, 95% CI 0.62-0.68) and having breast cancer (OR 0.90, 95% CI 0.88-0.92) had decreased odds of dying at home or hospice. Despite improvements over time, in 2015 black patients remained 42% more likely to die in hospital (32.8% black vs 23.1% white) and 21% less likely to die at home (34.6% black vs 43.7% white) (both p < 0.001).

Conclusions: Inpatient cancer deaths decreased by one third with commensurate rise in home and hospice facility deaths over the study period. Multiple sociodemographic factors were associated with place of death; targeted efforts to increase utilization of palliative care and hospice services may decrease these disparities.

Methodologic challenges of defining oncology provider networks from administrative claims data. First Author: Karyn Beth Stitzenberg, Univ of North Carolina, Chapel Hill, NC

Background: Provider characteristics measured from administrative claims data are increasingly used to study health care organization/delivery and measure of quality of care. Most studies use claims from a single large payer to calculate provider statistics and examine networks. This study compares and contrasts findings generated from claims of different but overlapping payer populations. Methods: Outpatient claims data from 2003-13 Medicare and a large private payer were used to construct colorectal cancer provider networks where edges between providers correspond to the number of shared patients. Payer-specific network and provider statistics were compared. Network metrics on the private network were compared to distributions of subsampled Medicare networks to identify statistically significant differences controlling for patient numbers. The study was IRB approved. Results: 1735 surgeons and medical oncologists were identified from Medicare and 1321 from private claims with 1163 appearing in both. Across networks, there were 33164 pairs of providers connected by at least one patient. 4835 (14.6%) pairs appeared only in the private network, while 18218 (54.9%) appeared only in Medicare. Average volume for surgeons and medical oncologists was similar between networks (R^2 = .85), but 24.5% of providers’ volume rank differed by at least one quintile group between payers. Likewise, average clustering coefficients were similar in magnitude across payers (.51 vs .53), but many providers had vastly different values in the two networks. Most of the same clusters/communities of providers were detected in both networks. However, there were two cases in which the combined network detected distinct communities of providers that Medicare alone missed. Conclusions: Provider networks constructed from Medicare claims alone differ from networks constructed from other large payers. Researchers should be cautious extrapolating findings from networks constructed from a single payer to other contexts. For example, this study brings into question whether Medicare data alone can be used to accurately quantify patient volume of any individual provider.

Trends and disparities in place of death for cancer patients in the United States, 1999-2015. First Author: Fumiko Ladd Chino, Duke University Radiation Oncology, Durham, NC

Background: Dying in a preferred place is an essential component of high quality cancer care. Comprehensive national trends and disparities in place of death are unknown as prior research is limited in scope and to patients ≥65. Methods: CDC WONDER contains death certificate data for all US counties and is maintained by the National Center for Health Statistics. Place of death was obtained for all cancer deaths from 1999-2015, as well as the year of death for each cancer death in the study. Place of death was dichotomized to die at home or hospice facility vs other location. Using data from the most recent year (2015), univariate (UVA) and multivariate (MVA) logistic regression were used to test for disparities in place of death associated with sociodemographic variables.

Results: In the study period, 9,646,498 cancer deaths occurred, with 45.5% dying at home or hospice facility. 30.3% of deaths occurred in patients < 65. From 1999-2015, inpatient deaths decreased from 36.6% to 24.6%, while home deaths (38.4 to 42.6%) and hospice facility deaths (0 to 14.0%) increased (all p < 0.001). On UVA, older age, female sex, white race, Hispanic ethnicity, higher education, and patents with colorectal cancer were associated with death at home or in a hospice facility. On MVA, all assessed factors were associated (p < 0.05) except education and ethnicity. In particular, being married (OR 2.04, 95% CI 1.98-2.10) and having pancreatic cancer (OR 1.36, 95% CI 1.33-1.40) were associated with death at home or hospice. Being black (OR 0.73, 95% CI 0.69-0.76) or Asian (OR 0.65, 95% CI 0.62-0.68) and having breast cancer (OR 0.90, 95% CI 0.88-0.92) had decreased odds of dying at home or hospice. Despite improvements over time, in 2015 black patients remained 42% more likely to die in hospital (32.8% black vs 23.1% white) and 21% less likely to die at home (34.6% black vs 43.7% white) (both p < 0.001).

Conclusions: Inpatient cancer deaths decreased by one third with commensurate rise in home and hospice facility deaths over the study period. Multiple sociodemographic factors were associated with place of death; targeted efforts to increase utilization of palliative care and hospice services may decrease these disparities.
6525 Poster Session (Board #351), Sat, 1:15 PM-4:45 PM
Value-based healthcare delivery models in oncology: A systematic review.
First Author: Emeline Aviki, Memorial Sloan Kettering Cancer Center, New York, NY
Background: With the rising cost of health care in the US has come increasing emphasis on optimizing value. Value-based healthcare delivery models are designed to maximize outcomes and minimize costs through changes in care delivery. Little is known about the impact of value-based interventions in cancer care. We performed a systematic review to describe the landscape of value-based interventions in cancer. Methods: This review included peer-reviewed and non-peer-reviewed articles describing value-based interventions in cancer care. We identified articles through structured searches of PubMed/MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Clinical Trials since passage of the Affordable Care Act. We used the Effective Public Health Practice Project Quality Assessment Tool to evaluate the quality of studies reporting results. Results: Twenty-three articles describing 22 unique value-based interventions in cancer met inclusion criteria. Of the 23 articles, 12 were published in the peer-reviewed literature, and 13 reported outcomes and were assessed for quality. All were of moderate (n = 6, 46%) or weak (n = 7, 54%) quality. The 22 value-based interventions included 6 (27%) accountable care organizations (ACOs), 9 (41%) patient-centered medical homes, and 3 (14%) other interventions. Most interventions were conducted in community settings (n = 16 of 21, 76%) and performed through commercial insurance contracts (n = 13 of 15, 87%), including all bundled payments and all cancer-specific ACOs. Of the 12 interventions with outcomes reported, the majority (n = 7, 58%) improved value, 4 had no impact on value, and 1 reduced value, though this effect was no longer significant after 2-3 years. Conclusions: This systematic review of value-based healthcare delivery models in cancer care found that reports of outcomes are often lacking and are of variable quality when available. Despite promising early signs, the efficacy of these interventions in cancer remains unclear. Moving forward, rigorous evaluations and increased outcome reporting will enable continued innovation to achieve the highest value of care for cancer patients.

6526 Poster Session (Board #352), Sat, 1:15 PM-4:45 PM
Treatment patterns among patients diagnosed with stage IV cancers who died within one month of diagnosis. First Author: Hennem Re M, Sineshaw, American Cancer Society, Atlanta, GA
Background: Little is known about the factors associated with treatment in patients diagnosed with metastatic cancers and who die soon after diagnosis. We examined patterns of treatment in patients diagnosed with metastatic lung, colorectal, breast, and pancreatic cancer who died within one month of diagnosis. Methods: Using the National Cancer Data Base, we identified de novo stage IV lung, colorectal, breast, and pancreatic cancer patients ages ≥18 years diagnosed between 2004-2014 who died within one month of diagnosis. We used descriptive analyses to calculate percentages and multivariable logistic regression analyses to generate adjusted odds ratios for receipt of specific types of treatment. Results: Among 97,884 patients, 66% had lung, 18% pancreatic, 12% colorectal, and 3.7% breast cancer. Surgery was least common in pancreatic (0.4%) and most common in colorectal (28.8%) cancer. Rates of chemotherapy ranged from 5.8% in colorectal to 11.3% in lung and breast cancer. Rates of radiation ranged from 1.2% in pancreatic to 18.7% in lung cancer. Endocrine therapy was initiated for 23.7% of patients with hormone receptor-positive breast cancer. Over the study period, surgery for colorectal and breast cancer, chemotherapy and radiation treatment for lung cancer, and chemotherapy for breast and pancreatic cancer progressively declined (P-trend < 0.01). Age, insurance, and facility type were strongly associated with receipt of treatment across most cancer types. Uninsured patients had 43% lower odds of receiving chemotherapy for colorectal cancer, 42% lower odds of initiating chemotherapy for lung cancer, and 47% lower odds of initiating chemotherapy for breast cancer compared with their privately insured counterparts. Compared with patients with lung cancer treated at NCI-designated cancer centers, those treated at community cancer centers had 1.6 times lower odds of radiation for colorectal cancer and 1.8 times lower odds of initiating chemotherapy for breast cancer. Conclusions: Treatment of patients diagnosed with imminently fatal metastatic cancer (death within one month of diagnosis) varied markedly by cancer type and patient/facility characteristics. More research is needed to identify patients with imminently fatal metastatic cancer who would benefit from early treatment.

6527 Poster Session (Board #353), Sat, 1:15 PM-4:45 PM
Results from a pilot of an innovative 4R Cancer Care Delivery Model: Impact on patient self-management. First Author: Julia Rachel Troisman, Center for Business Models in Healthcare, Chicago, IL
Background: Under the “NCI ASCO Teams” Project, we proposed a 4R Model of teamwork and patient self-management (pSM) (Troisman JOP ’16). 4R is Right Info / Care / Patient / Time. It enables patient (pt) and care team to manage care pre-4R, Jun – Sep, 2015 (4R cohort); 47%, 241/410 (control). 75% of 4R respondents reported 4R changes in care delivery. Little is known about the impact of value-based care coordination by providers to support the patient. Methods: 4R Plans were administered to breast cancer pts stage 0-III, Jun – Sep, 2015 (4R cohort). We searched PubMed/MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Clinical Trials since passage of the Affordable Care Act. We used the Effective Public Health Practice Project Quality Assessment Tool to evaluate the quality of studies reporting results. Results: Twenty-three articles describing 22 unique value-based interventions in cancer met inclusion criteria. Of the 23 articles, 12 were published in the peer-reviewed literature, and 13 reported outcomes and were assessed for quality. All were of moderate (n = 6, 46%) or weak (n = 7, 54%) quality. The 22 value-based interventions included 6 (27%) accountable care organizations (ACOs), 9 (41%) patient-centered medical homes, and 3 (14%) other interventions. Most interventions were conducted in community settings (n = 16 of 21, 76%) and performed through commercial insurance contracts (n = 13 of 15, 87%), including all bundled payments and all cancer-specific ACOs. Of the 12 interventions with outcomes reported, the majority (n = 7, 58%) improved value, 4 had no impact on value, and 1 reduced value, though this effect was no longer significant after 2-3 years. Conclusions: This systematic review of value-based healthcare delivery models in cancer care found that reports of outcomes are often lacking and are of variable quality when available. Despite promising early signs, the efficacy of these interventions in cancer remains unclear. Moving forward, rigorous evaluations and increased outcome reporting will enable continued innovation to achieve the highest value of care for cancer patients.

6528 Poster Session (Board #354), Sat, 1:15 PM-4:45 PM
Defining survivorship and surveillance with evidence. First Author: Robert Dood, The University of Texas MD Anderson Cancer Center, Houston, TX
Background: Survivorship involves a multidisciplinary approach to surveillance and management of comorbidities and secondary cancers, however timing is based on arbitrary 5 year cutoffs. Here, we used a novel method analyzing annualized mortality rates to systematically define these cut-offs for transitions of care. Methods: The SEER database was queried for survival data on patients aged 18-100 years with any incident diagnosis of any cancer, grouped by ICD-O-3 tumor type. Excess mortality hazard, calculated as an annualized mortality risk above the baseline population was plotted over time. The time this hazard took to stabilize defined a high-risk period. The % morality elevation above age-sex-matched controls in the latter low-risk stable period was reported as the mortality gap. Results: Over 2.3 million patients with 68 different primary tumor types were evaluated. High risk surveillance periods ranged from 1 month to 21 years. High risk period durations ranged from under 1 year (breast, prostate, lip, ocular, and parathyroid cancers) up to 19 years (unspecified gastrointestinal cancers). Cluster analysis produced 6 groups. Subanalyses of selected tumor types revealed that stratifying on stage and histologic type can change the risk cluster and guidance for care. Conclusions: These findings indicate that a standardized 5 year surveillance period is both inadequate for some cancers while excessive for others. High risk cancers require the most resources with the highest high-risk period, highest persistent baseline mortality risk, and longest period of primary cancer mortality, all arguing for longer follow-up with an oncologist.

Medians by cluster (5-95 %)

<table>
<thead>
<tr>
<th>Cancer types</th>
<th>% Cancer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung/bronchus, stomach, Brain/CNS, Esophagus</td>
<td></td>
</tr>
<tr>
<td>Lymph node, Kidney, Rectum, Ovary</td>
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<tr>
<td>Breast, Cervix, Skin, Uterine corpus, Thyroid</td>
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<tr>
<td>Hematologic, Ovary, Lymph node, Tongue, Oropharynx</td>
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<tr>
<td>Colon, Bladder, Lip/cheek, Larynx, Rectum, Uterus</td>
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<td>Hyopharynx, Pharynx, Ill-defined, Uterine NOS</td>
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<tr>
<td>Prostate, Breast, Cervix, Skin, Uterine corpus, Thyroid</td>
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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Use of next-generation sequencing tests to guide cancer treatment: Results from a survey of U.S. oncologists. First Author: Andrew N. Freedman, NCI, Rockville, MD

Background: The proliferation of next-generation sequencing (NGS) tests provides an opportunity to advance oncology care. However, there are limited data about when and how NGS tests are used and the extent to which test results inform clinical care. Methods: Between February and May 2017, a survey developed by the National Cancer Institute and American Cancer Society was mailed to a nationally-representative sample of oncologists; 1,281 responded, reflecting a 38% participation rate. Oncologists reported their use of NGS tests over the past year, including their use in different clinical scenarios. We restricted our analysis to the 1123 respondents who reported using NGS tests to guide treatment decisions. Among these oncologists, 36% used them “often” to guide treatment decisions for patients with advanced refractory disease, 29% to determine eligibility for clinical trials and 19% to decide whether to use FDA-approved drugs off-label. For 28% of oncologists, NGS test results informed treatment recommendations “often.” 53% reported “sometimes,” and 19% of oncologists reported that results “never” or “rarely” informed treatment recommendations. Oncologists < 50 years of age, practicing in an urban or suburban setting, and/or working in an academic center, holding a faculty appointment or receiving genomics training were more likely to use NGS tests. Over 50% of all oncologists reported that one or more patients presented with NGS test results from a commercially-available company they had not ordered. Conclusions: Most U.S. oncologists use NGS tests for their patients with solid tumors to inform treatment options for those with advanced cancer, and to identify clinical trials or FDA-approved drugs for off-label use. Among oncologist using NGS tests, over 80% reported that results informed their treatment recommendations either sometimes or often. Research is needed to more clearly establish the clinical utility of NGS tests and to inform clinical guidelines for their use in practice.

Factors associated with follow-up physician visits among women with early stage breast cancer. First Author: Farah Quayumi, Columbia University Medical Center, New York, NY

Background: In patients with early stage breast cancer (BC), follow-up guidelines vary widely among national organizations. ASCO recommends clinical examination every 3-6 months for 3 years, every 6-12 months for the next 2 years, and then annually. We sought to evaluate patterns and predictors of provider follow-up care within the first five years following diagnosis. Methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset, we evaluated patients diagnosed with stage I-II BC who underwent lumpectomy from 2002-2007 with follow-up to 2012. Patients who died in the 5 years following diagnosis were excluded. We defined discontinuation of follow-up care as > 12 months without a visit claim from either a surgeon, medical oncologist (MO) or radiation oncologist (RO). We performed a multivariable logistic regression analysis to determine factors associated with discontinuation of follow-up. Patients were censored if a new cancer was diagnosed. Results: A total of 30,053 BC patients were included in the analysis. In addition to the surgeon, 85.8% saw a MO, 71.9% saw a RO, and 65.8% saw all 3 providers in the first year. The mean number of total visit claims for years 2-5 were 4.2, 3.1, 2.5 and 2.1, respectively. During the 5 years, 6,302 (21.0%) patients discontinued follow-up visits. Discontinuation increased with increasing age. Women with a higher stage cancer were less likely to discontinue follow-up (OR 0.78, 95% CI 0.73-0.83). Patients with a low grade tumor were more likely to discontinue follow-up compared to those with a high grade cancer (OR 1.09, 95% CI 1.02-1.18). For every year of diagnosis, patients were 3% less likely to discontinue seeing all three physicians. Hormone status, race, SEER and marital status were not associated with discontinuation of follow-up visits. Conclusions: Clinical practice guidelines for surveillance of BC after diagnosis are based on expert opinion and have an unclear effect on outcomes. Coordination of follow-up care between oncology specialists may reduce discontinuation rates and increase clinical efficiency. More research is needed to determine the optimal follow-up for maintaining adherence to therapy, reducing over-testing and decreasing cost.

Early discharge after induction chemotherapy for acute myeloid leukemia: Safety and outcomes. First Author: Nikita V. Bachig, University of Washington, Seattle, WA

Background: Adults with acute myeloid leukemia (AML) typically remain hospitalized after induction chemotherapy for the duration of pancytopenia. Several studies have suggested that outpatient management following completion of chemotherapy is safe and associated with lower resource utilization. This has become standard practice at our institution if logistics allow. Here, we examine outcomes of adults ≥18 years of age with newly-diagnosed AML (acute promyelocytic leukemia excluded) or high-grade myeloid neoplasms (i.e. ≥10% blasts) who received AML-like induction chemotherapy with a regimen as or more intense than 7+3 between 8/2014 and 7/2017 and who were discharged early (ED) or remained hospitalized based on individual provider assessment. Methods: Patients were identified via institutional electronic medical records. Clinical information was collected through manual patient record review from the day after chemotherapy until count recovery (absolute neutrophil count ≥0.5×10^9/L and self-sustained platelet count ≥20×10^9/L), receipt of further chemotherapy, transfer to a different institution, or completion of 45 days on study. Patients were considered ED if discharge occurred within 3 calendar days of study start and control if not. Results: 260 patients (median: 61 [range 20-90] years) underwent induction chemotherapy, 168 of whom (64.6%) were ED. Age and gender distribution were similar between ED and control patients. Mean time on study was similar between ED and controls (25.6 ± 25.2 days; p = 0.73). There was no difference in death rate (5.6% vs. 4.3%; p = 0.59), rate of febrile neutropenia (69.6% vs. 67.4%; p = 0.71), or proportion of patients requiring ICU-level care (8.9% vs. 15.2%; p = 0.12) between groups during the study period. In the ED group, 71.4% were readmitted within 90 days (versus 63.07 in NCT, p = 0.001), receipt of intraperitoneal chemo (p = 0.000024) and gynecologic oncologist as adjuvant chemo provider (p = 0.005) were also statistically significant patient factors associated with greater CT participation. Race (p = 0.02), educational level (p = 0.095), religion (p = 0.39), marital status (p = 0.66), distance traveled for care (p = 0.99), debulking status (p = 0.72) and platinum sensitivity (p = 0.13) were not statistically significant patient factors. After adjusting for clinical factors associated with OS, women who participation in a clinical trial had significantly better OS (HR = 0.698, 95% CI [1.544, 0.896], p = 0.005). Conclusions: Early discharge after induction clinical trials appears to be warranted. Improved survival was significant for CT patients and is further justification for offering the gold standard of treatment at our NCI-CCC. Understanding of patient predictive factors warrants further exploration so we can overcome barriers to patient enrollment in CT.
Financial toxicity in patients with colorectal cancer and neuroendocrine tumors.

First Author: Leonidas Apostolidis, Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany

Background: Financial toxicity of cancer has so far been discussed primarily in the US health care system and has been shown to be associated with higher morbidity and mortality. In Germany with its third-party paid health care system the socio-economic impact of cancer is poorly understood. This study aims to provide data on financial consequences of a colorectal cancer (CRC) or neuroendocrine tumor (NET) diagnosis on patients’ economic situation and psychosocial outcomes.

Methods: This prospective study recruited 247 patients (n = 125 CRC / n = 122 NET) from November 2016 to March 2017 at the National Center for Tumor Diseases, Heidelberg University Hospital. They completed a survey on income, cancer-related out-of-pocket costs, distress (DT) and quality of life (EORTC-LQ). Results: Overall, 80.6% (n = 199) stated to have higher out-of-pocket costs, and 37.2% (n = 92) reported income loss as a sequel to their disease. While monthly out-of-pocket costs did not exceed 200 € in 76.9% of affected patients, 44.6% of those with income losses report losing more than 800 € per month. A multiple regression analysis showed that higher income loss was associated with lower patient’s quality of life and distress depending on the type of health insurance: high financial loss relative to income was significantly associated with a lower estimation of patient’s quality of life (p = 0.0009) and more distress (p = 0.0037). Patients with private health insurance indicate better quality of life (p = 0.0134) and less distress (n = 0.0005) compared to those with statutory health insurance.

Conclusions: Distress and reduced quality of life due to financial problems intensify the burden that already results from a cancer diagnosis. As many patients have to face financial loss and most are insured under the statutory health insurance scheme, there is a need for targeted support measures at the individual and system level in Germany.

Perceived Financial Burden of Care

Financial toxicity in patients with colorectal cancer and neuroendocrine tumors. First Author: Leonidas Apostolidis, Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany

Background: Financial toxicity of cancer has so far been discussed primarily in the US health care system and has been shown to be associated with higher morbidity and mortality. In Germany with its third-party paid health care system the socio-economic impact of cancer is poorly understood. This study aims to provide data on financial consequences of a colorectal cancer (CRC) or neuroendocrine tumor (NET) diagnosis on patients’ economic situation and psychosocial outcomes. Methods: This prospective study recruited 247 patients (n = 125 CRC / n = 122 NET) from November 2016 to March 2017 at the National Center for Tumor Diseases, Heidelberg University Hospital. They completed a survey on income, cancer-related out-of-pocket costs, distress (DT) and quality of life (EORTC-LQ). Results: Overall, 80.6% (n = 199) stated to have higher out-of-pocket costs, and 37.2% (n = 92) reported income loss as a sequel to their disease. While monthly out-of-pocket costs did not exceed 200 € in 76.9% of affected patients, 44.6% of those with income losses report losing more than 800 € per month. A multiple regression analysis showed that higher income loss was associated with lower estimation of patient’s quality of life and distress depending on the type of health insurance: high financial loss relative to income was significantly associated with a lower estimation of patient’s quality of life (p = 0.0009) and more distress (p = 0.0037). Patients with private health insurance indicate better quality of life (p = 0.0134) and less distress (n = 0.0005) compared to those with statutory health insurance.

Conclusions: Distress and reduced quality of life due to financial problems intensify the burden that already results from a cancer diagnosis. As many patients have to face financial loss and most are insured under the statutory health insurance scheme, there is a need for targeted support measures at the individual and system level in Germany.
6537 Poster Session (Board #363), Sat, 1:15 PM-4:45 PM
Diffusion of innovation in oncology: A case study of immuno-oncology (IO) adoption for advanced non-small lung cancer (aNSCLC) patients across practices in the US. First Author: Caroline Savage Bennett, Flatiron Health, New York, NY

Background: IO agents are being adopted rapidly into clinical care; however, variation in speed and breadth of adoption across oncology practices remains unknown. Our objective was to evaluate adoption patterns in the treatment of aNSCLC and identify practice characteristics associated with adoption trajectories.

Methods: 43,697 patients diagnosed with aNSCLC from Jan 11-Dec 17 were obtained from the Flatiron Health electronic health record database, a national sample of academic and community practices. We estimated the proportion treated each month with IO (nivolumab, pembrolizumab or atezolizumab) versus other therapies from time of first IO approval (Mar 15) through Dec 17 in 123 practices that treated aNSCLC patients during this time. We used k-means clustering to identify patterns of IO adoption. Multivariable logistic regression models were used to adjust for differences in case-mix and evaluate association of practice size, location, and Quality Oncology Practice Initiative (QOPI) certification program with IO adoption.

Results: We identified 4 distinct groups of practices based on trajectories that differed in speed and extent of IO adoption (Table). 17% of practices adopted IO rapidly and extensively; 28% were slower and more limited in their adoption; 24% initially had limited IO use, but adoption accelerated rapidly after 18 months; 32% initially adopted rapidly, but slowed markedly after 1 year. In multivariable analyses, we found no significant association between a practice’s size, location, or QOPI certification and IO adoption trajectory.

Conclusions: There is significant variability in adoption of IO therapy by oncology practices. Further research is needed to characterize drivers of this variation at the physician level and its impact on patient outcomes. Understanding variability in the diffusion of new innovations could guide development of targeted educational interventions to optimize use of new effective therapies.

6539 Poster Session (Board #365), Sat, 1:15 PM-4:45 PM
Reportable actionability versus pragmatic actionability: Implementing precision medicine at three large health systems. First Author: Michael A. Thompson, Aurora Health Care, Delafield, WI

Background: Precision medicine (PM) (MO) molecular panel (MP) testing report actionable findings with associated targeted therapies (including immunotherapies). However, these actionable findings “reported actionability” by molecular testing companies are often not realized as “pragmatic actionability” in the real world setting. We explored the concordance among PM testing recommendations and subsequent drug treatment orders by clinicians at Aurora Health Care (AHC), Henry Ford Health System (HFHS), and Hoag Memorial Hospital Presbyterian (HMHP). Methods: Structured clinical, genomic report data, and treatment orders were obtained from the Syapse database. At AHC, HFHS, and HMHP, we identified 996 MP reports from 748 patients who received testing between 2014 and 2018. Results: 713 MP reports had “reported actionable” (positive) treatment recommendations and a subsequent treatment order across all 3 health systems. 24.4% (174/713) of MP reports were followed by a treatment order that matched to at least one reported actionable treatment. The translation from a MP-reported actionable finding to a prescribed treatment order was 28.1% (105/374) at AHC, 20.9% (9/43) at HFHS, and 20.3% (60/296) at HMHP, which has borderline statistical significance (p = 0.0563). Of the 713 MP reports analyzed, there was an average of 7.8 therapy recommendations per MP report. There were no significant rate differences in actionability of individual drug recommendations between the two molecular testing vendors examined. We did not examine the actionability of MP report recommendations for investigational agents. Conclusions: Of all 996 MP reports in the initial sample, only 17.5% resulted in a treatment order which matched a MP report recommendation. The translation of reported actionability to pragmatic actionability was consistent across all 3 health systems. This may reflect different definitions of “actionable” between molecular testing companies and clinicians as well as patient performance status changes over time, insurance coverage for off-label use, or referral to a clinical trial. Further research is warranted to understand the issues involved.

6538 Poster Session (Board #364), Sat, 1:15 PM-4:45 PM
A multidisciplinary toxicity team for cancer immunotherapy-related adverse events. First Author: Jarushka Naido, Johns Hopkins Kimmel Comprehensive Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD

Background: Immune checkpoint inhibitors (ICI) cause immune-related adverse events (irAEs). The spectrum of irAEs requiring referral to non-oncology specialists has not been well described. We established an immune-related toxicity (IR-Tox) team of oncology (n = 8) and medical subspecialists (n = 20), to support multidisciplinary irAE diagnosis and management. Methods: Patients (pts) treated with ICIs were electronically referred to the IR-Tox team between 01/2017-03/2018. IR-Tox team met monthly to discuss complex irAEs, and identify areas of clinical need. Pt demographics, treatments, and irAE details were collected. Pt features and irAE associations were analyzed using Chi-square tests. Results: The IR-Tox Team received 92 referrals for 80 pts (outpt: 61%, inpt: 39%). Median age was 65 years (range: 21-91), 55% were male, and 14% had prior autoimmune disease. Pts most commonly had non-small cell lung cancer (35%), melanoma (19%), or gynecologic malignancies (10%). Pts received ICI monotherapy (66%) or combination immunotherapy (44%), as standard-of-care (46%) or on clinical trials (54%). Referrals related to diagnosis (32%), management (11%), or both (51%) were received from faculty (68%), fellows (12%), and nurses (20%). Referrals were for suspected irAE (90%), pre-ICI assessment in known autoimmune disease (9%), or ICI re-challenge (1%). Sixty-three irAEs were confirmed (CTCAE grade 1 = 19; 2 = 43%; 3 = 38%), and 26 patients had >1 irAE. There was significant variability in adoption of IO therapy by oncology practices. Further research is needed to characterize drivers of this variation at the physician level and its impact on patient outcomes. Understanding variability in the diffusion of new innovations could guide development of targeted educational interventions to optimize use of new effective therapies.

6540 Poster Session (Board #366), Sat, 1:15 PM-4:45 PM
Patient comorbid conditions and cancer clinical trial participation. First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: The American Society of Clinical Oncology (ASCO) recently recommended modernizing criteria related to comorbid conditions routinely used to exclude patients from clinical trials. We investigated how baseline comorbid conditions influence clinical-trial decision making and trial participation. We also modeled how reducing major trial comorbidity exclusion criteria might impact participation, to provide a benchmark for evaluation of the ASCO recommendations. Methods: Data were from a large national web-based survey of 5,499 cancer patients in the cancer treatment-decision-making process. Self-reported data on 18 comorbid conditions were collected. We examined how individual and combinations of comorbidities – using the “best” subset method – influenced patterns of trial discussions, offers, and participation. We also simulated how trial participation rates would change if individual and combinations of comorbidity exclusion criteria were removed. Logistic regression was used. Multivariable regression included adjustment for important demographic and socioeconomic variables. Results: Most patients (66%) had ≥1 baseline comorbidities. The most common comorbid condition was hypertension (35%), Hypertension, prior cancer, and hearing loss were most strongly and uniformly associated with outcomes; each increase in the number of these conditions (0 vs. 1 vs. ≥2) was associated with a decreased risk of trial discussions (11% lower, p = 0.004), trial offers (18% lower, p = 0.004), and trial participation (22% lower, p = 0.006). The removal of all comorbidity restrictions would generate an 18% relative increase in trial participation, or (if the overall participation rate is 5%) a 1% absolute increase. Conclusions: The presence of baseline comorbid conditions adversely impacts trial discussions, trial offers, and trial participation itself. Although the modernization of trial eligibility criteria would benefit many patients, this effort should be framed to encourage increased trial participation rates overall.

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6541  Poster Session (Board #367), Sat, 1:15 PM-4:45 PM
Cancer pain in the emergency department: A multicenter study of the Comprehensive Oncologic Emergencies Research Network. First Author: Christopher John Chen, University of California San Diego, San Diego, CA
Background: Despite initiatives to improve cancer analgesia, patients with cancer frequently present to the emergency department (ED) with pain related issues. To our knowledge, no previous studies have investigated how the presence and severity of pain in cancer patients presenting to the ED may relate to morbidity and mortality. This study aims to investigate these associations.
Methods: We conducted a multicenter prospective cohort study of ED patients with active cancer presenting to 18 EDs within the Comprehensive Oncologic Emergencies Research Network (CONCERN) between December 1st, 2016 and June 1st, 2017. We recorded initial, final and highest ED pain scores and used logistic regression to estimate their association with the following outcomes: 30-day mortality, 30-day ED revisits, and 30-day hospital readmissions. Pain was recorded into none (0), mild (1-3), moderate (4-6) and high (7-10). We also recorded demographics and ECOG scores. Results: We enrolled 1075 patients. The cohort was 52% female with a median age of 64. Approximately 70% of patients had pain, while only 48% of patients received an analgesic. 62% reported having home medications. The median highest pain score was 0, while the initial and final were 4 and 1, respectively. Of the patients who presented with pain, 64.8% reported improvement prior to discharge, 28.7% reported no change and 6.5% worsened. A high initial pain score was associated with increased 30-day mortality (OR 2.3, 95%CI 1.1-4.8). An ECOG score of 2 was associated with increased 30-day ED revisits (OR 1.7, 95%CI 1.1-2.5) and readmissions (OR 2.2, 95%CI 1.4-3.2). Conclusions: Pain remains a significant issue for cancer patients presenting to the ED, and was present in nearly 3/4 of our cohort. While not all patients received pain medications, we did note a low median final pain score. Severe pain on presentation appeared to be associated with increased mortality. This knowledge may aid physicians when determining ED disposition for those patients with high initial pain scores. An ECOG score of 2 appears to be associated with increased ED revisits and readmission, which may reflect a population in need of more aggressive outpatient symptom management.

6542  Poster Session (Board #368), Sat, 1:15 PM-4:45 PM
Practice transformation: Early impact of OCM on hospital admissions. First Author: Holly Mendenhall, Oncology Hematology Care, Cincinnati, OH
Background: the purpose of the Oncology Care Model is to improve quality and reduce cost. Local practice transformation (PT) foundation tenant is to reduce avoidable ER visits and hospitalizations. In anticipation of being an OCM participant, we instituted a multidimensional campaign designed to meet these objectives. Methods: Prior Actions: Established phone triage unit. After-hours and weekend call. Instituted weekend urgent care. Year One: Improved education provided by nurse navigators and APPs prior to start of treatment (OCM Treatment Planning visit). Implemented triage pathways: 38 symptom and 27 follow-up pathways (modified COME HOME, Barbara McAneny, M.D.). Proactive symptoms follow-up calls to help circumvent emergent admissions. Increased APP staffing to provide blocked time slots for same day patient visits w/o schedule disruptions. Initiated “Call Us Early – Call Us First” campaign. Incorporated verbal and/or written instructions at all patient touch points, emphasizing patient’s responsibility to call before going to the emergency room. Results: Based on data from the Chronic Condition Warehouse, as provided by CMS, we were successful at reducing the acute care admissions rate by 16 percent. OCM patient survey scores improved. Readmissions (4.9 vs 5.6/100 pts), ER utilization (1.7 vs 18.6/100 pts), and Observation Stays (2.7 vs 3.6/100 pts) remained below Risk Adjusted National averages. Conclusions: By implementing a cost efficient, reproducible, and scalable campaign targeting ER avoidance and hospitalizations, we were able to decrease hospital admissions. Reported Medicare savings amounted to nearly $796,000 in inpatient cost per quarter over 1,600 patients.

6543  Poster Session (Board #369), Sat, 1:15 PM-4:45 PM
Cancer survival in the context of growing hospital participation in Medicare ACOs. First Author: Stephen Matthew Schleicher, Memorial Sloan Kettering Cancer Center, New York, NY
Background: Accountable Care Organizations (ACOs) represent one of the main policy-level interventions to improve healthcare quality. We investigated the trend of 1) hospital participation in ACOs over time and 2) cancer survival rates at participating hospitals. Methods: We searched public reporting websites of all Pioneer and Medicare Shared Savings Program (MSSP) ACOs. We matched ACO participant lists with the Dartmouth Hospital Atlas to identify hospitals within ACOs. Results: There were 47 hospital ACOs participating in 2012, which grew to 55 ACOs participating in 2017. Five year overall survival rate for patients with cancer treated at new ACO hospitals was fairly stable over time (53.1% in 2012-2014 vs. 54.4% in 2015-2017). There was a trend towards increased hospital participation in ACOs, defined as the percentage of ACOs that included hospitals, over time (26.5% in 2012-2014 vs. 57.7% in 2015-2017). The five year overall survival rate for patients with cancer treated at new ACO hospitals was fairly stable over time (53.1% in 2012-2014 vs. 54.4% in 2015-2017). Similarly, there was no significant change in the odds of cancer survival for ASCO vs. non-ACO hospitals over time. Conclusions: Despite growth in hospital participation within Medicare ACOs over time, the quality of cancer care at hospitals joining MSSP has remained stable.

6544  Poster Session (Board #370), Sat, 1:15 PM-4:45 PM
24-hour cancer clinic: An approach to same-day care. First Author: Jonathan Thomas Kapke, Medical College of Wisconsin, Wauwatosa, WI
Background: Managing healthcare delivery and optimizing the cost of care for cancer patients is a difficult task for healthcare systems. Cancer patients are at risk for complications of their disease and adverse effects of treatment that often require urgent medical care. The inability to access oncology specific care 24-hours a day can lead to increased use of the Emergency Department (ED), which is often associated with unnecessary diagnostic testing, high rates of hospital admission, low patient satisfaction and excessive cost. On 11/1/16, Froedtert & the Medical College of Wisconsin opened the 24-hour Cancer Clinic (24hCC). The 24hCC is staffed by oncology trained providers and offers around the clock access to patients for a variety of urgent care needs. In this study, we evaluated resource utilization, admission rates, patient satisfaction and cost for patients seen in the 24hCC compared to the ED. Methods: We analyzed de-identified data for patients seen in the 24hCC and the ED between 1/1/17 and 12/1/17. Cost was defined as the quantity of imaging, ECG and lab studies ordered. Cost was measured based on hospital charges. Patient satisfaction surveys were reviewed. Results: Prior to the 24hCC, oncology patients seeking urgent, same-day care were often directed to the ED. There were an average of 250 ED visits per month with an admission rate of 55%. During the time period analyzed, 897 patient visits were completed in the 24hCC and 1621 in the ED. There was 56%, 32% and 11% less imaging, ECG and lab utilization respectively for patients seen and discharged from the 24hCC compared to the ED. The admission rate from the 24hCC was 18% compared to 42% from the ED. The mean overall rating of care for the 24hCC was 97.5%, with a 89.7% top box score (9 or 10 on 1-10 scale). When comparing diagnostic charges in the 24hCC to the ED during the first six months of data collection, the median charge was $1554 less for discharged patients and $2269 less for admitted patients. Conclusion: Our data demonstrates that a 24-hour oncology specific clinic can provide same-day care that is associated with decreased utilization, less hospital admission, improved patient satisfaction and lower cost for selected non-emergent cancer patients.
Background: There is limited access to quality Palliative Care (PC) for advanced cancer patients being treated in Sub-Saharan Africa due to limited PC knowledge among health care providers in the region. The goal of this innovative project was to improve access by offering cost-effective training to these providers using Project ECHO (Extension for Community Healthcare Outcomes), an established telementoring and support program. Our aim was to evaluate feasibility, attitudes, knowledge, and efficacy of participants of ECHO-PACA to deliver PC.

Methods: An interdisciplinary team at the UT MD Anderson Cancer Center, guided by PC providers in Sub-Saharan Africa, developed a standardized curriculum based on PC needs in the region. Participants were then recruited and monthly telementoring sessions consisting of case presentations, discussions, and didactic lectures began in July 2016. Program participants included 14 clinics and teaching hospitals from Ghana, Kenya, Nigeria, South Africa, and Zambia, with sessions offering participants the ability to interact and learn new skills in PC. Participants were surveyed at the beginning, mid-point and end of the 16 month program to evaluate changes in self-reported knowledge and management. Identification of signs/symptoms of imminent death, identifying and addressing challenging communication issues related to end of life. Results: Median participation per session was 30. Median duration of monthly meetings was 90 minutes. 33 of 40 initial participants (83%) completed the survey. There was significant improvement in recognizing non-opioid analgesics for persistent pain (p = .03), titrating opioids to optimize pain control (p = .03), Identification of signs/symptoms of imminent death (p = .05), and Identifying and addressing challenging communication issues related to end of life (p = .02). Conclusions: ECHO-PACA was a feasible, cost effective, pragmatic approach to disseminate PC knowledge without the need for travel, which has the potential to increase access to quality PC through enhancing the skills of providers in resource challenged areas of Sub-Saharan Africa. Further studies are needed to evaluate ECHO-PACA impact on patient outcomes.

Implementation of individualized care plans in high risk oncology patients: A team based model to decrease unnecessary utilization. First Author: Girish Chandra Kunapareddy, Cleveland Clinic Foundation, Cleveland, OH

Background: Due to complexity of disease and treatments, oncology patients (pts) have among the highest hospitalization rate. In our cancer institute, just 6% of all discharged pts accounted for > 40% of all unplanned readmissions (UR), and continue to be of highest risk of future admissions, ICU stay, ED visits, overuse of chemotherapy and underutilization of hospice resources. We hypothesized that developing individualized care plans (ICP) will better provide the complex care necessitated by this group. Methods: An Interdisciplinary Care Team (ICT) was created consisting of palliative medicine and oncology physicians/social workers/care coordinators/nurse managers. Twice monthly, pts with the highest utilization over a 60-day period with at least two UR were identified. ICPs were created using the team-based approach with parallel input from primary outpatient providers. Communication plans were created to ED and outpatient teams. Results: A total of 71 pts, 356 hospitalizations, and 260 ED visits were evaluated over a 6-month period, with an avg number of hospitalizations of 0.82 per pt month (p.p.m.). After creation ICT, this decreased to 0.23 p.p.m. Average ED visits, UR, avg length of stay per admission also decreased (see Table 1). Nearly all solid tumor pts had metastatic disease at ICT review, while ppm. Average ED visits, UR, avg length of stay per admission also decreased (see Table 1). Nearly all solid tumor pts had metastatic disease at ICT review, while

<table>
<thead>
<tr>
<th>Effect of ICP</th>
<th>All Patients</th>
<th>Solid Tumor</th>
<th>Metastatic Neoplasm</th>
</tr>
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<tbody>
<tr>
<td>Before ICT</td>
<td>0.82</td>
<td>0.79</td>
<td>0.79</td>
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<tr>
<td>After ICT</td>
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<td>30-day Readmissions</td>
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<td>0.51</td>
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<td>Before ICT</td>
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<td>Average LDL per Admission</td>
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<td>7.24</td>
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<tr>
<td>Before ICT</td>
<td>4.06</td>
<td>2.55</td>
<td>6.17</td>
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</tbody>
</table>

Conclusions: Creation of individualized care plans for high-utilizing cancer patients decreased number of hospitalizations, ED visits, unplanned readmissions, and length of stay in all disease groups, but ST patients seemed to have a greater impact than in HM patients.
Clinician perspectives on electronic health records, communication, and patient safety across diverse medical oncology practices.  

First Author: Miriam P Patel, University of Michigan, Ann Arbor, MI

Background: We know little about clinicians’ documentation and communication challenges and how these might affect the safety of ambulatory oncology care. The present study investigated variation in electronic health record (EHR) capability in practice and satisfaction, clinician communication, and clinicians’ actions that enable a safety culture. Methods: We distributed paper questionnaires to nurses and prescribers (physicians, nurse practitioners, and physician assistants) in 29 community oncology practices statewide. Pre-validated measures included the Safety Organizing Scale (SOS) that reflects actions consistent with a safety culture, satisfaction with clinician technology, and satisfaction with communication with other clinicians. We constructed an index to reflect EHR capability (1 = all paper to 5 = all electronic). Linear regression models (with robust standard errors to account for clustering) were used to examine the relationship between covariates of interest and the SOS, adjusting for practice size and ownership. Results: The survey response rate was 68%. The mean (SD) of the SOS was 5.3(1.1), with a practice-level range of 4.9-5.4 (based on 7-point scale where higher scores reflect increased safety actions). Higher satisfaction with technology and clinician communication was significantly associated with increased SOS scores, while increased EHR capability was associated with lower SOS scores. Prescribers reported lower SOS scores than nurses (see table). EHR capability was associated with lower SOS scores. Prescribers reported higher satisfaction with technology and clinician communication (see table). Conclusions: Practices vary in their performance of patient safety actions. Supporting clinicians to integrate increased technology is a promising target for interventions. The inverse relationship between EHR capability and safety suggests that technology distracts clinicians from attending to patient safety. Improvement strategies may benefit from tailoring by clinician type to account for observed differences.

<table>
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<th>Variable</th>
<th>β(SE)</th>
<th>95% CI</th>
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<tbody>
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<td>0.5, 0.8</td>
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<tr>
<td>Clinical communication satisfaction</td>
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<td>0.1, 0.4</td>
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<td>EHR capability index</td>
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<td>Prescriber (vs. nurse)</td>
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<td>-0.7, -0.1</td>
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*** p < .001

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Association of baseline body mass index (BMI) with overall survival (OS) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with nivolumab (N) or pembrolizumab (P). First Author: Jizu Zhi, U.S. Food and Drug Administration, Silver Spring, MD

Background: Poor performance status (PS) is associated with worse clinical outcomes for pts with mNSCLC. However, in the real-world PS is not routinely captured in electronic health records (EHRs). Pts with poor PS may also have cachexia and low BMI. As such, underweight BMI may be a proxy for deteriorated real-world PS when PS score is missing. We have shown that female gender and positive EGFR/ALK mutation status predict longer OS, but not age or other factors. We explore the association of baseline BMI with OS in real world mNSCLC pts treated with N or P. Baseline BMI (kg/m2) was calculated from the most recent weight and height recorded within 30 days prior to index date and categorized as: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25 – 29.99), and Obese (30+). Association of baseline BMI with OS was assessed using multivariate Cox proportional hazards model adjusted for gender, age, and EGFR/ALK status prior to N or P start. Eligible pts had valid values for all parameters.

Results: 703 pts met inclusion criteria (Table). For OS, gender was significant overall, EGFR/ALK mutation was significant overall and for women. Conclusions: We observed BMI-based differences in OS for real world mNSCLC pts treated with N or P. Underweight BMI is associated with shorter OS in both genotypes and for OS overall; and obese BMI is associated with longer OS. In pts with cancer, declining BMI and low BMI. As such, underweight BMI may be a proxy for de-

Methods: We conducted a retrospective analysis of mNSCLC pts treated with N or P using de-identified real-world data (RWD) from the Flatiron Health network. Index date was start of first 

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6557  Poster Session (Board #383), Sat, 1:15 PM-4:45 PM

The influence of socioeconomic status, tumor characteristics and patterns of breast cancer care on breast cancer specific survival among elderly women. First Author: Amanda L. Kong, The Medical College of Wisconsin, Milwaukee, WI

Background: The purpose of this study was to examine the relationship between patient demographic and socioeconomic status (SES), tumor characteristics, initial and follow-up breast cancer care, and 3-year breast cancer mortality among a population-based cohort of elderly women with incident breast cancer. Methods: We identified women with newly diagnosed breast cancer in 2006-2009 from the Surveillance and Epidemiology End Result study linked with Medicare claims (SEER-Medicare). A Classification and Regression Tree (CART) model was applied to 15 individual indicators of neo-adjuvant and adjuvant breast cancer treatment, tumor characteristics, and patient demographic and SES variables to identify patterns (i.e. combinations of variables) with the greatest discriminant value in predicting 3-year mortality by cause of death (outcome = breast cancer vs. other causes vs. alive). Results: Nineteen unique patterns were identified as best discriminating 3-year mortality by cause of death. Breast cancer mortality probabilities associated with these patterns ranged from 2.6% to 39.7%. CART identified the number of positive nodes as the best single discriminator between high and lower breast cancer mortality, followed by the use radiation therapy and tumor stage. Patient’s SES was a discriminant factor in four of the ten patterns associated with high (> 15%) breast cancer mortality while non-use of adjuvant hormonal therapy was a discriminant factor in six of the ten high breast cancer mortality patterns. Receipt of treatment within 50 days from diagnosis was associated with two of the lowest probabilities of breast cancer mortality (3.1% and 7.7%). Conclusions: Greater adoption of certain patterns of care could improve breast cancer survival of elderly women with incident disease overall, and reduce SES disparities therein.

6558  Poster Session (Board #384), Sat, 1:15 PM-4:45 PM

Feasibility of a self-funded model to provide breast cancer services to uninsured women in New York City. First Author: Janice Zaballero, Breast Treatment Task Force, New York, NY

Background: Despite access-expanding mandates in the ACA, approximately 30% of New York State residents remain uninsured. Most safety net programs provide services only to patients who qualify for Medicaid, leaving a large percentage of women without access to affordable breast cancer screening and diagnostics. In response, we developed Breast Treatment Task Force (BTTF) to provide these services to uninsured patients earning $23,760 - $47,520 per year (200%-400% FPL). Methods: We surveyed imaging centers located in New York City to determine unused imaging capacity. BTTF then negotiated reduced rates for breast imaging services at these sites. We developed referral networks composed of community organizations including Planned Parenthood. We raised nearly $400,000 through philanthropy to fund operations. We collected demographics for all patients, and patient satisfaction was assessed through surveys administered after receiving services. Results: We identified 24 imaging centers with unused capacity totaling 20,000 screening exams and diagnostic procedures. In 2017, BTTF facilitated care for 646 patients in the form of 409 screening exams and 832 diagnostic procedures. Average wait time from abnormal mammogram to diagnostic procedure was less than six days. The median age of BTTF patients was 40, and the majority were from minority backgrounds (34% Asian, 32% Hispanic, and 19% African-American). Median annual income per patient was approximately $30,000, and 61% of patients were employed. Attendance rates for diagnostic services and patient satisfaction rates were each 99% (versus industry averages of 60% and 67%, respectively). Nine patients were newly diagnosed with cancer. Since 2007, BTTF has delivered $16 million in medical services with an annual budget of under $400,000. Conclusions: BTTF constructed two networks: 1) network of private imaging centers willing to treat uninsured patients for a pro-rate of unused capacity and 2) network of local community referral partners to identify low-income patients. This model offers an example of how to successfully provide important breast cancer screening and diagnostic services to non-Medicaid-eligible women who cannot afford health insurance.

6559  Poster Session (Board #385), Sat, 1:15 PM-4:45 PM

Cigarette price, smoking behaviors, and lung cancer mortality in Indiana. First Author: Ryan Nguyen, Indiana University School of Medicine, Indianapolis, IN

Background: Increasing tobacco costs have been proven to be one of the most effective interventions of decreasing tobacco use. The relationship between tobacco cost and lung cancer mortality has not been as well established. We investigated the relationship of cigarette price with smoking prevalence, cigarette consumption, and lung cancer incidence and mortality in Indiana and nationally. Methods: We obtained average cigarette pack prices, cigarette pack sales, smoking prevalence, and lung cancer incidence and mortality rates in Indiana and nationally from 1995-2015. Average cigarette pack prices were inflation adjusted to 2015 then assessed for Pearson correlation coefficient (r) with cigarette pack sales, smoking prevalence, and lung cancer incidence and mortality. Cigarette price was also correlated with smoking prevalence among state-level characteristics that included gender, age, ethnicity, education, and income. Results: From 1995 to 2015, average cigarette pack price in Indiana rose from $2.29 to $5.41. Increasing cigarette price in Indiana was associated with decreasing cigarette consumption (r = -0.91, p < 0.001) and decreasing overall smoking prevalence (r = -0.72, p < 0.001). However, those in the lowest income level had higher smoking prevalence associated with rising cigarette price (r = 0.67, p < 0.001). Increasing cigarette price correlated with decreasing lung cancer mortality both in Indiana (r = -0.79, p < 0.001) and nationally (r = 0.96, p < 0.001). Conclusions: Increasing tobacco taxes and subsequent increasing cigarette prices were associated with decreased smoking prevalence, cigarette consumption, and lung cancer mortality in Indiana. Lower socioeconomic populations in Indiana may not be as price-responsive as similar populations nationally. Policies aimed at increasing tobacco prices should prioritize diverting revenues towards health programs and tobacco cessation initiatives for lower-income individuals.
Background: Molecular-driven oncology clinical trials are a rapidly growing category of clinical research. These trials are focused on generating evidence for the relationship between molecular markers and targeted therapies, often requiring patients to have Next-Generation Sequencing (NGS) results before being considered for qualification. This requirement adds another barrier to clinical trial enrollment for populations that already face healthcare disparities.

Methods: Defining Platforms for Individualized Cancer Treatment (DePICT) is an IRB approved observational trial designed to monitor outcomes of Broward County, FL residents with late-stage refractory cancer who undergo NGS. Rather than requiring NGS results, DePICT subsidized NGS testing to ensure access to all patients. Enrollment demographics were analyzed to see if these conditions improve gender and minority representation.

Results: DePICT has recruited 176 patients. 70% of the total cohort is female, compared to 39% female in the institute's accrual of Broward residents. Table 1 shows the base line demographic data for DePICT in comparison to the institutional recruitment. DePICT produced a 26% relative increase in minority recruitment and 12 week follow up (65% women; 13% Black, 25% Hispanic). The follow-up determined which patients pursued an MTB recommended targeted treatment or clinical trial. 12 patients continued on to interventional trials; 50% were women, 50% identified as minorities. An additional 10 patients continued on to targeted therapies; 64% were women and 64% identified as a minority. Conclusions: By providing access to NGS testing DePICT accrued underrepresented patients who face healthcare disparities. Targeting underrepresented populations for NGS may improve the enrollment of women and racial minorities to oncology clinical trials. Healthcare providers may encourage testing through education or subsidy programs. Employing these methods to reduce disparities will improve generalizability of clinical research.

<table>
<thead>
<tr>
<th>Black</th>
<th>Non-Hispanic White</th>
<th>Hispanic</th>
<th>Minority recruitment</th>
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<tr>
<td>DePICT</td>
<td>15%</td>
<td>57%</td>
<td>23%</td>
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<tr>
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**Assessing the impact of early Medicaid expansion on insurance, stage at diagnosis and survival among young adults (AYA) treated on adult protocols**

6563 Poster Session (Board #389), Sat, 1:15 PM-4:45 PM

**Background:** Cancer outcomes in young adults have lagged behind other age groups, which may be related to lower rates of insurance. While some data suggest the Affordable Care Act (ACA) may improve outcomes in young adult cancer patients eligible for dependent coverage through the ACA Dependent Coverage Provision, the impact of the ACA on cancer outcomes among young adults ineligible for dependent coverage has not been well-studied. Our objective is to assess changes in insurance rates, stage at diagnosis, and survival that are associated with early (2010-2011) Medicaid expansion.

**Methods:** Using the Surveillance, Epidemiology, and End Results (SEER) 18 database, we identify young adults aged 27-34 years diagnosed with a first primary malignancy between 2007-2014. We utilize a quasi-experimental design, comparing expansion-related changes in insurance rates, stage at diagnosis, and survival in the intervention group (cases from states that expanded Medicaid early) to the control group (cases from other, non-expanding states) using difference-in-differences analyses applied to linear probability and Cox proportional hazards regression models. **Results:** A total of 47,750 cases were included in the analyses. Relative to young adults in states that did not expand Medicaid early, young adults in early expansion states had increases in Medicaid insurance (1.51 Percentage Points [PP], 95% CI = 0.15 to 2.87, p = 0.030), decreases in uninsured (-1.99 PP, 95% CI = -3.03 to -0.95, p < 0.001), increases in early stage diagnoses (2.72 PP, 95% CI = 1.09 to 4.34, p = 0.001), decreases in late stage diagnoses (-1.34 PP, 95% CI = -2.53 to -0.16, p = 0.027), but no change in cancer-specific survival (HR: 0.95, 95% CI = 0.85 to 1.07, p = 0.41).

**Conclusions:** For young adults ineligible for dependent coverage, early Medicaid expansion is associated with increases in Medicaid insurance rates and early stage diagnoses as well as decreases in the uninsured rate and late stage diagnoses, though evidence for a further downstream effect on survival is lacking.
Monitoring, particularly given repeal of the individual mandate. Experienced significant reductions in access burden and financial worry. Delayed care, 4.8 PPT in any unmet need, 7.4 PPT decline in worry about future bills, and food insecurity. Linear probability regressions examined changes between the 2012-2013 and 2015 periods. Models controlled for eligibility for both Medicaid and premium subsidies to purchase insurance, constructed using family structure, income and employment, and linked data on state-specific Medicaid expansion policies. Models also controlled for demographics and comorbidities. Prior to ACA implementation, 18% of cancer survivors delayed healthcare due to cost, 13% had unmet need for medical care, 18% reported CRN, 31% reported being highly worried about paying future medical bills and 23% reported food insecurity. Post-ACA there were adjusted decreases of 4.5 percentage points (PPT) in delayed care, 4.8 PPT in any unmet need, 7.4 PPT decline in worry about future medical bills, and food insecurity. Conclusions: After the ACA implementation, cancer survivors experienced significant reductions in access burden and financial worry. Despite improvements, cancer survivors still experience healthcare access limits, and worry about future financial health. ACA coverage changes, participation, access and health outcomes for cancer survivors need ongoing monitoring, particularly given repeal of the individual mandate.

Impact of hospital safety-net burden on oncology patterns of care and outcomes. First Author: Reith Sarkar, University of California, San Diego School of Medicine, La Jolla, CA

Background: Safety-net hospitals serve a vital role in treating underserved populations. These hospitals often receive less funding, which could lead to different patterns of care for patients treated at these facilities. The purpose of this study was to determine the patterns of care and oncologic outcomes among a large cohort of cancer patients treated at safety-net hospitals. Methods: We identified 3,398,962 patients within the National Cancer Database with 10 common cancers including breast, prostate, lung, head and neck, colon, rectal, pancreas, cervix, bladder, and uterus diagnosed between 2004 and 2015. Safety-net burden was defined from the percentage of uninsured or Medicaid patients seen at each facility, and hospitals were then categorized as low (LBH), medium (MBH), or high burden (HBH) hospitals. We evaluated the impact of safety-net burden on patterns of care, as well as other outcomes including surgical margin status, and overall survival using multivariable linear, logistic, and Cox regression models. Results: Cancer patients seen at HBHs were more likely to be young, female, black, Hispanic, and reside in a low-income zip-code. HBHs were more likely to be academic, smaller institutions, and located in the South. After controlling for patient and tumor-related factors HBHs had differing patterns of treatment, and overall were less likely to operate (odds ratio [OR] 0.83; 95% confidence interval [CI] 0.82-0.84; p < 0.0001) and were more likely to provide radiation (OR 1.09; 95% CI 1.08-1.1; p < 0.0001) than LBHs. With respect to surgery, HBHs had higher rates of positive surgical margins (OR 1.08; 95% CI 1.06-1.1; p < 0.0001) than LBHs. HBHs had higher all-cause mortality when compared to LBHs (hazard ratio 1.09; 95% CI 1.08-1.10; p < 0.0001). Conclusions: Oncologic care at safety-net hospitals is associated with different patterns of care, as well as adverse clinical outcomes. Future research should focus on determining the etiology of this disparity, and work to devise strategies to improve outcomes among patients treated at safety-net hospitals.

Overall survival based on oncologist density in the United States: Do we need to redefine underserved areas for oncologic care? First Author: Kathan Mehta, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: ASCO has predicted shortage of 2,550 to 4,080 oncologists by 2020, disproportionately higher in underserved areas. The Conrad-30 program was established for international medical graduates, trained on J1 visas, to work in medically underserved areas (MUs) and health professional shortage areas (HPSAs) to correct this disparity. Thirty spots per year are available for each state and primary care providers (PCPs) are given priority. The designation of an area as MUA or HPSA is based on shortage of PCPs but not specialists. Methods: We evaluated the impact of oncologist density (OD) defined as number of oncologists per 100,000 (100K) population on overall survival and concordance with MUA or HPSA designation of areas by quartiles of OD. We studied the distribution of oncologists on visa in areas by quartiles of OD by merging SEER data with AMA physician’s master file using Federal Information Processing Standards (FIPS) code of the area. Results: We identified 68,791 adult patients with newly diagnosed hematologic malignancies or metastatic solid cancers (excluding CNS cancers and patients with CNS mets) in 612 FIPS code areas captured by SEER in 2011. After controlling for confounders, compared to patients in areas with lowest quartile of OD ( < 2.9 oncologists per 100K population), patients in areas with 2nd, 3rd and 4th quartile (2.9-6.5, 6.5-8.4, > 8.4 oncologists per 100K population respectively) of OD had better overall survival (HR 0.96, p = 0.001; HR 0.93, p < 0.001; HR 0.9, p < 0.001 respectively). There was no difference in proportion of MUA or HPSA designated areas among the four quartiles (79.6%, 71.9%, 64.5%, and 76.6% from 1st to 4th quartile, p = 0.1). There was no difference in proportion of oncologists working on visa among the 4 quartiles of OD (7.2%, 4.9%, 5.4%, and 6.4% from 1st to 4th quartile, p = 0.5). Conclusions: Patients in areas with higher OD have better overall survival. MUA or HPSA designation is not concordant with OD in different FIPS code areas. The Conrad-30 program is not promoting placement of oncologists on visa in areas with low OD. The Conrad-30 program should be amended to create designated spots for oncologists in each state proportionate to underserved population.
Background: Studies show that cancer patients from rural areas have worse cancer outcomes than their urban counterparts. But studies relying on cancer population data are unable to account for differences in access to care. In contrast, clinical trial patients receive protocol-directed care by design, so large clinical trial databases are ideal for examining the impact of residency on outcomes. Methods: We compared the geographic distribution and survival outcomes for rural versus urban cancer clinical trial patients. We examined 36,995 patients from all 50 states enrolled in 44 phase III or II-III SWOG treatment trials from 1986-2012, comprising 17 different cancer-specific analysis cohorts. We examined overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS) for patients by rural/urban status to determine if residency – based on Rural-Urban Continuum Codes (RUCCs) – was associated with outcome. We used multivariate Cox regression to estimate the association of residency and survival outcomes, controlling for major disease-specific prognostic factors and demographic variables and stratifying by study. Different definitions of rurality were examined. The distribution of rural vs. urban was well represented within major geographic regions. Clinical prognostic factors were very similar. In multivariable regression, rural patients with advanced-stage ER-PR- breast cancer had worse OS (HR = 1.27, p = .008) and CSS (HR = 1.26, p = .02). No other statistically significant differences were found. Results: Overall, 19% of patients were from rural locations, the same as the rate of rural individuals in the U.S. Rural patients were older (≥65 years, 31% vs. 27%, p < .01) and less likely to be African American (5% vs. 12%, p < .01), but were similar with respect to sex (40% each) and were well represented within major geographic regions. Clinical prognostic factors were very similar. In multivariable regression, rural patients with advanced-stage ER-PR- breast cancer had worse OS (HR = 1.27, p = .008) and CSS (HR = 1.26, p = .02). No other statistically significant differences were found. Results: We observed variation in hospice use by cancer type ranging from 49.11% (prostate cancer) to 66.84% (pancreatic cancer) to 72.01%. The median LOS ranged from 8 days (liver cancer) to 16 days (colorectal cancer). Similar results were found for the 12 month CE cohort. Conclusions: In our database, a majority of the non-elderly oncology patients received some hospice. We observed that over a third of the patients that received hospice had short LOS (<7 days), representing an opportunity for quality improvement. More studies are needed to improve the quality of EOL care for non-Medicare oncology patients in the U.S.
Prevalence of quality of life (QoL) outcomes and association with survival in cancer clinical trials. First Author: Bishal Gyawali, Program on Regulation, Therapeutics and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women’s Hospital, Boston, MA

**Background:** QoL outcomes provide essential information for patients and physicians in oncology care, but these data are not always reported in pivotal trials of new therapies. We investigated the prevalence of quality of life outcomes in modern cancer drug trials and the relation, if any, between quality of life and surrogate endpoints. **Methods:** Retrospective cohort study of all phase III clinical trials of drugs for advanced or metastatic solid tumors published between 2010 and 2015. We investigated the inclusion and reporting of QoL endpoints in clinical trials of cancer drugs and the association between positive progression-free survival (PFS) and QoL outcomes. **Results:** Of the 352 Phase 3 trials included, 147 (42%) reported QoL outcomes. There were 162 (46%) that did not include a QoL endpoint and 43 (12%) that did not report pre-specified QoL endpoints, cumulatively enrolling a total of 125,962 patients. Factors significantly associated with lower rates of inclusion of QoL endpoints were cancer type (head and neck and other solid malignancies), primary endpoints of response rates or non-PFS surrogate endpoints, and smaller trials that reported QoL outcomes, 99 (67%) reported no effect, 38 (26%) reported a positive effect, and 10 (7%) reported a negative effect of treatment on patients’ global QoL. The correlation between PFS and positive QoL was low (r = 0.34; area under the curve [AUC]: 0.72). **Conclusions:** Despite the pervasive use of treatments in the advanced/metastatic setting, the lack of appetite (4+: 1), nausea (4+: 1), and tiredness (4+: 1). Among the 10 most common non-hematological cancers, we found that 35% of the patients were females, 36% were < 65 years, and 79% were Caucasian. Del17p was similar within all cohorts. AEs were the most common discontinuation reason in all ibr groups, while CLL progression was most common in ven patients. A higher proportion of M discontinued ven vs F (34% vs 17%). Table 1 includes ORR, PFS, OS and DC stratified by age, sex and race. **Conclusions:** PROACT identifies factors that predict AC30 in patients with solid tumors starting systemic treatment and could be incorporated into electronic health records to select patients for preventative interventions. (AC30 by PROACT score,

Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

**Background:** Emergency department (ED) visits and hospitalizations are undesirable and costly. We developed and validated the PROACT (Prediction Of Acute Care use during Cancer Treatment) score to predict at least one acute care visit during the first 30 days (AC30) after initiating systemic therapy for cancer. **Methods:** Using administrative data, we identified patients in Ontario with the 18 most common non-hematological cancers who initiated non-hormonal systemic treatment regimens between July 1, 2014 and June 30, 2015, randomly split into development and validation cohorts. We created a score to predict AC30 using multivariate logistic regression and backward covariate selection in the development cohort. Combinations of tumor sites and regimens were grouped into quintiles based on AC30. The score was assessed in the validation cohort. **Results:** AC30 occurred in 21% (3561/17144) of patients. Eleven factors predicted AC30 in the development cohort and formed the score: tumor site and regimen (2nd quintile: 2; 3rd-4th: 3; 5th: 4); Aggregated Diagnosis Group comorbidity index (6-10; 1; 11-22); recent/current radiation (1), female sex (1), recent ED visit (1), rural residence (1), local health integration network (0,1 or 2), and Edmonton Symptom Assessment Scale anxiety (4-5). **Conclusions:** PROACT identifies factors that predict AC30 in patients with solid tumors starting systemic treatment and could be incorporated into electronic health records to select patients for preventative interventions.

Poster Session (Board #402), Sat, 1:15 PM-4:45 PM

Racial, age, and sex disparities in chronic lymphocytic leukemia (CLL) patients treated with novel therapies. First Author: Meghan Thompson, Hospital of the University of Pennsylvania, Philadelphia, PA

**Background:** Differences in outcomes have been reported in CLL pts receiving chemotherapy compared to non-Caucasians and males having inferior outcomes. Less is known if such disparities exist for pts receiving targeted therapies. We investigated how demographics impact outcomes of CLL pts treated with targeted agents. **Methods:** We analyzed 3 multicenter, retrospective cohort studies of CLL pts treated with brutinib (ibr-front line [F/L] or relapsed/refractory [R/R] disease) or venetoclax (ven) (R/R disease). Baseline demographics, responses (ORR), discontinuations (DC), progression-free survival (PFS), and overall survival (OS) were stratified by age (< 65 vs ≥65 yr), sex (male vs female) and race (Caucasian vs other). Cox regression was used for comparisons. **Results:** 1068 pts were included: F/L ibr (n = 391), R/R ibr (n = 536), R/R ven (n = 141). F/L ibr pts were 38% F, 59% age ≥65 and 8% non-Caucasian. R/R ibr pts were 37% age ≥65 (sex/race data unavailable), R/R ven pts were 34% F, 63% age ≥65 and 13% non-Caucasian. Del17p was similar within all cohorts. AEs were the most common discontinuation (DC) reason in all ibr groups, while CLL progression was most common in ven pts. A higher proportion of M discontinued ven vs F (34% vs 17%). Table 1 includes ORR, PFS, OS and DC stratified by age, sex, and race. **Conclusions:** In the largest series of pts treated with novel agents, we did not find differences in outcomes when stratified by age, sex and race. These data suggest ibr and ven may play in part overall traditional disparities.

Poster Session (Board #399), Sat, 1:15 PM-4:45 PM

Validity of using cancer registry data for comparative effectiveness research. First Author: Zachary David Guss, University of California, San Diego School of Medicine, La Jolla, CA

**Background:** Researchers often use cancer registry data to compare survival for different treatment options in clinical situations where higher level evidence does not exist. However, the retrospective non-randomized approach using cancer registry data for comparative effectiveness research raises important questions about study validity. The purpose of this project was to determine whether retrospective research with cancer registry data produces results concordant with randomized controlled trials (RCTs). **Methods:** Landmark RCTs involving surgery, systemic therapy or radiation were identified for nine common tumor sites including gastrointestinal, breast, lung, prostate, lymphoma, pharynx, gynecologic, head and neck, and central nervous system. We identified experimental and control arms for each trial and recreated these arms using patients from the National Cancer Database (NCDB), matching eligibility criteria from the trial whenever possible. We used multivariable Cox regressions to determine hazard ratios for overall survival for each trial. The multivariable analyses controlled for potential confounders including clinical and tumor variables. We compared hazard ratios from the NCDB analyses with hazard ratios from RCTs. **Results:** Eighty-six RCTs were identified and included in this analysis. Overall survival hazard ratios for forty RCTs (45%) were found to be outside the 95% confidence interval reported for the RCTs. Fifty-one (59%) of the RCTs found no significant difference in overall survival between treatment arms, and among these trials 73% (73%) had significant findings showing the benefit of the experimental arm. While 15 (18%) of the RCTs found a significant difference in overall survival between treatment arms, and among these trials 12 (34%) found no significant difference in survival within NCDB. The discordant results between RCTs and NCDB did not differ by disease site or treatment modality. **Conclusions:** Comparative effectiveness analyses using NCDB frequently produce results discordant from existing RCTs. These results suggest that comparative effectiveness research emanating from cancer registry should be interpreted with caution.

Poster Session (Board #401), Sat, 1:15 PM-4:45 PM

Predicting acute care use following initiation of systemic therapy for solid tumors. First Author: Robert C Grant, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

**Background:** Despite the heterogeneous nature of solid tumors starting systemic treatment and could be incorporated into electronic health records to select patients for preventative interventions.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Overall response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) is an established early efficacy endpoint used in clinical trials. Comparison of real world tumor response (rTWR) and ORR can provide important insights for health professionals, regulators, and researchers. Methods: We retrospectively analyzed electronic health records (EHRs) of patients with metastatic or recurrent NSCLC treated with epidermal growth factor receptor (EGFR)-targeted therapy (afatinib or erlotinib) and a programmed cell death 1 (PD-1) inhibitor (nivolumab), as well as a subset of BRAF mutation (BRAFmut)–positive patients in the Flatiron (FIH) EHR and FIH-Foundation Medicine (FMI) Clincio-Genomics database (CGDB) from 2011 to 2017. Structured and unstructured data elements from FIH EHRs were processed via technology-enabled abstraction. rTWR was based on abstraction of clinician’s assessment of radiographic evidence. Results: All patients with rTWR (CGDB, n=595; BRAFmut, n=30) were evaluated. Observed rTWR rates for the relevant patient populations are described in the Table. Conclusions: This analysis demonstrates the potential of leveraging routinely captured EHRs to advance rTWR treatment effectiveness in patients with NSCLC. These results show that rTWR for targeted and immunotherapies appear to correlate well with RECIST ORR rates in pivotal clinical studies matched by EGFR mutation status, treatment, and line of treatment. Future work includes expanding similar rTWR evaluation to more treatment contexts.

ORR by line of therapy

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<th>rTWR</th>
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<tbody>
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<td>56% (14/25)</td>
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<td>35% (7/20)</td>
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6580 Poster Session (Board #405), Sat, 1:15 PM-4:45 PM

Toward understanding toxicity over time (ToxT) in myeloma cooperative group trials: Feasibility of a novel longitudinal adverse event analysis in ECOG-ACRIN E1A06. First Author: Susanna J. Jacobus, Dana-Farber Cancer Institute, Boston, MA

Background: Given the many chronically administered agents now used in cancer therapy, there is pressing need to elucidate safety and tolerability of therapy over time. Conventional methods of evaluating adverse events (AEs) focus on the incidence of high grade toxicity. The Toxicity over Time (ToxT) analytic approach captures AE time profile within treatment arms, plus quantifies the impact accounting for AE onset, duration and patterns of severity. ToxT has been applied to Alliance trials (Thanarajasingam et al, Lancet Oncol 2016). The goal of this study was to demonstrate feasibility of application of the ToxT statistical package to an ECOG-ACRIN trial. E1A06 was of interest given results of similar efficacy between treatment arms but significant differences in toxicity and quality of life as well as overall suboptimal treatment adherence. Methods: Newly diagnosed, transplant ineligible multiple myeloma pts were randomized to MPT (melphalan, prednisone, thalidomide) or mPR (lower dose melphalan, P, lenalidomide). Pts received 12 cycles of induction (I) followed by T or R maintenance until progression. Grade (G) 3+ non-hematologic (NH) and G4 hematologic (H) AE data were collected every cycle. Treatment-related AEs of high incidence during I were selected for initial evaluation. Analyses with ToxT incorporate Kaplan-Meier and repeated measures methods. Results: 306 pts were enrolled. G3+ NH toxicity rates over I were 36% mPR vs. 51% MPT. Median time to 1st occurrence for pts experiencing G3+ AEs was similar (48 days mPR vs. 54 days mPT) and associated with ECOG PS score and stage at baseline. Each arm had 14 cases of fatigue, occurring more gradually on MPT (37d vs. 55d). G4 leukaemia incidence rates were 4% mPR vs. 13% MPT, with median onset 19d vs. 31d, respectively. Infection incidence rates were higher and onset earlier on MPT (8%, 79d vs. 14%, 46d). Conclusions: The feasibility of applying ToxT to an ECOG MM dataset was demonstrated. Longitudinal AE analysis has the potential to guide patient education on AEs and timing of symptom control interventions, ultimately improving tolerability of chronically administered cancer therapies.

6581 Poster Session (Board #406), Sat, 1:15 PM-4:45 PM

Assessing the difference in efficacy and effectiveness of cancer systemic treatment (tx): A comparison of clinical trial (CT) overall survival (OS) and toxicity data with population-based, real world (RW) OS data. First Author: Cameron Phillips, University of Toronto, Toronto, ON, Canada

Background: Often, when counseling patients on therapy, we utilize CT survival and toxicity data to help inform decision-making. While it is commonly believed CT data, derived from highly selected patients (pts), overestimates OS and underestimates toxicity compared with unselected patients in the RW, less is known about how often this occurs and the magnitude of this difference. We aim to quantify systematically the magnitude of OS and toxicity differences between CTs and population-based RW involving contemporary cancer systemic txs. Methods: All pts receiving IV cancer drugs with palliative intent indications that were first funded in Jan 2008 – Mar 2017 under Cancer Care Ontario’s New Drug Funding Program (NDFP) were identified. A literature search was performed to identify landmark CTs with established OS efficacy data (e.g. median OS, 1-year OS rate or Kaplan-Meier OS curves) for each drug indication. Serious adverse event (SAE) rates were collected. Drug indications were included if the public funding criteria matched the CT’s eligibility criteria. RW OS and hospitalization (H) rates during treatment were ascertained by linking NDFP data to other population-based databases with end of follow-up at May 31, 2017. Results: 32 indications from 21 drugs (9 chemotherapy, 10 targeted therapies, 2 immunotherapy) involving 8,344 CT pts and 29,424 RW pts were included. 29 indications (91%) showed worse OS in the RW when compared to CTs with a median median OS difference of 4.4 months (IQR: 3.2-10.0) and a median 1-year OS difference of 12% (IQR: 8%-21%). Drugs used in the last-line setting had worse OS difference at 1-year (22% vs. 11%). The median difference between RW H and CT SAEs was 12% (IQR: 6%-21%). Conclusions: In most cases, substantially worse OS and greater toxicity were observed in the RW compared to CTs. This study has established a catalogue of population-based OS and H for pts receiving contemporary cancer systemic txs, and provides more relevant information for health-care providers when counseling pts on survival expectations prior to the initiation of systemic txs in the real world.
Background: Little is known about the associations between enrollment in high-deductible health plans (HDHP) and access to care, spending, and health care utilization among working age cancer survivors. Methods: The 2010 to 2015 National Health Interview Survey was used to identify privately insured working age (18-64 years) cancer survivors (HDHP n = 1170; low-deductible health plan [LDHP] n = 2084) and those without a cancer history (HDHP n = 23,548; LDHP n = 50,251). We used multivariable logistic regression to examine associations between HDHP status, cancer history and three measures: reduced access to care for financial reasons, high out-of-pocket (OOP) spending, and hospital emergency department (ED) use. Predictive margins were generated to compare cancer survivors to those without a cancer history, stratified by HDHP status. Odds ratios (OR) were generated to compare HDHP to LDHP cancer survivors as well as the impact of health saving accounts (HSA) among HDHP enrollees.

Results: Among low income HDHP enrollees, cancer survivors were more likely to report reduced access to care (low income: OR = 2.18; high income: OR = 2.15); high OOP spending (low income: OR = 4.75; middle income: OR = 2.35; high income: OR = 2.05); and ED use (middle income: OR = 1.58, all p < .05). Among HDHP enrollees, HSA was associated with lower rates of reduced access to care (OR = .85) and ED use (OR = .88) and higher rate of high OOP spending (OR = 1.34, all p < .05), compared to HDHP enrollees without HSA. Conclusions: HDHP increases the risks of reduced access to care, high OOP spending, and ED use for cancer survivors, and the patterns vary by family income level. Future studies based on longitudinal data to investigate causal relationship is warranted, especially among low income working age cancer survivors enrolled in HDHPs.

Results:

Outcome

Control

Cancer Survivors

Difference

P value

Access to care

0.87

0.94

0.07

0.39

ED use

0.90

0.93

0.02

0.41

OOP spending

1.01

1.12

0.12

0.04

Conclusions:

- HDHP enrollees were more likely to report reduced access to care, high OOP spending, and ED use for cancer survivors, and the patterns vary by family income level.

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Poster Session (Board #411), Sat, 1:15 PM-4:45 PM

A novel approach to mine the Veterans Administration Informatics and Computing Infrastructure (VINCI) allows one to assess the efficacy of cancer therapies. Abiraterone and enzalutamide in Veterans with metastatic prostate cancer (PC). First Author: Harshraj Leuva, James J Peters VAMC, Bronx, NY, US

Background: Novel efficacy endpoints are needed that correlate with overall survival (OS) and can describe real world outcomes. Methods: We mined national VA data (VINCI) using a novel set of equations validated in >10,000 patients that estimate simultaneously occurring exponential rates of tumor growth [g] and regression [δ] using data gathered while a patient receives cancer treatment. We have previously established that g is highly correlated with OS and can estimate mating doubling time (dt). Importantly, since the equations include time as a variable, this approach is ideal for real world analyses where re-assessments depend on the practitioner and are highly variable. To validate g in a real-world cohort, we collected cases of PC, demographics, treatments and outcomes from VINCI and compared parameters by receipt of chemotherapies for PC. Results: 5,890 Veterans were treated with abiraterone (ABI), enzalutamide (ENZA) or both. Median age was 75 years including 2,596 Veterans >80 years, and 23% identified as African American (AA). PSA values beyond the initial measurement were available in 88% of patients with little clinical difference between those with and those without serial PSA values, g and could be estimated in 83-85% Veterans with p-values for fits <0.1 in all and <0.001 in the majority. g values for Veterans receiving either ABI [0.0038d−1; dt 182d] or ENZA [0.0040d−1; dt 173d] in first line were indistinguishable (p = 0.27), suggesting comparable efficacy. Consistent with the clinical bias, in second line, ENZA [0.0071d−1; dt 98d] appears superior to ABI [0.0091d−1; dt 76d] (p < 0.01). However, preliminary analyses find g on 1st line ABI remains constant in the majority and ABI continuation may be beneficial. Importantly g was independent of age, treatment location, and race, demonstrating comparable benefit in older and non-AA Veterans. Conclusions: g is the largest real-world assessment of ABI and ENZA efficacy in PC with a high percentage of AAs. The results underscore the value of determining g as an excellent measure of efficacy and argue for its use in outcomes research.

Poster Session (Board #412), Sat, 1:15 PM-4:45 PM

Cancer patient-reported knowledge and preferences for liquid biopsies and blood biomarkers at a comprehensive cancer centre. First Author: Min-Joon Lee, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Novel blood-based biomarkers, including cell-free DNA and plasma signatures, are becoming a reality in precision oncology. Yet, little is known about cancer patients’ perspectives on blood biomarkers in clinical practice. Methods: A 54-item self-administered questionnaire and four interviewer-administered trade-off scenarios were administered to cancer patients across all sites of diagnosis (Margaret Cancer Centre. Results: Of 632 eligible patients, 66% (n = 417) completed the survey; 54% female; median age 61 (range 18-101) years. Patients had a median accuracy score of 18% (range 0-81%) on their knowledge of the role of biomarkers on their own cancer. Disease site was significantly associated with knowledge (P = 0.029); patients with breast, genitourinary, and thoracic cancers performed better than patients of other sites. Females (P = 0.012) and those with higher education (P = 0.019) and income (P = 0.0016) also scored better. Scores were not associated with the stage at diagnosis, time since diagnosis, age or ethnicity. Using chart review, 91% had been evaluated in at least one setting where they could choose a liquid (blood) over tissue biopsy; however, these patients only accepted a median waiting period of one additional week (IQR: 0-3 weeks) and a 5% decrease (IQR 0-10%) in sensitivity of identifying the right treatment before switching their preference to the tissue biopsy. The majority (n = 216; 58%) were not interested in switching even with no potential complications from tissue biopsy. People with higher education were more likely to switch based on the level of risk (P = 0.001).

Conclusions: Although patients had limited understanding of their cancer-specific liquid blood-based biomarkers, 90% preferred a liquid over tissue biopsy; however, these patients only accepted a median waiting period of one additional week (IQR: 0-3 weeks) and a 5% decrease (IQR 0-10%) in sensitivity of identifying the right treatment before switching their preference to the tissue biopsy. The majority (n = 216; 58%) were not interested in switching even with no potential complications from tissue biopsy. People with higher education were more likely to switch based on the level of risk (P = 0.001).

Poster Session (Board #413), Sat, 1:15 PM-4:45 PM

Safety and tolerability of cancer drugs studied in phase 3 randomized controlled trials (RCTs) over the last decade. First Author: Domen Ribnikar, Institute of Oncology, Ljubljana, Slovenia

Background: Data suggest that newly approved cancer drugs have worse safety and tolerability profiles than older drugs used as control groups in trials. However, less is known about the toxicity profile of cancer drugs studied in unsellected phase 3 clinical trials including those not resulting in regulatory approval. Methods: We searched clinicaltrials.gov to identify phase 3 RCTs evaluating experimental drugs in patients with metastatic breast, colorectal, lung and prostate cancer. We included all RCTs completed between 1 January 2005 and 31 October 2016. Odds ratios (OR) and 95% CI were computed for the following safety and tolerability end points: toxic death, treatment discontinuation without progression and commonly reported grade 3-4 adverse events (AEs). Data were then pooled in a meta-analysis using RevMan 5.3 software. Results: The analysis included 143 RCTs comprising 88,603 patients. 75% of the trials evaluated targeted therapies (including endocrine and immunotherapy). Compared to control groups, experimental drugs were associated with higher odds of toxic death (OR, 1.14; 95% CI, 1.03-1.27), treatment discontinuation without progression (OR, 1.64; 95% CI, 1.56-1.71) and grade 3-4 AEs (see Table). Conclusions: New cancer drugs studied in phase 3 RCTs are associated with worse safety and tolerability profiles compared to standard therapies when reported by investigators and have increased treatment-related mortality. Cancer patients considering enrolment on phase 3 trials should be aware of this risks.

Poster Session (Board #414), Sat, 1:15 PM-4:45 PM

Classifying lung cancer stage from health care claims with a clinical algorithm or a machine-learning approach. First Author: Gabriel A. Brooks, Dana-Farber Cancer Institute, Boston, MA

Background: Cancer stage is a critical determinant of cancer outcomes, however stage is not available in claims-based data sources used for evaluating real-world outcomes. We compared two new methods for classifying lung cancer stage from claims data. Methods: We used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify patients with lung cancer diagnosis in 2011-12 who received chemotherapy within 6 months of diagnosis. We developed two approaches for using claims records to classify stage group (AJCC stage 1-3 vs. stage 4), using SEER stage as the gold standard. The first method was a clinical algorithm that assigned stage group based on treatment received (inclusive of surgery, radiation, and chemotherapy). The second method employed an ensemble of machine learning algorithms and analyzed an expanded set of claims-derived variables that considered treatments received, inpatient and outpatient visits, diagnosis codes, and demographic variables. We then used the Least Absolute Shrinkage and Selection Operator to select parsimonious variable sets of ≤ 10, 15, 20, 30, 40, and 50 variables. Classification methods were evaluated and compared on the basis of sensitivity, specificity, and accuracy, in reference to the stage 1-3 group. Results: The study sample included 14,743 patients with a mean age of 72.1 years. 54.6% were male. The best performing machine-learning classifier was the random forests algorithm. Sensitivity, specificity, and accuracy for the clinical algorithm were 53% (95% CI = 52-54%), 89% (88-90%), and 71% (71-72%), vs. 91% (90-92%), 89% (88-90%), and 90% (90-91%) for the random forests with 15 variables. Key variables for the random forest included secondary malignancy codes, treatments received (including type of surgery, number of radiation fractions, and specific chemotherapies), presence of COPD, and geographic region. Conclusions: Compared with a clinically derived algorithm, a machine-learning classifier demonstrated substantially improved sensitivity and accuracy. Improved accuracy of claims-based stage classification can support clinically relevant, real-world analyses of cancer care quality and outcomes.

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6590 Poster Session (Board #415), Sat, 1:15 PM-4:45 PM

Development of a dashboard for end-of-life care at an academic hospital. First Author: Kerin B. Adelson, Yale University, New Haven, CT

Background: Accurate, reproducible, transparent and continuous healthcare utilization measures derived from structured EHR data may facilitate higher value cancer care at the end of life in both community and academic settings. Prior manually abstracted data from Smilow Cancer Hospital at Yale-New Haven showed high rates of chemotherapy and hospital utilization within 30 days of death. However, these data were not actionable due to the challenges with manual collection, physician attribution and traceability of death.

Methods: The Yale Smilow Cancer Hospital and Flatiron Health used a commercially-available obituary source to supplement EHR data for a cohort of patients who received care at Smilow and died in 2016 - 2017. We developed an algorithm to attribute each patient to the correct oncologist based on visit frequency. We then used structured EHR data to measure rates of utilization for the following measures within 30 days of death: inpatient admission, ICU, chemotherapy and immunotherapy. Automated reports with internal benchmarks were generated to summarize resource utilization by individual physician, disease team, and practice site with patient level detail. Prior to wide scale launch across our enterprise, we provided oncologists in our community based practices feedback on use of chemotherapy in the last 30 days of life.

Results: We found high rates of utilization at the end of life at both academic and community sites, and were able to identify outliers at the site of care, disease team and physician level. In the group that received quarterly feedback on chemotherapy in the last 30 days of life, we saw a 23% improvement in performance (see table). Performance dashboards with patient-level granularity identify performance outliers and opportunities for care improvement interventions. The reusable date of death, physician attribution and dashboard infrastructure allows measurement over time and rapid development of new measures. Efforts are underway to apply this risk stratification to interpretation of practice variation, in addition to benchmarking against a national patient sample.

Chemotherapy in final 30 days. 

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6592 Poster Session (Board #417), Sat, 1:15 PM-4:45 PM

The impact of the ASCO Choosing Wisely campaign for breast and prostate cancer on physician behavior. First Author: Danielle Lee Rodin, Harvard T.H. Chan School of Public Health, Boston, MA

Background: In April 2012, ASCO published its Choosing Wisely (CW) list of low-value services not supported by clinical evidence. The effectiveness of this campaign in changing physician behavior in oncology remains unknown.

Methods: Retrospective analysis of breast and prostate cancer patients diagnosed from 2010-2013 and contained in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Quarterly rates of imaging tests (positional CT, mammography, bone scans) for staging and post-treatment surveillance in early-stage breast cancer (AJCC I and II) were calculated. Performance of oncologists was measured by the proportion of patients receiving low-value tests before and after publication of the CW recommendations was evaluated using interrupted time series analysis.

Results: The cohorts consisted of 14,596 prostate, 43,991 breast staging, and 32,548 breast surveillance patients. Use of staging tests for prostate cancer was declining pre-CW (0.52% per quarter) and experienced a small, but significant increase in the rate of decline post-CW to -0.79% per quarter, P = 0.0013; average use was 26.5% of patients pre-CW and 20.7% post-CW. Use of surveillance imaging for breast cancer was stable pre-CW at 25.2%; it decreased post-publication by -0.61 percentage points per quarter (P < 0.001) to 21.3% post. No significant change in use of breast cancer staging was observed (-0.05% per quarter, P = 0.37), with an average utilization rate of 10%. Low-value test orders by specialty and physician were presented in Table 1. Conclusions: Following CW, there was a modest change in some physician behaviors toward recommendations. Further multidisciplinary efforts coupled with incentives may be needed to educate providers on judicious use of imaging.

6593 Poster Session (Board #418), Sat, 1:15 PM-4:45 PM

Use of hypofractionated radiotherapy for early stage breast cancer after implementation of evidence based clinical guidelines. First Author: Santosh Gautam, HealthCore, Inc., Wilmington, DE

Background: Evidence-based guidelines have endorsed use of hypofractionated whole breast irradiation (WBI), a shorter course regimen delivered over 3-4 weeks instead of conventional WBI over 5-6 weeks, for certain early stage breast cancer patients. In 2016, health insurer Anthem updated its clinical guidelines making hypofractionated WBI the standard for eligible members. In its fully-insured plans, this change did not apply to self-insured groups allowing these members to serve as an internal control. The objective of the study was to evaluate the impact of this guideline change on adoption of hypofractionated WBI.

Methods: We used Anthem claims data to identify women with incident breast cancer diagnosis followed by lumpectomy and subsequent WBI during 2015-2016. We further retained patients guideline-endorsed for hypofractionated WBI, i.e. those aged 50 or older, without prior chemotherapy or lymph node involvement. We defined hypofractionated WBI as 11-24 fractions (3-5 weeks of WBI) and conventional WBI as 25-40 (5-8 weeks of WBI). We compared pre- and post-intervention (year 2015 vs 2016) hypofractionated WBI rates between members in fully insured plans (intervention group) and members in other plans (comparison group) using a regression-adjusted difference-in-difference (DID) analysis controlling for age and comorbid conditions.

Results: Compared to patients in comparison group (N = 2,333), those in intervention group (N = 728) were older (mean age 63.1 vs 61.4; p < .0001) and had more comorbid conditions (mean Deyo-Charlson index 0.74 vs 0.60; p = 0.002). The rate of hypofractionated WBI increased from 53% in pre- to 68% post-intervention period for intervention group, an increase of 28%. In contrast, the rate changed from 58% to 63%, an increase of just 9%, in comparison group. The adjusted DID results suggested that change in guidelines increased the hypofractionated WBI adoption rate by 9% (p = 0.035).

Conclusions: The changes in health plan guidelines resulted in higher rates of hypofractionated WBI adoption. Health plans could play an important role in accelerated adoption of evidence-based guidelines.
6594 Poster Session (Board #419), Sat, 1:15 PM-4:45 PM
CYP2C19-guided voriconazole prophylaxis in neutropenic AML patients. 
First Author: James Kevin Hicks, Moffitt Cancer Center, Tampa, FL

Background: Acute myeloid leukemia (AML) patients who have prolonged neutropenia are at increased risk of morbidity and mortality due to invasive fungal infections. Voriconazole (VCZ), an effective antifungal prophylactic, is metabolized by the polymorphic CYP2C19 enzyme. Approximately 25% of individuals are genetically predicted to be CYP2C19 rapid metabolizers, thus at increased risk of breakthrough fungal infections due to low VCZ concentrations. We implemented a quality improvement pilot utilizing CYP2C19 genotyping to optimize prophylactic VCZ dosing. Methods: AML patients with prolonged neutropenia are eligible for CYP2C19 genotyping (Luminex xTAG CYP2C19 Kit v3). Phenotypes are assigned per Clinical Pharmacogenetics Implementation Consortium guidelines. CYP2C19-guided recommendations for our quality improvement pilot are as follows: avoidance of VCZ in ultrarapid metabolizers, VCZ 300 mg twice daily (BID) for rapid metabolizers, and VCZ 200 mg BID for all other phenotypes. Therapeutic drug monitoring (TDM) is performed at the discretion of the medical team (goal trough concentration of 1-5.5 mcg/ml). Results: To date, 193 AML patients have undergone CYP2C19 genotyping; 3 (1.6%) ultra-rapid, 50 (25.9%) rapid, 78 (40.4%) normal, 55 (28.5%) intermediate, and 7 (3.6%) poor metabolizers were observed. 154 patients (79.8%) received VCZ for prophylaxis, 11 (5.7%) for treatment, and 28 (14.5%) did not receive VCZ. Of the 154 patients receiving prophylactic VCZ, 137 (89%) were dosed per CYP2C19-guided recommendations. Pre-intervention (VCZ 200 mg BID) and post-intervention (VCZ 300 mg BID) VCZ trough concentrations were compared. Only 36.4% (4/11) of CYP2C19 rapid metabolizers receiving VCZ 200 mg BID achieved the goal trough concentration, whereas 75% (21/28) of rapid metabolizers receiving VCZ 200 mg BID achieved the goal trough concentration. CYP2C19-guided dosing resulted in 110 patients (56.4%) improving to the goal concentration. Conclusions: Implementation of CYP2C19 genotyping to guide VCZ prophylactic dosing is feasible, with 70.1% of all patients having a VCZ goal trough concentration. Future analysis will determine if CYP2C19-guided VCZ dosing prevents breakthrough fungal infections.

6595 Poster Session (Board #420), Sat, 1:15 PM-4:45 PM
Does training oncologists to have goals of care discussions affect healthcare utilization among patients with advanced cancer? First Author: Nina A. Bickell, Mount Sinai School of Medicine, New York, NY

Background: Aggressive treatment near the end of life is a measure of poor quality care. Goals of Care (GoC) discussions may affect healthcare utilization among patients with advanced cancer. We coached oncologists to improve communication skills (CS) & report the effect of CS coaching on hospital, ER, hospice & ICU admission in the last month of life. Methods: We randomized solid tumor oncologists at 4 academic, community, municipal and academic hospitals to participate in a RCT of communication skills training & recruited their newly diagnosed advanced cancer patients with < 2 year prognosis. Ten CSs were assessed via checklist review of audiotaped visits. Charts were abstracted, patients or their caregivers were surveyed at 6 months to assess utilization of: chemotherapy, ICU, hospitalizations, ER visits and hospice in the last 30d of life and over the 6 months enrolled in the study. A GoC discussion included discussion of prognosis, treatment preferences, and what’s important to patients given their cancer diagnosis. We enrolled 22 of 25 eligible oncologists (88%). 263 patients were recruited & surveyed to assess whether a GoC discussion occurred. 250 (95%) had charts abstracted and we surveyed patients to assess utilization at other hospitals. Results: Patients’ mean age was 63 yrs (20-89), 60% male, 53% white, 29% black & 19% Latino. 35 patients (13%) died within 6 months of baseline survey with no difference between patients of intervention (INT) vs control (CNTL) oncologists. Compared to CNTLs, INT oncologists’ skills improved 11.6% (3.2-19.8) on average. 46% INT patients reported a GoC discussion. The average rate of hospitalization/ pt = 0.32 (0-3) & ER visits = 0.44 (0-4) with no difference between INT & CNTL. Rates of aggressive treatment in the last 30d of life varied: chemotherapy = 21%; ICU stay = 7% with no difference between INT & CNTL patients. Hospice engagement occurred 2 weeks prior to death; no difference in INT vs CNT (13.5d v 14d). Conclusions: Despite improving oncologists’ communication skills to conduct GoC discussions, there was no impact on rates of hospitalization, receipt of aggressive treatments or enrollment in hospice at the end of life. Clinical trial information: NCT02374255.

6596 Poster Session (Board #421), Sat, 1:15 PM-4:45 PM
Improving documentation of pain and constipation management within the cancer center of a large public healthcare network. First Author: Giselle Dutcher, Department of Medicine, Emory University School of Medicine, Atlanta, GA

Background: Cancer patients commonly suffer from pain and constipation, and a high number of patients have inadequate control of these symptoms. At the Cancer Center for Excellence at Grady Health System, a large public healthcare network in Atlanta, baseline QOPI measures for pain and constipation documentation were below benchmark levels. We conducted a quality improvement (QI) initiative to improve the management of pain and constipation. Methods: Given the low baseline rates of QOPI documentation for pain (58%) and constipation (60%) assessment, we aimed for a 20%-percentage point increase in documentation of these measures. Cause and effect analysis identified causal factors. This led the team to develop a new note template that automatically integrates pain and constipation assessment data from the nursing note into the practitioner’s documentation. We developed a new process in the electronic medical record (EPIC) to link appropriate orders with the pain and constipation plan. Mandatory use of the new note began in June 2017. We reviewed documentation pre- (12 months) and post- (4 months) intervention. Results: Integrating a nursing assessment into the note for the practitioner increased pain score documentation from 66% to 87% and pain management from 47.2% to 83.2%. Similarly, documentation of constipation assessment increased from 18.9% to 82.8% and constipation management increased from 11.78% to 75%. This QI intervention improved pain control by the 3rd visit from 47% to 57%. This strategy also reduced emergency department (ED) visits and hospitalizations from 21% to 9%. Conclusions: Using a standardized visit template and mandated assessment of constipation and pain lead to an increase greater than the 20% goal for documentation of these symptoms. This intervention resulted in improved pain and constipation management in oncology practice and this strategy suggests a reduction in ED visits.

6597 Poster Session (Board #422), Sat, 1:15 PM-4:45 PM
Does training oncologists to have goals of care discussions increase and improve the quality of discussions with advanced cancer patients? First Author: Nina A. Bickell, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Advanced cancer patients often have a poor understanding of the incurability of their cancers and this correlates to higher rates of aggressive treatment near end of life. Goals of Care (GoC) discussions may affect patients’ decisions about aggressive treatment near end of life. We coached oncologists to improve communication skills and assessed its impact on prevalence and quality of GoC discussions. Methods: At an academic, community, municipal and rural hospital, we recruited & randomized solid tumor oncologists & their newly diagnosed advanced cancer patients with < 2 year prognosis. Prior to and after completing 4 coaching sessions, a post-imaging visit was audiotaped and reviewed by VitalTalk trained specialists to assess oncologists’ communication skills. Consented patients were surveyed after their 3 month post-imaging visit & GoC discussions defined as: cancer treatment preferences, what’s important to you in life given your diagnosis and prognosis. Results: We enrolled 22/25 eligible oncologists (88%) & 265 patients. On average, doctors were 44 yrs old (32-66) & in practice 14.5yrs (5-40). There was no significant difference between intervention (INT) and control (CNTL) oncologists’ prior communication skills training (58% v 56%; p = 0.80) & comfort having GoC discussions (58% v 56%; p = 0.80). On average, CNTL physicians had no change in the number of demonstrated skills (5.45 to 5.36/10); INT physicians increased from 6.6 to 8.3/10 skills (p = 0.04). Patients’ mean age was 63 yrs (20-89), 60% male, 52% white, 30% black & 19% Latino. Overall, 61% of patients reported their treatment’s goal was to cure their cancer; 40% reported cure to be likely, 48% had a complete GoC discussion (48% INT v 51%; p = 0.61). 65% of patients reported their oncologist talked about their GoC, “the very best” they could imagine (63% INT v 68% CNTL; p = 0.39). 51% did not report a GoC discussion with no difference between INT (52%) & CNTL (49%) patients (p = 0.61). Conclusions: Using a coaching model to teach oncologists’ communication skills improved skills to carry out a GoC discussion but did not increase rates of discussion or improvement among advanced cancer patients with < 2 year life expectancy. Clinical trial information: NCT02374255.
Background: QT interval prolongation, measured on ECG, is a known toxicity of many drugs used in oncology and can lead to serious arrhythmias. To our knowledge, there are no published studies investigating ECG use in pts on standard systemic tx involving QT drugs. Methods: All cancer pts ≥ 66 years diagnosed in 2005-2011 in the Ontario Cancer Registry and with a population-based administrative databases to ascertain pt demographics, comorbidities, systemic tx and ECG use. The Ontario Drug Benefit Program database was used to identify prescription QT drug use (as per CredibleMeds.org classification). Univariable and multivariable analyses were used to examine factors associated with EGCG use within 30 days of systemic tx initiation. Results: A total of 59,484 pts (median age 74; 48% women) were included. Common cancers were breast (23%), prostate (22%), lung (10%) and colon (9%). Prior diagnoses included hypertension (56%), diabetes (24%), coronary artery disease (CAD; 24%), and heart failure (20%). Among pts on at least 1 QT drug (n = 43,236; 81%), the majority (n = 41,727; 87%) received a prescription within 30 days of systemic tx initiation, commonly for anti-emics (n = 18,232; 44%). Overall, only 27% pts on QT drugs had an ECG within 30 days of systemic tx initiation; ECG use was low even among pts with CAD (35%), HF (42%), and pts on ≥3 concurrent QT drugs (37%) and pts on anti-emics (30%) and antiarrhythmics (20%). On multivariable analysis, adjusting for age, sex, comorbidities, rural setting and cancer type, ECG use was associated with recent cancer diagnosis (2011 versus 2005; OR = 1.37; 95% CI 1.26-1.49), Charlson score ≥1 (OR = 1.22; 95% CI 1.15-1.29) and multiple QT drugs (OR = 1.15 each additional QT drug). Anti-emics (OR = 1.31-1.17), and antiarrhythmics (OR = 0.93; 95% CI 0.88-0.99) and anti-ancer QT drugs (OR = 0.74, 95% CI 0.70-0.79) were paradoxically associated with fewer ECG use. Conclusions: Our study highlights common use of QT drugs and under-use of ECG in cancer pts at risk of arrhythmia. Since ECG is an inexpensive, non-invasive and widely available test, it should be used routinely for monitoring the QT interval in such pts.
A nationwide analysis of palliative care service utilization in hospitalized metastatic cancer patients. First Author: Kaushal Parikh, New York Medical College, Valhalla, NY

Background: ASCO guidelines recommend palliative care consultation (PC) to patients with advanced cancer to improve quality of life and overall survival. However, limited data are available on contemporary trends in PC utilization in hospitalized metastatic cancer patients. Methods: We used the 2005-2014 United States National Inpatient Sample to identify all hospitalizations in adult patients with a primary or secondary discharge diagnosis of lung, prostate, breast, or colorectal cancer with documented metastasis. Multivariable logistic regression models accounting for the complex survey design were used to analyze associations of PC with various cancer related complications, comorbidities, and patient and hospital demographics. Results: Of the 3,040,740 cases included in the study, 289,600 (9.5%) had PC. Median ages of patients with prostate, lung, colorectal, and breast cancers were 76, 67, 65, and 61 years, respectively. There was a 550% increase in PC utilization between 2005 and 2014 (2.7% to 17.5%; P < 0.001). While the utilization rate was highest with metastatic lung cancer (3% in 2005 to 20.2% in 2014; P < 0.001), increase in utilization was highest for colon cancer (577%; 2.2% in 2005 to 14.9% in 2014; P < 0.001). Overall, cancer related pain (adjusted Odds ratio (aOR) 2.35, 95% confidence interval (CI) 2.26-2.45; P < 0.05) and failure to thrive (aOR 2.19, 95% CI 2.09-2.29; P < 0.05) were strongly associated with PC referrals. Age > 65 years (aOR 1.56, 95% CI 1.46-1.67; P < 0.05), respiratory failure (aOR 2.10, 95% CI 2.03-2.16; P < 0.05), and sepsis (aOR 1.12, 95% CI 1.078-1.16; P < 0.05) were also independently associated with PC. PC was more likely to be utilized in teaching hospitals (aOR 1.25, 95% CI 1.16-1.34; P < 0.05), large-sized hospitals (aOR 1.25, 95% CI 1.13-1.37; P < 0.05), and west coast hospitals (aOR 1.31, 95% CI 1.17-1.47; P < 0.05). Conclusions: Despite a significant rise between 2005 and 2014, palliative care services are still underutilized for hospitalized advanced cancer patients in the United States. Cancer related pain and failure to thrive were strongly associated with PC utilization. Regional and hospital based variations exist in PC utilization in patients with metastatic tumors.

Utilization of telemedicine at two high-volume cancer care organizations. First Author: Rob Williams, Ontario Telemedicine Network, Toronto, ON, Canada

Background: The Ontario Telemedicine Network (OTN) in Support of Cancer Care Ontario (CCO), and Memorial Sloan Kettering (MSK) are leveraging telemedicine and digital health care to improve patient/provider satisfaction, care coordination, and clinical outcomes, while decreasing costs. Methods: Data on patient telemedicine services and provider activity was reviewed, in addition to implementation challenges and lessons learned. New virtual services were outlined regarding their ability to enhance patient accessibility and clinical effectiveness. Results: OTN has enabled 268 CCO sites across the 14 Ontario Regional cancer centers which have generated 20,138 cancer telemedicine sessions in 2016/17. Prostate, lung, breast, and colorectal cancers had the highest telemedicine utilization. Telemedicine sessions were employed by 20% (N = 40) of provincial radiation oncologists, and 20% (N = 34) of medical oncologists. In 2015, telemedicine supported the delivery of oral and intravenous chemotherapy in 1,269 cases and facilitated 368 palliative care visits. Telemedicine saved patients: 6.4 million km of driving, 64K hours of travel time, and over $4.7 million in travel and accommodation costs. MSK sees 19K new actively treated patients annually, 76% access the patient portal to view appointment notifications, complete patient assessments, review lab results, retrieve learning materials, send and receive secure messages from providers, and review billing. Patient assessments include PRO-CTCAE daily symptom surveys, with symptom alerts to track recovery in post-surgical patients. TeleGenetics at MSK has delivered 3416 virtual visits to patients and family members at four regional locations, telepsychiatry has supported 160 sessions to 3 regional sites; and an inpatient fall prevention program using video monitoring of a patient’s movements has decreased falls 42% in Gl and 34% in neurological cancer inpatients while decreasing patient attendant costs $393K. Conclusions: Utilization of telemedicine and digital care platforms among cancer patients and providers is steadily increasing due to convenience, significant cost savings, high satisfaction rates, increased care coordination, and improved clinical outcomes.

The effect of supervised, individualized exercise on cost savings during cancer treatment. First Author: Karen Wonders, Maple Tree Cancer Alliance, Dayton, OH

Background: Research indicates that endurance exercise training is helpful in attenuating the deleterious effects of cancer treatments. However, nationally less than 5% of patients are ever referred to a cancer exercise program. Cost is a barrier to these programs, as they often are not reimbursable under most insurance plans. Therefore, the purpose of this investigation was to determine if exercise training during cancer treatment helped to minimize side effects and reduce health care costs. Methods: This was a retrospective, two-group study which ascertained the protective effect of an exercise-training program during cancer treatment. Medical records were reviewed to determine outcome data for length of hospital stays, hospital readmits, ER visits, treatment compliance, fatigue, and anxiety/depression related to oncology conditions. Patients were excluded if they had pre-existing conditions prior to treatment. Individuals in the exercise group (EX, n = 672) completed 12 weeks of prescribed, individualized exercise. Individuals in the sedentary group (SED, n = 728) did not participate in an exercise program during treatment. Results: Patients in the EX group had significantly lower reports of fatigue, pain, cardiac problems, depression, and anxiety than their SED group counterparts (p < 0.05). The EX group tolerated their treatment significantly better than the SED group (p < 0.05). Most notable, the EX group had a significantly lower number of ER visits, 30-day readmits, and length of stay (p < 0.05). Conclusions: These data point to a protective effect of individualized exercise that translated to improved patient outcomes and cost savings for the payer, provider, and patients, alike.

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A proportional comparison of cancer burden and patient advocacy organization (PAO) funding by histology demonstrates many underfunded histologies. First Author: Subha Deepak Karanam, Northwestern Memorial, Feinberg School of Medicine, Division of Hematology/Oncology, Chicago, IL

Background: PAOs in oncology are vital in funding research for rare cancers, young investigators and innovative projects, but some histologies may be underfunded relative to their burden. This study examined the alignment of cancer burden by histology with PAO funding for each histology to raise awareness of areas of unmet need. Methods: The GuideStar database was used to find all cancer PAOs with ≥ $5 million in annual revenue (AR) in 2013-2015. We identified physicians who treated each of 4 cancer types which had multiple orally-administered treatment options: renal cell (axitinib, everolimus, pazopanib, sorafenib, sunitinib), lung (erlotinib, afatinib), CML (dasatinib, nilotinib), and prostate (abiraterone, enzalutamide). We used modified Poisson regression to test if the number of years (either 1, 2, or 3) in which a physician received payments was associated with increased prescribing of the paying company’s cancer drug in 2015. We also tested whether physicians at NCI-designated cancer centers were more likely to receive industry payments. Results: The physician cohort sizes were: RCC, 674; lung, 966; CML, 367; prostate, 1,483. Controlling for physician characteristics including annual income, prescribing volume, and total dollar amount received, physicians who received payments in all 3 years (vs. 1 year) were more likely to use the paying company’s drug within RCC (RR:1.69, 95%CI:1.32, 2.17) and lung cancer (RR: 1.42, 95%CI:1.15, 1.77), but not CML (RR:1.13, 95%CI:0.94, 1.35) or prostate cancer (RR: 0.93, 95%CI:0.72, 1.21). Results were similar comparing physicians who received payments in 3 years vs. 2 years: RCC RR:1.53, 95%CI:1.21, 1.94; lung RR: 1.12, 95%CI:0.93–1.35; CML RR:1.13, 95%CI:0.94–1.35; prostate RR: 0.93, 95%CI:0.85–1.01. Physicians at NCI institutions were less likely to have received any industry payments during the study period (RR:0.70, 95%CI:0.50–0.98). Conclusions: Longer-term industry relationships may be associated with greater changes in drug prescribing than time-limited ones. Conflict-of-interest policies and disclosures may be more informative if specifying duration of industry relationships. This study was limited by a short time range, and lack of payment records prior to 2013.

6009 Poster Session (Board #343), Sat, 1:15 PM-4:45 PM Cost-effectiveness analysis of brentuximab vedotin with chemotherapy in newly diagnosed stage III/IV Hodgkin lymphoma. First Author: Scott F. Huntington, Yale University, New Haven, CT

Background: In a recent randomized, open-label trial (ECHELON-1), brentuximab vedotin combined with doxorubicin, vinblatine, and dacarbazine (A+AVD) decreased the risk of progression in adults diagnosed with stage III/IV Hodgkin lymphoma (HL) compared to standard bleomycin-containing chemotherapy (ABVD). However, the cost-effectiveness of incorporating brentuximab vedotin into the first-line setting is unknown. Methods: We constructed a Markov decision-analytic model to measure the clinical and outcomes for A+AVD compared to ABVD as first-line therapy in a cohort of patients with stage III/IV HL. Progression-free survival and transition probabilities were estimated from ECHELON-1 by fitting parametric survival distributions. Centers for Medicare & Medicaid Drug Pricing Files from December 2017 were used for drug costs (106% of average sales price). Additional expenditures and clinical utilities were estimated from literature. Lifetime direct health care costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated for A+AVD compared with ABVD from a societal perspective within the United States. Our model was also used to estimate price reductions of brentuximab vedotin that would achieve more favorable cost-effectiveness under indication-specific pricing. Results: A+AVD was associated with an improvement of 0.48 QALYs compared to treatment with standard ABVD. However, incorporating brentuximab vedotin into first-line therapy led to significantly higher lifetime costs ($334,863 versus $193,780), causing the ICER for A+AVD compared with ABVD to be $292,266/QALY. If indication-specific pricing was implemented, price reductions of brentuximab vedotin by 40% to 60% in the first-line setting would produce ICERs of $100,000 to $150,000/QALY. Conclusions: Substituting brentuximab vedotin for bleomycin during first-line therapy for stage III/IV HL is unlikely to be cost-effective under current drug pricing. Should indication-specific pricing be implemented, discounting brentuximab vedotin in the first-line setting by 40% to 60% could reduce ICERs to widely acceptable values.
Background: Chimeric antigen receptor T-cell (CAR-T) therapy is a new class of cancer therapy with promising results, but comes at a high upfront cost. We sought to evaluate the cost-effectiveness of CAR-T therapy among pediatric patients with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL). Methods: We built a microsimulation model for pediatric patients with r/r ALL who received either CAR-T therapy or standard of care chemotherapy. Outcomes modeled included costs, quality of life (health utility), treatment complications, and survival, all of which were estimated from published literature. Long-term survival beyond the time-frame of clinical trial data was estimated using Social Security actuarial life-tables adjusted with standardized mortality ratios. Cost-effectiveness was measured with the incremental cost-effectiveness ratio (ICER), with ICERS under $100,000 per quality-adjusted life year (QALY) considered cost-effective. One-way and probabilistic sensitivity analyses were used to assess overall stability of the model. Results: Compared to standard of care chemotherapy CAR-T increased the total cost of treatment by $378,600 and increased effectiveness by 6.72 QALYs, resulting in an ICER of $56,300 per QALY. The probabilistic sensitivity analysis of CAR-T was cost-effective in > 99% of iterations at a willingness to pay of $100,000 per QALY. Conclusions: Despite its high cost, CAR-T therapy has an acceptable cost-effectiveness profile for pediatric r/r ALL. Additional follow-up of this cohort is required to establish long-term outcomes and further inform questions about the cost-effectiveness of CAR-T therapy.
A value framework analysis of the Canadian Cancer Trials Group. First Author: Joseph Del Paggio, Department of Medicine, University of Toronto, Toronto, Canada

Background: To identify new therapies that offer substantial benefit to patients, investigators and research funding bodies may wish to consider value framework thresholds in the design of clinical trials. To our knowledge, existing value frameworks have not been applied to the research output of a cooperative cancer trials group. Herein, we apply the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to the published output of the Canadian Cancer Trials Group (CCTG).

Methods: Statistical design, study characteristics, and results of all published phase III trials of the CCTG were abstracted. Studies that showed a statistical significance in favor of the experimental therapy were graded using ESMO-MCBS v1.1. To identify the proportion of all trials that were designed to detect a difference which would be considered meaningful, we also applied the ESMO-MCBS to the statistical power calculations. We defined “substantial benefit” as trials that met a grade of A, B, 5, or 4 for the ESMO-MCBS.

Results: During 1979-2017, CCTG published 477 trials. 132 trials were phase III and formed the study cohort; 49% of these trials were statistically “positive”. The most common disease sites were breast (18%), hematologic (17%), and lung (13%). Forty-six percent of trials were conducted in the palliative setting. Experimental therapies included cytotoxic (36%), molecular (20%), and hormonal (10%) agents. Median sample size was 490. In 40% of trials the primary endpoint was overall survival; a survival surrogate was used in 33% of trials. Among the 58 positive trials for which the ESMO-MCBS could be applied to power calculation for 79 trials; 70% of these trials were designed to detect an effect size that could meet ESMO-MCBS thresholds for substantial benefit. The ESMO-MCBS could be applied to the power calculation for 79 trials; 70% of these trials were designed to detect an effect size that could meet ESMO-MCBS thresholds for substantial benefit.

Conclusions: The majority of CCTG phase III trials are designed to detect clinically meaningful differences in patient outcome. However, only one quarter of all trials ultimately yield results that meet ESMO-MCBS thresholds for substantial benefit.

Immunotherapy (IO) versus non-IO for oncology drugs: Comparing survival benefits (SB) using restricted mean survival time. First Author: Amanda Pattie Rahamadian, Sunnybrook Research Institute, Toronto, ON, Canada

Background: Current measures of absolute SB (median survival time/rate at fixed times on Kaplan-Meier (KM) curves) and relative SB (hazard ratios) are limited in properly capturing SB for IO trials. Restricted mean survival time (RMST) captures entire area under KM curves, directly measuring SB. This study aimed to quantify the magnitude of SB in recent oncology drugs using RMST differences and RMST ratio (absolute and relative SB, respectively), and compare those of IO and non-IO. Methods: All Food and Drug Administration approved oncology drugs from 01/2011-11/2017 and randomized control trials (RCTs) used for approval were identified. RCTs with overall survival (OS) or progression-free survival (PFS) as primary endpoints and published KM curves were included. Curves were extracted using established methods (Guyot et al., 2012) with DigitizeIt. RMST differences, ratios, and confidence intervals (CI) were calculated and meta-analyzed using random-effects models to estimate overall absolute and relative SB of contemporary oncology drugs, and to compare those of IO and non-IO. Meta-regression was used to adjust for confounders (crossover, time horizon, year approved, trial phase, companion diagnostics, and approval type).

Results: 94 RCTs with 51 639 patients were included (13 IO and 81 non-IO). Overall RMST differences (absolute SB) were 1.55 mos for OS (95% CI 1.32-1.77) and 2.99 mos for PFS (95% CI 2.65-3.33). Overall RMST ratios (relative SB) were 1.11 for OS (95% CI 1.09-1.13) and 1.42 for PFS (95% CI 1.36-1.48). IO PFS RMST difference was less than non-IO (0.55 mos vs. 1.43 mos, p = 0.02). IO OS RMST difference was larger than non-IO by 1.56 mos (2.02 mos vs. 0.46 mos, p = 0.01). IO OS relative RMST was larger than non-IO (0.56 mos vs. 0.33 mos, p = 0.00001), while RMST ratios were similar (1.33 vs. 1.43, p = 0.16). Conversely, IO OS RMST difference was larger than non-IO by 0.6 mos (2.02 mos vs. 1.43 mos, p = 0.02). IO OS RMST ratios were slightly larger for IO than non-IO (1.18 vs. 1.09, p = 0.0006). Meta-regression showed the adjusted SB for OS was 0.83 mos greater for IO vs. non-IO, p = 0.01. Conclusions: Overall, absolute SB of recent oncology drugs are modest. Unlike popular belief, observed SB of IO drugs are not dramatically superior to non-IO drugs. RMST differences and ratios of oncology drugs in clinical trials should be routinely reported to fully measure SB.

Background: Invasive fungal infections (IFI) are a cause of morbidity, mortality and increased health costs in patients with Acute Leukemia (AL) and hematopoietic stem cell transplant (HSCT). With this study, we aim to examine trends of IFI related hospitalizations in patients with AL and HSCT in the United States. Methods: We utilized Nationwide Inpatient Sample (NIS) data from 2005–2014 and identified patients with AL (acute lymphoblastic leukemia and acute myelogenous leukemia) and HSCT hospitalization using ICD 9 CM codes. Patients with missing information on age, gender and mortality were excluded. Patients with age < 18 years were excluded as well. IFI (candidemia, aspergillosis, zygomycosis) were identified by using appropriate ICD 9 codes in secondary diagnosis field. P-values for trends were generated using Cochran Armitage test. Results: A total of 666,567 hospitalizations with HM were identified. Out of which 15,316 (2.31%) had IFIs. A majority were males (57.8%), Caucasian (58%) and belong to age group 50-64 (36.8%). Overall Incidence of fungemia was 2.3% and remained stable over 11 years (2.16% in 2005 to 2.2% in 2011, relative increase = 7.25%, p trend ≤0.0064). Overall In-hospital mortality was 21.84% (unchanged over 11 years with a relative decrease of 8.1 % with p trend ≤ 0.131. After stratifying for specific IFIs, in-hospital mortality for candidemia (35.0%), zygomycosis (25.51%) and aspergillosis (18.8%). None of which have changed over 1 decade. Future studies to identify limiting factors are needed to provide crucial information to prevent fungemia and improve outcomes.

TPS6621 Poster Session (Board #446a), Sat, 1:15 PM-4:45 PM A randomized, controlled trial to assess a multi-level intervention to improve adherence to oral cancer medications. First Author: Rashmika Potdar, Einstein Medical Center Philadelphia, Newtown Square, PA

Background: Cancer treatment with oral cancer medication is complex. Cancer patients require substantial skills to adhere to- and achieve the goals of therapy. Medication adherence among cancer patients is increasingly important, as treatment with oral medications is increasingly prevalent. The rates of adherence to oral therapy vary widely by population, cancer type, and level of education. To date, however, there is no clear evidence on the effect of improvements in health literacy on patients’ adherence to oral cancer medications. We hypothesize that compared to usual care, the addition of a multilevel intervention will result in greater adherence to oral cancer medications. Methods: In a single-center, patients are randomized 1:1 to receive usual care, including cancer care plus education by a registered nurse (Arm 1), or the addition of a multilevel intervention (Arm 2). The multilevel intervention includes a brief web-based educational video on cancer and oral cancer drugs, periodic reinforcement of educational messages with videos, brief phone calls 24 hours and 2 weeks after each encounter, and offer of facilitative services, if needed. Health literacy is recorded at baseline, using REALM R. Adult cancer patients on any oral cancer medication are eligible to participate in the study. Exclusion criteria include ECOG ≥3, concurrent chemo-radiation, hormonal therapy, non-adherence (defined as history of missing 2 or more Oncology clinic appointments), pregnancy, residence in a nursing home, dementia, or lacking decisional capacity. The primary outcome of interest is medication adherence, indicated by the proportion of expected refills completed for oral cancer medications during the follow up period. Secondary outcomes include adherence to follow up visits, adherence to other prescribed medications, healthcare utilization, and other healthcare outcomes. With a onesided alpha = 0.05, the target sample size of 110 patients, would yield 90% power to test the primary hypothesis. To date, we have randomized 19 participants, and enrollment proceeds as planned. Clinical trial information: NCT03245411.
Ambulatory cancer care electronic symptom self-reporting (ACCESS) for surgical patients: A randomized controlled trial. First Author: Cara Stabile, Memorial Sloan Kettering Cancer Center, New York, NY

Background: An increasing proportion of cancer surgeries are ambulatory (≤ 1 day in hospital) procedures. Providing patients and their caregivers with ongoing, real-time support after discharge is imperative to delivering high-quality postoperative care in this new health care environment. Despite abundant evidence that patient self-reporting of symptoms improves quality of care, Reference: 1. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *Journal of Clinical Oncology.* 2014;32(14):1480-1501. the most effective way to monitor and manage such data remains unknown. Methods: This is a two-armed, prospective randomized controlled trial evaluating two approaches to the management of patient-reported data: (1) Team Monitoring—symptom monitoring by the clinical team, with nursing outreach if symptoms exceed normal limits; and (2) Enhanced Feedback—real-time feedback to patients about expected symptom severity, with patient-activated care as needed. It is hypothesized that Enhanced Feedback about expected symptom severity would be more effective than Team Monitoring in improving patient-centered outcomes and the patient/caregiver experience. Breast, prostate, gynecologic, and head and neck cancer patients undergoing ambulatory cancer surgery (n = 1,700) will complete an electronic survey about their symptoms for up to 30 days after surgery. Information provided to patients in the Enhanced Feedback group is procedure-specific and based on continuously updated survey data from previous patients. Qualitative interviews will also be performed. Accrual began in August 2017. Primary outcomes will evaluate unplanned emergency department visits within 30 days. Secondary outcomes will assess the patient/caregiver experience (i.e., patient engagement, patient anxiety, and caregiver burden). Findings will be relevant in designing future coordinated care models targeting improved health care quality and patient experience. Clinical trial information: NCT03178045.
Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study. 
First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** IVO is an oral, targeted inhibitor of mutant isocitrate dehydrogenase 1 (mutIDH1) that is being evaluated in a phase 1 dose escalation and expansion study of mutIDH1 advanced hematologic malignancies (NCT02074839). Here we report updated efficacy and safety data from all patients with R/R AML receiving IVO 500 mg once daily (QD). 

**Methods:** The primary efficacy endpoint was the CR+CRh rate (complete remission [CR] according to modified IWG-2006 criteria plus CR with partial hematologic recovery [CRh]). CRh was defined as absolute neutrophil count > 0.5 × 10^9/L and platelet count > 50 × 10^9/L. The overall response rate (ORR) comprised CR, CR with incomplete hematologic or platelet recovery, partial response, and morphologic leukemia-free state. The data cutoff date for this analysis was Nov 30, 2017. 

**Results:** A total of 258 patients were treated with IVO. Among 179 R/R AML patients who received IVO 500 mg QD, 17 (9.5%) remained on treatment at data cutoff. In R/R AML patients, the CR+CRh rate was 3.1% (95% CI: 25.1%, 39.2%), including CR in 24.0% (95% CI: 18.0%, 31.0%). Median duration of CR+CRh was 8.2 months (95% CI: 5.6, 12.0), and median duration of CR was 10.1 months (95% CI: 6.5, 22.2). The ORR was 41.9% (95% CI: 34.6%, 49.5%). Treatment was well tolerated; the most common adverse events (AEs) of any grade, irrespective of causality and occurring in ≥25% of 179 R/R AML patients were diarrhea (33.5%), leukocytosis (31.3%), nausea (31.3%), febrile neutropenia (29.1%), fatigue (28.5%), and infection (28.5%). The majority of these AEs were grades 1–2 and unrelated to treatment. 

**IDH differentiation syndrome (IDH-DS):** At 12 mo of follow-up, 19 of 179 (10.6%) patients, including grade ≥3 IDH-DS in 9 (5.0%) study drug was held owing to IDH-DS in 6 patients (3.4%), and no instances of IDH-DS led to dose reduction, permanent treatment discontinuation, or death. Updated mutation clearance results will be provided. 

**Conclusions:** In a high-risk, molecularly defined R/R AML patient population, IVO induced durable remissions and was well tolerated. Studies in previously untreated AML populations are ongoing. Clinical trial information: NCT02074839.

**7002 Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Bosutinib vs imatinib for newly diagnosed chronic myeloid leukemia in the BF-RE trial: 24-month follow-up. 
First Author: François-Xavier Mahon, Cancer Center of Bordeaux, Institut Bergonié, INSERM U1218, University of Bordeaux, Bordeaux, France

**Background:** Bosutinib is a dual Src/Abl tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia (CML) in chronic phase (CP) and CML resistant/intolerant to prior therapy. Here we compare efficacy of first-line bosutinib and imatinib after ≥24 mo (median: 27 mo) of follow-up. 

**Methods:** In the ongoing, open-label, phase 3 BF-RE trial (NCT02130557), 536 patients with CP CML were randomized 1:1 to bosutinib (n = 268) or imatinib (n = 268 [3 untreated]). 

**Results:** Higher molecular and complete cytogenetic response (MR and CCyR) rates were observed for bosutinib vs imatinib at 12 mo; these differences continued after ≥24 mo (Table). 

**Time to response (based on cumulative incidence), hazard ratio (HR)†**

<table>
<thead>
<tr>
<th>Time to response</th>
<th>Bosutinib</th>
<th>Imatinib</th>
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</thead>
<tbody>
<tr>
<td>MR4</td>
<td>25.7</td>
<td>19.0</td>
</tr>
<tr>
<td>MR4.5</td>
<td>28.6</td>
<td>22.2</td>
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<tr>
<td>MMR</td>
<td>67.2</td>
<td>57.5</td>
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</tbody>
</table>

**MMR, %**

| At 12 mo | 46.6 | 36.2 | 0.013 |
| At 24 mo | 61.2 | 50.7 | 0.015 |
| At 36 mo | 20.5 | 11.6 | 0.005 |
| At 48 mo | 32.8 | 25.7 | 0.73  |
| At 60 mo | 7.5  | 3.0  | 0.220 |
| At 72 mo | 19.2 | 7.5  | 0.001 |

**Overall survival (OS), %**

| At 12 mo | 51.5 |
| At 24 mo | 39.1 |
| At 36 mo | 22.2 |
| At 48 mo | 14.2 |

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Moxetumomab pasudotox was evaluated in a Phase 1 clinical trial for the treatment of relapsed/refractory acute lymphoblastic leukemia (R/R ALL). The study included adult patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). Therapy was given to adult patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). The primary end point of the trial was the durable complete remission (CR) rate in adult R/R ALL patients. The trial was conducted at 24 sites in the United States and included 80 patients who received the investigational drug.

Methods: Eligible patients (≥18 years) with relapsed or refractory acute lymphoblastic leukemia (R/R ALL) were enrolled in the trial. The primary end point was the percentage of patients achieving complete remission (CR) with an immunophenotypic (IHP) minimal residual disease (MRD) status of ≤5% at 2 months after infusion. Secondary end points included stability of the IHP MRD status, duration of MRD CR, and overall survival.

Results: Of the 80 patients enrolled, 63 had relapsed and 17 had refractory disease. The median number of prior systemic therapies was 3 (range, 1 to 6). The median age was 51 years (range, 18 to 71 years). The most common prior therapies were chemotherapy (93% of patients) and hematopoietic stem cell transplantation (69% of patients). The CR rate was 56% (44/80), with 32% (26/80) of patients achieving MRD CR. The median time to CR was 31 days (range, 14 to 70 days). The median time to MRD CR was 2.3 months (range, 0 to 15 months). The median follow-up duration after infusion was 16.7 months (range, 1 to 30 months).

Conclusions: Moxetumomab pasudotox achieved a high rate of independently assessed durable CR, with the ability to eradicate MRD in heavily pretreated HCL patients, and showed a favorable safety profile without immunosuppression. Clinical trial information: NCT02614066.

Moxetumomab pasudotox was administered intravenously on days 1, 3, and 5 of a 28-day cycle. The initial dose was 400 mg/kg, and subsequent doses were adjusted based on the pharmacokinetic profile and safety data. The drug was well tolerated, with most treatment-related adverse events being manageable and reversible. The most common adverse events were infections, such as neutropenia, and capillary leak syndrome. Hemolytic uremic syndrome (4 patients) and capillary leak syndrome (4 patients) were the most severe adverse events. No patients required plasma exchange for these events.

Conclusion: Moxetumomab pasudotox was well tolerated and achieved a high rate of independently assessed durable CR, with the ability to eradicate MRD in heavily pretreated HCL patients, and showed a favorable safety profile without immunosuppression. Clinical trial information: NCT02614066.

Background: Moxetumomab pasudotox is a monoclonal antibody that targets CD40L, a co-stimulatory molecule present on tumor cells. It is being evaluated for the treatment of R/R ALL in a Phase 2 clinical trial. The primary end point of the trial is the percentage of patients achieving MRD CR. The secondary end points include overall survival, duration of MRD CR, and infusion-related adverse events.

Methods: Patients with R/R ALL were enrolled in the trial at 24 sites in the United States. The primary end point was the percentage of patients achieving MRD CR. The secondary end points included overall survival, duration of MRD CR, and infusion-related adverse events. The trial was designed to accrue 80 patients. The primary exclusion criteria were active severe infection or other uncontrolled infection, active malignancy other than ALL, and active autoimmune disease.

Results: Of the 80 patients enrolled, 63 had relapsed and 17 had refractory disease. The median number of prior systemic therapies was 3 (range, 1 to 6). The median age was 51 years (range, 18 to 71 years). The most common prior therapies were chemotherapy (93% of patients) and hematopoietic stem cell transplantation (69% of patients). The CR rate was 56% (44/80), with 32% (26/80) of patients achieving MRD CR. The median time to CR was 31 days (range, 14 to 70 days). The median time to MRD CR was 2.3 months (range, 0 to 15 months). The median follow-up duration after infusion was 16.7 months (range, 1 to 30 months).

Conclusions: Moxetumomab pasudotox achieved a high rate of independently assessed durable CR, with the ability to eradicate MRD in heavily pretreated HCL patients, and showed a favorable safety profile without immunosuppression. Clinical trial information: NCT02614066.
Durable response with venetoclax in combination with decitabine or azacitidine in elderly AML patients with acute myeloid leukemia (AML). First Author: Jonathan Michael Gerber, Levine Cancer Institute, Atrium Health, Charlotte, NC

**Background:** MRD has emerged as a significant prognostic factor in ALL, but even levels <0.1% still carry a risk of relapse. It is theorized that relapse is due to resistant LSCs, which survive after therapy. Consistent with this, MRD in acute myeloid leukemia patients was enriched for LSCs, which were CD34+ with intermediate (int) levels of aldehyde dehydrogenase (ALDH) activity. It is postulated that residual LSCs are more resistant than the bulk leukemic cells to therapy. The LSCs serve as a highly sensitive test for MRD. These findings merit validation in a larger cohort.

**Methods:** PB, BM, and peripheral blood samples were collected from 36 patients with AML. Flow cytometry and/or PCR were used to detect MRD. Twenty-four patients were followed post therapy, 5 of whom achieved complete remission with <0.1% detectable MRD by clinical flow cytometry and/or PCR. Whereas clinical FACS detected a mean of 0.0116% MRD in the 5 cases, the LSCs constituted 31.95 ± 0.1% detectable MRD by clinical flow cytometry and/or PCR.
Center, Houston, TX

Impact of minimal residual disease (MRD) status in clinical outcomes of patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) treated with inotuzumab ozogamicin (InO) in the phase 3 INO-VATE trial. First Author: Elias Jabbour, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MRD negativity is a key prognostic indicator of patient (pt) outcome in ALL and is predictive of improved survival and disease-free status. In the INO-VATE ALL trial (Kantarjian, NEJM 2018), pts with R/R ALL who received InO vs standard chemotherapy (SC) achieved greater remission (CR/CRi; 81% vs 29%) and MRD negativity (78% vs 28%), in pts with CR/Cri) and had improved overall survival (OS): 7.7 vs 6.7 months. This analysis was conducted to assess prognostic value of MRD negativity by end of treatment (EOT) with InO.

Methods: INO-VATE pts who received InO (n = 164) were included. Among pts with CR/Cri, MRD status (by multiparametric flow cytometry at a central lab) was defined as negative (MRD-1 ≤ 1 × 10^−9) blasts/nucleated cells (n = 81), or positive (MRD+; n = 83), based on assessment by EOT. OS, progression-free survival (PFS), and predictors of MRD status (by multivariable logistic regression) are reported from final study data as of Jan 4, 2017.

Results: MRD- status with CR/Cri was associated with significantly improved OS and PFS (Table) vs MRD+ status with CR/Cri: unstratified HR 0.512; 1-sided P = 0.009 for OS and HR 0.423; P = 0.0001 for PFS. Exploratory multivariate analyses indicated that 2nd salvage compared to first salvage (OR 0.098, P = 0.03) was associated with lower likelihood of achieving MRD- status, while 1×10^9/L absolute circulating blast count at baseline (OR 3.231, P = 0.002) and longer duration of remission (OR 1.033, P = 0.005) were associated with increased likelihood of achieving MRD- status. Clinical trial information: NCT01564784.

Conclusions: Among pts who received InO in the INO-VATE trial, having CR/Cri and MRD- status at EOT was associated with the greatest survival outcomes. However, pts who achieved an MRD+ CR/Cri had much greater survival than those who did not have CR/Cri in R/R ALL, use of InO may optimize chances to attain the primary goal of complete remission and MRD- status.

7015 Poster Discussion Session: Displayed in Poster Session (Board #75), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Profilming the immune checkpoint pathway in acute myeloid leukemia. First Author: Paola Dama, University of Chicago, Chicago, IL

Background: The immune checkpoint pathways in AML patients especially during the course of chemotherapy induction were seldom studied. This study was to characterize these pathways in AML patients treated on a prospective clinical trial to combine Selinexor with high-dose cytarabine (HiDAC) with mitoxantrone (Mito) (NCT02573363). Flow cytometry parameter flow-cytometry was utilized to monitor the changes in expression of immune checkpoint receptors using bone marrow and peripheral blood samples at diagnosis and following remission induction therapy in 26 patients with AML enrolled to the study. Expression of CD47, PD-L1, PD-L2 and Gal-9 was assessed on CD34+ AML blasts and CD34- cell populations. In parallel, we evaluated expression of inhibitory (PD1, CTLA4, Lag3, Tim3) and stimulatory co-receptors (CD28, ICOS, CD137, OX40L, HLA-DR) on CD4+ and CD8+ T cell subsets. Flow cytometry data were analyzed with FlowJo-10 software. The Mann Whitney Test, Wilcoxon Rank test and Spearman’s rank correlation analysis were applied. Results: The percentage of CD34+ Gal9+ cells was significantly higher in patients who experienced treatment failure (TF) after chemotherapy, compared with those in complete remission (CR), with median of 36.9% (range: 1.7% - 98.3%) versus a median of 3.8% (range: 0.18% - 60.1%; p < 0.05). There was no difference of PD-L1 expression in these two groups. CD69 is a marker of the immune activation status of AML. We observed significant increase of expression of PD-L1 on BM CD34-, Tim3 on BM CD4+ and CD8+ T cells, as well as co-stimulatory checkpoint receptors: CD137 (4-1BB), HLA-DR on BM CD4+ cells, and OX40 on BM CD8+ T cells. In peripheral blood, the PD1 expression on CD4+ cells was much higher at the time of remission comparing to that at diagnosis. These data suggested an exhausted T cells status at the time of disease remission on the clinical trial treatment. Conclusions: Our small study demonstrated high level expression of Gal9 in CD34- cells in the BM at diagnosis in patients who failed induction chemotherapy. Increased expression of Tim3 and OX40 in peripheral CD4+ T cell at the disease remission suggested an exhausted immune status, which could be targeted with checkpoint inhibitors.
Background: First-generation (1st gen) FLT3 TKIs such as sorafenib (SOF) or midostaurin (M) are increasingly used for treatment of FLT3-mutated (FLT3–ITD) acute myeloid leukemia (AML). Quizartinib (Q) is a high-affinity and selective FLT3 inhibitor with strong clinical antileukemic activity in pts with FLT3–ITD mR/R AML. Analyzing the clinical activity of Q in pts with prior TKIs may provide early insights into an important clinical question about potential benefit of agents with varying kinase and safety profiles. Methods: This post hoc exploratory analysis was done in two phase 2 trials of Q monotherapy in FLT3–ITD mR/R AML (Studies A [NCT01565668], B [NCT00989261]) to assess Q activity in pts w/ FLT3–ITD mR/R AML. This post hoc exploratory analysis was done in two phase 2 trials of Q monotherapy in FLT3–ITD mR/R AML. In part 1, 212 pts were evaluated (117 in Study A (Q 90, 1 SOF, 1 M) and 95 in Study B (Q 30 or 60 mg/d)). In both studies, Q was given for 28-day cycles until relapse, intolerance, or proceeding to HSCT. Results: In Study A, complete response (CR = CR+PR+CRI) and overall response rates (ORR = CR+PR+CRI+PR) with Q were 33% (9/27) and 67% (18/27), respectively, in pts with prior TKIs (117 evaluable cases). Complete response rate (4/27, 15%) was achieved in cases with FLT3–ITD mu pts received prior TKI (1/27, 4%). In Study B, CR and ORR were 36% (4/11) and 45% (5/11), respectively, in prior-TKI-treated pts, compared with 48% (29/61) and 69% (42/61), respectively, in the TKI-naive pts. Median survival durations in Study A were 24, 6, and 24 weeks for prior-TKI-treated pts and 24, 22, and 24 weeks for pts who were TKI-naive. Conclusion: This analysis demonstrates meaningful clinical activity of Q in FLT3–ITD mR/R AML pts with prior 1st gen FLT3–ITD TKI exposure. Limitations are well tolerated with most AEs being mild or moderate in severity. 2 pts achieved PR (30) in Study A and 30 pts were evaluable. 1 pt died of bleeding complications while on treatment. Median survival duration of 8.6 months was achieved. Conclusion: This analysis demonstrates meaningful clinical activity of Q in FLT3–ITD mR/R AML pts with prior 1st gen FLT3–ITD TKI exposure. Limitations in Study B, CR and ORR were 36% (4/11) and 45% (5/11), respectively, in prior-TKI-treated pts, compared with 48% (29/61) and 69% (42/61), respectively, in the TKI-naive pts. Median survival durations in Study A were 24, 6, and 24 weeks for prior-TKI-treated pts and 24, 22, and 24 weeks for pts who were TKI-naive. Conclusion: This analysis demonstrates meaningful clinical activity of Q in FLT3–ITD mR/R AML pts with prior 1st gen FLT3–ITD TKI exposure. Limitations the safety and efficacy of Q in AML and MDS. These data suggest that expanded late-stage antileukemia activity is at baseline. AML was well tolerated and showed antileukemic effects in pts with RR AML. Clinical trial information: NCT01565668, NCT00989261.

7019 Posterior Discussion Session; Displayed in Poster Session (Board #79), Mon, 8:00-AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30-AM-12:45 PM First-in-human study of ABBV-075 (mivebrasil), a pan-inhibitor of bromodomain and extra terminal (BET) proteins, in patients (pts) with relapsed/refractory (RR) acute myeloid leukemia (AML): Preliminary data. First Author: Gautam Barthakur, The University of Texas MD Anderson Cancer Center, Houston, TX Background: Pts with RR AML have a poor prognosis. BET proteins bind acetylated histone tails, leading to the upregulation of oncogenic target genes through inhibition of their recruitment to chromatin and increased release of reticulocytes, supplementing erythropoiesis. Our laboratory previously demonstrated that late-stage erythropoiesis is associated with a response to luspatercept as an erythroid-maturation agent (EMA). Clinical trial information: NCT01749514, NCT02268383.

7020 Posterior Discussion Session; Displayed in Poster Session (Board #80), Mon, 8:00-AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30-AM-12:45 PM Analysis of anti-leukemic activity, predictive biomarker candidates, immune activation and pharmacodynamics in RR AML and MDS in response to treatment with bemcentinib (BGB3234), a first-in-class selective AXL inhibitor, in phase II open-label, multi-centre study. First Author: Bjorn T. Gjertsen, Center for Cancer Biomarkers CCBIO, Department of Clinical Science, University of Bergen, Bergen, Norway

Background: Bemcentinib (BGB3234) is a first-in-class, oral selective inhibitor of the RTK AXL currently in phase II clinical development across several cancer types. AXL overexpression has been established as an independent negative prognostic factor in AML whereas AXL inhibition via bemcentinib has shown anti-leukemic activity and immune activation in pre-clinical models of AML and other cancers. Methods: N = 35 R/R AML or MDS (interm-2 and high-risk) pts received bemcentinib monotherapy in this two part 3+3 dose escalation and cohort expansion study. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in a selection of pts pre-dose and at C2D1. Gene expression analysis was carried out by ncRR using TCGA. Phosphorylation of AXL and downstream targets PLCγ1, Erk, MapK and Akt was carried out by single cell flow and mass cytometry. Clonal evolution was analysed by exome sequencing and TruSight myeloid panel. The TCRb and IGH repertoire was investigated using Biomed TCRb-A/B and Biomed2 FR-2/3 primer pools and NGS on an Illumina MiSeq platform. Results: Treatment was generally well-tolerated with most AEs being mild or moderate in severity. 2 pts achieved complete responses with incomplete recovery of peripheral counts (CRI) and 5 achieved partial responses (PR). 8 pts reported disease stabilisation for more than 4 months. Levels of plasma soluble AXL and angiogenin and BM SFRF-1 expression were associated with pt benefit. Whole exome and sequencing analysis showed conservation of clones which may limit the evolution of resistant blasts. Immune activation was observed by T- and B-cell receptor diversification. PhosphoFlow analysis of AXL and downstream signalling intermediates evidenced targeted inhibition. Conclusions: Bemcentinib is well tolerated in MDS and AML, and a new therapeutic option is supported by the demonstration of multiple mechanisms including immune modulation. Pt benefit (CRI/PR/SD > 4 mths) is predictable by measurement of plasma markers soluble AXL and angiogenin. Clinical trial information: NCT02488408.
Is there a benefit of re-induction therapy in adult patients with AML with <20% blasts? First Author: Kayva Kannam Kanran, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Decision on re-induction (RI) therapy in adult patients with newly diagnosed acute myeloid leukemia (AML) who have received induction chemotherapy (ICT) when there are less than 20% blasts on day 14 nadir bone marrow biopsies, is difficult due to the lack of reliable data and the toxicity associated with RI. We sought to determine the utility of RI in this group of patients.

Methods: We identified 270 adults with AML treated at Wake Forest Baptist Health with ICT between 2002-2009. We excluded 37 patients who did not have a NBMB. NBMB was classified as negative (< 5% blasts), suspicious (< 5% blasts), morphological suspicion for residual disease or 5-20% blasts) and positive (> 20% blasts) for residual disease. Complete remission (CR) was achieved if recovery BM had < 5% blasts along with platelet recovery to at least 100,000 cells/microliter and absolute neutrophil count of at least 1000 cells/microliter. A CRi was defined as having either platelet or neutrophil recovery but not both. Kaplan Meier estimation was used to calculate the median OS and survival estimates at 1, 2, and 3 years post induction.

Results: Of the 233 patients, 106 (45.5%) had NBMB findings suspicious for residual disease (SRD). Of these patients, 66 (62.3%) underwent RI and R0 (37.7%) did not. Of those who received RI, 52 of 66 (78.8%) achieved a CRiCR. In the patients who did not receive RI, 32 of 40 (80.0%) achieved a CRiCRI. There was no statistical difference in median OS with and without re-induction in patients with SRD overall and when sub classified into favorable, intermediate and poor cytogenetic categories.

Conclusions: Our retrospective analysis raises questions about the utility of RI in adult patients with AML with less than 20% blasts on nadir marrow. This finding warrants prospective trials for further validation.

2023 Poster Discussion Session; Displayed in Poster Session (Board #83), Mon, 8:00-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Impact of numerical variation, allele burden and mutation length on outcomes in acute myeloid leukemia with fms-like tyrosine kinase-receptor-3 internal tandem duplication (FLT3-ITD) mutation. First Author: Ahmad Ghorab, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: While high allelic burden is known to be associated with adverse outcomes in FLT3-ITD mutated AML, the impact of numerical variation and insert size on clinical outcome is less well studied. Methods: Analysis included 330 newly diagnosed AML pts with FLT3-ITD mutation diagnosed between 3/1999 and 11/2015. Overall survival (OS) was calculated from the time of diagnosis to death/last follow up time. Relapse free survival (RFS) was calculated from response to frontline ICT. Results: Table 1 summarizes patient characteristics, response and OS, RFS by numerical variation, size, allelic burden and stem cell transplantation (SCT). Because of the time frame, only 20% pts had frontline exposure to FLT3 inhibitors. Conclusions: Numerical variation and insert length had no significant impact on outcomes while lower allelic burden, FLT3 inhibitor therapy trended towards better RFS. SCT had a significant favorable impact on both OS and RFS.An expanded contemporary cohort analysis is ongoing.

2024 Poster Discussion Session; Displayed in Poster Session (Board #84), Mon, 8:00-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Clonal evolution in acute myeloid leukemia (AML): Relapse after a long remission period. First Author: Musa Yilmaz, Baylor College of Medicine, Houston, TX

Background: Late relapse in AML occurring more than 5 years after achieving remission is uncommon and underlying biological events are poorly understood. We aim to determine the clonal events resulting in late relapse of AML. Methods: We identified patients (pts) with AML who received intensive induction chemotherapy between 1990 and 2017, achieved complete remission (CR), and remained in CR for at least 5 years. A total 349 pts were identified, and 15 (4%) relapsed beyond 5 years. Whole exome-sequencing was performed in diagnosis (dx) and 1 relapse bone marrow samples (available in 10 pts). Results: A total of 43 driver mutations were identified in 10 pts, of which 12 were primary tumor specific, 18 relapse-specific, and 13 were shared between primary and relapsed tumor (Table). Twenty-seven of 43 driver mutations (63%) were nonsynonymous SNV and 16 (37%) were indels. At relapse, 3 clonal evolution patterns were identified: pattern 1, the founding clone in the primary tumor gained additional mutations and evolved into the relapse clone and assumed dominance of the BM, pattern 2, the founding clone in the primary tumor gained additional mutations at relapse (UPN 9, 10, 12, and 14); and pattern 3, relapsing clone harbored none of the primary tumor mutations, thus it represented a new clone (UPN 3 and 15). Conclusions: Relapse after a long remission in pts with AML is associated with persistence of the founding clone and acquisition of new relapse-specific mutations in the majority. Understanding the mechanisms of such quiescence may assist in increasing CR duration in pts with AML.

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7025 Poster Session (Board #85), Mon, 8:00 AM-11:30 AM

Determining the sensitivity of primary acute myeloid leukemia (AML) samples with FLT3-ITD or FLT3-D835 mutations to FLT3 inhibitors using an ex vivo drug sensitivity screen

Authors: First Author: Mara Rosenberg, Oregon Health & Science University, Portland, OR

Background: AML has high molecular complexity and certain markers are predictors of overall survival. Mutations in FLT3-ITD, for example, lead to a poor prognosis with outcomes further worsened by co-occurring mutations in DNMT3A. Small molecule inhibitors have been developed to target a select number of these mutations such as Midostaurin on FLT3-ITD and FLT3-D835. However, the impact of the specificity of mutation or the effect of co-occurring mutations in DNMT3A and NPM1 on drug sensitivity is not fully known. Methods: We identified 503 primary AML samples tested with an ex vivo drug sensitivity screen that includes 130 small-molecule inhibitors and over 10 FLT3 inhibitors. Mononuclear cells were screened, metabolic viability assessed, and drug response summarized by area under the curve (AUC). Results: FLT3-ITD was the strongest indicator for response to FLT3 inhibitors (Table 1). Sensitivities were similar with DNMT3A and/or NPM1 co-mutations. Further, FLT3-D835 mutant samples showed no increased sensitivity to FLT3 inhibitors compared to non-FLT3 mutated samples. Conclusions: The similar ex vivo drug sensitivity screen (FLIT3-ITD AML with or without DNMT3A and/or NPM1 mutations suggest co-treatment with FLT3 inhibitors will allow for improved overall survival in these cohorts. Additional clinical testing may further characterize the effect of FLT3-D835 mutations on targeted therapies and the impact of co-mutations. Some FLT3-ITD inhibitors were associated with increased potential for FLT3-D835 and Midostaurin suggesting alternative treatment choices for select AML patients.

Mean AUC values (% confidence interval) for each drug by sample classification.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Quizartinib</th>
<th>KW-2469</th>
<th>Cobasentinib</th>
<th>Sorafenib</th>
<th>Sunifatinib</th>
<th>Midostaurin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITD+</td>
<td>37(4±3)</td>
<td>55(±5)</td>
<td>45±4</td>
<td>52±4</td>
<td>54±4</td>
<td>56±4</td>
</tr>
<tr>
<td>ITD+ / DNMT3A+</td>
<td>36(4±5)</td>
<td>55(±5)</td>
<td>41(7±4)</td>
<td>48±7</td>
<td>54±7</td>
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<tr>
<td>ITD+ / NPM1+</td>
<td>35(4±4)</td>
<td>53(±4)</td>
<td>51(3±11)</td>
<td>59(8)</td>
<td>61(8)</td>
<td>69±9</td>
</tr>
<tr>
<td>FLT3-</td>
<td>57(2±2)</td>
<td>77(2)</td>
<td>67(2)</td>
<td>73(2)</td>
<td>74(2)</td>
<td>76(2)</td>
</tr>
</tbody>
</table>

*Drug AUC differs from Midostaurin (p < 0.001); Sample classification differs from FLT3 Negative cohort (p < 0.001).

7027 Poster Session (Board #87), Mon, 8:00 AM-11:30 AM

CX-01, an inhibitor of CXCL12/CXCR4 axis and of platelet factor 4 (PF4), with azacitidine (AZA) in patients with hypomethylating agent (HMA) refractory AML and MDS.

First Author: Eric Huselton, Washington University in St. Louis, St. Louis, MO

Background: Outcomes are poor for older patients with AML and MDS who progress on HMAs. Blocking the CXCL12/CXCR4 axis may be therapeutic as this is essential for retention of malignant stem cells in the bone marrow (BM), where they may be protected from the genotoxic stresses of chemotherapy. CX-01 is a low molecular weight heparin derivative with minimal anticoagulant activity that disrupts the CXCL12/CXCR4 axis, and neutralizes the activity of PF4, a negative regulator of megakaryopoiesis. We hypothesized that CX-01 would re-sensitize patients with HMA-refractory AML and MDS to AZA and mitigate thrombocytopenia. Methods: Patients with HMA-refractory INT-1 or greater MDS and AML received 7 day continuous infusion of CX-01 with or without AZA. Dose-escalation to 40 mg of LY2510924 is planned to achieve 50% decrease in CXCR4 mean fluorescence intensity. Results: Eleven pts have been enrolled with a median age of 55 (range, 19-70) years. Of 10 pts tested, 2 (20%) had complex cytogenetics. Median prior therapies were 1 (1-3). Six pts were treated at dose level ‘0’ (10 mg) and 5 at dose level ‘1’ (20 mg); 3 of 5 treated at dose level ‘1’ had known fluorodeoxiglucose (FDG) PET scan, and 2 were evaluable for treatment response. Combination of CX-01 and AZA appears to have an encouraging response rate in HMA-refractory AML and MDS. Treatment was feasible with no instances of grade ≥3 toxicity. Conclusion: Combination of CX-01 and AZA is feasible in HMA-refractory AML and MDS to AZA and mitigate thrombocytopenia.

7026 Poster Session (Board #88), Mon, 8:00 AM-11:30 AM

Initial report of a phase I study of LY2510924 with iraducibin and cytarabine (IA) in relapsed/refractory (R/R) AML. First Author: Prajwal Boddu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: LY2510924 is a peptide antagonist of CXCR4, a key component of the CXCR4/SDF-1 signaling axis that is critical for homing of stem cells in the bone marrow and activation of downstream pathways involved in cell proliferation and survival. In a preclinical AML model, LY2510924 showed significant activity as a single agent and in combination with chemotheraphy (Cho et al. Blood 2015). Methods: A phase I study was designed to determine the safety and toxicity profile of combination therapy of LY2510924 with IA in patients (pts) with R/R AML. Pts aged 18 to 70 years who failed prior therapy (≤ salvage 3) were eligible. LY2510924 is administered from days 1-7 followed by IA starting day 8. In responders, 4-6 consolidation cycles were administered. Two dose escalation levels (10 and 20 mg) were planned, according to a 3+3 design: up to 12 pts to be enrolled in phase I portion. Results: Eleven pts have been enrolled with a median age of 55 (range, 19-70) years. Of 10 pts tested, 2 (20%) had complex cytogenetics. Median prior therapies were 1 (1-3). Six pts were treated at dose level ‘0’ (10 mg) and 5 at dose level ‘1’ (20 mg); 3 of 5 treated at dose level ‘1’ had known fluorodeoxiglucose (FDG) PET scan, and 2 were evaluable for treatment response. Combination of CX-01 and AZA appears to have an encouraging response rate in HMA-refractory AML and MDS. Analysis from INO-VATE by bone marrow blast percentage (BMB%)

First Author: Anjali S. Advani, Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: InO is a calcineutrin-conjugated antibody targeting CD22 on ALL blast cells. Here we report outcomes in R/R ALL patients (pts) receiving InO or standard care chemotherapy (SC) in the phase 3 INO-VATE trial according to baseline BMB%, an indicator of disease burden. Methods: Adults with CD22+ ALL due to receive salvage treatment were randomized 1:1 to InO (n = 164) or SC (n = 162). Dosing and methods were published previously (Kantarjian et al, NEJM 2016). BMB% was defined as low (< 50%), moderate (50-90%), and high (> 90%) at start of treatment. Results: At baseline, characteristics across all groups were balanced and median BMB% was 28%, 78% and 95% in the low, moderate, and high disease burden subgroups. Complete remission rates were significantly higher in InO vs SC pts, with 74% vs 46%, 75% vs 48%, and 70% vs 17% achieving CR/CRi in low, moderate, and high BMB% subgroups. Significantly more pts in the InO arm achieved minimal residual disease negativity: 29/53 (55%), 52/79 (66%), and 16/30 (53%) for low, moderate, and high BMB% compared with 10/48 (21%), 11/83 (13%), and 2/30 (7%) for SC, respectively. InO-treated pts also had improved progression-free survival vs SC, with hazard ratios of 0.44 (95% CI, 0.26-0.74, 1-sided P = 0.001) for low, 0.50 (95% CI, 0.34-0.75, P<: 0.001) for moderate, and 0.33 (95% CI, 0.16-0.69, P = 0.0002) for high BMB%. Overall survival (OS) was favored in the InO arm across groups (Table) with potentially the greatest difference seen in pts with high BMB% (HR = 0.60 (95% CI 0.32-1.29, 1-sided P = 0.033) Clinical trial information: NCT01564784. Conclusions: InO treatment resulted in superior efficacy over SC across all BMB% subgroups out to 2 years follow-up, particularly in patients with the greatest disease burden by BMB%.

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Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

7029 Poster Session (Board #89), Mon, 8:00 AM-11:30 AM

Extensive safety profile of inotuzumab ozogamicin (InO) in relapsed/refractory acute lymphoblastic leukemia (ALL) patients enrolled in the phase 3INO-VATE trial.

First Author: Vineeta R. Kapila, Inotuzumab Ozogamicin Development, Washington School of Medicine and Fred Hutchinson Cancer Research Center, Seattle, WA

Background: In INO-VATE, patients (pts) treated with InO vs standard chemotherapy (SC) had significantly greater remission rates and longer overall survival (OS), with 23% reduced risk of death (Kantarjian et al, NCIJ 2016). Here we report detailed safety outcomes from this trial. Methods: InO was given as 4 doses. One dose-limiting toxicity (DLT) of reversible G4 encephalopathy was observed in the majority of pt samples by rtPCR. Eleven pts received at least 1 dose of InO. Pegzilarginase was given at 0.12 to 0.48 mg/kg. Low ASS1 expression was observed in blasts. ASL, & OTC in blasts.

Primary endpoint was MTD. Other endpoints included safety, PK, PD (arginine & arginase). Study methods were previously published. Adults with C022+ ALL in 1st or 2nd salvage were randomized 1:1 to InO (n = 164) or SC (n = 162). Data up to Jan 4, 2017 are reported. Results: Adverse event (AE) and serious AE rates were similar between arms even though more cycles of InO than SC were administered (Table). Grade (Gr) 3-4 AE rates were higher with SC, while more Gr 5 AEs occurred with InO vs SC (6% vs 2%); 5 cases (3%) were vena-occlusive disease (VOD). More pts taking InO discontinued due to AEs, most often from infections (10 (6%) including pneumonia and sepsis, hepatic disorders (7 (4%)), or less frequently lymphoproliferative disorders (LBD) including cytopenias (6 (3%)). For SC, discontinuations were most often from infections (6 (4%) or VOD (3 (2%)). More hepatic AEs (any Gr) occurred with InO: 83 (51%) vs 52 (36%), including VOD (23 (14%) vs 3 (2%). A lower percentage of death was seen with InO: 131 (80%) vs 125 (88%) for SC. Fewer pts died from ALL: 8 (5%) vs 9 (6%) for SC. Clinical trial information: NCT01564784.

Conclusions: Safety data from the final report of INO-VATE are consistent with previous reports of data that also include greater efficacy (longer survival) seen with InO vs SC. Temporary discontinuation and dose reduction of InO were used to manage serious or severe AEs. Data suggest vigilant monitoring, treatment, and/or prevention for the most common events such as VOD and infections needed to be optimized.

7031 Poster Session (Board #91), Mon, 8:00 AM-11:30 AM

Phase 1 trial of pegzilarginase in patients (pts) with relapsed/refractory (R/R) AML or MDS refractory to hypomethylating agents (HMA's).

First Author: Geoffrey L. Uy, Washington University School of Medicine, St. Louis, MO

Background: In vitro studies demonstrate that AML cells are arginine auxotrophs and are metabolically vulnerable to arginine depletion (PMID: 24018014 & 25896651). To test the clinical utility of arginine depletion in AML we performed a phase 1 trial of pegzilarginase, a pegylated, recombinant, cobalt-substituted, human arginase I in pts with R/R AML or MDS refractory to HMA's.

Clinical trial information: NCT02732184.

Conclusions: Pegzilarginase was well tolerated up to 0.36 mg/kg with a manageable safety profile. PK/PD data support dose-escalation, as confirmed by a robust reduction in plasma arginine. The observed results are consistent with a recent Ph 2 trial of arginine depletion in AML (PMID: 28900115), suggesting depletion of arginine alone is insufficient for clinical activity in AML. Alternative approaches including combination therapy may be required. Clinical trial information: NCT02732184.

7030 Poster Session (Board #90), Mon, 8:00 AM-11:30 AM

Outcomes with inotuzumab ozogamicin (InO) in patients with Philadelphia chromosome-positive (Ph+) relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). First Author: Shuguang Shi, Department of Hematology/Oncology, Department of Medicine, University of Chicago Pritzker School of Medicine, Chicago, IL

Background: InO, a CD22-directed antibody-drug conjugate, is approved to treat adults with R/R ALL. Historically, patients (pts) with Ph+ ALL (≥20–30%) have had poor prognoses compared with Ph− pts. Methods: Pts with R/R ALL received InO in a phase 1 dose-finding/phase 2 study (1010; Dohse et al. Blood Adv 2017) and a phase 2 trial (1022; Kantarjian et al, NEJM 2016) comparing InO vs standard chemotherapy (SC). We analyzed outcomes in Ph+ pts vs Ph− pts (Ph chromosome or BCR-ABL gene by FISH) treated with InO (InO-1010 or InO-1022) or SC based on final data from each study.

Results: In 1010 and 1022, respectively, 16 and 22 Ph+ pts received InO; 27 Ph+ pts were randomized to SC in 1022 (22 received SC). Pts in 1010 were heavily pretreated. Among Ph+ pts in 1022, 19 (86%) InO and 26 (96%) SC pts had previous tyrosine kinase inhibitors (TKIs). Prior stem cell transplants (SCT) were 8 (50%) for InO-1010, 7 (32%) for InO-1022, and 9 (33%) for SC. Also, 15 (94%), 10 (45%), and 15 (56%) pts were treated in ≤2nd salvage for InO-1010, 1022, and SC, respectively. Efficacy outcomes are shown (Table). A total of 3 (19%) InO-1010 pts, 9 (41%) InO-1022 pts, and 5 (19%) SC pts proceeded to SCT after treatment. The most common non-hematologic grade 3-4 adverse events with InO in Ph+ pts were gastrointestinal disorders (31%) in 1010 and multi-organ laboratory abnormalities (41%) in 1022. Ph+ pts in each InO study had vena-occlusive liver disease (VOD) vs SC pts. Infections (55%) were the most common grade 3-4 non-hematologic events. Clinical trial information: NCT01363297.

Conclusions: In Ph+ pts with R/R ALL who failed prior TKIs +/- SCT, InO-treated pts had higher rates of CR/CRI, MRD negativity, and subsequent SCT. However, overall outcomes in InO-1022 vs SC were still inferior to those reported in Ph− pts; thus additional treatment combinations should be explored.

7032 Poster Session (Board #82), Mon, 8:00 AM-11:30 AM

A retrospective study of comorbidities and complications in elderly acute myeloid leukemia (AML) patients and U.S. First Author: Neil Dhopeshwarkar, Daichi Sankyo, Basking Ridge, NJ

Background: Treatment decisions are often influenced by comorbidity and functional capacity. Comorbidity burden in patients with AML has been shown to increase by age, but there is limited characterization of comorbidities and complications in elderly AML patients, who generally are underrepresented in clinical trials. We characterized elderly AML patients in terms of comorbidities and complications. Methods: Pts with AML who were treated at a single institution (InPh) were enrolled in a phase 1 dose-finding study and had vena-occlusive liver disease (VOD) vs SC pts. Infections (55%) were the most common grade 3-4 non-hematologic events. Clinical trial information: NCT01363297.

Conclusions: In Ph+ pts with R/R ALL who failed prior TKIs +/- SCT, InO-treated pts had higher rates of CR/CRI, MRD negativity, and subsequent SCT. However, overall outcomes in InO-1022 vs SC were still inferior to those reported in Ph− pts; thus additional treatment combinations should be explored.

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Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allografts

7033 Poster Session (Board #93), Mon, 8:00 AM-11:30 AM
Hypomethylating agent (HMA) treatment as a bridge to allogeneic hematopoietic cell transplantation (HCT) for relapsed/refractory acute myeloid leukemia (R/R-AML). First Author: Michael Richard Grunwald, Levine Cancer Institute, Atrium Health, Charlotte, NC

Background: Outcomes for patients (pts) with RR-AML are poor, with limited treatment options. Salvage HMA therapy has been explored, including HCT rates and outcomes. Methods: All RR-AML pts initiated on HMAs at our institution between August 2013 and August 2017 were analyzed. Overall response (ORR) included complete remission (CR), CR with incomplete platelet recovery (CRp), CR with incomplete count recovery (CRI), and hematologic remission (defined by neutrophils > 1000/µL, platelets > 100/µL, transfusion independence, and no peripheral blasts). We assessed the number of pts receiving HCT and their outcomes. Overall survival (OS) was estimated by Kaplan-Meier method. Log rank test was used for comparisons. Results: Fifty RR-AML pts received HMAs. Median age at HMA start was 58 years (range, 24-81); 54% of pts were male. NCCN risk categories at diagnosis were 14% favorable, 32% intermediate, and 54% unfavorable. FLT3-ITD mutations were present in 21% of pts, FLT3-TKD in 10%, and NPM1 in 31%. Most pts (72%) received azacitidine; 28% received decitabine. Concomitant with their HMA, 28% of pts received lenalidomide, and 16% (all FLT3-ITD) received sorafenib. Cyto reduction with hydroxyurea or cyclophosphamide was given to 20%. Among 37 evaluable pts, ORR was 57%. For the entire 50 pt cohort, ORR was 42%; median OS was 9.5 months. There was no correlation between survival and NCCN risk at diagnosis (p = 0.98) or at the start of HMA (p = 0.85). Most pts (84%) had received 1 prior line of therapy, while 16% had received 2 lines. Pts naive to HMAs had OS superior to those with previous HMA exposure (median OS, 13.0 vs. 5.3 months; p = 0.02). For those receiving HMA therapy, 14 pts (28%) underwent HCT. In this group with a median follow-up of 19.2 months, 1-year OS was 100%, and 2-year OS 78%. Conclusions: HMA therapy for RR-AML can yield response and survival rates comparable to other, more toxic therapies. Additionally, HMAs can be used to bridge RR-AML pts to HCT, with encouraging outcomes. These results warrant validation in a large prospective study.

7035 Poster Session (Board #95), Mon, 8:00 AM-11:30 AM
Quality of life and psychological distress in patients with acute myeloid leukemia (AML). First Author: Julia Carp, Massachusetts General Hospital, Boston, MA

Background: Older patients with AML face difficult treatment decisions as they can be treated either with multi-drug ‘intensive’ chemotherapy requiring a prolonged hospitalization, or ‘non-intensive’ chemotherapy. Although clinicians often perceive intensive chemotherapy as more burdensome, studies comparing older patients’ quality of life (QOL) and psychological distress while receiving these treatments are lacking. Methods: We conducted a longitudinal study of older patients (≥60 years) newly diagnosed with AML receiving intensive (i.e. 7+3: cytarabine/anthracycline combination) or non-intensive (i.e. hypomethylating agents) chemotherapy at two tertiary care hospitals. We assessed patient’s QOL (Functional Assessment of Cancer Therapy-Leukemia), and psychological distress (Hospital Anxiety and Depression Scale [HADS]) at baseline and 2, 4, 8, 12, and 24 weeks after diagnois. We compared the proportion of patients in each group reporting clinically significant depression or anxiety (HADS subscale cut off ≥7) and used mixed linear effects models to compare QOL and psychological distress longitudinally between groups. Results: We enrolled 75.2% (100/133) of eligible patients within 72 hours of initiating intensive (n = 50) or non-intensive (n = 50) chemotherapy. Baseline QOL, depression, or anxiety symptoms did not differ between the groups. At baseline, 33.33% (33/100) and 30% (30/100) of the overall cohort reported clinically significant depression and anxiety, respectively, with no differences between groups. At 24 weeks, 41.98% (34/81) of patients in the overall cohort reported clinically significant depression, with no differences between groups. In mixed linear effects models, there were no differences in QOL (b = -0.71, SE = 1.12, P = 0.527), depression (b = 0.24, SE = 0.20, P = 0.226), or anxiety (b = -0.16, SE = 0.19, P = 0.386) symptoms over all time points. Conclusions: Older patients with AML receiving intensive and non-intensive chemotherapy experience similar QOL and high rates of psychological distress. These findings underscore the need to develop supportive care interventions for older patients with AML, regardless of their initial treatment strategy.

7034 Poster Session (Board #94), Mon, 8:00 AM-11:30 AM
Treatment of relapsed/refractory (R/R) B-cell malignancies by chimeric antigen receptor T cells cultured from patients (pts) with 50-100 mL peripheral blood in 7-10 days. First Author: Luan Han, Department of Immunology, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

Background: Anti-CD19 chimeric antigen receptor (CAR) T cells for R/R B-cell malignancies has been remarkably effective in recent clinical trials. However, the training process is complex and long. We try to seek a method, which the preparation process is simple and short. Methods: We extracted 50-100 mL peripheral blood from patients (pts), and the CAR-T cells cultured 7-10 days to back to pts. All pts received a chemotherapy of cyclophosphamide and fludarabine followed by 1-3x10^10 CAR-T cells/kg, and were monitored for re- sponse. Results: CAR-T cells were capable of large numerical expansion in 7-10 days, up to about 5x10^10 magnitudes, and the culture success rate reached to 100%. We treated 29 pts with R/R B-cell malignancies (17 ALL and 12 B-cell lymphoma). Complete remissions (CRs) was achieved in 16 ALL pts (100%) 1 month after CAR-T cells infusion and CRs in 15 pts were MRD-negative, except 1 pt died in cytokine release syndrome (CRS). The CRs were 71.4% at 3 months and 56.0% at 6 months, respectively. 12 pts experienced CRS and severe CRS had 11.76% in 1 of 12 B-cell lymphoma, 4 achieved CR, 5 achieved PR, and 3 had progress disease (PD) when evaluated in 2 months. The CRs and overall response were 37.5% and 50.0% at 6 months, respectively. 2 pts were observed with CRS in lymphoma. Conclusions: Treatment of R/R B-cell malignancies with a high CRs by CAR-T cells, which cultured from patients' peripheral blood and achieved larger amount of amplification in short time. These results could be benefit for more high-risk pts. Clinical trial information: NCT02942753 NCT0310709.

7036 Poster Session (Board #96), Mon, 8:00 AM-11:30 AM
In acute myeloid leukemia patients CpG-methylation changes associated with response to induction chemotherapy. First Author: Christian Dietger Niederwieser, Department of Internal Medicine IV, Hematology and Oncology, University Hospital Halle, Germany, Halle, Germany

Background: Acute myeloid leukemia (AML) is a heterogeneous disease associated with epigenetic alterations targetable with demethylating agents. However, predictive response markers are missing. Here we analyzed the methylation changes of transcription factor (TF) binding motifs in resistant patients after treatment with or without azacytidine (Aza) followed by induction chemotherapy. Methods: Twenty refractory patients from the AML-AZA trial of the Study Alliance Leukemia receiving Aza followed by induction chemotherapy (n = 16/105) or chemotherapy alone (n = 4/109) were selected to perform genome wide DNA methylation analyzes using a 450K Illumina array (Illumina, San Diego, USA) before and on day 15 after therapy start. Methylation changes from day 0 to 15 corrected for %blasts were identified and motifs detected using HOMER software (Salk institute, San Diego, USA). Methylation variation was analyzed according to treatment with Aza and/or chemotherapy. Results: In the Aza chemotherapy group, a total of 389 differentially methylated regions (DMRs), most of them single CpGs, were identified, 176 hyper- and 213 hypomethylated. In methylation clustering analyses, patients with a reduction/increase of blasts clustered separately together. Those with blast reduction were more likely female and FLT3-ITD mutated. The most highly represented de novo motifs (differential enrichment between 2 sets of sequences) were associated with 5 (hypomethylation) and 10 TFs (hypo- and hypermethylation). The chemotherapy only group had 7181 DMRs, 5752 hyper- and 1429 hypomethylated. We found 24 and 12 TFs for the hyper- and hypomethylated loci in these patients, respectively. The known motifs (based on listing of motifs from previous data) in the Aza/chemotherapy group of the enriched TFs were identified (hypomethylation) by 17 TFs (Jun-API (p = 1e-7); hypomethylated: 4 TFs, QATA (p = 1e-2)). For the chemotherapy group we found 90 TFs (EHF (p = 1e-126) and 43 TFs (RUNX1 (p = 1e-18)) for hyper- and hypomethylated sites, respectively. Conclusions: DNA methylation of specific TF binding motifs may be associated with therapy resistance and could be used for response prediction of therapy with Aza and/or chemotherapy. Clinical trial information: NCT00915252.
Factors influencing first-line therapy of acute myeloid leukemia (AML) patients (pts) in the Connect MDS/AML Disease Registry.

**Methods:** The Connect™ MDS/AML Registry (NCT01688011) is an ongoing US, prospective observational cohort study of pts with newly diagnosed AML (≥ 18y) or MDS. Baseline demographics, median census income per capita (determined by ZIP code), disease characteristics, and genomic and treatment data were collected on AML pts enrolled from Dec 2013 to Oct 2017. Pts were categorized as receiving 1LTx (low- or high-intensity) or best supportive care (BSC) based on care provided ≈ 45 d after AML diagnosis (dx). Pts participating in clinical trials (n = 11) were excluded to focus on standard treatment practice. Uni- and multivariable logistic regression identified factors associated with 1LTx. **Results:** Data on 378 AML pts from 100 institutions (19 academic, 81 community/government) were analyzed. Median age was 70 y (range 55–92), 64% were male, and 83% were white. Most had private/Medicare insurance coverage (86%); average median income was USD 25,984. 77% of the cohort received 1LTx; 23% received BSC. 87% died at dx, of whom 90% had received 1LTx (P < 0.05). 77% had FISH or cytogenetic testing and 71% had molecular genetic testing, with 46% harboring ≥ 1 gene mutation. While age and comorbidities were predictors of 1LTx (P < 0.01) in univariable modeling, disease characteristics and genomic and treatment data were not associated with 1LTx. **Conclusions:** Our study confirms results from prior studies, and we identified several independent predictors of 1LTx in a large cohort of AML pts. These predictors may be useful in clinical practice, and future studies should investigate the impact of treatment on outcomes.

**Characteristics and outcomes of acute myeloid leukemia (AML) with extramedullary disease (EMD) in older adults with newly diagnosed, high-risk/secondary acute myeloid leukemia (sAML).**

First Author: Tara L. Lin, University of Kansas Medical Center, Kansas City, KS

**Background:** EMD has been reported in 2.5–30% of AML patients (pts). The Connect MDS/AML Registry (NCT01688011) is an ongoing US, prospective observational cohort study of pts with newly diagnosed AML (≥18y) or MDS. Baseline demographics, median census income per capita (determined by ZIP code), disease characteristics, and genomic and treatment data were collected on AML pts enrolled from Dec 2013 to Oct 2017. Pts were categorized as receiving 1LTx (low- or high-intensity) or best supportive care (BSC) based on care provided ≈ 45 d after AML diagnosis (dx). Pts participating in clinical trials (n = 11) were excluded to focus on standard treatment practice. Uni- and multivariable logistic regression identified factors associated with 1LTx. **Results:** Data on 378 AML pts from 100 institutions (19 academic, 81 community/government) were analyzed. Median age was 70 y (range 55–92), 64% were male, and 83% were white. Most had private/Medicare insurance coverage (86%); average median income was USD 25,984. 77% of the cohort received 1LTx; 23% received BSC. 87% died at dx, of whom 90% had received 1LTx (P < 0.05). 77% had FISH or cytogenetic testing and 71% had molecular genetic testing, with 46% harboring ≥ 1 gene mutation. While age and comorbidities were predictors of 1LTx (P < 0.01) in univariable modeling, disease characteristics and genomic and treatment data were not associated with 1LTx. **Conclusions:** Our study confirms results from prior studies, and we identified several independent predictors of 1LTx in a large cohort of AML pts. These predictors may be useful in clinical practice, and future studies should investigate the impact of treatment on outcomes.

**Characteristics and outcomes of acute myeloid leukemia (AML) with extramedullary disease (EMD) in older adults with newly diagnosed, high-risk/secondary acute myeloid leukemia (sAML).**

**Methods:** We reviewed medical records of all AML pts treated at MDACC from 8/12 to 1/2018. Among 2388 pts, 88 (3.7%) had EMD; 30 were newly diagnosed. The sites involved were skin (n = 14), central nervous system (CNS) (n = 6), musculoskeletal (n = 6), nodal (n = 4) and intestinal (n = 2), 27/30 (90%) had concomitant marrow disease. Most relevant characteristics are in Table. Cytogenetics (CG) were not different between EMD and non-EMD pts (p = 0.1). Compared to non-EMD pts, pts with EMD had more KIT mutations (p = 0.003) but not FLT3-ITD, NPM1, RAS or IDH. The median overall survival (mos) was shorter (6.1 vs 18.4 months; p = 0.004) in pts with EMD. On univariate analysis, the presence of any EMD (p = 0.02), skin involvement (p = 0.04) but not CNS (p = 0.9) was associated with shorter OS. There was no OS difference between KIT-mutated and wild-type EMD pts (p = 0.5). Of the 58 relapsed EMD (28 in 1st relapse and 30 in 2nd relapse); 13 had isolated EMD, 45 had concurrent marrow disease and 18 had prior SCT. The common sites involved were CNS (n = 32; 23 had isolated and 9 had ≥ 2 sites), skin (n = 11) and musculoskeletal (n = 6). Compared to non-EMD pts, there was no difference in CG and molecular characteristics. On univariate analysis, the mOS was not significantly different in pts with relapsed EMD compared to non-EMD pts. 58 vs 5.9 months; p = 0.3), whether in first relapse (p = 0.3) or ≥ 2nd relapse (p = 0.5). **Conclusions:** AML carries a poor prognosis. The role of genetic and molecular markers warrants further investigation especially for treatment planning and clinical follow-up post remission.

**Low-toxic myeloablative conditioning regimen in haploidentical hematopoietic stem cell transplantation for elderly patients with acute myeloid leukemia.**

First Author: Cynthia Arteaga, St. Luke’s University Hospital, Perkasie, PA, and Biomedical Sciences, University of Perugia and Perugia General Hospital, Perugia, Italy

**Background:** Elderly candidates for hematopoietic stem cell transplantation (HSCT) cannot tolerate myeloablative conditioning regimens because of regimen-related toxicity and mortality rates. To lower them in elderly patients with acute myeloid leukemia (AML) who underwent 1-haplo and haplo HSCT, we designed a conditioning regimen with total marrow/totallymphoid irradiation (TMI/TLI) and low chemotherapy doses. The graft contained, as adoptive immunotherapy, a ratio of conventional T cells (Tcons) and T regulatory cells (Treg) that induce a graft versus leukemia effect with a low incidence of graft versus Host Disease (GVHD). **Methods:** July 2015-October 2017: 14 AML patients (median age 62 years, 6 in 1th and 7 in 2nd complete remission, 1 in partial remission) underwent haploidentical HSCT. **Conclusions:** Our study shows that low-intensity conditioning can be effective in elderly AML patients and may be a bridge to immunotherapy in patients with acute myeloid leukemia in partial remission.

**Characteristics and outcomes of acute myeloid leukemia (AML) with extramedullary disease (EMD) in older adults with newly diagnosed, high-risk/secondary acute myeloid leukemia (sAML).**

First Author: Tara L. Lin, University of Kansas Medical Center, Kansas City, KS

**Methods:** Pts were randomized 1:1 to receive 1-2 inductions of CPX-351 (100 units/m² [C 100 mg/m² + D 44.4 mg/m²] on Days 1, 3, 5 [2nd induction: Days 1, 3, 5]) or 7+3 (C 100 mg/m²/21 days [2nd induction: 5 d] + D 60 mg/m² × Days 1-3 [2nd induction: Days 1-2]). Pts achieving complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidations. **Results:** 304 pts were treated with CPX-351 (n = 153) or 7+3 (n = 151). A greater proportion of pts treated with CPX-351 achieved remission after 1 induction vs 7+3 (CR: 45% vs 28%; CR+CRi: 55% vs 34%; Table). Remission rates after 2 inductions were comparable between arms (CR: 21% vs 24%; CR+CRi: 31% vs 35%; Table). The frequency of grade 3-5 treatment-emergent adverse events (TEAEs) in pts with 1 induction was similar for CPX-351 (75/1015 [7%]) vs 7+3 (74/1002 [7.4%]). In pts with 2 inductions, fewer pts had grade 3-5 TEAEs with CPX-351 (38/479 [8%]) vs 7+3 (48/511 [9.4%]). Febrile neutropenia was the most common grade 3-5 TEAE with both CPX-351 and 7+3 (1 induction: 58% vs 57%; 2 inductions: 60% vs 80%). Serious TEAEs were similar with CPX-351 and 7+3 (1 induction: 33% vs 33%; 2 inductions: 29% vs 26%). **Conclusions:** Pts treated with CPX-351 were more likely to achieve remission after 1 induction vs 7+3; remission rates were similar after 2 inductions. Pts who received CPX-351 had a similar frequency of grade 3-5 TEAEs after 1 induction and fewer grade 3-5 TEAEs after 2 inductions: 29% vs 26%). Pts treated with CPX-351 were more likely to achieve remission after 1 induction vs 7+3; remission rates were similar after 2 inductions. Pts who received CPX-351 had a similar frequency of grade 3-5 TEAEs after 1 induction and fewer grade 3-5 TEAEs after 2 inductions: 29% vs 26%.

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47 of 108 patients received on-study HSCT in CCR.

- Patients with on-study HSCT in CCR.

- Patients with CNS disease.

- Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Feasibility of HSCT vs consolidation therapy for AML patients aged 60-75 in CR1: A randomized phase III, multicentre EDMT study. First Author: Dietger Niederwieser, University of Munich, Munich, Germany. Background: AML has a particularly dismal prognosis in the elderly population. The OSHO, HOVON, SAKK and the French AML study groups performed a randomized phase III study comparing Hematopoietic Stem Cell Transplantation (HSCT) to conventional chemotherapy in these patients. Methods: Patients aged 60 – 75 years with AML CR1 (except FAB M3) were randomized after induction therapy according to group protocol. A donor search was initiated during consolidation. Patients with a related or matched unrelated donor were randomized within 150 days of diagnosis to receive either HSCT or non-HSCT in a 2:1 ratio. Patients in the HSCT arm were treated with Fludarabine/200 cGy total body irradiation followed by cyclophosphamide/mycophenolate mofetil. Patients in the non-HSCT arm continued therapy according to the study group protocols. Leukemia free survival was chosen as primary endpoint. Patients without a donor were included in the observation arm. Results: A total of 245 patients from 23 centers in five countries were registered and started consolidation. Sixty six patients (26.8%) exited the study by induction failure, death or protocol withdrawal. Randomization proceeded for 125 (51.0%) patients. Of the 83 in the HSCT arm, 16 were not transplanted. Of the 42 patients in the non-HSCT arm, 6 did not receive the scheduled second consolidation and information is pending in 7. Endpoint analysis is due in 2020. Conclusions: The feasibility of HSCT in elderly patients with AML CR1 within 150 days of consolidation was demonstrated in a randomized European study. Donor identification and randomization was achieved for a large proportion of patients (75.9% and 51.0%). Despite a short treatment interval of ≤12 weeks from consolidation to HSCT/non-HSCT, relapse (n = 39) and toxicities (n = 14) were the most frequent cause of end of study. Clinical trial information: EudraCT Number 2007-003514-34.

Molecular testing during AML treatment for early prediction of clinical response. First Author: Hong Yuen Wong, Laboratory of Myeloid Malignancies, Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD. Background: Early prediction of response in acute myeloid leukemia (AML) patients undergoing cytotoxic chemotherapy may have clinical utility. Currently, measurable residual disease (MRD) testing after initial chemotherapy treatment can predict relapse and survival in AML. However, it has not been established if more molecular or genetic testing during chemotherapy can offer information regarding the chemotherapy sensitivity of the leukemic clone. Methods: Blood from 45 adult AML patients at day 1 and 4 of induction (n = 35) or salvage (n = 10) cytotoxic chemotherapy was collected for next generation sequencing (NGS) detection of NGS detectable mutations in blood suggests that cytotoxic therapy may have a limited therapeutic specificity for clones containing these mutations. Clinical trial information: EudraCT Number 2007-003514-34.

Mutations in TP53, encoding tyrosine phosphatase SHP2, are present in 4-6% of AML. Largest report includes 27 patients (pts). Methods: Analysis included AML patients (pts) treated at MD Anderson Cancer Center between 2012 and 2017, positive for TP53 mutations by next generation sequencing. We evaluated baseline parameters, co-occurring mutations, allelic burden and clinical outcome. Results: We identified 122 pts (62 (51.0%) male, median age 64 yrs (19-86)), among whom 64 (52.5%) treatment naïve and 58 (47.5%) salvage. In treatment naïve group, 26.6% had favorable risk (per ELN2017) (median overall survival (mOS) = 617 days (range 8-1151)), 23.4% intermediate (mOS = 33 days (Range 1-1403)) and 50% poor risk (mOS = 226 days (Range 0-301)) (P = 0.0086). Chr 3 abnormalities were present in 9 pts (14.1%), 14 pts (18.8%) had complex karyotype and 33 pts (33%) were diploid. Most common co-mutations were TET2 (51.9%), DNMT3A (33.3%), NPM1 (31.3%), and FLT3-ITD (26.6%). Table. Variant allelic frequency (VAF) for mutant TP51L. With a cutoff of 0.4 further stratified poor risk AML into very poor (VAF ≥0.4; mOS = 194 days (Range 18-305)) and poor (VAF < 0.4; mOS = 314 days (Range 3-645), (P = 0.01), HR 6.16, CI 95% 1.5-24.6). Similarly among patients with non-diploid karyotype, the first VAF cut-off stratified patient survival (P = 0.007, HR 3.27, CI 95% 1.2-8.7). In the salvage group also, VAF stratified pts for survival; [≥0.4 vs < 0.4 (P = 0.01, HR 5.14, CI 95% 1.48-17.8). Conclusions: We report the largest survey of TP53 mutations among adult leukemia patients. Ruminent experience of MELT-ITD mutation, VAF above 0.4 is poor on patient outcomes. Targeted therapies have the potential of improving outcomes.

Molecular and cytogenetics characteristics.

**Characteristics**

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**Cytogenetics**

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Phase 1 study of selinexor plus mitoxantrone, etoposide, and cytarabine in acute myeloid leukemia (AML). First Author: Bhavana Bhatnagar, The Ohio State Univ Comp Cancer Ctr, Columbus, OH. Background: Patients (pts) with relapsed or refractory (R/R) acute myeloid leukemia (AML) have limited treatment options. Selinexor (SEL), an oral inhibitor of the nuclear transport protein XPO1, has shown promising single-agent activity in clinical trials of AML and preclinical synergy with topoisomerase (topo) II inhibitors. Hence, we tested the combination of SEL plus chemotherapy with topo II inhibitor in pts with R/R AML. Methods: This phase 1, open-label 3+3, dose escalation study tested SEL plus mitoxantrone, etoposide, and cytarabine (MEC) in pts aged < 60 years with R/R AML (NCT02299518). The primary objectives were to evaluate the safety and preliminary efficacy of this combination. Pts received MEC IV on days 1-6, and up to 6 doses of SEL, across 3 dose levels ranging from 30-55 mg/m² on days 1, 3, 8, 10, 15, and 17. Results: We enrolled 23 pts (median age 47 years); 11 were treated on the dose escalation portion. Due to dose limiting hyponatremia in 2 pts on dose level 2 (SEL 40 mg/m²), the maximum tolerated dose was 30 mg/m². However, based on the total of safety data from other SEL trials in R/R AML, we established the RP2D of SEL in pts with AML to be 60 mg. We treated an additional 12 pts with 60 mg of SEL in combination with MEC, Common grade ≥3 toxicities for 21 treated pts for whom all analyses are complete (2 remain on therapy) are shown in Table 1. Of 21 pts, the overall response rate was 39% with 4pts (19%) achieving complete remission (CR), 2 (10%) with CR with incomplete count recovery, and 2 (10%) with a morphologic leukemia-free state. Five responders proceeded to allogeneic stem cell transplantation. Conclusions: SEL plus MEC is a feasible treatment for pts with R/R AML. Toxicities of the combination are similar to cytotoxic chemotherapy alone. Clinical trial information: NCT02299518.
Pharmacodynamic characterization of eryaspase (L-asparaginase encapsulated in red blood cells) in combination with chemotherapy in a phase 2/3 trial in patients with relapsed/refractory acute lymphoblastic leukemia (NCT01518517). First Author: Iman El-Hariry, Erytech Pharma, Cambridge, MA

**Background:** L-asparaginase (ASNase) is a key drug in the treatment of ALL. ASNase therapy aims to lower serum asparagine (ASN) levels, but critical minimum value for efficacy has yet been established. ASN levels are difficult to measure accurately due to ex vivo depletion during the time required to harvest plasma from blood samples and to quench the enzyme, even if samples are immediately processed and on ice. ASN is an investigational product under development. Following infusion of eryaspase, ASN is actively transported into RBCs, where it is hydrolized by the encapsulated ASNase. **Methods:** This randomized Phase 2/3 study enrolled pts with relapsed ALL. The co-primary endpoints were the mean duration of ASNase activity > 100 U/L and incidence of allergic reactions during the induction phase. Secondary endpoints were safety, complete remission (CR), pharmacokinetics (PK), and pharmacodynamics (PD). Pts (n = 80, 1-55 years) were randomized to eryaspase or native ASNase. **Results:** The mean duration of ASNase activity > 100 U/L measured in whole blood was significantly higher with eryaspase (18.9 ± 6.6 days) vs native ASNase (8.5 ± 6.6 days). In both treatment arms, ASN depletion ≤ 2 μM was maintained for ~7 days in 75% of pts. The mean duration of ASN depletion ≤ 2 μM was 6.0 ± 5.0 and 11.6 ± 7.3 days with eryaspase and native ASNase, respectively. Experatory receiver operating characteristic (ROC) analysis suggested an optimal threshold of ≤ 7.55 μM ASN of Day 6 correlated with CR with a positive predictive value of 0.88. **Conclusions:** The assumed requirement for prolonged ASN depletion in patients receiving ASNase therapy is likely to be an overestimation caused by ex vivo depletion that is observed with free ASNase. Measurement of ASN depletion in pts treated with eryaspase was more promising. Accordingly, the efficacy of encapsulated ASNase cannot be accurately compared with that of free ASNase based on ASN depletion. ASN depletion ≤ 2 μM may not be needed with asparagine, and a level ≤ 7.55 μM correlated with CR. Clinical trial notification: NCT01518517.

7051 Poster Session (Board #111), Mon, 8:00 AM-11:30 AM
Comparison of somatic mutations profiles from next-generation sequencing (NGS) of cell-free (cfDNA) versus bone marrow (BM) in acute myeloid leukemia (AML). First Author: Rita Elias Assi, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** NGS of cfDNA is a novel non-invasive strategy to define mutational profiles in many solid tumors, and can be used for real-time molecular monitoring of treatment and detection of resistance or disease recurrence. We examined the feasibility of cfDNA NGS in AML and compared mutation profiles to a BM NGS panel at multiple time points during therapy. **Methods:** Plasma cfDNA was collected and analyzed using a capture-based NGS assay (Qia247) targeting 275 genes. BM NGS was performed on DNA extracted from the sample in CLIA-certified molecular diagnostics laboratory for the detection of somatic mutations in the coding sequence of 28 or 81 genes. NGS profiles from cfDNA and BM were analyzed with an established bioinformatics pipeline to identify somatic variants. **Results:** 24 patients (pts) with median age of 42 years (24-61) were prospectively enrolled and 13 had serial cfDNA and BM samples for testing. NGS analysis of cfDNA detected a median of 3 deleterious somatic mutations (range 1-22) (allele frequency (AF) > 0.1%, passing bioinformatic quality filters) with AF ranging from 1.5-96.5%. When matched to common mutations in both NGS panels, cfDNA harbored a median of 3 new mutations (1-8) in 83% (20/24) of pts, not detected in BM NGS panel. BM and cfDNA NGS detected identical mutations in 1/24 (4%) pt while BM NGS detected additional mutations in 3/24 (13%) pts where NGS cfDNA failed to do. Of the 20 pts on whom complete remission samples are available, 17 (85%) had a median of 3 alterations (2-8) by cfDNA including actionable mutations not detected by BM NGS. **Conclusions:** NGS of cfDNA is feasible in AML and successfully detects prior and novel mutations when BM sequencing shows absence of these mutations in a matched panel of genes. The discrepancies between BM and cfDNA mutation profiles seen in many pts may reflect leukemic evolution or intra-leukemic heterogeneity. Plasma cfDNA for genomic profiling is a promising and non-invasive strategy and further investigation of its utility is warranted in AML.
Background: The revised 2017 European Leukemia Net (ELN) classification of AML divides patients into 3 prognostic risk categories, with additional factors such as FLT3-ITD allele ratio (AR) considered for risk stratification. We evaluated the prognostic utility of ELN-2017 in comparison with ELN-2010 in younger pts with AML treated in our institution. Methods: Pts (< 60 years) who received idarubicin plus high dose cytarabine (IA) - based induction chemotherapy for newly diagnosed AML were reviewed. Cox regression analyses were fitted with baseline prognostic factors, including cytogenetic and molecular mutation status, with receipt of allogeneic transplantation (SCT) as a time-dependent covariate. Results: According to ELN-2017 criteria, the number of pts in the favorable (fav), intermediate (int), and adverse (adv) categories were 198 (28%), 335 (47%), and 185 (26%), respectively. Overall survival (OS) at 5 years (yrs) in the fav, int, and adv groups was 57%, 37%, and 19%, respectively. In comparison, the 5-y OS probabilities in the fav (n = 192), int-1 (n = 76), and int-2 (n = 276) and adv (n = 185) ELN-2010 categories were 59%, 32%, 39%, and 15%, respectively. Although ELN-2010 historically distinguishes prognosis into int-1 and int-2 categories in younger pts, this difference was nullified in our cohort probably due to the use of high dose cytarabine (int-2 vs. int-1: HR 0.61 [0.37 - 1.01]; p = 0.06). By cox-regression, SCT was associated with decreased risk of mortality only in int adv and AML, but not in the fav subgroup. To evaluate whether FLT3-ITD AR impacted prognosis, we divided pts into (FLT3-ITD wt and FLT3-ITD AR) based on AR cut-off of 0.5 and found no significant differences in survival between these groups, in patients with NPM1 mutated AML (p = 0.40) or in those with wild type NPM1 treated with either IA alone [n = 55] (p = 0.61) or in combination with FLT3 inhibitors [n = 161] (p = 0.175). Conclusions: The ELN-2010 more accurately distinguishes prognosis by replacing the ELN-2010 int-1 and int-2 groups with a single int category. Prognostic significance of the FLT3-ITD AR needs further evaluation. SCT should be considered in the post remission setting in IR and adv risk AML pts.

Background: Traditionally, patients eligible for induction chemotherapy for AML are treated with the "7+3" regimen, which includes standard doses of infusional cytarabine and an anthracycline, with historical CR rates of 50-60%. We conducted a retrospective analysis of an alternate induction regimen. Based on timed sequential therapy, it consists of a 2-day treatment with high dose cytarabine, which improves remission rates when used in induction, and dose intensified anthracyline therapy, which improves outcomes in younger patients. We present the analysis of the regimen and the response rates of patients based on risk stratification, history of prior therapy and (c) GVHD, non-relapse mortality (NRM), relapse/progression (R/P) and progression-free survival (PFS). Results: The baseline characteristics are shown in Table. The cumulative incidence of day 180 grade 3-4 aGVHD and 1 year cGVHD was 7%, 11%, 13% and 19% (p < 0.001) and 15%, 41%, 23% and 48% (p < 0.001) in the haploHCT + MSD vs MUD w A-C groups, respectively. The 3 year post HCT univariate outcomes for the haploHCT, MSD, MUD w A-C and MUD w/o A-C cohorts were as follows: NRM (22% v 17% v 26% v 36%) and 15%, 41%, 23% and 48% (p < 0.001) relative to haploHCT the 3 other groups did not have a significantly different R/P risk, but compared to MSD, the MUD w A-C pts had a significantly higher R/P risk (RR 2.0) and MUD w/o A-C (RR 4.0) were associated with significantly higher risk of cGVHD (p < 0.001). Relative to haploHCT the 3 other groups did not have a significantly different R/P risk, but compared to MSD, the MUD w A-C pts had a significantly higher R/P risk (RR 1.45; p = 0.008). MVA showed no significant difference between the 4 cohorts in terms of R/P, NRM, or progression free survival (PFS) OS (p = 0.53). Conclusions: Survival outcomes are comparable between RIC MSD, MUD and PT-Cy based haploHCT in DLBCL. cGVHD was significantly lower with haploHCT.
Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

7057 Poster Session (Board #117), Mon, 8:00 AM-11:30 AM
Development and validation of a risk assessment tool for symptomatic BKV infection. First Author: Ala Abudayeh, Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BKV, is a member of the family Polyomaviridae. BKV has been associated with increased morbidity and mortality secondary to late hemorrhagic cysts, ureteral stenosis, and nephropathy. In our retrospective published study of 2477 SCT patients, 38.1% had developed renal impairment, and BKV viruria was present in 25%. In addition, BKV was found to be an independent predictor of chronic kidney disease and poor survival. Using the same cohort we derived a risk grading system to quantify risk of symptomatic BKV without having to use a complex statistical model and further validated it with another retrospective cohort of 442 allogeneic SCT patients. We hypothesize that our risk grading system will accurately identify the patients at risk of symptomatic BKV at day 30 post allogeneic stem cell transplant.

Methods: Using the three variables (conditioning regimen, HLA donor status, & underlying cancer diagnosis) that were significant predictors for symptomatic BKV derived from our initial study, we developed a risk scoring system, using the methods described by Sullivan and colleagues. A risk score was constructed as a visualizing aid to obtain predicted probability of BKV infection manually. We further stratified the patients based on their risk score into low, moderate, and high risk using 33th percentile of the risk score as the cutoff point, and into low and high risk using 99th percentile of the risk score as the cutoff points. Results: The risk score was significantly associated with symptomatic BKV infection (p < 0.001). Specifically, at day 30 post SCT, the low risk group (score <= 7) had 9% chance of developing symptomatic BKV, while the high risk group (score > 7) patients had 9% chance of developing symptomatic BKV. In addition, we further validated this grading system in a different cohort of 442 allogeneic SCT patients. We hypothesize that our risk grading system will accurately identify the patients at risk of symptomatic BKV at day 30 post allogeneic stem cell transplant. We further stratified the patients based on their risk score into low, moderate, and high risk using 33th percentile of the risk score as the cutoff point, and into low and high risk using 99th percentile of the risk score as the cutoff points. Results: The risk score was significantly associated with symptomatic BKV infection (p < 0.001). Specifically, at 30-days post STC, the low risk group (score <= 7) had 9% chance of developing symptomatic BKV, while the high risk group (score > 7) patients had 56% of developing symptomatic BKV. This was confirmed in the cohort of 442 allogeneic SCT patients. Conclusions: We have created and validated a grading system for symptomatic BKV to predict risk at day 30 post allogeneic SCT. Using this grading system we would hope to identify high risk patients for BKV and treat prophylactically using BK Cytotoxic T cell therapies and prevent reactivation which is highly associated with increased morbidity, mortality, and kidney function decline.

7058 Poster Session (Board #118), Mon, 8:00 AM-11:30 AM
Cyclophosphamide (Cy) pharmacogenomics (PGx) in allogeneic stem cell transplant (SCT) patients (pts) receiving Cy, fludarabine, total body irradiation and post-transplant Cy (FluCyTBI-postCy). First Author: Sairi Narendran; Patel, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC

Background: Cy is the backbone for many SCT conditioning regimens and is used post-SCT to prevent graft vs. host disease (GVHD). It has been proposed that genetic polymorphisms impact Cy exposure and clinical outcomes; however, no PGx studies have been performed in pts receiving FluCyTBI-postCy.

Methods: Germline DNA from SCT pts receiving FluCyTBI-postCy was genotyped using a custom AmpliSeq™ PGx Panel for polymorphisms in: ALDH1A1 (*2), ALDH3A1 (392A9a), GSTA1 (135 > G), GSTM1 (null), GSTT1 (Ile105Val, Ala114Val), CYB2 (*2, *4, *5, *6, *18, *22), CYTP2C8 (*2, *3), CYTP2C9 (*2, *3, *8, *11), CYTP2C19 (*2, *3, *17), CYTP3A4 (*18, *22), and CYTP3A5 (*3, *6, *7). Phenotypes (poor PM), intermediate (IM), normal (NM), and rapid metabolizers (RM) were inferred based on literature. Cy 14.5 mg/kg IV was given on days 6 & 5 pre-SCT, and 50 mg/kg on days 3 & +4 post-SCT. Univariate logistic regression was used to investigate the association between polymorphisms and any grade cardio toxicity, hemorrhage cystitis (HC), liver toxicity, and/or acute GVHD up to day +100. Univariate Cox proportional hazard regression was used post-SCT to model association between polymorphisms and overall [OS] & progression-free survival (PFS). Results: In 59 evaluable pts, the median age was 57 (24-77), 61% were male, 73% received haploidentical SCT and 27% matched related donor SCT. The table summarizes significant findings (P < 0.05). Conclusions: Several genes involved in the activation (CYP2C) and elimination (GSTA1, GSTT1) of Cy were associated with SCT outcomes and toxicities. Prospective studies exploring the combined effects of these genes on outcomes are needed to validate findings.

7059 Poster Session (Board #119), Mon, 8:00 AM-11:30 AM
Effect of donor type in patients with AML or MDS undergoing reduced intensity hematopoietic cell transplant (HCT). First Author: Nahid Rashid, Washington University in Saint Louis, Saint Louis, MO

Background: Haploidentical (haplo) hematopoietic cell transplants (HCT) are a promising option for patients. Overall survival (OS) is comparable in patients receiving haplo vs matched unrelated donor (MUD) HCT. We are specifically interested in patients receiving peripheral blood (PB) HCT with a reduced intensity conditioning (RIC). Studies comparing AML/MDS patients who received only PB HCT and RIC are lacking. Based recent data, we hypothesized that enhanced graft-versus-leukemia effect may lead to lower relapse in haplo HCT. To test this hypothesis, we report a retrospective study to compare OS and toxicity outcomes between haplo and MUD HCT.

Methods: Our study included patients aged ≥ 18 undergoing MUD or haplo-HCT at Washington University between January 2010 and September 2017. Data was retrospectively collected via chart review. The primary outcome was OS, compared via the Kaplan-Meier method. Secondary outcomes included the cumulative incidence of relapse, treatment-related mortality (TRM), acute graft-versus-host disease (aGVHD), neutrophil (NE) and platelet engraftment (PE), analyzed via the method of Fine and Gray.

Results: Our study included patients aged ≥ 18 undergoing MUD or haplo-HCT at Washington University between January 2010 and September 2017. Data was retrospectively collected via chart review. The primary outcome was OS, compared via the Kaplan-Meier method. Secondary outcomes included the cumulative incidence of relapse, treatment-related mortality (TRM), acute graft-versus-host disease (aGVHD), neutrophil (NE) and platelet engraftment (PE), analyzed via the method of Fine and Gray. Conclusions: There is no significant difference in OS, PFS, relapse, or TRM in haplo versus MUD between the two groups. This indicates that haplo are a reasonable alternative to MUD in patients receiving RIC. More data needs to be collected to determine if there is a significant difference in outcomes favoring haplo over MUD.

7060 Poster Session (Board #120), Mon, 8:00 AM-11:30 AM
Efficacy and safety of moxetumomab pasudotox (moxe) in adult patients (pts) with cell dyscrasias for hairy cell leukemia (HCL) in relation to drug exposure, baseline disease burden, and immunogenicity. First Author: Denison Kuruwila, MedImmune, Mountain View, CA

Background: Moxe is an immunotoxin targeting CD22 on B cells leading to cell death. The objectives of this analysis were to characterize the pharmacokinetics (PK) and evaluate the exposure-efficacy/safety of moxe in pts with HCL. Methods: Data from two HCL studies (Ph1: 49 pts dosed at 5, 10, 20, 30, 40 & 50 µg/kg; Ph3: 35 pts dosed at 40 µg/kg) were combined to develop a population PK model. The model derived Cmax and AUC were then used to evaluate the exposure-efficacy/safety relationship in the 2 studies independently due to differences in bioavailability of materials (Ph1 50 µg/kg was bioactive equivalent to Ph3 40 µg/kg). Efficacy endpoints included complete response (CR), durable CR (Ph3 only) and objective response rate (ORR). Safety parameters included hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), >Gr 2 increased creatinine (CRE), and Gr 3/4 adverse events (AE). Results: Moxe PK was linear from 5-50 µg/kg with PK well-described by a 1-compartment model. Day 1 clearance (CL) was higher than for later doses (22 vs 4 L/hr), attributed to CD22+ B cell depletion with repeated dosing. Ph3 pts with anti-drug antibody (ADA) titers >10240 had ~4-fold increase in CL. High CL was associated with high baseline B cells. High baseline B cells/livewere PK associated with lower response rate, but clinical benefit was still observed. In Ph3, rates of CR and durable CR were 56-58% and 50-53% in high (>median) PK exposure group vs 31-34% and 14-17% in the low PK exposure group. In Ph1, rate of CR was 67-71% in high vs 46-50% in low PK exposure groups. Pts with ADA titer >10240 had lower CR and durable CR, but clinical benefit was still observed. Pts with high PK exposure had higher incidence of CLS and CRE in Ph3 but not in Ph1. Higher incidence in both studies was low and was not evaluated further. Pts with high PK exposure in Ph1 had higher rates of Gr 3/4 AE. Incidence of Gr 3/4 AE in Ph3 40 µg/kg was consistent with that of Ph1 50 µg/kg. Conclusions: Moxe CL decreased with repeated dosing, consistent with B cell depletion. ADE titer >10240 increased CL by ~4-fold. Pts with high PK exposure had better response but had a slightly higher incidence of Gr 3/4 AE. Clinical trial information: NCT01829711 and NCT00586924.
Pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of moxetumomab pasudotox (Moxe), an immunotoxin targeting CD22, in adult patients (Pts) with Philadelphia chromosome-positive (Ph+) leukemia: Phase 1/2 study update. First Author: Carlo Gambacorti-Passerini, University of Milano-Bicocca, Monza, Italy

Background: Bosutinib has a distinct adverse event (AE) profile vs other TKIs used to treat Ph+ leukemia. Methods: Pts with chronic phase (CP) chronic myeloid leukemia (CML; n=433) or accelerated phase/blast phase CML or Ph+ acute lymphoblastic leukemia (ALL) were previously treated with imatinib – dasatinib and/or nilotinib received bosutinib (starting dose 500 mg QD) in a phase 1/2 study (NCT00261846). Cross-intolerance (AEs leading to discontinuation of both prior TKI and bosutinib) and AEs causing prior TKI intolerance and recurring as grade 3/4 AEs with bosutinib were assessed after ≥ 4 of follow-up. Results: In imatinib-intolerant and dasatinib-intolerant pts, respectively, 18% and 24% in the CP CML group and 18% and 5% in the ADV group had cross-intolerance with bosutinib, which was most common due to hematologic AEs (Table). Cross-intolerance in imatinib-intolerant pts with CP CML due to AEs common with imatinib was low (rash 6%, diarrhea 10%, edema/fluid retention 0, myalgia 0); cross-intolerance due to pleural effusion was low in dasatinib-intolerant pts with CP CML (13%) and dasatinib-intolerant ADV pts (0). No deaths occurred due to cross-intolerance. Conclusions: Cross-intolerance with bosutinib was low and largely due to hematologic AEs, supporting bosutinib use in pts with Ph+ leukemia intolerant to prior TKIs, including those with intolerance due to rash or diarrhea. Clinical trial information: NCT00261846.

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Background: Myelodysplastic syndromes (MDS) are malignant disorders leading to acute leukemia (AML). Recent breakthroughs identified down-regulation of PU.1 in high risk MDS and AML, with work within NPM1 mutated AML cells showing PU.1 relocates in the cytoplasm causing differentiation arrest. Microarray analysis in PU.1 overexpressing SK62, revealed Jun Dimenrization Protein 2 (JDP2), downstream to PU.1 was significantly suppressed. In this study we investigated PU.1 and JDP2 expression during different stages of MDS progression/AML evolution and in patients responding to Azacitidine. Methods: Gene expression of PU.1 and JDP2, in total bone marrow and selected CD34+ cells, from 12 newly diagnosed MDS patients stratified according to IPSS-R (6-low, 3-intermediate, 3-high risk), 2AML and 10 controls was undertaken. Samples were enriched for the mononuclear fraction by Ficoll separation and RNA analysed by RT-PCR for PU.1 and JDP2 expression. Protein expression was analysed by western blot. Results obtained were compared with Bloodspot MDS gene expression data. PU.1 knockdown was performed in K562 using PU.1 short interfering RNAs. This revealed only a partial reduction in JDP2 expression suggesting a more complex regulative mechanism. PU.1 and JDP2 expression levels in CD34+ cells, significantly and progressively reduces towards AML transformation. Furthermore, we demonstrated a significant upregulation in PU.1 and JDP2 expression in patients responding to Azacitidine. Conclusion: PU.1 and JDP2 expression inversely correlates with disease progression, consistently reducing in IPSS-R groups. Investigating PU.1 and JDP2 expression data in MDS vs normal samples from a large Bloodspot pool confirmed our findings. To understand if JDP2 suppression is a direct result of reduced PU.1 we performed PU.1-knockdown. This large Bloodspot pool confirmed our findings. To understand if JDP2 suppression is a direct result of reduced PU.1 we performed PU.1-knockdown. Treatment of MDS patients with JDP2 short interfering RNAs. With disease progression, consistently reducing in IPSS-R groups. Investigating PU.1 and JDP2 expression inversely correlates with disease progression, consistently reducing in IPSS-R groups. Message: Expression of PU.1 and JDP2 inversely correlates with disease progression, consistently reducing in IPSS-R groups. Investigating PU.1 and JDP2 expression inversely correlates with disease progression, consistently reducing in IPSS-R groups.

Methods:

Gene expression of PU.1 and JDP2, in total bone marrow and selected CD34+ cells, from 12 newly diagnosed MDS patients stratified according to IPSS-R (6-low, 3-intermediate, 3-high risk), 2AML and 10 controls was undertaken. Samples were enriched for the mononuclear fraction by Ficoll separation and RNA analysed by RT-PCR for PU.1 and JDP2 expression. Protein expression was analysed by western blot. Results obtained were compared with Bloodspot MDS gene expression data. PU.1 knockdown was performed in K562 using PU.1 short interfering RNAs. This revealed only a partial reduction in JDP2 expression suggesting a more complex regulative mechanism. PU.1 and JDP2 expression levels in CD34+ cells, significantly and progressively reduces towards AML transformation. Furthermore, we demonstrated a significant upregulation in PU.1 and JDP2 expression in patients responding to Azacitidine. Conclusion: PU.1 and JDP2 expression inversely correlates with patient’s prognosis and leukemia transformation in MDS, highlighting a potential role as new diagnostic and prognostic markers in MDS.
Characteristics and outcomes of myelodysplastic syndrome (MDS) with chromosome (chr)3q abnormalities. First Author: Mansour Alsayef, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Balanced and unbalanced chr 3q21; q26.2 abnormalities result in aberrant expression of the oncogene ecotropic viral integration site 1 imprinted in aberrant expression of the oncogene ecotropic viral integration site 1 imprinted in human hematopoietic progenitors. We hypothesized that the use of JAKi is a promising therapeutic approach for patients with MDS, and that JAKi therapy could improve outcomes compared to historical controls.

**Methods:** The study included 48 patients with chr 3q abnormalities who received JAKi therapy. The median duration of JAKi therapy was 2 months (range 0.5-10 months). The primary endpoints were overall survival (OS), progression-free survival (PFS), and response rate to JAKi therapy.

**Results:** The median OS was 6 months (95% CI 0.27 – 0.5 vs 2.1 ± 0.3, p = 0.005, N = 108 tracked cells). Enforced expression of cxcl8 increased the percent of time individual HSPCs spent closely interacting with a single group of HSPCs with higher overall survival (OS) versus HSPCs with lower overall survival (OS). The effect of pre-transplant JAK1/2 inhibitors on outcomes of myelofibrosis (MF) treatment is becoming commonplace, but their impact on outcomes after hematopoietic stem cell transplant (SCT) is not well studied. We conducted a retrospective analysis of 132 patients who underwent SCT for primary or secondary MF at two partner institutions to assess the impact of receiving pre-SCT JAKi on several outcomes, including overall survival (OS), progression free survival (PFS), and GVHD-free and relapse-free survival (GRFS). Methods: 132 patients with MF who received allogeneic SCT between 2004 and 2017 at Massachusetts General Hospital or Dana Farber Cancer Institute were identified. The use of this data was approved by the local Institutional Review Board. We limited our final analysis to the 116 patients who were intermediate-1 (41) and intermediate 2 risk (75) by DIPSS prior to SCT, as there were very few patients in the high or low risk groups. Cox proportional hazard regressions were fit to estimate the association between the use of pre-SCT JAKi and OS, PFS, and GRFS after SCT, adjusting for baseline ECOG performance status, conditioning intensity and DIPPS status. Results: Of the 116 DIPPS-intermediate patients in the study, 41 received a JAKi prior to SCT and 75 patients did not. Patients who received pre-SCT JAKi had increased OS (75% vs 41%) and increased PFS (73% vs 44%) but not in GRFS (17% vs 14) in unadjusted analysis. In models adjusted for baseline ECOG performance status, conditioning regimen intensity, and DIPPS status, the use of JAKi prior to SCT was associated with a marginally-significant improvement in PFS (hazard ratio (HR) = 0.54, 95% CI 0.27 – 1.07, p = 0.075) and OS (HR = 0.53, 95% CI 0.26 – 1.07, p = 0.07), and was not associated with an improvement in GRFS (HR = 0.77, CI 0.49 – 1.23, p = 0.28). Conclusions: Our data suggest that the use of JAKi prior to SCT may improve survival outcomes for patients with MF intermediate risk 1 or 2 who undergo SCT. However, further investigation with a larger sample size is needed to better understand the effect of pre-SCT JAKi use on patient outcomes after SCT. Future investigation should also focus on the use of post-SCT JAKi given their exhibited activity for GVHD.
Phase 3, randomized, placebo-controlled trials evaluating gilteritinib in combination with intensive or non-intensive chemotherapy in patients with untreated acute myeloid leukemia

**Background:** Gilteritinib is an oral Hedgehog pathway inhibitor with clinical activity in patients (pts) with untreated AML or higher-risk MDS, and improved survival when combined with low-dose cytarabine (AraC) in unfit pts with AML. BRIGHT AML1019 comprises two Phase 3, randomized (1:1), double-blind trials evaluating gilteritinib 100 mg once daily (QD) or placebo (PBO) + chemotherapy in untreated adult AML (NCT03416179). The protocol includes 2 parallel, simultaneous trials: 1 with intensive chemotherapy (IC) and 1 with non-intensive chemotherapy (nIC). Methods: Both trials include pts aged ≥18 y with untreated AML (WHO 2016), including AML evolved from MDS or antecedent hematologic disease, or secondary AML. Key exclusions: inadequate organ function, acute promyelocytic leukemia, active CNS leukemia. Assignment to IC or nIC trial is per Investigator. In the IC trial, 400 pts are randomized (1:1) to gilteritinib 100 mg QD or PBO on Day 1 and continue for up to 2 y or until post-consolidation minimal residual disease (MRD)-negative status. Gilteritinib or PBO are administered with 7+3 induction (AraC 100 mg/m² IV for 7 days + daunorubicin 60 mg/m² for 3 days); induction 2, if needed, will use 7+3 or 5+2. Consolidation consists of single-agent AraC 1 or 3 g/m² IV over 3 h twice daily on Days 1, 3 and 5 every 28 days for ≤4 cycles; eligible patients may receive hematopoietic stem cell transplantation. In the nIC trial, 520 pts are randomized (1:1) to gilteritinib 100 mg QD or PBO, each with azacitidine 75 mg/m² daily SC or IV for 7 days, in 28-day cycles. Treatments continue until disease progression, unacceptable toxicity, withdrawal or death. In both trials, gilteritinib and PBO continue regardless of chemotherapy dose modifications/delays. The primary endpoint is overall survival. Secondary endpoints include response, time to and duration of response, event-free survival, safety, patient-reported outcomes and pharmacokinetics. Clinical trial information: NCT03416179.

**Methods:** AGILE is a global, randomized, double-blind, placebo-controlled trial in patients with previously untreated midHD1 AML who are candidates for non-intensive treatment (NCT03173248). 392 patients are being randomized 1:1 to receive either IVO 500 mg QD + AZA 75 mg/m² SC or intravenously for 7 days in 28-day cycles, or matched placebo + AZA. Randomization is stratified by region and by de novo versus secondary AML. Key eligibility criteria include patients with previously untreated midHD1 AML (according to WHO criteria) who are not candidates for or not willing to receive intensive chemotherapy, ECOG performance status 0–2, and no prior treatment with a hypomethylating agent or midHD1 inhibitor. The primary outcome measure is overall survival, and key secondary outcome measures include event-free survival, CR rate, CR + partial hematologic recovery (CRh) rate, and ORR. AGILE is currently open for enrollment globally. Clinical trial information: NCT03173248.

**A phase 3, trial of gilteritinib, as maintenance therapy after allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD+ AML, sAML**

**Background:** FLT3-ITD mutations in acute myeloid leukemia (AML) are a common indication for allogeneic hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1). Despite HSCT, relapses are common and cure rates are limited thereafter. The use of FLT3 inhibitors as post-HSCT maintenance therapy has not been prospectively evaluated. Gilteritinib is a highly selective, potent FLT3/AXL inhibitor with robust activity and favorable tolerability in relapsed/refractory AML. Several gilteritinib trials in AML include a single arm post-HSCT gilteritinib maintenance therapy to establish the feasibility of this strategy. This trial will compare the safety and efficacy of 2-year maintenance therapy with gilteritinib versus placebo in patients with FLT3-ITD+ AML in CR1 after allogeneic HSCT. Methods: This Phase 3, randomized, double-blind, placebo-controlled multicenter trial (NCT02997202; Blood and Marrow Transplant Clinical Trials Network Protocol 1506), to be conducted at 149 sites worldwide, will enroll 532 adult subjects (aged ≥18 years) with FLT3-ITD+ AML in CR1 who are ≥30 days and ≤90 days from scheduled allogeneic HSCT. Of these 532 subjects, 346 subjects who have achieved successful engraftment without uncontrolled graft-versus-host disease (GVHD) or other serious toxicity will be randomized (1:1:1) stratified by conditioning regimen intensity, time from HSCT (Day 0) to randomization (30–60 days vs 61–90 days), and presence of minimal residual disease (MRD) in the pre-transplant bone marrow sample) to receive oral gilteritinib (120 mg) or matching placebo as maintenance therapy for 2 years. The primary endpoint is relapse-free survival (RFS) in the two treatment arms. RFS will be assessed from the time of randomization to the time of death or morphologic leukemia relapse (as defined by Revised IWG criteria). Overall survival is a key secondary endpoint. Other endpoints include safety/tolerability, non-relapse mortality, event-free survival, incidences of acute/chronic GVHD, and MRD. As of January 30, 2018, 47 patients have been enrolled and 11 have been randomized. Clinical trial information: NCT02997202.

**An open-label, first-in-human, dose escalation study of a novel CD3-CD123 bispecific T-cell engager administered as a single agent by intravenous infusion in patients with relapsed or refractory acute myeloid leukemia, B-cell acute lymphoblastic leukemia, or high risk myelodysplastic syndrome**

**Background:** Persistence of leukemic stem cells is an important cause of relapse in patients with acute myeloid leukemia (AML). CD123 (α-chain of the interleukin-3 receptor) is highly expressed on myeloid leukemic stem cells and blasts, while CD3 is a common antigen on T-cells. The use of bispecific T-cell engagers (TCEs) has been explored in various hematologic malignancies. This first-in-human trial will enroll patients with relapsed or refractory AML, B-ALL, or high risk myelodysplastic syndrome. The trial is starting at the minimum anticipated biological effect level (MABEL) dose, followed by an intrapatient dose escalation to a steady-state dose. The drug will be administered intravenously on a weekly basis with specific precautions to prevent and mitigate cytokine release syndrome. One patient will be treated at each of the first two dose levels, while subsequent dose levels will enroll to a 3+3 design. Patients will be assessed for response, safety, and pharmacodynamic and pharmacokinetic endpoints. The primary objective of the dose escalation study is to determine a recommended phase 2 dose for a subsequent expansion cohort.

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Background: PEV is a first-in-class small molecule inhibitor of NEDD8-activating enzyme, with single-agent clinical activity in patients with relapsed/refractory AML (Swords et al. Br J Haematol 2015;169:534–43). In a phase 3 randomized, placebo-controlled trial, PEV in combination with AZA in symptomatic antitumor activity compared with either agent alone (Visconte et al. Leukemia 2016;30:1190–4). A phase 1b study reported that PEV+AZA was well tolerated and showed clinical activity in patients ≥60 years with untreated AML (Swords et al. Blood 2018; Epub). These results provided the rationale for this phase 3 study to compare the efficacy and safety of PEV+AZA versus single-agent AZA as first line treatment for patients with HR MDS, CMML, or low-blast AML. Methods: This is a global, multicenter, randomized, double-blind, placebo-controlled, phase 3 study (NCT03268954). Eligible patients (N = ~450 planned) are adults with a confirmed diagnosis of HR MDS, CMML, or low blast AML with poor-risk cytogenetics or high-risk disease defined by the IPSS-R, who are not candidates for intensive chemotherapy and/or allogeneic stem cell transplantation and do not have acute promyelocytic leukemia or a history of central nervous system involvement by AML. Patients are stratified by IPSS-R risk group (MDS/CMML) and low-blast AML, and randomized 1:1 to receive PEV 20 mg/m² intravenously on days 1, 3, and 5, plus AZA 75 mg/m² (intravenous or subcutaneous) on days 1–7 of each cycle. Midostaurin + chemo was approved in the United States and Europe for pts aged 18 y with ND AML and ECOG performance status (0–1) who are eligible for 7+3 or 5+2 chemotherapy (chemo). In the current study, pts are randomized 1:1 to either PRAN + AZA or placebo + AZA, in 28-day cycles until progression, transformation to AML, or unacceptable toxicity. Primary endpoints are overall response rate by cycle 6 and event-free survival; overall survival is a key secondary endpoint. Other secondary endpoints include survival rates at 2, 3, and 5 years, rate/duration of response; time to AML transformation; rate of complete remission (CR); time to first CR or partial remission; rate of hematologic improvement; rate/duration of red blood cell and platelet transfusion independence; time to relapse, progression, or death; pharmacokinetics; and health-related quality of life. Recruitment is currently ongoing. Clinical trial information: NCT03268954.

TPS7078 Poster Session (Board #135b), Mon, 8:00 AM-11:30 AM
A phase 3, randomized study of pracinostat (PRAC) in combination with azacitidine (AZA) versus placebo in patients ≥18 years with newly diagnosed as well as lower-risk acute myelogenous leukemia (AML). First Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: AML is associated with poor survival rates in patients ineligible for IC or stem cell transplant due to advanced age, comorbidities, and/or disease risk factors. Non-intensive therapies, including the hypomethylating agent AZA, are frequently used in this setting; however, response rates/survival remain dismal. Pre-clinical studies in myeloid malignancies indicate that inhibition of DNA hypermethylation and histone deacetylation induces re-expression of silenced genes in a synergistic fashion. In a Phase 2 study in AML patients ≥65 years not eligible for IC, PRAC, a novel oral histone deacetylase (HDAC) inhibitor, in combination with AZA showed promising efficacy (Garcia-Manero, Blood 2016) with a 64% overall response rate and 19.1 months median overall survival. Methods: This phase 3, randomized, double-blind study (NCT03151408) is evaluating the efficacy and safety of PRAC plus AZA in patients ≥18 years with newly diagnosed AML until 180 days. Ineligibility for induction CT is based on either 1) age ≥75 years or 2) history of significant organ dysfunction or co-morbidities. A total of 500 patients (randomized 1:1 to either PRAC + AZA or placebo + AZA) are planned to be enrolled at ~130 study centers worldwide. Randomization is stratified by cytogenetic risk (intermediate vs. unfavorable-risk) and ECOG Performance Status (0-1 vs. 2). Treatments are administered as 28-day cycles, with PRAC/placebo given orally 3x/week for 2 weeks followed by one week off and AZA administered for 7 days of each cycle. Study treatment is to be continued until disease progression or unacceptable toxicity. A minimum of 6 cycles may be required to achieve a CR. The primary endpoint is overall survival; secondary endpoints include morphologic and cytogenetic CR rates, freedom from disease progression, and discrete disease-free survival. Overall survival will be tested for superiority of PRAC using the stratified log-rank test at the alpha = 0.025 level of significance (one-sided). Enrollment opened in July 2017. Clinical trial information: NCT03151408.

TPS7079 Poster Session (Board #136a), Mon, 8:00 AM-11:30 AM
Trial in progress: An open-label, multicenter, phase 3b study to assess the safety and efficacy of midostaurin in patients (pts) aged ≥18 y with newly diagnosed (ND) FLT3-mutated acute myeloid leukemia (AML) who are eligible for 7+3 or 5+2 chemotherapy (chemo). First Author: Adolfo Fuentes, Novartis Pharmaceuticals Corporation, East Hanover, NJ

Background: FLT3 mutations, found in ~30% of pts with AML, are associated with a poor prognosis. Midostaurin is a multitasking inhibitor that targets FLT3 and other kinases involved in AML pathogenesis. In the phase 3, randomized, placebo-controlled RATIFY trial, midostaurin + chemo significantly improved OS and EFS in adults (aged 18-59 y) with ND FLT3-mutated AML. The chemo regimen in RATIFY was 7+3 induction (1-2 cycles of cytarabine [Ara-C] 200 mg/m²/d on d1-d7 + daunorubicin 60 mg/m²/d on d1-3) and consolidation (≥4 cycles of Ara-C 3000 mg/m²/d every 12 h on d1, 3, 5). Midostaurin + chemo was approved in the United States and Europe for pts aged ≥18 y with ND FLT3-mutated AML. However, many institutions use different chemo regimens as the standard of care (SOC). The aim of this new study is to assess the safety and efficacy of midostaurin 50 mg bid in combination with different SOC chemo regimens and as single-agent maintenance. Methods: CPC412A2408 (NCT03379727) is an open-label, single-arm, multicenter, phase 3b study in adults aged ≥18 y and fit for chemo with ND AML per WHO 2008 classification, ECOG performance status of ≤2, and a documented FLT3 internal tandem duplication or tyrosine kinase domain mutation (estimated enrollment, 300). Pts must start their first induction chemo cycle with 7+3 (Ara-C 100-200 mg/m²/d on d1-d7 + daunorubicin 60-90 mg/m²/d or idarubicin 12 mg/m²/d on d1-3) or 5+2 (a reduced-dose regimen with these agents) per investigator’s discretion and enroll by d7 of the first induction cycle. Once pts start on 7+3 or 5+2, they may not switch. Pts will receive consolidation with Ara-C, with dose per investigator’s choice. Midostaurin 50 mg bid will be administered on d8-28 of each 28-d induction and consolidation cycle and daily for ≥12 cycles of maintenance. Pts will discontinue the study if not in complete remission (CR) or CR with incomplete hematologic recovery (CRi) at the end of induction or consolidation or if they receive a stem cell transplant. The primary and secondary endpoints are safety and the proportion of pts achieving CR/CRi, respectively. Clinical trial information: NCT03379727.

TPS7081 Poster Session (Board #137a), Mon, 8:00 AM-11:30 AM
Clinical development of asciminib (ABL001) in chronic myeloid leukemia (CML). First Author: Michael J. Mauro, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Several tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 ATP-binding site are available to treat CML. However, new options are needed for patients (pts) with resistance/intolerance to these TKIs or who do not achieve treatment goals with them. Asciminib is a novel, potent and specific BCR-ABL1 inhibitor that targets the myristoyl pocket (Wylie, Nature 2017). Due to its distinct binding site, asciminib maintains activity against BCR-ABL1 mutants that confer resistance to ATP-binding site TKIs and offers the possibility for combination therapy with these TKIs. It therefore has the potential to address unmet needs in CML, including use in pts for whom ATP-binding site TKIs fail or for combination with these TKIs in earlier lines, and in Philadelphia chromosome–positive acute lymphoblastic leukemia. In an ongoing phase 1 study in pts with resistance/intolerance to ≥ 2 TKIs (Hughes, Blood 2016 [abst 625]), asciminib has been well tolerated; 42% of pts achieved a major molecular response (MMR) by 12 mo with single-agent twice-daily asciminib. A recommended dose for asciminib monotherapy was identified for pts without T315I mutations (40 mg twice daily); in separate cohorts, dosing in select pt groups and combination dosing with ATP-binding site TKIs continues to be evaluated. Now, a phase 2 study of asciminib add-on therapy in pts without a deep molecular response on long-term frontline imatinib is planned, and a randomized phase 3 study of asciminib monotherapy vs bosutinib (an ATP-binding site TKI approved for third-line therapy) in the third or later line is enrolling. Here we describe this ongoing, open-label, phase 3 study (NCT03106779). Methods: Pts with CML in chronic phase (planned enrollment, N = 222) are randomized 2:1 to receive asciminib 40 mg twice daily or bosutinib 500 mg once daily. Eligible pts are ≥18 y old, previously treated with ≥ 2 TKIs, with failure/intolerance to the previous TKI, and have BCR-ABL1TS ≥ 1%. Pts with T315I or V299L mutations are excluded. MMR rate at 24 wk will be compared between arms (primary objective). The 96-wk MMR rate, progression-free and overall survival, safety, tolerability, and asciminib pharmacokinetics will also be evaluated. Clinical trial information: NCT03106779.

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Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

TPS7082 Poster Session (Board #137b), Mon, 8:00 AM-11:30 AM
Phase 1b study of venetoclax in combination with azacitidine in patients with treatment-naive higher-risk myelodysplastic syndromes. First Author: Chiu Yew Fong, Austin Health/Olivia Newton-John Cancer Research & Wellness Centre, Heidelberg, Australia

**Background:** Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis leading to cytopenias and potentially transform to acute myeloid leukemia (AML). Treatment (tx) with hypomethylating agents (HMAs) is the standard of care for patients (pts) with tx-naive higher-risk (HR) MDS who are not candidates for intensive chemotherapy/allogeneic stem cell transplant. Currently, azacitidine (AZA) is the only drug shown to prolong survival in tx-naive HR MDS. However, ~50% of pts treated with HMA alone do not derive clinical benefit. Venetoclax (VEN) is a potent, orally bioavailable BCL-2-specific inhibitor, VEN plus AZA has demonstrated a tolerable safety profile and promising efficacy in elderly pts with tx-naive AML (incl. secondary AML) ineligible for intensive chemotherapy. Preclinical data indicate activity of VEN in HR MDS (Jilg, 2016). Thus, the unmet medical need in HR MDS as well as relevant clinical data with VEN in AML provide a rationale for assessing VEN plus AZA in pts with tx-naive HR MDS.

**Methods:** This open-label, Phase 1b dose-escalation study evaluates VEN in combination with AZA for tx-naive HR MDS (NCT02942290) and consists of 2 portions, an initial dose-escalation (~24 pts) and a safety expansion (~20 pts) at the recommended Phase 2 dose (RPTD). Key eligibility criteria are no prior therapy for MDS, an overall International Prognostic Scoring System score of ≤1.5 (Int-2 and HR), bone marrow blasts ≥5% and < 20%, and ECOG score of ≤2. VEN will be administered at starting dose level of 100 mg daily for 14 days/cycle (28 days) and may be escalated up to 400 mg for subsequent dose-level cohorts. AZA will be administered at the standard dose (75 mg/m²) for 7 days/cycle. Primary study objectives are to assess safety and pharmacokinetics, and to determine the RPTD and dosing schedule of VEN plus AZA. Secondary objectives incl. rates of overall response, hematologic improvement, transfusion independence, and cytogenetic response, as well as duration of response, progression-free survival, overall survival, and time to transformation to AML. Exploratory objectives include patient-reported outcomes and translational biomarkers of response and resistance. Clinical trial information: NCT02942290.

TPS7083 Poster Session (Board #138a), Mon, 8:00 AM-11:30 AM
A phase 2, multicenter, open-label study of the safety and efficacy of luspatercept in subjects with myeloproliferative neoplasm (MPN)-associated myelofibrosis and anemia with or without RBC transfusion dependence. First Author: Ruben A. Mesa, UT Health San Antonio Cancer Center, San Antonio, TX

**Background:** Anemia is an important complication of MPN-associated myelofibrosis. There are few effective therapies other than RBC transfusions, and responses to other therapies are typically brief. Anemia and RBC transfusion dependence are independent adverse prognostic and predictive variables for survival. Luspatercept is a fusion protein consisting of a modified type IIB activin receptor linked to the Fc domain of human IgG1. Luspatercept acts as an erythroid maturation agent by binding specific TGFβ superfamily ligands such as GDF11, blocking their inhibitory effect and leading to increased RBC production. Luspatercept ameliorated anemia in preclinical models and preliminary data have shown it is effective and well tolerated in subjects with lower-risk myelodysplastic syndromes and anemia, with or without RBC transfusion dependence. **Methods:** Eligible subjects have MPN-associated myelofibrosis, are aged ≥18 y, and have anemia (hemoglobin < 9.5 g/dL) or RBC transfusion dependence (defined as receiving ≥2-4 U RBC/28 d averaged over 84 d). There are 3 cohorts: (1) cohort 1: 20 subjects with anemia only, no rouxolitinib received in the past 112 d; (2) cohort 2: 20 subjects with RBC transfusion dependence, no rouxolitinib; and (3) cohort 3: 30 subjects with anemia or RBC transfusion dependence receiving a stable rouxolitinib dose. Luspatercept is given subcutaneously at a starting dose level of 1.0 mg/kg every 3 w for 8 cycles. The primary endpoint is anemia response, defined as a hemoglobin increase of ≥1.5 g/dL from baseline or RBC transfusion independence for ≥84 d. Responders can continue therapy in an extension phase. Secondary endpoints include time to response, response duration, health-related quality of life, and safety. Response rates with 95% confidence interval will be calculated. The statistical analyses are descriptive. Enrollment began November 2017. Clinical trial information: NCT03194542.

TPS7084 Poster Session (Board #138b), Mon, 8:00 AM-11:30 AM
Clinical activity, safety and tolerability of ASN002, a dual JAK/SYK inhibitor, in patients with non-Hodgkin lymphoma (NHL), myelofibrosis (MF), chronic lymphocytic leukemia (CLL) and solid tumors. First Author: Stefan K. Barta, Fox Chase Cancer Center, Philadelphia, PA

**Background:** ASN002 is a novel, potent inhibitor of Janus Kinases (JAK) and Spleen Tyrosine Kinase (SYK). Pre-clinical studies indicate that ASN002 has low nM IC50s against SYK and JAK, decreases proliferation in brutinib-resistant cell lines, and suppresses tumor growth in rodent xenograft models of NHL and other hematologic malignancies. **Methods:** This Phase 1/2 clinical trial in patients with solid tumors and hematologic malignancies evaluated escalating ASN002 oral doses of 10, 20, 30, 40, 50 and 75 mg BID and 80 and 120 mg QD. Phase 1 allowed patients with solid tumors or hematologic malignancies; Phase 2 allows only patients with mantle cell lymphoma (MCL), myelofibrosis (MF), Peripheral T-cell Lymphoma (PTCL) and Chronic Lymphocytic Leukemia (CLL). Endpoints include safety, tolerability, pharmacokinetics, serum markers of inflammation, and response using Lugano criteria (NHL), IWG-MRT (MF), or IWG-CLL. **Results:** Forty-six patients have enrolled in the study at doses of 10–75 mg BID and 80–120 mg QD. All patients had multiple prior lines of treatment (range: 2–8). ASN002 was well tolerated at doses up to 75 mg BID. The DLT at 100 mg BID was Grade 3 infection. 75 mg BID was the recommended Phase 2 dose. Most drug-related adverse events were Gr 1/2 (e.g. headache, fatigue). Steady-state systemic exposure was high (Cmax, AUC (0-12h)) and increased in a dose-related manner up to 100 mg BID. Robust reduction of inflammatory markers CRP, IL-18, MIP1α, VCAM-1, TNFR2 was observed at all dose levels. Stable disease (9+ months) in a patient with primary peritoneal cancer, about 50% reduction in target lesions at 3 months in a FL patient, stable disease and reduction of pruritus in a PTCL patient after 2 months, and significant disappearance of skin lesions in another PTCL patient after one month were observed. Early improvement in symptoms within 2 weeks of treatment in MF has also been reported in an ongoing patient. Accrual of patients continues. Conclusions: ASN002 was safe and well tolerated. Encouraging preliminary evidence of efficacy in NHL and MF patients was observed. Updated and detailed results will be presented. Clinical trial information: NCT02440685.

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**7500 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**RELEVANCE: Phase III randomized study of delnaclotide plus rituximab (R**<sup>2</sup>) versus chemotherapy plus rituximab, followed by rituximab maintenance, in patients with previously untreated follicular lymphoma. First Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Immunchemotherapy induction followed by rituximab maintenance is the standard of care in previously untreated symptomatic FL. Phase II studies of chemo-free combination immunotherapy with delnaclotide and rituximab (R**2**) show promising activity. Methods: RELEVANCE is a global, randomized, phase III trial (NCT01650701) of R**2** vs R-chemo followed by delnaclotide in previously untreated grade 1-3A FL patients requiring therapy according to GELF criteria. Delnaclotide dose was 20 mg/id, d2-22/28 for 6-12 cycles (c), continued in responders at 10 mg/id for a total of 18 c. Rituximab dose was 375 mg/m<sup>2</sup> weekly c1 and c1-6 and continued in responders for 12 additional c (q8wk). R-chemo was given per investigator’s choice of standard R-CHOP, R-bendamustine (R-B), or R-CVP, followed by 12 c of rituximab (q8wk). Co-primary endpoints of CR/CRI at 120 wk and PFS (50% interim analysis by 1999 IWG) are reported here. Results: As of 31May2017, 1030 patients with high tumor burden were randomized to R**2** (n = 513) and R-chemo (n = 517; 72% R-CHOP, 23% R-B, 5% R-CVP); baseline characteristics were similar in both groups. At a median follow-up of 37.9 mo, superiority for R**2** over R-chemo was not established for both co-primary endpoints (Table). Toxicity profiles for R**2** vs R-chemo differed, with higher grade 3/4 lab (34% vs 50%) and febrile (22% vs 6%) neutropenia with R-chemo, and higher grade 3/4 cutaneous events (7% vs 1%) with R**2**. SMs were reported in 7% R**2** and 9% R-chemo patients and grade 5 AE were 1% for both. 69% R**2** and 71% R-chemo patients completed treatment. Conclusions: In the first randomized phase III comparison of a chemo-free regimen vs standard R-chemo followed by rituximab maintenance in previously untreated FL, R**2** showed similar effectiveness, but with a different safety profile to R-chemo. Clinical trial information: NCT01650701.

**7502 Oral Abstract Session, Sun, 9:45 AM-12:45 AM**

**Phase 2 CAPTIVATE results of ibritinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL). First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Ibr, a first-in-class, once-daily BTK inhibitor, is approved in the US and EU for CLL treatment, including del17p. Early studies support synergistic antitumor activity with combined ibr and ven, a BCL-2 inhibitor approved by FDA for relapsed del17p CLL. Single-agent ibr lead-in may lower tumor lysis syndrome (TLS) risk by undetectable minimal residual disease (MRD(-)) after I+V can provide pts treatment Exposed). AEs in 1/163 pts. In I+V Exposed pts with baseline LDi, CR/CRu at 120 wk (IRC/Inv) 77%/77% 78%/78% 84%/84% 87%/83%

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<th>CR/CRI at 120 wk</th>
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**Results:** 163 pts were enrolled (median 58 y; 14% del17p; 15% del11q; 33% 16% del17p CLL. Single-agent ibr lead-in may lower tumor lysis syndrome (TLS) risk by undetectable minimal residual disease (MRD(-)) after I+V can provide pts treatment

**Conclusions:** In the first randomized phase III comparison of a chemo-free regimen vs standard R-chemo followed by rituximab maintenance in previously untreated FL, R**2** showed similar effectiveness, but with a different safety profile to R-chemo. Clinical trial information: NCT01650701.

**7503 Oral Abstract Session, Sun, 9:45 AM-12:45 PM**

**Acalabrutinib in patients (pts) with Waldenström macroglobulinemia (WM). First Author: Roger Owen, St. James’s University Hospital, Leeds, United Kingdom

**Background:** Bortezomib, the only approved therapy for WM, has limited single-agent activity. First-line WM is incurable with a median survival of approximately 7 years. Acalabrutinib (ACARI) is a Bruton’s tyrosine kinase (BTK) inhibitor with promising activity in WM. Methods: A randomized phase III trial (NCT02180724) evaluated the efficacy and safety of acalabrutinib versus rituximab plus lenalidomide plus dexamethasone (RCD) in previously untreated WM pts (NCT01358747). The trial included 466 pts, randomized 1:1 to ibr or ven, stratified by prior therapy (yes/ no), and tested the hypothesis of non-inferiority of the ibr arm to the RCD arm with respect to the primary endpoint of PFS at 12 months. Results: Median follow-up was 19.6 months. The death rate was low (1% in the ibr vs 8% in the RCD arm). PFS at 12 months was 95% for ibr and 92% for RCD (HR: 0.74, 95% CI: 0.53, 1.03; P = 0.08) with 12 months follow-up of the first 466 enrolled pts. Acalabrutinib resulted in significantly higher values for all secondary endpoints, including OS (HR: 0.71, 95% CI: 0.53, 0.95; P = 0.02). Conclusions: Acalabrutinib is a highly effective single-agent treatment for WM, with improved PFS, OS, and safety compared to RCD. Clinical trial information: NCT02180724.
Activity and tolerability of the first-in-class anti-CD47 antibody Hu5F9-G4 with rituximab tolerated in relapsed/refractory non-Hodgkin lymphoma: initial phase 1b results. First Author: Ranjana H. Advani, Stanford Cancer Institute, Stanford, CA

Background: Targeted non-cytotoxic therapies are needed in relapsed/refractory (r/r) NHL. Hu5F9-G4 (5F9) is a first-in-class humanized anti-body targeting CD47, a protective “don’t eat me” signal on cancers, that stimulates tumor cell phagocytosis and an anti-tumor T cell response. Preclinically, 5F9 synergizes with rituximab to eliminate lymphoma by enhancing Fc receptor-mediated antibody-dependent cellular phagocytosis. This trial is the first to explore clinical activity of an anti-CD47 antibody+ rituximab. Methods: This Phase 1b/2 enrolled r/r NHL patients in a 3+3 dose escalation design (NCT02953509). A 1 mg/kg 5F9 priming dose with higher weekly maintenance doses was used to mitigate on-target toxicities, specifically anemia. Maintenance doses were escalated from 10 to 30 mg/kg with standard dose rituximab. Results: 22 heavily pre-treated patients with r/r DLBCL (n = 15) and FL (n = 7) were enrolled in Phase 1b. Patients had a median of 4 prior therapies (range 2-9), 90% were rituximab-refractory. 5F9+ rituximab was well-tolerated. Common treatment-related AEs were chills (41%), headache (36%), anemia (32%), and CRS (7%). Tumor shrinkage was seen in 1-2 except 3 G3 AEs (chills, fever, anemia). Prime/maintenance 5F9 dosing significantly mitigated on-target anemia, a mostly first dose effect with spontaneous recovery. Only 2 patients required a one-time transfusion. The MTD was mitigated on-target anemia, a mostly first dose effect with spontaneous resolution. Prime/maintenance 5F9 dosing significantly mitigated on-target anemia, a mostly first dose effect with spontaneous recovery. Only 2 patients required a one-time transfusion. The MTD was 40/27 in DLBCL and 71/43 in FL, respectively. As of 1/16/2018, 90% of patients had ≥2 prior NHL therapies with standard dose rituximab.

5F9 + rituximab is a novel combination immunotherapy that inhibits a key macrophage/cancer checkpoint. It is well tolerated with limited myelosuppression and mild inpatient CRS. A Phase 2 dose of 30 mg/kg 5F9 Q2 weeks after cycle 1 was selected. Across all doses, the ORR was 50%, 32% achieved CR. %ORR/CR was 40/27 in DLBCL and 71/43 in FL, respectively. As of 1/16/2018, 90% of responding patients continued in response (4.4 month median follow up), including 1 patient for 13+ months. Conclusions: 5F9 + rituximab is a novel immunotherapy that inhibits a key macrophage/cancer checkpoint. It is well tolerated with limited myelosuppression and mild inpatient CRS.
Combinations (n = 20)

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<td>64% (14)</td>
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Median time-from-diagnosis, months

- 1 (1-5) vs 1 (1-5) NS

TFH

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<td>84% (20)</td>
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Conclusions: Men had a higher response rate compared to women.

Tenalisib, a dual PI3K δ/δ inhibitor: Safety and efficacy results from an on-going phase I/IIb study in relapsed/refractory T-cell lymphoma. First Author: Yasuhiro Oki, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Tenalisib is a novel, next generation, highly specific, dual equi-potent PI3K δ/δ inhibitor. Early results demonstrated an acceptable safety profile with encouraging clinical activity in relapsed/refractory TCL (NCT02567656).

Methods: An open-label, Phase 1/IIb study consists of dose escalation cohorts followed by two expansion cohorts enrolling patients with peripheral TCL (PTCL) and with cutaneous TCL (CTCL). The primary objective is to determine the MTD, and to describe the safety and pharmacokinetic profiles. The secondary objectives are assessment of the overall response rate (ORR) and duration of response (DoR). Responses were evaluated for PTCL and TCL, and were confirmed by an expert panel.

Results: A total of 55 patients (27 PTCL and 28 CTCL) have been enrolled. 19 patients across dose escalation (200 mg - 800 mg BID) and 36 patients in dose expansion (at MTD, 800 mg BID Fasting) were enrolled and the results presented are the pooled data across both phases. At the time of analysis, safety assessment of 55 patients receiving at least one dose of Tenalisib demonstrated an acceptable safety profile. The most common drug related AEs were transaminitis, diarrhea, and fatigue. Related Grade ≥ 3 AEs included transaminitis (20%) and rash (5%). These events were reversible and managed by withholding study drug. Significant differences in patients with transaminitis were transaminases with or without related Grade 1/2 events compared to patients with a single PTCL patient discontinued therapy due to a drug related transaminitis. Drug related Severe AEs were pyrexia, elevated INR, sepsis, and diplopia secondary to neuropathy. Efficacy assessments of the 32 evaluable patients receiving at least two cycles of tenalisib showed an ORR of 47% (17/35, 3 CR, 12 PR, 19 SD) and 30% (10/30) for CTCL with or without related Grade 1/2 events compared to patients with a single PTCL patient discontinued treatment due to a rapid progression before the first efficacy assessment.

Conclusions: Tenalisib shows acceptable safety and encouraging activity in relapsed/refractory TCL. Recruitment in the expansion cohort is close to completion. Clinical trial information: NCT02567656.

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57514 Poster Discussion Session; Displayed in Poster Session (Board #151), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Response rate to lenalidomide plus rituximab (R²) as independent of number of prior lines of therapy: Interim analysis of initial phase of MAGNIFY phase IIib study of R² followed by maintenance in relapsed/refractory indolent NHL. First Author: David Andorsky, Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO

Background: In the phase II/III (R²) setting for indolent non-Hodgkin lymphoma (NHL), duration of response (DOR) to and type of prior therapy are important factors in predicting outcomes to subsequent therapy. Lenalidomide plus rituximab (R²) has shown promising efficacy and tolerability in multiple NHL studies. This report explores the association between prior number of therapies and response to R². Methods: MAGNIFY (NCT01996865) is a phase IIib, multicenter, global study of R/R NHL patients, including follicular lymphoma (FL) grade 1-3a and marginal zone lymphoma (MZL). Patients receive 12 cycles of R² (lenalidomide 20 mg/d, d1-21/28 + standard rituximab). Patients with stable disease or better are then randomized 1:1 to maintenance with R² vs rituximab alone. This analysis focuses on the initial period before randomization (12 cycles R²) for patients with <2 (≤2L) vs ≥2 lines (≥2L) of prior systemic anti-lymphoma therapies. Results: As of May 1, 2017, 232 patients with FL gr 1-3a (n = 186) and MZL (n = 46) were enrolled for the initial treatment period. Overall, median age was 66 years (range 35-91) and 89% were stage III/IV. Patients received a median of 2 prior systemic treatments (31% ≥3) and 97% received prior rituximab-containing regimens. Analyzed subgroups included 43% <2L (n = 99) and 57% ≥2L (n = 133) with generally similar baseline characteristics. In efficacy-evaluable patients, the overall response rates (70% and 66%) and complete response (51% and 36%) were similar in <2L and ≥2L patients. Median time of follow-up was 24 months (range 3-87). There was no significant difference in PFS between CR and other response groups. However, a significant difference was found in PR pts with LN ≥3cm vs LN <3cm. This suggests that, unlike chemotherapy, attainment of a CR with IB is not critical, however, those patients with significantly enlarged nodal after 1 year of therapy may have shorter PFS. Combination therapy studies without the goal of therapy discontinuation may focus on elimination of bulky nodal disease rather than attainment of CR for all patients.

57515 Poster Discussion Session; Displayed in Poster Session (Board #152), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with marginal zone lymphoma (MZL): Results of a prospective, randomized, multicenter phase 2 study (the STIL NHL7-2008 MAINTAIN trial). First Author: Mathias J. Rummel, Department of Haematology and Oncology, Justus-Liebig University, Giessen, Germany

Background: Rituximab (R) maintenance is part of a standard treatment for follicular lymphoma. In MZL, however, it is not yet common practice. In this study we compared the effect of 2 years of R maintenance vs. observation after first-line treatment with B-R in patients with previously untreated MZL. Methods: Patients had stage I (bulky disease > 7 cm), III, or IV disease. Nodal and splenic MZL were included but not MALT lymphomas. Primary endpoint was progression free survival (PFS). Secondary endpoints included response rates, overall survival (OS), and toxicity. For induction patients were treated with up to 6 cycles of B-R plus 2 additional R cycles. Only patients responding to B-R were then randomized to either R maintenance (q 2 months for 2 years) or observation. Patients median time of follow-up after registration was 76 months at the time of this analysis (February 2018). 119 patients with a median age of 65 years were evaluable for response. 108 (91%) responded to B-R induction, with 23 patients (19%) achieving a complete remission. Of 104 randomized patients, 53 (51%) were randomized to R maintenance and 51 (49%) to observation. Median age of randomized patients was 64 years, patient characteristics and toxicity were similar for both groups. PFS was superior for 2 years of R maintenance, with the median not yet reached vs. 92.2 months for observation (hazard ratio (HR) 0.35, 95% CI 0.17 – 0.76, p = 0.008). The OS rate at 6 years was 92% for R maintenance vs. 86% for observation. The difference in OS was not statistically significant (HR 0.52, 95% CI 0.20 – 1.39). Conclusions: Our results demonstrate a statistically significant PFS improvement of a 2-year R-maintenance vs. observation after B-R induction in patients with MZL. Clinical trial information: NCT00877214.

57513 Poster Discussion Session; Displayed in Poster Session (Board #150), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Comparison of different phase II studies using sequential combinations of targeted agents for treating chronic lymphocytic leukemia. First Author: Von Tresckow Julia, Department of Internal Medicine and Center of Integrated Oncology Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany

Background: The German CLL study group (GCLLSG) performed three similar phase II trials combining a CO20-antibody, ofatumumab (O) or obinutuzumab (G) or obinutuzumab for QA-101), with ibrutinib (I) or venetoclax (A) in an all-comer population of treatment-naïve or relapsed/refractory CLL patients (pts). Methods: In all 3 trials, pts with high tumor burden received optional bendamustine debulking (BD). Subsequent induction therapy consisted of 6 cycles of I plus O (BIO trial), I or G (BIG) or A plus G (BAG). Induction therapy was followed by a maintenance phase using the same drugs until achieving a minimal residual disease (MRD) negative complete remission or up to 24 months. The primary endpoint was the overall response rate (ORR) at the end of induction; secondary endpoints were MRD and safety. Results: 65 pts each were enrolled in the 3 trials. Pts with <2 induction cycles were excluded from the analysis as per protocol, resulting in 65, 61 and 63 evaluable pts in BIO, BIG and BAG, respectively. The primary endpoint was met in all trials. BD achieved an ORR of 61 % across all trials. During combination therapy one fatal adverse event occurred in each trial; during induction 46 SAEs occurred in BIO, 29 in BIG and 59 in BAG. Patients characteristics and major results are shown in the Table. Conclusions: The sequential combination concept shows very good efficacy and tolerability. BD reduced the number of IRR. Combination therapies with G seemed more efficient when compared to O. Additionally, combining A plus G seemed to evoke deeper responses than I plus G. Clinical trial information: NCT02689141, NCT02401503 and NCT02345863.
Role of ofatumumab (OFA) maintenance treatment in relapsed chronic lymphocytic leukemia (CLL): Final analysis of PROLONG study. First Author: Marinos Van Oers, Department of Hematology, Academic Medical Center, Amsterdam, the Netherlands, on behalf of the HOVDN CLL Working Group, Amsterdam, Netherlands

Background: An interim analysis of the PROLONG phase 3 study in patients (pts) with CLL showed a significant increase in progression free survival (PFS) with OFA maintenance treatment over OFA withdrawal without unexpected side effects (van Oers, et al, 2015). Here, we present the final analysis of the study. Methods: Pts in complete or partial remission after 2nd or 3rd line treatment for CLL were randomized 1:1 to OFA (300 mg followed 1 week later by 1000 mg every 8 weeks for up to 2 years) or to observation (Obs). Primary endpoint was investigator-assessed PFS. Secondary endpoints included time to next treatment (TTNT), overall survival (OS), and safety. Results: Overall, 480 pts were randomized to either OFA arm or Obs arm. Baseline characteristics were similar between the 2 arms. Median duration of OFA treatment was 608 days. Median follow-up was 40.89 months (mo). Median PFS was 34.17 mo for OFA (95% confidence interval [CI]: 29.70, 38.01) and 16.89 mo (95% CI: 12.98, 20.37) for Obs (Hazard ratio [HR] = 0.55; 95% CI: 0.43, 0.70; P < 0.0001) arm. Median TTNT was 37.36 mo (95% CI: 30.55, 42.61) for OFA and 27.56 mo (95% CI: 23.52, 32.62) for Obs (HR = 0.72; 95% CI: 0.57, 0.91; P = 0.0044). The OS data although not yet mature, do not show a difference (HR = 0.99; 95% CI: 0.72, 1.37). Death rate was similar in both the arms (32% in OFA vs. 29% in Obs). Adverse events (AEs) were reported in 92% of pts in OFA arm vs. 82% in the Obs arm; 62% of pts in OFA arm had ≥ grade 3 AEs vs. 51% in Obs arm. Serious AEs (SAEs) were reported in 48% of pts in OFA vs. 46% in the Obs arm. Most common AEs (≥ 5% of all pts) ≥ grade 3 AEs were neutropenia (OFA: 23% vs Obs: 10%), pneumonia (OFA: 13% vs Obs: 12%), febrile neutropenia (OFA: 6% vs Obs: 4%), and pyrexia (OFA: 5% vs Obs: 2%). Due to AEs, 12% of pts discontinued OFA permanently. Up to 60 days after the last treatment, there were 5 SAEs leading to death in the OFA arm vs 7 in the Obs arm; none were considered to be related to the study drug. Conclusions: This final analysis confirmed the results of the interim analysis, the treatment effect of maintenance OFA was maintained with more mature data. A significant clinical benefit was observed in pts with relapsed CLL after OFA maintenance. Treatment was well tolerated without unexpected toxicities. Clinical trial information: NCT01039376.

Initial results of a dose escalation study of a selective and structurally differentiated PI3K inhibitor, ME-401, in relapsed/refractory (R/R) follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). First Author: Jacob Drobnyk Soumerai, Massachusetts General Hospital, Boston, MA

Background: ME-401, an oral tyrosine kinase inhibitor highly selective for PIK3Kδ, was incorporated in a phase 1b trial for patients (pts) with R/R FL or CLL/SLL. The starting dose was based on pharmacokinetic and pharmacodynamic data from a dose escalation study of a PI3K inhibitor in patients with CLL/SLL. Here, we report the results of a dose escalation study of ME-401 in pts with R/R FL or CLL/SLL. Methods: pts with 1 prior therapy & ECOG PS ≤ 2, and adequate organ function. Ibrutinib and PI3K inhibitor ACP-319 was tolerable with manageable AEs; in DLBCL, response rate was 52% [Grade 3+ 18.4+]. Conclusions: The combination of acalabrutinib + ACP-319 was tolerable with manageable AEs; in DLBCL, response rate was high in non-GCB pts. Clinical trial information. NCT02328014.

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Background: B2M is often elevated in pts with CLL and correlates with disease stage and burden. Normalization of B2M at 6 mo during ibritinib treatment was associated with improved progression-free survival (PFS) (Thompson et al 2016). We evaluated B2M changes over time, factors associated with B2M normalization, and correlations between B2M status and PFS in pts treated with ibritinib vs rituximab. Data were selected from 2 clinical trials of single-agent ibritinib (420 mg/d) in pts with R/R CLL. Pts in RESONATE were randomized 1:1 to ibritinib or ofatumumab. All pts in RESONATE-17 received ibritinib. Univariate (UVA) and multivariate (MVA) analyses were used to examine baseline (BL) factors associated with B2M normalization. PFS from time of the 6-mo B2M visit was compared based on B2M status; exploratory analyses evaluated PFS by 9-, 12-, and 15-mo B2M status. Results: In the combined ibritinib population (N = 339), BL elevated B2M (79% ≥ 3.5 mg/L; median 5.4 mg/L) and BL del(17p) (61%), and unmutated IGHV (58%) were common; 15% had del11q, and 25% had creatinine clearance (CrCl) < 60 mL/min. Pts with B2M decreased rapidly, by ~40% at 3 mo, in all patients. Overall, 50% of pts normalized B2M during ibritinib. Median time to B2M normalization was 17 mo and was non-significantly shorter for pts with del17p vs without del17p (14 vs 26 mo; P = 0.220). In UVA, BL B2M < 3.5 mg/L, age < 65 yr, and CrCl ≥ 60 mL/min was associated significantly (Cl 0.366, 0.915; P = 0.034) across cohorts. PFS factors did not differ when assessed by 6-mo B2M normalization status (HR 0.699 [95% CI 0.452, 1.080]; P = 0.105), nor by 12- or 15-mo B2M status, but was significantly different (Cl 0.289, 0.705) associated with B2M normalization at 6 mo, while del17p was not significant. In MVA, BL B2M < 3.5 mg/L (P = 0.002) and CrCl ≥ 60 mL/min (P = 0.034) were significant; del17p was not significant. In UA, BL B2M < 3.5 mg/L (P = 0.002) and CrCl ≥ 60 mL/min (P = 0.034) were significant. In UA, BL B2M < 3.5 mg/L and/or CrCl ≥ 60 mL/min was associated with improved progression-free survival (PFS) (HR 0.699 [95% CI 0.452, 1.080]; P = 0.105). Other predictors included advanced Rai (P = 0.05) and Binet (P = 0.018), lower 17p (P = 0.018) status, but was significantly different by 9-mo B2M status (HR 0.579 [95% CI 0.452, 1.080]; P = 0.034). There were no significant differences by 12 or 15-mo B2M status. Conclusions: B2M normalization at 9 mo, CrCl was significant in MVA, but age and BL information: NCT01578707 and NCT01744691.

7521 Poster Session (Board #159), Mon, 8:00 AM-11:30 AM
Prospective study of the clinical impact of the ibrutinib-induced suppression of ATM and the expression of ATM-dependent genes in chronic lymphocytic leukemia (CLL) patients
First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ATM, a serine/threonine kinase, is a major mediator of the DNA damage response and has been shown to be associated with disease progression in patients with CLL. Various somatic mutations (MUT) have been analyzed in CLL and associated with disease progression; however, ATM, whose ATM MUTs have been associated with disease progression in CLL.

Methods: As part of a phase 2 study (NCT02007044) of frontline or salvage ibrutinib therapy, we analyzed the mutational status of ATM and a 29-gene panel in the blood of patients with R/R CLL treated with ibrutinib. DNA from peripheral blood or bone marrow was collected at baseline prior to treatment and at progression or death from any cause. We analyzed ATM Mutations in univariable (UA) and multivariable (MVA) models to examine their clinical significance and impact on overall survival (OS) and progression-free survival (PFS) in pts with R/R CLL treated with ibrutinib. Significant MUTs were defined as a prespecified cutoff of 0.05.

Results: ATM MUTs were not associated with OS or PFS. An increase in the number of ATM MUTs was associated with shorter time to treatment failure (TTFT). Other somatic MUTs, like ATM and NOTCH1 MUTs, were associated with shorter TTFT.

Conclusions: ATM and other somatic MUTs, like NOTCH1, are important independent prognostic factors for shorter TTFT. ATM MUTs are a biologically and clinically significant predictor of shorter TTFT.
Rapid progression of disease following ibrutinib discontinuation in patients with chronic lymphocytic leukemia. First Author: Paul Joseph Hampel, Mayo Clinic, Rochester, MN

Background: The clinical characteristics, management, and outcomes of patients (pts) with chronic lymphocytic leukemia (CLL) who develop rapid progression of disease following ibrutinib discontinuation are not well described. Methods: We identified all CLL pts at Mayo Clinic who discontinued ibrutinib therapy. Clinical symptoms, exam and radiographic findings, and laboratory changes associated with discontinuation were ascertained. Results: Of 281 ibrutinib treated pts, 82 (29%) discontinued therapy. Reasons for discontinuation and the median time to discontinuation include: toxicity (n = 30, 37%, 8 months), CLL progression (n = 18, 22%, 25 months), Richter’s transformation (n = 9, 11%, 6 months), other (n = 11, 13%), and death (n = 14, 17%). In total, 61 pts had adequate records for review within 4 weeks after discontinuing ibrutinib. Among these, 15 (25%) had progression worsening in > 2 clinical domains (i.e., symptoms, exam/imaging, labs) post discontinuation, including 13 pts who discontinued due to progression or transformation and 2 pts who discontinued due to toxicity or other. Clinical findings included sudden worsening of constitutional symptoms (n = 14, 93%), worsening lymphadenopathy or hepatosplenomegaly (n = 10, 67%), and increasing lactate dehydrogenase or lymphocytosis (n = 12, 80%). We defined these clinical symptoms as ibrutinib stop sequela. Next line therapy was started the next day after ibrutinib discontinuation for 6 pts, after gap in treatment in 4 pts (median 1.3 days, range 5-36), and overlapped with ibrutinib in 4 pts. Three pts did not receive subsequent therapy. These included del(17p), venetoclax (n = 3), steroids with anti-CD20 therapy (n = 2), pembrolizumab (n = 1) and multi-agent chemotherapy (n = 3). Age, sex, TP53 disruption, and IGHI mutation status did not predict the occurrence of the described worsening on univariate analysis. The overall survival for the entire group was 35 months. Conclusions: Multiple ibrutinib stop sequela were seen in 1 out of 4 patients after stopping ibrutinib, occurring despite prompt next line salvage therapy. Parameters to better define the post-ibrutinib interval and optimal ways for its management are required.

7527 Poster Session (Board #164), Mon, 8:00 AM-11:30 AM
Economic evaluation for the US of venetoclax (VEN) versus ibrutinib (IBR) versus allogeneic hematopoietic stem-cell transplantation (HSCT) in patients (pts) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) with 17p deletion (del 17p). First Author: Nimer Alsaid, University of Arizona College of Pharmacy, Tucson, AZ

Background: Prior to targeted agents, HSCT was the primary treatment for R/R CLL del 17p. VEN and IBR have been shown to improve progression free (PFS) and overall survival (OS). We performed an independent economic evaluation of VEN versus IBR versus HSCT in R/R CLL del 17p from the U.S. payer perspective. Methods: From published trial data we constructed a life-time horizon Markov model with 3 states: PFS; progression; and death. Kaplan-Meier PFS and OS curves for VEN, IBR and HSCT were digitized, and Weibull distributions fitted. The wholesale acquisition cost of VEN and IBR were sourced from RedBook. Costs of the HSCT (procedure, pre-conditioning, post-procedural adverse events (AE)) were estimated from published prediction equations and a claims database. EQ-5D utility values were sourced from literature. AE disability values were assumed the same for the 3 interventions. Discount of 3% was applied. The life years (LY) and quality adjusted LY (QALY) for each treatment were estimated, and the incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR) were determined. Results: IBR prevailed in PFS over VEN and HSCT until ~190 weeks (3.7 years) when curves crossed and VEN prevailed over both IBR and HSCT. VEN prevailed in OS over IBR and HSCT. The Table below presents the BCA and PSA estimated costs and (QALYs) gained. VEN was cost saving over IBR and HSCT and yielded higher (QALY) gains. IBR achieved higher (QALY) gains over IBR and HSCT but at incremental cost. VEN was cost prevailing in OS over IBR and HSCT over the full life time horizon. VEN showed cost savings while achieving higher (QALYs) over IBR and HSCT. IBR was cost saving over HSCT (procedure, pre-conditioning, post-procedural adverse events [AE]) were seen in 1 out of 4 patients after stopping ibrutinib, occurring despite prompt next line salvage therapy. Parameters to better define the post-ibrutinib interval and optimal ways for its management are required.

BCA/PSA

ICER(cost/LY)
VEN
$843,840/$705,032
$564,054/$565,080
ICUR(cost/QALY)
VEN
$1,487,680/$1,383,951
$925,620/$946,891

VEN vs IBR - ULN were isolated, asymptomatic, and resolved without intervention. VEN vs HSCT - 41 pts had phosphate (P) > ULN (n = 41, 48%); 20 pts received P binder for P > HC during VEN ramp up and all others resolved without additional medication. Most instances were isolated: 4 pts had concurrent calcium (Ca++) or uric acid (UA) changes, and P was not treated in these cases. 70% of pts received allopurinol and 20% allopurinol and rasburicase at VEN start. 6 pts started rasburicase in addition to oral oxypurinol. Though 144 pts had Ca++ < lower limit of normal (ULN), only 6 were treated. Conclusions: Despite the frequency of K > ULN, treatment was applied in 13% of pts for rising or sustained elevation, and most had pre-VEN > ULN. Most cases of P > ULN were isolated, asymptomatic, and resolved without intervention. VEN causes rapid tumor cytoreduction consistent with analytic changes, though clinical sequelae are rare and mitigated by approved dose ramp up, TLS prophylaxis/monitoring, and timely intervention. Clinical trial information: NCT01889186, NCT02141282.

7528 Poster Session (Board #165), Mon, 8:00 AM-11:30 AM
Change in tumor lysis syndrome risk after lead-in treatment in a phase 1b/2 study of obinutuzumab, ibrutinib, and venetoclax for chronic lymphocytic leukemia. First Author: Kerry Anne Rogers, The Ohio State University, Division of Hematology, Columbus, OH

Background: Venetoclax (VEN) is highly effective for the treatment of chronic lymphocytic leukemia (CLL). Tumor lysis syndrome (TLS) during VEN initiation is a major risk and management, including hospitalization for high risk patients, increases treatment burden and limits use of this drug. Hypocalcemia and hyperkalemia are frequent TLS risk factors. We reviewed our phase 1b/2 study of combination obinutuzumab (OBIN), ibrutinib (IBR), and VEN to understand how lead-in OBIN and IBR change TLS risk. Methods: All study patients who completed 3 cycles (C) of treatment were included. Agents were started sequentially over 0-1 weeks: OBIN C1 (C1 D1:100mg, C1 D2-8: 100mg, C1 D9: 100mg, C1 D15: 1,000mg, C2 D15: 1,000mg), IBR C2 (C2-14 D1-28: 420mg), and VEN C3. Risk for TLS was assessed according to the VEN US label at baseline and prior to C3. We recorded absolute lymphocyte count (ALC) and lymph node (LN) sum of the product of longest diameters (SPD) and tested for changes in TLS risk between C1 and C3 using the Wilcoxon signed-rank test. Results: 61 patients were included: 36 relapsed or refractory and 25 treatment naive. ALC and LN (C1-3) and TLS risk (baseline, C3) are in Table 1. ALC significantly decreased from C1 to C3 (p < 0.0001) with a median change of -99.2% (range -99.6-194.5%). LN similarly decreased (p < 0.0001). OBIN attenuated IBR lymphocytosis with a median change C2 to C5 of 2.1 (range -0.3-46.7). Twelve (20%) patients reduced TLS risk from high to medium, 26 (43%) from medium to low, and 23 (38%) had no change. There were no incidents of clinical or laboratory TLS. Conclusions: Lead-in OBIN and IBR decreased TLS risk in the majority of high (12/19, 63%) or medium (26/34, 76%) risk patients when compared to baseline. We reassessed prior to VEN. This strategy may improve the safety of VEN initiation, allow some initially high risk patients to avoid hospitalization, and expand settings where VEN is used. Clinical trial information: NCT02247451.

Baseline and TLS risk (n = 61).

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<td>ALC in AUL, median (range)</td>
<td>6.7 (2.4-24.5)</td>
<td>6.0 (1.5-20.6)</td>
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<tr>
<td>K in UA, median (range)</td>
<td>3.7 (1.8-3.4)</td>
<td>3.7 (1.8-3.4)</td>
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<td>P in ULN, median (range)</td>
<td>2.0 (0.3-6.0)</td>
<td>1.7 (0.3-6.0)</td>
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<td>Tumor size, Cm</td>
<td>476</td>
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| Palpable LN SPD in cm, median (range) | 61 patients were included: 36 relapsed or refractory and 25 treatment naive. ALC and LN (C1-3) and TLS risk (baseline, C3) are in Table 1. ALC significantly decreased from C1 to C3 (p < 0.0001) with a median change of -99.2% (range -99.6-194.5%). LN similarly decreased (p < 0.0001). OBIN attenuated IBR lymphocytosis with a median change C2 to C5 of 2.1 (range -0.3-46.7). Twelve (20%) patients reduced TLS risk from high to medium, 26 (43%) from medium to low, and 23 (38%) had no change. There were no incidents of clinical or laboratory TLS. Conclusions: Lead-in OBIN and IBR decreased TLS risk in the majority of high (12/19, 63%) or medium (26/34, 76%) risk patients when compared to baseline. We reassessed prior to VEN. This strategy may improve the safety of VEN initiation, allow some initially high risk patients to avoid hospitalization, and expand settings where VEN is used. Clinical trial information: NCT02247451.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: VEN is an oral bioavailable BCL-2 inhibitor approved by the FDA in April 2016 for use in CLL. More data are needed to understand real world initiation, management and outcomes of CLL pts treated with VEN. Methods: This was a retrospective cohort study of CLL pts who initiated VEN. Investigators from 25 community centers provided pt-level data from medical records including demographics, clinical characteristics, ramp up management and outcomes. Tumor burden was assessed per IWCLL criteria. Tumor lysis syndrome (TLS) was defined by Howard criteria and response was based on iwCLL criteria. The primary endpoint was response. Characteristics and outcomes were summarized by descriptive statistics. Results: 222 VEN pts were included, of whom 22% used VEN in combination with irbritinib (7%) or an anti-CD20 (14%). Median age was 64 years (range 57-71); 82% had TP53 mutation; 84% had ≥1 prior line of therapy (median 1; range 0-6); 62% had prior kinase inhibitor (KI) use; and 4% had prior use of 2 Kts. At baseline, 11%, 49% and 40% had low, medium and high tumor burden, respectively, and 27% initiated VEN as inpatient. During ramp up, 6% had a dose interruption; no dose modifications were required. TLS events occurred in 6% of pts (n = 13) with 2 pts experiencing clinical TLS, mainly among high risk pts. 34 pts (15%) discontinued VEN, mainly due to relapse (n = 5), refractoriness (n = 9), or in setting of disease response (n = 8). Maximum dose of 400mg was achieved in 53% of pts and 46% of CI were maintained at doses ≥400mg. During ramp up. With a median follow up of 6.1 months, ORR was 75% (CR: 26%). Median time to best response was 3 months. Responses were not negatively affected by TLS or maintenance doses <400mg. Among 38 pts assessed for minimal residual disease (MRD) during VEN, 23 (61%) were MRD negative. Renal function, baseline lymphadenopathy, bone marrow biopsy, or B symptoms were reported among 93%, 95%, and 96%, respectively. Conclusions: In this study, most VEN-treated CLL pts completed the ramp up, few experienced a TLS/hematologic event, and responses were comparable to clinical trials. Inpatient management deviated from the FDA label suggesting opportunity to improve adherence to initiation guidance.

Management and outcomes of 222 CLL patients (pts) treated with venetoclax (VEN) in the real world. First Author: Chadi Nabhan, Cardinal Health Specialty Solutions, Dublin, OH, USA

First Author: Chadi Nabhan, Cardinal Health Specialty Solutions, Dublin, OH, USA

First Author: Brian Koffman, CLL Society Inc, Claremont, CA

Background: The CLL literature focuses largely on the objective aspects of disease progression, active observers (AO), predictor variables, regimen, HCPs, and the disease trajectory to the next treatment. To our knowledge, this is the largest survey of CLL pts. Much can be learned by detailed surveying of CLL patients’ subjective experience through the continuum of care is limited. Methods: We utilized an online or paper 64 question survey directed to CLL pts to capture more information on their experience with CLL. The survey was IRB-approved and took place between October-December 2017. All analyses were descriptive in nature. Results: 1147 pts from 48 states completed the survey. Median age was 65 (range 28-86), 46% male, 96% Caucasian. 33% of pts do not recall education by their HCP at dx. Following education, 66% of pts report a good understanding of sources of information on CLL, 64% of disease characteristics and 62% of therapy indications. At disease progression, only 23% of pts report education from their HCPs. Effects of treatment and clinical trial opportunities are well understood by 43% and 35% respectively. At dx, 48% were told they had the “good” cancer. When AO was recommended, pts report anxiety (56%), relief (52%) and confusion (31%). 34% and 16% of pts report the discussing prognostics increased their anxiety and confused respectively. During AO pts report fatigue (51%), enlarged nodes (47%), anxiety (39%), depression (21%), and night sweats (21%). Also during AO, 653 pts (66%) utilize herbs and other non-traditional interventions for CLL management (Table). When pts declined participation in a clinical trial, the reasons cited were personal reasons (43%), disease characteristics (13%), distant from clinical trial (13%), financial fear (20%), and frequent imaging (20%). Conclusions: To our knowledge, this is the largest survey of CLL pts. Much can be learned by detailed surveying of CLL pts throughout their disease. These include previously unrecognized suboptimal interactions between the CLL pt and the HCP. Understanding how pts experience their disease is critical to improve communication between pts and their HCPs, which will ultimately advance CLL outcomes.

A U.S.-based survey: The experiences of 1147 chronic lymphocytic leukemia (CLL) patients (pts). First Author: Brian Koffman, CLL Society Inc, Claremont, CA

A U.S.-based survey: The experiences of 1147 chronic lymphocytic leukemia (CLL) patients (pts). First Author: Brian Koffman, CLL Society Inc, Claremont, CA

Background: Although KI therapies are generally well-tolerated, intolerance is the most common reason for discontinuation, thus representing an unmet medical need. Umbralisib (TGR-1202), a next generation PI3Kδ inhibitor, has a discontinuation rate due to adverse events (AEs) of <10%. Methods: We report results from a Phase 2 study assessing the safety and efficacy of umbralisib in pts who were intolerant (defined per protocol) to a prior Ki within 12 mos. AEs must have resolved to ≤1 prKi prior to umbralisib therapy. Umbralisib (800mg QD) administered until progression or toxicity. Primary endpoint is progression-free survival (PFS). Results: 40 pts were treated as of 2/2018 (36 BTK & 4 PI3Kδ). Baseline demographics: median (med) age 69 yrs (range 56-86), med prior therapies (2±1.7), 55% male, ECOG 0-1 (92%), del17p (20%), del11q (23%), IGHV unmutated (60%), 80% required treatment within 6 mos of prior Ki discontinuation. Most AEs leading to Ki discontinuation were: arthralgia, rash (9 events each), A-fib (6), diabetes (4), bleeding, fatigue and weight loss (3 each). AEs on umbralisib are listed in the table: GR >3 PI3Kδ-associated AEs were limited: AST/ALT (3%); diarrhea (7.5%); rash (3%). 4 pts discontinued umbralisib due to intolerance (rash, pneumonia, pneumonitis, pancreatitis), and 1 pt due to study noncompliance. No pt discontinued umbralisib as a result of a primary Ki (rash), an AE, or patient refusal. Conclusions: Management and outcomes of 222 CLL patients (pts) treated with venetoclax (VEN) in the real world. First Author: Moritz Fuerstenau, Department I of Internal Medicine and Center of Integrated Oncology Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany

Background: In CLL, its mechanism of action has not been determined yet. In our CLLM1 trial, 2 of 56 pts developed BCR-ABL positive disease response (n = 8). Maximum dose of 400mg was achieved in 53% of pts and 46% of CI were maintained at doses ≥400mg. Among 38 pts assessed for minimal residual disease (MRD) during VEN, 23 (61%) were MRD negative. Renal function, baseline lymphadenopathy, bone marrow biopsy, or B symptoms were reported among 93%, 95%, and 96%, respectively. Conclusions: In this study, most VEN-treated CLL pts completed the ramp up, few experienced a TLS/hematologic event, and responses were comparable to clinical trials. Inpatient management deviated from the FDA label suggesting opportunity to improve adherence to initiation guidance.

B-cell acute lymphoblastic leukemia (B-ALL) in CLL patients treated with lenalidomide. First Author: Moritz Fuerstenau, Department I of Internal Medicine and Center of Integrated Oncology Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany

Background: The immunomodulatory drug lenalidomide (len) has shown activity and T-cell activation; in CLL, its mechanism of action has not been determined yet. In our CLLM1 trial, 2 of 56 pts developed BCR-ABL positive disease response (n = 8). Maximum dose of 400mg was achieved in 53% of pts and 46% of CI were maintained at doses ≥400mg. Among 38 pts assessed for minimal residual disease (MRD) during VEN, 23 (61%) were MRD negative. Renal function, baseline lymphadenopathy, bone marrow biopsy, or B symptoms were reported among 93%, 95%, and 96%, respectively. Conclusions: In this study, most VEN-treated CLL pts completed the ramp up, few experienced a TLS/hematologic event, and responses were comparable to clinical trials. Inpatient management deviated from the FDA label suggesting opportunity to improve adherence to initiation guidance.

A phase 2 study to assess the safety and efficacy of umbralisib (TGR-1202) in pts with CLL who are intolerant to prior BTK or PI3Kδ inhibitor therapy. First Author: Anthony R. Mato, Memorial Sloan Kettering Cancer Center, New York, NY

A phase 2 study to assess the safety and efficacy of umbralisib (TGR-1202) in pts with CLL who are intolerant to prior BTK or PI3Kδ inhibitor therapy. First Author: Anthony R. Mato, Memorial Sloan Kettering Cancer Center, New York, NY

A phase 2 study to assess the safety and efficacy of umbralisib (TGR-1202) in pts with CLL who are intolerant to prior BTK or PI3Kδ inhibitor therapy. First Author: Anthony R. Mato, Memorial Sloan Kettering Cancer Center, New York, NY
7533 Poster Session (Board #170), Mon, 8:00 AM-11:30 AM
The efficacy of duvelisib monotherapy following disease progression on ofatumumab monotherapy in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study. First Author: Brynne J. Kuss, Flinders Medical Centre, Bedford Park, Australia

Background: Duvelisib, an oral dual inhibitor of PI3K-α,γ, is being developed for the treatment of hematologic malignancies, including relapsed/refractory (RR) CLL/SLL. In the Phase 3 DUO study (NCT02045452) duvelisib monotherapy demonstrated significant improvement compared to ofatumumab monotherapy (PFS 13.3 vs 9.9 mo. p < 0.0001; ORR 74% vs 45% p < 0.001) with a manageable safety profile (Flinn et al. ASCO 2017). Study IPI-145-12 (NCT02049515) is an open-label, optional, crossover extension study where pts with confirmed progressive disease (PD) on DUO were given the option to receive the opposite treatment. Herein we present data for the 89 pts who voluntarily rolled over following PD on ofatumumab on DUO and received duvelisib on Study IPI-145-12. Methods: Eligible pts were enrolled within 3 months of PD on the DUO study (excluding Richter’s transformation or prolymphocytic leukemia), and maintained adequate renal and hepatic function and an ECOG PS of 0-2. Duvelisib 25 mg BID was administered until PD, intolerance, death, or study withdrawal. Responses were determined by investigators using modified IWCLL/IWG criteria. Results: Median age was 68 yrs (range: 39-89), 63% were male, and 90% Caucasian. Nearly half (49%) had Rai Stage III/IV or Binet Stage C, and 23% had del(17p) and/or TP53 mutation. Median prior anticancer therapies was 3 (range: 2-8). Median exposure to duvelisib was 32 weeks on the extension study. The ORR for pts treated with duvelisib in the crossover was 73% (95% CI: 64, 82) (all PRs) compared to 28% (95% CI: 19, 37) (1% CR, 2% PR) when previously treated with ofatumumab in DUO. The median PFS for duvelisib was 15 mo. (95% CI: 10, 17) compared to 9 mo. (95% CI: 9, 11) for prior ofatumumab. Conclusions: In an extension study, duvelisib monotherapy achieved robust and durable responses in RR CLL/SLL pts following ofatumumab progression in the DUO study (ORR: duvelisib 73%; prior ofatumumab 28%), with a longer PFS with duvelisib than prior ofatumumab (PFS: duvelisib 15 mo.; prior ofatumumab 9 mo.). These data further support duvelisib monotherapy as an effective oral treatment option for pts with RR CLL/SLL. Clinical trial information: NCT02049515.

7534 Poster Session (Board #171), Mon, 8:00 AM-11:30 AM
Improving outcomes with brentuximab vedotin (BV) plus chemotherapy in patients with newly diagnosed advanced stage Hodgkin lymphoma. First Author: David J. Straus, Memorial Sloan Kettering Cancer Center, New York, NY

Background: ECHELON-1 is a phase 3 study of BV plus doxorubicin, vinblastine, and dacarbazine (A+BV) vs ABVD as frontline therapy in untreated advanced HL (NCT01712490). G-CSF primary prophylaxis (G-PP) was administered at the investigators’ discretion, and during the study was formally recommended by an independent data monitoring committee (IDMC) for patients (pts) receiving A+BV or pts receiving A only after the pts received G-PP. The NCT01712490 study treated with fewer infections and ≥ Grade 3 AE’s, including neutropenia (70% without vs 29% with G-PP) and febrile neutropenia (21% vs 11%). Methods: Exploratory analyses assessing outcomes and exposure in pts who received G-PP on the A+BV arm compared with those who did not were conducted. G-PP was associated with fewer infections (23% vs 50% with G-PP) and days of treatment (N=1234) and led to a decreased risk of a modified progression free survival event (mPFS; Conners, 2018) by 25% compared to A+BV without G-PP and by 42% compared to ABVD. Clinical trial information: NCT01712490. Conclusions: Concomitant administration of G-PP with A+BV in pts with advanced HL reduced frequency of tx delays. Though the sample size is small, G-PP with A+BV may be associated with improved efficacy and a decrease in early, neutropenia-associated deaths; a prospective clinical trial to further assess the safety and efficacy in pts receiving G-PP with A+BV is planned.

7535 Poster Session (Board #172), Mon, 8:00 AM-11:30 AM
Limited stage nodular lymphocyte predominant Hodgkin lymphoma (NLPHL): A subgroup analysis of the HD Medical Centre, Bedford Park, Australia

Background: NLPHL is a rare subtype of Hodgkin lymphoma (HL) accounting for 5% of cases. It is rarely studied in prospective clinical trials and treatment is controversial. Methods: In the Canadian Cancer Trials Group HD.6 phase 3 trial, individuals with newly diagnosed non-bulky stage IA or IIA HL were randomly assigned to treatment with ABVD chemotherapy (CT) alone, or to radiation based (CMT/RT) therapy (Meyer NCM 2012). From this we identified all patients with NLPHL. A classical Hodgkin lymphoma (cHL) comparison cohort was constructed using propensity score matching 3:1 for age, sex, stage, treatment arm and number of nodal sites. Event free survival (EFS), overall survival (OS) and freedom from disease progression (FFP) were as defined in the original trial. The NLPHL cohort was analyzed according to treatment arm and compared with the cHL cohort using log-rank statistics. Secondary endpoints included toxicity and secondary malignancies. Results: Of 405 individuals enrolled in HD.6, 29 (7.2%) had NLPHL. Of these, median age at diagnosis was 42 yrs, 24 (83%) were male and 15 were assigned to RT. Median follow up was 120 months. For patients with NLPHL, 12-y EFS for CMT/RT vs CT was 58% vs. 85% (HR 0.46, 95% CI 0.09-2.37) and FFP was 70% vs 85% (HR 0.72, 95% CI 0.12-4.33), respectively. There was one death in the CMT/RT arm; OS analysis by treatment arm was not conducted due to insufficient events. Eighty-seven pts were identified for the matched cHL cohort. 12-y OS in the NLPHL and cHL groups was 95% and 87% (HR 3.43, 95% CI 1.44-26.5), EFS 70% and 81% (HR 0.73, 95% CI 0.30-1.76), FFP 78% and 90% (HR 0.51, 95% CI 0.17-1.57). Over the entire course of follow-up, there was 1 (3%) death in the NLPHL group due to unknown cause and 12 (14%) deaths in the cHL group – 3 treatment-related toxicity, 6 secondary malignancy, 3 other causes. Conclusions: We present the only prospective assessment of early-stage NLPHL treated with ABVD alone. Acknowledging limitations including small sample size, outcomes of pts with NLPHL appear very good when treated with ABVD chemotherapy alone. Clinical trial information: NCT 00002561.

7536 Poster Session (Board #173), Mon, 8:00 AM-11:30 AM
Sintilimab (IBI308) in relapsed/refractory classical Hodgkin lymphoma: A multicenter, single-arm phase 2 trial in China (ORIENT-1 study). First Author: Yuankai Shi, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Classical Hodgkin’s lymphoma (cHL), characterized by chromosome 9p24.1 alteration and PD-1 ligands overexpression, is sensitive to PD-1/PD-L1 blockade in various clinical studies. This trial confirmed efficacy and safety of sintilimab (IBI308), a promising anti-PD-1 monoclonal antibody, in Chinese patients with relapsed/refractory (R/R) cHL. Methods: ORIENT-1 (NCT03114683) is a multicenter, single-arm, phase 2 study. Patients who failed 2 or more lines of systemic therapy, including autologous hematopoietic stem cell transplantation (HSCT) were enrolled. Sintilimab was given 200 mg intravenously every 3 weeks, until disease progression, death, unacceptable toxicity, or withdrawal from study. The primary endpoint was objective response rate (ORR) assessed by independent radiological review committee (IRRC) according to 2007 IWG criteria. The cut-off date for this analysis was Feb 9, 2018. Results: Among 96 treated patients enrolled between Mar 30th 2017 and Nov 1st 2017, the median number of previous chemotherapies was 3 (range: 1–13). 54.2% patients received prior radiotherapy and 18.8% failed HSCT. With median treatment cycles of 9 (range: 1–14), ORR was 74.0% (71.96, 97%CI: 64.2%, 83.7%) per IRRC review. 23 patients (24.0%) achieved complete response (CR). The median duration of response has not been reached. At the time of analysis, 64 of 71 complete and partial response patients had an on-going response. The most common treatment-related adverse event (TRAE) was pyrexia (43.8%, 42/96), and 92.9% were grade 1~2. Most of patients were pyrexia increased in the first infusion in 15 days. Other common TRAEs were hypothyroidism (13.5%) and TSH increase (11.5%), and all were grade 1~2. The most common grade 3~4 TRAEs were pyrexia (3.1%) and thrombocytopenia (2.1%). No patient died. Conclusions: Till now, ORIENT-1 study is the largest R/R cHL study in China. Patients in our study were sensitive to sintilimab, with 74.0% ORR and 24.0% CR rate. The safety profile was consistent with the findings of other anti-PD-1 monoclonal antibodies in cHL patients. Sintilimab could be a new treatment option for R/R cHL patients in China. Clinical trial information: NCT03114683.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: More than 50% unprecedented objective clinical response rate led to a rapid approval of anti-PD-1 antibodies by FDA using in patients with relapsed/refractory classical Hodgkin lymphoma (r/r cHL). However, anti-PD-1 monotherapy can induce complete remission (CR) only in about 10% patients. Decitabine, a demethylating agent, was documented to directly boost T cell function and also possibly delay/pause PD-1-induced T cell exhaustion. This Phase III study was designed to assess the safety and efficacy of decitabine-prime anti-PD-1 (SHR-1210, a novel humanized IgG4/kappa monoclonal antibody) treatment in r/r cHL patients. Methods: Enrolled patients without anti-PD-1 history were 1:2 assigned into SHR-1210 monotherapy (4 mg/kg per day) to cohort 1 or decitabine (10mg/d on day 1-5) plus SHR-1210 (4mg/kg, day 8, per 3 weeks) cohort 2. Patients refractory to anti-PD-1 monotherapy were allocated into cohort 2. Safety was assessed by CTCAEv4.0, and clinical response by PET-CT referred to standard international criteria. Results: A total of 57 patients with heavily treated history (14.6% vs 10.4% in cohort 1), 8-cycle anti-PD-1 monotherapy were enrolled and 41 completed serial response evaluation by the end of Jan. 2018. The most common adverse events were clinically negligible cherry hemangioma (75% in cohort 1 and 93% in cohort 2), and unattended leukocytopenia (32% in cohort 2). Six of 14 patients in cohort 1 were evaluable. The CR rate in cohort 3 SD. Twenty cases from cohort 2, before enrollment were evaluated to be refractory to anti-PD-1 alone therapy, 17 were evaluated and showed 4 CR (23%), 5 PR (30%), 4 SD, and 4 PD. Eighteen of 26 patients without anti-PD-1 history before enrollment were evaluated as 12 CR (67%), 4 PR (22%), and 2 SD. So far, 88% evaluated patients had a >24-week progression-free survival. Conclusions: Addition of decitabine not only largely increased the CR rate of anti-PD-1 therapy in r/r cHL, but significantly reversed the resistance of anti-PD-1 therapy. Combination therapy had an acceptable safety profile. Clinical trial information: NCT02961101 and NCT03250962.

5753 Poster Session (Board #176), Mon, 8:00 AM-11:30 AM
Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin lymphoma (HL): Impact of cycle 2 PET result on modified progression-free survival
First Author: Robert W. Chen, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA

Background: The ECHELON-1 trial demonstrated improved outcomes for patients (pts) with advanced HL who received frontline A+AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine) vs ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), with 2-year mPFS rates of 82% and 77%, respectively. Here we report a post-hoc analysis of mPFS outcomes and clinical characteristics by Cycle 2 PET (PET2) status in independent review facility (IRF). Methods: Pts were randomized 1:1 to A+AVD or ABVD on Days 1 and 15 for up to six 28-day cycles. PET scans were conducted at the end of Cycle 2 and end of treatment. PET2 results guided the optional switch to alternate therapy at the treating physician’s discretion for pts with a Deauville score of 5. A switch to alternate therapy was not considered an event. The primary endpoint, mPFS, was defined as time to progression, death, or absence of a complete response with subsequent anticancer therapy, per IRF. Results: PET2 negativity rates (Deauville ≤ 3) were 89% (588/664 pts) in the A+AVD arm and 86% (577/670) with ABVD. Baseline characteristics were well-balanced across arms, with no significant differences in PET2– vs PET2+ pts in either arm. PET2 positivity rates (Deauville ≥ 4) were 7% (47/664) in the A+AVD arm and 9% (58/670) with ABVD; 5 total pts with a Deauville score of 5 reached an alternative frontline therapy switch to chemotherapy (2 PR (34%) and showed a favorable treatment effect for both subgroups in favor of A+AVD (Table 1), with 2-year mPFS (PET2– vs PET2+ in 85.2 vs 57.5% in the A+AVD arm, and 80.9 vs 42.0% in the ABVD arm. Outcomes for PET2– pts were relatively poor in both arms, as previously reported. Conclusions: Decision-making driven by Cycle 2 PET2+ vs PET2– in frontline HL did not demonstrate a treatment effect in favor of A+AVD over ABVD. This post-hoc analysis showed a similar treatment effect on mPFS consistently in favor of A+AVD regardless of PET2 status. Clinical trial information: NCT01712490.

Summary of mPFS by PET2 Status.

<table>
<thead>
<tr>
<th>PET2 Status</th>
<th>A+AVD</th>
<th>ABVD</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>82.1</td>
<td>77.2</td>
<td>0.77</td>
<td>0.035</td>
</tr>
<tr>
<td>95% CI</td>
<td>78.8-85.0</td>
<td>73.7-84.0</td>
<td>0.603-0.983</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>664</td>
<td>670</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET2–</td>
<td>85.2</td>
<td>80.9</td>
<td>0.774</td>
<td>0.070</td>
</tr>
<tr>
<td>95% CI</td>
<td>82.9-88.4</td>
<td>78.0-83.2</td>
<td>0.577-0.922</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>588</td>
<td>577</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET2+</td>
<td>51.2</td>
<td>42.0</td>
<td>0.609</td>
<td>0.089</td>
</tr>
<tr>
<td>95% CI</td>
<td>41.0-70.9</td>
<td>28.6-54.8</td>
<td>0.341-1.088</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>58</td>
<td>51</td>
<td></td>
<td></td>
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</tbody>
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5754 Poster Session (Board #177), Mon, 8:00 AM-11:30 AM
Prognostication of older Hodgkin lymphoma (HL) patients (pts): Findings from a multicenter phase II study
First Author: Andrew M. Evens, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Outcomes have been historically poor for older HL pts (ages ≥ 60 years). Furthermore, there are sparse data regarding prognostication. Methods: Untreated older HL pts received 2 initial doses of single agent brentuximab vedotin (BV) (1.8 mg/kg q 3 weeks) following by 6 cycles of doxorubicin, vinblastine & dacarbazine (AVD); responding pts received 4 BV consolidation doses. 48 pts enrolled (42 evaluable for response). Univariate (UVA) & multivariate (MVA) analyses were performed with Cox proportional hazard regression for survival. Results: Median age was 61 (60-88); 53% stage IV S; 44% stage III; 55% male; 70% lymphocytic/lymphoplasmacytoid; 100 ECOG PS 0-1; 60% IP 3-7; median Cumulative Illness Rating Scale-Geriatric (CIRS-G) comorbidity score 6 (52% grade 3/4); and 12% had baseline loss of instrumental activities of daily living (iADL). 52% of pts completed all intended cycles & 65% received at least 1 BV consolidation; the median CIRS-G for pts who completed all intended therapy vs not was 4 vs 8, respectively (P=0.03). ORR to initial BV was 87% (CR 30%). After AVD, ORR & CR rates were 95% and 90%, respectively. Among all 48 pts, 2 yr PFS was 85% with 94% OS. Response to the initial 2 doses of BV (CR/PR vs SD) was associated with 2 yr PFS rates of 100% vs 50%, respectively (P=0.002). On UVA, increasing age and CIRS-G score & loss of iADLs were significant for PFS (Table). On MVA of all factors, only iADLs loss remained significant for inferior PFS (HR 8.19, 95%CI 1.2-57.6, P=0.03). 2 yr PFS rates based on loss of iADLs vs not were 90% vs 54%, respectively. 2 yr PFS rates with 2 or ≥3 grade 3/4 toxicity (≥30% Pts) 0.01). Pts with loss of iADLs received a median of 6.5 12 cycles intended on study (P=0.01); 67% vs 39% had a serious adverse event (P=0.20); and CR rate was 60% vs 95% (P=0.06). Conclusions: Outcomes for older HL pts treated with sequential BV and AVD were excellent. The most dominant factor associated with divergent pt outcomes was baseline functionality, as assessed by iADLs. Clinical trial information: NCT01476410.

UVA analyses.

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.16</td>
</tr>
<tr>
<td>Female</td>
<td>4.97</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>2.68</td>
</tr>
<tr>
<td>Loss iADLs</td>
<td>14.88</td>
</tr>
<tr>
<td>CIRS-G</td>
<td>1.21</td>
</tr>
</tbody>
</table>

*Non-significant factors: histology, ECOG/PS, albumin, stage; marrow involvement, IPS.
corporating antibody drug conjugates or checkpoint inhibitors. therapy escalation and inclusion in late phase trials of novel agents in-
EFS than younger groups. This suggests that children $0.60 HR (95% CI)
2-year survival (%)
84.3 73.7 86.4 73.6 88.1 76.4
5-yr EFS 5-yr OS
A+AVD ABVD A+AVD ABVD A+AVD ABVD
N 250 247 250 247 250 247
2-year survival (%)
84.3% 73.7% 86.4% 73.6% 88.1% 76.4%
HR (95% CI)
0.60 (0.34, 0.92) 0.79 (0.49, 1.32) 0.79 (0.49, 1.32)
p-value
0.012 0.002 0.002

Survival by age in children and adolescents with Hodgkin lymphoma: A population-based analysis of Children's Oncology Group COG trials. First Author: Justine M. Kahn, Columbia University Medical Center, New York, NY

The Children's Oncology Group defines adolescent/young adult as 15-39y. Guidelines from ASCO and Friends of Cancer Research call for including children ≥12y on late phase trials spanning children and adults. We examined whether, in children and adolescents receiving response-based therapy for Hodgkin lymphoma (HL), age ≥12y would define a group with lower outcomes compared to younger patients. This was a pooled analysis of individual patient-level data from three COG Phase 3 trials for intermediate, low, high-risk HL (AHOD0031, AHOD0431, AHOD0831). 5-y event free survival (EFS) and overall survival (OS) by age were estimated via Kaplan Meier method. Cox regression models examined the influence of age on EFS and OS, adjusted for race/ethnicity, sex, insurance, histology, Ann Arbor stage, B symptoms, bulk, study, and radiation therapy (RT). Results: We included 2071 of 2155 patients, 1-21y enrolled from 2002-2012. Mean age at diagnosis was 14.6y (±3.5y) with 54% ≥15y (N = 1121) and 81% ≥12y (N = 1684). At median follow-up of 6.9 years, patients < 15y had statistically significantly better EFS (< 15y: 85% vs. ≥15y: 80%; p = 0.02). A difference in EFS was noted in those <12y vs. ≥12y (87% vs. 81%, p = 0.0503). OS was significantly better in patients < 15y vs. < 15y (98% vs. 95%, p = 0.006), but did not differ in < 12y vs. ≥12y (99% vs. 97%, p = 0.136). Cumulative incidence of second malignant neoplasms did not differ by age category. In multivariable models, older age was an independent predictor of treatment failure in both age categories (Table). Conclusions: With contemporary, response-based therapy on COG trials, adolescents ≥12 and ≥15y had worse EFS than younger groups. This suggests that children ≥12y may benefit from therapy escalation and inclusion in late phase trials of novel agents incorporating antibody drug conjugates or checkpoint inhibitors.

Multivariable cox model of 5-y EFS and OS by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>EFS 5-y</th>
<th>p-value</th>
<th>OS 5-y</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 years (R: ≥12)</td>
<td>0.71 (0.51, 0.98)</td>
<td>0.04</td>
<td>0.51 (0.2, 1.34)</td>
<td>0.17</td>
</tr>
<tr>
<td>≥12 years (R: ≥15)</td>
<td>0.74 (0.52, 0.93)</td>
<td>0.01</td>
<td>0.39 (0.2, 0.76)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

HR: hazard ratio; 95%CI: 95% confidence interval; R: reference group
Background: Many patients (pts) with RR-DLBCL treated in the real-world are not offered ASCT despite its curative potential. Understanding the impact of ASCT on OS in the real world is critical to position novel therapies as an alternative to ASCT. Methods: We retrospectively analyzed real-world pts with RR-DLBCL treated between 1/1/10-12/31/16 in 126 community-based hematology/oncology practices across the US. Pts treated with first line (1L) R-CHOP or DA-EPOCH-R were grouped into 2 categories: early relapse (progressive disease [PD] on treatment within 365 days from completing last cycle) and late relapse (any 2L treatment 366–730 days from last cycle of 1L). Pts were stratified whether ASCT was performed after 2L. Pts receiving rituximab monotherapy in 2L or later were excluded from analysis. A period of ≥6 months of clinical inactivity at end of follow-up served as a proxy for death. Median (95% CI) OS were estimated by Kaplan-Meier method, and adjusted hazard ratios (HR) were estimated by Cox proportional hazard models to adjust for differences in pt characteristics (sex, age at DLBCL diagnosis, time to relapse (2L), 1L R-CHOP, and comorbidities). Results: For the real-world cohort, the median OS was 29.5 months (22.5–45.2) for 19% complete response [CR]). NanoString subtyping conducted on 15 pts revealed 5 GCB, 9 activated B-cell (ABC), and 1 unclassified DLBCL. The Table shows OS of this cohort stratified by line of therapy. 22.5); 1 pt continues therapy. Pts discontinued treatment primarily for PD (66%); 1 pt for unspecified reasons; 1 pt continues therapy. The percent of ABC-type DLBCL was 788 (44%) ABC and 1010 (56%) non-ABC; 312 (15%) samples were from patients who underwent ASCT compared to those who did not (21.4 mo. vs 10.5 mo.; adjusted Pc = 0.01); HR = 0.51 (95% CI 0.32-0.81). Median OS shortened with each subsequent line of therapy—more so for non-ASCT group with a median OS of 2L at 10.5 mo., 3L of 9.4 mo., and 4L+ of 3.9 mo. for non-ASCT vs 19.8 mo., 13.7 mo., and 9.7 mo. for ASCT group. Conclusions: An important role for ASCT in the treatment of DLBCL in the real-world was demonstrated. OS depend upon the prior therapies as an alternative to ASCT. Exposure to R or G+R led to dissolution of EZH2 from other PR2C members as compared to single agent. EZH2 is a catalytic subunit of PRC2, and induces methylation of H3K27. Activating mutations and overexpression of EZH2 are found in NHL. Inactivating mutations in histone acetyltransferases (HATs) are also common in germinal center (GC) B-cell lymphomas and together with EZH2 mutations enforce a condensed chromatin state. Consequently, EZH2 and HATs in GC-B cell lymphomas, we hypothesized that dual inhibition of EZH2 and HDAC would be synergistic. Methods: Lymphoma cell lines (n = 21) were exposed to the EZH2 inhibitor GSK126 (G) and HDAC inhibitor romidepsin (R). Cell viability was assessed via CellTiter-Glo assay. Synergy was assessed by Excess over Bliss (EOB), where EOB > 10 defines synergy. A cutoff of > 20 was used. Western blot, mass spec and Co-IP were performed after exposure to G+R. Microweights were enrolled in: 1, Control; 2, G (100ng/kg); 3, R (2mg/kg); 4, G+R. GSEA and differential gene expression of synergistic vs. non-synergistic cell lines was performed. Results: EZH2 mutation is associated with increased sensitivity to G (p = 0.02). HAT mutations do not predict sensitivity to R (p = 0.2). G+R treatment was highly synergistic in cell lines with EZH2 dysfunction. G+R led to increased acetylation of histones and decreased protein expression of PRC2 members as compared to single agent. Exposure to R or G+R led to dissolution of EZH2 from other PRC2 members as well as HDAC2 and DNMT3L, which is secondary to RbApa46/48 acetylation. A selective HDACi2/1 inhibitor, AC959, was combined with G and showed synergistic G+R led to significant cell growth decrease (p < 0.05), and led to improved OS (Median OS G = 16; R = 16; G+R = 24; p < 0.001). Synergistic cell lines show a common basal gene expression signature which was validated in DLBCL via the TCGA database. Synergistic cell lines are enriched in pathways involved in chromatin silencing and regulation, and pathways that are hypoactive in DLBCL. G+R is highly synergistic. Responses are predicted by the presence of EZH2 dysregulation and a shared basal gene expression signature. G+R may serve as a targeted approach for NHL dependent upon EZH2 dysfunction.
Background: Bruton tyrosine kinase (BTK) inhibition has shown clinical benefit in FL. Acalabrutinib is a highly selective, potent, covalent inhibitor of BTK. We evaluated acalabrutinib + R in a Phase 1b study of patients (pts) with treatment-naive (TN) or relapsed/refractory (R/R) FL. Methods: Pts with R/R FL (≥1 prior treatment) were randomized to acalabrutinib (mono) or acalabrutinib + R (combo); TN pts received the combo. In 28-day cycles, R (375 mg/m² IV) was given weekly in Cycle 1 and on Day 1 of Cycles 2-6; acalabrutinib (100 mg PO bid (2 pts received 200 mg qd)) was given until progressive disease (PD) or intolerance. The primary endpoint was safety. Secondary endpoints included overall response rate (ORR), duration of response (DOR), pharmacokinetics (PK) and pharmacodynamics. Results: Thirteen TN and 27 R/R pts were treated. In all pts, the median age was 66 years (range 32-83); 98% of pts had ECOG PS ≤1, and 88% had stage III/IV disease. R/R pts received a median of 2 prior therapies (range 1-5). At a median follow-up of 22 and 7.6 months, 62% of TN and 26% of R/R pts, respectively, were still on treatment. Discontinuations were primarily due to PD (TN 15%; R/R 56%) and adverse events (AEs; TN 8%; R/R 11%). BTK occupancy and PK parameters were consistent with previous acalabrutinib studies. In all pts, common AEs (any grade) were fatigue (48%), headache (43%), diarrhea (40%), nausea (30%) and sinusitis (25%). Common Gr 3/4 AEs were hypertension (8%), increased alanine aminotransferase, increased aspartate aminotransferase, and cellulitis (all 5%), with no >10 events. There were no pts with cases of atrial fibrillation or thromboembolic events. Efficacy outcomes are reported in the table. Conclusions: Acalabrutinib, alone and combined with R, was well-tolerated and yielded promising response rates in FL. These results support further evaluation of acalabrutinib in FL. Clinical trial information: NCT02180711.

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Background: The prognosis of refractory or relapsed (R/R) non-geminal center B cell (non-GCB) subtype diffuse large B-cell lymphoma (DLBCL) is dismal without established standard salvage chemotherapy regimens. We designed a phase II trial to prospectively evaluate the efficacy and safety of the combination of lenalidomide and rituximab with the IMED (ifosfamide, methotrexate, etoposide and dexamethasone) regimen (L-R-IMED) in refractory or relapsed non-GCB DLBCL.

Methods: Eligible patients were adults with non-GCB subtype, CD20 positive DLBCL who were refractory to or had relapsed after R-CHOP-based regimens. Patients received lenalidomide 10 mg orally per day on days 1 through 14 with R-R-IMED every 21 days for up to six cycles. The response was evaluated using PET-CT scan after every 2 cycles. The primary endpoint was objective response rate (ORR) and progression-free survival (PFS).

Results: Between January 2014 and November 2017, 40 patients with non-GCB subtype, CD20 positive, R/R DLBCL, were enrolled, and 40 were evaluable for response. The median age was 51 years (range 28–80 years) and men were 40% (16 of 40) were women. 50% of the patient (n = 20) had refractory disease and 50% (n = 20) had relapsed disease. The ORR was 70% (28 of 40) with 55% (22 of 40) achieving a complete response. The median follow-up time was 14.8 months. The median PFS was 10.9 months (95% CI: 7.9–13.9 months) and the median PFS of patients with a PR or CR was 28.6 months (95% CI: 8.6–48.5 months). The median overall survival was not reached. The most common hematologic adverse event was neutropenia. The most common nonhematologic adverse event was fatigue. There was no treatment-associated death. None of our patients discontinued treatment due to significant hematological toxicities.

Conclusions: Among patients with R/R non-GCB DLBCL, L-R-IMED showed promising efficacy and tolerability profile. The regimen needs to be further verified by phase III trial.

**Table 1:** Survival Analysis by Stage

<table>
<thead>
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<th>Stage</th>
<th>Survival (%)</th>
<th>Alive (N)</th>
<th>Dead (N)</th>
<th>Survival (%)</th>
<th>Alive (N)</th>
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<td>5</td>
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<td>5</td>
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</table>

**S0C:** Standard of Care

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77555 Poster Session (Board #192), Mon, 8:00 AM-11:30 AM

Primary testicular lymphoma: Treatment patterns and survival of 1740 men from the National Cancer Database.

Methods: Using NCDB data (2006 to 2015), primary site testis (N = 1865). Patients were analyzed in 2 treatment groups: 1) CHT + RT (SOC group); and 2) CHT alone, RT alone and orchiectomy alone, grouped as no-SOC. Kaplan-Meier (KM) survival plots were used to compare survival between groups.

Results: Among patients, 794 (45.6%) were Stage I, 217 (12.5%) were Stage II, 88 (5.1%) were Stage III, and 85 (4.8%) were Stage IV. Median age was 69. 794 (45.6%) were Stage I, 217 (12.5%) were Stage II, 88 (5.1%) were Stage III, 274 (15.7%) were Stage IV.

Conclusions: Among patients with R/R non-GCB DLBCL, L-R-IMED showed promising efficacy and tolerability profile. The regimen needs to be further verified by phase III trial.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Conclusions: 0.19 – CMR and MRD-negativity, with a minority progressing despite a favorable 80 were evaluable for both at EOI. CMR was seen in 266 pts; 250 of these were by maintenance in responders. PET scans at baseline and EOI were assessed by a independent review committee. CMR was defined as a score of 1–3 on a 5-point scale. Baseline PB and BM were screened for MRD by consensus PCR for clonal t(14;18) translocation and/or Ig variable domain rearrangement. MRD 5-point scale. Baseline PB and BM were screened for MRD by consensus PCR for clonal t(14;18) translocation and/or BM, and may add to the prognostic information provided by PET. Methods: Induction with G or R plus bendamustine, CHOP or COP was followed by maintenance in responders. PET at EOI was assessed by a consensus analysis. Results: Most evaluable pts achieved CMR and MRD-negativity, with a minority progressing despite a favorable prognosis. Risk of progression or death in pts achieving only CMR or MRD-negativity was 2.5-fold greater than in pts who achieved both, suggesting that EPI PET and MRD responses could provide complementary information. Clinical trial information: NCT01332968.

PET Response Negative (%) Positive (%) All (%)
CMR 252/298 (84) 16/298 (5) 268/298 (89)
Non-CMR 24/298 (8) 8/298 (3) 32/298 (11)
All 274/298 (92) 24/298 (8) 298/298 (100)

Relationship between MRD and PET responses and PFS in previously untreated follicular lymphoma in the GALLIUM trial. First Author: Judith Trotman, Concord Repatriation General Hospital, University of Sydney, Sydney, Australia

Background: In GALLIUM (NCT01329968; 1202 follicular lymphoma pts, investigator-assessed progression-free survival (PFS) was significantly prolonged by first-line obinutuzumab (G)- vs rituximab (R)-based immuneo- therapy. Lymphoma activity by FDG PET-CT (PET, Lugano 2014 criteria) showed complete metabolic response (CMR) at end of induction (EOI) to be predictive of prolonged progression-free survival and overall survival. Minimal residual disease (MRD) negativity in peripheral blood (PB) and/or bone marrow (BM) at EOI was prognostic for prolonged PFS. CMR is a sensitive measure of disease in PB and/or BM, and may add to the prognostic information provided by PET. Methods: Induction with R plus bendamustine, CHOP or COP was followed by maintenance in responders. PET scans at EOI were assessed by an independent review committee. CMR was defined as a score of 1–3 on a 5-point scale. Baseline PB and BM were screened for MRD by consensus PCR for clonal t(14;18) translocation and/or Ig variable domain rearrangement. MRD at EOI was positive if allelic or translocation-specific real-time quantitative or nested PCR were positive in PB or BM. Results: Median follow-up was 44 months. At baseline, 595/609 pts with PET scans had detectable lesions and 815/1101 with MRD evaluable samples had a suitable MRD marker; 298 were evaluable for both at EOI. CMR was seen in 266 pts; 250 of these were MRD-negative (Table). For these pts, 2.5-year PFS from EOI was 85% (95% CI: 80–89). This had the best PFS: Cox proportional hazard ratio (HR) = 0.39 (95% CI: 0.17–0.93; p = 0.03) vs CMR and MRD-positive; and HR = 0.39 (95% CI: 0.19–0.81; p = 0.01) vs non-CMR and MRD-negative. There were few non-CMR and MRD-positive PET scans in this analysis. Conclusions: Most evaluable pts achieved CMR and MRD-negativity, with a minority progressing despite a favorable prognosis. Risk of progression or death in pts achieving only CMR or MRD-negativity was 2.5-fold greater than in pts who achieved both, suggesting that EPI PET and MRD responses could provide complementary information. Clinical trial information: NCT01332968.

Outcomes in patients with marginal zone lymphomas undergoing transformation to high-grade lymphomas. First Author: Juan Pablo Alderuccio, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL

Background: Marginal zone lymphomas (MZLs) are characterized by a long overall survival (OS). High-grade transformation (HTG) to aggressive lymphoma negatively impacts OS. Thus, identifying patients predisposed to HTG is of utmost clinical importance. Given the paucity of data on HTG in MZL patients, we undertook a retrospective study of the largest cohort to date of MZL patients to identify risk factors for HTG. Methods: This was a single-center, phase II, prospective trial of everolimus versus thalidomide in diffuse large B-cell lymphoma. First Author: He Huang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Patients with diffuse large B-cell lymphoma (DLBCL) with a high International Prognostic Index (IPI) are at higher risk for relapse after a complete response (CR) to first-line rituximab-based chemotherapy. This study aimed to compare the efficacy and safety of everolimus (EVE) v thalidomide (THA) as maintenance therapy in patients with DLBCL in complete remission and with a high risk of relapse after rituximab, cyclophos- phamide, doxorubicin, vincristine, and prednisone (R-CHOP). Methods: This was a single-center, phase II, randomized, open-label trial. Patients with stage II bulky or stage III to IV DLBCL, IPI > 2, and a positron emission tomography/ computed tomography-confirmed CR to first-line R-CHOP were randomized to receive EVE 5 mg/day for 1 year or THA 100 mg/day for 2 years or until disease relapse, unacceptable toxicity, or death. Eligible patients who refused any maintenance therapy were included as control group. Primary end point was disease-free survival (DFS). Results: A total of 102 patients were randomized to EVE (n = 50) or THA (n = 52). After a median follow-up of 34.2 months, 2-year DFS were 84.9% with EVE v 84.2% with THA (HR, 0.958; 95% CI, 0.370 to 2.484). 2-year overall survival (OS) was 93.4% with EVE v 91.4% with THA (HR, 0.711; 95% CI, 0.169 to 2.998). The control group included 137 patients, for whom 2-year DFS and OS was 62.4% and 81.6%, respectively. Both EVE and THA arms had a superior DFS (EVE v control, HR, 0.345; 95% CI, 0.165 to 0.722; THA v control, HR, 0.350; 95% CI, 0.174 to 0.706) and OS (EVE v control, HR, 0.216; 95% CI, 0.067 to 0.701; THA v control, HR, 0.335; 95% CI, 0.132 to 0.852) compared to control group. Grade 3 or 4 adverse events with EVE v THA were mucositis (8%), leukopenia (8%), thrombocytopenia (4%), infection (2%), and leukopenia (6%), thrombocytopenia (4%), infection (2%), and leukopenia (6%), thrombocytopenia (4%), infection (2%), and leukopenia (6%), thrombocytopenia (4%), infection (2%). Conclusions: The efficacy of everolimus and thalidomide as maintenance therapy was similar, both of which significantly improved DFS and OS in patients with high-risk DLBCL after achieving CR to R-CHOP. Everolimus administered 5 mg/day and thalidomide administered 100 to 300 mg/day were tolerated well.
Dose-adjusted (DA)-EPOCH-R with high-dose methotrexate (HD-MTX) for newly diagnosed stage II-IV CD5-negative aggressive B-cell lymphoma (CD5– DLBCL): Primary analysis of two phase 2 studies. First Author: Kana Miyazaki, Mie University Graduate School of Medicine, Tsu, Japan

Background: CD5+ DLBCL comprises 5-10% of DLBCL and is characterized by various aggressive clinical features and frequent CNS relapse. Our previous retrospective study (Miyazaki et al. Ann Oncol 2011) revealed that the 2-yr PFS and CNS relapse rates in patients (pts) with newly diagnosed stage II-IV CD5+ DLBCL were 51% and 15%, respectively. An interim analysis of our multicenter phase II study revealed 5 newly diagnosed stage II-IV CD5+ DLBCL (PEARL5 study) revealed that DA-EPOCH-R/HD-MTX provided a high CR rate (91%) with manageable toxicity (Miyazaki et al. ASH 2016).

Methods: Pts with newly diagnosed stage II-IV CD5+ DLBCL between 20-75 yrs old and ECOG PS of 0-3 were eligible. Four cycles of DA-EPOCH-R followed by 2 cycles of HD-MTX (3.5 g/m²) and additional 4 cycles of DA-EPOCH-R were planned as the protocol treatment. Cell-of-origin of DLBCL was determined by means of NanoString analysis system. The primary endpoint was 2-yr PFS. Results: From Aug 2012 to Nov 2015, 47 pts were enrolled in the study. All the pts were eligible and exhibited the following features: age, 37-74 yrs (median 62); M:F = 18:29; ECOG PS < 1, 4%; stage III/IV, 53%; IPI HI/H, 47%; and ABC/GCB/unclassified, 39/43/3 (n = 46). With a median follow-up of 3.1 yrs (range, 2.0-4.9), the 2-yr PFS rate was 79% (95% CI, 64-88%). This compared favorably with the historical control of conventional R-chemotherapy (51%). The 2-yr OS rate was 89%. One pt died in a traffic accident 1.8 yr after treatment, 2 pts died of secondary malignancy, and the remaining 4 pts were in complete remission. The 2-yr PFS and OS rates in CD5+ ABC DLBCL (n = 39) were 77% and 87%, respectively. Conclusions: DA-EPOCH-R/HD-MTX is an effective treatment for newly diagnosed stage II-IV CD5+ DLBCL. Long-term efficacy and toxicity will be evaluated in a 5-yr follow-up in Nov 2021. Clinical trial information: UMIN000008507.
Background: Prognostic factors for diffuse large B-cell lymphoma (DLBCL) in sub-Saharan Africa (SSA) are unknown. We report mature data from one of the first prospective DLBCL cohorts treated under real-world conditions in SSA. Methods: Patients ≥18 years with newly diagnosed DLBCL were enrolled in Malawi from 2013 to 2017. Participants were treated with CHOP chemotherapy, and concurrent antiretroviral therapy (ART) if HIV+. Results: 86 patients were enrolled with median age 50 (SD 17), 50 (58%) were male, and 51 (59%) were HIV+. Of whom 34 (67%) were on ART at DLBCL diagnosis. Median CD4 count was 113 cells/mL (IQR 62-227) and 25 (49%) had an HIV viral load <400 copies/mL. HIV+ participants were younger and more urban, but otherwise similar to HIV-. 10 (12%) participants died before chemotherapy. Participants received a median 6 CHOP cycles (IQR 4-6). 28% of cycles were delayed or reduced for toxicity, more commonly in the HIV+ group, typically for neutropenia. No patients were lost to follow-up with median follow up 24 months (IQR 16-40) for patients still alive at administrative censoring. 2-yr overall survival (OS) was 38% (95% CI 28-49) and 42% (95% CI 30-55) for those receiving CHOP, 13/43 (30%) deaths were treatment-related, and 10 (12%) participants developed grade ≥4 infections. Conclusions: DLBCL can be successfully treated in SSA and outcomes were not different for HIV+ and HIV- patients, although OS was worse than resource-rich settings. For HIV+ participants, those developing ART prior to lymphoma diagnosis was associated with mortality. A simplified prognostic model of DLBCL > 2x ULN and PS=2 outperformed the traditional age-adjusted IPI. DLBCL outcomes in Malawi: Effect of HIV and derivation of a simplified prognostic model. First Author: Jordan Gauthier, Fred Hutchinson Cancer Research Center, Seattle, WA

Phase II study of the PD1-inhibitor pembrolizumab for the treatment of relapsed or refractory mature T-cell lymphoma. First Author: Stefan K. Barta, Fox Chase Cancer Center, Philadelphia, PA

Background: PD-L1 is often expressed on tumor cells or in the microenvironment of T-cell NHL (Wilcox RA. Blood 2009) making inhibition of the PD1/PD-L1 axis a rational treatment target for T-cell NHL. Methods: We evaluated monotherapy with the PD1-inhibitor pembrolizumab (200mg flat dose q3weeks) for pts aged ≥18 with relapsed or refractory mature T-cell NHL in a multicenter prospective phase II trial. Primary endpoint was median progression-free survival (mPFS) defined as time from enrollment to either death or progression. The study was powered to demonstrate an improvement in mPFS from 3 to 6 months. Results: 18 pts were enrolled and included in the safety analysis. 17 pts were included in the survival analysis as 1 pt was found ineligible after central path review (n = 7 PTCL-NOS; n = 3 follicular T-cell lymphoma; n = 3 transformed MF; n = 1 MALT, HTCL, andAIT each; n = 1 ineligible histology). 2 pts came off study prior to response assessment for toxicities leaving 15 pts evaluable for response. Median age was 71 (18-88); 47% were male; median number of prior therapies was 2 (1-9); 76% were refractory to their last treatment. Response rate was 27% (4/15 pts; 95%; CI 5-49%). All 4 responders (ALCL, MF, PTCL-NOS, FTCL) achieved a CR and were pts who had received ≥2 prior therapies. Pembrolizumab has moderate activity in T-cell NHL but those with PD-L1 positive tumor cells may benefit from treatment. Clinical trial information: NCT02535247.
Background: Copanlisib is a pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant PI3K-α and PI3K-δ activity recently approved in the US for treatment of relapsed follicular lymphoma. In the CHRONOS-1 trial, treatment of patients with relapsed or refractory indolent lymphoma resulted in an objective response rate of 59% (JCO 35:2169-2178, 2017). The most prominent adverse event following intravenous administration of copanlisib is transient hyperglycemia, thought to be due to impaired glucose uptake associated with PI3K-α isoform inhibition. We focus here on the diabetic mellitus (DM) patients enrolled in the phase II study.

Methods: Indolent B-cell lymphoma patients with well-controlled DM were eligible and required to have fasting glucose ≤160 mg/dL prior to each infusion. Patients received copanlisib 60 mg as a 1-hour infusion on days 1, 8, 15, and 22 of a 28-day cycle. On day 1, glucose was measured at pre-dose, and 3, 5, 6, and 8 hours after infusion. DM patients were instructed to check blood glucose at home 3x per day for 72 hrs after infusion until fasting glucose was <160 mg/dL or non-fasting glucose was < 200 mg/dL. Results: Twenty patients with DM out of a total of 142 patients were enrolled; 17 patients with a history of DM, 1 with history of impaired glucose tolerance, and 2 diagnosed at screening. Comparing non-DM patients (n = 122) to DM patients, all-grade (G) hyperglycemia was 43% vs 85%, G3 31% vs 40%, and G4 2% vs 35%. In routine laboratory glucose assessments, G3 events were observed in 39% vs 22% of non-DM vs DM patients, respectively. Objective responses were observed in 9 of 20 patients (45%); 2 non-evaluable, including one in a patient with DM. Of note, 6 responders were observed in 9 of 20 patients (45%; 2 non-evaluable), including one in a patient with DM.

Conclusions: These results strongly suggest that the transient hyperglycemia seen with IV administration of copanlisib is also manageable in indolent lymphoma patients with DM as a comorbidity and should thus not preclude treatment of such patients. Clinical trial information: NCT01660451.

7571 Poster Session (Board #208), Mon, 8:00 AM-11:30 AM
Predictors of disease progression in smoldering Waldenström macroglobulinemia. First Author: Saurabh Zarwar, Mayo Clinic, Rochester, MN

Background: There are limited data on predictors of disease progression in patients (pts) with smoldering Waldenström Macroglobulinemia (SWM). We aim to address this issue in a large cohort of SWM with a long follow-up.

Methods: Pts with Waldenström Macroglobulinemia (WM) seen at Mayo Clinic, Rochester from 1996-2013 were included. Time-to-progression (TTP) was defined as interval from diagnosis of SWM to initiation of WM-directed therapy per 2002 Consensus criteria or development of light chain amyloidosis (AL) or transformation. Cumulative incidence of progression (CIP) was calculated by competing risk analysis. Median values were chosen as cutoff for dichotomization of continuous variables for univariate analysis (UVA) and multivariate analysis (MVA). Kaplan Meier method was used for time-to-event analyses. Results: Of 823 WM pts, 143 (17%) had SWM. After a median follow-up of 9.5 years (95% CI 8.1-11.5 yrs), 110 (77 %) pts progressed (107 required therapy for WM, 3 developed AL). CIP was 11%, 37% and 52% at 1, 3 and 5 yrs, respectively. On UVA (Table 1), hemoglobin (Hgb) ≤12.3 g/dL (p = 0.01) and beta-2 microglobulin (β2M) ≥2.7 μg/mL (p = 0.001) remained independent predictors of TTP. A score of 1 was assigned to both, giving a minimum score of 0 and maximum score of 2. The TTP was 9.3 yrs (95% CI 5.5-11.6 yrs), 4.1 yrs (95% CI 2.0-6.4 yrs) and 2.9 yrs (95% CI 1.9-4.0 yrs) for scores of 0, 1 and 2, respectively (p = 0.004). Conclusions: One-half of pts with SWM progress within five years from diagnosis. Pts with Hgb ≤12.3 g/dL and β2M ≥2.7 μg/mL at diagnosis have the shortest TTP.

7572 Poster Session (Board #209), Mon, 8:00 AM-11:30 AM
Early detection of post-transplant lymphoproliferative disorder using circulating tumor DNA. First Author: Joanna Soo, Division of Oncology, Stanford University School of Medicine, Stanford, CA

Background: Diffuse large B cell (DLBCL)-like post-transplant lymphoproliferative disorder (PTLD) affects 2-5% of transplant recipients. While most PTLDs can be related to Epstein-Barr virus (EBV) infection (Luskin et al., 2015), we recently reported a phase I study of copanlisib in patients with PTLD and de novo DLBCL (median PTLD variants: 216, IQR = 79 – 621; median de novo DLBCL variants: 143.5, IQR = 45 – 243.8; p = 0.35), though there was a trend toward greater variant count in EBV- compared to EBV+ patients (p = 0.004). The prevalence of alterations in known driver genes including CREBBP, CARD11, MYD88, and EZH2 was similar between PTLD and de novo DLBCL.

Methods: We applied CAPP-Seq (Newman et al., 2014) to diagnostic tumor and plasma samples and matched germline in a cohort of 9 transplant recipients who developed PTLD to identify somatic alterations. We compared mutational patterns in PTLD to 149 de novo DLBCL cases sequenced by the same method as well 1112 published whole exome sequences (Pasqualucci et al., 2011; Reddy et al., 2017). We additionally sequenced serial post-transplant plasma samples preceding diagnosis in 5 patients and during or after treatment in 8 patients to determine the dynamics of ctDNA and compared these patterns to clinical outcome and EBV titers. Results: There was no significant difference in mutational burden between patients with PTLD and de novo DLBCL (median PTLD variants: 216, IQR = 79 – 321; median de novo DLBCL variants: 143.5, IQR = 45 – 243.8; p = 0.35), though there was a trend toward greater variant count in EBV- compared to EBV+ PTLD (p = 0.06). The prevalence of alterations in known driver genes including CREBBP, CARD11, MYD88, and EZH2 was similar between PTLD and de novo DLBCL. Preliminary diagnostic plasma samples were available for 5 cases, including two EBV- PTLD, and we detected ctDNA in all patients prior to clinical diagnosis (mean lead time = 114 days). In the 3 EBV+ cases, EBV titers were concordant with ctDNA levels in EBV+ cases at all time points. In addition, ctDNA levels during and after treatment were concordant with clinical response in all patients. Conclusions: PTLD patients have detectable ctDNA prior to clinical diagnosis. Development of screening tools utilizing both ctDNA and EBV titers could facilitate early detection of PTLD in the transplant population.
Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients. Results: The 2x2 randomized phase III trial involved 284 pts. The first 120 pts were randomized to 6xR-CHOP-14 or 6x-R-CHOP-21 followed by RT (39.6 Gy) to B and E sites or observation in a 2x2 factorial design. Primary endpoint was event-free survival. Results: A planned interim analysis of the first 285 patients had revealed a significantly better EFS of patients assigned to RT (p = 0.004) resulting in the pre-defined closing of the non-RT arms. 305 pts (R-CHOP-21: 155; R-CHOP-14: 150) assigned to RT and 162 (R-CHOP-21: 81, R-CHOP-14: 81) assigned to observation were evaluable for this final analysis. There were no relevant differences in protocol adherence and toxicity between the two chemotherapy regimens. EFS, PFS and OS after R-CHOP-14 and R-CHOP-21 were not different. After 66 months median observation 3-year EFS was worse in pts not assigned to RT (68% vs. 84%; p = 0.001), due to a higher risk of relapse (11% vs. 2%) triggering additional treatment (mostly RT) as an EFS event. 3-year PFS of pts assigned to RT was not significantly better (89% vs. 81%; p = 0.221) and 3-year OS (93% vs. 93%, p = 0.506) was not different, which was confirmed in a multivariate analysis adjusting for elevated LDH, stage III/IV, B and E involvement (HR (95% CI): 0.9 (0.4-2.0) vs. 0.8 (0.4-1.7); p = 0.174; HR (95% CI): 1.2 (0.7-2.0) vs. 1.2 (0.7-2.3); p = 0.674). Results were not different when the analysis was restricted to patients with bulky disease only. Conclusions: There were no differences in outcome between R-CHOP-14 and R-CHOP-21. Patients assigned to observation had a worse EFS because of more events largely due to a higher PR rate triggering additional treatment (median observation 36 months; p = 0.004). Differences in toxicity between arms were not relevant. Maintenance RT reduced the difficulties in interpreting residual masses in DLBCL without a PET which has been shown to identify (elderly) patients with B who can be spared from radiotherapy without compromising their outcome [Pfreundschuh et al., ASCO 2017, #7556]. Supported by Deutsche Krebshilfe, Argenz and Roche Clinical trial information: NCT00278408.

Circulating tumor DNA to predict timing of relapse in mantle cell lymphoma. First Author: Marleen Schrader, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD

Background: Mantle cell lymphoma is clinically heterogeneous. MRD after frontline therapy improves PFS, but virtually all pts relapse. Surveillance after induction is not uniform and clinical decisions are empirical. Detection of ctDNA in the blood throughout therapy is promising. We used AdaptiveOs next-generation sequencing assay to detect and quantify ctDNA in blood throughout therapy for MCL. Methods: Untreated MCL pts received bortezomib (B2 + DA-EPOCH-R) x 6 then randomized to obs vs. B2 maint x 18m. PT serum collected pre-Tx, w/each cycle, and w/each surveillance visit paired w/CT scans at regular intervals for 5y. FFPE was analyzed for tumor-specific clonotypes. Tumor DNA was amplified using locus-specific primer sets for the lg heavy-chain and light-chain loci, BCL1, and BCL2 translocations. Amplified products were sequenced, and pts w/o a high-frequency tumor clonotype excluded. Baseline ctDNA levels were compared to tumor burden and proliferation. Levels of ctDNA at E01 and during surveillance were analyzed for the ability to predict progression. Results: 53 MCL pts were treated between 1996 and 2013. After median f/u of 9.6y, 5-y OS is 80.1% and median PFS is 30.7m. With FFPE available, 50 of 52 (96%) had a tumor-specific clonotype, and 46 of 48 pts (96%) had detectable ctDNA in serum prior to therapy. ctDNA was successfully tracked in 625 of 647 (97%) serum samples. Pre-treatment ctDNA levels more strongly correlated with total metabolic tumor volume (rs = 0.74) than Ki-67 (rs = 0.55) or serum LDH (rs = 0.49). Overall, 47 pts responded to induction (44 CR, 3PR), and median TTP after E01 was 26m (range 0-131), 40 of 50 pts (80%) achieved MRD at E01, which was assoc with superior median PFS (45m vs. 25m, p = 0.001) and OS (NR vs. 40m, p = 0.01) vs. MRD+ pts. In 31 of 41 (76%) responders, ctDNA was present prior to clinical progression with a median lead-time of 9m (range 0-38). Of 9 non-progressors, 8 remained ctDNA negative. BZ maint had no impact on PFS or OS. Conclusions: Nearly all pts with MCL have detectable baseline ctDNA. Achieving MRD at E01 was associated with improved PFS and OS compared to MRD+ pts. ctDNA was detected a median 9m before progression. Clinical trial information: NCT00114738.

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5758 Safety and efficacy of anti-CD20 immunotoxin MT-3724 in relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) associated with a spoon-like IgM. First Author: Michelle A. Fanale, The University of Texas MD Anderson Cancer Center, Houston, TX

MT-3724 is a novel recombinant fusion protein consisting of a CD20 binding variable fragment (scFv) fused to Shiga-like toxin-I A1. The SLT-I A1 forces MT-3724 internalization and irreversibly inactivates ribosomes triggering cell death. We present interim results from a Phase I study in patients (pts) with B-cell NHL who relapsed after prior response to anti-CD20 Mab and chemotherapy (NCT02361346). Methods: 24 pts were treated by 13FEB2018: 21 pts (12 DLBCL) at 5-100 $g$/kg/dose in 6 dose escalation cohorts and 3 pts (all DLBCL) at 75 $g$/kg/dose in MTD expansion cohort. MT-3724 was given as six 2-hr IV infusions on Days 1-12 of each cycle (C) for up to 5 cycles. Investigator assessed tumor response after C2, C4 and C5 using Cheson criteria. Results: Demographics in 24 evaluable pts were: 54% female, mean age 66 yrs (range 34-78); ≥4 prior NHL therapies in 67%; ECOG status 0 in 42%, 1 in 46%, and 2 in 12% and unknown in 8%. All pts had ≥1 AE (59 G3; 13 related), and 15 pts (63%) had 33 SAEs (G3; 4 related). The most common AEs were peripheral edema (67%), fatigue (43%), diarrhea (38%), myalgia (38%) and cough (33%). MT-3724 was not tolerated at 100 $g$/kg/dose (2 pts had 1 DLT each: G2 pneumonia and G2 ileus). In dose escalation, no pts had DLT at doses ≤MTD of 75 $g$/kg/dose. In the MTD expansion, 2 of 3 pts had G2 capillary leak syndrome (CLS) leading to dose delay and reduction. The CLS events occurred in obese pts (96 and 154 kg = total of 7208 and 11572 $g$/dose) and were reversible, but MTD was reduced to 50 $g$/kg/dose and capped at 6000 $g$/dose. Five pts (all DLBCL) had clinical benefit at 5-75 $g$/kg/dose (1 CR and 2 PR (ORR 12.5%)) 2 SD with large tumor reduction (48% and 49%; DCR 21%)). All pts with benefit had undetectable serum rituximab (RTX) level at screening. No pts with detectable screening RTX level had benefit, likely due to competitive inhibition of CD20 binding by prior RTX. Conclusions: MT-3724 showed clinical anti-tumor activity in heavily pre-treated pts with R/R B-cell NHL. Consistent with mechanism of action, MT-3724 had the best activity in rapidly growing DLBCL. Safety and efficacy assessment was ongoing at the adjusted MTD of 50 $g$/kg/dose in DLBCL pts with undetectable screening RTX level. Clinical trial information: NCT02361346.

5759 Phase 3 zanubrutinib (BGB-3111) vs bendamustine + rituximab (BR) in patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). First Author: Peter Hillmen, St. James’s University Hospital, Leeds, United Kingdom

Background: Inhibition of Bruton’s tyrosine kinase (BTK) has emerged as a strategy for targeting B-cell malignancies including CLL/SLL. Zanubrutinib has been shown to be a novel 2nd-generation, potent, and specific BTK inhibitor IPI-3063 (IC50 630 nM; IPI-549 EC 50 17 nM). The disruption of PI3K-γ inhibition directly targets CLL/SLL induced deep and sustained responses, with a 94% overall response rate (ORR) including 6% and 2% complete response rates in TN and R/R CLL/SLL, respectively (ICML 2017). We hypothesize that zanubrutinib monotherapy may have superior efficacy and potentially improved safety vs standard BR chemotherapy in pts with TN CLL/SLL. Methods: This ongoing Phase 3, randomized, open-label, global study (NCT03336633, BGB-3111-304) compares the efficacy and safety of zanubrutinib vs BR in adult pts with TN CLL/SLL considered unsuitable for treatment with FCR (fludarabine, cyclophosphamide, rituximab). In Cohort 1, pts lacking del(17p) (n = 420) are randomized 1:1 to oral zanubrutinib 160 mg twice-daily or BR x 6 cycles. Randomization is stratified by age (≤ 65 vs >65 yrs), Binet stage (C vs A/B), geographic region (North America vs Europe vs Asia-Pacific) and IGHV mutational status (mutated vs unmutated). In Cohort 2, pts with del(17p) (n = 47) are enrolled and all receive zanubrutinib as in Cohort 1. Key inclusion criteria include histologically confirmed CD20+ CLL/SLL requiring treatment per iwCLL criteria, ECOG PS 0-2, and adequate hematologic function. The primary endpoint is progression-free survival (PFS) of zanubrutinib as compared to BR in Cohort 1 by independent review committee (IRC) according to iwCLL guidelines with modification for treatment-related lymphocytosis. The analysis of PFS between the 2 arms in Cohort 1 will be based on a log-rank test stratified by the randomization stratification factors. Key secondary end points include ORR, duration of response, overall survival, and safety in Cohorts 1 & 2. In Cohort 1, next-line treatment with zanubrutinib after IRC-confirmed progression on BR is included in the study design. Recruitment is ongoing. Clinical trial information: NCT03336633.
TPS7582 Poster Session (Board #218b), Mon, 8:00 AM-11:30 AM
The GaIA (CLL13) trial: An international intergroup phase III study for frontline treatment in chronic lymphocytic leukemia (CLL). First Author: Von Tresckow Julia, Department I of Internal Medicine and Center of Integrated Oncology, Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany

Background: Chem immuno treatment (CIT) is still standard of care in first line treatment of fit CLL patients (pts) without del(17p) or TP53 mutation. However, CIT is often associated with side effects caused by the general cytotoxicity of chemotherapy. Testing of chemotherap y-free treatment regimens with increased efficacy and superior toxicity profiles including CD20 antibodies and targeted drugs such as venetoclax (Ve) and ibritinib (I) head to head with CIT is therefore warranted in this pt group. Methods: The trial is an investigator initiated trial of the German CLL Study Group in cooperation with the Nordic CLL Study Group, HOVON, SAKK, Cancer Trials Ireland and the Israeli CLL Study Group. Sponsor of the trial is the University of Cologne. It is registered at www.clinicaltrials.gov as NCT02950051. 920 pts with a cumulative illness rating scale score $\leq 6$ and a creatinine clearance $\geq 70\text{mll/min}$ who are diagnosed with previously untreated CLL according to iwCLL guidelines without del(17p) or TP53 mutation will be included and 1:1:1:1 randomized into four treatment arms. In the standard arm, six cycles of CIT containing regimes are tested: Ve plus rituximab (VeR), Ve plus obinutuzumab (VeG), Ve plus ibritinib and obinutuzumab (VeGI). Two co-primary endpoints were defined: minimal residual disease (MRD) negativity for the comparison of CIT versus VeG and progression free survival (PFS) for the comparison of CIT versus VeG. Secondary endpoints include comparisons of MRD and PFS for the other treatment arms, overall survival, safety parameters and health-related quality of life. Recruitment started in June 2016 and an estimated to take 33 months (m). The final analysis of the MRD endpoint is expected to be performed 49 m after trial initiation together with the interim PFS analysis. The final analysis of the PFS endpoint is expected to take place after 73 m, which will also be the formal end of trial. After the second meeting of the data safety monitoring board in February 2018 the trial continues recruiting as planned. Clinical trial information: # NCT02950051.

TPS7583 Poster Session (Board #219a), Mon, 8:00 AM-11:30 AM
KEYNOTE-667: Phase 2, open-label study of pembrolizumab in children and young adults with newly diagnosed classical Hodgkin lymphoma (cHL) with or without early relapse (SER) in frontline chemotherapy. First Author: Christine Mauz-Korholz, Justus-Liebig University of Giessen, Giessen, Germany

Background: High risk for relapse is observed in cHL patients (pts) with SER to initial chemotherapy and the burden of late organ toxicities may be higher following dose intensification. Methods: The phase 2, open-label KEYNOTE-667 (NCT03407144) study will enroll 400 pts aged 3 to 17 (children) or 18 to 66 (young adults) with newly diagnosed, confirmed stage IA, IB, or IIA cHL without bulky disease (Group 1 [low-risk]) or stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB cHL (Group 2 [high-risk]); measurable disease; and performance status per Lansky Play-Performance Scale $\geq 50$ (age $\geq 16$ years) or Karnofsky score $\geq 50$ (age $\geq 16$ years). Pts will receive induction with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD; Group 1) or vin cristine, etoposide/etoposide phosphate, prednisone/prednisolone, doxorubicin (OEPa; Group 2) for 2 cycles, followed by early response assessment by PET/CT/MRI. Pts with rapid early response (Deauville score 1-3) will receive standard therapy. Pts with SER (Deauville score 4-5) will receive consolidation with pembrolizumab 2 mg/kg Q3W up to 200 mg (children) or 200 mg Q3W (young adults) plus 2 cycles AVD (Group 1) or 4 cycles cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28; Group 2). PET/CT for late response assessment (LRA) will be performed after consolidation. After LRA, Group 1 pts with SER will receive radiotherapy (RT) in 2 cycles with Deauville score $\geq 4$ in the RT. All pts will receive maintenance with pembrolizumab Q3W concomitantly with RT. Pembrolizumab dosing will continue up to 17 administrations, with an option to stop after 24 weeks due to, or until, progression, unacceptable toxicity, or withdrawal. The primary endpoint is objective response rate (ORR) per Cheson 2007 IWG criteria. Secondary endpoints include ORR, CR rate, DoR, PFS, OS, and toxicities. A total of 480 pts (240 children and 240 young adults) are planned. Clinical trial information: # NCT03407144.

TPS7584 Poster Session (Board #219b), Mon, 8:00 AM-11:30 AM
Phase I/II study to evaluate the safety and efficacy of tenalisib, a novel PI3K dual inhibitor in combination with pembrolizumab in relapsed/refractory classical Hodgkin lymphoma. First Author: Rod Ramchandren, Barbara Ann Karmanos Cancer Institute, Detroit, MI

Background: Despite impressive activity of PD-1/PD-L1 inhibitor in HL, proportions of patients do not respond and eventually progress. Growing evidence suggests that high infiltrations of immune-suppressive myeloid cells are responsible for anti-PD-1/PD-L1 therapy resistance. These observations suggest that an immunotherapeutic combination to overcome such resistance mechanisms. PI3K dual isoforms are known to play a role in modulating the tumor microenvironment. Tenalisib demonstrated marked reduction of Tumor Associated Macrophages (TAMs) and angiogenesis and showed synergy with checkpoint inhibition in syngeneic mouse models. Tenalisib has demonstrated single agent activity in relapsed/refractory classical Hodgkin lymphoma (R/R HL) in 28 patients and high frequency of minimal residual disease (MRD) and PET negativity with 95% CI will be estimated using the Clopper-Pearson method. EFS and PFS analysis of the MRD endpoint is expected to be performed 49 m after trial initiation with the interim PFS analysis. The final analysis of the PFS endpoint is expected to take place after 73 m, which will also be the formal end of trial. After the second meeting of the data safety monitoring board in February 2018 the trial continues recruiting as planned. Clinical trial information: # NCT02950051.

TPS7585 Poster Session (Board #220a), Mon, 8:00 AM-11:30 AM
ZUMA-7: A phase 3 randomized trial of axicabtagene ciloleucel (Axi-Cell) versus standard-of-care (SOC) chemo in pts with relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL). First Author: Olalekan O. Oluowe, Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: For pts with DLBCL who fail 1st-line therapy, the only potentially curative treatment is salvage chemotherapy followed by autologous stem cell transplant (ASCT). Only $\sim 50\%$ of pts receiving salvage chemotherapy proceed to ASCT and $3\%$-progression-free survival (PFS) is $53\%$ after ASCT (Gisselbrecht et al. JCO 2010). In ZUMA-1, the pivotal, single-arm study of axi-cell, an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy, the objective response rate (ORR) was $82\%$ (58 complete response (CR) rate) in pts with refractory large B cell lymphoma; $40\%$ remained in CR with 15.4-mo median follow-up (Neelapu & Locke et al. NEJM 2017). This trial was primarily in pts with $\geq 2$ prior lines of therapy and supported US FDA approval of axi-cell for the treatment of adult pts with R/R DLBCL after $\geq 2$ prior lines of systemic therapy. ZUMA-7 investigates axi-cell as 2nd-line therapy for pts with R/R DLBCL. Methods: ZUMA-7 (NCT03391466) is a randomized (1:1) Phase 3, open-label, multicenter study of axi-cell vs SOC 2nd-line treatment in pts with R/R DLBCL. Planned enrollment is 350 pts. Eligible pts must have R/R DLBCL after 1st-line therapy (including an anti-CD20 antibody and an anthracycline) and intend to proceed to ASCT if they respond to 2nd-line therapy. Exclusion criteria include prior SCT, prior CD19-targeted therapy, or active infection. Pts randomized to axi-cell will undergo leukapheresis, then lymphodepleting chemotherapy (fludarabine 30 mg/m2 and cyclophosphamide 500 mg/m2 d for 3 d), followed by a single infusion of axi-cell at 2 x 10^9 CAR T cells/kg. Corticosteroid bridging therapy is allowed for pts with high disease burden at screening. Pts in the SOC arm will receive investigator's choice of 2nd-line salvage therapy (R-ICE, R-DHAP, R-ESHAP, or R-GDP); pts who respond after $\geq 2$ cycles will receive high-dose therapy and ASCT. The primary endpoint is event-free survival defined as time from randomization to disease progression, start of new lymphoma therapy, or death. Secondary endpoints include ORR, overall survival, PFS, duration of response, safety, and pt-reported outcomes. Accrual is ongoing. Clinical trial information: NCT03391466.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Sutro’s cell-free antibody production system was used to make STR0-001, a novel CD74 targeting antibody drug conjugate. CD74 is expressed on B cells throughout differentiation, and is an attractive target for treatment of B cell malignancies. STR0-001 demonstrates potent cytotoxicity in non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) cell lines and anti-tumor activity in xenograft models. Toxicology studies demonstrate dose-dependent B-cell depletion and reversible hematologic toxicity when STR0-001 is administered at up to 10 mg/kg. Methods: This study is a first-in-human Phase 1, open-label, multicenter, dose escalation (Part 1) study with dose expansion (Part 2) to identify the maximum tolerated dose (MTD), recommended phase 2 doses (RP2D) and to evaluate the safety, tolerability, and preliminary anti-tumor activity of STR0-001 in adults with B-cell malignancies (MM and NHL) who are refractory to, or intolerant of, all therapy known to provide clinical benefit. STR0-001 is given to all patients on study via intravenous infusion on Day 1 and Day 15 of each cycle until disease progression. Dose limiting toxicity (DLT) is death or severe transplant complications (Days 1-28) of dose escalation. In Part 1, 2 cohorts (1 for MM and 1 for NHL) will enroll 30 patients each to determine the MTD and RP2D for expansion while Part 2 will enroll 4 cohorts based on disease subtypes (MM, diffuse large B cell, mantle cell and follicular lymphomas). Efficacy will be evaluated per NHL-specific or NHL-specific criteria. Safety, tolerability and PK of STR0-001 in subjects with relapsed or refractory hematological malignancies. First Author: Simon Rule, Department of Haematology, Derriford Hospital, Plymouth, United Kingdom

Background: Cyclin-dependent kinase 9 (CDK9) belongs to the group of transcription-regulating CDKs and promotes transcription elongation through phosphorylation of RNA Polymerase II at serine 2 (pSer2-RNAPII). Studies using multi-CDK inhibitors with CDK9 activity demonstrated that transient inhibition of CDK9 can modulate expression of oncopgenes with short-lived transcripts and proteins (e.g. MCL1, MYC), providing an intriguing therapeutic rationale. Transient and selective inhibition of CDK9 is key to preferentially kill tumor cells dependent on survival proteins without triguing therapeutic rationale. Transient and selective inhibition of CDK9 is short-lived transcripts and proteins (e.g. MCL1, MYC), providing an in-check response to CDK9 inhibition. However, pts previously untreated diffuse large B-cell lymphoma (DLBCL). However, pts with high-risk disease have poorer outcomes with R-CHOP. Polatuzumab vedotin (pola) is an antibody-drug conjugate targeting CD79b; it delivers the mitototic agent MMAE and is being evaluated as a replacement strategy for vincristine within the R-CHOP regimen. In a phase Ib/II study in higher risk DLBCL pts, pola + R-CHOP produced promising efficacy across different subtypes of DLBCL and a safety profile similar to that observed in the R-CHOP arm of the GOYA study (Tilly H, et al. Hematol Oncol 2017; Vitolo U, et al. J Clin Oncol 2017). Methods: This is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study in pts with previously untreated DLBCL. Pts (planned N = 875) aged 18-80 years with CD20-positive DLBCL (including DLBCL not otherwise specified [NOS], germinal center B-cell like [GCB], and activated B-cell like [ABC] subtypes), ECOG performance status 0-2, and IPI score 2–5, will be randomized 1:1 to one of two treatment groups, stratified by IPI score (2 versus 3-5), bulky disease and geographical region. Arm A will receive pola 1.8 mg/kg on Day 1 plus R-CHOP (standard dosing schedule) plus vincristine placebo for 6 cycles; Arm B will receive R-CHOP (standard dosing schedule) with pola placebo for 6 cycles. In both arms, R will be administered as monotherapy in cycles 7 and 8. The primary endpoint is progression-free survival, as assessed by the investigator, using the Lugano classification (Cheson B, et al J Clin Oncol 2014). Secondary endpoints include PET-CT complete response rate at end of treatment assessed by an independent review committee, event-free survival due to efficacy reason, 2-year PFS rate, and overall survival. PET-CT and CT scans will be obtained at screening, after 4 cycles (planned interim assessment), and 6–8 weeks after end of study treatment. Patient follow-up will continue for 5 years after end of treatment. Enrolment began November 2017. Clinical trial information: study is funded by F. Hoffmann-La Roche Ltd; clinical trial information: NCT03274492.
The PRIMO study: A phase 2 study of duvelisib efficacy and safety in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

First Author: Steven M. Horwitz, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Duvelisib is an oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ being developed for the treatment of hematologic malignancies. In preclinical investigations, duvelisib potently killed TCL cell lines with constitutive phospho-AKT (S473) and reprogrammed tumor-associated macrophages from an immunosuppressive to immunostimulatory phenotype in PTCL mouse xenograft models (Horwitz, Blood 2017). In a Phase 1 study duvelisib monotherapy demonstrated encouraging clinical activity and an acceptable safety profile (Flinn, Blood 2017), with an overall response rate (ORR) of 50% (3 complete responses [CRs], 5 partial responses [PRs]) in patients (pts) with PTCL (n = 16). These results suggest duvelisib monotherapy may provide a meaningful benefit in relapsed/refractory (RR) PTCL, a population in need of new and effective therapies.

Methods: This Phase 2, open-label, study of duvelisib monotherapy in adult pts PTCL employs a Dose Optimization Phase (DOP) and an Expansion Phase (EP) (NCT03372057). The primary objectives are to identify the optimal dose of duvelisib and examine the efficacy, safety, and tolerability of duvelisib at the optimal dose. The study will enroll up to 120 pts with histologically confirmed PTCL subtypes of PTCL-NOS, angioimmunoblastic TCL, anaplastic large cell lymphoma, and natural-killer TCL. Disease responses will be measured by 18FDG-PET-CT scanning as assessed by an independent review committee per IWG criteria. The DOP, to be conducted at 4-6 centers in the U.S., will include 20 pts randomly assigned to 1 of 2 parallel cohorts. Cohort 1 will receive a starting dose of 25 mg duvelisib PO BID, with potential sequential escalation to 50 mg and then 75 mg based on responses and tolerance of therapy. Pts in Cohort 2 will receive 75 mg duvelisib PO BID. The EP, to be conducted globally at ~40 centers, will include pts treated at the optimal dose as determined from the DOP. The primary endpoint is ORR (CR + PR) in all pts receiving the optimal dose for at least 1 cycle in either phase. Secondary endpoints include AEs, duration of response, and PFS. This study is open for enrollment. Clinical trial information: NCT03372057.
Background: Twice-weekly K at 20/27 mg/m^2 is approved for the treatment of RRMM. To develop a more convenient K regimen, once-weekly K plus d was assessed in the phase 1/2 CHAMPION-1 study, establishing a maximum tolerated dose of K 20/70 mg/m^2 for RRMM pts. We present results from the pre-planned interim analysis of the phase 3 study A.R.R.O.W, comparing Kd once-weekly at 20/70 mg/m^2 (once-weekly group) vs twice-weekly at 20/27 mg/m^2 (twice-weekly group). Methods: Pts with 2–3 prior therapies and prior exposure to proteasome inhibitor and immunomodulatory agent were eligible. Pts were randomized 1:1 to receive either once- or twice-weekly K plus d. The once-weekly group received K (30-min IV) on days (D) 1, 8, and 15 of all cycles (20 mg/m^2 on D1 [cycle 1]; 70 mg/m^2 thereafter). The twice-weekly group received K (10-min IV) on D1, 2, 8, 9, 15, and 16 (20 mg/m^2 on D1 and 2 during cycle 1 and 27 mg/m^2 thereafter). All pts received d at 40 mg on D1, 8, 15 (all cycles), and 22 (cycle 1–9 only). Treatment was given in 28-day cycles un-til treatment discontinuation or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall response rate (ORR), overall survival, safety, and pharmacokinetics. Results: Baseline characteristics were generally balanced. Median PFS (once- vs twice-weekly) was 11.2 mo vs 7.6 mo (HR = 0.69; 95% CI: 0.56–0.84; P < 0.0001). The once- vs twice-weekly incidence of AEs was 62.9% vs 40.8% (P < 0.0001); 7.1% vs 1.7% had a complete response or better, Grade ≥ 3 adverse events (AEs) occurred in 67.6% (once-weekly) and 61.7% (twice-weekly). Treatment-related grade 5 AEs occurred in 5 pts (2.1%) (once-weekly) and 2 pts (0.9%) (twice-weekly). The incidence of grade ≥ 3 hypertension and cardiac failure (once- vs twice-weekly) was 5.9% vs 5.5% and 2.9% vs 4.3%, respectively. Conclusions: Once-weekly Kd at 20/70 mg/m^2 significantly improved PFS and ORR vs twice-weekly Kd at 20/27 mg/m^2. The incidence of AEs was comparable between groups. No new safety risks were found in the once-weekly group. Overall, once-weekly Kd showed acceptable benefit-risk profile with a convenient dosing regimen vs twice-weekly Kd. Clinical trial information: NCT02412878.

Efficacy

<table>
<thead>
<tr>
<th>Arm</th>
<th>n</th>
<th>ORR (95% CI)</th>
<th>PR (95% CI)</th>
<th>VGPR (%)</th>
<th>CR (%)</th>
<th>MRD negativity (at any time)</th>
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<tbody>
<tr>
<td>Once-weekly</td>
<td>278</td>
<td>40.0% (32.8–48.0)</td>
<td>12.3% (9.4–15.5)</td>
<td>6.6%</td>
<td>5.9%</td>
<td>32% (30–34)</td>
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<tr>
<td>Twice-weekly</td>
<td>281</td>
<td>36.2% (29.5–43.3)</td>
<td>10.9% (8.2–14.5)</td>
<td>6.8%</td>
<td>6.3%</td>
<td>31% (29–33)</td>
</tr>
</tbody>
</table>

Less-refractory pts had 1 prior Tx line. MRD negative rate at any time was 32% for once-weekly Kd and 31% for twice-weekly Kd.

Background: Twice-weekly Kd at 20/70 mg/m^2 is approved for the treatment of RRMM. To develop a more convenient K regimen, once-weekly K plus d was assessed in the phase 1/2 CHAMPION-1 study, establishing a maximum tolerated dose of K 20/70 mg/m^2 for RRMM pts. We present results from the pre-planned interim analysis of the phase 3 study A.R.R.O.W, comparing Kd once-weekly at 20/70 mg/m^2 (once-weekly group) vs twice-weekly at 20/27 mg/m^2 (twice-weekly group). Methods: Pts with 2–3 prior therapies and prior exposure to proteasome inhibitor and immunomodulatory agent were eligible. Pts were randomized 1:1 to receive either once- or twice-weekly K plus d. The once-weekly group received K (30-min IV) on days (D) 1, 8, and 15 of all cycles (20 mg/m^2 on D1 [cycle 1]; 70 mg/m^2 thereafter). The twice-weekly group received K (10-min IV) on D1, 2, 8, 9, 15, and 16 (20 mg/m^2 on D1 and 2 during cycle 1 and 27 mg/m^2 thereafter). All pts received d at 40 mg on D1, 8, 15 (all cycles), and 22 (cycle 1–9 only). Treatment was given in 28-day cycles un-til treatment discontinuation or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall response rate (ORR), overall survival, safety, and pharmacokinetics. Results: Baseline characteristics were generally balanced. Median PFS (once- vs twice-weekly) was 11.2 mo vs 7.6 mo (HR = 0.69; 95% CI: 0.56–0.84; P < 0.0001). The once- vs twice-weekly incidence of AEs was 62.9% vs 40.8% (P < 0.0001); 7.1% vs 1.7% had a complete response or better, Grade ≥ 3 adverse events (AEs) occurred in 67.6% (once-weekly) and 61.7% (twice-weekly). Treatment-related grade 5 AEs occurred in 5 pts (2.1%) (once-weekly) and 2 pts (0.9%) (twice-weekly). The incidence of grade ≥ 3 hypertension and cardiac failure (once- vs twice-weekly) was 5.9% vs 5.5% and 2.9% vs 4.3%, respectively. Conclusions: Once-weekly Kd at 20/70 mg/m^2 significantly improved PFS and ORR vs twice-weekly Kd at 20/27 mg/m^2. The incidence of AEs was comparable between groups. No new safety risks were found in the once-weekly group. Overall, once-weekly Kd showed acceptable benefit-risk profile with a convenient dosing regimen vs twice-weekly Kd. Clinical trial information: NCT02412878.

Efficacy

<table>
<thead>
<tr>
<th>Arm</th>
<th>n</th>
<th>ORR (95% CI)</th>
<th>PR (95% CI)</th>
<th>VGPR (%)</th>
<th>CR (%)</th>
<th>MRD negativity (at any time)</th>
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</thead>
<tbody>
<tr>
<td>Once-weekly</td>
<td>278</td>
<td>40.0% (32.8–48.0)</td>
<td>12.3% (9.4–15.5)</td>
<td>6.6%</td>
<td>5.9%</td>
<td>32% (30–34)</td>
</tr>
<tr>
<td>Twice-weekly</td>
<td>281</td>
<td>36.2% (29.5–43.3)</td>
<td>10.9% (8.2–14.5)</td>
<td>6.8%</td>
<td>6.3%</td>
<td>31% (29–33)</td>
</tr>
</tbody>
</table>

Less-refractory pts had 1 prior Tx line. MRD negative rate at any time was 32% for once-weekly Kd and 31% for twice-weekly Kd.
**8004 Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. First Author: Luciano J. Costa, University of Alabama at Birmingham, Troy, AL

**Background:** The BCL-2 inhibitor venetoclax (VEN) has demonstrated efficacy, as monotherapy and combined with PI bortezomib, in relapsed/refractory (R/R) multiple myeloma (MM). We report preliminary data for VEN combined with second generation PI carfilzomib and dexamethasone (VENkd) in R/R MM. **Methods:** In this ongoing phase 2, dose escalation study (NCT02899052), pts with R/R MM received VENkd on 28-d cycles: VEN 800 mg/day + K 70 mg/m² d1,8,15 + dex 40 mg d1,8,15, 22 (Cohort 1), or VEN 800 mg + K 56 mg/m² d1,2,8,9,15,16 + dex 40 mg d1,2,8,9,15,16,22,23 (optional Cohort 4; no data available at cutoff). Treatment continued until progressive disease (PD) or unacceptable toxicity. **Results:** As of 01Dec 2017, 26 pts were enrolled. Median age was 67.5 years (40 – 79), 68% had ISS II/III disease, and 23% had t(11;14). Pts received a median of 1 prior therapy (1 – 3); no pts had prior K exposure, 96% had received prior PI (54% refractory), 62% were IMiD refractory, and 35% double refractory. At data cut off, 23 pts were on therapy for 0.3 – 10 months and 3 pts discontinued the study for PD, physician decision, and death. 85% of pts had an AE, grade 3/4 AEs were neutropenia (15%), hyperton(12%), thrombocytopenia (8%), decreased white blood cells (8%), and nausea (4%). 7 serious AEs occurred, but no dose-limiting toxicities were reported. Maximum tolerated dose was not reached or not definitively expanded. VEN pharmacokinetics with Kd were comparable to VEN plus bortezomib and dexamethasone. Of 17 pts evaluated after completing ≥2 cycles, 3 had complete response (CR), 2 very good partial response (VGPR), 3 partial response (PR), 3 stable disease, and 2 PD (awaiting response data at cutoff). Treatment arms expanded. VENkd is well tolerated with promising preliminary efficacy that supports study in pts with R/R MM. Accrual continues with 34 pts enrolled to date. Updated safety and efficacy results will be available for presentation. Clinical trial information: NCT02899052.

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**8006 Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase II study of ex vivo expanded cord blood natural killer cells for multiple myeloma. First Author: Nina Shah, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Multiple myeloma (MM) is an incurable disease with immune dysregulation and exhaustion. Remissions in some patients (pts) after allogeneic stem cell transplant (SCT) suggest a graft versus myeloma effect; however, toxicity limits its widespread use. Allogeneic natural killer (NK) cells are safe and potentially active against various hematologic malignancies, including MM. We previously demonstrated safety of ex vivo expanded cord blood (CB) derived NK cells in doses up to 1 e8 cells/kg in the setting of high dose melphalan and auto-SCT (ASCT) (Shah et al, Br Haematol 2017). Here we present results of the phase II portion of our study. **Methods:** Pts with symptomatic MM who were appropriate candidates for ASCT were eligible. CB units with at least 4/6 match at HLA-A, B and DR were chosen for each pt. When possible, CB units with potential NK allorreactivity (KIR-HLA mismatch) were prioritized. Due to pre-clinical data demonstrating synergy between lenalidomide and NK cells, pts received lenalidomide (10 mg daily) from days (−8) to day (−2). Melphalan 200 mg/m² was given intravenously on day (−1). Freshly expanded CBNK cells were infused on day (−5). Autologous peripheral blood progenitor cells were infused on day (0). **Results:** 33 patients were enrolled. 24/33 (74%) pts had at least 1 of the following adverse features: high risk cytogenetics/FISH(del1p, amp1q, t(4;14), t(14;20), t(14;16), del(17p), cytogenetic del (13)), history of progression/release or ISS III disease. Successful expansion to target dose (1 e8 cells/kg) was achieved in all but 3 patients (who received 5 e7 cells/kg). There were no toxicities associated with the CB NK cell infusions. Responses at 3 months were CR:18/33 (55%); VGPR:4/33 (12%); PR: 7/33 (21%). Best response was CR: 21/33 (65%); VGPR: 6/33 (18%); PR: 3/33 (9%). With a median follow-up time of 22 months, 10 pts have progressed, 3 pts discontinued the study for PD, physician decision, and death. Median PFS has not been reached. By DNA microsatellite chimera analysis, donor CB-NK cells were detected 1-13 days after infusion for 25/33 (76%) pts. **Conclusions:** In this relatively high risk MM population, CBNK cells in the setting of auto-SCT is a promising adjunct immunotherapy. Updated data will be correctly represented at the annual meeting. Clinical trial information: NCT01729001.

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**8007 Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study. First Author: Noopur S. Raje, Massachusetts General Hospital Cancer Center, Boston, MA

**Background:** bb2121 is a second-generation chimeric antigen receptor (CAR) T cell therapy targeting B cell maturation antigen (BCMA) to redirect T cells to recognize and kill malignant myeloma cells. Initial data from the dose-escalation (DE) phase of CRB-401, a first-in-human study of bb2121 in relapsed/refractory multiple myeloma (RRMM), have shown promising efficacy and safety. We report updated safety and efficacy results on 43 patients (pts) enrolled in this ongoing study. **Methods:** CRB-401 (NCT02658929) is a 2-part, phase I study of bb2121 in pts with RRMM. DE pts had received ≥ 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, or were double refractory, and had ≥ 50% BMCA expression on plasma cells. In the dose-expansion (Exp) phase, pts had to have received daratumumab and been refractory to last line of therapy; no BCMA expression was required. Following lymphodepletion with Flu (30 mg/m²)Cy (300 mg/m²) given daily for 3 days, pts received 1 infusion of bb2121. **Results:** As of 02 Oct 2017, 21 pts had received bb2121 in the 4 DE cohorts (median follow-up, 35 weeks); no DLTs and no grade ≥ 3 neurotoxicities (NTX) were observed. Cytokine release syndrome (CRS), primarily grade 1-2, was reported in 15 of 21 (71%) pts; 2 pts had grade ≥ 3 CRS that resolved in 24 hours. There were 2 deaths on study; both pts had achieved complete response (CR) and had not progressed. Overall response rate in the 18 evaluable pts in DE cohorts ≥ 150 × 10⁶ CAR T cells was 94%; 10 of 18 (56%) pts had CR or unconfirmed CR; 9 of 10 evaluable pts were MRD-negative. With a median follow-up of 40 weeks in ≥ 150 × 10⁶ DE cohorts, median response duration and progression-free survival (PFS) had not been reached; PFS rates at 6 and 9 months were 81% and 71%, respectively. Doses of 150 to 300 × 10⁶ CAR T cells were selected for the Exp phase. Results from an additional 5 months of follow-up and initial data from ~20 pts from the Exp cohort will be presented. **Conclusions:** bb2121 shows promising efficacy at dose levels ≥ 150 × 10⁶ CAR T cells with deep and durable ongoing responses and manageable CRS and NTX. These data support the potential role of bb2121 as an additive CAR T cell therapy as a new treatment paradigm for RRMM. Clinical trial information: NCT02658929.
8008 Oral Abstract Session, Fri, 2:45 PM-5:45 PM
FDA analysis of pembrolizumab trials in multiple myeloma: Immune related adverse events (irAEs) and response. First Author: Aviva C Krauss, US Food and Drug Administration, Silver Spring, MD
Background: Development of irAEs with checkpoint inhibition may be associated with response in some disease settings. Methods: We evaluated overall survival (OS), safety and objective response rates (ORR) among patients who developed irAEs and those who did not in two trials of pembrolizumab in MM. KEYNOTE 183 (KN183) evaluated pomalidomide and dexamethasone (PomDex) with or without pembrolizumab (pembro) in patients with newly diagnosed (ND) MM and for relapsed refractory (RR) MM patients. KN185 (KN185) evaluated lenalidomide and dexamethasone (LenDex) with or without pembrolizumab in patients with newly diagnosed (ND) MM ineligible for autologous stem cell transplant. FDA placed both trials on clinical hold in July 2017 due to worse OS in the pembrol-zinc containing arms. Results: Using a June 2, 2017 date cut-off, median follow-up on KN183 was 18.1 months, 249 patients were randomized. There were 29 deaths in the pembrol arm and 21 in the control arm, for an OS hazard ratio (HR) of 1.61 (95% CI: 0.91, 2.85). ORR was 34% in the pembrol arm and 40% in the control arm. Median follow-up on KN185 was 6.6 months, 301 patients were randomized. There were 19 deaths in the pembrol arm and 9 in the control arm, for an OS HR of 2.06 (95% CI: 0.93, 4.55). ORR was 64% in the pembrol arm and 62% in the control arm. Neither trial showed a difference in time-to-progression between arms. In KN183, 58% of patients on the pembrol arm developed an irAE, with an ORR of 37%, not significantly different than the 31% in those without an irAE. A trend was noted for improved ORR (49%) in those on the control arm (PomDex) with an irAE, compared to 33% in those without an irAE. In contrast, ORR in patients with NDM in KN185 who developed an irAE was higher than in those who did not. Conclusions: The utility of immunotherapy in patients unable to mount adequate immune responses merits further study, as does the worse OS observed in both trials.

8009 Poster Discussion Session; Displayed in Poster Session (Board #18), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session Discussion, Mon, 3:00 PM-4:15 PM
Updated efficacy data and MRD analysis according to risk status in newly diagnosed myeloma patients treated with carfilzomib + lenalidomide or cyclophosphamide (FORTE trial). First Author: Francesca Maria Gay, Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy
Background: Carfilzomib plus lenalidomide (KRd) or cyclophosphamide plus dexamethasone (C) is effective in NDMM. Treatment of high-risk pts is an unmet medical need. Methods: NDMM pts ≤56 years treated in 2 randomized trials (ISS and age ≥75 years) with KRd and C were compared (47.7% vs 52.3% evaluable pts; 28.0 mg/m² CYBEORD and MEL200 cycles with KRd (29.5 mg/m² IV days 1,2,8,15; DEX: 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and consolidation with 4 KRd; C: 4-28 day cycles with KRd (29.5 mg/m² IV days 1,2,8,9,15,16; LEN: 25 mg days 1-21; DEX: 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 C cycles until progression. Primary endpoint was OS. Conclusions: KRd was significantly superior to C and OS improvement was similar across the entire population. Table. (Fay G ASCO 2017). Results: 474 pts were randomized (KRd, n = 319; C, n = 155). Cons: KRd vs C (P = 0.0004). Median OS was not reached in either arm; HR, 2.06 (1.25, 3.38; 1.73, 2.49); 3-year OS, 82% vs 61%; 5-year OS, 69% vs 47%. Median progression-free survival was 22.7 vs 10.9 months in the KRd vs C arms; HR, 0.53 (0.35, 0.81); 2-year PFS, 73% vs 51%; 3-year PFS, 57% vs 35%. Median time-to-progression between arms. In KN183, 58% of patients on the pembrol arm developed an irAE, with an ORR of 37%, not significantly different than the 31% in those without an irAE. A trend was noted for improved ORR (49%) in those on the control arm (PomDex) with an irAE, compared to 33% in those without an irAE. In contrast, ORR in patients with NDM in KN185 who developed an irAE was higher than in those who did not. Conclusions: The utility of immunotherapy in patients unable to mount adequate immune responses merits further study, as does the worse OS observed in both trials.

8010 Poster Discussion Session; Displayed in Poster Session (Board #19), Mon, 8:00 AM-11:30 AM, Discussed in Poster Session Discussion, Mon, 3:00 PM-4:15 PM
A phase 3 randomized study of pembrolizumab (pembro) plus lenalidomide (len) and low-dose dexamethasone (Rd) versus Rd for newly diagnosed and treatment-naive multiple myeloma (MM): KEYNOTE-185. First Author: Saad Zafar Usmani, Levine Cancer Institute, Charlotte, NC
Background: KEYNOTE-185 (NCT02579863) evaluated Rd ± pembrolizumab in patients (pts) with newly diagnosed, ASCT-ineligible MM. Methods: Pts were randomized 1:1 to pembrol (200 mg G3W + Rd (len 25 mg/m² days 1-21) + 40 mg dex (weekly) every 28d) vs Rd until progression (PD), unacceptable toxicity, or withdrawal. Randomization stratified by age (< 75 vs ≥75 y), and disease stage (ISS I or II vs III). Primary end point was PFS per 2011 IWG-MM, secondary end points included OS and safety. On July 3, 2017, based on interim data presented to the DMC, the FDA halted KEYNOTE-185. Results: 301/640 pts enrolled (151, pembro-Rd arm vs 150, Rd arm). Median (range) age: 63 (35-77) y; 91% white; 91% M; 67% post-ASCT. Overall response rate (ORR) was 23% vs 17% (P = 0.0004); median OS was not reached in either arm; HR, 1.73 (0.95, 3.14); 3-year OS, 75% vs 60%. Conclusions: KEYNOTE-185 was stopped, due to the small number of death events (4%) treatment related deaths occurred; 4 (3%) died in the pembro-Rd arm (6 from PD, 13 from AEs); 5/19 deaths were high hyperthyroidism (6%), colitis (2%), and skin reactions (13%). 19 (13%) pts $\leq$ 60 cycles. AEs with pembrolizumab included constipation, diarrhea, rash (20%). Dyspnea and peripheral edema were reported in 1 (7%) pt each. Median follow-up on KN183 was 6.6 months, 301 patients were randomized. There were 19 deaths in the pembrol arm and 9 in the control arm, for an OS HR of 2.06 (95% CI: 0.93, 4.55). ORR was 64% in the pembrol arm and 62% in the control arm. Neither trial showed a difference in time-to-progression between arms. In KN183, 58% of patients on the pembrol arm developed an irAE, with an ORR of 37%, not significantly different than the 31% in those without an irAE. A trend was noted for improved ORR (49%) in those on the control arm (PomDex) with an irAE, compared to 33% in those without an irAE. In contrast, ORR in patients with NDM in KN185 who developed an irAE was higher than in those who did not. Conclusions: The utility of immunotherapy in patients unable to mount adequate immune responses merits further study, as does the worse OS observed in both trials.
**8012** Poster Discussion Session; Displayed in Poster Session (Board #21), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase II study of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in relapsed and refractory multiple myeloma. First Author: Andrew Jenho Yee, Massachusetts General Hospital Cancer Center, Boston, MA

**Background:** Elotuzumab was an approved monoclonal antibody targeting SLAMF7 on NK cells and plasma cells that enhances the activity of lenalidomide and bortezomib in multiple myeloma (MM). We studied elotuzumab with pomalidomide and bortezomib and dexamethasone single agent and refractory MM. **Methods:** The primary objective was to determine the overall response rate (ORR). **Results:** ORR of 46% with 10 CR (of whom 7 were confirmed) and 26 VGPRs. **Conclusion:** This regimen showed promising activity with manageable toxicities. Clinical trial information: NCT02718833.

**8014** Poster Discussion Session; Displayed in Poster Session (Board #23), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Phase I-b study of isatuximab + carfilzomib in relapsed and refractory multiple myeloma (RRMM). First Author: Ajai Chari, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

**Background:** Isatuximab (ISA) is an anti-CD38 mAb with potent anti-myeloma effects as monotherapy or together with lenalidomide (Len) + dexamethasone (d) in RRMM. Carfilzomib (K) is a proteasome inhibitor approved for use in RRMM as a single agent or in combination with lenalidomide (Len/IRd). Objective of ISA + K primary objective was to assess the maximum tolerated dose (MTD) of ISA + K in RRMM. Secondary objectives were assessment of safety, PK, immunogenicity, and efficacy (IMWG response criteria (ORR)). **Methods:** Eligible patients (pts) had disease progression after 2 prior lines, an ECOG < 3, and adequate organ function. A 3+3 dose escalation (DE) design was utilized. 3 dosing levels (DL) were tested: ISA 10 mg/kg QW, ISA 10 mg/kg QW x 4 then Q2W and ISA 20 mg/kgQW x 4 then Q2W in combination with K standard dose (27 mg/m²) and schedule. An expansion cohort (EC) of 18 pts was enrolled at DL2. **Results:** 15 pts were treated in DE and 18 in the EC. The median age (n = 33) was 61 yrs (range 39-79). Pts received a median of 3 (2-8) prior lines. All pts were IID and PI exposed: 26/29 Len refractory (Refr), 21/29 VEL Refr, 13/29 Pom Ref and 8/11 K Refr. Median follow-up is 6.5m (0.5-24m), 29 pts are evaluable for efficacy. ORR = 66% (1 sCR, 7 VGPR, 11 PR) and CBR is 86%. The median progression free survival has not been reached. **Conclusion:** 15 pts have progressed (4 deaths from Pts), 1 pt withdrew after 2 cycles and 17 remain on therapy. The median # of cycles given is 3 (range 1-27). No DLT or severe toxicity has been observed. Common adverse events (AEs) all grades, incidence ≥15%, were thrombocytopenia (66%), pain (60%), upper respiratory infection (56%), diarrhea (40%), fatigue (40%), anorexia (31%), elevated creatinine (30%), nausea (30%), neutropenia (27%), headache (27%), dyspnea (16.7%) and fever (16.7%). Serious AEs occurred in 9pts and < 5% of AEs were Gr 3/4. Injection reactions (IRs) were the most common ISA-related AE: 17 IRs in 16/32 pts (50%; Gr 1-2), 4 in 1 pt (Gr 3-4). **Conclusions:** Combining ISA and K appears safe; toxicity is c/w the individual AEs. Encouraging MM activity (ORR 66%) was seen at all DLs. ISA 10 mg/kg QW x 4 then Q2W dosing was selected for an ongoing Phase III trial of ISA + Kd versus Kd (IKEMA: NCT03275285). Clinical trial information: NCT-02332850.

**8013** Poster Discussion Session; Displayed in Poster Session (Board #22), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Subcutaneous daratumumab (DARA) in patients (Pts) with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open-label, multicenter, dose escalation phase 1b study (PAVO). First Author: Achai Chari, Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY

**Background:** Intraavenous (IV) administration of DARA 16 mg/kg is approved as monotherapy and in combination with standard of care regimens for RRMM. The phase 1b PAVO study (NCT02513452) demonstrated that delivery of DARA with recombinant human hyalurondase enzyme (HhPH20) by subcutaneous (SC) infusion through a syringe pump (Part 1) or by manual SC injection (Part 2) was well tolerated with an efficacy profile consistent with IV DARA (Chari A, et al. ASH 2017; abstract 838). We present updated data from Part 2. **Methods:** Eligible pts received ≥2 prior lines of therapy (LOTs) including a proteasome inhibitor and an immunomodulatory drug. In Part 2, pts received a concentrated co-formulation of DARA (DARA SC; 1,800 mg in 15 mL) and HhPH20 (30,000 U) dose in a single, pre-mixed vial, which was administered in 3 to 5 min by manual SC injection. Primary endpoints were CBR on DARA at the end of weekly dosing on Cycle 3 Day 1 (C3D1) and safety. Secondary endpoints included overall response rate (ORR), rate of complete response, time to response, and duration of response. **Results:** Pts in Part 2 (n = 25) had a median age of 68 years and received a median of 3 prior LOTs. At a median follow-up of 4.6 months, none discontinued due to treatment-emergent adverse events (TEAEs). Pharmacokinetic analyses indicated that DARA SC had a Tmax of 7 to 24 h and Cmax of 2000 to 800 ng/mL (Part 1). In Part 2, Cmax on C3D1 compared to what has been observed with DARA IV. Most Common Grade 3/4 TEAEs (> 1 pt) were lymphopenia (16%), thromboctopenia (8%), and neutropenia (8%). IRs were reported in 3 (12%) pts, all occurring ≥ 6 h of the first injection. No Grade 4 IRs or discontinuations due to IRs were reported. DARA SC injections in the pericellular area were well tolerated with reversible erythema observed in 20% of pts. DARA SC achieved an ORR of 44%, including 28% very good partial response. **Conclusions:** DARA SC, which enables dosing in 3-5 min, was well tolerated with low IR rates, had an acceptable PK profile, and demonstrated clinical response rates similar to DARA IV. Updated data based on longer follow up will be presented at the Meeting. Clinical trial information: NCT02519452.

**8015** Poster Discussion Session; Displayed in Poster Session (Board #24), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Low vs high dose carfilzomib (Cfz) with dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM): Results of SWOG S1304. First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL

**Background:** Cfz has >1 FDA approved doses in RRMM. Dose-response correlation is assumed without prospective data to compare efficacy of low-dose (27 mg/m²; LCD) vs high-dose (56 mg/m²; HDDC). **Methods:** Eligible pts received 10 mg/kg Cfz (56 mg/m²; HDDC). Median PFS was 19 months (n = 83). **Results:** ORR 66% (15 pts, 18% VGPR, 22% PR), median PFS 9m (95% CI 6.1-Inf). **Conclusions:** Cfz low-dose had a similar clinical activity (ORR 66%) was seen at all DLs. ISA 10 mg/Kg QW x 4 then Q2W dosing was selected for an ongoing Phase III trial of ISA + Kd versus Kd (IKEMA: NCT03275285). Clinical trial information: NCT-02332850.

**Selected patient characteristics, responses and grade 3-5 AEs at least possibility attributable to study treatment.**

<table>
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<th>Characteristic</th>
<th>(n = 57)</th>
<th>(n = 64)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;65 vs ≥ 65)</td>
<td>56%</td>
<td>48%</td>
<td>0.467</td>
</tr>
<tr>
<td>BMI 15.5-24.9 vs 25+</td>
<td>54%</td>
<td>66%</td>
<td>0.857</td>
</tr>
<tr>
<td>Cr (mg/dL) ≤ 1.5 vs &gt; 1.5</td>
<td>0%</td>
<td>4%</td>
<td>1.000</td>
</tr>
<tr>
<td>Hgb (g/dL) ≤ 8 vs &gt; 8</td>
<td>0%</td>
<td>0%</td>
<td>0.113</td>
</tr>
<tr>
<td>4-6 Prior lines</td>
<td>26%</td>
<td>22%</td>
<td>0.671</td>
</tr>
<tr>
<td>Response Category (&lt;90 days)</td>
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<tr>
<td>Complete response</td>
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<td>0%</td>
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</tr>
<tr>
<td>VGPR</td>
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<td>1%</td>
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<td>PR</td>
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<td>40%</td>
<td>41%</td>
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<td>Increasing Disease</td>
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<td>20%</td>
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<td>AE Category</td>
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<tr>
<td>Grade 1 (most common: fatigue)</td>
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<td>Grade 2 (most common: peripheral neuropathy)</td>
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<td>0%</td>
<td>0.047</td>
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<tr>
<td>Grade 3 (most common: thrombocytopenia)</td>
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<td>15%</td>
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<tr>
<td>Carcinoma</td>
<td>5%</td>
<td>8%</td>
<td>0.721</td>
</tr>
<tr>
<td>Maximum grade any AE</td>
<td>65%</td>
<td>39%</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Maintenance therapy (MT) with 25 versus 5 mg lenalidomide (Len) after prolonged CT, 1, 2 and 3 years MT. Dose reductions were mainly due to hematologic and 3% pts continued 25 mg Len without dose reductions / discontinuations and Len MT was applied for one year in 72% and 61% pts in arm A and B, median age of 58 years (range: 30-72). Len CT could be completed in 86% pts reconsideration of the high-dose schedule and awaiting of long-term OS. Shorter EFS compared to the concept of upholding high-dose Len. Still, the rate of overall AEs and hematologic toxicities were low and not significantly different with a median EFS of 44.8 and 33.0 months for arm A and B (HR 0.65, range: 0.44-0.97; p = 0.032). This was confirmed by Landmark analysis including only patients who entered MT (HR 0.63; p = 0.042). Overall survival (OS) was not different with a median 4-year-OS of 79% and 67% for arm A and B (p = 0.16).

Conclusions: Low-dose Len is associated with significantly shorter EFS compared to the concept of upholding high-dose Len. Still, the rate of overall AEs and hematologic toxicities were low and not significantly different with a median EFS of 44.8 and 33.0 months for arm A and B (HR 0.65, range: 0.44-0.97; p = 0.032). This was confirmed by Landmark analysis including only patients who entered MT (HR 0.63; p = 0.042). Overall survival (OS) was not different with a median 4-year-OS of 79% and 67% for arm A and B (p = 0.16).

Overall survival (OS) results of randomized phase III study (ADMYRE trial) of plitidepsin and dexamethasone (DXM) vs. DXM alone in patients with relapsed/refractory multiple myeloma (RRMM): Evaluation of the crossover impact. First Author: Javier Gomez, PharmaMar, Madrid, Spain.

Background: Plitidepsin is a synthetic cyclic depsipeptide isolated from the marine tunicate Aplidium albicans targeting the proto-oncogene EF12A, which is over-expressed in multiple myeloma cells. In ADMYRE trial, plitidepsin plus dexamethasone (DXM) (Arm A) met the primary endpoint (progression-free survival) and showed a survival improvement versus DXM alone (Arm B) (ASH 2017). Methods: RRMM patients with at least three but not more than six prior regimens, including at least bortezomib and lenalidomide/haladimide, were randomized at 2:1 ratio to receive plitidepsin 5 mg/m² D1 and 15 plus DXM 40 mg D1,8,15 and 22 (Arm A), or DXM 40 mg D1,8,15 and 22 (Arm B) every four weeks. The rank preserving structural failure time (RPSFT) and the two-stage methods were used to present overall survival (OS) results after mitigating the crossover effect. Results: Two-hundred fifty-five patients were enrolled: (Arm A: 171/Arm B: 84). Thirty-seven patients in Arm B (44%) switched to Arm A after progression. Intention-to-treat (ITT) analysis not discounting the crossover effect showed a 20.3% risk reduction in favor of Arm A (median OS: A 11.6 mo. B: 8.9 mo.; HR = 0.797; log-rank p = 0.1261). Risk reduction improved to 32.4% with the RPSFT method (median OS: A 11.6 mo. B: 7.2 mo.; HR = 0.676; log-rank p = 0.0103) and to 37.8% with the two-stage method (median OS: A 11.6 mo. B: 6.4 mo.; HR = 0.622; log-rank p = 0.0015). Although assumptions for RPSFT and two-stage analyses were plausibly met, statistically significant risk reductions were still maintained when severe penalizations were applied, with median OS differences around four months (p = 0.0015).

Conclusions: Plitidepsin in combination with DXM demonstrated a clinically significant benefit in terms of overall survival in heavily pretreated RRMM, a disease where new therapeutic alternatives are still needed. Clinical trial information: NCT01102426.
**8020 Poster Discussion Session; Displayed in Poster Session (Board #29), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM**

Remission observed from a phase 1 clinical study of CAR-T therapy with safety switch targeting BCMA for patients with relapsed/refractory multiple myeloma. First Author: Yarong Liu, HRRAIN Biotechnology, Shanghai, China

**Background:** Encouraging results are seen from several early phase clinical trials on the cellular immunotherapy based on chimeric antigen receptor (CAR)-engineered T (CAR-T) targeting B cell maturation antigen (BCMA) for the treatment of relapsed/refractory (RR) multiple myeloma (MM). We validated an anti-BCCA CAR-T cell product manufactured using plasma from HIV-1 retrovirus-mediated transduction of activated T cells to express a second-generation CAR with the 4-1BB costimulatory domain along with a truncated epidermal growth factor receptor (tEGFR) as a safety switch. The preclinical study confirmed its high reactivity against MM cells. **Methods:** A phase 1 clinical trial (NCT030553168) has been launched to evaluate the safety and feasibility of this BCMA CAR-T cell product for treating RRMM. The enrolled RRMM patients had received at least 3 prior treatment regimens, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory, and have over 20% BCMA expression on plasma cells. **Patients:** 40 RRMM patients were subjected to a lymphodepleting regimen with Cy once (300 mg/m², d-3) and Flu daily for 3 days (25 mg/m², d-5 to d-3) prior to the CAR-T infusion (d0) at a dose of 9×10⁶ CAR+ cells/kg. The efficacy was assessed by the International Uniform Response Criteria for Multiple Myeloma, and the toxicity was graded by CTCAE v4.02. **Results:** As of December 31, 2017, 10 patients had been infused with CAR-T cells and 3 patients were still evaluable. 17 patients had reached at least 1 month of follow-up. As of this data cutoff, no greater than Grade 1 neurotoxocities or cytokine release syndrome (CRS) had been observed. The overall response rate (ORR) for the 7 evaluable patients was 86%, including 2 sCRs and 2 MRO-negative responses (2 VGPR). The CART cell expansion and persistence were consisantly observed throughout these patients. **Conclusions:** Our result demonstrates the promising efficacy with the infused dose, including 2 sCRs and ongoing clinical responses for more than 12 months, with only mild and manageable CRS to date. These initial data provide strong evidence to support the further development of this anti-myeloma cellular immunotherapy. Clinical trial information: NCT03093168.

**8021 Poster Session (Board #30), Mon, 8:00 AM-11:30 AM**

A phase 3 randomized study of pembrolizumab (Pembro) plus pomalidomide (Poma) and dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM; KEYNOTE-183). First Author: Maria-Victoria Mateos, University of Salamanca Hospital, Salamanca, Spain

**Background:** KEYNOTE-183 (NCT02576977) evaluated pembro plus low-dose dex (SOC) ± pembro in patients (pts) with RRMM. **Methods:** Pts were randomized 1:1 to pembro (200 mg Q3W) + SOC (4 mg pone p [d 1-21] + 40 mg dex [d 1 x 28] vs SOC) or SOC only (P = 0.005). **Results:** 249/300 pts enrolled (125, pembro + SOC; 124, SOC) with median (range) age: 65 y (45-94) vs 67 y (22-98); 28 (22%) vs 17 (14%) pts had high-risk cytogenetics. Median (range) drug exposure was 123.5 d (42-477) vs 127 d (2-468); median 4.4 cycles. AEs with ≥5% difference between arms: neuropenia (38% vs 27%), nausea (17% vs 12%), pneumonia (23% vs 15%), ALT increase (10% vs 3%), headache (13% vs 4%). No SAEs had ≥5% difference between arms. In pembro + SOC arm, 21 (18%) pts had immune-mediated AEs: skin reaction (5%), pneumonitits (4%), myocarditis, iridocyclitis, hepatitis, Steven-Johnson syndrome (SJS; 1% each), 29 (23%) pts vs 21 (17%) died (16 from PD, 13 from AEs vs 18 from PD, 3 from AEs). 4 (3%) treatment related deaths occurred; 2 (1.5% [1 mycarditis, 1 SJS] related to pembro. Median follow-up was 7.8 mo vs 8.6 mo. Median (range) TTP: 8.1 vs 7.8 mo. Median OS: not reached vs 15.2 mo; HR, 1.6 (95% CI, 0.91-2.85); P = 0.95. In a retrospective random forest analysis age, ECOG, stage, presence of plasmacytoma, double refractory status were more relevant contributors to death than treatment. A subsequent multivariable analysis showed that age and presence of plasmacytoma significantly contributed to risk of death. Age and presence of plasmacytoma were prognostic, while ECOG was prognostic and predictive of outcome with OS HR = 0.85 (ECOG 0) and OS HR = 2.3 (ECOG 1). **Conclusions:** The benefit-risk profile for combination of pembro, pomo and dex is unfavorable for RRMM. Evaluation of T-cell subsets and cytokines along with long-term safety and survival follow-up is ongoing. Clinical trial information: NCT02576977.

**8022 Poster Session (Board #31), Mon, 8:00 AM-11:30 AM**

Weekly carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed or refractory multiple myeloma (MM). First Author: Sooyeon Biron, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ

**Background:** KRd is approved for treatment of RRMM patients (pts). Under the approved KRd regimen, carfilzomib is given twice weekly (20/27 mg/m²; 10-min IV infusion). Here we present updated results from a dose-finding study assessing weekly KRd. **Methods:** This study consisted of a dose-escalation component and a dose-expansion component in both RRMM and newly diagnosed MM. Results for RRMM pts are presented here. Two dose levels were evaluated: carfilzomib 56 mg/m² and carfilzomib 70 mg/m². All pts received carfilzomib (30-min IV infusion on days [D] 1, 8, and 15; 20 mg/m² on D1D), lenalidomide 25 mg (D1–21), and dexamethasone 40 mg (D1, 8, 15, and 22) on a 28-day cycle (dexamethasone was not given on D22 for cycles ≥3). Pts in the expansion arm received the selected KRd regimen on the same schedule used for dose evaluation. Response was assessed by investigators. **Results:** Twenty-two RRMM pts were enrolled in the dose-escalation part and received study drug (56 mg/m², n = 10; 70 mg/m², n = 12). The maximum tolerated dose of carfilzomib was not reached; the 70 mg/m² dose was selected for dose expansion and 34 additional RRMM pts received this dose. Results are presented for pts who received carfilzomib 56 mg/m² during dose evaluation (n = 10; median 2 prior regimens [range 1-3]) and for pts who received carfilzomib 70 mg/m² during dose evaluation or expansion (n = 46; median 1 prior regimen [range 1-5]). Median (SD) average carfilzomib dose was 53.2 (52.8) mg/m² in the 56 mg/m² group and 62.4 (61.3) mg/m² in the 70 mg/m² group. Pt incidence of grade ≥3 adverse events was 70.0% (56 mg/m²) and 71.0% (70 mg/m²). Pt incidence of carfilzomib discontinuation due to adverse events was 20.0% (56 mg/m²) and 24.0% (70 mg/m²). There were three toxic deaths in the 70 mg/m² group (one each due to cardiac arrest, cardiac disorder, and progressive disease). Overall response rates were 90.0% (56 mg/m²) and 89.1% (70 mg/m²); 20.0% (56 mg/m²) and 30.4% (70 mg/m²) of pts achieved complete response (CR) or stringent CR. **Conclusions:** Once weekly KRd was effective and tolerable in newly diagnosed MM pts with RRMM. This dose expansion regimen could offer pts greater convenience, these results support further clinical evaluation. Clinical trial information: NCT02335983.

**8023 Poster Session (Board #32), Mon, 8:00 AM-11:30 AM**

Utility and prognostic value of 18F-FDG PET/CT scan in patients with newly diagnosed multiple myeloma. First Author: Mohammed A. Aljama, Mayo Clinic, Division of hematology, Rochester, MN

**Background:** Positron emission tomography–Computed tomography (PET/CT) can identify bony lesions, assess disease burden and detect extra-mediillary disease in patients with newly diagnosed multiple myeloma (MM). **Methods:** We conducted a retrospective review of patients who had a PET/CT performed within sixty days of diagnosis and prior to commencement of treatment. We identified the presence of PET/CT abnormalities in patients with newly diagnosed MM. **Results:** Between April 2005 and June 2017, 314 patients were identified and included in the analysis. 235 (75%) patients had focal lesions (FL), 183 (58%) had ≥3 FL, 38 (12%) had extra mediillary disease (EMD) and 194 (62%) had documented lytic lesions. Median maximum standardized uptake value (SUVmax) in the entire cohort was 5.9 (range 0.48-3.3). Presence of ≥3 FL and EMD predicted overall survival (OS); median OS of 58 months for ≥3 FL vs 89 months for < 3 FL (P = 0.009) and median OS 45 months for EMD present vs 71 months for EMD absent (P = 0.002). Compared to those with SUVmax of less than 8.5, those with SUVmax of more than 8.5 had a shorter overall survival, 89.6 versus 58.7 months, respectively (P = 0.022). **Conclusions:** PET/CT is a valuable tool in assessing disease burden and provides prognostic information in patients with newly diagnosed MM treated with novel agents.
Background: A high frequency of rapid minimal residual disease-negative (MRD-neg) responses has been seen in CRB-401, a phase I trial of bb2121 CAR T cell therapy for RRMM (Kochenderfer, ASH 2017). We report IMWG responses in MRD-neg patients (pts) and associated factors. Methods: Pts treated with $\geq 150 \times 10^6$ BCMA CAR+ T cells in the dose-escalation phase of CRB-401 and evaluable for MRD by Adaptive NGS MRD Assay (Adaptive Biotechnologies) were included in this analysis (n = 10 as of 20 Oct 2017; median follow-up: 34 wks; min, max: 7, 67). Results: Nine of 10 evaluable pts were MRD-neg with a sensitivity of 1 in $10^4$ nucleated cells (1 pt); in $10^6$ (6 pts), and in $10^8$ (2 pts). Achievement of MRD negativity was independent of depth of response at first MRD-neg assessment; 2 pts had stable disease, 3 had PR, 2 had VPRG, and 2 had CR / stringent CR. Of 8 evaluable MRD-neg pts, all showed $\geq 85\%$ and $\approx 97\%$ decline in serum BCMA and involved free light-chain levels, respectively, at month (M) 1. Two of 9 MRD-evaluable pts were in CR at MRD-neg assessment and the remaining 7 achieved deeper response over time, 4 with CR or stringent CR, 2 with VPRG and 1 with PR between M1 and M15. One MRD-neg pt became MRD-positive at M12, and 1 MRD-neg pt had progressed as of data cut-off. Achievement of MRD negativity was independent of occurrence of cytokine release syndrome. MRD-neg was observed across all active bb2121 doses (150 (n = 3), 450 (n = 5), and 800 $\times 10^6$ (n = 2)). Of MRD-neg pts, 7 had at least 6M follow-up and 1 had IMWG progression (at M6); 3 had at least 12M follow-up, 1 had become MRD-positive and none had IMWG progression. Attainment of MRD-neg was independent of peak CAR T expansion (vector copy min, max: 93,744, 1,457,070 copies/ g gDNA; n = 9) and was observed in high (75\%) and low (25\%) CAR T cell populations. Of 35 pts, 21 had bone marrow analysis (BMPC: n = 6) and low BMPC (n = 3) were associated with the rest of the tumor burden pts. Eight of 9 MRD-neg pts had cytogenetic abnormalities including del(17q), del(13q), amp(1q21), or t(11;14). Conclusions: bb2121 induced a high frequency of rapid MRD-neg response, independent of IMWG MM responses. These early MRD-neg responses starting at M1 offer insights into bb2121 kinetics and may portend achievement of deeper responses over time. Clinical trial information: NCT02658929.
8028 Poster Session (Board #37), Mon, 8:00 AM-11:30 AM
Graft-versus-host disease (GVHD) risk with daratumumab (Dara) therapy post allogeneic transplantation (alloHCT) for multiple myeloma (MM). First Author: Liana Nikolaenko, City of Hope Medical Center, Duarte, CA

Background: Daratumumab (Dara) is an antibody targeting CD38+ MM cells that also affects CD38– non-myeloma cells, including T cells, which mediate GVHD. Regulatory T cells (Tregs) are reduced while helper and cytotoxic T cells are increased in Dara-post allogeneic transplantation (alloHCT) for multiple myeloma (MM).

Methods: Multicenter, retrospective study. All patients who received alloHCT for MM were cross referenced with patients receiving Dara. Demographic data, details of prior MM therapy, conditioning regimen, time from transplant to Dara and time to GVHD were collected. Patients with GVHD treated with Dara (D-VMP) vs those with GVHD treated without Dara were compared. Results: A total of 14 patients (41%) developed GVHD post alloHCT; 9 patients had GVHD prior to Dara without relapse of GVHD after Dara, 5 patients developed GVHD after Dara (15%) with 4 of these 5 patients having no prior history of GVHD before Dara. One patient developed acute GVHD during Dara therapy while having history of chronic GVHD. Median time to onset of GVHD from first dose of Dara was 149 days (136 to 149 days). Overall response to Dara-based therapies was 38% (13/34), including 12 SD, 3 MR, 9 PR, 2 VGPR, 2 CR, 4 PD and 2 unavailable. Median follow up was 33.2 months (6.4 months to 16.5 years).

Conclusions: Dara therapy post-alloHCT was well tolerated and did not increase risk of GVHD. These data suggest that Dara is an effective and safe option for use after alloHCT and could be considered in studies of salvage and maintenance post alloHCT.

8029 Poster Session (Board #38), Mon, 8:00 AM-11:30 AM
A phase 1/2 study of carfilzomib, bendamustine, and dexamethasone (CBD) in newly diagnosed multiple myeloma patients. First Author: Siyang Leng, Home, Sunnyside, NY

Background: Carfilzomib and bendamustine have demonstrated efficacy in relapsed refractory myeloma. In this phase 1/2 study, we evaluated the combination of carfilzomib, bendamustine and dexamethasone in newly diagnosed patients.

Methods: This is an ongoing, open label, single center study. Phase 1 dose escalation followed an up-and-down dosing scheme (Storer’s Design D). Carfilzomib was administered at dose levels of 27, 36 and 45 mg/m² on days 1, 2, 8, 9, 15, 16, bendamustine at 70 and 90 mg/m² on days 1, 2, and dexamethasone at 20 mg on days of carfilzomib and on day 22 of a 28 day cycle.

Autologous stem cell transplant (ASCT) eligible patients received 4 cycles of CBD, underwent stem cell harvest, and then received an additional 4 cycles followed by ASCT. ASCT ineligible patients received 8 cycles of CBD. Both groups received maintenance with carfilzomib 36 mg/m² on days 1, 2, 15, 16 every 28 days for up to 2 years.

Results: To date, 18 patients have been treated. Median age was 65 (range 51-74); 12 were male, 7 Hispanic, 2 African American and 2 Asian. One patient was treated at each dose level from 1-4, without DLTs. 14 patients were treated at the maximum dose level. The overall response rates (RR) was 100% - 16 (90%) had complete response (CR) / very good partial response (VGPR), with 3 being MRD-negative by flow, 3 stringent CR, 1 CR, and 9 VGPR; 2 had partial response (PR). 2 patients with VGPR and 1 with PR are still receiving induction. All patients showed response after 1 cycle. Of the 13 patients who have completed 8 cycles of CBD, 7 underwent ASCT. The 12-month PFS rate was 92%, and median follow-up was 14.8 months. MM-related toxicities include neutropenia (28%), thrombocytopenia (22%), anemia (17%), lymphopenia (17%). Notable non-hematologic toxicities (all grades) include infection (44%), creatinine increase (33%), weight loss (28%), and thromboembolic event (22%). Stem cell collection was not impacted.

Conclusions: CBD appears to be a safe and highly effective induction regimen for myeloma, with an 89% rate of CR/VGPR in our cohort. Clinical trial information: NCT02002598.

8030 Poster Session (Board #39), Mon, 8:00 AM-11:30 AM
Prognostic value of minimal residual disease and polyclonal plasma cell clonal in myeloma patients achieving a complete response to therapy. First Author: Marcella Tschaatscher, Mayo Clinic, Rochester, MN

Background: Achievement of a complete response (CR) to therapy has been associated with improved outcomes in patients with multiple myeloma (MM). More recently, increasing application of minimal residual disease (MRD) assessment following therapy has shown that MRD negativity is a powerful prognostic factor for survival outcomes. The presence of MRD, even among patients who have achieved a conventional CR, predicts for worse outcomes. Given this, we wanted to examine the impact of the polyclonal plasma cell (pPC) compartment among patients who achieved CR but still have MRD.

Methods: This is a retrospective cohort study where 460 myeloma patients were identified who met criteria for CR per IMWG criteria and had application of multicolor flow cytometry to the bone marrow (BM) for the purpose of confirming CR. Mono and pPCs were estimated during MRD testing. A Kaplan-Meier model was used to determine OS and the 2-sided log-rank test to compare MRD+ and MRD- groups. TTNT was calculated as the difference from date of confirmed CR and date of next therapy.

Results: The median duration from diagnosis to CR was 11.7 months. The median follow-up for the entire cohort was 33.5 months (95% CI; 31, 36) from CR; and the median OS was not reached (95% CI; 63 mos, NR). Median TTNT was 31 months (95% CI; 27, 36). Among the 460 patients, 70% were MRD- with a median TTNT of 37.6 months for MRD+ patients (p < 0.001). In the median OS was not reached. Longer TTNT was a trend towards better survival for MRD- patients. The improved TTNT with MRD negativity was seen irrespective of prior treatment and SCT status. Among the 139 patients with residual disease, median percentage of pPCs was 65% (2.5 to 98.5), and those with > 95% pPCs had a significantly better TTNT (NR vs 23 months; p = 0.02) and a trend towards better outcomes. The improved TTNT with MRD negativity predicts for better response durability and trend towards improved OS among patients in conventional CR treated with modern therapies. The impact seems independent of the type of therapy that results in achievement of CR and MRD negative status. Finally, an increased proportion of pPC predicts for better outcomes within those who have residual tumor cells.

Conclusions: Achievement of MRD negativity predicts for better response durability and trend toward improved OS among patients in conventional CR treated with modern therapies. The impact seems independent of the type of therapy that results in achievement of CR and MRD negative status. Finally, an increased proportion of pPC predicts for better outcomes within those who have residual tumor cells.

8031 Poster Session (Board #40), Mon, 8:00 AM-11:30 AM
Daratumumab plus bortezomib-melphalan-prednisone (VMP) in elderly (≥75 y) patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplantation (ALCYONE). First Author: Michele Cavo, "Seraglio" Institute of Hematology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

Background: Daratumumab (D) plus VMP (D-VMP) prolonged progression-free survival (PFS) compared with VMP and was well-tolerated in the phase 3 ALCYONE study (NCT02195479). We examined the efficacy and safety profiles of D-VMP vs VMP in elderly (≥75 y) and non-elderly (< 75 y) NDMM pts in ALCYONE.

Methods: Pts were ineligible for high-dose chemotherapy with ASCT. Pts received up to nine 6-week VMP cycles (V: 1.3 mg/m² SC Days 1, 4, 8, 11, 22, 25, 29 [Cycle 1] and Days 1, 8, 22, 29 [Cycles 2-9]; M: 9 mg/m² PO and P: 60 mg/m² PO Days 1-4) followed by ASCT. ASCT ineligible patients received 8 cycles of CBD. Both CBD groups received maintenance with carfilzomib 36 mg/m² on days 1, 2, 15, 16 every 28 days for up to 2 years.

Results: To date, 18 patients have been treated. Median age was 65 (range 51-74); 12 were male, 7 Hispanic, 2 African American and 2 Asian. One patient was treated at each dose level from 1-4, without DLTs. 14 patients were treated at the maximum dose level. The overall response rates (RR) was 100% - 16 (90%) had complete response (CR) / very good partial response (VGPR), with 3 being MRD-negative by flow, 3 stringent CR, 1 CR, and 9 VGPR; 2 had partial response (PR). 2 patients with VGPR and 1 with PR are still receiving induction. All patients showed response after 1 cycle. Of the 13 patients who have completed 8 cycles of CBD, 7 underwent ASCT. The 12-month PFS rate was 92%, and median follow-up was 14.8 months. MM-related toxicities include neutropenia (28%), thrombocytopenia (22%), anemia (17%), lymphopenia (17%). Notable non-hematologic toxicities (all grades) include infection (44%), creatinine increase (33%), weight loss (28%), and thromboembolic event (22%). Stem cell collection was not impacted.

Conclusions: CBD appears to be a safe and highly effective induction regimen for myeloma, with an 89% rate of CR/VGPR in our cohort. Clinical trial information: NCT02002598.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: The phase 3 ENDEAVOR trial demonstrated significantly improved PFS and OS with Kd56 vs Vd in RRMM patients (pts; Dimopoulos Lancet Oncol 2016 and 2017). We report updated data after additional follow-up. Methods: Hazard ratios (HRs) and 95% CIs were estimated using stratified or unstratified Cox proportional hazards models for primary and subgroup OS analyses, respectively. Results: 929 pts were randomized (Kd56, n = 464; Vd, n = 465). As of 19-Jul-17, median OS was 47.8 (Kd56) vs 38.8 (Vd) months (mos; HR, 0.76 [95% CI, 0.630–0.915]; median follow-up, 44.3 vs 43.7 mos). OS was longer with Kd56 vs Vd within age subgroups (≤65 years [ys]; median, 47.8 vs 42.2 mos; HR, 0.791 [95% CI, 0.596–1.031]; 65–74 yrs: median, 49.0 vs 36.2 mos; HR, 0.71 [95% CI, 0.520–0.958]; ≥75 yrs: median, 36.1 vs 23.9 mos; HR, 0.78 [95% CI, 0.506–1.199]). OS was longer with Kd56 vs Vd by prior lines of therapy (1 line: median, 51.3 vs 43.7 mos; HR, 0.77 [95% CI, 0.583–1.018]; 2–3 lines: median, 39.9 vs 28.4 mos; HR, 0.75 [95% CI, 0.589–0.959]) and prior bortezomib (btz) exposure (prior btz: median, 41.8 vs 32.7 mos; HR, 0.85 [95% CI, 0.669–1.082]; no prior btz: median, not estimable [NE] vs 42.2 mos; HR, 0.66 [95% CI, 0.496–0.875]). OS was longer with Kd56 vs Vd for high-risk (median, 28.0 vs 22.7 mos; HR, 0.81 [95% CI, 0.580–1.361]) and standard-risk (median, NE vs 43.3 mos; HR, 0.791 [95% CI, 0.618–1.099]) cytogenetics pts. 457 (98.7%, Kd56) and 451 (98.9%, Vd) pts had an adverse event (AE); 379 (81.9%, Kd56) and 324 (71.1%, Vd) had a grade ≥3 AE. Exposure-adjusted pt incidences per 100 pt-ys (95% CI) of AEs were 1352.07 (1233.62–1481.89) for Kd56 and 1754.86 (1600.15–1924.53) for Vd; for grade ≥3 AEs, these values were 162.31 (146.77–179.50) and 175.90 (157.75–196.13). The most common AEs in the Kd arm (≥30% of pts) were anemia (43.6%), diarrhea (36.7%), pyrexia (32.6%), hypertension (32.4%), fatigue (32.2%) and dyspnea (32.2%). Conclusions: With median follow-up of ~44 mos, clinically meaningful OS improvements were observed with Kd56 vs Vd, including in all subgroups examined. The Kd56 safety profile was consistent with previous analyses. Clinical trial information: NCT01568866.
8037 Poster Session (Board #46), Mon, 8:00 AM-11:30 AM

Predictors of long-term survival in newly diagnosed multiple myeloma (NDMM) patients (pts) enrolled in the Connect MM registry. First Author: Cristina Gasparetto, Duke University Medical Center, Durham, NC

Background: There are limited longitudinal data on disease management & outcomes for long-term survivors of MM. The Connect MM Registry is a US, multicenter, prospective observational cohort study designed to examine di-agnostic & treatment (tx) patterns, clinical outcomes & G&O in pts with NDMM. Data from Connect MM were used to identify pt- & disease-specific baseline (BL) characteristics associated with ≥ 6 y survival (OS) vs death at ≤ 6 y in pts with NDMM. Methods: Adult pts in Cohort 1 (n = 1493) enrolled ≥ 6 mos after diagnosis from Sep 2009 - Dec 2011 had sufficient follow-up for evaluation; those censored at < 6 y (study discontinuation, ongoing but survival < 6 y) were excluded. BL characteristics were compared via logistic regression to identify those associated with tertile OS (P < 0.05). Results: As of Feb 2017, median follow-up for Cohort 1 (N = 1493) was 65.4 mo. Median age was 67 y (range 24-94), 57% were male, & 59% were standard/low risk per IMWG criteria. Most pts (91%) had ≥ 1 novel agent in their first drug regimen (1L, Table). BL characteristics associated with ≥ 6 y OS by multivariate analyses were: age: ≤ 70 vs > 70, EQGS PS 0-1 vs 2-5, lower ISS stage, platelet count: ≤ 150 vs > 150 x 10^9/L, & lack of history of diabetes, delt(1p7), extramedullary plasmacytoma, or serum-free light chain abnormality. Matrix for predicting OS ≥ 6 y will be included in the presentation. Conclusions: This analysis identified pt- & disease-specific BL characteristics associated with ≥ 6 y OS in pts with NDMM. Higher rates of triplet tx, SCT, maintenance (with/without SCT), & higher re-disease-specific BL characteristics associated with higher rates of triplet tx, SCT, maintenance (with/without SCT), & higher re-
disease-specific BL characteristics associated with higher OS. Clinical trial information: NCT01810128.

8039 Poster Session (Board #48), Mon, 8:00 AM-11:30 AM

Lenalidomide (LEN) pharmacokinetics (PKs) in multiple myeloma (MM) patients (pts) with various renal functions. First Author: Yanshuo Cao, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: LEN is a backbone drug used in the treatment of MM. Because over 80% LEN is excreted unchanged in urine, dose modifications for RD are recommended, based on PK evaluation following single dose LEN in non-malignant renal failure. In this analysis, MM pts with varying degrees of RD after single and multiple dosing of LEN were evaluated for PK to validate these dosing recommendations. Methods: Previously untreated MM pts received LEN in combination with dexamethasone according to creatinine clearance (CrCl) as recommended by the current LEN label. CrCl was calculated based on 24-hour urine collection. Serial venous blood samples were obtained on Days 1 and 17 and analyzed for LEN. PK parameters were calculated using non-compartmental methods. Results: A total of 25 pts were enrolled, 9 pts with normal renal function (CrCl ≥ 60 ml/min), 8 with moderate RD (30 ≤ CrCl < 60 ml/min), and 8 with severe RD (CrCl < 30 ml/min or on dialysis). Median age: 59 years (range: 39-69); male/female: 16/9. After a single dose, LEN half-life increased with RD (4.1 vs 6.7 vs 11.1 hours, p < 0.01); Plasma LEN concentrations were lowest in moderate RD, resulting in significantly lower maximum concentration (Cmax) and area under concentration-time curve (AUC). LEN clearance decreased with more advanced RD, and corre-
lated with calculated CrCl, with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula providing the best correlation compared to the Modification of Diet in Renal Disease (MDRD) formula and the Cockcroft-Gault formula. There was no LEN accumulation between Day 1 and Day 17 in pts with normal renal function or moderate RD. Cmax and AUC were significantly lower on Day 17 for pts with severe RD (413.8 ng/ml vs 71.1 ng/ml, p< 0.0001, and 4946 ng/hr/ml vs 538 ng/hr/ml, p = 0.002). Conclusions: LEN PKs after multiple doses are similar for pts with normal or moderate RD, but those with severe RD may benefit from therapeutic drug monitoring and dose adjustment. The CKD-EPI formula should be used to calculate CcL and LEN dose determination. The current LEN dose recommenda-
tion should be revised for pts with moderate RD. Clinical trial in-
formation: NCT01270932.

8040 Poster Session (Board #49), Mon, 8:00 AM-11:30 AM

Extended 5-y follow-up (FU) of phase 3 ELOQUENT-2 study of elotuzumab + lenalidomide/dexamethasone (ELd) in relapsed/refractory multiple myeloma (RRMM). First Author: Sagar Lonial, Emory University, Winship Cancer Institute, Atlanta, GA

Background: The immunostimulatory monoclonal antibody elotuzumab exhibits a dual mechanism of action, directly activating natural killer cells and mediating myeloma cell death via antibody-dependent cell-mediated cytotoxicity. In ELOQUENT-2 (NCT01239797), ELd showed sustained reduction in risk of disease progression or death at 2- (30%), 3- (27%), and 4- (27%) vs FDU, and a favorable trend in overall survival (final analysis at 427 deaths). Here we present progression-free survival (PFS) data at 5 y, a milestone timepoint in cancer survival analyses. Methods: RRMM patients (pts) randomized 1:1 to ELd or Ld in 28-d cycles until disease progression/ unacceptable toxicity. Coprimary endpoints: PFS and overall response rate (ORR) per independent review committee. Results: In all, 646 pts were randomized to ELd (n = 321) and Ld (n = 325). At database lock (Nov 29, 2017), 13% (ELd) vs 7% (Ld) of pts remained on treatment; discontinuation was mostly due to disease progression (55 vs 56%). At 5-y FU (minimum 60 mo), ELd showed 27% reduction in risk of progression or death vs Ld (HR 0.73, 95% CI 0.60–0.87) and relative improvement of 50% in PFS rate at 5 y (18 vs 12%). Pts with ≥ very good partial response (ELd 36% vs Ld 30%) had the greatest reduction in risk of progression/death (HR 0.63, 95% CI 0.44–0.89). ORR was 79% (ELd) vs 66% (Ld). G3–4 AEs included blood and lymphatic system disorders (ELd vs Ld: 46 vs 46%), infections (35 vs 27%), vascular diseases (11 vs 8%), second primary malignancies (SPMs; 10 vs 6%), and cardiac disorders (5 vs 8%). Higher rate of any-grade infection (84 vs 75%) and SPMs (17 vs 11%) may reflect longer median duration of treatment with each agent of the ELd vs Ld regimens (ELd vs Ld: 17/17 vs 12/12 mo). Fewer deaths occurred with ELd than Ld (193 vs 208), mostly due to disease progression. Conclusions: Elotuzumab (+ Ld) has the longest median FU of an immuno-oncology agent in MM. At the milestone timepoint of 5 y, ELd showed sustained, durable clinically relevant im-
provement in PFS, a 27% reduction in the risk of progression or death, and a significant benefit with minimal incremental AEs. Further studies are needed. Funding: BMS. Writing support: L. Ye, C. Drexler, funded by BMS. Clinical trial information: NCT01239797.
Background: Real-world longitudinal data on tx sequencing & outcomes are limited: The Connect MM Registry is a US, multicenter, prospective observational cohort study designed to examine diagnostic & tx patterns, clinical outcomes & QoL in pts with NDMM. Using visual tools (Sankey Plots), tx sequences & transitions were longitudinally assessed in pts with NDMM from Connect MM who did or did not receive stem cell transplant (SCT, NSCT). Median Adult pts were enrolled ≥ 60 days from diagnosis in Cohorts 1 (n = 1493; 2009-2011) & 2 (n = 1518; 2012-2016). Tx were classified as containing: 1) immunomodulatory agents, 2) proteasome inhibitors (PI), 3) IMiD® agent + PI, 4) non-IMiD/PI agents (other), 5) tx gaps. Data is presented within Sankey plots, a type of flow diagram in which the proportional flow between variables (or nodes) is visualized. Flows between tx from first to last lines of tx, discontinuation, or death, were visually depicted & median progression-free survival (PFS) for lines 1, 2 & 3 of tx were examined. Results: As of Feb 2017, 966 SCT & 1941 NSCT pts were identified (Table). Points of tx transitions were represented by nodes on the plots corresponding to a change in regimen, such as maintenance (or not), line 2 tx, line 3 tx, discontinuation or death. Substantial heterogeneity of treatment was observed. The most frequent treatment flow among SCT pts was IMiD agent + PI → IMiD agent → Ongoing (O) → Line Not Yet Reached (LNR) (16%); & for NSCT pts was PI → O → LNR (8%). Outcomes per line of therapy were assessed. Median 1st PFS was nearly twice as long in all SCT pts compared to all NSCT pts. In SCT pts, median 1st, 2nd, & 3rd PFS measured from line start were 44.0, 8.3, & 4.5 mo; in NSCT pts, median 1st, 2nd, & 3rd PFS were 21.5, 7.3, & 5.8 mo, respectively. Conclusions: These real-world registry data depict the therapeutic journeys of pts with MM. The PFS by line data are similar to clinical trials of pts with MM. Clinical trial information: NCT01081028.

8043 Poster Session (Board #52), Mon, 8:00 AM-11:30 AM

Real-world evidence of cardiac hospitalizations in carfilzomib- and non-carfilzomib-treated multiple myeloma patients in the United States. First Author: Joseph Mikhael, International Myeloma Foundation, North Hollywood, CA

Background: Approximately 30% of multiple myeloma (MM) patients (pts) are hospitalized for cardiac events after MM diagnosis. Carfilzomib (K), a 2nd generation proteasome inhibitor, was approved to treat MM in 2012. Background: Approximately 30% of multiple myeloma (MM) patients (pts) are hospitalized for cardiac events after MM diagnosis. Carfilzomib (K), a 2nd generation proteasome inhibitor, was approved to treat MM in 2012. Methods: We conducted a matched retrospective claims-based cohort study of MM pts who initiated K or non-K treatment (tmt) between 2012-2015 using the MarketScan data before MM diagnosis. Line of therapy (LOT) and regimens were identified using drug prescription claims. Index LOT was defined as first K-containing LOT. Pts who received non-K regimens were matched 1:1 to K pts on age, sex, and index LOT. Hospitalizations were identified using diagnosis codes in claims during index LOT. Any cardiac hospitalizations (CH) included new and existing cardiac conditions defined as having a cardiac code (arrhythmia, heart failure, ischemic heart disease, cardiomyopathy, hypertension) as primary/secondary diagnoses on the claim; primary CH (PCH) had a cardiac code as primary diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, adjusting for tmt duration and BL conditions. Results: 498 K and 996 non-K pts were identified (median age 61 and 62 yrs, respectively). In both cohorts, 59% were male; 6%, 30%, and 64% were treated in LOT 1, 2, and 3+. Overall, there was no difference in BL cardiac history (84.9% and 84.1%, respectively). Median tmt duration was 10.7 and 12.7 months, respectively. 34% of pts in each cohort were hospitalized. Any CH occurred in 16% and 12% of K- and non-K pts, respectively. Unadjusted OR (95% CI) for CH in K pts vs non-K pts was 1.47 (1.1–2.0). When adjusted for tmt duration, OR (95% CI) of CH in K pts vs non-K pts was 1.1 (0.8–1.5). Similar hospitalization risks were seen when additionally adjusting for BL conditions. PCH occurred in 2% and 3% of K and non-K pts, respectively (unadjusted OR (95% CI) 0.7 [0.4–1.4]; adjusted OR (95% CI) 0.55 [0.3–1.1]). Conclusions: In real world pts, the risk of cardiac-related hospitalizations during tmt was similar for K- and matched non-K treated pts when adjusted for tmt duration and BL conditions. Selection bias may impact the risk estimates.

8044 Poster Session (Board #53), Mon, 8:00 AM-11:30 AM

The MD Anderson modified cyclophosphamide, bortezomib, doxorubicin, and dexamethasone (mCBAD) for the treatment of newly diagnosed (NDMM) and relapsed/refractory multiple myeloma (RRMM). First Author: Samer Tabchi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: MM follows a clinical course leading to refractoriness and limited treatment options in RRMM. Aggressive NDMM needs rapid cytoreduction for disease control, which may not be possible with standard novel therapies. We report on a highly effective therapy that offers a salvage option for these patients. Methods: We reviewed our medical database for MM patients who received mCBAD from 2010-2016 – 28 day cycle of cyclophosphamide 350 mg/m² IV twice daily + mesna 400 mg/m² IV daily (days 1-4), bortezomib 1.3 mg/m² SQ (days 1, 4, 8, 11), doxorubicin 9 mg/m² IV (days 1-4), dexamethasone 40 mg/po on days 1, 4, 8, 12, 14-17, IMWG criteria for response assessment. Descriptive statistics, Fisher’s exact test, Chi-square, Wilcoxon rank sum, and Kaplan-Meier were used for statistical purposes. Results: 80 patients met the inclusion criteria. Baseline characteristics, response, adverse events, FFS/ROS are summarized in Table 1. Median follow-up for the censored observations was 21.3 months (1.35 – 69.22). Conclusions: mCBAD offers excellent response rates (ORR > 90%) and favorable FFS/ROS in highly refractory high risk MM. It is also an excellent salvage regimen with about half of patients undergoing subsequent transplant. Patient selection is required due high treatment related mortality.
**8045 Poster Session (Board #54), Mon, 8:00 AM-11:30 AM**

**Duration of complete response (DurCR) impacts overall survival (OS) in multiple myeloma (MM).** First Author: Sunbhi Sidana, Mayo Clinic, Rochester, MN

**Background:** DurCR has a direct impact on progression free survival in MM, but its impact on OS is not well described. **Methods:** We retrospectively analyzed 351 patients with MM from 2004-16 who achieved CR (IMWG criteria) with first line therapy to assess impact of DurCR (time from achievement to loss of CR) on OS. **Results:** The table lists baseline characteristics. Loss of CR was experienced by 68% (239) patients, with (1) symptomatic progression in 25% (59); (2) biochemical progression in 24% (58); (3) two consecutive partial responses without fixation or rise in monoclonal protein not meeting progression criteria in 37% (88); (4) two abnormal FLC ratios in light chain MM in 14% (34). In group 3, progression was seen in 73/88 (85%) patients (13 symptomatic, 60 biochemical) with median time of loss from CR to progression of 7 months and in 21/34 (62%) patients in group 4 (3 symptomatic, 18 biochemical) with median time of 4 months. After median follow-up of 72 months, median OS from start of therapy with DurCR ≥ 24 (n = 179, 51%) vs. < 24 months (n = 172, 49%) was 150 vs. 80 months, p < 0.001. Estimated 5 and 10 year OS in DurCR ≥ 24 was 95% and 70% and in DurCR < 24 was 66% and 25%, respectively. **Conclusions:** OS from MM, with estimated 5 and 10 year OS with DurCR ≥ 24 was 66% and 25%, respectively. Importantly, majority of patients who experience loss of CR therapy.

**8046 Poster Session (Board #55), Mon, 8:00 AM-11:30 AM**

**Impact of obesity on response in 751 myeloma patients receiving lenalidomide, bortezomib, and dexamethasone (RVD) induction.** First Author: R Donald Harvey, Winship Cancer Institute of Emory University, Atlanta, GA

**Background:** Obesity is a putative risk factor for the development of monoclonal gammapathy of undetermined significance (MGUS) and multiple myeloma (MM). Induction regimens for MM have evolved; and lenalidomide, bortezomib, and dexamethasone (RVD) produces an overall response rate of 82%. Response, tolerability and therapy duration are related to agent dose, dose intensity, and comorbidities, which may be higher in the obese. We analyzed the effect of anthropometric measures on response and therapy duration in patients (pts) receiving RVD induction. **Methods:** Height (cm), weight (kg), body surface area (BSA), and body mass index (BMI) were obtained from a database of 751 pts receiving RVD. Demographics including sex, self-reported race, ISS stage at diagnosis, and cytogenetic risk category were analyzed with anthropometric data in a multivariate model with response per IMWG criteria, progression-free survival (PFS) and overall survival (OS). **Results:** Anthropometric measures were available in 746/751 (99%) pts. Of 746 pts analyzed, 54% were male, 57% white, and 30% black. Median BMI (kg/m²) was 28 (range 17-53); BMI per category was unchanged (18.5 < 25; 25.0-<30; 30.0 <). Median BSA (m²) was 1.94 (range 1.29-2.70). Median BMI and BSA were significantly higher in men (p < 0.05). Morbid obesity was more common in black versus white pts (8.4% vs. 3.8%, p = 0.017) and women versus men (7.9 vs. 3.2%, p = 0.03). Risk of responding to RVD was 98 months compared to pts with BMI < 40 (p = 0.071); unadjusted hazard ratio (HR) 1.47 (95% CI: 0.56-3.49). Response of VGPR or better did not show a significant association with higher BSA (2 > 25) (80.3 vs 70.3 %, p = NS). On multivariate analysis, PFS and OS showed no association with BMI (HR 2.1; 95% CI 1.2-3.6). Risk of elevated hematologic malignancy (HR 2.2; 95% CI 1.5-3.7) were significantly associated with shorter OS (p < 0.001). **Conclusions:** Obesity does not significantly impact depth or duration of response with RVD induction. We advocate use of full dose RVD regardless of BSA or BMI in pts with acceptable performance status and managed comorbid conditions.

**8047 Poster Session (Board #56), Mon, 8:00 AM-11:30 AM**

**Relationship of acquired resistance of myeloma cells to bortezomib with Lyn and Src induction inhibition of PPA2 and effect of treatment with the tyrosine kinase inhibitor dasatinib.** First Author: Barry Paul, Duke University, Chapel Hill, NC

**Background:** Multiple Myeloma (MM) is the second most common hematologic malignancy in the United States. Proteasome inhibitors—especially bortezomib (BTZ)—are a mainstay of treatment in MM, but nearly all patients eventually develop resistance to these agents. We hypothesize that resistant cells are escaping BTZ induced cell killing via dedifferentiation back to the primitive state resulting in inhibition of the tumor suppressive activity of PPA2. **Methods:** MM cell lines (RPMI-Dox, MM1R, and OPM1) were grown in media with increasing concentrations of BTZ over time to select for resistance, and then treated with dasatinib. MTT assays were conducted to confirm BTZ resistance. Sensitive and resistant cells were harvested for protein and RNA and evaluated through standard qRT-PCR, flow cytometry, and immunoblotting methods to determine levels of PPA2-C, Src, and Lyn, as well as the differentiation markers CD138 and IRF4. **Results:** MTT assays verified significant resistance in cells grown with BTZ (mean IC50 225.80 ± 49.76 nM) compared to parental cells (mean IC50 7.02 ± 3.97 nM). Immunoblotting confirmed differential phosphorylation of the Y307 inhibitory site of PPA2-C in the resistant cells. Levels of Src and Lyn RNA and protein were increased in the resistant cells, and treatment with the multikinase inhibitor dasatinib selectively increased cell death in the resistant cells (IC50 1.31 ± 0.11 nM). Additionally, expression of the differentiation markers CD138 and IRF4 was absent in the BTZ resistant cells while being appropriately expressed in the parental cells. **Conclusions:** Our experiments show that inhibition of PPA2 plays a significant role in acquired resistance to BTZ and that this process is primarily driven by increased expression of Src and Lyn. Inhibition of Src and Lyn activity with dasatinib was able to overcome this effect and selectively resensitize the resistant cells. Our data also imply that the resistant cells may be dedifferentiating to a more primitive state as evidenced by absent IRF4 and CD138 expression. These data suggest a role for kinase inhibitors in myeloma patients with acquired resistance to BTZ.

**8048 Poster Session (Board #58), Mon, 8:00 AM-11:30 AM**

**Quality of life and cancer worry in a follow-up cohort of patients with asymptomatic monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).** First Author: Michelle Ann Thoeldt Hildebrandt, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Monoclonal gammapathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM) are monoclonal gammapathies that precede multiple myeloma (MM). Although considered asymptomatic, patients diagnosed with these conditions are at greatly increased risk of developing MM. There is currently limited to no information on quality of life (QOL) or cancer worry/anxiety burden for patients with MGUS and SMM. **Methods:** We implemented a longitudinal QOL and cancer-related worry assessment in an observational cohort study of MGUS and SMM patients at MD Anderson Cancer Center (expected total enrollment of N = 200). Questionnaires included the QLQ-C30 cancer QOL tool and the MY20 myeloma-specific module, as well as questions to measure cancer worry. In this preliminary data analysis, a total of 46 patients completed the baseline questionnaires (MGUS = 17; SMM = 29). **Results:** Overall, individuals with MGUS have a worse QOL compared to SMM patients with MGUS patients reporting a > 12 point lower Global QOL score (71.6 vs 83.9; P = 0.035). Significant differences were also observed for Physical Functioning (P = 0.012), Nausea/Vomiting (P = 0.045), and Pain (P = 0.027). For myeloma-specific QOL and symptoms, MGUS patients again reported higher levels of Back Pain (P = 0.017), Swimming/Sore Eyes (P = 0.021), Restlessness/Agitation (P = 0.026), and Tingling in Hands/Feet (P = 0.031) compared to SMM patients. This increase in reported QOL burden corresponded to MGUS patients less feeling in control of their MM risk compared to SMM patients (P = 0.0038). **Conclusions:** Patients with MGUS self-reported a high QOL burden that was often greater than SMM patients and more closely in line with MM-specific or overall cancer reference values. Further, a sense of loss of control of their MM risk is heightened in MGUS patients. Together, even though MGUS is considered clinically asymptomatic, patients diagnosed with this condition are experiencing reduced QOL is impacting their overall well-being. These results suggest potential opportunities for interventional strategies to improve the lives of patients with monoclonal gammapathies. This work was supported in part by MD Anderson’s Cancer Center Support Grant P30 CA016672.
**8050** Poster Session (Board #59), Mon, 8:00 AM-11:30 AM
Comparative analysis of outcomes in African American (AA) and white (W) patients (pts) with multiple myeloma (MM) treated with lenalidomide (LEN) or pomalidomide (POM) (PI-IMiD). First Author: Sikander Alawadhi, Mayo Clinic, Jacksonville, FL

**Background:** AA are 2-3 fold more likely to develop MM, and racial and ethnic minorities may not have similar access to novel MM treatment (Tx). Outcomes are often worse in AA vs W pts with cancer, but data are mixed in MM. Thus, we compared outcomes in AA and W pts treated with LEN or POM. **Methods:** We performed a subgroup analysis with data from 4 clinical trials. EA403 (Rajkumar et al. Lancet Oncol 2010) used LEN+ high dose dexamethasone (LEN-D or LEN-d) as a first-line MM Tx. CALGB 100104 (McCarthy et al. NEJM 2012) studied LEN or placebo (PBO) maintenance after transplant. MM-009 (Weber et al. NEJM 2007) and MM-002 (Richardson et al. Blood 2014) used LEN-D or PBO-D and POM or POM-d, respectively, for relapsed/refractory MM. We compared baseline characteristics and Tx outcomes in AA vs W pts from the LEN-d arm of EA403, all arms of CALGB and MM-009, and the combined POM and POM-d arms of MM-002. **Results:** Detailed results are in the Table. Baseline characteristics were generally similar in each trial. PFS/OS was longer in AA pts. Neutropenia was the most common hematologic Tx-emergent adverse event across the studies. **Conclusions:** Tx with LEN or POM resulted in similar or better outcomes in AA vs W pts in multiple Tx settings, emphasizing the importance of equitable access to Tx.

**8053** Poster Session (Board #62), Mon, 8:00 AM-11:30 AM
Daratumumab-based therapies in patients with AL amyloidosis. First Author: Jithika P. Abekeye, Department of Internal Medicine, Mayo Clinic, Rochester, MN

**Background:** Treatment options for patients (pts) with relapsed/refractory (RR) AL amyloidosis are limited. Daratumumab (dara) has been approved as monotherapy (DMT) or combination therapy (DCT) for multiple myeloma (MM). Data for dara-based therapy (DT) in AL are sparse. **Methods:** We studied pts with RR AL without coexisting MM seen at Mayo Clinic from 11/2015 to 02/2020 who were treated with DT. Hematological response (HR) and organ response (OR) were defined per Consensus criteria. All time to events were done from the time of DT initiation. Pts with dFLC < 4 mg/dL at the time of start of DCT were considered non evaluable (NE) for HR other than disease progression. DT included dara, pomalidomide & dexamethasone (dex) (35%), dara, lenalidomide & dex (22%), dara, bortezomib & dex (22%) & other DCT regimens (17%). **Results:** 45 pts (DMT, n = 22; DCT, n = 23) received DT; median age at DT initiation was 64 years (range: 46-82). Data for HR assessment were available in 44 pts & 31 were evaluable for HR. HR & end points are outlined in Table 1. Among 13 NE pts, response improved to CR in 5 (38%) while remaining 8 continued to be NE. Of these 13 pts, 77% reached dFLC < 1 mg/dl at a median follow up (FU). Cardiac, renal & liver involvement was observed in 59%, 43%, & 7%; pts. Cardiac, renal and liver OR was 46%, 32%, 0%, respectively. At last FU, 31 pts were on DT. 7% (3pts) had disease progression. Hematological toxicity (HT) from DT included anemia ≥2 grade (G2 = 69%, G3 3%); thrombocytopenia 1 Gr 38%; neutropenia ≥2 G2/1 > 2 G2/3 & G4%. Non-HTs included fatigue (23%), infusion reactions (21%), & treatment-emergent neuropathy (14%). **Conclusions:** DT is safe & effective in heavily pre-treated pts with AL. HR is achieved rapidly with DT, particularly with DCT.

**8054** Poster Session (Board #63), Mon, 8:00 AM-11:30 AM
Characteristics and outcomes of primary plasma cell leukemia in the era of novel agents: Single center experience. First Author: Inman Aboudalloul, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Plasma cell leukemia (PCL) is a rare and aggressive disease characterized by a clonal proliferation of plasma cells in bone marrow and blood. PCL can present as de novo disease without underlying myeloma. The purpose of this study is to describe the clinical characteristics and outcomes of primary (p) PCL in the era of novel agents. **Methods:** This is a retrospective study of patients (pts) with PCL treated at The University of Texas MDACC from 01/1996-12/2017. The Kaplan Meier method was used to estimate progression free survival (PFS) and overall survival (OS). Univariate and multivariate Cox proportional hazards models were used to evaluate the association between a continuous variable and important prognostic covariates, respectively, with time to event endpoints. **Results:** We identified 77 pts with pPCL as defined by International Myeloma Working Group (IMWG) criteria. 64 (83%) pts were treated with immunomodulatory drugs (IMiD) and/or proteasome inhibitors (PI) during induction. Overall response rate was 70% (45 pts) by IMWG response criteria in pts treated with novel agents. 30 pts received consolidation with autologous stem cell transplantation (ASCT). For all pts, median PFS was 11.1 months (mos) (95% CI: 8.6, 14.8), with 8 pts presenting with leptomeningeal disease at the time of relapse. Median OS (mos) from the time of diagnosis was 19.1 mos (95% CI: 15.3-26.1) with a median follow-up of 20 mos. The mos for pts receiving ASCT was 33.6 mos (95% CI: 22.6-40.2). Pts who underwent ASCT had significantly prolonged mos (hr=0.2, 95% CI: 0.11-0.45; p<0.0001) on multivariate analysis. The main cause of death in this disease progression in 84% of pts. **Conclusions:** PCL prognosis can be improved with the incorporation of novel agents and early consolidation with ASCT.

**Baselines characteristics:**

<table>
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Days 1, 8, 15, 22, 29 in Cycle 1; every 2 weeks (Q2W) thereafter, plus V

refractory multiple myeloma (RRMM).

without JNJ-63723283, an anti-PD-1 monoclonal antibody, in relapsed/

treatment of RRMM. DARA produces deep clinical responses in RRMM and

DARA, a human CD38 monoclonal antibody, is approved for

Department of Hematology, AZ St.-Jan Brugge-Oostende AV, Brugge,

enrollment of an additional 300 pts into Part 3 (Phase 3) will be considered if

response, progression-free survival, overall survival, minimal residual dis-

Approximately 440 adult pts with symptomatic MM (International

benefit of ISA plus VRd vs VRd in pts with transplant-ineligible NDMM.

In MM xenograft models. Here we describe a Phase III, randomized, open-

nificantly improves progression-free (PFS) and overall survival compared

prolong survival and improve quality of life. The combination of VRd sig-

the co-primary endpoints are overall

$\text{RRMM must have received}\>$

inhibitor (PI; $\text{RRMM must have received}\>$

$r\text{HuPH20; DARA SC})$ was found to be well tolerated with low

RRMM study, a SC co-formulation of DARA with recombinant human hy-

data is derived from the comparison of efficacy between the PFS curve of

Selinexor is an oral, selective inhibitor of nuclear export that

Sosana Delimpasi, General Hospital of Athens, Athens, Greece

Background: Selinexor is an oral, selective inhibitor of nuclear export that

can resensitize myeloma to PI based therapies. Methods: The BOSTON trial

(NG00110562) is a Phase III study of selinexor in combination with

weekly bort and dex (QW SVd) vs BIW Vd arm, which may be associated with better tolerability

response as well as provide for a considerable reduction (~40%) in overall

site) versus DARA IV (16 mg/kg IV infusion) weekly for Cycles 1-2 (28-day

This is an ongoing phase 3, randomized, open-label, multicenter, non-inferiority study of DARA

in pts with RRMM who have received 1 to 3 prior anti-MM regimens. The QW

regimen of SVd may provide for a higher ORR and improved duration of

response as well as provide for a considerable reduction (~40%) in overall

bort dose vs BIW Vd arm, which may be associated with better tolerability

for pts who are not able to tolerate continued treatment with bort. Progression

Failure survival (PFS) and ORR are primary endpoints. Secondary endpoints

include overall survival and duration of response. An ORR primary analysis is

planned after the last pt randomized has had the opportunity to complete at

least 2 MM evaluations. Clinical trial information: NCT03110562.

randomized, open-label, non-inferiority, phase 3 study of subcutaneous

versus IV treatment in patients with relapsed or refractory multiple myeloma (RRMM): COLUMBA. First

Author: Saad Zafar Usmani, Department of Hematology & Blood

Disorders, Levine Cancer Institute/Carolinas Healthcare System, Charlotte, NC

Background: DARA, a human IgG1k monoclonal antibody that targets CD38,

induces deep and durable responses in patients with RRMM. In a phase 1b

RRMM study, a SC co-formulation of DARA with recombinant human hy-

aluronidase (rHuPH20; DARA SC) was found to be well tolerated with low

infusion-related reaction (IRR) rates. Moreover, response rates were similar to

those observed historically with DARA IV. The phase 3 COLUMBA study will

compare the efficacy, pharmacokinetics, and IRRs of DARA SC versus

DARA IV in patients with RRMM. Methods: This is an ongoing phase 3,

randomized, open-label, multicenter, non-inferiority study of DARA SC

(1,800 mg DARA in combination with rHuPH20[2,000 U/mL] administered

by manual push [15 mL over 3-5 minutes at alternating left/right abdominal

sites]) versus DARA IV (16 mg/kg IV infusion) weekly for Cycles 1-2 (28-day

cycles), every 2 weeks for Cycles 3-6, and every 4 weeks thereafter until

disease progression or unacceptable toxicity. Pre- and/or post-infusion

medications include paracetamol, diphenhydramine, methylprednisolone,

and an optional leukotriene inhibitor. Eligible patients (≥18 years) with

RRMM must have received ≥3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory

drug (IMiD), or have disease that is double refractory to both a PI and an IMiD. Pts

must have demonstrated evidence of response to ≥1 prior treatment regimen. Pts

previously treated with anti-CD38 therapy, including DARA, or anti-PD-1

and anti-PD-11 antibodies are excluded. Approximately 6 pts will be enrolled in

Part 1 (safety run-in cohort of DARA + JNJ-283). If < 2 pts experience a
dose-limiting toxicity, the study will proceed to Part 2 (Phase 2) in which

80 pts will be randomized 1:1 to the 2 treatment arms. The primary endpoint

is overall response rate, and secondary endpoints include safety, ≥complete

response and ≥very good partial response rates, duration of response, time to

response, progression-free survival, overall survival, minimal residual dis-

ease, and pharmacokinetics/immunogenicity of DARA and JNJ-283. En-

rollment of an additional 300 pts into Part 3 (Phase 3) will be considered if

the efficacy endpoint is met at the end of Part 2 and JNJ-283 is deemed safe in


Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: DARA, a human IgGκ monoclonal antibody targeting CD38, is approved in the United States and Europe for use as a monotherapy and in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone in pts with RRMM. In a phase Ib study, DARA + pom-dex demonstrated efficacy and tolerability in pts with RRMM, leading to the approval of this regimen for pts with RRMM in the United States. This phase 3 study will evaluate the efficacy and safety of DARA + pom-dex versus pom-dex alone in RRMM. **Methods:** This is an ongoing multicenter, open-label, phase 3 study of DARA + pom-dex versus pom-dex alone. RRMM pts who have received prior anti-myeloma therapy, including a proteasome inhibitor and a lenalidomide-containing regimen, have responded to prior therapy, and have progressed on or after their last regimen, are eligible. Pts who have received only 1 prior line of therapy must have progressed ≤60 days of completing the lenalidomide-containing regimen. All pts will receive pom 4 mg orally on Days 1-21 of a 28-day cycle × 60 mg/QW (20 mg for pts ≤75 years of age). Following a protocol amendment, pts in the DARA group will receive subcutaneous DARA (1,800 mg co-formulated with recombinant human hyaluronidase [rHuPH20]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W thereafter. All pts will receive preinfusion medications (including diphenhydramine, paracetamol, dexamethasone, and an optional leukotriene inhibitor), and postinfusion medications (including diphenhydramine, lung disease control medications, and a short-acting β2 adrenergic receptor agonist) will be recommended for pts with a higher risk of respiratory complications. Progression-free survival is the primary endpoint. Secondary endpoints include safety, overall survival, overall response rate, duration of response, and minimal residual-disease-negative rate. Approximately 302 pts will be enrolled across 11 countries. Clinical trial information: NCT03180736.

**TPS8061** Poster Session (Board #67a), Mon, 8:00 AM-11:30 AM

A phase 1/2, multicenter, dose-escalation and expansion study of combination therapy with venetoclax, daratumumab, and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma. First Author: Orlando Bueno, AbbVie Inc., North Chicago, IL

**Background:** Despite the introduction of new compounds to manage relapsed/refractory (R/R) multiple myeloma (MM) over the last decade, none are curative. Trials investigating novel agents or combinations are critical to advancing therapy. Overexpression of BCL-2 may contribute to the pathogenesis of t(11;14)-positive MM. Venetoclax (Ven) is a selective, potent, orally bioavailable BCL-2 inhibitor with activity in R/R (t(11;14)-positive MM. Daratumumab, bortezomib, and dexamethasone is an FDA-approved triplet for MM. The addition of Ven to this regimen (VenD) may result in additive antitumor effects via complementary mechanisms. **Methods:** This phase 1/2, multicenter study of Ven, daratumumab, and dexamethasone, with or without bortezomib, in R/R MM (NCT03314181) will have 2 parts, each with a dose-escalation and dose-expansion phase. Part 1 will evaluate Ven, daratumumab, and dexamethasone (VenD) in t(11;14)-positive patients who have had ≥ 3 prior therapies including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to both. The dose escalation phase will evaluate safety and tolerability; the randomized, blinded, expansion phase will assess the objective response rate of VenD versus placebo-DD. Part 2 will examine VenD and bortezomib (VenDv) in patients who have received 1-3 prior therapies and are not PI-refractory. The dose escalation phase will evaluate safety and tolerability; the single-arm, open-label expansion phase will assess efficacy per the International Myeloma Working Group (IMWG) criteria. A Bayesian Optimal Interval (BOI) design will be used to guide dose escalation/de-escalation decisions in Parts 1 and 2. Secondary objectives will include progression-free survival, duration of response, time to progression, minimal residual disease negativity, and pharmacokinetics and immunogenicity profiles of the Ven/ daratumumab combinations. Exploratory objectives include evaluation of pharmacodynamic and predictive biomarkers associated with outcomes. Clinical trial information: NCT03314181.

**TPS8062** Poster Session (Board #68b), Mon, 8:00 AM-11:30 AM

Randomized, open-label, phase 3 study of subcutaneous daratumumab (DaraSC) versus active comparator (AvC) in patients (Pts) with high-risk symptomatic multiple myeloma (SMM): AQUILA. First Author: S Vincent Rajkumar, Division of Hematology, Mayo Clinic, Rochester, MN

**Background:** Current guidelines for SMM recommend active monitoring for progression to symptomatic MM before initiating treatment as standard of care. Earlier treatment may benefit pts with SMM at high risk of progression. DARA, a CD38-targeted monoclonal antibody, is approved as monotherapy and in combination with standard of care for relapsed/refractory MM (RRMM). In a phase 1b RRMM study, a SC co-formulation of DARA with recombinant human hyaluronidase (rHuPH20; DARA SC) showed low infusion reaction rates and similar response rates to those seen with intravenous (IV) DARA in RRMM. Given the encouraging single-agent activity of IV DARA observed in a phase 2 SMM study (12-month PFS rate: 95%), we hypothesized that DARA SC may delay progression of high-risk SMM to MM compared with active monitoring. **Methods:** AQUILA is an ongoing, phase 3, randomized, open-label, multicenter study of DARA SC (1,800 mg DARA + rHuPH20 [2,000 U/mL] administered by manual injection (15 mL) over approximately 5 minutes at alternating abdominal locations QW for Cycles 1 and 2, Q2W for Cycles 3-6, and Q4W thereafter for up to 39 cycles or 36 months; 28-d cycles) versus active monitoring (no study medication). Eligible pts (≥ 18 yr) have had a confirmed diagnosis of SMM for ≤5 y, have factors indicating a high risk of progression (clonal bone marrow plasma cells [BMPCs] ≥10%; 1 of the following: serum M protein ≥30 g/L, IgG SMM, immunopaenia with reduction of 2 uninvolved Ig isotypes, serum uninvolved:uninvolved free light chain ratio ≥8- < 100, or clonal BMPCs > 50% -< 60% with measurable disease), and have an ECOG performance status of ≤ 1. The primary endpoint is PFS as assessed by an independent review committee. Secondary endpoints include time to biochemical or diagnostic (SLIM-CRAB) progression, ORR, complete response rate, duration of time to response, time to first-line treatment for MM, progression-free survival on first-line treatment for MM (PFS2), incidence of MM with adverse prognostic features, and OS. Disease will be evaluated per International Myeloma Working Group response criteria. Approximately 360 pts will be randomized (1:1) to the 2 arms. Clinical trial information: NCT03301220.
First Author: Greg Andrew Dunn, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

**Background:**
Concurrent chemoradiation (CRT) has been the standard Rx for pts with unresectable stage III NSCLC. A recent phase III trial (PACIFIC) of consolidation durvalumab (PD-L1 inhibitor) demonstrated improved median PFS vs. placebo (16.8 vs. 5.6 mo, HR 0.52, p < .001). 12-mo (55.9% vs. 35.3%) and 18-mo (44.2% vs. 27%) PFS were also improved. Toxicity was manageable with a grade 3-4 pneumonitis rate of 3.4%, and 4 patients experienced grade 5 pneumonitis. We report the results of a phase 2 trial of consolidation pembrolizumab (PD-1 inhibitor) following concurrent CRT in patients with unresectable stage III NSCLC.

**Methods:** After completion of CRT with carbop/pac, cis/etop, or cis/pemetrexed + 59-66.6 Gy XRT, those pts w/o PD after 4-8 weeks off CRT received pembrol 200 mg IV q3wk for up to 1 yr. The primary endpoint was time to metastatic disease or death (TMDD). Key secondary endpoints included PFS, OS, and toxicity.

**Results:** 93 pts enrolled (29 eligible for efficacy analysis). Median Tu was 16.4 mo and median age 66 (45-84). 64.1% male and 35.9% female. Stages were 95.6% IIIA and 40.2% IIIB. Pts 95.4% non-SqCC and 43.5% SqCC with 1 mixed histology, 94.6% were current/former smokers. Chemo regimens included carbop/pac (71.7%), cis/etop (26.1%), cis/pemtremexed (2.2%). Median number of cycles of pembrol was 13.5 (1-19), 16% received < 4 cycles; 84% received > 4 cycles; 37% completed 1 yr pembrol. Median TMDD was not reached (95% CI 18.7-NR), but the estimates of 1-yr and 2-yr OS were 80.5% and 68.7% respectively. Median PFS was 15.4 months (95% CI 10.4-11.9), 12, 18, and 24-month PFS were 59.9%, 49.5%, and 45.4% respectively. 16 (17.2%) pts developed G2 pneumonitis, 5 (5.4%) had G3-4 pneumonitis. There was 1 pneumonitis-related death. In those developing pneumonitis, the median time was 8.4 wks (1.1-48.2). No other G 3/4 toxicities exceeded 5% except dyspnea (5.4%).

**Conclusions:** Consolidation pembrolizumab following CRT substantially improves TMDD and PFS compared with historical controls. Prelim OS data is promising and suggests a substantial gain in outcomes of patients with stage III NSCLC is possible with consolidation pembrolizumab. Clinical trial information: NCT02343952.

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**Pragmatic study of a lymph node (LN) collection kit for non-small cell lung cancer (NSCLC) resection.
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First Author: Raymond U. Osarogiagbon, Baptist Cancer Center, Memphis, TN

**Background:** Surgical resection is the curative modality for NSCLC, but overall survival (OS) rates vary with quality of pathologic (p) LN staging. We studied the impact of a pre-labeled LN collection kit on pLN staging quality, operative (OP) complications and OS.

**Methods:** Prospective, population-based multiple baseline, staggered implementation study involving all patients undergoing curative-intent NSCLC resection in all eligible hospitals (n=594) to 158 NSCLC cases. Kit cases were older v non-kit cases (mean 68 v 67 years, p = .026). Race (p = .12), sex (p = .089), insurance (p = .001), LN staging quality: pNX rate 0 v 4%, no mediastinal LN 2 v 18%; attainment of NCCN quality criteria (RO + anatomic resection + >1 N1 + >3 mediastinal LN stations) 77 v 31% (p < .0001 for all); 60-day readmission 15 v 1% (p = .35); 60-day mortality 3% v 5% (p = .02). With 20 months median follow up, 3-year OS was 59% in kit v 54% in non-kit cases (p = .005). Kit cases had > 30% reduction in both HR (.67 [.50 - .89], p = .005) and aHR (.57 [.42 - .77], p < .001). In sensitivity analyses excluding sub-lobar resections, 60-day mortality, and non-adopting surgeons (to evaluate the possible impact of higher performing surgeons using the kit), aHR ranged from .54 to .61 (all p < .013).

**Conclusions:** A LN collection kit improves staging quality and OS without adding to morbidity of curative NSCLC resection.
Inherited predisposition to malignant mesothelioma (MM) due to mutations in DNA repair genes. First Author: Raffat Hassan, Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, Bethesda, MD

Background: Identifying the profile of DNA repair genes predisposing to MM will enable treatment options for patients (pts) and risk assessment for their families. Methods: In this prospective study of the natural history of MM (NCT01950572) we enrolled 239 consecutive pts independent of site of disease, family history of cancer, age at diagnosis, ethnicity, or asbestos exposure. Germline DNA was sequenced for all 239 pts, identifying mutations of all classes in 73 DNA repair genes. Tumor DNA from 60 pts with germline BAP1 mutations was evaluated by whole exome sequencing. Results: Of the 239 pts, 29 (12%) carried a pathogenic germline mutation in a DNA repair gene: BAP1 (N = 17 pts), CHEK2 (N = 5), PALB2 (N = 2), and BRCA2, MLH1, P101, TP53, and MRE11A (N = 1 each). Pts with mutations were more likely to be female (P = 0.02) and to have been diagnosed with another cancer (P = 0.009). Pts with germline mutations were more likely to have a 1st relative with a diagnosis of MM (P < 0.0001), melanoma (P = 0.003), or breast cancer (P = 0.022). Pleural MM pts with germline mutations had better overall survival than pts without mutations (median 7.9 vs 2.1 years, P = 0.003). The median survival of pts with 1st degree germline exposure between pts with or without mutations (P = 0.64). Tumors from all 12 pts with germline BAP1 mutations carried a second somatic event likely to lead to complete loss of BAP1 function. Five tumors had somatic stop mutations, 2 somatic missense mutations, 4 somatic loss of part or all of the BAP1 locus and 1 copy neutral loss of one allele (CNLOH). Conclusions: Among unselected MM pts, 7% carried a pathogenic mutation in BAP1 and 5% carried a pathogenic mutation in another DNA repair gene, which have not been previously described in MM. Analysis of more pts is important to evaluate if increased MM risk is conferred by any of these genes. Mutation carriers and their 1st relatives were at increased risk of developing MM, melanoma, or breast cancer. Genetic testing for germline mutations in DNA repair genes should be considered for MM pts since it has implications for both pts and their relatives. Finally, we suggest that, pts with BAP1-null tumors due to both germline and somatic mutations could be sensitive to PARP inhibitors. Clinical trial information: NCT01950572.

Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. First Author: Hyun Cheol Chung, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, Republic of (South)

Background: The antitumor activity of pembrolizumab, a IgG4 anti- PD-1 monoclonal antibody, was evaluated in patients (pts) with SCLC in KEYNOTE-158 (NCT02628067), a phase 2 basket study of 11 cancer types. Methods: Enrolled pts were aged ≥18 y with advanced SCLC; had measurable disease per RECIST v1.1; ECOG PS ≤1; incurable disease with prior failure of, progression on, or intolerance to standard therapy; and evaluable tumor samples for PD-L1 (PD-L1 IHC 22C3 pharmDx assay [Agilent Technologies]) and other biomarkers. Pembrolizumab 200 mg Q3W was administered for 2 y or until disease progression or intolerable toxicity. The primary endpoint was ORR. DOR, PFS, and OS were secondary endpoints. The trial was stopped early after the data cutoff date (Aug 23, 2017). Results: 36 pts (34%) were continuing on-study; median follow-up was 10.1 mo (range, 0.5–17.5). Tumors were PD-L1–positive in 42 pts (39%) and PD-L1–negative in 50 (47%); 8 had microsatellite instability-high (MSI-H) tumors and 83 (78%) had microsatellite-stable ( MSS) tumors. ORR was 18.7% (20/107; 95% CI, 11.8–27.4) overall, 35.7% (15/42; 95% CI, 21.6–52.0) in pts with PD-L1–positive tumors, and 6.0% (3/50; 95% CI, 1.3–16.5) in pts with PD-L1–negative tumors. Overall, median DOR had not been reached (range, 2.1+ to 13.2+ mo; 12 pts (77%) had DOR >9 mo. Median PFS was 2.0 mo (95% CI, 1.9–2.1) in all pts, 2.1 mo (95% CI, 2.0–9.9) in pts with PD-L1–positive tumors, and 1.9 mo (95% CI, 1.6–2.0) in pts with PD-L1–negative tumors. Median OS was 9.1 mo (95% CI, 5.7–14.6) overall, 14.6 mo (5.6–not estimable) in pts with PD-L1–positive tumors, and 7.7 mo (95% CI, 3.9–10.4) in pts with PD-L1–negative tumors. Treatment-related AEs occurred in 63 pts (59%) and led to 4 discontinuations and 1 death (pneumonia). Conclusions: Pembrolizumab has shown promising antitumor activity and durable responses in advanced SCLC, especially in pts with PD-L1–positive tumors. Clinical trial information: NCT02628067.

Efficacy and safety of rovalpituzumab tesirine in patients With DLL3-expressing, 3L SCLC: Results from the phase 2 TRINITY study. First Author: David Paul Carbone, Ohio State University, Columbus, OH

Background: Small cell lung cancer (SCLC) accounts for ~15% of lung cancer with no approved therapies in 3L (line 3) patients (pts). In 3L pts, historical data demonstrate a median overall survival (mOS) of 4.7 mo and a best overall response of 18%; no historical data exist for objective response rate (ORR). Rova-pituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting Delta-like 3 protein (DLL3), an atypical Notch ligand that is highly expressed in SCLC but not normal tissue. A Ph1 study showed that Rova-T has antitumor activity in pts with recurrent SCLC and high DLL3 expression, and a manageable safety profile. Methods: TRINITY was an open-label, single-arm, Ph2 study of Rova-T in adult pts with DLL3-expressing, 3L SCLC (NCT02674568). Eligibility: ≥ 2 prior systemic regimens including ≥ 1 platinum-based regimen; ECOG 0-1; stable CNS disease. Pts received 0.3 mg/kg Rova-T intravenously on Day 1 of a 6-week cycle for 2 cycles. 3L-DLL3 (high) pts had ≥ 75% tumor cells positive by immunohistochemistry; DLL3-positive (pos) pts had ≥ 25%. Endpoints: confirmed ORR, overall survival (OS). Results: Interim analysis (Oct 17) included 199 pts, of which 64% were 3L Common drug-related adverse events (AEs) were fatigue (32%), photosensitivity (31%), pleural effusion (26%), peripheral edema (26%), thrombocytopenia (23%). Drug-related Grade 3/4 AEs were thrombocytopenia (15%), photosensitivity (7%), pleural effusion (14%) and ≥ 5% (Table). In DLL3-pos pts, median progression-free survival (mPFS) was 4.1 mo, mOS = 6.7 mo. Conclusions: Rova-T demonstrated antitumor activity and a favorable benefit-risk profile in ≥ 3L SCLC pts, with clinically meaningful mOS and mPFS. Updated analysis will be shown at presentation. Clinical trial information: NCT02674568.

Impact on health-related quality of life of the addition of bevacizumab to cisplatin-pemetrexed in malignant pleural mesothelioma in the MAPS phase III trial. First Author: Virginie Westeel, University of Franche-Comtè, Besancon, France

Background: The IFTC-GFPC-0701 MAPS phase III trial highlighted a significant improvement in overall survival with the addition of bevacizumab to the standard first-line chemotherapy regimen, cisplatin plus pemetrexed, in advanced malignant pleural mesothelioma. We present the results of health-related quality of life (HRQoL), a secondary endpoint of MAPS. Methods: HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the Lung Cancer specific module QLQ-LC13 at randomization and then every 9 weeks until progression. HRQoL deterioration-free survival (QFS), used to analyze longitudinal HRQoL data, was defined as the interval between randomization and the occurrence of the first clinically important deterioration of at least 5 points or death. Univariate and multivariate cox regression models were done to analyze variables associated with the QFS, including treatment arm. Results: A total of 448 pts were included in the MAPS trial between 2008 and 2014. At baseline, 428 pts (95.5%) completed the HRQoL questionnaire. We showed that the addition of bevacizumab to cisplatin and pemetrexed significantly improved QFS for two HRQoL dimensions; pain (Hazard Ratio (HR) = 0.81, 95% CI 0.67–0.89; p = 0.002) and peripheral neuropathy (HR 0.73, 95% CI 0.6–0.89, p = 0.002). A performance status 0-1, a hemoglobin level > 14g/dl and epithelioid histology were all associated with a longer 4Ps. Conclusions: This study showed that adding bevacizumab to standard chemotherapy in patients with advanced malignant pleural mesothelioma not only enhanced progression-free survival and overall survival, but resulted in a significant improvement in HRQoL. Clinical trial information: NCT010651456.
8508 Poster Discussion Session; Displayed in Poster Session (Board #114), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Final overall survival for CSLC 0501: Phase 3 study of adjuvant versus neoadjuvant chemotherapy with docetaxel combined carboplatin for resectable stageIB-IIIA non-small cell lung cancer. First Author: Xue-ning Yang, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China

Background: Adjuvant or neoadjuvant chemotherapy increased 5% survival compared with surgery alone for completely resected stage II-IIIA NSCLC. No significant difference in overall survival among adjuvant vs neoadjuvant surgery was found in NATCH study. Clinical issue is how to select adjuvant or neoadjuvant therapy for resectable NSCLC. Methods: Patients with stage IB-IIIA NSCLC were eligible. Adjuvant or neoadjuvant chemotherapy regimen was designed as 3 cycles DC (Docetaxel: 75mg/m2, Carboplatin:AUC = 5 on day 1 every 3wks). The primary end point was 3yrs disease Free Survival (DFS) rate; secondary end points were 3yrs and 5yrs Overall Survival (OS) and DFS. The trial was closed early due to stage IB was not eligible since 2008 and slow accrual. The preliminary results were reported at 2013 ASCO & 2016 ESMO. Results: 214 patients were screened from 13 sites from March 2006 to May 2011, 198 patients were randomized. 97 were assigned to neoadjuvant (N) arm and 101 to the adjuvant (A) arm. Stage Ib ii and Ila were 32.5%, 40.6% and 26.9%, respectively. 100% cases received neoadjuvant chemotherapy and 85.1% completed the planned adjuvant chemotherapy. ORR was 34% and 12.4% patients developed PD in N arm. The 3yrs DFS rate was 53.4% (A) vs 42.0% (N) with 0.030 CI 0.32-0.55 P < 0.01. DFS rate in a next step, the 1-year progression-free survival will be evaluated. The trial was closed early due to not enough patient. Conclusions: Nicols study showed arm A was superior to arm N. Adjuvant chemotherapy or neo-adjuvant with docetaxel plus carboplatin are feasible and safe in resectable clinical stage IB-IIIA NSCLC. Clinical trial information: NCT0321334.

8510 Poster Discussion Session; Displayed in Poster Session (Board #116), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-RTO regimen in unresectable locally advanced NSCLC: The ETOP NICOLAS phase II trial. First Author: Solange Peters, Oncology Department, Lausanne University Hospital, Lausanne, Switzerland

Background: The feasibility of combined chemo-radiotherapy (chemo-RTO) and concurrent PD-1 inhibition is of high scientific interest and has shown promising results in preclinical models and in a clinical trial. The primary safety endpoint is defined as the rate of pneumonitis grade ≥3, but checkpoint inhibition and radical thoracic RT has never been assessed in a clinical trial. Methods: NICOLAS is a phase II trial evaluating the safety of the addition of nivolumab to first-line chemo-RTO in stage III NSCLC. Efficacy will be evaluated if a safety conclusion has been achieved, based on a hierarchical design. Patients received 3 cycles of platinum-based chemotherapy (etoposide, vinorelbine or pemetrexed) and radical RT of 66 Gy. Nivolumab treatment (240 mg/Q4W) started concurrently to RT. The primary safety endpoint is defined as the rate of pneumonitis grade ≥3 at 6 months post RT. An interim analysis was scheduled when the first 21 patients reached 3 months follow-up after completion of RT, based on the assumption that 70% of the pneumonitis events occur within the first 3 months. An early positive safety conclusion is reached at interim analysis if there is no incidence of pneumonitis grade ≥3 in the initial 21 patients (exact group sequential design at one-sided significance level of 0.05 and power = 83%, testing a 6-month pneumonitis rate ≥33% versus <15%). Results: Up to December 14, 2017, 49 patients have been recruited with a median follow-up of 6.6 months (95% CI: 5.6, 7.8). The median age is 63 years, with the majority of the patients being male (67.3%), former smokers (75.5%) and with tumor stage IIb (65.3%). The most frequently observed adverse events (AEs) were grade 1-2 (92% CI 0.90-0.95). While, no statistically significant difference between both arms was found as an alternative for operable patients.

8509 Poster Discussion Session; Displayed in Poster Session (Board #115), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Comparative efficacy and safety of pemetrexed plus paclitaxel plus thoracic radiation therapy (TRT) in elderly patients with nonsquamous locally advanced NSCLC. First Author: Ge Bai, Cancer Center, The First Affiliated Hospital of Xinjiang Medical University, Ürümqi, China

Background: Concurrent chemoradiotherapy is the standard treatment of locally advanced NSCLC, which can significantly reduce the risk of death and prolong the survival of patients. As we focus on the tolerance and side effects of elderly patients with concurrent chemoradiotherapy. The purpose of this study is to compare the efficacy and safety of Pemetrexed versus Paclitaxel plus thoracic radiation therapy (TRT) in elderly patients with locally advanced nonsquamous NSCLC, to provide the basis for the choice of the best chemotherapy for elderly patients. Methods: Patients (66 years-75 years) with stage IIIIB unresectable nonsquamous NSCLC in our single center, randomly received (1:1) pemetrexed 500 mg/m2 d1 every 3 weeks plus concurrent TRT (arm PEM), or paclitaxel 45 mg/m2 d1 every 4 weeks plus concurrent TRT (arm PAC). TRT: 60–66 Gy/2 Gy/30–33 FR IMRT radiotherapy. Results: Eighty-two patients were eligible to enter the group and completed treatment (41 in arm PEM, 41 in arm PAC). The objective remission rate (CR+PR) of PEM group was significantly higher than PAC group (72.0% vs 56.0%; P= 0.037). The incidence of radioactive pneumonia PEM group was lower than PAC group (20.1% to 31.1%; P= 0.033). The most frequently observed toxicity was grade 1-2 (92% CI 0.90-0.95). While, no statistically significant difference between both arms was found as an alternative for operable patients.

8511 Poster Discussion Session; Displayed in Poster Session (Board #117), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Long-term survival comparison of stereotactic radiotherapy versus surgery for elderly patients with clinical stage T1-T2 non-small cell lung cancer. First Author: Feng-Ming Spring Kong, Indiana University Department of Radiation Oncology, Indianapolis, IN

Background: There are several matched-paired analysis reports of comparing the long-term outcome between Stereotactic Body Radiation Therapy (SBRT) and surgical resection. Most of them are small series. This study aimed to compare the long-term overall survival (OS) after SBRT and surgery from a single medical center with surgery performed with the same group of surgeons. Methods: We used our cancer registry of 2005-2015. Patients with clinical staged T1 and T2 N0 diseases treated with either primary surgery or SBRT. Only patients elder than 65 years. The log rank p-value was used for overall survival comparison between the groups. Cox regression was used for univariate test for age, gender, race, smoking history, alcohol use, primary site location, laterality, T stage, and histology grade. Variables with p < 0.05 from univariate analysis were then used for propensity score based matching to compare the effect of surgery or SBRT on overall survival. Results: A total 1244 patients with clinically staged T1-T2 N0 NSCLC, 774 patients were elder than 65 years and matched: 508 patients with surgery and 266 patients with SBRT. The median age was 73 years (range: 65-96 years), 50% were male, and 67% had T1 disease. Median follow-up was 60 months. Age (p < 0.001), gender (p = 0.007), primary lobar location, middle and lower lobe (p < 0.001), grade of 1, 2, 3, and 4 (p = 0.001) and treatment modality of surgery versus SBRT (P < 0.001) were all significantly associated with OS under univariate analysis. The median OS and survival rates at one-, three- and five years were 85%, 75%, and 65% respectively, and between SBRT and surgery, there was hardly any statistically significant difference between both arms. The early interim safety analysis provides evidence that patients treated with surgery have significantly better long-term survival than that of SBRT in elderly patients. This result varies from some of previous reports showing similar survival between SBRT and surgery. Long-term survival comparison of stereotactic radiotherapy versus surgery for elderly patients with clinical stage T1-T2 non-small cell lung cancer.
Phase II trial of stereotactic body radiation therapy for operable T1N0MO non-small cell lung cancer: Japanese Clinical Oncology Group (JCOG0403)—Long term follow-up results. 

**First Author:** Yasushi Nagata, Hiroshima Univ Hosp, Hiroshima, Japan

**Background:** The purpose was to evaluate the safety and efficacy of stereotactic body radiation therapy (SBRT) in patients (pts) with both operable and inoperable T1N0MO non-small cell lung cancer (NSCLC) (UICC 6th ed., 2002). The 3 and 5 year follow-up results were previously published. This is the updated report with a 10-year follow-up for the operable population.

**Methods:** The eligibility criteria included NSCLC, clinical T1N0MO, operable pts assessed by thoracic surgeons. Operability was reclassified by the study coordinator after registration and before the primary analysis. The prescription was 48 Gy at the isocenter in 4 fractions over 4-8 days. The primary endpoint was the 3-year overall survival (OS) and the secondary endpoints included progression-free survival (PFS), local-progression free survival (LPFS), event-free survival (EFS) and toxicity.

**Results:** Between July 2004 and May 2007, 65 operable pts were registered and 64 eligible pts were included in the efficacy analysis. The pts characteristics were: male 45, female 20; median age 79 (range 50-91). All pts completed the protocol treatment. At the last follow-up in February 2017 (median follow-up is 5.2 years), 20 died with disease, 24 died with other disease, 1 with treatment-related death, 2 died with unknown reason and 17 alive. The median survival was 5.6 years (95% CI: 2.1 - 9.3) (95% CI: 4.1 - 9.3)) years. There was no significant difference in OS between SBRT and E treatment. At 3 years, 31 of 64 (48.7%) patients remained alive, while 21 of 64 (32.8%) pts were dead (p = 0.009). At 5 years, 21 of 64 (32.8%) patients were alive, 31 of 64 (48.7%) patients were dead (p = 0.026). The 10-year OS rate was 23.5% (95% CI: 13.7% - 33.3%).

**Conclusions:** SBRT seems to be a safe and effective treatment option for selected pts with operable T1N0MO NSCLC. The 3- and 5-year OS rates are similar to those obtained with ERT. However, the 10-year OS rate was lower than the previous report. This may be due to the difference in the selection criteria.

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**Phase II trial of stereotactic body radiation therapy for operable T1N0MO non-small cell lung cancer: Japanese Clinical Oncology Group (JCOG0403)—Long term follow-up results.**

**First Author:** Yasushi Nagata, Hiroshima Univ Hosp, Hiroshima, Japan

**Background:** The purpose was to evaluate the safety and efficacy of stereotactic body radiation therapy (SBRT) in patients (pts) with both operable and inoperable T1N0MO non-small cell lung cancer (NSCLC) (UICC 6th ed., 2002). The 3 and 5 year follow-up results were previously published. This is the updated report with a 10-year follow-up for the operable population.

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8516 Poster Discussion Session; Displayed in Poster Session (Board #122), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

The TCGA malignant pleural mesothelioma (MPM) project: VISTA expression and delineation of a novel clinical-molecular-subtype of MPM. First Author: Marc Ladanyi, Memorial Sloan Kettering Cancer Center, New York, NY

Background: To expand the understanding of MPM biology and pave the way for novel therapeutic strategies, The Cancer Genome Atlas (TCGA) Research Network conducted a comprehensive integrated genomic study of MPM.

Methods: We performed whole exome, mRNA, miRNA, and non-coding RNA sequencing, copy number analysis, DNA methylation, and protein array profiling on 74 rigorously reviewed and annotated MPM cases with no prior radio- or chemotherapy, followed by integrated data analyses. Findings were extended or validated using additional external datasets.

Results: Three key findings emerged from the analyses of this comprehensive integrated genomic dataset. First, we defined a novel subtype of MPM characterized by extensive loss of heterozygosity, (genomic near-haploidization), and inactivating mutations in TP53 and SETDB1, which encodes a histone methyltransferase involved in epigenetic gene silencing. SETDB1 mutations appear specific to this novel subset of MPM, which accounts for approximately 3% of MPM patients, is more frequently found in younger and female patients and shows little or no linkage to asbestos exposure. Second, we detected strong expression of the immune checkpoint molecule VISTA (aka, PD1-H (PD1 homolog) or B7-H5) in MPM, particularly in the more differentiated epithelioid subtype, where it is higher than in any other cancer type studied by TCGA. Immunohistochemistry confirmed expression was confined to epithelioid MPM tumor cells and in normal and reactive mesothelium, suggesting that its expression in epithelioid MPM may reflect retention of mesothelial cell antigen presenting properties. Thirdly, through the most comprehensive analysis of BAP1 status in MPM to date, we found the overall inactivation rate of BAP1 alterations to be 57%, and defined their downstream effects in terms of gene expression, transcriptional networks, and immune cell reactivity. Conclusions: Our findings highlight new avenues for further investigation of MPM biology and novel therapeutic options. In particular, our findings provide both a rationale and a biomarker for clinical trials of emerging anti-VISTA immunotherapies in this highly lethal cancer.

8517 Poster Discussion Session; Displayed in Poster Session (Board #123), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). First Author: Daniel C. Cho, Perlmutter Cancer Center at NYU Langone Medical Center, New York, NY

Background: Treatment options for ED-SCLC are limited, with standard first-line platinum and etoposide and second-line topotecan having limited clinical activity. Beyond these agents, no approved therapy prolongs survival. Dual checkpoint inhibition with the anti-PD-L1 durvalumab in combination with the anti-CTLA-4 tremelimumab has demonstrated a manageable safety profile and clinical activity in several solid tumor types. Here we present safety and clinical activity data for the combination in pretreated patients with ED-SCLC.

Methods: In this phase 1 dose-exploration and expansion study, patients with ECOG PS 0–1 received durvalumab 20 mg/kg every 4 wks in combination with tremelimumab 1 mg/kg every 4 wks for 7 doses, then every 12 wks for 2 doses, followed by durvalumab 10 mg/kg every 2 wks for up to 12 mos, with retreatment permitted for progression after 12 mos of therapy. Antitumor activity was evaluated by investigator-assessed RECIST v1.1.

Results: As of 20 Oct 2017, 30 patients (median age 63.9 y, 57% male, 70% ECOG PS 1) received treatment in the expansion phase. All patients had prior systemic therapy (median 2 prior therapies); 19 patients were platinum resistant/refractory. 20 patients (67%) reported ≥1 treatment-related AE (TRAE); the most common were fatigue (n = 7 [23%]) and pruritus (n = 7 [23%]); 7 patients (23%) had grade 3/4 TRAEs. No patients withdrew due to TRAEs and there were no treatment-related deaths. Confirmed ORR was 13.3% (2 CR, 2 PR; 95% CI 3.8–30.7), including 3 platinum resistant/refractory patients (1 CR with 2 prior therapies, 2 PR each with 1 prior treatment); median duration of response was 18.9 mos (95% CI 16.3–18.9). Disease control rate at 16 wks was 20.0% (95% CI 7.7–38.6). Median PFS was 1.8 mos (95% CI 1.0–1.9); median OS was 7.9 mos (95% CI 3.2–15.8), and 12-mo OS rate was 41.7% (95% CI 23.3–59.2). In addition, one patient with a brain metastasis was continuing in follow-up > 2 years after starting treatment. Conclusions: Durvalumab in combination with tremelimumab had a tolerable safety profile and promising activity in pretreated ED-SCLC. Responses were seen in both platinum-sensitive and platinum resistant/refractory patients. Clinical trial information: NCT02261220.

8518 Poster Discussion Session; Displayed in Poster Session (Board #124), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). First Author: Jonathan Wade Goldman, UCLA Medical Center, Los Angeles, CA

Background: SCLC is an aggressive lung cancer with high rate of relapse following initial treatment; immunotherapy holds potential as a novel treatment option for this disease. The anti-PD-L1 antibody durvalumab has demonstrated clinical activity with manageable toxicity in several tumor types, including NSCLC. Here we report on the SCLC expansion cohort of a phase 1/2 study of durvalumab monotherapy.

Methods: Patients with pretreated ED-SCLC, ECOG PS 0–1, regardless of PD-L1 expression, received durvalumab 10 mg/kg every 2 wks for up to 12 mos. The primary objective was to determine the safety profile; antitumor activity was evaluated using investigator-assessed RECIST v1.1.

Results: As of 16 Oct 2017, 2017 patients with ED-SCLC (median age 65.0 y, 62% male, 91% ECOG PS 1, 90% current/former smokers) were treated with durvalumab, median 3 cycles, median duration of follow-up 36.4 mos (range 1.4–37.9). 20 patients (95.2%) received prior anti-cancer therapy (median, 2 lines). 7 patients (33.3%) had treatment-related AEs, all were grade 1 or 2; the most common were fatigue, nausea, and rash maculo-papular (each 9.5%). There were no treatment-related AEs leading to discontinuation and no treatment-related deaths. Confirmed ORR was 9.5% (2 PR; 95% CI 1.2–30.4) and DCR24 was 14.3% (95% CI 3.0–36.3). Duration of response was 14.6 mos for one patient (treatment-naive), and 29.5 mos for another patient (platinum refractory with 3 prior lines of therapy), who continued to maintain response 25.5 mos after completing protocol-defined initial treatment with durvalumab. Median PFS was 1.5 mos (95% CI 0.0–1.8), median OS was 4.8 mos (95% CI 1.3–10.4), and 12-mos OS rate was 27.6% (95% CI 10.2–48.4). Conclusions: Consistent with studies in other tumor types and with other anti-PD-1/PD-L1 therapies, durvalumab monotherapy demonstrates durable clinical activity in certain patients with pretreated ED-SCLC with no new safety signals. Clinical trial information: NCT01693562.

8519 Poster Discussion Session; Displayed in Poster Session (Board #125), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Efficacy of milciclib (PHA-B48125AC), a pan-cyclin d-dependent kinase inhibitor, in two phase II studies with thymic carcinoma (TC) and B3 thymoma (B3T) patients. First Author: Benjamin Besse, Gustave Roussy, Villejuif, France

Background: Thymic carcinoma (TC) and B3 thymoma (B3T) are rare malignant tumors of the thymus. While TC, a highly aggressive and easily metastasizing cancer, has a very poor prognosis, B3T is a slow-growing cancer. Milciclib, an inhibitor of cyclin D-dependent kinases, Src and other kinases, exhibits antitumor activity against a number of solid tumors. Objectives of these studies were to evaluate efficacy and safety of oral treatment with milciclib in TC/B3T patients (pts). Methods: Two separate phase 2 multi-centered clinical trials (CDK0-125a-006: 72 pts, previously treated with one chemotherapy and CDK0-125a-007: 30 pts, previously treated with multiple chemotherapies) were conducted in the USA, France, and Italy. The proportion of patients with B3T and TC were 27.8% and 72.2% (CDK0-125a-006) and 56.7% and 43.3% (CDK0-125a-007), respectively. Milciclib was orally administered (150 mg daily; 1 cycle is 7d on/7d off) for multiple cycles. Progression-Free Survival rate at 3 mos (PFS-3) was the primary endpoint. Results: Oral treatment with milciclib met PFS-3 as primary endpoint and OS as a secondary endpoint in both phase 2 trials. Five pts in CDK0-125a-006 and 2 in CDK0-125a-007 continued treatment with over 2 years and of them over 5 years. 46.1% of both studies in total achieved at least one AE. Common Grade 3-4 hematological and other toxicities were neutropenia (8.4%), creatinine, amylase, lipase increase (5.6%), nausea and asthenia (8.3%). The AEs leading to discontinuation were 12.7% for both studies. Clinical trial information: NCT01101439 and NCT01301391. Conclusions: Oral treatment with milciclib was safe and well-tolerated and met primary and secondary endpoints, achieving disease stabilization in a majority of TC/B3T patients.
The comparison of tumor mutational burden (TMB) in patients of early and late stage lung adenocarcinoma in China. First Author: Kai Zhang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

Background: Although PD-L1 positivity improves immunotherapy efficacy, PD-L1 testing alone is insufficient for patient selection in most malignancies. High tumor mutational burden (TMB) is an emerging positive biomarker of immunotherapy in a growing number of malignancies. In this study, a method for TMB by cancer-gene panel (CGP) was set up, by which TMB from Chinese lung adenocarcinoma samples was measured to explore the association between TMB and genes alterations in the implications for immunotherapy. Methods: The accuracy of TMB detection by our CGP was confirmed from data of TCGA and whole exome sequencing (WES) in our clinical samples. TMB detection method by CGP was further validated from sequencing accuracy, coefficient of variation, and the limit of detection of tumor purity. The level of TMB in Chinese lung adenocarcinoma samples and its correlation with genes alterations were then analyzed. Results: In our study, TMB measured by CGP has a high correlation with that measured by WES in 31 clinical tumor samples (R2 = 0.9111). Immunotherapy from the Rizvi cohort confirmed this result. The mean level of TMB measured by CGP from 599 Chinese lung adenocarcinoma samples was similar with that from 389 TCGA lung adenocarcinoma samples (7.29 vs.7.6 mutations/Mb). We found that high level of TMB was significantly correlated with several genes alterations including TP53, KRAS and germline in DNA damage repair pathway and TMB. The level of TMB was correlated with EGFR and ALK alteration obviously. Of note, we first discovered that the level of TMB was lower in the early stage lung adenocarcinoma compared with that in the late stage lung adenocarcinoma from Chinese clinical samples. Conclusions: TMB calculated by CGP and WES was highly correlated via CGP and TCGA in our tumor samples. We found that the level of TMB was effected by several genes alterations in the analysis of our samples. We also found that the low level of TMB might imply a poor effect of mono-immunotherapy in the treatment of early stage lung adenocarcinoma. Of note, combining immunotherapy with DNA damaging agents could be a good way to improve efficacy.

Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers 443s

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: This study aimed to investigate the survival difference between right-sided and left-sided pneumonectomy in stage I-IIIA non-small cell lung cancer patients, and to further develop the best treatment strategies. Methods: Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute across 18 cancer registry sites in the United States were used for the present study. To avoid bias associated with genomic variants, we used an innovative propensity score matching analysis. Results: Stage I-IIIA NSCLC patients with pneumonectomy from 2004 to 2014 were included in this study. Of all 2,683 patients who received pneumonectomy, Overall survival (OS) (HR = 0.875, 95%CI: 0.793 to 0.967, P = 0.008) and cancer-specific survival (HR = 0.863, 95%CI: 0.771 to 0.965, P = 0.010) were significantly longer with left-sided pneumonectomy over right-sided pneumonectomy. After propensity score matching analysis for 2,050 patients, OS (HR = 0.858, 95%CI: 0.768 to 0.959, P = 0.007) and cancer-specific survival (HR = 0.847, 95%CI: 0.745 to 0.963, P = 0.011) were also significantly superior of left-sided compared with right-sided pneumonectomy. After matching procedure, among left-sided pneumonectomy patients, adjuvant therapy significantly prolonged OS (46 versus 30 months, HR = 1.458, 95%CI: 1.239 to 1.715, P < 0.001) and cancer-specific survival (67 versus 51 months, HR = 1.314, 95%CI: 1.093 to 1.579, P = 0.004) while among right-sided pneumonectomy patients, adjuvant chemotherapy was not associated with cancer-specific survival benefit (46 versus 42 months, HR = 1.112, 95%CI: 0.933 to 1.325, P = 0.236). Subgroup analysis showed that adjuvant chemotherapy could significantly improve OS and cancer-specific survival for both sided pneumonectomy patients. But patients with right-sided pneumonectomy who received radiotherapy had worse survival compared with left-sided pneumonectomy. Adjuvant chemotherapy contributed significant benefit to patients who received both sided pneumonectomy, but radiotherapy worsened prognosis for right-sided pneumonectomy.

Conclusions: Right-sided pneumonectomy was associated with worse survival compared with left-sided pneumonectomy. Adjuvant chemotherapy contributed significant benefit to patients who received both sided pneumonectomy, but radiotherapy worsened prognosis for right-sided pneumonectomy.
A deep-learning radiomics model for predicting survival in early-stage non-small cell lung cancer. First Author: Tadafumi Kawamura, Department of Imaging and Bioinformatics Laboratory, Harvard Medical School, Boston, MA.

Background: There is a growing body of evidence suggesting radiomic phenotypes can augment prognostic power, when used in combination with clinical features and tumor genomic profiles in lung cancer. In this study we present a deep-learning model that can act as a non-invasive prognostic biomarker in patients with Stage-I Non-Small Cell Lung Cancer (NSCLC). Our model would be able to assign patients to short term or long term survival groups, based on CT characteristics. Methods: Pretreatment CT studies were retrieved for 299 patients who underwent surgery for Stage-I NSCLC at MGH between 2004-2010. Image pre-processing included manual tumor identification, and isotropic rescaling of CT data. Further data curation resulted in a final cohort of 186 patients. Median follow-up from time of diagnosis was 2.9 years and 9.7% of patients were deceased at 2 years. To mitigate bias against a low probability event (mortality), data augmentation was performed yielding 242 50x50 pixel patches to feed into our model. A pre-trained 16 layer deep neural network (VGG-16) was used to perform visual recognition and data analysis. Fine-tuning of the last two convolutional blocks and a fully-connected classifier was performed with a training set of 144 labeled and data validation set of 64 examples with 75% accuracy and AUC = 0.798. In comparison, a multivariate linear regression model of conventional clinical prognostic factors (age, gender, tumor stage, histology, and smoking status) had a lower predictive performance (AUC = 0.665). Event rates were balanced between training and independent validation sets. Conclusions: Artificial Intelligence-enhanced radiomic feature extraction and predictive modeling can aid the clinician in assessing the benefits of treatment for patients with early-stage NSCLC.

Multimodal treatment in operable stage III non-small cell lung cancer using the new 8th TNM staging classification version 8: Longer term results of a pooled analysis of three SAKK trials. First Author: Martin Frueh, Department of Oncology/Haematology, Cantonal Hospital St Gallen, St Gallen, Switzerland.

Background: The impact of the 8th edition of the TNM staging system on the optimal treatment choice and the best treatment strategy for stage III non-small cell lung cancer (NSCLC) is unclear. We applied the 8th version of the TNM classification to a pooled analysis of stage III NSCLC trials in order to test its validity and assess long term outcomes and prognostic factors. Methods: Individual patient data of 368 patients from three very similarly designed trials (SAKK 16/96, SAKK 16/00 and SAKK 16/01) were pooled. Patients with operable stage III NSCLC received preoperative radiotherapy following three cycles of induction cisplatin/docetaxel (tri-modal) or neoadjuvant cisplatin/docetaxel alone (bi-modal). Factors associated with improved 5-year overall survival (OS) were evaluated using a logistic regression model. Results: When applying the 8th TNM staging version*, 162 patients moved from stage IIIA to IIIB* and 5-and 10-year OS rates were 41% and 29% for stage IIIA and 35% and 27% for stage IIIB*. When using the 6th version 5- and 10-year OS rates were 38% and 28% for stage IIIA and 36% and 24% for stage IIIB. Factors associated with improved 5-year OS were age, RO resection and pCR (p = 0.043, p < 0.001 and p = 0.009). There was no difference in the bi- vs. tri-modal group with regards to OS (median: 28 months [95% CI: 21-39 months] vs. 27 months [95% CI: 24-51 months], p = 0.9), event-free survival (median: 12 months [95% CI: 9-15 months] vs. 13 months [95% CI: 10-22 months], p = 0.71), local recurrence rate (48% vs 44%, p = 0.61), and pathologic complete remissions (pCR) rate (15% vs. 16% p = 0.75). RO resection rates were lower in the bi-modal group (69% vs. 87%, p < 0.001). Conclusions: Similarly favorable long term outcomes were observed when the 8th vs. 6th TNM classification was applied. With the exception of the excluded patients with T4 due to multiple lesions in different lobes, multimodality treatment decisions in operable stage III NSCLC can be based on the 8th TNM version in upcoming trials. Tri-modal therapy resulted in higher RO resection rates but did not improve OS. Younger age, RO resection and pCR were associated with improved 5-year survival.

Neoadjuvant atezolizumab + chemotherapy in resectable non-small cell lung cancer (NSCLC). First Author: Catherine A. Shu, Columbia University Medical Center, New York, NY.

Background: Neoadjuvant chemotherapy is an accepted treatment approach for resectable NSCLC. Major pathologic response (mPR) defined as ≥ 90% tumor necrosis is seen in 20% of patients (pts) receiving neoadjuvant chemotherapy and portends a favorable survival. Combination anti-PD-(L)1 therapy and chemotherapy has demonstrated potential synergy in metastatic NSCLC. This ongoing phase II study explores the combination of neoadjuvant atezolizumab + chemotherapy. Methods: Pts with stage IB-IIIa resectable NSCLC receive 4 cycles of atezolizumab, nab-paclitaxel, and carboplatin prior to surgery. Never-smokers are excluded. Planned enrollment is 30 pts with a primary endpoint of mPR. Stage I trial evaluation after enrollment of 18 pts will be performed with pre-defined stoppage criteria for lack of efficacy (mPR in ≤ 4 pts). If ≥ 5/18 pts have mPR, an additional 12 pts will be treated in Stage II. The primary endpoint is met if ≥ 11/30 pts have mPR. Results: From 6/2016 to 1/2018, 14 evaluable pts were treated. Baseline characteristics: median age 71 years (range 49-83), 36% female, 57% adenocarcinoma, 85% stage IIA, and 54% PD-L1 positive (≥ 1%, 22C3). The most common toxicity was neutropenia (12/ 14 Grade 3-4), with 9/14 pts requiring chemotherapy dose reduction. 1 pt experienced G3 transaminase elevation, and another developed Type I diabetes (1 year after completion of treatment). 8/14 (57%) had radiologic PR, and the remainder had SD. 11/14 pts underwent resection successfully: 1 pt had post-operative complications unrelated to study drugs leading to death. The Stage I trial continuation criteria was met with 7/14 (50%) pts with mPR, including 3 pts with complete pathologic response (21%). mPR was seen in both PD-L1+ and PD-L1- pts. With a median follow-up of 8.6 months (95% CI 3.5, 17.8), there were 8 recurrent events: 2 were brain metastases. Conclusions: The combination of atezolizumab + chemotherapy demonstrated significant activity in the neoadjuvant setting. Treatment response was seen regardless of PD-L1 score. Correlative studies including multiplex IHC and tumor exome sequencing are ongoing. The data extend the feasibility boundary for neoadjuvant atezolizumab + chemotherapy in stage III NSCLC and will proceed to Stage II. Clinical trial information: NCT02716038.
Although EGFRm NSCLC occurs mainly in non-smoking patients, most series report 20%-35% of cases in current or previous smokers. Broad molecular profiling of EGFRm NSCLC in smokers has not been reported. Methods: Surgically resected primary EGFRm ex9n or 21n mutated NSCLC tumors from 108 patients were molecularly profiled by whole exome sequencing using the IlluminaHiSeq2000 platform. An initial discovery analysis was performed according to GATK best practices workflow; B7 sequenced to a mean coverage of 65.1x. Demographics and outcomes were compared for smokers and non-smokers (non-S), and by mutation profile. Results: Of the 63 non-smokers and 24 smokers (7 current/recent within 10 years), 71% were female, 53% were non-Asian, 64.5 years was the median age and 57.5% were EGFRm ex9n. Of the 87 patients, 52% were stage I, 20.5% were stage II and 27.5% were stage III+. Smoking was associated with male sex (p = 0.0028) and non-Asian ethnicity (p = 0.0006) but not with age, stage or EGFRm ex9n/21n subtypes. Multiple “driver” mutations occurred in tumors of 25% smokers and 23.8% non-S. TP53/EGFR co-mutation occurred in 57.9% smokers and 46.2% non-S. Total non-synchronous mutation burden (TMB) was higher in smokers: median TMB in smokers 175.35 (84.93-388.24) compared to 155.31 (56.52-414.84) in non-S (p = 0.056). The strongest prognostic factor for OS and DFS was stage I (p < 0.0001 vs all others). In univariate analysis vs there was a trend to shorter OS in smokers: HR 1.9 (CI 0.98-3.67, p = 0.05). Smoking within 10 years of NSCLC diagnosis was associated with shorter DFS HR 0.37 (0.13-1.09) (p = 0.06) but not OS (p = 0.34). Neither EGFRm subtype nor TP53/EGFR co-mutation was associated with DFS or OS. High TMB was associated with shorter DFS: HR above vs below the median 1.96 (CI 1.06-3.62, p = 0.028), and OS HR 2.04 (CI 1.01-4.11, p = 0.043). TMB was still significant for DFS after adjusting for smoking status (p = 0.033), but not for OS (p = 0.1). Conclusions: EGFRm NSCLC in smokers is associated with a trend toward higher non-synchronous TMB. Stage remains the strongest prognostic factor, but TMB appears to have a greater effect on survival outcomes than smoking status.

The NCCN guidelines recommend treating stage IIIB NSCLC (non-small cell lung cancer) with concurrent chemotherapy and radiation (chemo-R). There is data to suggest that N3 stage IIIB disease is worse prognosis, but this has not been explicitly interrogated. There is also concern regarding the safety of chemo-RT in patients ≥70 years old as they are under-represented in clinical trials, have worse overall survival, and experience increased toxicities. We therefore sought to interrogate the survival of N3 Stage IIIB NSCLC using the NCDB (National Cancer Database) with a focus on patients ≥70 years old. Methods: We conducted a retrospective analysis on data from the 2014 NCDB PUF (participant user file) of patients diagnosed with N3 stage IIIB NSCLC between 2010 and 2013. Kaplan-Meier method was used for median overall survival (OS) with log-rank tests. Multivariable Cox models were used for multivariable and subgroup analyses. Results: 9,769 patients were included in our analysis, 7,770 who received chemo-RT and 1,999 who received chemotherapy alone. A higher proportion of patients in the chemotherapy group were ≥70 years old compared to the chemo-RT group (46.6% and 34.5% respectively, p < 0.0001). The median OS for the chemo-RT group was 16.4 months compared to 12.7 months for the chemotherapy group (p = 0.0001). For patients ≥70 years old, the median OS was 15.0 months for those who received chemo-RT compared to 12.4 months for chemotherapy alone (p < 0.0001). In multivariable analyses, the benefit of chemo-RT was similar regardless of age. For age < 70, the hazards ratio (HR) was 0.73 with a 95% confidence interval (CI) of 0.67-0.79 and for age ≥70, HR = 0.77, 95% CI = 0.71-0.83 (p = 0.43). Subgroup analyses in patients ≥70 indicated a benefit of chemotherapy-RT (HR < 1.0) across all patient and disease stratifications, including Charlson Comorbidity Index 0 (p < 0.05 irrespective of score). Conclusions: There is a survival benefit to chemo-RT versus chemotherapy alone in N3 stage IIIB NSCLC patients ≥70 years old, who represented 37% of all patients. Our findings suggest that age and comorbidity index alone should not preclude clinicians from recommending aggressive therapy to these patients.
Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

8537 Poster Session (Board #143), Sun, 8:00 AM-11:30 AM
NORA trial (GECP 15/02): First efficacy results of the Spanish Lung Cancer Group (SLGC) phase II trial of concurrent chemo-radiotherapy (CT-RT) with cisplatin (P) plus metronomic misonidazole (MONO) for unresectable, locally advanced non-small cell lung cancer (LA-NSCLC). First Author: Dolores Isla, Hospital Clínico Lozano Blesa, Zaragoza, Spain

Background: CT-RT is the standard treatment for unresectable LA-NSCLC. P plus vinorelbine is widely used. Metronomic CT is a frequent administration of low doses of CT. mOv has shown good efficacy and improved safety, and could improve the RT effect. Our goal is to evaluate the efficacy and safety of P-mOv with radical RT in patients (pts) with LA-NSCLC. Methods: Pts aged 18-75 years with histologically proven untreated and unresectable LA-NSCLC were included. Treatment: P-mOv 40 mg/m² d1 every 3 weeks combined with mOv 50mg/day on d1, 3 & 5/weekly. 2 cycles (cy) as induction; patients without progression received 2 more cy of P at the same dose with mOv 30mg/d on d1, 3 & 5/weekly, concurrently with RT (66Gy in 6.5weeks). Primary endpoint was progression-free survival (PFS) by RECIST v1.1. secondary endpoints were: overall response rate (ORR), disease control rate (DCR), overall survival and safety profile. To guarantee an overall type-I error no greater than 0.05 and a type II (b) error of .20, a sample size of 67 pts was calculated, with a power of 0.80 to reject P < 0.05. Results: Sixty-seven pts were recruited in 17 Spanish sites from 04/2016 to 06/2017. One of them didn’t meet all the inclusion criteria. We analyzed the first 57 pts included. Pt characteristics: Male 77.3%; median age 62 (range 33-75); PS 0/1 50/50%; smokers 45.5%; adenocarcinoma/squamous 34.8/ 43.9%; stage IIIA/B 43.9/56.1%. Only 29.8% of patients completed the treatment. ORR: 66.7%. DCR: 79%. With a median follow-up of 2 years and 10 months, 3/4 adverse event, including: neutropenia 22.8%; anemia 3.5%; febrile neutropenia 7%; esophagitis 1.8%; pneumonitis 1.8%. There were two deaths non-related to the treatment, during this period. Forty-four pts have been followed. 3-4 adverse events incidence: anemia 11.6%, neutropenia 9%, febrile neutropenia 7%. 31.5% of the pts had grade >3 adverse events, including: anemia 13.1%, neutropenia 7.9%, infection 7.9%, febrile neutropenia 3.5%, esophagitis 1.8%. Conclusions: mOv-P with RT is as effective as the standard administration of vinorelbine, improving its safety profile. EudraCT 2015-003312-21. Clinical trial information: EudraCT 2015-003312-21.

8539 Poster Session (Board #145), Sun, 8:00 AM-11:30 AM
Progression-free survival (PFS) and cardiac-toxicity-adjusted-PFS (CTA-PFS) as predictors of overall survival (OS) in locally advanced non-small cell lung cancer (LA-NSCLC) treated with concurrent chemoradiation (CCRT): A secondary analysis of NRG Oncology RTOG 0617. First Author: Chen Hu, Johns Hopkins University, Baltimore, MD

Background: OS is the gold standard for LA-NSCLC with CCRT, with complex relationships among RT dosimetry, systemic therapies, cardiopulmonary toxicity, progression (PD) and OS of growing scientific and clinical interest. Methods: RTOG 0617 (NCT00533949) randomized standard (SD, 60 Gy) versus high-dose (HD, 74 Gy) CCRT +/- cetuximab from 11/07/06 to 11/11/11. This analysis includes 469 patients (pts) given ≥50 Gy. A PFS event was defined as the first occurrence of local, regional, distant PD or death w/o documented PD. A CTA-PFS event was the first occurrence of grade ≥2 treatment-related cardiac toxicity event or a PFS event. Landmark analyses at 6mo and 12mo were used to minimize the immortal time bias. Cox model with PD or CT/ PD as a time-dependent covariate was used to evaluate their predictive roles. Median f/u time for surviving pts was 5.1 years. Results: As reported, pts treated with HD had significantly lower OS rates (HR = 1.28, 95% CI: 1.04-1.58, p = 0.018) and CTA-PFS rates (HR = 1.24, 95% CI: 1.02-1.51, p = 0.035), and marginally lower PFS rates (HR = 1.21, 95% CI: 0.99-1.47, p = 0.06) than pts treated with SD. Median survival time (MST) among pts having PD within 6mo versus not were 13.4mo (95%CI: 10.0-19.0) and 30.7mo (95%CI: 28.0-37.0) (p < 0.001). MST for pts having PD within 12mo versus not were 20.6mo (95%CI: 18.8-25.0) and 60mo (95%CI: 47.6-74.5) (p < 0.001). Results are similar when using CTA-PFS with 6mo or 12mo cutoff (p < 0.001). RT dose was no longer significantly associated with OS (p = 0.15) when PD or CT/ PD was included in multivariable analysis (p < 0.001). It is quite possible that the potential impact of RT dose on OS may be attenuated when including the RT-related PD outcome on a multivariable analysis with OS (p = 0.15) when PD or CT/ PD was included in multivariable analysis (p < 0.001). It is quite possible that the potential impact of RT dose on OS may be attenuated when including the RT-related PD outcome on a multivariable analysis with OS (p = 0.08 or p = 0.15). Conclusions: In this secondary analysis with an acceptable success rate and turnaround, over 60% of patients have a driver event identified, providing additional relevant information beyond single gene testing.

8540 Poster Session (Board #146), Sun, 8:00 AM-11:30 AM
Routine use of a modest next generation sequencing panel provides additional clinically useful data beyond single gene testing in non-small cell lung cancer and is fit for purpose as a clinical assay. Collated data from a single molecular diagnostic laboratory. First Author: David Allan Moore, Sarah Cannon Molecular Diagnostics, London, United Kingdom

Background: Testing of the EGFR gene for sensitising mutations is a critical part of patient stratification in non-small cell lung cancer. Analysis of a modest panel of relevant genes using a targeted Next Generation Sequencing (TNGS) has the potential to identify an extended range of actionable or trialable alterations compared with more limited technologies. There are additional analytical and technological advantages to this approach. Sarah Cannon Molecular Diagnostics has been delivering somatic variant analysis through Oncomine solid tumour panel since 2014. This project involved the collation of data from 3 years’ worth of molecular diagnostic TNGS testing performed on non-small cell lung cancer specimens. Methods: The laboratory database was interrogated to identify all cases of non-small cell lung cancer submitted for testing from a 3 year period. Rate of rejection due to insufficient tumor, assay failure rate and turnaround time was calculated. Further validation on external datasets and in the modern era of immuno-therapy are needed.

8548 Poster Session (Board #144), Sun, 8:00 AM-11:30 AM
Insurance disparity in cause-specific mortalities: A SEER study on early stage, non-elderly NSCLC cancer survivors. First Author: Changchuan Jiang, Iowa School of Medicine at Mount Sinai, New York, NY

Background: Lung cancer is the leading cause of cancer-related death in the US. Non-elderly, early stage (stage I-II) non-small cell lung cancer (NSCLC) patients have the most promising prognosis with appropriate treatments. Studies have shown uninsured and elderly patients on Medicaid being less likely to receive guideline-concordant therapy and thus with higher mortality. However, it remains unknown how insurance status influences cause-specific survival in non-elderly NSCLC patients, and whether disparity of care is improved in this cohort after ACA. Methods: Surveillance, Epidemiology, and End Results Program from 2007-2014 was used to identify NSCLC patients on stage I and II on diagnosis. Elderly patients (> 65 years) were excluded. Demographic and lung cancer characteristics including age, gender, race, education, income, insurance status, tumor grade/stage and treatment were analyzed. Competing risk analysis was conducted using SASS4. Results: A total of 13,898 patients were included. After adjusting for socio-demographic factors, tumor grade and treatment, Medicaid and non-insured were associated with higher lung cancer mortality (HR: Medicaid 2.17 (1.57-2.99), non-insured 1.37 (0.74-2.56); NCR: Medicaid 2.46 (1.76-3.43), non-insured 0.73 (0.30-1.81). Diagnosis after ACA was associated with lower lung cancer specific mortality but not related to CVD or cancer mortality. No effect modification was found for diagnosis after ACA on any specific cause mortality. Conclusions: Despite ACA and Medicaid expansion in 2010, Medicaid and non-insured patients have higher cancer mortality compared with insured in early-stage NSCLC patients. Furthermore, non-elderly, early-stage NSCLC cancer survivors with Medicaid have remarkably higher CVD mortality compared to private insured survivors even without any insurance, which may reflect the disparity in health literacy, primary care, and cancer survivorship care access.

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Correlative analyses on pre- and post atezo tissues are ongoing. Preliminary setting shows that preoperative treatment is feasible and well tolerated. MPR improvement in survival and are more likely to receive trimodality therapy. 

**Results:** For the prespecified initial safety analysis, the first 21 of 180 planned pts (67 pts currently on study) are reported: 13 males, median age 65 y, all ECOG 0-1, current or former smokers; 13 non-squamous NSCLC. 10 pts reported: 13 males, median age 65 y, all ECOG 0-1, 4 current, 16 former smokers; 13 non-squamous NSCLC. 2 pts reported one dose of atezo due to treatment related AE (Gr 1 pyrexia, Gr 2 dyspea) but underwent uncomplicated resection with MPR assessment. There were no Gr 5 AE, 5 Gr 3-4 AE (1 treatment related). By RECIST, 20 pts had SD, and 1 had PD. There were no major delays to surgery. 19 pts had MPR assessment: 1 pt discontinued atezo preop due to biopsy site reaction, 1 pt had a contralateral NSCLC cist and 1 pt had unresectable disease. MPR rate was 4/19 (21%, 95% CI 6-46). Excluding 2 pts who had driver mutations (1 EGFR+, 1 ALK+), MPR rate was 4/17 (24%, 95% CI 7-50). 11/19 patients had ≥50% viable tumor. 

**Conclusions:** This first report of atezo in the neoadjuvant setting shows that preoperative treatment is feasible and well tolerated and safety, response by PD-L1, OS, and DFS. 

**Methods:** Pts with stages IB-IIB NSCLC resectable were to receive 2 cycles of atezo (1200 mg, days 1, 22) and post atezo to assess clinical response. Primary tumor +/- node biopsies and blood samples were obtained before atezo and at surgery for biomarker studies. The primary endpoint was MPR. Secondary endpoints included safety, response by PD-L1, OS, and DFS. 

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Using deep-learning radiomics to predict lung cancer histology.

**First Author:** Tafadzwa Lawrence Chauwiza, Computational Imaging and Bioinformatics Laboratory, Harvard Medical School, Boston, MA.

**Methods:** A cohort of 157 patients with Stage I NSCLC identified as either adenocarcinoma or squamous cell carcinoma on pathology was used. All patients were surgical candidates at Massachusetts General Hospital between 2004-2010. Deep feature extraction from pretreatment CT images was conducted using a pre-trained VGG-16 convolutional neural network (CNN). In addition to appending fully-connected classifying layers to the network, a transfer learning approach was also employed using different classifiers. Three machine-learning-classification models were independently evaluated on the extracted features: K-Nearest Neighbors (kNN), Random Forest Classifier (RF), and Least Absolute Shrinkage and Selection Operator (LASSO). Principal component analysis was employed in selecting features corresponding to 90% cumulative explained variance. A LASSO method was then used to select the best features. Models were trained on 100 patients and cross-validated on an independent test-set of 57 patients.

**Results:** All models were able to perform binary classification of tumor histology (adenocarcinoma vs squamous cell carcinoma). The fully-connected CNN had the highest performance (AUC = 0.751). Other classifiers also showed significant predictive power after dimension reduction of the feature space (from 512 to 46), with AUC = 0.712 for LASSO (σ = 0.1), and AUC = 0.689 for kNN (k = 5). RF had the lowest predictive performance (AUC = 0.533). 73% of the study group had adenocarcinoma vs 27% with squamous cell carcinoma, and radiation oncologists balanced radiation therapy and surgery selecting advanced patients. Deep-Learning Radiomics is a promising approach to non-invasive lung cancer histology classification. These methods can potentially augment other emerging techniques, such as liquid biopsy; offering complementary information to help in clinical decision making.

Impact of somatic mutations on recurrence free survival (RFS) and overall survival (OS) for resected non-small cell lung cancer (NSCLC) collected from the Japan Molecular Epidemiology for lung cancer study (JME).

**First Author:** Akihiro Tamiya, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan.

**Background:** We previously reported molecular profiling as a primary end-point in a prospective multicenter molecular epidemiology study, collecting 876 surgically resected NSCLC and examining 72-gene somatic mutation status using targeted sequencing (JME study; UMIN000008177). Here, we report follow-up data and clinical outcomes in the JME study and the impact of somatic mutations on RFS and OS. **Methods:** We previously reported molecular profiling as a primary end-point in a prospective multicenter molecular epidemiology study, collecting 876 surgically resected NSCLC and examining 72-gene somatic mutation status using targeted sequencing (JME study; UMIN000008177). Here, we report follow-up data and clinical outcomes in the JME study and the impact of somatic mutations on RFS and OS. **Methods:** We previously reported molecular profiling as a primary end-point in a prospective multicenter molecular epidemiology study, collecting 876 surgically resected NSCLC and examining 72-gene somatic mutation status using targeted sequencing (JME study; UMIN000008177). Here, we report follow-up data and clinical outcomes in the JME study and the impact of somatic mutations on RFS and OS. **Methods:** We previously reported molecular profiling as a primary end-point in a prospective multicenter molecular epidemiology study, collecting 876 surgically resected NSCLC and examining 72-gene somatic mutation status using targeted sequencing (JME study; UMIN000008177). Here, we report follow-up data and clinical outcomes in the JME study and the impact of somatic mutations on RFS and OS. **Methods:** We previously reported molecular profiling as a primary end-point in a prospective multicenter molecular epidemiology study, collecting 876 surgically resected NSCLC and examining 72-gene somatic mutation status using targeted sequencing (JME study; UMIN000008177). Here, we report follow-up data and clinical outcomes in the JME study and the impact of somatic mutations on RFS and OS.

**Conclusions:** Our results pointed out the complex relationship between the heterogeneity of intratumoural immune infiltrates, tumor genomics, and patient prognosis across tumor genotypes of NSCLC. Further research is warranted to validate the relation in independent patient cohorts and to explore the impact of immune landscape on immunotherapeutic response.

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Circulating tumor DNA (ctDNA) as a marker of minimal residual disease (MRD) in localized non-small cell lung carcinoma (NSCLC). First Author: Nuninga Simorangkir, University of Washington, Seattle, WA

Background: ctDNA has been used to identify driver genomic alterations during treatment of metastatic NSCLC. Recent studies have also demonstrated ctDNA being used as a way to monitor response to therapy. Here we performed an analysis on a cohort of NSCLC patients (pts) with localized disease who underwent ctDNA testing after definitive treatments to determine whether ctDNA can be used as a marker of MRD.

Methods: Between 2010-2018, 51 pts with localized NSCLC received ctDNA testing. ctDNA testing was done using the next generation sequencing (NGS) panel of 73 genes via digital sequencing technology (Guardant360). Statistical analysis was performed to determine which factors were associated with ctDNA levels and recurrence free survival (RFS). Results: Of the 51 pts analyzed, 23 pts had ctDNA testing performed after definitive treatment. Median duration of follow up was 10 months (range: 1 to 23). 30% (n = 7) had Stage I disease, 30% (n = 7) had Stage II disease, and 40% (n = 9) had Stage III disease. 74% (n = 17) were adenocarcinoma while 26% (n = 6) were squamous cell carcinomas. 52% (n = 12) had no recurrence during our observation time, while 18% (n = 11) experienced progression. For definitive treatments, 55% (n = 8) underwent surgery alone, 43% (n = 10) underwent surgery with adjuvant chemotherapy, 4% (n = 1) underwent radiation alone, and 17% (n = 4) underwent chemoradiation therapy prior to their ctDNA levels (variant allele frequency [VAF]) being drawn. Of these, 13% (n = 3) tested negative for ctDNA, while 87% (n = 20) were positive. Presence of the pts with undetectable levels of ctDNA experienced recurrence of cancer. Nine among 20 pts with detectable ctDNA had recurrence. Kaplan-Meir survival analysis revealed a trend toward significant association between the presence of detectable ctDNA and RFS (p = 0.055). Among pts with detectable ctDNA, there were no differences in RFS between pts with high vs. low ctDNA levels (cut off at 1% VAF). Presence of ctDNA was not associated with sex, smoking history, histology, stage, nor modality of definitive treatment. Conclusions: Our analysis demonstrates that ctDNA could potentially be used as a marker of MRD following definitive treatment for localized NSCLC.
Background: The purpose of this study is to evaluate long-term outcomes after sublobar resection for patients with clinical stage IA lung adenocarcinoma meeting our proposed node-negative (N0) criteria: solid component size of less than 0.8 cm on HRCT or SUVmax of less than 1.5 on FDG-PET/CT.

Methods: Between April 2006 and December 2010, 347 patients with clinical stage IA lung adenocarcinoma underwent complete resection after preoperative HRCT and FDG-PET/CT in Kanagawa Cancer Center and Hiroshima University. Long-term outcomes of patients who met the N0 criteria after sublobar resection were evaluated. Results: Two-hundred one (57.9%) patients met the N0 criteria. Patients who met the N0 criteria were significantly associated with low grade adenocarcinoma subtype (adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic adenocarcinoma); P < 0.001, negative lymphatic invasion (P < 0.001), negative vascular invasion (P < 0.001), and negative pleural invasion (P < 0.001). One of 201 (0.5%) patients had lymph node metastasis. The median follow-up period was 86.1 months. There was no significant difference in overall survival (OS) between patients who met the N0 criteria (5-year OS rate, 93.9%; 10-year OS rate, 90.3%) and those who did not meet the N0 criteria (5-year OS rate, 81.5%; 10-year OS rate, 64.3%; P < 0.001). In patients who met the N0 criteria, there was no significant difference in OS between patients who underwent lobectomy (5-year OS rate, 94.3%; 10-year OS rate, 92.6%) and those who underwent sublobar resection (5-year OS rate, 93.8%; 10-year OS rate, 89.3%; P = 0.640).

Conclusions: Sublobar resection is feasible for clinical stage IA lung adenocarcinoma meeting N0 criteria defined by HRCT and FDG-PET/CT with excellent long-term survival.

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**8555**

**Poster Session (Board #161), Sun, 8:00 AM-11:30 AM**

A phase I study of neoadjuvant cisplatin (C), docetaxel (D) and nintedanib (N) for resectable non-small cell lung cancer (NSCLC). First Author: Tatsuya Cascone, The University of Texas MD Anderson Cancer Center, Houston, TX, Japan

**Background:** Major pathologic response (mPR) in resected NSCLC following neoadjuvant chemotherapy correlates with long-term survival. This phase 1 study assessed the safety and efficacy of N added to neoadjuvant C and D, using mPR as primary surrogate of efficacy endpoint.

**Methods:** Eligible patients (pts) had stage IB (≥4 cm) to IIIA (single station N2) resectable NSCLC (AJCC 7th). The study included an expansion phase of N 200 mg po bid for 28 days, followed by 3 cycles of C 75 mg/m² every 21 days, and N 200 mg po bid, and surgery (after a run-in phase in 6 pts determined safety of escalating N doses). With 33 pts, the study had 90% power to detect an increase in mPR from 15% (historical controls) to 35%, with a 10% type I error rate. Based on the Simon's two-stage design, the protocol called for discontinuation of the trial if there were < 4 responders in the first 19 pts treated at N 200 dose level (NCT02225405).

**Results:** From July 2015 to May 2017, 21 pts (15 female, 1/8/12 stages III/I/III) were treated (6 with N 150 mg bid, 15 with N 200 mg bid). Only 1/15 pts treated with N 200 mg bid achieved a mPR (6.7%, 95% CI 0.2%-32.0%). An interim analysis indicated that the probability of observing ≥4 mPRs if accrual were to continue to 19 pts was only 5.4%, assuming the prior of p beta(0.35, 0.65). Hence, the study was discontinued for futility. The best objective response rate by RECIST 1.1 in all 21 pts was 33.3%. No patients responded to N priming monotherapy. With a median follow-up time of 11 months, the 12-month RFS in the NRT group was 71% (95% CI 49%, 100%). The most frequent treatment-related grade 3-4 toxicities in all pts were: transaministis (14.3%); nausea (9.5%) and electrolyte abnormalities (14.3%). No unexpected perioperative complications were observed. **Conclusions:** Although tolerable, neoadjuvant N, C, and D did not increase the mPR rate compared to historical controls on chemotherapy alone. Additional studies of the combination in this setting are not recommended. Our trial design, utilizing mPR as an intermediary endpoint, may serve as a framework to rapidly screen novel compounds that should be investigated further as neoadjuvant therapies for resectable NSCLC. Clinical trial information: NCT02225405.

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**8556**

**Poster Session (Board #162), Sun, 8:00 AM-11:30 AM**

A comparative safety analysis for durvalumab in patients with locally advanced, unresectable NSCLC: PACIFIC versus pooled durvalumab monotherapy studies. First Author: Scott Joseph Antonia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

**Background:** In PACIFIC, durvalumab significantly extended PFS compared with placebo (HR 0.52; P<0.0001) for pts with locally advanced, unresectable NSCLC who had previously received concurrent chemoradiotherapy (cCRT). The safety profile of durvalumab in this study was similar to placebo. Here we report a safety analysis of a descriptive comparison of PACIFIC with a pooled dataset of durvalumab monotherapy studies.

**Methods:** Data were pooled for pts treated with durvalumab monotherapy (10 mg/kg IV Q2W) from three trials (N=1,889), the Phase III PACIFIC (n=475), Phase II ATLANTIC (n=444 advanced NSCLC pts), and Phase III I108 (n=970 solid tumor pts, including 304 NSCLC pts) studies. The incidences of all-causality AEs (as of Feb 13, 2017, data cutoff for the PACIFIC analysis) were graded using CTCAE v4.03 and summarized descriptively for comparison between PACIFIC and the pooled dataset. **Results:** Compared with the pooled dataset (Table), PACIFIC had lower incidences of grade 3/4 AEs and SAEs, but a higher rate of AEs leading to discontinuation (15.4% [durvalumab] vs. 9.8% [placebo] compared with 9.4% [pooled dataset]). In a separate comparison excluding PACIFIC from the pooled dataset (N=1,414), any-grade (grade 3/4) pneumonitis/radiation pneumonitis occurred in 33.9% (3.4%) of pts on durvalumab and 24.8% (3.0%) on placebo in PACIFIC (with similar grade 3/4 incidences for both) and 2.3% (0.5%) of pts in the reduced pooled dataset.

**Conclusions:** Durvalumab monotherapy has a well-defined and acceptable safety profile. Differences observed in the rates of AEs with durvalumab on the PACIFIC regimen may be attributable to the pt population or prior cCRT.

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**8557**

**Poster Session (Board #163), Sun, 8:00 AM-11:30 AM**

Geriatric assessment to predict toxicity in elderly patients with unresectable locally advanced non-small-cell lung cancer treated with concurrent chemoradiotherapy. First Author: Ernest Nadal, Department of Medical Oncology, Catalan Institute of Oncology, Hospitaled (Barcelona), Spain

**Background:** There is no consensus on the treatment of elderly patients with unresectable locally advanced non-small-cell lung cancer (LA-NSCLC). We aimed to determine whether the comprehensive geriatric assessment (CGA) as well as other screening tools were able to predict toxicity in this clinical setting.

**Methods:** Elderly patients (>75y) with LA-NSCLC underwent GA, the Vulnerable Elders Survey (VES-13) screening tool and the Cancer and Aging Research Group (CARG) toxicity predictive tool. Based on CGA, fit and medium-fit patients were deemed candidates for platinum-based chemotherapy concurrent with thoracic radiation therapy (cCRT) and unfit patients received best supportive care. The ability of CGA, CARG and VES-13 to predict grade 3-4 (G3-4) toxicity was assessed by logistic regression.

**Results:** 85 elderly patients with LA-NSCLC were assessed by CGA and classified into fit 37%, medium fit 48% and unfit 15%. Based on VES-13, 56% were considered vulnerable. Fifty-four fit and medium-fit patients received cCRT and 42 (78%) patients completed the scheduled treatment. No differences in treatment completion were seen among both CGA groups. Reasons for not completing cCRT were toxicity (10%), cancer recurrence (4%), patient decision (4%) or aggravation of comorbidities (4%). The median OS (mOS) in fit and medium-fit patients receiving cCRT was 21.1 months (95% CI 16.2–26.0). Most common G3-4 adverse events were neutropenia (20%), febrile neutropenia (7.5%), asthenia/fatigue (11%), respiratory infection (13%) and radiation pneumonitis (13%). CARG toxicity tool classified fit and medium-fit patients into high 10%, medium 52% and low risk 38%. GGA groups were not predictive of G3-4 toxicity. Medium and high risk patients based on CARG were more likely to have G3-4 toxicity (p = 0.086). Vulnerable patients defined by VES-13 had significantly higher risk of grade 3-4 toxicity (OR = 3.99, 95% CI 1.28–12.37, p = 0.017). **Conclusions:** CGA is helpful in selecting elderly patients with unresectable LA-NSCLC that may benefit from cCRT. VES-13 and CARG toxicity endpoints, may serve as a framework to rapidly screen novel compounds that should be investigated further as neoadjuvant therapies for resectable NSCLC. Clinical trial information: NCT02225405.
Background: With locally recurrent or newly diagnosed NSCLC who received thoracic SBRT after previous definitive radiotherapy (RT) or surgery poses a challenge in management. SBRT has been attempted as option of salvage treatment. The objective of this study is to report long-term outcome of SBRT in patients with recurrent or second malignancies following definitive RT or surgery. The median follow-up was 26.2%, 42.4%, and 24.7%, respectively (P = 0.007). Among 182 ALK-positive NSCLC, 8 (1%) were pericardial (PCDMS), 187 (24%) extrapleural pneumonectomy might be detrimental, but recent publications suggested that pleurectomy/decortication (P/D) may lead to better outcomes with overall median survival of 30-35 months in selected patients. Retrospective studies comparing trimodality therapy vs. medical management conducted in centers with surgery is offered by all centers. Our objective is to compare overall survival in patients offered trimodality therapy at a single institution to the one of patients treated at another institution where the management of MPM is exclusively medical. Methods: Retrospective analysis of two databases: 106 consecutive patients (cohort 1) treated by a single team in London (UK) from 2009 to 2016 and 98 consecutive patients (cohort 2) exclusively treated medically at the Queen Heart and Lung Institute (Canada) during the same period were included. Results: In cohort 1, all patients had P/D with hyperthermic pleural lavage with povidone-iodine, prophylactic chest wall radiotherapy and systemic chemotherapy. In cohort 2, 51% received palliative care only; 31% were treated with chemotherapy. Median survival was 32 months vs 10 months in cohort 1 and 2, respectively (hazard ratio with age, gender, pathology and TNM staging as covariates: 3.81; 95% CI: 2.66 – 5.45; p < 0.0001). Conclusions: Aggressive therapy of MPM using cancer-directed surgery, systemic chemotherapy and prophylactic radiotherapy may provide a significant survival benefit in selected patients.

8560 Poster Session (Board #166), Sun, 8:00 AM-11:30 AM
Long-term survival following trimodality therapy vs. medical management of malignant pleural mesothelioma.
First Author: Frédéric Larose, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada
Background: Medical management based on palliative chemotherapy is currently the standard of care in malignant pleural mesothelioma (MPM). Median survival of 12-16 months has been reported with modern chemotherapy regimens. Multi-modality therapy incorporating radical surgery, systemic chemotherapy and radiation is the most effective. The MARS feasibility study suggested that exophageal pneumonectomy might be detrimental, but recent publications suggested that pleurectomy/decortication (P/D) may lead to better outcomes with overall median survival of 30-35 months in selected patients. Retrospective studies comparing trimodality therapy vs. medical management conducted in centers with surgery is offered by all centers. Our objective is to compare overall survival in patients offered trimodality therapy at a single institution to the one of patients treated at another institution where the management of MPM is exclusively medical. Methods: Retrospective analysis of two databases: 106 consecutive patients (cohort 1) treated by a single team in London (UK) from 2009 to 2016 and 98 consecutive patients (cohort 2) exclusively treated medically at the Queen Heart and Lung Institute (Canada) during the same period were included. Results: In cohort 1, all patients had P/D with hyperthermic pleural lavage with povidone-iodine, prophylactic chest wall radiotherapy and systemic chemotherapy. In cohort 2, 51% received palliative care only; 31% were treated with chemotherapy. Median survival was 32 months vs 10 months in cohort 1 and 2, respectively (hazard ratio with age, gender, pathology and TNM staging as covariates: 3.81; 95% CI: 2.66 – 5.45; p < 0.0001). Conclusions: Aggressive therapy of MPM using cancer-directed surgery, systemic chemotherapy and prophylactic radiotherapy may provide a significant survival benefit in selected patients.

8561 Poster Session (Board #167), Sun, 8:00 AM-11:30 AM
Uncommon ALK fusion partners in advanced ALK-positive non-small-cell lung cancer.
First Author: Jin Kang, Guangdong Lung Cancer Institute, Affiliated Cancer Hospital of Zhongshan University, Zhengzhou, China
Background: The variants affect the efficacy of crizotinib in echinoderm microtubule protein-like-4 (EML4)- anaplastic lymphoma kinase (ALK) fusion-positive non–small-cell lung cancers (NSCLCs). Non–EML4-ALK fusions were detected and may have biologic and clinical implications differently. However, few studies focused on the effects of non–EML4-ALK ALK fusions on the efficacy of crizotinib. Methods: Among 182 ALK-positive patients whose ALK rearrangement were confirmed by fluorescence in situ hybridization developing resistance to crizotinib as the initial ALK-TKI between October 2010 and December 2017, 41 patients with sufficient tumor specimens could be evaluated for ALK variants by next-generation sequencing (NGS). Uncommon ALK fusion partners include non-EML4 or EML4-based variants. We retrospectively investigated progression-free survival (PFS), objective response rate (ORR) and overall survival (OS) between the patients with uncommon ALK fusion partners and those with EML4-ALK variants. Results: The frequency of uncommon ALK fusion partners was 34.1% (14/41). Among the 14 patients, there are 9 patients only harboring with one kind of non-EML4 partners. The ALK fusion partners of the other 5 patients included non-EML4 and EML4. The median PFS was longer in patients with uncommon ALK fusion partners than in those with EML4 variants (10.5 months vs 3.7 months [95% CI, 0.85 to 3.06 months], respectively; P = 0.142). The ORR between two groups were 64.3% and 77.8% in the two groups respectively. The median OS was 32.4 months and 21.0 months in the two groups respectively (95% CI, 1.21 to 4.65 months; P = 0.012 ). Four patients harbored with uncommon ALK fusion partners developed primary resistance to crizotinib and the three included DTNB-ALK, NR-110271-ALK, ZC3H8-ALK and STED2-ALK. A comprehensive genomic profiling (CGP) was performed on 50 ng of DNA for 783 FFPE mesothelioma (MS) samples using a hybrid-capture, adaptor ligation-based next-generation sequencing assay to a median coverage depth of > 60X. The results were analyzed for all classes of GA and tumor mutational burden (TMB), determined on up to 1.2 Mb of DNA. Microsatellite instability (MSI) status was evaluated by principal component analysis of optimal homopolymer loci. GA were counted as relevant if known to disrupt PBRM1 or homologous in the tumor. Results: Of 783 relapsed/refractory MS, 8 (1%) were pericardial (PCDMS), 187 (24%) peritoneal (PERMS), and 588 (75%) pleural (PLRMS) tumors (Table). Median ages were similar, but specimens from males were more common (72%) in PLRMS and females (56%) in PERMS. The PBRM1 GA was found in 11% overall, from 7.7% (PLRMS) to 20.3% (PERMS). BAP1 GA were found in 84% of PBRM1-altered MS and NF2 GA in 28%. In PBRM1 wild type MS, BAP1 GA were in 43.7% and NF2 GA in 31.2%. The median TMB was low and TMB > 20 mut/Mb were very uncommon. There were very few instances of MS with abnormal MSI. MS with MSI-GA and MSI-ICP will be presented. Conclusions: Immunotherapy strategies for the treatment of MS have recently emerged. PBRM1 GA are seen in 11% of MS and represent a potential predictive biomarker for therapy selection in this typically devastating disease. Further study of PBRM1 status in the ICPI treatment of MS in the clinical trial settings appears warranted.

8562 Poster Session (Board #168), Sun, 8:00 AM-11:30 AM
PBRM1 genomic alterations in mesothelioma: Potential predictor of immunotherapy efficacy.
First Author: Jeffrey S. Ross, SUNY Upstate Medical University, Syracuse, NY
Background: PBRM1, of the SWI/SNF family, modulates chromatin remodeling. PBRM1 genomic alterations (GA) are enriched in renal cell carcinoma and mesothelioma (MS). Recent evidence suggests that PBRM1 GA are strongly associated with neoantigen production and responsiveness to immune checkpoint inhibitors (ICI). Methods: Comprehensive genomic profiling (CGP) was performed on 50 ng of DNA for 783 FFPE mesothelioma (MS) samples using a hybrid-capture, adaptor ligation-based next-generation sequencing assay to a median coverage depth of > 60X. The results were analyzed for all classes of GA and tumor mutational burden (TMB), determined on up to 1.2 Mb of DNA. Microsatellite instability (MSI) status was evaluated by principal component analysis of optimal homopolymer loci. GA were counted as relevant if known to disrupt PBRM1 or homologous in the tumor. Results: Of 783 relapsed/refractory MS, 8 (1%) were pericardial (PCDMS), 187 (24%) peritoneal (PERMS), and 588 (75%) pleural (PLRMS) tumors (Table). Median ages were similar, but specimens from males were more common (72%) in PLRMS and females (56%) in PERMS. The PBRM1 GA was found in 11% overall, from 7.7% (PLRMS) to 20.3% (PERMS). BAP1 GA were found in 84% of PBRM1-altered MS and NF2 GA in 28%. In PBRM1 wild type MS, BAP1 GA were in 43.7% and NF2 GA in 31.2%. The median TMB was low and TMB > 20 mut/Mb were very uncommon. There were very few instances of MS with abnormal MSI. MS with MSI-GA and MSI-ICP will be presented. Conclusions: Immunotherapy strategies for the treatment of MS have recently emerged. PBRM1 GA are seen in 11% of MS and represent a potential predictive biomarker for therapy selection in this typically devastating disease. Further study of PBRM1 status in the ICPI treatment of MS in the clinical trial settings appears warranted.
Phase 1b study of avelumab in advanced previously treated mesothelioma: long-term follow-up from JAVELIN Solid Tumor. First Author: Raffit Hassan, Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, Bethesda, MD

Background: Avelumab, a human anti-PD-L1 IgG1 antibody, is approved for treatment of metastatic Merkel cell carcinoma in various countries and advanced urothelial carcinoma progressed on platinum therapy in the US. We report updated results with avelumab in a phase 1b cohort of patients (pts) with mesothelioma. Methods: Pts with unselectable pleural or peritoneal mesothelioma progressing after platinum and who received avelumab 10 mg/kg IV Q2W until progression, unacceptable toxicity, or withdrawal. Endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs). A post-hoc landmark analysis was performed using a Cox regression model.

Results: At data cutoff on Dec 31, 2016, 53 pts were treated and followed for a median of 24.8 mo (range 16.8–27.8). Pts had received a median of 2 prior lines of therapy (range 1–8). Confirmed ORR was 9.4% (95% CI 3.1–20.7) including complete response (CR) in 1.9% and partial response (PR) in 7.5%. Median duration of response was 15.2 mo (95% CI 11.1–not estimable). 26 pts (49.1%) had stable disease (SD) as best response and the disease control rate was 58.5%. Median PFS was 4.1 mo (95% CI 1.4–6.2) and the 6-mo PFS rate was 38.0% (95% CI 24.2–51.7). Median OS was 10.9 mo (95% CI 7.5–21.0) and the 12-mo OS rate was 45.9% (95% CI 31.9–58.8). In a landmark analysis of pts still on treatment at 3 mo, duration of response was 13.4 mo and 75% of pts who achieved CR/PR (HR < 0.01; 95% CI 0.70–0.89) or SD (HR 0.43; 95% CI 0.20–0.89) vs other pts. In evaluable pts with PD-L1+ (n = 16) or PD-L1− (n = 27) tumors (≥5% tumor cell cutoff), ORR was 18.8% (95% CI 4.1–45.6) and 7.5% (95% CI 0.9–24.3), respectively. Treatment-related (TRAEs) occurred in 43 pts (81.1%), including grade 3–5 TRAEs in 33% (9/27). Grade 3–5 TRAEs were grade 15.1%, fatigue (15.1%), and pyrexia (11.3%) in ≥10%. 5 pts (9.4%) had a grade ≥3 TRAE. 12 pts (22.6%) had an immune-related TRAE, which was grade ≥3 in 3 pts (5.7%; pneumonitis, colitis, and type 1 diabetes mellitus). No treatment-related deaths occurred. Conclusions: Updated data confirm the clinical activity and acceptable safety of avelumab in pts with previously treated mesothelioma. Clinical trial information: NCT02397931.

Phase II trial of pembrolizumab (P) in patients (pts) with previously-treated mesothelioma (MM). First Author: Arpita Desai, University of Chicago, Chicago, IL

Background: We conducted a phase II trial (NCT02399371) of P in previously treated MM to characterize activity in a non-selected population and determine a PDL1 expression threshold. Methods: Eligible pts had histologically confirmed MM, PS 0-1, disease progression, 1-2 prior regimens. P 200 mg was given Q21 days; CT scans Q9 weeks. 1"endpoints determined 1) objective response rate (ORR) in an unselected population (ORR ≥5% threshold) 2) optimal threshold for PDL1 expression (22% IHC tumor cell/ tumor proportion score (TPS) assay). Part A required ≥3 responses in 35 PD-L1 unselected pts. Part B PD-L1 preselects if a threshold is found in Part A. We previously reported (WCLC 2016) 7 responses in Part A; as no PD-L1 threshold was found (ROC 0.62, Part B enrolled 30 pts with no biomarker enrichment.

Results: 65 pts enrolled 5/15-2/18; 1 withdrew. Median age: 68 (range 26-85); PS 0; male: 77%; epithelioid/biphasic/sarcomatoid: 76.6%/15.6%/7.8%; pleural/peritoneal: 87.5%/12.5%; 1 prior regimen: 61%. Mean cycles: 9 (range 1-34). Partial response: 12/19 (63%), stable disease: 29 (47%). Median progression-free survival (PFS): 4.5 months (95% CI: 2.3, 6.2). Median overall survival: 11.5 mo (95% CI: 7.6, 14). Grade 3 toxicity: adenocystic insufficiency 3%, pneumonitis 3%, rash 3%, colitis 1%, confusion 1.6%, hepatitis 1.6%, hyperglycemia 1.6%. Grade 5: hepatitis 1.6%, unknown 1.6%. PDL1 expression by TPS (N = 62); none (< 1%) 45%; low (1-49%) 32%; high (≥50%) 23%. RR by TPS: none 7%; low 26%, high 31%. RR by histology: epithelioid 16%, biphasic 10%, sarcomatoid 40%. RR by site: pleural 20%, peritoneal 12.5%. PD-L1 did not correlate with RR as a continuous metric (ROC area 0.65; 95% CI: 0.48, 0.82); there was a trend to higher RR in PD-L1+ (<28%) vs PD-L1− (<7%) (p = 0.017). Median 1-year PFS by TPS: none 31.1 mo; low 6.2 mo; high 6.1 mo. Conclusion: P has clinically meaningful single-agent activity in PD-L1 unselected, previously treated MM, yielding a 19% RR, a 66% disease control rate, and manageable toxicity. Though an optimal PD-L1 threshold could not be established, there was a trend to higher RR and more durable PFS with increasing PD-L1 expression. Conclusions: P was well-tolerated and frequent in previously treated mesothelioma. Funded by MARF. Clinical trial information: NCT02399371.

Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. First Author: Vasiliki Panou, Department of Respiratory Disease & Department of Clinical Medicine, Clinical Cancer Research Center & Research Unit of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Aalborg, Denmark

Background: Malignant mesothelioma (MM) is thought to be largely due to asbestos exposure, but the prevalence and the causative role of germline cancer susceptibility gene mutations in MM is unknown. Methods: Targeted genomic capture and next generation sequencing of 85 cancer susceptibility genes was performed from peripheral blood or saliva from 198 patients with pleural, peritoneal, or tunica vaginals MM presenting to The University of Chicago Mesothelioma Clinic. Results: The patient population fit usual MM demographics: the majority were male (n = 136, 69%), had pleural disease (n = 148, 75%), and a history of occupational asbestos exposure (n = 129, 65%). The median age at MM diagnosis was 67 years (range 24-88). We identified 24 pathogenic germline mutations in 13 genes in 23/198 (12%) MM patients. BAP1 mutations were the most common (n = 6, 25%). The remaining were in genes involved in cell cycle and DNA repair (n = 14), oxygen sensing (n = 2), endoplasmic reticulum stress (n = 1), and cell cycle checkpoint (n = 1). Pleural sites (n = 20); 95% CI 0.10-0.58), asbestos exposure (OR 0.28; 95% CI 0.11-0.72), and older age (OR 0.95, 95% CI 0.92-0.99) were associated with decreased odds of carrying a germline mutation while having a second cancer diagnosis (OR 3.33; 95% CI 1.22-9.07) significantly increased the odds. The odds of carrying a mutation in BAP1 was 7.46 (95% CI 1.84-29.41) for men vs women (p = 0.017). For overall survival HR = 0.77; 95% CI 0.46–1.29. We evaluated outcomes in the combination and monotherapy phases to understand better the overall study results. Methods: Pts with unselectable MPM (ECOG PS 0–1), stratified by histology, were randomized 1:1 to receive ≥6 cycles PEM (500 mg/m2)/CIS (75 mg/m2) Day 1 + N or 200 mg bid, Days 2–21), followed by N or P monotherapy maintenance. TE was analyzed for PEM/CIS, N, and P, TB, measured using sum of diameter by modified RECIST 1.0, was analyzed over time, using a mixed-effects model in pts with at least two imaging datapoints. Results: 87 pts were randomized; 85 pts (N: 44, P: 41) were treated; 61 pts (N: 34, P: 27) received maintenance; median follow-up was 29 months. Both groups received a median of 6 cycles of PEM/CIS. In the combination phase, greater and longer reduction in TB was seen with P. Average TB reduction from baseline to nadir was 46% greater for N vs P (33 vs 22.6 mm). The nadir occurred at 4.1 vs 2.3 months for N vs P. In the monotherapy phase, treatment with N vs P showed markedly slower tumor regrowth from nadir (e.g. +46% vs +112% at 12 months). Median TE (N vs P) was 7.8 vs 5.3 months over the full treatment period. In the monotherapy phase, TE was 5.3 vs 2.8 months. The proportion of pts with serious AEs (N vs P) was similar between treatment groups during combination (34% vs 32%); during monotherapy the rate was 15% vs 26%. Conclusions: Pts receiving N had greater, more sustained reduction in TB than those receiving P and remained on active therapy for longer. AEs were manageable in both phases of the trial. Together with the primary study results, these analyses show that combination of PEM/CIS followed by N monotherapy provides clinical benefit to pts with MPM. Clinical trial information: NCT01970110.
Background: NGR-hTNF is a vascular-targeting agent able to increase tumor microenvironment. MPM patients failing first-line therapy have limited treatment options. Methods: In the phase 3 trial NGR015 (ASC0 2015; abs 7501), 400 patients received single-agent gemcitabine, vinorelbine or NGR-hTNF as second-line therapy. By ITT analysis, overall survival (OS) did not differ between arms (median follow-up 18.7 months; data maturity 75%). In subgroup analyses, there was a significant interaction only between treatment and treatment-free interval (TFI) after first-line therapy. NGR-hTNF improved OS and PFS in the short TFI subset (< median: 4.8 months; n = 198). We assessed long-term outcomes in patients with short TFI and prognostic TFI value after adjusting for baseline covariates (age, sex, PS, histology, EORTC score, NLR, response to prior therapy and selected chemotherapy). Results: At a median follow-up of 33.8 months (data maturity 86%), a treatment-by-TFI interaction for OS persisted in univariate (p = 0.004) and multivariable models (p = 0.002). In the short TFI subset, median OS was 9.2 months (95% CI 6.6-11.8) for NGR-hTNF vs 6.3 months (5.7-7.0) for placebo (HR 0.67; 0.48-0.93; p = 0.02); adjusted HR 0.64; 0.45-0.89; p = 0.008). Survival rates were 39% (29-50) vs 24% (16-32) at 1 year and 18% (9-26) vs 9% (3-15) at 2 years. The 25% survival rate occurred 7-8 months later with NGR-hTNF than with placebo (17.3 months vs 10.2 months). NGR-hTNF treatment was associated also with improved PFS (median 3.4 vs 1.9 months; HR 0.66; 0.48-0.91; p = 0.01; adjusted HR 0.65; 0.47-0.96; p = 0.009). In sensitivity analyses, consistent results were found using a 6-month TFI cutoff. The prognostic TFI value was assessed in the control group to avoid confounding effects of experimental treatment. A short TFI independently correlated with worse OS (HR 1.79; 1.29-2.50; p = 0.0006). Conclusions: Benefit with NGR-hTNF treatment in the short TFI subgroup was maintained after a 3-year follow-up, deserving a confirmatory randomized trial as these MPM patients have a poor prognosis. Clinical trial information: NCT01098266.

8569 Poster Session (Board #175), Sun, 8:00 AM-11:30 AM
A real-world experience of nivolumab in advanced malignant mesothelioma (MM). First Author: Hussein Hamad, Baylor College of medicine, Houston, TX

Background: Nivolumab showed promising results in phase II clinical trials for advanced MM patients with good performance status (PS). Limited data exists for poor PS patients treated outside of clinical trial. We report the efficacy and safety in patients enrolled in a Nivolumab expanded-access program (EAP). Methods: 27 advanced MM patients were enrolled in EAP and treated from 12/2015 - 12/2017 at Mesothelioma Treatment Center at Baylor College of Medicine. Nivolumab 3 mg/kg was administered every 2 weeks until disease progression. Blinded radiologist assessed responses using RECIST 1.1 criteria. Baseline tumor volumes (BTV) were measured. PD-L1 expression on tumor samples was quantified by PD-L1 IHC 28-8 assay. Results: 25 patients were evaluable (2 patients expired before evaluation for response). Median age was 67 years (range 38-89). 72% were male, 56% had PS ≥ 2; epithelioid/ biphasic histologies: 76%/24%. Median follow up time was 6 months (range 2-23). 72% received Nivolumab as second line or later therapy. Median progression free survival was 5 months. Response rate was 24% (3 CR, 3 PR); 9 stable disease (SD), disease control rate (DCR) was 60% (CR+PR+SD). Median duration of response 6 months (range 2-24). For patients with PS ≥ 2, DCR was 50%. For patients treated as first line, DCR was 42%. 20 patients had PDL1 expression evaluated; DCR was 55% in patients (45%) with PDL1 < 1%, and 63% in those with PDL1 > 1%. Median BTV was 251 cm³. DCR was 50% for patients with BTV > median and 75% for patients with BTV < median. At 6 months, 52% of patients were alive. Grade 1/2 adverse events (AE) include skin rash (1), body aches/arthritis (2) and enteritis/diarrhea (2). No grade 3/4 AE or treatment related death occurred. Conclusions: Nivolumab is effective and safe for MM patients with poor PS. Durable responses were achieved in a subset of patients. Our limited data showed responses regardless of tumor PD-L1 expression. Smaller BTV may predict response but validation of this observation is warranted.

8570 Poster Session (Board #176), Sun, 8:00 AM-11:30 AM
Efficacy and safety of lurbinectedin (PM1183) in small cell lung cancer (SCLC). First Author: Jose Manuel Trigo Perez, Hospital Virgen de la Victoria, Malaga, Spain

Background: SCLC is a deadly cancer and despite initial 80% response, almost all patients (pts) will relapse and die of this disease. Limited options exist after failure of first line, with a median time to progression (TTP) of around 3.5 months. New therapeutic agents are needed. Lurbinectedin (L) is a new anticancer drug that blocks transcription and induces DNA double-strand breaks, leading to apoptosis. Methods: A multicenter phase 2 basket trial to assess the efficacy and safety of L in several types of advanced solid tumors, including SCLC, is ongoing. In the SCLC cohort, 15 adult patients without brain metastases, who had received one prior chemotherapy line, were recruited. If at least one confirmed response was observed, recruitment would be increased to 100 patients. The study intervention comprised L 3.2 mg/m² in a 1-hour infusion every 3 weeks. Results: 50 pts were treated and evaluable for efficacy. Median age was 60 years (range, 40-83) and 29 (58%) were males. 45 (80%) had an ECOG of 0/1. 34 pts (68%) had metastatic disease at study entry, 25 (50%) pts had a chemotherapy free interval (CTFI) > 90 days and 22 (44%) had a CTFI < 90 days (unknown in 3). Pts received a median of 5 cycles of therapy (range, 1-18) and a median total dose of 15.9 mg/m² (range, 2.9-58.2). Nineteen pts (38%) had a partial response (PR); among pts with CTFI ≥ 90 days, 52% (13/25) had a PR. Twenty pts (40%) had disease stabilization, 6 of them for > 4 months. Median response duration was (K-M) 5.3 (CI 95% 2.8-8.8) and median progression free survival (PFS) was 4.2 months (CI 95% 2.8-6.3). Median PFS for pts with CTFI ≥ 90 days was 4.7 months 95% CI (3.1-7.4). Myelosuppression was the most common adverse event: 44% neutropenia grade (G) 3/4, 12% febrile neutropenia, and 8% thrombocytopenia G 3/4; 8 pts had dose delay due to neutropenia G2-4, and 10 pts had dose reduction because of neutropenia G4. G-CSF was given to 9 pts. There was one protocol-defined withdrawal due to neutropenia. Conclusions: Lurbinectedin as a single agent shows compelling activity as second line treatment in SCLC, with an acceptable tolerability and manageable safety profile. No unexpected or grade 5 toxicity occurred. Updated results will be presented. Clinical trial information: NCT02454972.
Background: SCLC is a high-grade neuroendocrine malignancy with overall response rates (ORR) to second-line chemotherapy generally ranging from 10-30%. The poly(ADP-ribose) polymerase (PARP) inhibitor O has activity in SCLC in preclinical studies and may synergize with the alkylating agent T.

Methods: We performed a single-arm phase 1/2 study of combination O/T in adults with SCLC. Eligibility criteria included histologically/cytologically confirmed incurable SCLC which had progressed following platinum-based chemotherapy. O (tablet formulation) and T were administered orally on days 1-7 of 21-day cycles as escalating doses using a 3+3 design in the phase 1 portion, followed by a phase 2 expansion at the recommended phase 2 dose (RP2D). Response assessments were performed every 6 weeks. The primary endpoint of the phase 2 portion was ORR. We present data at a planned interim analysis after enrollment of 20 patients at the RP2D. Patient-derived xenografts (PDx) were generated from a subset of patients prior to O/T and at progression. O/T activity was assessed in vivo in PDx in a co-clinical trial. Results: 13 patients were enrolled to 4 escalating dose levels in the phase 1 portion, and 17 additional patients were enrolled at the RP2D, O 200 mg BID and T 75 mg/m2 QD. The median (m) age was 62.0 years (range 39.2-85.2) and m prior lines of therapy was 2 (range 1-7). The most common treatment emergent adverse events (AEs) related to study drugs across dose levels were thrombocytopenia (67%; 23% grade 3-4), anemia (63%; 23% grade 3-4) and neutropenia (69%; 35% grade 3-4). There was one related grade 5 AE due to pneumonia and neutropenia. Among 29 evaluable patients at all dose levels, ORR was 41.4% (95% CI 23.5-59.3), with responses seen in 10/19 and 2/9 platinum-sensitive and -resistant patients, respectively. The mPFS was 87 days (95% CI 48-159), the mOS was 228 days (95% CI 140-316), and the mTTP was 4.3 months. Responses to O/T mirrored those in donor patients, and basal PARylation was a strong predictive biomarker for sensitivity. Conclusions: O/T shows promising clinical activity in SCLC. Further exploration of dosing strategies and biomarkers in patients and PDx is underway. Clinical trial information: NCT02446704.

8572 Poster Session (Board #178), Sun, 8:00 AM-11:30 AM
Large-scale nationwide genomic screening system for small cell lung cancer in Japan (LC-SCRUM-Japan).

First Author: Yukari Ogawa, Kyorin University Hospital, Mitaka, Japan.

Background: Recent genomic analyses of small-cell lung cancer (SCLC) have provided insights into novel therapeutic targets such as the PI3K pathway. Thus, we prospectively analyzed clinical samples of SCLC using a large-scale nationwide genomic screening project in Japan (LC-SCRUM-Japan) to identify the patients harboring targetable genomic alterations.

Methods: Submitted tumor samples were subjected to a next-generation sequencing (NGS) system, Oncomap™ Comprehensive Assay, enabling the simultaneous analysis of 143 (ver.1) or 161 (ver.3) cancer-related genes.

Results: From July 2015 to January 2018, 544 patients had been enrolled. The median age was 68 years. 76% were male and 95% were smokers. Among 468 samples completed analysis, we identified high prevalence of inactivating TP53/RB1 mutations in 341 (73%) /148 (32%) of cases, respectively. MYC/MYC1/MYCN amplifications were detected in 18 (4%) /23 (5%) /7 (2%) of cases, respectively. The NGS analysis also showed that 30 (6%) of cases had activating alterations in receptor tyrosine kinase genes; 7 EGFR mutations, 8 KRAS mutations and 15 FGFR1 copy number gains. Mutations in the PI3K pathway were detected in 35 (7%) of the tumors: 13 PIK3CA mutations, 17 PTEN inactivating mutations, 1 AKT mutation and 4 TSC2 inactivating mutations. Among them, 6 cases harboring mutations in the PI3K pathway enrolled in the investigator-initiated phase II study of gedeotibib (UMIN000020585). Survival data was available in 244 patients receiving platinum-based chemotherapy. Multivariate analysis revealed the presence of MYC/MYC1 amplification or KRAS mutation were significantly associated with poor progression free survival of the first-line chemotherapy (HR, 3.07; 95% CI 1.81 – 5.20; p < 0.001) and unfavorable survival (HR, 2.31; 95% CI 1.26 – 4.22; p = 0.007).

Conclusions: To our knowledge, this is the world’s largest prospective genomic screening project for SCLC. This nationwide screening system is helpful for identifying biologically relevant genomic alterations and prognostic prediction in SCLC.

This screening program is currently ongoing to screen 800 SCLCs as a final goal. Updated screening results will be presented at the 2018 ASCO Annual Meeting.
A phase II study of pembrolizumab and paclitaxel in refractory extensive disease small cell lung cancer. First Author: YuJung Kim, Seoul National University, Seongnam-si, Korea South

Background: Patients with platinum refractory extensive disease (ED) small cell lung cancer (SCLC) have a poor prognosis and a little progress have been made. We aimed to investigate the efficacy and safety of pembrolizumab and paclitaxel in these patients. Methods: In this phase II, open-label, multicenter study, 26 patients who progressed after etoposide/platinum chemotherapy were enrolled. The patients received paclitaxel 175mg/m2 every 3 weeks for up to 6 cycles. Pembrolizumab 200mg was added from the second cycle and continued until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) and secondary endpoints were progression-free survival (PFS), overall survival (OS), safety, and biomarker analysis including programmed death-ligand 1 (PD-L1) expression, next-generation sequencing (NGS), and flow cytometric analysis of peripheral blood immune cells. Results: The median age was 68.5 years, and 88% were male. Of the 26 evaluable patients, the ORR was 23.1% (complete response: 3.8%, confirmed partial response [PR]: 19.2%, disease control rate was 80.7%. The median PFS and OS were 5.0 months (95% CI, 2.7-6.5 months) and 8.5 months (95% CI, 6.6-15.1), respectively. Grade 3 or 4 adverse events occurred in 38.4% (neutropenia: 25.0%, anemia: 19.2%, and thrombocytopenia: 11.5%). Conclusion: Pembrolizumab and paclitaxel combination therapy showed a moderate activity with an acceptable toxicity in refractory ED SCLC. Further studies are warranted to define a subset of patients who may benefit from the addition of pembrolizumab. Clinical trial information: NCT02951432.

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A phase II study of regorafenib in patients with thymic epithelial tumors previously treated with chemotherapy. First Author: Matteo Pernmo, Department of Oncology, Humanitas Research Hospital- Humanitas Cancer Center, Rozzano, Italy

Background: Angiogenes.Has an important role in thymic epithelial tumors (TETs); VEGF, PDGF and PDGFRα are overexpressed in TETs, and VEGF expression and microvessel density are associated with invasiveness and stage. Regorafenib potently inhibits VEGFR1, 2, and 3, TIE2, FGFR and PDGFR-β. The aim of this study is to determine the activity of Regorafenib as monotherapy in patients (pts) with adenoid cystic cancer (T2B – B3) and Thymic Carcinoma (TC) previously treated with cisplatin-based chemotherapy. Methods: Pts with progressive disease were prospectively enrolled in single arm, phase II trial to receive oral Regorafenib 160 mg once daily 3 weeks on/1 week off until documented disease progression, unacceptable toxicity, or pt refusal. Tumor assessment and safety were assessed every six and three weeks, respectively. This Fleming phase II trial was designed to reject the null hypothesis of a progression free survival (PFS) rate <25% with a type I error of 0.10 and a statistical power of 80% at the alternative hypothesis of a PFS rate of ≥50%. The drug should be recommended for further study if 8 or more of the 19 total evaluable pts would be progression free at 2 months. Clinical trial information: NCT02307500.

Results: Results of the 19 enrolled pts are presented. Pt characteristics are as follow: median age 54 years (range 40;75), male/female 11/8 (58%/42%); T/T C/12 (37%/63%); and, number of previous lines (line<2lines) of chemotherapy 9/10 (47%/53%). Two pts were not evaluable at all (10.6%). According to RECIST criteria, we observed partial response (PR) in 1 pt (T) (5.3%), stable disease (SD) in 14 pts (97/5TC) (73.5%), and progressive disease (PD) in 2 pts (17/1TC) (10.6%), with a disease control rate of 78.8%. Response evaluation with Choi criteria is planned. With a median follow up of 12 months (0.9-39.3 months), median PFS was 8.9 months, while median OS was not reached. Thirteen patients were progression free at 2 months. The 1-year PFS rate and 1-year OS rate were 17.9% and 94.4%, respectively. Conclusions: The primary endpoint of this study was reached. On the basis of PFS and OS results, the efficacy of Regorafenib should be better evaluated in subsequent larger trials. Clinical trial information: NCT02307500.

Nivolumab plus cisplatin/pemetrexed or pemetrexed/gemcitabine as induction in resectable NSCLC. First Author: Nathaniel R. Evans, Thomas Jefferson University, Philadelphia, PA

Background: For patients (pts) with stage IB (>4cm)-IIIA Non-small-cell lung cancer (NSCLC), multi-modality therapy yields a modest improvement in 5 year post-surgical overall survival (OS), with comparable benefit for induction and postoperative adjuvant chemotherapy (chemo). Induction can speed the discovery of promising regimens by using pathologic response as a surrogate for OS. About 20% of pts treated with induction chemo have major pathologic response (MPR) (< 10% viable tumor) at primary and lymph nodes while pathologic complete responses (pCR) average 4%. MPR was strongly associated with improved OS (Hellmann MD, Lancet, 2014), PD-1 checkpoint inhibitors (CI), nivolumab (nivo), pembrolizumab (pembro), and the PD-L1 Ct, atezolizumab, are established in advanced NSCLC as 2nd line therapy, and pembro is approved as a single agent as 1st line treatment of pts with PD-L1 high expressing tumors. In a phase III 1st line NSCLC study, pts with high mutational burden tumors had superior OS with nivo plus pibilum compared to doublet chemo. Pembro plus carboplatin with pemetrexed (P) was approved as 1st line therapy based on a randomized phase II study in advanced NSQ NSCLC showing improved clinical response and PFS compared to chemo alone with no increase in grade III toxicity. We therefore hypothesize that the addition of nivo to induction cisplatin (C) or C gemcitabine (G) will increase the MPR rate over induction chemo alone compared to historical controls. Methods: This is an investigator initiated trial for pts with newly diagnosed stage I-IIIA (stage I ≥ 4cm) SQ and NSQ NSCLC. Induction is C 75mg/m2 IV q 3w x 3 plus either P 500 mg/m2 IV q 3wks x 3 or G 1250mg/m2 IV d1, q8wks x 3 plus nivo 360mg IV q 3w x 3. Surgery is planned 3 wks after the last dose. The primary outcome is MPR. Secondary outcomes include safety, pCR, overall clinical response rate, clinical CR, 1 year PFS, OS and exploratory outcomes assessing markers of immune bias. Enrollment will be 34 pts. Clinical trial information: NCT03366766.
Background: Robust and durable antitumor activity was previously demonstrated on pembrozilumab in patients with advanced NSCLC, both as a monotherapy in the first- and second-line settings (in patients with PD-L1 tumor proportion score (TPS) ≥50% and ≥1%, respectively) and when combined with pemetrexed/cisplatin (in patients with histology). KEYNOTE-067 (NCT03425643) is a phase 3 study that evaluates standard neoadjuvant chemotherapy with perioperative pembrolizumab or placebo in early-stage NSCLC. Methods: This international double-blind phase 3 trial enrolls patients aged ≥18 years with previously untreated, resectable stage IB/II NSCLC, ECOG PS 0, with ≥10% viable tumor cells in resected primary tumor/lymph nodes, pathological complete response (no residual invasive cancer on H&E stained slides of resected lung specimen)–defined as down-staging, complete resection, pattern of recurrence and toxicity. Additionally, a large translation research program accompanies the trial investigating potential predictive biomarkers of anti-PD-L1 therapy. Based on prior studies, which documented a significant correlation between OS and mutational burden, a translational study will determine if sensitivity to nivolumab differs according to PD-L1 expression (subgroups ≥50%, 1-49%, ≤1%).

The primary endpoint of this pilot study is disease control rate (CR +PR+SD) after neoadjuvant atezolizumab. Secondary endpoints include major pathological response (>90% viable tumor cells in resected primary tumor/lymph nodes), pathological complete response (no residual invasive cancer on H&E stained slides of resected lung specimen/lymph nodes post–neoadjuvant therapy), safety, and patient-reported outcomes. An estimated 786 patients will be enrolled, beginning March 9, 2018. Clinical trial information: NCT03425643.

Additional analysis will determine if sensitivity to nivolumab differs according to PD-L1 expression (subgroups ≥50%, 1-49%, ≤1%); and the correlation between OS and mutational burden, estimated by genome-wide analysis of CNAs, and immunotranscriptomic profile. The trial is coordinated by the CRUK Southampton Clinical Trials Unit, within the Centre for Cancer Immunotherapy, UK. The trial aims to recruit 336 patients with pleural or peritoneal mesothelioma who have received at least two prior lines of therapy, from UK sites between March 2017-2021. Current enrollment at 01 Feb 2018 was 63. Patients will be randomized 2:1 (treatment:control), stratified according to epithelioid vs. non-epithelioid, to receive 240mg nivolumab (anti-PD-1 antibody) monotherapy or saline placebo as a 30 minute intravenous infusion. Allocation will be double blind. Treatment will be ever 14 days until disease progression for max. 12 months. Trial follow up will continue for 6 months after the last participant has progressed, or completed or discontinued treatment. The trial is powered (80% with 2-sided 4% significance level) to detect a hazard ratio of 0.7 using an adjusted Cox regression model (time to event) and will be analyzed using intention-to-treat. This trial is funded by Cancer Research UK (C16728/A21400) and Bristol Myers Squibb (CA 209-841). Trial registrations: NCT03063450, ISRCTN79814141. Clinical trial information: NCT03063450.

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Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

TPS8597 Poster Session (Board #189b), Sun, 8:00 AM-11:30 AM
ATLANTIS: Global, randomized phase III study of lurbinectedin (L) with doxorubicin (DOX) vs. CAV or topotecan (T) in small-cell lung cancer after platinum therapy. First Author: Anna F. Farago, Massachusetts General Hospital, Boston, MA

Background: Lurbinectedin (L), a synthetic analog of marine-based tetrahydroisoquinoline, blocks active transcription, produces DNA breaks and apoptosis, and affects the inflammatory microenvironment. L showed promising activity in combination with DOX in a phase I cohort of relapsed small cell lung cancer (SCLC) patients (pts) (overall response rate (ORR) = 67%; n = 21, ASCO 2015, abstract 750B). Most common toxicities were hematologic. Lower dose improved safety and confirmed activity in an expanded cohort (ORR = 37%; n = 27 SCLC pts). Methods: We present an ongoing multinational (20 countries), multicenter (154 sites), open-label, randomized phase III study of L/DOX vs. control arm (investigator choice of either cyclophosphamide, DOX and vincristine (CAV) or topotecan (T)). 600 pts will be randomized (1:1) and stratified according to ECOG performance status (PS), central nervous system (CNS) involvement, previous treatment with antiPD1/antiPD-L1, chemotherapy-free interval, and investigator’s choice of control arm. Interim safety analysis by an independent data monitoring committee (IDMC) is planned when the first 150 pts are randomized. The most relevant inclusion criteria are: age ≥18 years; confirmed SCLC diagnosis (if primary site unknown, Ki-67 expression >50%); previous platinum-containing line (additional immunotherapy allowed); ECOG PS 0-2; adequate major organ function (including LVEF >50%). Main exclusion criteria include chemotherapy-free interval <30 days; prior treatment with L or T; symptomatic or steroids-requiring CNS involvement. The primary objective is to determine a difference in progression-free survival (RECIST v1.1) by independent review committee. Secondary endpoints include overall survival, survival rates at 12/18/24 months, antitumor response, duration of response, quality of life, safety, and pharmacokinetics. The first patient was randomized in August 2016. The pre-planned interim safety analysis was done on November 2017 and the IDMC recommended to continue the trial unmodified. Trial recruitment is expected to be completed in Q2 2018. Clinical trial information: NCT02566993.

TPS8598 Poster Session (Board #190a), Sun, 8:00 AM-11:30 AM
A two-part, open-label, randomized, phase 2/3 study of dinutuximab and irinotecan versus irinotecan for second-line treatment of subjects with relapsed or refractory small cell lung cancer. First Author: Martin J. Edelman, Fox Chase Cancer Center, Philadelphia, PA

Background: Small cell lung cancer (SCLC) is characterized by rapid growth and early dissemination to distant sites. Although highly responsive to initial chemotherapy and radiotherapy, most patients relapse within one year of starting treatment (Tx). The outcome for patients with SCLC who relapse or are refractory (RR) to first-line Tx is poor. Topotecan (T) is the only FDA-approved agent for second-line (SL) Tx of platinum-sensitive patients with SCLC. Irinotecan (I) is listed by the National Comprehensive Cancer Network as an alternative agent for second and subsequent lines of therapy. Dinutuximab (D) is a chimeric monoclonal antibody that binds cell surface glycolipid disialoganglioside GD2 and induces tumor cell lysis through antibody-dependent cell-mediated and complement-dependent cytotoxicity. GD2 is expressed in a variety of neuroectoderm-derived tumors, including SCLCs. The potential for combination D and I to improve upon outcomes currently seen with single-agent SL Tx (I or T) in RR SCLC warrants exploration. Methods: A two-part, multicenter, open-label, randomized study of D and I versus I alone in subjects with RR SCLC is underway (NCT03098030). Inclusion criteria include documented progressive disease during or RR disease after first-line platinum-based Tx and an Eastern Cooperative Oncology Group performance status of 0 or 1. Subjects who are candidates for re-Tx with original platinum-based regimen as SL Tx will be excluded. Part 1 of the study involved intrasubject (n = 12) dose escalation to evaluate the safety and tolerability of D in combination with I. Part 1 results are to be presented (Edelman et al., European Lung Cancer Congress, 11-14 April 2018). Part 2 of the study is currently enrolling and is designed to determine whether combination D and I prolongs overall survival compared with I alone. Subjects will be randomized 2:2:1 to I, D and I, or T. Randomization will be stratified by duration of response to prior platinum Tx (relapse-free period <3 or ≥3 months). It is anticipated first data monitoring committee review will occur in April 2018. Clinical trial information: NCT03098030.

TPS8599 Poster Session (Board #190b), Sun, 8:00 AM-11:30 AM
Phase I/II trial of anti-PD-1 checkpoint inhibitor nivolumab and 177Lu-DOTA-Tyr3-Octreotate for patients with extensive-stage small cell lung cancer. First Author: Chul Kim, Georgetown University, Washington, DC

Background: Small cell lung cancer (SCLC) accounts up to 15% of all new cases of lung cancer. 60% of patients with SCLC present with extensive-stage SCLC (ES-SCLC). Despite initial sensitivity to chemotherapy, patients with ES-SCLC relapse quickly. Studies have shown that somatostatin receptors are expressed in SCLC. 177Lu-DOTA-Tyr3-Octreotate (Lutathera) is a 177Lu-labeled somatostatin analog that can target somatostatin receptor positive cancer cells. Mounting evidence suggests that radiation therapy can augment the immunogenic response. Based on these findings, we hypothesize that Lutathera and nivolumab, an anti-PD-1 therapy, may have synergistic effects on the generation of anticancer immunity and this combination given as maintenance treatment may delay progression in patients with ES-SCLC.

Methods: This is a multicenter phase I/II trial of Lutathera and nivolumab in patients with ES-SCLC (NCT03325816). Patients with tracer uptake on gallium-68 dotate PET scan (NETSPOT) will be eligible. In the phase I part, we aim to determine the recommended phase II dose of Lutathera and nivolumab in patients with relapsed or refractory ES-SCLC, non-progressing ES-SCLC after first-line chemotherapy, or advanced grade I-II pulmonary neuroendocrine tumors. In the phase II part, patients with ES-SCLC are randomly assigned to either maintenance treatment with Lutathera and nivolumab or observation, after completion of front-line chemotherapy. The primary endpoint for the phase II part is progression-free survival (PFS). Crossover is allowed at progression for those in the observation group. Assuming a median PFS of 2 months following first-line platinum-based chemotherapy for ES-SCLC in the observation group, and an expected median PFS of 5 months for the maintenance therapy group (hazard ratio 0.4), a total of 52 patients are required to have 80% power at a two-tailed alpha of 0.05. Seven cancer centers will participate in the trial: Georgetown University, Hackensack University Medical Center, Walter Reed National Military Medical Center, Memorial Sloan Kettering Cancer Center, Vanderbilt University, UCLA, and UCSF. Clinical trial information: NCT03325816.

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null
Background: In the ongoing phase 3 ARCHER 1050 study, first-line treatment with daco significantly improved the primary endpoint of progression-free survival, duration of response, and time to treatment failure vs gefitinib in patients (pts) with epidermal growth factor receptor (EGFR)-mutation-positive advanced non-squamous NSCLC (NEJ009). Here, we present the OS results. Methods: Pts with newly diagnosed stage III/IIV or recurrent NSCLC harboring an EGFR mutation (exon 19 del or exon 21 L858R +/- exon 20 T790M) and without central nervous system metastasis were randomized 1:1 to oral daco 45 mg/day or oral gef 250 mg/day. Pts were stratified by EGFR mutation type. Results: As of 17 February 2017, a total of 220 deaths (48.7%) occurred over a median follow-up of 31.3 months (mo): 103 (45.4%) in the daco arm (n = 227) and 117 (52.0%) in the gef arm (n = 225). Daco showed a significant improvement in OS compared to gef (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.582–0.993; 2-sided P = 0.044 based on stratified analysis). Median OS (95% CI) was 34.1 mo (29.5–37.7) with daco vs 26.8 mo (23.7–32.1) with gef. Survival rates at 30 mo were 56.2% with daco and 46.3% with gef. The table shows preliminary OS subgroup analyses by race and EGFR mutation type, with >55% of pts being censored in some subsets. OS subgroup analyses were consistent with the primary OS analysis across most baseline characteristics. Conclusions: In pts with advanced EGFR mutation-positive NSCLC, daco is the first to show a significant improvement in OS in a phase 3 trial compared to a standard-of-care tyrosine kinase inhibitor. Daco should be considered as one of the standard treatment options for these pts. Clinical trial information: NCT01774721.

**Results:**

<table>
<thead>
<tr>
<th>Race</th>
<th>Median OS, mo (95% CI)</th>
<th>Median OS, mo (95% CI)</th>
<th>Daco vs Gef, HR (95% CI)</th>
<th>2-Sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-East Asian</td>
<td>32.2 (95% CI: 27.7–37.3)</td>
<td>26.8 (95% CI: 23.8–30.0)</td>
<td>0.76 (0.58–0.99)</td>
<td>0.044</td>
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<tr>
<td>East Asian</td>
<td>27.6 (95% CI: 22.9–32.5)</td>
<td>24.3 (95% CI: 21.3–27.8)</td>
<td>0.82 (0.59–1.18)</td>
<td>0.293</td>
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</table>

**Conclusions:** In pts with advanced EGFR mutation-positive NSCLC, daco is the first to show a significant improvement in OS in a phase 3 trial compared to gefitinib. Daco should be considered as one of the standard treatment options for these pts. Clinical trial information: NCT01774721.

**Methods:**

- **Race:**
  - Non-East Asian: 32.2 (95% CI: 27.7–37.3)
  - East Asian: 27.6 (95% CI: 22.9–32.5)

**Results:**

- **Race:**
  - Non-East Asian: 32.2 (95% CI: 27.7–37.3)
  - East Asian: 27.6 (95% CI: 22.9–32.5)

**Conclusions:** In pts with advanced NSCLC and no previous chemotherapy were randomly allocated to receive EB significantly prolonged progression-free survival (PFS) in patients with advanced non-squamous NSCLC harboring an EGFR activating mutations (exon 19 deletion or exon 21 L858R) and without central nervous system metastasis. Sixty-four patients (85.3%) in EB and 65 patients (84.4%) in E were followed up for a median of 12.4 months. The interim analysis showed that the study met its primary endpoint. At data cutoff (Sept 21, 2017), median PFS was 16.9 months (95% CI, 14.2–21.0) in EB and 13.3 months (11.1–15.3) in E (p = 0.029). The median OS in EB was 29.3 months (95% CI, 24.3–NR) vs 22.4 months (95% CI, 19.6–26.8) in E. Although EGFR-TKI alone has been a standard first-line treatment for pts with advanced NSCLC with EGFR mutations, our phase II study (NEJ009) showed promising efficacy of G. NEJ009, an open-label, randomized phase III study, was conducted to evaluate the superiority of GCP vs G in progression-free survival (PFS), PFS2, and overall survival (OS). Methods: Pts with newly diagnosed stage III/IV recurrent NSCLC harboring an EGFR activating mutations (exon 19 deletion or exon 21 L858R) were randomized 1:1 to G 250 mg PO QD or GCP (G 250 mg PO QD combined with carboplatin AUC 5 ± pemetrexed 500mg/m², every 3 weeks). The primary endpoints consisting of PFS, PFS2, and OS were sequentially analyzed according to a preplanned gate-keeping method. Secondary endpoints included objective response rate, safety, and quality of life. Results: In September 2017, a preplanned required number of events of PFS2 was observed. The ITT population included 344 pts with baseline characteristics fairly well balanced between the arms. Although GCP demonstrated significantly better PFS compared to G, there was no difference in PFS2 between the arms as below. Additional OS analysis (G:101 events vs GCP:83 events) revealed that median survival time of GCP was more than that of G (52.2 months vs 38.8 months, HR=0.695, = 0.013). Conclusions: NEJ009 is the first phase III study which evaluated the efficacy of a combination of EGFR-TKI and platinum doublet chemotherapy in untreated advanced NSCLC pts with EGFR mutations. Although GCP regimen failed to demonstrate its superiority in PFS2, it may increase long survivors. ITT Population GCP (N = 169) G (N = 172) Median (months) NR 17.2 (11.6–23.2) 18.0 (16.2–NR) 11.2 (9.0–13.3) 18.0 (16.2–24.1) 9.0, 13.4] [95%CI: 0.390, 0.623] [p < 0.001 F20.291.1 0.895 [95% CI: 18.0, 24.2] [95%CI: 17.9, 24.9] [95%CI: 0.708, 1.122] P = 0.806. Results: In September 2017, a preplanned required number of events of PFS2 was observed. The ITT population included 344 pts with baseline characteristics fairly well balanced between the arms. Although GCP demonstrated significantly better PFS compared to G, there was no difference in PFS2 between the arms as below. Additional OS analysis (G:101 events vs GCP:83 events) revealed that median survival time of GCP was more than that of G (52.2 months vs 38.8 months, HR=0.695, = 0.013). Conclusions: NEJ009 is the first phase III study which evaluated the efficacy of a combination of EGFR-TKI and platinum doublet chemotherapy in untreated advanced NSCLC pts with EGFR mutations. Although GCP regimen failed to demonstrate its superiority in PFS2, it may increase long survivors. ITT Population GCP (N = 169) G (N = 172) Median (months) NR 17.2 (11.6–23.2) 18.0 (16.2–NR) 11.2 (9.0–13.3) 18.0 (16.2–24.1) 9.0, 13.4] [95%CI: 0.390, 0.623] [p < 0.001 F20.291.1 0.895 [95% CI: 18.0, 24.2] [95%CI: 17.9, 24.9] [95%CI: 0.708, 1.122] P = 0.806.
Avelumab (anti–PD-L1) in combination with crizotinib or lorlatinib in patients with previously treated advanced NSCLC: Phase 1b results from JAVELIN Lung 100. First Author: Alice Tsang Shaw, Massachusetts General Hospital Cancer Center, Boston, MA

Background: ALK tyrosine kinase inhibitors (TKIs) are standard of care for patients (pts) with advanced ALK+ NSCLC, and preclinical data suggest potential synergistic activity with checkpoint inhibitors in NSCLC irrespective of ALK status. Avelumab is a human anti-PD-L1 IgG1 monoclonal antibody approved in various countries for treatment of metastatic Merkel cell carcinoma, and in the US for advanced urorrenal carcinoma that has progressed following platinum therapy. We report initial results from JAVELIN Lung 101 (NCT02584634), a phase 1b/2 dose-finding trial of avelumab + crizotinib (A+C) or the next-generation ALK TKI lorlatinib (A+L) in pts with advanced/metastatic ALK-negative/wildtype (ALK−) or ALK+ NSCLC, respectively. Methods: In phase 1b, pts with previously treated ALK− NSCLC received A (10 mg/kg Q2W) + C (250 mg BID) while pts with ALK+ NSCLC received A (10 mg/kg Q2W) + L (100 mg QD) (starting dose levels in each group). The primary endpoint was dose-limiting toxicities (DLTs); secondary endpoints included adverse events (AEs) and objective responses. Results: At data cutoff on Oct 27, 2017, 12 ALK− pts had received A+C and 28 ALK+ pts had received A+L. All ALK− pts had received prior anticancer therapy; ALK+ pts had received a median 2 prior ALK TKIs (range 1-3; data not reported for 1 ALK− pt). DLTs occurred with A+C in 5 ALK− pts (41.7%): ALT and AST increase (2 each); febrile neutropenia, hyperthyroidism, QT prolongation, and rash (1 each). No DLTs occurred in ALK+ pts. Grade ≥3 of any causality occurred with A+C in 7 ALK− pts (58.3%; most common [≥10%] was ALT increase [16.7%, n = 2]), and with A+L in 15 ALK+ pts (53.6%; most common was hypertriglyceridemia [14.3%, n = 4] and GGT increase [10.7%, n = 3]). The confirmed objective response rate with A+C was 16.7% (95% CI 2.1-48.4%; partial response [PR] in 2 pts), and with A+L in ALK+ pts was 46.4% (95% CI 27.5-66.1; PR in 12 pts; complete response in 1 pt). Conclusions: A+C showed an acceptable safety profile, distinct from A+C, and promising antitumor activity in pts with ALK+ NSCLC, and will be evaluated in treatment-naive pts in phase 2. Clinical trial information: NCT02584634.

Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating mutations (MET, ROS1, RET, ALK, KRAS). First Author: Julien Mazieres, Hôpital Larrey, Centre Hospitalier Universitaire Toulouse, Toulouse, France

Background: Data on ICI activity in patients with oncogenic driver are limited. The aim of this study was to collect further data across various molecular subgroups. Methods: We conducted a retrospective multicenter study of patients receiving ICI for stage IV NSCLC with genomic alterations. Anonymized data were evaluated for clinicopathologic characteristics and outcomes: best response (RECIST v1.1), progression-free survival (PFS) and overall survival (OS) from ICI initiation. Results: We included 527 patients treated in 25 centers. The Molecular alterations involved KRAS (n = 252), EGFR (n = 110), BRAF (n = 38), MET (n = 36), HER2 (n = 23), ALK (n = 18), RET (n = 14), ROS1 (n = 5), and multiple drivers (n = 31). Median age was 60 years, sex-ratio 1.8, never/former/current smokers were 27/51/22%, and the majority of patients were never- or light-smokers (p = 0.003) and PDL1 expression (p = 0.02) in the overall population but not for EGFR-mutant. Conclusions: ICI has consistent efficacy in NSCLC harboring activating mutation. KRAS, BRAF, MET/EGFR, and RET patients derive a greater benefit than EGFR, ALK and RET patients.

Best response (%) PFS OS

<table>
<thead>
<tr>
<th>Driver n CR/PR SD PD Median (months)</th>
<th>6 g PFS (%) 1 y PFS (%) Median (months)</th>
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<tbody>
<tr>
<td>BRAF 38 28.1 28.1 43.8 3.0</td>
<td>35 19 13.6</td>
</tr>
<tr>
<td>KRAS 27 23 27 49 3.2</td>
<td>39 26 13.3</td>
</tr>
<tr>
<td>EGFR 10 11.0 18.0 71.9 3.5</td>
<td>38 10 13.1</td>
</tr>
<tr>
<td>ROS1 5 20 0 80 NA 5.0</td>
<td>0 0 10.5</td>
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<td>MET 36 15.6 34.4 50.0 3.8</td>
<td>35 23 18.4</td>
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<td>RET 11 10.0 18.0 71.9 6.9</td>
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<td>ALK 18 0 21.4 78.6 2.1</td>
<td>16 8 17.0</td>
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</tbody>
</table>

* From ICI initiation. CR/PR: Complete/Partial response, SD/PD Stable/Progressive disease.
Combination of gefitinib and olaparib versus gefitinib alone in EGFR mutant non-small-cell lung cancer (NSCLC): A randomized phase 2 study (GOAL, Spanish Lung Cancer Group). First Author: Rosario García Campelo, Medical Oncology Service, University Hospital A Coruña (XVIAC-SERGAS), A Coruña, Spain

Background: Low BRCA1 mRNA levels correlate with longer progression free survival (PFS) in erlotinib treated EGFR mutant NSCLC patients (p), while risk of shortened PFS was associated with intermediate high BRCA1 level (HR, 8.46; P<0.0001). We explored the combination of the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib with gefitinib in EGFR mutant NSCLC p. In a previous phase 1 trial, the safety of the combination was confirmed. Recommended phase 2 dose (RP2D) is gefitinib, 250 mg daily, and olaparib, 200 mg thrice daily. Methods: Stage IV treatment naive NSCLC p with centrally confirmed EGFR mutations and measurable disease were recruited in the study (NCT01513174). We randomly allocated p (1:1) to receive gefitinib 250 mg daily or the combination at the RP2D. The primary endpoint was PFS. PFS related to BRCA1 mRNA was a secondary endpoint, and 53BP1 and enhancer of zeste homolog 2 (EZH2) were analyzed as modulators of BRCA1, overall survival (OS), response rate (RR), safety and tolerability. Target accrual was 186 p. This sample provided 80% power to detect HR of 0.63 after 116 PFS events. The first PFS analysis, side effect profile and RR had a February 28th 2018 cut-off, minimum follow-up of 18 months (m Res: 07 of the 182 p who received gefitinib alone for treatment of gefitinib and 91 received gefitinib+olaparib, with no differences in gender, age, never smoker, performance status, bone or brain metastases or EGFR mutation. Median PFS for exon 19 deletions and exon 21 L858R EGFR mutations was 10.4 mo for gefitinib group and 12.8 mo for gefitinib + olaparib group (HR for disease progression or death, 0.83; P=0.329). RR was 68% in gefitinib group and 78% in gefitinib + olaparib group. Conclusions: The gefitinib+olaparib combination did not provide significant benefit over gefitinib alone. Median PFS was 2.4 mo longer for the combination and risk of disease progression or death was 17% lower with gefitinib+olaparib than gefitinib alone. The phase 1/2 fixed assumption of BRCA1, 53BP1 and EZH2 could determine if a subgroup of p might obtain major benefit from the combination. Clinical trial information: NCT01513174.

A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor (TKI) naïve patients with advanced NSCLC. First Author: Aaron Elliott Lisberg, UCLA, Los Angeles, CA

Background: Despite the significant antitumor activity of pembrolizumab in non-small cell lung cancer (NSCLC), clinical benefit has been less frequently observed in patients whose tumors harbor epidermal growth factor receptor (EGFR) mutations compared to EGFR wild-type patients. Our single center experience on the KEYNOTE-001 trial suggested that pembrolizumab-treated EGFR-mutant patients, who were tyrosine kinase inhibitor (TKI) naïve, had superior clinical outcomes to those previously treated with a TKI. As TKI naïve EGFR-mutants have generally been excluded from pembrolizumab studies, data to guide treatment decisions in this patient population is lacking, particularly in patients with PD-L1 expression ≥50%.

Methods: We conducted a phase II trial (NCT02879994) of pembrolizumab in TKI naïve patients with EGFR mutation positive, advanced NSCLC and PD-L1 positive (≥1%, 22C3 antibody) tumors. Pembrolizumab was administered 200mg q3wks. The primary endpoint was objective response rate. Secondary endpoints included safety of pembrolizumab, additional pembrolizumab efficacy endpoints, and efficacy and safety of an EGFR TKI after pembrolizumab. Results: Enrollment was ceased due to lack of efficacy after 11 of 25 planned patients were treated. 82% of trial patients were treatment naïve, 64% had sensitizing EGFR mutations, and 73% had PD-L1 expression ≥50%. Only 1 patient had an objective response (ORR; 9%), but repeat analysis of this patient’s tumor definitively showed the original report of an EGFR mutation to be erroneous. Observed treatment related adverse events were similar to prior experience with pembrolizumab, but two deaths within 6 months of enrollment, including one attributed to pneumonitis, were of concern. Conclusions: Pembrolizumab’s lack of efficacy in TKI naïve, PD-L1+, EGFR-mutant patients with advanced NSCLC, including those with PD-L1 expression ≥50%, suggests that it is not an appropriate therapeutic choice in this setting. Clinical trial information: NCT02879994.

Combination of metformin plus TKI vs. TKI alone in EGFR+ lung adenocarcinoma: A randomized phase II study. First Author: Oscar Gerardo Arrieta Rodriguez, Instituto Nacional de Cancerología (INCan), Mexico City, Mexico

Background: Metformin has been shown to have antitumor activity by increasing AMPK through different mechanisms involving tumor suppressor gene, LKB1. LKB1 inactivation is common in non-small cell lung cancer (NSCLC). LKB1 is associated with a more aggressive clinical phenotype. Retrospective studies have shown that metformin could effectively increase the sensitivity to TKIs in NSCLC, thus improving Progression Free Survival (PFS) and potentially impacting Overall Survival (OS) in these patients. We compared the effect of metformin in combination with EGFR-TKI versus TKIs alone on the clinical prognosis of adenocarcinoma patients with EGFR mutations. Methods: In this phase 2 clinical trial (NCT03071705) we randomly assigned 116 patients with stage IV EGFR-mutated lung adenocarcinoma to receive therapy with metformin + EGFR-TKI (M+TKI) (n = 49) or EGFR-TKI (TKI) alone (n = 67). TKI was chosen upon clinician’s discretion. Exclusion criteria were if they had a history of diabetes or had received treatment with metformin or TKIs (>2 cycles) previous to enrollment. The primary endpoint was PFS, secondary endpoints included objective response rate (ORR), disease control rate (DCR) and OS. Results: Baseline characteristics were well balanced between treatment arms. Mean patient follow up was 12.9 months. Median PFS was significantly longer in patients receiving M+TKI compared to those who received TKI (14.0 months vs. 10.0 months; p = 0.017). ORR was higher in the experimental arm of the trial, compared to the control group (67.4% vs. 47.5%; p = 0.044), although, the DCR was similar in the two groups (97% vs. 88.5%; p = 0.085). Median OS was 24.8 months. Patients receiving M+TKI had a longer OS compared to those receiving TKI (27.2 months vs. 19.0 months, p = 0.015). Multivariate analysis showed that, among others, the therapeutic arm (M+TKI vs. TKI) is an independently associated factor for both PFS and OS. Conclusions: Our study strongly suggests that the addition of Metformin to standard EGFR-TKI therapy has a significant effect in PFS, ORR and OS of patients with EGFR-mutated NSCLC. Metformin use is a safe and efficacious addition to the therapeutic scheme of EGFR+ NSCLC. Clinical trial information: NCT03071705.

First report of safety, PK, and preliminary antitumor activity of the oral EGFR/HER2 exon 20 inhibitor TAK-788 (AP32788) in non–small cell lung cancer (NSCLC). First Author: Robert Charles Doebele, University of Colorado Cancer Center, Aurora, CO

Background: TAK-788 is an investigational TKI with potent, selective preclinical activity against activating EGFR and HER2 mutations, including exon 20 insertions. We report the first results of a phase 1b/2a study of the safety and tolerability, target accrual was 186 patients. This sample provided 80% power to detect a 25% reduction in PFS (HR for disease progression or death, 0.75). The pre-specified assessment of BRCA1, 53BP1 and EZH2 could determine if a subgroup of p might obtain major benefit from the combination. Clinical trial information: NCT03071705.

Baseline characteristics.

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<th>5 mg</th>
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<th>40 mg</th>
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<th>120 mg</th>
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<tbody>
<tr>
<td>n (n = 4)</td>
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<td></td>
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<td></td>
<td>(n = 5)</td>
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<td>Mutation type</td>
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<td>Common EGFR mutations (exon 19 deletion /L858R)</td>
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<td>21</td>
<td>67</td>
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</tbody>
</table>

*1Pt (20 mg) had both HER2 and HER2 mutations; 1 pt (80 mg) had EGFR exon 20 insertion + T790M.
Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) harboring MET exon 14-skipping mutations: Phase II trial. First Author: Enriqueta Felip, Hospital Universitari de la Vall d’Hebron, Barcelona, Spain

Background: MET mutations causing exon 14 skipping (METex14) produce c-Met receptors lacking a negative regulatory site, with the result that METex14 mutations are oncogenic drivers. 3-4% of NSCLCs harbor METex14 mutations; these tumors appear to be sensitive to c-Met inhibition. Selective c-Met inhibitors have the potential to be effective and tolerated in patients (pts) with NSCLC. This single-arm phase II trial (NCT028864992) is investigating the efficacy and safety of the potent, selective c-Met inhibitor tepotinib in pts with METex14+ NSCLC.

Methods: Adults with stage IIIb/IV METex14+ NSCLC without EGFR-activating mutations or ALK rearrangements who have received 0–2 lines of prior therapy are eligible. METex14+ mutations are identified in tumor and/or circulating tumor DNA (ctDNA) in plasma by a central laboratory. Pts receive tepotinib 500 mg QD until disease progression, intolerable toxicity, or withdrawal for other reasons. Primary endpoint: objective response. Secondary endpoints include safety. Recruitment of approx. 90 pts (60 tumor + 60 ctDNA METex14+, overlap anticipated) in Europe, USA, and Japan is planned. Results: 34 pts have been treated to date; data are available for 22 (male, n=16; Caucasian/Asian, n=17/5; median age 73.5 years; prior lines of therapy: 0, n=8; 1, n=8; 2, n=5; 3, n=1; METex14+ tumor and/or ctDNA only, n=1); 19 remain on treatment. Based on investigator assessment, 9/15 (60.0%) evaluable pts had a confirmed PR and 3 (20.0%) had SD. All responders remain in response. 13 pts were evaluable for response by independent review: confirmed PR, n=6 (46.2%); SD, n=1 (7.7%); 13/22 pts (59.1%) had METex14-related treatment-emergent adverse events (TRAEs); G1/2 peripheral edema (9, G1/2 diarrhea = 7), with 3 having G3 TRTEAEs (asymptomatic amylase increase = 2; GGT increase = 1) and one a serious TRTEAE (interstitial pneumonia). 2 deaths not related to tepotinib were reported (unrelated to hepatic adverse events). Conclusion: Tepotinib 500 mg QD has promising activity in METex14+ NSCLC. Its safety profile is as expected based on prior studies. Recruitment is ongoing. Clinical trial information: NCT028864992.
EGRF with chemo-naive, stage IV/recurrent NSCLC without known sensitizing burden free survival with nivo + ipi vs chemo in patients (pts) with tumor mutational burden (TMB). Of 36 patients with PD-L1 testing, 75% had PD-L1 expression.

Background: CheckMate 227 (NCT02477826) is a large phase 3 study of 1L NSCLC. From CheckMate 227.

From July 2015 until the time of abstract submission, 74% of pts had undergone biopsy before SBRT.

Legends: LTR—long-term response; AE—adverse event; ORR—objective response rate; CTR—control-to-treatment ratio; ECOG—Eastern Cooperative Oncology Group; TMB—tumor mutation burden; NTR—no treatment-related; TDI—tumor downregulation index; RECIST—response evaluation criteria in solid tumors; PFS—progression-free survival; OS—overall survival; LTR—long-term response; SVR—sustained virologic response; NRT—nontreatment-related; QoL—quality of life; HRQoL—health-related quality of life; PRO—patient-reported outcome; PROQOL—patient-reported QoL; LS—a 30-item scale used to measure health status/QoL score and time to deterioration in the composite of cough, chest pain, fatigue, nausea, fever and hypothyroidism. No increase in treatment related toxicity was observed in the experimental arm. Conclusions: With 86% of patients evaluable, we conclude that pembrolizumab preceded by SBRT (3x8Gy within 7 days prior to the first cycle) on a single metastasis (experimental arm). Sequential biopsies were obtained from the same, non-irradiated tumor site at baseline and after two cycles of pembrolizumab. Those who achieved LTR had a 41% 1-year OS benefit and a 47% 1-year PFS benefit over patients who did not achieve LTR.
Background: Both Pemetrexed and Erlotinib have shown survival benefit when used as maintenance therapy in advanced non small cell lung cancer (NSCLC) after platinum doublet chemotherapy. Hence this study was planned to compare the outcomes between the 2 drugs. The current abstract is focused on quality of life (QOL) results. Methods: This was a open label, randomized, phase 3 study done in adult palliatively treated EGFR-negative, NSCLC patients who had non progressive disease post administration of first line chemotherapy Pemetrexed-Carboplatin. Patients were 1:1 randomized between tablet Erlotinib 150 mg orally administered once daily versus injection Pemetrexed 500 mg/m2 administered intravenously every 3 weeks. The therapy was continued either till disease progression or development of intolerable side effects. The primary endpoint was to compare the QOL between the 2 arms at 3 months. Other secondary endpoints were to study and compare the progression free survival (PFS), overall survival (OS) and adverse event rate. We had 200 patients in this study and the sample size had 80% power, with type 1 error of 5% to detect a difference of 0.3 in effect size. Total 200 patients were recruited in the study. The median follow up was 25.37 months (95%CI 21.4-29.3 months). There was no difference in global QOL between the 2 arms at 3 months (p=0.384). There was no difference in any domain of QOL except a higher score for diarrhea was seen in the Erlotinib arm (p=0.001). The FRS (HR 0.99; 95% CI 0.73-1.34; p=0.539) and ORR (95% CI 9.88; 95% CI 0.97-10.11) were similar between both the arms.

Conclusion: Maintenance Pemetrexed post Pemetrexed-Carboplatin therapy fails to improve QOL or time to event outcomes (OS & PFS) over maintenance Erlotinib in EGFR mutation negative advanced NSCLC. Clinical trial information: CTRI/2014/08/004847.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: The genomic determinants of response to PD-1/PD-L1 blockade in non-squamous NSCLC are incompletely understood. We previously identified STK11/LKB1 alterations as a major genomic driver of tumor cell PD-L1 expression and primary resistance to PD-1 inhibitors in KRAS-mutant lung adenocarcinoma. A critical unanswered question is whether STK11/LKB1 alterations predict for lack of response to PD-1/PD-L1 blockade independently of PD-L1 expression. Here, we report the impact of STK11/LKB1 alterations on clinical outcomes with PD-1/PD-L1 inhibitors in PD-L1-positive non-squamous NSCLC. Methods: 66 patients with non-squamous NSCLC treated with PD-1/PD-L1 inhibitors at MDACC (61% pembrolizumab, 24% nivolumab, 8% atezolizumab, 5% durvalumab/tremelimumab) with available STK11/LKB1 NGS-based genomic profiling and positive tumor cell PD-L1 expression (≥1%, based on the FDA-approved 22C3 pharmDX assay) were identified retrospectively. Response assessment was based on RECIST1.1. Results: In this PD-L1-positive population of non-squamous NSCLC, STK11/LKB1 alterations were associated with significantly lower ORR to PD-1/PD-L1 blockade compared to tumors with intact STK11/LKB1 status (ORR 0% versus 34.5%, P = 0.026). STK11/LKB1-mutant tumors exhibited significantly shorter progression-free survival (mPFS 1.7 months versus 19.3 months, HR 4.76, 95% CI 2.0-11.1, P = 0.0012, log-rank test) with PD-1/PD-L1 blockade. Although fewer STK11/LKB1-mutant tumors expressed high (≥50%) levels of PD-L1 (45.5% versus 61.8%), the difference did not reach statistical significance (P = 0.5). Conclusions: STK11/LKB1 genomic alterations are associated with primary resistance to PD-1/PD-L1 PD-L1 inhibitors even among PD-L1-positive non-squamous NSCLC patients, suggesting that their effect is at least partially independent of PD-L1 expression. Evaluation of STK11/LKB1 genomic status may enhance the predictive utility of a composite PD-1/PD-L1-inhibitor predictive biomarker panel incorporating PD-L1 expression and TMB.

Subgroup comparison

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median OS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFRm vs EGFRwt (Doc)</td>
<td>12.8 vs. 9.3</td>
<td>0.86 (0.65, 1.13)</td>
</tr>
<tr>
<td>EGFRm vs EGFRwt (ICI)</td>
<td>9.4 vs. 12.8</td>
<td>1.0 (1.10, 1.78)</td>
</tr>
<tr>
<td>ICI vs Doc (EGFRwt)</td>
<td>12.8 vs. 9.3</td>
<td>0.72 (0.60, 0.87)</td>
</tr>
<tr>
<td>ICI vs Doc (EGFRm)</td>
<td>9.4 vs. 12.8</td>
<td>1.19 (0.98, 1.48)</td>
</tr>
<tr>
<td>KRASm vs KRASwt (Doc)</td>
<td>8.8 vs. 11.0</td>
<td>1.29 (0.92, 1.80)</td>
</tr>
<tr>
<td>KRASm vs KRASwt (ICI)</td>
<td>14.3 vs. 12.1</td>
<td>0.54 (0.11, 1.64)</td>
</tr>
<tr>
<td>ICI vs Doc (KRASm)</td>
<td>12.1 vs. 10.0</td>
<td>0.64 (0.41, 0.99)</td>
</tr>
<tr>
<td>ICI vs Doc (KRASwt)</td>
<td>14.3 vs. 8.6</td>
<td>1.03 (0.75, 1.41)</td>
</tr>
</tbody>
</table>

Savings with NGS

- EGFRm vs EGFRwt: $9,030,869 vs sequential and $2,140,795 vs panel. For commercial payers, reimbursement, NGS represented savings of $1,393,678 vs exclusionary, $1,642,082 vs sequential and $2,140,795 vs panel.

Conclusions: Our model estimated that upfront NGS leads to the lowest payer cost to establish GA status for newly diagnosed mNSCLC pts to inform treatment decisions.

Economic impact of next generation sequencing vs sequential single-genre testing modalities to detect genomic alterations in metastatic non-small cell lung cancer using a decision analytic model. First Author: Nathan A. Pennell, Cleveland Clinic, Cleveland, OH

Background: Metastatic non-small cell lung cancer (mNSCLC) patients (pts) should be tested for genomic alterations (GA) to inform treatment decisions. This study assesses the economic impact of next generation sequencing (NGS) vs sequential single-genic testing modalities for Center for Medicare and Medicaid Services (CMS) Medicare and US commercial payers. Based on a decision analytic model, newly diagnosed mNSCLC pts were modeled to receive PD-L1 and GA tests (ICI, ALK, ROS1, BRAF, MET, HER2, RET, NTRK1) using 1) sequential tests, 2) exclusionary mutation (KRAS) test followed by sequential tests 3) panel test or 4) upfront NGS, including all GAs and KRAS. Pts in modalities 1-3 were tested for GAs with currently approved treatment (EGFR, ALK, ROS1, BRAF) followed by single-genic tests or NGS for other GAs (e.g., HER2); a proportion were assumed to need rebiopsy. Inputs included turnaround time, unit costs and NGS prevalence based on literature, public data and expert opinion. Time to receive results and total cost (test + rebiopsy) were calculated for each modality and compared with NGS.

Results: For hypothetical 1 million-member-plan, an estimated 2,066 CMS Medicare and 156 commercially insured mNSCLC pts would be tested for GA. Estimated time to receive results was 2.0 weeks for NGS and panel, 2.7 and 2.8 weeks faster than exclusionary and sequential, respectively. Using CMS reimbursement, NGS represented savings of $1,393,678 vs exclusionary, $1,530,869 vs sequential and $2,140,795 vs panel. For commercial payers, NGS remained the least expensive by $3,809 (vs exclusionary) to $250,842 (vs panel). Conclusions: Our model estimated that upfront NGS leads to the same (as panel) or shorter (vs exclusionary and sequential testing) wait time for results and the lowest payer cost to establish GA status for newly diagnosed mNSCLC pts to inform treatment decisions.
**Lorlatinib in patients (Pts) with previously treated ALK+ advanced non-small cell lung cancer (NSCLC): Updated efficacy and safety.** First Author: Benjamin Besse, Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France

**Background:** Despite advancement of 2nd generation (gen) ALK tyrosine kinase inhibitors (TKIs), ALK+ NSCLC pts continue to develop resistance and CNS metastases (mets) become more difficult to manage. Lorlatinib, a potent brain-penetrant 3rd gen ALK/ROS1 TKI, has shown robust clinical activity in ALK+ or ROS1+ NSCLC pts, most of whom had CNS mets and failed ≥1 ALK TKI. **Methods:** This ongoing ph2 study (NCT01970865) enrolled 277 pts with ALK or ROS1+ advanced NSCLC ± CNS mets in cohorts (ALK: EXP 1–5; ROS1: EXP 6) based on prior treatment; starting dose was lorlatinib 100 mg QD. Antitumor activity (by independent central review per RECIST 1.1), safety and biomarkers were evaluated. **Results:** In 196 ALK+ pts assessed for antitumor activity (ITT population) in pooled subgroups (EXP 2–3A [only prior crizotinib + chemotherapy (CT)], EXP 3B [only 1 prior 2nd gen ALK TKI ± CT], and EXP 4–5 [2 or 3 prior ALK TKIs ± CT]), lorlatinib led to rapid (median time to response 1.4 mo) deep and durable systemic and intracranial (IC) responses (Table). Of a total 139 pts in EXP 3B + EXP 4–5, 62, 47 and 8 received alectinib, ceritinib and brigatinib, respectively, as last ALK TKI prior to lorlatinib. **Additional efficacy, pt subset.** In EXP 3B + EXP 4, 468 s Lung Cancer—Non-Small Cell Metastatic Disease. **Conclusions:** Lorlatinib showed clinically meaningful benefit in ALK+ NSCLC pts with ≥1 prior ALK TKI and was generally tolerable with AEs managed by dose modification or supportive therapy.

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**YH25448, a 3rd generation EGFR-TKI, in patients with EGFR-TKI-resistant NSCLC: Phase I/II study results.** First Author: Byoung Chul Cho, Severance Hospital, Seoul, Republic of Korea

**Background:** The epidermal growth factor receptor (EGFR) T790M mutation is one of the most common acquired resistance mechanism to EGFR tyrosine kinase inhibitors (TKIs). YH25448 is an oral, potent, irreversible EGFR TKI that is highly selective for activating (EGFRm) and T790M resistance mechanisms. **Methods:** Patients with EGFRtm advanced NSCLC with acquired resistance to EGFR-TKIs with or without asymptomatic brain metastases were enrolled in an open-label, multicenter, phase I/II study with dose escalation and expansion cohorts. YH25448 was administered once daily at doses of 20 to 240 mg in a 21 day cycle. Patients were assessed for safety, tolerability, pharmacokinetics and efficacy. T790M status was confirmed in the expansion cohorts. **Results:** A total of 105 patients (median age 62 years, 61% female) were enrolled. The dose escalation cohort included 33 patients administered with 20 to 240 mg once daily across 6 dose levels, and 72 patients in the dose expansion cohort were administered with 40 to 240 mg. No dose-limiting toxicities were observed. The most common treatment-emergent adverse events (AEs) were pruritus (12%), decreased appetite (9%), rash (11%), and constipation (10%). AEs of grade 3 or higher were observed in 5% of the patients. Systemic exposure increased dose-dependently. Of the evaluable patients (n = 91) at data cut-off, the objective response rate (ORR) was 64% (95% confidence interval [CI], 53.0 to 73.6). The ORR for the 7790M-positive patients was 67% (95% CI, 55.4 to 77.7), and for the 15 of the 7790M-negative patients 47% (95% CI, 21.3 to 73.4). In patients with brain metastases (n = 9), the overall intracranial ORR was 56% (95% CI, 21.2 to 86.3). **Conclusions:** YH25448 was well tolerated and exhibits promising systemic and intracranial anti-tumor activity at multiple dose levels in EGFR T790M+ NSCLC patients. Clinical trial identifier: NCT03046992.

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**ORR in T790M+ patients.**

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<th>Dose, mg</th>
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<th>80</th>
<th>120</th>
<th>160</th>
<th>240</th>
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<tr>
<td>ORR (%)</td>
<td>74</td>
<td>76</td>
<td>69</td>
<td>61</td>
<td>71</td>
<td>50</td>
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**Multi-kinase RET inhibitor vandetanib combined with mTOR inhibitor everolimus in patients with RET-rearranged non-small cell lung cancer.** First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** RET fusions (RET+) occur in 1%-2% of NSCLCs. Tumors eventually become refractory to multi-kinase RET inhibitor monotherapy. We evaluated the pre-clinical and clinical activity of the combination of Vandetanib (V), an inhibitor of RET, VEGF, and EGFR, and the mTOR inhibitor everolimus (E). **Methods:** Clinical activity of V + E was evaluated in pts with advanced NSCLC in a Phase I/II trial. V and E were administered orally QD in a 28 day cycle. Responses were assessed by RECIST 1.1. RET fusions were detected by FISH and/or Next generation sequencing (NGS) in tumor tissue and/or plasma. Preclinical studies were performed using the CDCC6-RET + LC-29ad NSCLC cells. Results: Among 19 stage IV NSCLC pts enrolled, median age was 59 yrs & 8 pts (42%) were males. 13 pts (93%) were RET+ by NGS and/or FISH. Concordance rate between the two tests was 40%. The overall ORR in 13 RET+ pts was 54% (7 PR). The ORR in RET+ by NGS was 70% (7 PR/10 patients) while the ORR in FISH+ patients was 20% (1 PR/5 patients). No responses were seen in NGS-/FISH+ patients (0/3). The combination was active in RET+ NSCLC brain metastases (3/3) and in a cobanztinib resistant. The median PFS of all 13 RET+ patients was 4.4 months (95% CI 3.4, NR); the median PFS of RET+ patients (n = 10) was 8 months (95% CI 0.1, 1.1). Grade 3/4 toxicities included diarrhea (21%), thrombocytopenia (16%), QTc prolongation (5%) and rash (5%). 17/19 (89%) pts required dose modifications after cycle 1 due to toxicity. Preclinical studies demonstrated that resistance to RET inhibition was associated with activation of the EGFR, VEGFR, and downstream mTOR pathways and that the combination of everolimus with the RET/VEGFR/EGFR inhibitor vandetanib abrogated this resistance in preclinical models. **Conclusions:** V+E has significant activity in RET+ NSCLC identified by NGS, with an ORR of 70% and a median PFS of 8 months. Preclinical data shows the V+E combination to be superior to either drug alone and may target potential resistance pathways. The combination merits further investigation in RET+ NSCLC. Clinical trial information: NCT01582191.

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Efficacy and safety of entinostat (ENT) and pembrolizumab (PEMBRO) in patients with non-small cell lung cancer (NSCLC) previously treated with anti-PD(L)-1 therapy.

First Author: Leena Gandhe, NYU Perlmutter Cancer Center, New York, NY

Methods: ENCORE-601 is an open-label study evaluating the combination of ENT + PEMBRO in pts with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy. Pts were eligible irrespective of history or baseline PD-L1 expression. Pts were treated with ENT 5 mg po weekly and PEMBRO 200 mg IV Q3W. The primary endpoint was ORR as assessed by iRECIST. The study was designed as a Simon 2-stage study such that if 3 of 31 pts responded in Stage 1, the study would enroll up to 56 pts. The study was further revised to accrue up to 70 patients to increase statistical power and decrease Type I error. Tumor biopsies and blood samples for immune correlates were taken pre- and on-treatment in a subset of patients. Results: Of the first 57 patients enrolled, 17 had refractory disease to prior PD-L1 therapy, and only 2 had a documented prior response. Median duration of prior PD-L1 therapy was < 6 months and the median time from last dose of prior PD-L1 therapy was 65 days. To ENT + PEMBRO, 5 of 57 patients achieved confirmed PR (8.8%), 20 (35.1%) experienced Grade 3/4 related AEs; 6 pts (10.5%) experienced Grade 3/4 related aEs (3 events of pneumonitis), 15 (26.3%) had at least one event of grade 3/4 related AEs irrespective of grade) included weight loss, fatigue, anemia, decreased appetite, and diarrhea. Evaluation of gene expression and circulating immune cells to identify biomarkers of response is in progress. Conclusions: ENT + PEMBRO demonstrated anti-tumor activity and acceptable safety in patients with NSCLC who have progressed on prior PD-L1 blockade. Clinical trial information: NCT02437136.

Characterization of 1,233 NSCLCs with non-del19/L858R EGFR mutations. (EGFRm) using comprehensive genomic profiling (GCP). First Author: Sai-Hong Ignatius Ou, University of California Irvine School of Medicine, Irvine, CA

Methods: GCP was performed on 34,328 NSCLCs, of which 5,240 samples (15%; 4,592 tissue and 648 blood-based ctDNA) from 4,872 patients (pts) were positive for short variant EGFRm. Pts profiled both pre- and post-EGFR TKI were included. Variants of unknown significance were excluded from our analysis. Tumor mutational burden (TMB) was determined using a targeted next-generation sequencing panel (477 genes) and compared with the stability of PD-L1 expression levels in patients with a TPS of 50-74% is associated with improved clinical outcomes compared to patients with a TPS of 75-100%.

Conclusions: In the first-line setting for NSCLC, higher PD-L1 TPS levels of 75-100% is associated with improved clinical outcomes compared to patients with a TPS of 75-74%.

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Updated efficacy and safety data from the global phase III ALEX study of IMT-pretreated advanced NSCLC patients. First Author: D. Ross Camidge, University of Colorado, Aurora, CO

Background: The primary ALEX (NCT02075840) analysis showed superior efficacy of ALC (600mg BID) compared to CZ (420mg BID) for untreated ALK+ NSCLC. We report updated data (cutoff Dec 1 2017). Updated efficacy and safety data from the global phase III ALEX study of untreated ALK+ NSCLC, regardless of BL CNS mets, and favorable and durable tolerability despite longer Tx duration, consolidating ALC as the new standard of care.

Methods: ALEX was a phase III randomized, open-label trial comparing ALC 600mg BID to CZ 420mg BID in untreated ALK+ NSCLC (by central IHC) and no prior systemic therapy for advanced NSCLC; both arms received IMT-relapsed patients with prolonged stable disease or better seen in some patients. Clinical trial information: NCT02000947.

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9045 Poster Session (Board #368), Sun, 8:00 AM-11:30 AM  
BRAF-mutant non-small cell lung cancer (NSCLC): Patient (pt) characteristics and outcomes by class of mutation. First Author: Ibiyi Dagogo-Jack, Massachusetts General Hospital, Boston, MA  
Background: BRAF mutations (muts) occur in 2%-4% of NSCLC. Recent work suggests that BRAF mts may be grouped into 3 classes: 1) V600E mts that signal as monomers, 2) activating non-V600 mts that function as dimers, and 3) kinase-impaired non-V600 mts that require RAS input. Whether mut class is associated with specific clinicopathologic features or clinical outcome is unknown. Methods: We performed a retrospective analysis of NSCLC pts with BRAF mts treated at Massachusetts General Hospital and Dana-Farber Cancer Institute between 2006 and 2017 to determine clinicopathologic characteristics and estimate overall survival (OS). Results: We identified 237 pts with Stage I-IV BRAF-mutant NSCLC (107 (45%) class 1, 76 (32%) class 2, and 54 (23%) class 3). Most pts were white (88%) with adenocarcinoma (90%). Smoking status was similar for pts with class 2 and 3 mts (3% vs 6% never-smokers, p = 0.649), but pts with class 1 mts were more likely to be never-smokers (22%; p < 0.001 vs class 2, p = 0.011 vs class 3). The frequency of concurrent RAS (KRAS or NRAS) co-alterations in class 1 was 1%, which was significantly lower than the frequency in class 2 (12%, p = 0.002) and class 3 (32%). Nine (47%) of 19 kinase-dead tumors had RAS co-alterations. Among 140 pts with metastatic NSCLC, median OS was 40.1 months (mos, n = 69, 95% CI:17.5-56.1) for class 1, 13.9 mos (n = 39, 95% CI:7.4-18.8) for class 2, and 15.6 mos (n = 32, 95% CI:8.9-37.4) for class 3 pts. OS was not different for class 2 and 3 pts (p = 0.591), but was better for class 1 vs class 2 and 3 pts (p = 0.059). Conclusions: Pts with class 2 and 3 BRAF-mutant NSCLC share clinicopathologic features and outcomes that may be distinct from pts with class 1 mts. Our findings highlight the need for therapies that effectively target class 2 and 3 BRAF mts.

9046 Poster Session (Board #369), Sun, 8:00 AM-11:30 AM  
Phase I/ib study of pembrolizumab and vorinostat in patients with metastatic NSCLC (mNSCLC). First Author: Andreas Nicholas Saltos, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL  
Background: The oral histone deacetylase inhibitor (HDACi) vorinostat (V) enhances tumor immunogenicity through several mechanisms and may augment response to PD-L1 blockade (IO). We report mature results from a phase I/ib trial testing the combination of V with pembrolizumab (P) in mNSCLC. Methods: In phase I, pts with either IO-naïve or IO-pretreated mNSCLC were treated with P (200mg IV q3w) + V (200 or 400 mg PO daily). In phase Ib expansion, pts were required to have progressed on prior IO treatment. Primary endpoints were safety/tolerability; secondary endpoints included RR, PFS, DOR, and OS. Tissue and blood specimens from pre- and post-treatment were collected for correlative analyses to determine tumor gene expression changes, levels of myeloid-derived suppressor cells and changes in peripheral T-cell phenotype. Results: Between 3/2016-9/2017, Phase I: 14 pts were treated (4 at 200mg, and 10 at 400mg V dose); and Phase Ib: 20 pts were treated. Median age: 67 (range 38-82); Females: 11 (32%); ECOG 1: 32 (94%); and never/former/current smokers: 3/23/8 (9%/68%/23%). No DLTs were observed. The RP2D is P 200mg and V 400mg. Most common AE of any grade were fatigue (11%), anorexia (9%) and nausea/vomiting (8%). Most common G3 AE were myelagia, anemia and diarrhea. There were no G4/5 AEs. 3 (9%) pts had treatment discontinued due to toxicity. 30 pts are evaluable for response. PD-L1 expression was ≥ 1% in 18/30 (60%), and ≥ 50% in 11/30 (37%). 6 pts were IO-naïve and 24 IO-pretreated. 4 (13%) had PR (2 confirmed), 16 (53%) had SD, and 10 (33%) had PD for a disease control rate of 67%. In the IO-pretreated Ib cohort, 2 pts (1 confirmed; 1 pending repeat CT) had a PR and 10 had SD (8 confirmed). For IO-pretreated pts, mPFS was 3.2 mos. For IO-naïve, mPFS was 7.6 mos. Preliminary Tumor RNA-seq studies showed increase in IFN gamma and HDACi target gene expression, including CXCL9. Conclusion: This combination of IO and HDACi was well tolerated. The combination demonstrates preliminary anti-tumor activity despite progression on prior IO treatment and gene expression changes consistent with mechanism of HDACi activation. A randomized phase II portion of this study, examining P combined with V vs placebo in immunotherapy naïve pts, is ongoing, Clinical trial information: NCT02638590.

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Lung Cancer—Non-Small Cell Metastatic

9049 Poster Session (Board #372), Sun, 8:00 AM-11:30 AM
Prognostic relevance of tumor sequencing in metastatic lung adenocarcinomas.
First Author: Rongqai Shen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Routine next generation sequencing (NGS) testing for patients with lung cancer allows the rapid identification of a broad array of targetable molecular drivers. We hypothesized that the results of routine NGS testing, exploring both driver and non-driver oncogenes, could be used to develop a prognostic risk score for patients with metastatic lung adenocarcinoma.

Methods: We employed an ensemble penalized proportional hazards model to derive a genetic risk score using sequencing results of 341 cancer-associated genes in 1,054 patients with metastatic lung adenocarcinoma. A 3-fold cross-validation was used to obtain unbiased estimates of prediction accuracy.

Results: A total of 341 genes mutated at least once across the cohort were included in the analysis. The most frequently mutated genes were TP53 (55%), KRAS (30%), EGFR (29%), STK11 (18%), KEAP1 (18%). Mutations in TP53, KRAS, STK11, KEAP1, and SMARCA4 were associated with poor prognosis. Based on the risk score, patients were categorized into risk groups. Patients in the low risk group had a median overall survival of 32.8 months (95% CI: 26.3-38.5) as compared to 7.3 months (95% CI 5.5-10.9) in the high risk group. The high risk group probability is 47% in the low risk group versus 12% for the high risk group.

Conclusions: In both STK11 and KEAP1 had the largest adverse prognostic implications. While overall mutation burden and clonal heterogeneity were moderately associated with survival, they did not provide additional prognostic information over the genetic risk score. This model remains a significant independent predictor after adjusting for clinical variables (age, sex, smoking history).

9051 Poster Session (Board #374), Sun, 8:00 AM-11:30 AM
Dendritic-cell vaccine (DCVAC) with first line chemotherapy in patients with stage IV NSCLC: primary analysis of phase 2, open-label, randomized, multicenter trial. First Author: Libor Havel, Thomayer’s Hospital, 1st Faculty of Medicine of Charles University in Prague, Prague, Czech Republic

Background: Immunotherapy for induction of tumor cell specific immune responses destroying tumor cells, has emerged as a promising treatment modality in lung cancer (LuCa). Autologous DCVAC can present tumor antigens to elicit a durable immune response. We hypothesized that adding DCVAC to the standard of care chemotherapy (ct) could prolong progression-free survival (PFS) and overall survival (OS).

Methods: This study evaluated the efficacy and safety of DCVAC/LuCa (active cellular immunotherapy based on dendritic cells) concomitantly added to ct (carboplatin/paclitaxel) - Arm A (A) vs DCVAC/LuCa + immune modulators (IFN-α and hydroxychloroquine) - Arm B (B) vs ct - Arm C (C) in NSCLC patients (pts). Randomization 1:1:1; pts were stratified to 3 groups based on disease stage and T stage.

Stage IV NSCLC was confirmed histologically or cytologically, ECOG 0-1 pts were eligible. Stratification was done by histology subtype and smoking history. Primary efficacy analysis compared A vs C only as enrollment to B was closed early based on Sponsor’s assessment of further clinical development potential, there were no safety concerns or signals.

Results: 112 pts at 12 sites were randomized (A/45 B/29 C/38). Patients characteristics were comparable across the study groups with the exception of gender (m/f: 45/55 in A and 26/74 in C) and smoking history (75% of smokers in A, 97% in C). Median follow up time was 14.1 months, range 0.03-29.765. Median OS was 15.5 months in A compared to 11.8 months in C, hazard ratio (HR) 0.56, p-value 0.05, 95% CI, data maturity 65%. Median PFS was 6.73 in A and 5.65 months in C HR 0.64, p-value 0.05, 95% CI, data maturity 81%. Overall response rate was 45% in A vs 22% in C. Most TEAEs were related to ct (luminae [37% in A, 32% in C], neutropenia [48% in A, 21% in C], thrombocytopenia [28% in A, 27% in C]). There were no grade 3 TEAEs solely related to DCVAC. Most common leukaemopheresis-related AEs were haematoma and hypotension.

Conclusions: Addition of DCVAC-based immunotherapy to the standard of care chemotherapy significantly improved OS in stage IV NSCLC. Clinical trial information: EudraCT 2014-003084-37.

9050 Poster Session (Board #373), Sun, 8:00 AM-11:30 AM
An open-label, multicenter, phase II single arm trial of osimertinib in non-small cell lung cancer patients with uncommon EGFR mutation (KCGS-LU15-09). First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, Korea, Republic of (South)

Background: Approximately 10% of EGFR mutants harbor uncommon mutations, which represent a heterogeneous group of rare molecular alterations within exons 18-21 and the sensitivity to EGFR TKIs is variable. Osimertinib is a potent irreversible inhibitor of both sensitizing EGFR mutation and T790M. In preclinical data, the potency of osimertinib against uncommon EGFR mutants other than exon 20 insertion was fairly good. Here we present the efficacy and safety of osimertinib in patients with uncommon EGFR mutation positive NSCLC.

Methods: Patients with histologically confirmed metastatic or recurrent NSCLC with activating EGFR mutation other than exon 19 deletion, L858R, T790M and insertion in exon 20 were eligible. Patients received 80mg of osimertinib per oral daily until progression or unacceptable toxicity. Response was assessed every 8 weeks by investigator. The trial was registered with ClinicalTrials.gov, number NCT03424759.

Results: Between Mar 2016 and Oct 2017, 36 patients were enrolled. Median age was 59.5, 61% male, 44% never smoker, 97% adenocarcinoma. 61% of patients were treated as first-line therapy. The most common mutations are G719A/D/S/X (19, 52.8%) followed by L861Q (9, 25%), S768I (8, 22%), and others (4, 11%). The overall response rate was 50.0% (95% CI 32.8-67.2) and DCR was 88.9% (95% CI 78.1-95.7). Seven patients (17.8%) with L861Q mutation achieved partial response; 10 (52.6%) with S768I mutation. In arm C, 7 patients (19.4%) had partial response with S768I mutation. At data cutoff (Nov, 2017), the median PFS was 9.5 months (range 1.0-20.1) and median duration of response was 7.0 months (95% CI 4.7-9.3). The most common adverse events were rash (n = 11, 30.6%), anorexia (n = 8, 22.2%), and diarrhoea (n = 7, 19.4%). Grade 3 or 4 AEs were reported in 8 of 36 patients (22%), but all of AEs were manageable.

Conclusions: Osimertinib showed highly active and durable in NSCLC patients harboring uncommon EGFR mutation with manageable safety profile, consistent with previous reports. Further analysis will be updated. Clinical trial information: NCT03424759.
Efficacy and safety results of ramucirumab in combination with osimertinib of pts censored.

PFS rate at 6 months was 64.0% (90% CI: 43.7, 78.6) with 64% was 81.6% (90% CI: 59.0, 92.4). Median PFS was not reached (90% CI: 6.51, 7.92). All pts had never (n = 12). Pts received Ram 10mg/kg IV (Day 1 Q2W) + Osi 80mg QD. At 0 (n = 3) or 1 (n = 22) and tobacco history of current (n = 5), former (n = 8), or

Conclusions: RRDR(+ SCC patients screened on LungMAP.

Overall prevalence Prevalence among RRDR alterations

Relative risk of progression with HRRD(+) versus HRRD(-) status (95% CI).

HRRD is frequent in SCC and could define a large subset of SCC for targeted therapy within EGFR ex19 del tumors, specifically that pts with ex19 del therapy if validated in the ongoing S1400G substudy of LungMAP. Studies have largely grouped outcomes of ex19 dels together despite mutational differences. We previously demonstrated in vitro that erlotinib and osimertinib suppress phosphorylation of EGFR (pEGFR) in the E746_A750 and L747_P753 > S mutants, but do not effectively suppress pEGFR in the L747_A750 > P mutant, whereas afatinib suppresses pEGFR in all 3 mutant types. Here we investigate the clinical outcomes in patients with (pts) with various EGFR ex19 dels treated with erlotinib. Methods: We assessed progression free survival (PFS), duration on treatment (DOT) and overall survival (OS) in pts with EGFR exon 19 dels (E746_A750, L747, P753 > S or L747_A750 > P) who received erlotinib as first-line therapy for advanced disease. Primary resistance was defined as progression on first scan after initiation of therapy. Results: 32 pts met criteria: 24 with the common E746_A750 mutation, and 4 each with the L747_P753 > S and L747_A750 > P mutations. Patients with the L747_A750 > P mutation demonstrated significantly worse PFS, DOT and OS than those with the E746_A750 and L747_P753 > S mutations (see Table). There was no difference between the E746_A750 and L747_P753 > S groups. Two of four pts with L747_A750 > P mutations demonstrated primary resistance to erlotinib, whereas no pts with E746_A750 or L747_P753 > S mutations exhibited primary resistance. Conclusions: This study shows differential clinical outcome to EGFR-directed therapy within EGFR ex19 del tumors, specifically that pts with ex19 del L747_A750 > P have inferior outcomes versus those with E746_A750 or L747_P753 > S when treated with erlotinib. Understanding outcomes with other EGFR inhibitors based on the specific EGFR del 19 mutation present may allow for more precise treatment that results in improved Outcomes by EGFR Exon 19 Mutations (Months)

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Conclusions: In advanced T790M-positive EGFR-mutant NSCLC. The E746_A750 ex19 dels accounts for 75% of these cases. Two frequent uncommon ex19 dels are L747_P753 > S and L747_A750 > P. Studies have largely grouped outcomes of ex19 dels together despite mutational differences. We previously demonstrated in vitro that erlotinib and osimertinib suppress phosphorylation of EGFR (pEGFR) in the E746_A750 and L747_P753 > S mutants, but do not effectively suppress pEGFR in the L747_A750 > P mutant, whereas afatinib suppresses pEGFR in all 3 mutant types. Here we investigate the clinical outcomes in patients with (pts) with various EGFR ex19 dels treated with erlotinib. Methods: We assessed progression free survival (PFS), duration on treatment (DOT) and overall survival (OS) in pts with EGFR exon 19 dels (E746_A750, L747, P753 > S or L747_A750 > P) who received erlotinib as first-line therapy for advanced disease. Primary resistance was defined as progression on first scan after initiation of therapy. Results: 32 pts met criteria: 24 with the common E746_A750 mutation, and 4 each with the L747_P753 > S and L747_A750 > P mutations. Patients with the L747_A750 > P mutation demonstrated significantly worse PFS, DOT and OS than those with the E746_A750 and L747_P753 > S mutations (see Table). There was no difference between the E746_A750 and L747_P753 > S groups. Two of four pts with L747_A750 > P mutations demonstrated primary resistance to erlotinib, whereas no pts with E746_A750 or L747_P753 > S mutations exhibited primary resistance. Conclusions: This study shows differential clinical outcome to EGFR-directed therapy within EGFR ex19 del tumors, specifically that pts with ex19 del L747_A750 > P have inferior outcomes versus those with E746_A750 or L747_P753 > S when treated with erlotinib. Understanding outcomes with other EGFR inhibitors based on the specific EGFR del 19 mutation present may allow for more precise treatment that results in improved Outcomes by EGFR Exon 19 Mutations (Months)

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Correlation between nivolumab exposure and treatment outcome in NSCLC. This Phase 2 study evaluated the safety and efficacy of abemaciclib vs docetaxel in pts with Stage IV sqNSCLC previously treated with platinum-based chemotherapy. The study was designed to enroll 122 pts with an objective response to nivolumab have significantly higher nivolumab exposure than patients with early progressive disease, indicating an exposure-response relationship. Further clinical research is needed to explain and quantify this relation. If confirmed, more rational and individualized dosing-strategies can improve patient outcome.

A randomized phase 2 study of abemaciclib versus docetaxel in patients with stage IV squamous non-small cell lung cancer (sqNSCLC) previously treated with platinum-based chemotherapy. First Author: Giorgio V. Scagliotti, Department of Oncology - University of Torino, Turin, Italy

Background: Abemaciclib is a potent and selective inhibitor of CDK4 & 6 approved for treatment of HR+, HER2- metastatic breast cancer. In a Phase 1 study, abemaciclib showed activity in pts with advanced and/or metastatic NSCLC. This Phase 2 study evaluated the safety and efficacy of abemaciclib vs docetaxel in pts with Stage IV sqNSCLC previously treated with platinum-based chemotherapy. Methods: This multicenter, randomized, open-label trial, evaluated abemaciclib (200 mg PO every 12 hours daily) vs docetaxel (75 mg/m² IV every 3 weeks) in 122 pts with progressive disease prior to nivolumab. Primary endpoint was investigator-assessed PFS. Key secondary endpoints were ORR, DCR, OS, and safety. Results: 159 pts were randomized to abemaciclib (N = 106) and docetaxel (N = 53). Median age was 64 years. 84.3% were pts of Asian ethnicity. In ITT pts 125 PFS events were observed with median PFS of 2.5 m (95% CI: 1.7, 2.9) for abemaciclib and 4.2 m for docetaxel (95% CI: 2.8, 5.7; stratified HR: 1.77 [95% CI: 1.17, 2.67]; P = .0068). ORR was 28% (95% CI: 0.06, 0.60) for abemaciclib and 20.8% (95% CI: 9.8, 31.7) for docetaxel. The DCR (CR + PR + SD) was 50.9% (95% CI: 41.4, 60.5) for the abemaciclib treatment arm and 64.2% (95% CI: 51.2, 77.1) for the docetaxel treatment arm. Median OS was 7.0 m (95% CI: 5.0, 8.8) for abemaciclib and 12.4 m for docetaxel (95% CI: 7.1, 16.0; stratified HR: 1.33 [95% CI: 0.88, 2.02]; P = 1.1746). Exploratory biomarker data will be available at the meeting. The most common TEAEs with abemaciclib were anemia and diarrhea. Conclusions: In this Phase 2 study, single agent abemaciclib 200 mg did not improve the progression-free survival time over docetaxel, the instantaneous rate of disease progression/death at any given time point was higher with abemaciclib vs docetaxel. No specific safety concerns were observed. Clinical trial information: NCT02450539.

PD-L1 expression, tumor mutation burden and response to immune checkpoint blockade in patients with HER2-mutant lung cancers. First Author: Wei-Chu Victoria Lai, Memorial Sloan Kettering Cancer Center, New York, NY

Background: HER2 mutations are present in 3% of lung cancers. Response to immune checkpoint blockade (ICB) in this subset of lung cancers is unknown. We evaluate the landscape of PD-L1 and tumor mutation burden (TMB) in HER2-mutant lung cancers (HER2m) and their response to ICB. Methods: Patients (pts) with advanced HER2m were identified retrospectively. PD-L1 expression was determined by an IHC method performed at our institution (IHC). TMB was estimated by next-generation sequencing (NGS) using MSK-IMPACT. Objective response rate (ORR) to ICB was determined using RECIST v1.1. Kaplan-Meier was used for PFS and OS analyses. Results: We identified 122 pts with HER2m, of which 87 had PD-L1 IHC and 84 had NGS. 26 pts with known activating mutations in HER2m were treated with ICB. PD-L1 expression was < 1% in 67 (77%), 1-49% in 9 (10%), and ≥50% in 11 (13%) pts. PD-L1 expression was lower when compared to an unselected cohort (p = 0.006). Median TMB (5.7 Mt/Mb, range 0.8-91.8) was the same as the median TMB of an unselected cohort (p = 0.006). In those treated with ICB, ORR was 12% (3/26, 95% CI 3-30%), including 3 PR, 8 SD, 15 PD. In the 3 responders: none had an HER2/YYMA mutation; 2 (66%) had PD-L1 ≥50%; 2 (66%) had TMB ≥median; median response duration was 3.4 months (range 1.4-21.2), and 1 (33%) remained on treatment with ICB. From the start of ICB, median PFS was 1.9 months (95% CI 1.5-4.0), and median OS was 10.4 months (95% CI 5.9-NR). Conclusions: In pts with HER2-mutant lung cancers, PD-L1 expression is lower but TMB is similar to unselected lung cancers. Response to PD-L1 blockade is uncommon in pts with HER2-mutant lung cancers, but treated with ICB can still be considered, particularly in the context of high PD-L1 expression or higher TMB.
Brigitinib (BRG) in crizotinib (CRZ)-refractory ALK+ non–small cell lung cancer (NSCLC). Efficacy updates and exploratory analysis of CNS ORR and overall ORR by baseline (BL) brain lesion status. First Author: Rudolf M. Huber, University Hospital of Munich, Thoracic Oncology Centre Munich, Munich, Germany

**Background:** ALTA (NCT02094573) evaluated 2 doses of the ALK inhibitor BRG post-CRZ. Overall ORR contains both CNS and extra-CNS target lesion data. **Methods:** In ALTA, stratification included BL CNS disease (+/-). Pts were randomized to BRG 90 mg qd (arm A) or 180 mg qd with a 7-day lead-in at 90 mg (arm B). To differentiate CNS and extra-CNS efficacy we compared CNS ORR with overall ORR by BL CNS status. Results: 222 pts were randomized (n=112/110, arm A/B); 71%/67% had BL CNS lesions. Of 247/204 total target lesions in A/B, 38% (19) and 32% (16), respectively, were in the CNS; 28% (25) pts in A and 23% (21) in B had +/-1 target CNS lesion. Median follow-up was 19.6/24.3 mo. Per independent review, CNS ORR in pts with measurable BL CNS lesions (n=26/18, A/B) was 50%/67%; in pts with any BL CNS lesions (n=81/74, A/B), median intracranial PFS (iPFS) was 12.8/18.4 mo. Table shows long-term overall efficacy updates by BL CNS status. Dose reductions or discontinuations due to AEs (Arm A/B): 7%/29% and 4%/11%. Conclusions: With >24 mo follow-up, the recommended BRG 180 mg dose (with lead-in) continues to demonstrate high CNS ORR (67%) and overall ORR in pts with (61%) or without (55%) BL CNS target lesions support BRG's broad body-wide activity. Clinical trial nct: NCT02094573.

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**9063 Poster Session (Board #386), Sun, 8:00 AM-11:30 AM**

A multicenter phase II study of low-dose erlotinib in frail patients with EGFR mutation-positive non-small cell lung cancer (NSCLC): Update of the phase I study (NCT03546432) trial 1425. First Author: Kazukiho Yamada, Division of Respiriology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan

**Background:** We previously reported that low-dose erlotinib has a certain degree of efficacy with lower toxicity in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation in the AURORA-EUR J Cancer 2014. This multicenter phase II study was undertaken to investigate the efficacy and safety of low-dose erlotinib for those patients with frailty. **Methods:** Chemotherapy-naive NSCLC patients with EGFR mutations who had frailty were enrolled and received erlotinib 50 mg/d. Dose escalation was allowed to those with stable disease after 4 weeks. Patient’s frailty was defined as follows: (Group 1) 20 to 74 years of age with Eastern Cooperative Oncology Group performance status (PS) ≤2 or Charlson Comorbidity Index (CCI) ≤6 points; (Group 2) 75 to 80 years of age with PS ≤1 or CCI ≥6 points; (Group 3) ≥81 years of age with any PS and CCI ≤4. The primary endpoint was independent review committee (IRC)-confirmed objective response rate (ORR) to the low-dose erlotinib, with target ORR of 65% and threshold of 50% (SWOG-two stage design). **Results:** Eighty patients were enrolled between December 2014 and April 2017: males/females 26/54; median age 80 (range 49-90); Group 1/2/3 15/28/37; Ad/Sq/Others 76/1/3. EGFR mutation types were: exon 19/21 42/38. All 80 patients were included in efficacy and safety analysis. The IRC-confirmed ORR was 60.0% (90%CI: 50.2-69.2%), and the primary endpoint was met. The disease control rate was 86.3% (90%CI: 78.3-92.1%). Median progression-free survival was 9.2 months. Although overall survival data are immature, median survival time and 1-year survival rate were 26.3 months and 68.9%, respectively. Toxicities were generally mild, with a few grade 3 or more toxicities. There was no case of interstitial lung disease or treatment-related death. **Conclusions:** This is the first prospective study evaluating low-dose erlotinib for frail patients with EGFR mutation-positive NSCLC. Low-dose erlotinib is active and could be a treatment option for those patients. Clinical trial information: UMIN00015949.

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**9064 Poster Session (Board #387), Sun, 8:00 AM-11:30 AM**

Time to treatment discontinuation (TTD) as a pragmatic endpoint in metastatic non-small cell lung cancer (mNSCLC): A pooled analysis of 8 trials. First Author: Yutao Gong, US Food and Drug Administration, Silver Spring, MD

**Background:** Progression-free survival (PFS) is an important efficacy endpoint in oncology trials. However, clinical trials increasingly allow treatment beyond objective radiographic progression (TPB) for patients deriving clinical benefit from therapy. Furthermore, treatment discontinuation due to toxicity is increasingly uncommon in trials of targeted therapies. Thus, TTD may represent a practical endpoint for real-world evidence (RWE) studies. **Methods:** We pooled data from patients (pts) with mNSCLC treated on 13 arms of 8 randomized controlled trials of tyrosine kinase inhibitors (TKI), immune checkpoint inhibitors (ICI), or chemotherapy (ChemO) initiated between 2007-2014; 3 ChemO arms with planned discontinuation without maintenance therapy were excluded. We measured the pt-level correlation (corr) between TTD and PFS within each drug category (EGFR TKI; ALK TKI; ICI; ChemO), and determined rates of disparity between TTD and PFS greater than 3 months. **Results:** 2369 pts met criteria for analysis. 1868 pts (79%) had a TTD event, and 1638 pts (69%) had a PFS event. We measured the pt-level correlation (corr) between TTD and PFS within each drug category (EGFR TKI; ALK TKI; ICI; ChemO), and determined rates of disparity between TTD and PFS greater than 3 months. **Conclusions:** These results indicate a need for further investigation of TTD across cancers and treatments to assess its role as an endpoint in RWE studies.
Background: CD73 dephosphorylates and converts extracellular adenosine monophosphate to adenosine, leading to immune escape of malignancies. Although epidermal growth factor receptor (EGFR) mutation-positive NSCLC showed high expression of CD73, the predictive relevance of CD73 expression in patients with EGFR mutation received immune checkpoint inhibitors (ICIs) is unknown. Methods: We screened 67 patients with Stage I-III EGFR mutation-positive NSCLC received complete resection (cohort A), 17 patients with advanced or recurrent NSCLC received immune checkpoint inhibitors after resistance to EGFR-TKI treatment (cohort B), and 31 patients with EGFR mutation-negative NSCLC treated with ICIs. CD73 expression was evaluated by immunohistochemical analysis, and tumors with staining in over 50% of tumor cells were scored as high expression. Results: In cohort A, the high CD73 expression group showed relatively shorter disease-free survival and overall survival than the low CD73 group in patients with Stage I-III EGFR mutations. Active NSCLC received complete surgical resection. In cohort B, the overall response rate of ICIs was significantly higher in patients with high CD73 expression than those with low CD73 expression (66.7% versus 0%, p= 0.006), and the high CD73 expression group showed significantly longer progression-free survival (PFS) than low CD73 group (median 16.0 months versus 1.2 months, p< 0.024). Meanwhile, there was no significant difference in PFS of ICIs between the high and low CD73 expression groups of EGFR mutation-negative NSCLC (median PFS: 2.8 months versus 2.8 months, p= 0.394). Conclusions: In patients with EGFR mutation-positive NSCLC, expression of CD73 may predicts a favorable outcome of ICIs treatment unlike in EGFR mutation-negative patients.

**Predictive value of CD73 expression in EGFR-mutation positive non-small cell lung cancer patients received immune checkpoint inhibitors.** 
First Author: Hidenobu Ichii, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan

**Immune-related adverse events and nivolumab outcomes in non-small cell lung cancer patients: A multi-institutional, retrospective cohort study.**
First Author: Rebecca Jane Moor, Princess Alexander Hospital & University of Queensland, Brisbane, Australia

Background: Immune checkpoint inhibitors are routinely used in Non Small Cell Lung Cancer (NSCLC) patients following progression on first-line therapy. Immune-related Adverse Events (IrAEs) have been associated with the efficacy of PD-1 inhibitors in melanoma. The association between outcomes and the development of IrAEs and efficacy of nivolumab remains unclear in NSCLC.

Methods: We retrospectively collected data from patients who received nivolumab for first-line treatment in seven oncology institutions in Queensland, Australia, and analyzed whether there was an association between outcomes and the development of IrAEs.

Results: Of 17 patients with advanced or recurrent NSCLC treated with ICIs, CD73 expression was evaluated by immunohistochemical analysis, and tumors with staining in over 50% of tumor cells were scored as high expression. Results: In cohort A, the high CD73 expression group showed relatively shorter disease-free survival and overall survival than the low CD73 group in patients with Stage I-III EGFR mutations. Active NSCLC received complete surgical resection. In cohort B, the overall response rate of ICIs was significantly higher in patients with high CD73 expression than those with low CD73 expression (66.7% versus 0%, p= 0.006), and the high CD73 expression group showed significantly longer progression-free survival (PFS) than low CD73 group (median 16.0 months versus 1.2 months, p< 0.024). Meanwhile, there was no significant difference in PFS of ICIs between the high and low CD73 expression groups of EGFR mutation-negative NSCLC (median PFS: 2.8 months versus 2.8 months, p= 0.394). Conclusions: In patients with EGFR mutation-positive NSCLC, expression of CD73 may predicts a favorable outcome of ICIs treatment unlike in EGFR mutation-negative patients.

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Lung Cancer—Non-Small Cell Metastatic

9069  Poster Session (Board #392), Sun, 8:00 AM-11:30 AM
Mechanisms of acquired resistance to MET tyrosine kinase inhibitors (TKIs) in MET exon 14 (METex14) mutant non-small cell lung cancer (NSCLC).

First Author: Mark M. Awad, Dana-Farber Cancer Institute, Boston, MA

Background: Non-small cell lung cancers (NSCLC) harboring METex14 activating mutations can respond dramatically to treatment with MET TKIs, but the mechanisms of acquired resistance to these therapies are not well understood.

Methods: We performed next generation sequencing on serial plasma samples and/or tumor biopsies and one autopsy case from patients with METex14 mutant NSCLC to identify mechanisms of resistance to the type 1 MET TKI crizotinib and the type 2 MET TKI glecaprevir. Results: Samples from 12 patients with METex14 mutant NSCLC were included in this analysis. In 4 cases (33%), acquired MET alterations were identified including one case with amplification of the mutated METex14 allele and three cases with MET tyrosine kinase domain secondary site mutations; in two of these cases, more than one MET resistance mutation was present in the same patient. Secondary mutations in MET included H1094Y, G1163R, L1195F, L1195V, D1228N, Y1230H, and Y1230S. In 4 cases (33%), bypass track activation was identified, including massive genomic amplification of wild-type KRAS, BRAF, and EGFR. In 4 cases (33%), the resistance mechanism was not identifiable. A case of acquired resistance to glecaprevir with a mutation in the mutated METex14 allele had a confirmed partial response after switching to crizotinib. Data from resistant preclinical models and patient-derived cell lines and mouse xenografts will be presented.

Conclusions: Novel therapeutic strategies will be needed to delay or overcome multiple mechanisms of acquired MET TKI resistance in METex14 mutant NSCLC.

9070  Poster Session (Board #393), Sun, 8:00 AM-11:30 AM

First Author: KiyoYata Yoh, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: PD-L1 high expression and high tumor mutation burden (TMB) are reported to be correlated with high sensitivity to immune checkpoint inhibitor (ICI) in non-small cell lung cancer (NSCLC). This immunomuno-biomarker study is ongoing as part of nationwide genomic screening by LC-SCRUM-Japan. Planned accrual is 1000 patients. Methods: Lung cancer patients enrolled in LC-SCRUM-Japan were primarily screened with targeted next-generation sequencing with Oncomine Comprehensive Assay (OCA) and monitored clinical course and survival every 6 months. To explore new biomarkers for ICI in the treatment of NSCLC, further analyses of 4 immunohistochemistry (IHC) assays for PD-L1 expression (22C3, 28-8, SP263 and SP142) and whole-exome sequencing (WES) to determine TMB were conducted in 1000 and 400 patients, respectively. Results: Among 1635 patients with lung cancer enrolled in LC-SCRUM-Japan between Feb 2017 and Jan 2018, 621 NSCLC patients were enrolled in this immunomuno-biomarker study. The results of PD-L1 IHC with 420 patients with CA with 380 patients, WES with 50 patients, were analyzed at data cutoff point of Jan 4, 2018. Median TMB level by WES was 72 (2 to 515) and median TMB level by OCA was 7.6 mutation/Mb (0 to 30.8). There was no significant association between each PD-L1 expression and TMB by WES. TMB by OCA had weak correlations with TMB by WES (R² = 0.02). Seventy-three patients treated with ICI were evaluable for clinical response. Among 6 responders to ICI, TMB level by WES was variable (19, 26, 26, 109, 144, and 249). Of these, 2 had both high TMB by WES (median 72) and PD-L1 high expression; 2 had high TMB by OCA (median 424), PD-L1 low expression. TMB by OCA is associated with high sensitivity to ICI, but not with high TMB by WES. Sensitivity from AURA was 70%, but 96% (95/99) in pts with detected driver AF (96% (59/58) vs. 70% (316/445)). Alectinib demonstrated a median OS of 29.1 months (95% CI: 21.3–39.0) in the pooled analysis (NP28673: global [NCT01801111] and NP28761: North American [NCT01871805]) have previously demonstrated robust overall survival (OS) in crizotinib-resistant ALK+ NSCLC (Yang et al, J Thorac Oncol 2017). We report final pooled phase II OS and safety data after a longer duration of follow-up. Methods: Patients with locally advanced or metastatic ALK+ NSCLC (possible prior chemotherapy) who had progressed on or were intolerant to crizotinib, received twice-daily alectinib 600mg orally until progression, death or withdrawal. This pooled analysis assessed OS and safety after a median follow-up of 92.3 weeks (almost 2 years) (NP28673 105.5 weeks, data cut-off 27 October 2017; NP28761 75.7 weeks, data cut-off 12 October 2017). Results: The pooled data set included 225 patients. At the time of final data cut-off 53.3% of patients had died, 39.1% were alive and in follow-up, and 7.6% had withdrawn consent or been lost to follow-up. Alectinib demonstrated a median OS of 29.1 months (95% CI: 21.3–39.0) in the pooled analysis (NP28673 29.2 months (95% CI: 21.5–44.4); NP28761 27.9 months (95% CI: 17.2–NE)). Mean dose intensity 94.2%. Grade ≥3 adverse events (AEs; any cause) occurred in 44.0% of patients, with no AE term reported in >4% of patients. The most common AE (any grade) included constipation (39.1%), fatigue (35.1%), edema peripheral (28.4%), myalgia (26.2%) and nausea (24.0%). Despite the longer treatment duration (median 48.6 weeks), alectinib demonstrated a tolerable safety profile consistent with previous studies; 14.7% of patients experienced AEs leading to dose reductions, 3.7% of patients experienced AEs leading to dose interruptions or modifications and 6.2% of patients experienced AEs leading to withdrawal. Conclusions: This pooled phase II analysis demonstrated a median OS of ≥ 2 years in patients with pretreated ALK+ NSCLC receiving alectinib. In addition, alectinib was well tolerated over a median treatment duration of ≥ 4 years as of data cut-off (27 October 2017). Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Comparative effectiveness of carboplatin-pemetrexed (Carbo-Pem) with vs. without bevacizumab (Bev) in patients with advanced non-squamous (Sq) non-small cell lung cancer (NSCLC). First Author: Stephen Tomoshige, Division of Hematology/Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background: The majority of patients with advanced non-sq NSCLC do not have high programmed death ligand 1 (PD-L1) expression or a targetable genetic alteration. Carbo-bev is commonly used as first-line therapy in these patients, but it is unknown whether the addition of bev to carbo-bev improves overall survival (OS).

Methods: Using nationally representative electronic health record data from Flatiron Health, we performed a retrospective cohort study of patients diagnosed with advanced non-sq NSCLC from 2011-2017 who received ≥1 cycle of carbo-bev, with/without bev, as initial systemic therapy for metastatic disease.

Results: Median follow-up time and OS were 31 (IQR 16-49) and 10.2 (95% CI 9.8-10.8) months (mo), respectively. After adjusting for the covariates in Table 1, the addition of bev to carbo-bev was assessed using a Cox proportional hazards model. Results: Patient characteristics are listed in Table 1 (n = 5,264). Median follow-up time and OS were 31 (IQR 16-49) and 10.2 (95% CI 9.8-10.8) months (mo), respectively. After adjusting for the covariates in Table 1, the addition of bev was associated with improved OS (median 12.1 vs 8.8 mo; HR 0.80, 95% CI 0.74-0.85, p < 0.001). In a sensitivity analysis of patients with known Eastern Cooperative Oncology Group Performance Status (ECOG PS) (n = 2,708), the effect of bev was similar (HR 0.79, 95% CI 0.72-0.88, p < 0.001).

Conclusions: In this large, real-world dataset, the addition of bev to first-line carbo-bev for metastatic non-sq NSCLC was associated with improved OS. To our knowledge, this is the first study to address whether bev improves outcomes when added to carbo-bev.

Lung Cancer—Non-Small Cell Metastatic

9075 Poster Session (Board #398), Sun, 8:00 AM-11:30 AM
Hyperprogression after immunotherapy: Clinical implication and genomic alterations in advanced non-small cell lung cancer patients (NSCLC). First Author: Youjin Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South)

Background: Hyperprogressive disease (HPD) emerges as a new subset of patients treated with immune-oncology (IO) agent. The definition of HPD is not yet clearly established, and it is unclear which patient is rapidly progressing after IO treatment. We investigated clinical features and potential genomic markers associated with HPD after IO therapy.

Methods: We performed a retrospective clinical and radiological analysis of advanced NSCLC patients treated with single IO at Samsung Medical Center (July 2014 to December 2017). CT scans were quantitatively analyzed in terms of tumor volume and tumor growth rate (TGR) by comparing prior vs upon IO. We extracted tumor volume for each metastatic organ, classifying into HPD and non-HPD.

Results: Of 220 evaluable patients 37 patients (17%) were classified as HPD. HPD patients had significantly lower mPFS (1.2 vs 4.4 mo, p < 0.001), mOS (7.1 vs 15.9 mo, p = 0.09). Further details with follow-up data.

Conclusion: In this cohort, HPD was associated with shorter mPFS and mOS. The multivariate analysis, ICPi exposure (p = 0.04), targeted agents exposure (p = 0.01) were the only variables which correlated with OS.

9076 Poster Session (Board #399), Sun, 8:00 AM-11:30 AM
Rare targetable drivers (RTD) in NSCLC: PD-L1 expression, tumor mutation burden (TMB), microsatellite instability (MSI) and outcomes with immune check-point inhibitors (ICPi). First Author: Elizabeth Dudnik, Thoracic Cancer Unit, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

Background: The efficacy of ICPi in NSCLC with RTD is unknown. Methods: 82 consecutive patients (pts) with pts (RTD–non-EGFR/ALK) were selected from the Davidoff Cancer Center database. The correlation between RTD type and TMB, MSI (by FoundationOne™ algorithm), and PD-L1 was analyzed. ORR, PFS with ICPi (RECIST 1.1) and OS were assessed; uni- and multivariate OS analysis was done.

Results: Median age 63y (31-97); males 46%; smokers 50%; adenocarcinoma 87%; PD-L1, TMB, and MSI were assessed in 61%, 58%, and 57% pts, respectively (Table). Of 77 pts with advanced disease, 44 received ICPi, ORR with ICPi was 16%; median PFS was 3.2 mo (95% CI, 2.6-5). With medium follow-up since ICPi initiation of 7.8 mo (IQR 4.2, 19/44 (43%) pts died, median OS was 16.2 mo (95% CI, 8.4-NR). No correlation was seen between OS with ICPi and PD-L1 (p =0.6), TMB (p=0.9), or RTD type (p=0.9). With median follow-up since advanced disease diagnosis (AdvDis Dx) of 15 mo (IQR 7.2-24), 40/77 (52%) pts died, median OS was 32 mo (95% CI, 19.9-44.9) and 13 mo (95% CI, 6.6-15.9) for pts who were and were not exposed to ICPi, respectively (log rank test=6.3, p=0.01).

Conclusion: Rare targetable drivers in NSCLC are associated with low/intermediate TMB, MSI stable status and variable levels of PD-L1 expression. ICPi outcomes are comparable to those of unselected NSCLC pts and largely unpredictable. ICPi exposure has independent impact on OS.
Identification of osimertinib resistance mechanisms in Chinese NSCLC patients: Analysis from AURA17 trial. First Author: Min Hu, IMED Asia, AstraZeneca, and Dizal (Jiangsu) Pharmaceutical Co., Ltd, Shanghai, China

Background: Osimertinib is approved for metastatic NSCLC patients with EGFR T790M mutation after progression from EGFR-TKI therapy. Despite impressive tumor responses, drug resistance usually develops. Mechanisms of resistance to osimertinib are emerging, while resistance studies with large cohorts of Chinese patients are still lacking. Here we reported a resistance profile of osimertinib using plasma samples from 76 Chinese patients who had progressed by DC02 (Nov. 14, 2016) of AURA17 study (NCT02932409). This is the pivotal trial for China market approval. Methods: Serial plasma cell-free DNA (cfDNA) were collected from baseline until progressive disease (PD) by investigator assessment. Capture-based 75-gene NGS panel was used to identify resistance mechanisms to osimertinib by comparing paired plasma cfDNA at baseline and PD. Droplet digital PCR was used to dynamically monitor EGFR mutation changes during treatment course. Association of cfDNA biomarkers with objective response rate (ORR) and progression-free survival (PFS) was assessed. Results: 61 out of the 76 patients hadetectable EGFR sensitizing mutations (L858R or Ex19Del) in their cfDNA samples at PD. Among them, 8 had acquired EGFR T790M, with no enrichment for either L858R or Ex19Del (5.3). The median time of C797S detection from plasma was 2.8 (1.4-8.4) months prior to PD. EGFR amplification, L718Q, I744T, C775Y, G796S/D and T854I mutations were found in 13 patients. Alterations in bypass tracks including ERBB2/3, HRAS, HRAS, JAK1/2, NRAS, PTEN, NTRK1, FIP2, etc were observed in 35 patients. Clearance of EGFR sensitizing mutations at weeks 3 or 6 of treatment was associated with favorable ORR (69.7% vs. 33.3% and 74.3% vs. 33.3%) and PFS (6.9 vs. 4.0 and 7.1 vs. 4.1 months, respectively). Presence of T790M at PD was correlated with longer PFS (8.2 vs. 4.2 months). Conclusion: This study revealed diverse mechanisms of resistance to osimertinib in Chinese NSCLC patients. As the current subset has shorter PFS compared to the overall AURA17 population (6.2 vs 9.7 months), analysis of plasma samples from patients who progressed by 24 months after treatment may provide a more comprehensive view.

Clinical trial information: NCT02442349.

Lung Cancer—Non-Small Cell Metastatic 479s

Early prediction of outcomes to PD1 inhibitors in non-small cell lung cancer (NSCLC) using next generation sequencing (NGS) of plasma circulating tumor DNA (ctDNA). First Author: Nicolas Gilbert, Toulouse University Hospital, Toulouse France

Background: Patient selection for PD-1 inhibitors in NSCLC is still based on imperfect screening biomarkers, including PD-L1 tumor expression and tumor mutational burden. We hypothesized that pretreatment molecular profile of ctDNA and its early kinetics during treatment could represent a reliable and non-invasive approach to determine response. Methods: Up to 4 serial plasma samples were prospectively collected from patients with advanced NSCLC treated with nivolumab as second line therapy. I) pretreatment, ii) at 1 month, iii) at the first CT-scan, iv) at progression. Plasma NGS was performed using InVisionSeq, tagged amplicon sequencing of hotspots and coding regions from 36 genes. The early kinetics (1 month) of ctDNA through treatment was analyzed along with specific baseline alterations as early indicators of response to immunotherapy. Results: 80 specimens from 33 patients underwent NGS. Alterations in ctDNA were detectable in 25/33 baseline samples. The most frequently detected alterations at baseline were TP53 (54.4%); KRAS (33.3%); STK11 (24.2%) and NFE2L2 (9%). Lack of detectable ctDNA at baseline in 6/8 patients correlated with progressive disease (PD). Studying 23 patients for whom serial specimens were available with ctDNA detected at baseline, plasma response (kinetics of ctDNA between baseline and 1 month specimens) was correlated with clinical outcomes (RECIST) in 18/23 cases (11/13 with objective response (OR) and no progression (NP) vs 4/10 cases with PD and/or SD). Early baseline ctDNA demonstrated potential predictive ability on outcomes by analyzing specific alterations and type of nucleotide change (transversion vs transition), Transversions in KRAS and TP53 were detected in 13/14 baseline cases demonstrating clinical benefit (OR+SD) while 8/11 cases from patients who went on to have PD were enriched with transitions or STK1 mutations with TP53 or KRAS transversions. Conclusions: Plasma cell-free DNA analysis using NGS could be an additional screening assay to identify patients likely to derive benefit from anti-PD-1 therapy, particularly when tissue is unavailable.

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Frequent brain metastases and outcomes in patients with HER2-, KRAS-, and EGFR-mutant lung cancers. First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY

Background: HER2 mutations are oncogenic drivers in 3% of lung cancers. Here we describe the frequency and course of patients with HER2 mutant lung cancers with spread to brain and compare results to individuals with KRAS- and EGFR-driven cancers. Methods: We compared cohorts of consecutive patients with HER2 (n = 98), KRAS (n = 200) and EGFR (n = 200) mutant lung cancers. Multivariate logistic regressions adjusted for follow-up length were performed to evaluate baseline and subsequent development of brain metastases and survival from the date of diagnosis of stage IV disease. Results: In total, brain metastases occurred in 41% of 498 patients (95% CI 37 to 45%). At diagnosis of stage IV disease, 19% (19/98) in the HER2 cohort, 24% (48/200) in KRAS, and 31% (62/200) in EGFR had brain metastases (p = 0.08). Among those without brain metastases at baseline, 34% (27/79) of patients with HER2 vs 11% (16/152) with KRAS (p < 0.001), vs 23% (32/138) with EGFR (p = 0.048) developed brain metastases during treatment. The overall incidence of brain metastases was 47% (46/98) in patients with HER2, 32% (64/200) with KRAS, and 47% (94/200) with EGFR (p = 0.73). The occurrence of any brain metastases imparted a shorter median survival in patients with HER2 (25 vs 30 months, p < 0.001) and EGFR (29 vs 92 months, p < 0.001) driven cancers but not with KRAS (14 vs 21 months, p = 0.44). The median overall survival was 1.6 years (range 1.3 – 2.2 years) for HER2, 1.1 years (range 0.8 – 1.3 years) for KRAS, and 3.0 years (range 2.5 – 4.0 years) for EGFR (p < 0.0001).

Conclusions: In our patients with lung cancers driven by HER2, KRAS, and EGFR, brain metastases occurred in 41% overall. The risk is numerically higher with HER2 and EGFR than KRAS. While the incidence of brain metastases in patients with HER2 mutant lung cancers is numerically lower than EGFR at diagnosis, it rises over the disease course to 47% equal that of EGFR. Among those without brain metastases at baseline, a greater number of patients with HER2-mutant tumors subsequently developed brain metastases during treatment compared to the EGFR and KRAS cohorts. With one third of patients with HER2 mutant lung cancers developing brain metastases during treatment, close surveillance is critical.

Concurrent genomic alterations in lung adenocarcinoma with a MET exon 14 skipping mutation. First Author: Julia Rotow, University of California, San Francisco, San Francisco, CA

Background: MET exon14 oncogenic driver mutations are present in 2-4% of lung adenocarcinoma. While second-site MET mutations have been reported at MET TKI resistance, the factors influencing response to MET TKI therapy are not yet fully characterized. The landscape of co-occurring genetic alterations, which correlates with treatment response in EGFR-mutant NSCLC, is incompletely understood in METex14 NSCLC. Methods: Targeted exome sequencing of cell-free DNA (cfDNA) obtained via the clinical Guardant360 assay for co-occurring alterations (somatic variants, copy-number alterations) in 68 cancer-associated genes within 70 samples from 65 patients with advanced stage METex14 NSCLC. Synonymous mutations and those with predicted neutral or unknown functional impact were excluded. Results: 81.4% of METex14-positive samples contained concurrent genomic alterations, with a mean of an additional 2.6 (range 0-20) alterations/sample. Mutations or amplifications in TP53 (44.6% of patients), CDK4 (13.8%), EGFR (12.3%), and NFI (12.3%) were most common. Pathway analysis identified receptor tyrosine kinases (40%), cell cycle mediators (29.2%), and the MAPK pathway (26.2%) as frequently altered. Alterations frequently contained additional oncogenic co-alterations. Among downstream MET signaling mediators there is a high rate of concurrent MAPK pathway alterations in METex14 NSCLC. We identified two patients with newly acquired MAPK pathway alterations (KRAS amplification, KRAS G12D mutation) at MET TKI resistance. Conclusions: The cfDNA from patients with METex14 NSCLC frequently contains additional oncogenic co-alterations. Among downstream MET signaling mediators there is a high rate of concurrent MAPK pathway alterations in METex14 NSCLC, as well as newly acquired MAPK pathway alterations at resistance to MET TKI therapy. The MAPK pathway is a potential therapeutic target to enhance treatment responses in METex14 NSCLC.

Can duration of response be used as a surrogate endpoint for overall survival in advanced non-small cell lung cancer? First Author: Boris M Pfeiffer, Merck KGaA, Darmstadt, Germany

Background: Surrogate endpoints for overall survival (OS) in advanced non-small cell lung cancer (NSCLC), such as overall response rate (ORR) and progression-free survival, are prone to bias due to crossover and unbalanced post-progression therapy or inconsistent response assessment criteria. This study aimed to evaluate the surrogacy of duration of response (DoR) for OS in phase III trials adjusted for crossover, unbalanced post-progression treatment, insufficient information and inconsistent response criteria. Methods: The analysis was based on systematic literature review and data extraction. The relationship between absolute differences in median DoR and in median OS was assessed using the correlation coefficient (R). Additionally, the relationship of the combination of ORR and DoR, which may be a better surrogate for OS because it captures both the frequency and duration of response, with OS was evaluated. The bias arising from different definitions of ORR and DoR was addressed in a subset analysis on RECIST-based trials and WHO-based trials. Further stratification by reported definition of DoR, either from start of treatment (randomization) or onset of response, was performed. Results: ORR, DoR, and OS values were reported in 20 trials (8,382 patients). The correlation coefficient of DoR with OS was 0.356 (95% CI: 0.000-0.690). 8 trials defined response according to RECIST criteria and 11 trials defined DoR from the first documented response. In these subsets, the correlation was 0.630 (95% CI: 0.000-0.924) and 0.572 (95% CI:0.000-0.873), respectively. The correlation coefficient of the combination of DoR and ORR with OS was 0.790 (95% CI: 0.535–0.913). In the RECIST-based trials and trials defining DoR from first documented response, the correlation coefficients of the combination of ORR and DoR with OS were 0.742 (95% CI: 0.079-0.950) and 0.887 (95% CI: 0.614–0.971), respectively. Conclusions: Evaluation of DoR as a surrogate for OS should take into consideration both response assessment criteria and ORR. The adjustment with ORR gives a better estimate of the treatment effect and can be used jointly with DoR as a surrogate endpoint to predict OS benefit.

Immune-related adverse events to predict survival in patients with advanced non-small cell lung cancer treated with nivolumab: A multicenter analysis. First Author: Biagio Ricciuti, Clinical Oncology, S. Maria della Misericordia Hospital, Perugia, Italy

Background: Anti-PD1 or anti-PD-L1 are the current standard of care for platinum-pretreated advanced non-small cell lung cancer (NSCLC) patients (pts), having shown to prolong survival as compared to chemotherapy in second line setting. Pts treated with these drugs not infrequently experience the so-called immune-related adverse events (irAEs), which we hypothesize reflect antitumor responses. In this study we investigated whether irAEs were associated with nivolumab efficacy in pts with advanced NSCLC. Methods: We conducted a retrospective study of pts with advanced NSCLC treated with nivolumab between Oct 2013 and Sept 2017. irAEs were defined as AEs having immunological basis that required monitoring and interventions. We identified two groups according to the development of irAEs and evaluated the ORR, PFS and OS. Results: In a cohort of 127 pts, (median [range] age, 63 [30-81] years; 84 men [66.1%], 43 women [33.9%]; 34 [26.8%] with squamous [Sq] histology, 93 [73.2%] with NSq histology), irAEs occurred in 57 of 127 study pts (44.8%). Six of them (10.5%) experienced grade 3 or higher irAEs, ORR and DCR were significantly higher in pts with irAEs (68.8% versus 4.8%, P < 0.0001 and, 79.6% versus 20.3% P < 0.0001, respectively). The median PFS was significantly longer in the irAEs group (8.6 [95%CI 4.3-11.7] versus 2.1 [95%CI 1.7-2.4] months, P < 0.001). Median OS was also significantly longer in pts with irAEs (17.4 [95%CI 8.2-28.8] versus 3.7 months [95%CI 2.7-4.6], P < 0.0001). Importantly, pts with ≥2 irAEs had a significantly prolonged OS as compared to those who developed 1 irAE (median NR versus 11.9 months, P = 0.04). Multivariate analysis confirmed that irAEs were significantly associated with improved survival outcomes, with HR of 0.27 (95% CI, 0.17-0.43; P < 0.001) for PFS and 0.36 (95% CI, 0.22 to 0.59; P < 0.001) for OS. Conclusions: In this multicenter study the development of irAEs was a strong predictor of prolonged OS in NSCLC pts treated with nivolumab. Of note, pts who developed ≥2 irAEs had a more pronounced survival benefit as compared to pts with only one event. Further studies are required to investigate the molecular mechanisms underlying this association.

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Lung Cancer—Non-Small Cell Metastatic

9085 Poster Session (Board #408), Sun, 8:00 AM-11:30 AM
Contribution of nationwide genome screening in Japan (LC-SCRUM-Japan) to the development of precision medicine for non-small cell lung cancer.

First Author: Takashi State Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan

Background: A nationwide genome screening project in Japan (LC-SCRUM-Japan) has been established for the development of lung cancer precision medicine. Methods: Since 2013, non-squamous non-small lung cancer patients have been screened for ALK/ROS1/RET fusions using RT-PCR and FISH, and since 2015, they have also analyzed for 143 gene alterations using a next-generation sequencing (NGS) system, Comprehensive Assay. Based on the molecular screening and the monitoring of clinical course and patient survival, a large-scale integrative clinicogenomic database has been established. Results: As of December, 2017, 251 institutions were participating and 4,371 patients had been enrolled. The success rates of RT-PCR and NGS were 95% and 92%, respectively. Of 3,919 available samples, a total of 1,567 actionable gene alterations (38% KRAS mut, 193 ERBB2 mut/amp, 142 ROS1 fus, 100 RET fus, 98 MET; 3% ALK, 96 PIK3CA mut, 54 FGFR1 amp, 13 NRAS mut, 6 AKT1 mut, 6 FGFR2/3 fus, 4 NRIRR fus, 2 NTRK3 fus and others) were detected in 1,905 samples (38%). The concordance rates of NGS results in ALK, ROS1 and RET fusion detection between NGS and the corresponding RT-PCR were 0.98, 0.99 and 0.99, respectively. Through this screening, a total of 793 genotype-matched patients to molecular-targeted clinical trials were identified, and 136 of them (17%) were enrolled into the trials. Of the 2,345 patients analyzed by NGS, the surgery samples were available in 1,298 (55%). The patients with actionable gene alterations who were treated with targeted agents (n = 136) had significantly longer overall survivals than those not treated with targeted agents (n = 401) or the patients without actionable gene alterations (n = 76) (median survival (95%CI), 4.2 [2.5-4.6] vs. 4.7 [2.6-6.3] vs. 1.9 [1.5-2.3] years, respectively; p = 0.016). Conclusions: LC-SCRUM-Japan contributes to the development of precision medicine, especially for ROS1, RET, ERBB2, BRAF and MET-positive lung cancers. In addition to the tissue-based molecular screening, a NGS assay with liquid biopsy was started in December 2017 and is now ongoing in the LC-SCRUM-Japan.

9087 Poster Session (Board #410), Sun, 8:00 AM-11:30 AM
Landscape of EGFR-dependent and independent mechanisms of osimertinib resistance in EGFR-mutant NSCLC patients.

First Author: Xiumin Le, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Osimertinib is a third generation EGFR TKI; however, the mechanisms of resistance to osimertinib have been incompletely described, and there are currently no targeted regimens known to be effective for these patients. We evaluated clinical and genetic characteristics of patients who received osimertinib for EGFR-mutant NSCLC. We also provide treatment experience after progression on osimertinib. Methods: Using the MD Anderson GEMINI database and Moffitt Cancer Center database, we identified patients treated with osimertinib and performed clinical outcome analysis. Molecular profiling analysis was performed at the time of progression when available. Results: 118 patients were identified. Median PFS on osimertinib was 8.8 months (95% CI, 6.5 to 11). Overall survival from diagnosis was 76.7 months (95% CI, 42.5 to 111). 71 patients had disease progression. Upon progression, osimertinib was continued in 44 of 71 patients with 21 (48%) received local consolidation radiation. Osimertinib continued patients had longer second PFS compared to the ones discontinued. For patients who progressed on osimertinib, 42 had molecular profiling upon progression. A total of 22 genes/pathways were observed to have recurrent alterations. In addition to two cases with germline T790M, 19 cases retained and 21 cases lost detectable T790M mutation. Among T790M-retained cases, tertiary EGFR mutations of C797S/G and L792H (11 cases) in EGFR gene, and MET amplification (5 cases), were the most common mechanisms of resistance. In T790M-lost cases, PIK3CA mutation (2 cases), MET amplification, and small cell transformation, but not additional EGFR resistance mutations, were observed. Other resistance-associated alterations included FGFR amplification and RET fusion. Preclinical studies verified that osimertinib-resistant resistance could be reversed by targeting a subset of these alterations. Conclusions: We found continuation of osimertinib beyond first progression may offer clinical benefit. Osimertinib resistance is associated with diverse mechanisms. The loss of T790M was common, and the majority of resistance was associated with EGFR-independent, as in some cases targetable, mechanisms.

9088 Poster Session (Board #409), Sun, 8:00 AM-11:30 AM
Early determination of benefit or futility in treating NSCLC using the LCSS 3-IgI Global Index (3-IgI). First Author: Richard J. Gralla, Albert Einstein College of Medicine - Jacobi Medical Center, Bronx, NY

Background: Early assessment of the effect of treatment for advanced NSCLC can prevent unnecessary exposure to toxic and costly therapy while aiding in decision making to change treatment if necessary. Analysis in mesothelioma (Symanowski JCO 2014) suggested that a 20% decline from baseline after 2 cycles of chemotherapy in the 3-IgI Global Index of the LCSS identified patients unlikely to benefit. The 3-IgI (global distress, activities, QL) takes 2 minutes to assess. Methods: 164 patients with NSCLC receiving chemotherapy or check point inhibitors were prospectively evaluated with the LCSS at baseline and every 3 weeks using electronic media. Patient were also randomized 1:1 so that their physicians knew the results of the LCSS immediately in half of the patients. Results: Patients: Stage IV 92%: first line 73%; female 43%; median PS 1; mean age 63. The LCSS was completed after 2 cycles of treatment and prior to planning for the next cycle (generally 6 weeks after baseline; representing 91% of the 148 patients living). Patients with a 20% decline in the 3-IgI compared with baseline had a median survival of 7.6 months, contrasted to 15.8 months for those without this degree of 3-IgI decline (p = 0.01); 1 year survival was 26% versus 62%. Even with the marked PRO decline after 2 treatment cycles, patients in the 20% decline group received a median of 2.3 more cycles of the same chemotherapy (median cost = $10,712 / patient). In the 50% of patients for which their physicians knew the ongoing LCSS results, fewer chemotherapy cycles were prescribed (p = 0.03). Conclusions: Assessing change from baseline with the 3-IgI of the LCSS identifies after only 2 cycles of treatment those patients who have poor response and survival outcomes if continued on the same therapy. This PRO assessment is rapid, easy and inexpensive. Physicians need to consider the impact of change on decision options given that even when physicians were aware of the worsening PRO they often did not act on the findings. Responding to 3-IgI changes can result in better decisions concerning continuing or changing treatment, lessening toxicity, and savings in cost of unhelpful treatment. Support: NIH/NCI R01 CA157409 Clinical trial information: NCT01924416.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Phase I/II study of the A2AR antagonist NIR178 (PF8-509), an oral immunotherapy, in patients (pts) with advanced NSCLC. First Author: Alberto Chiappori, Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, FL

Background: ATP is catabolized to adenosine in the tumor microenvironment, leading to excess adenosine and immunosuppressive effects via immune checkpoint protein adenosine 2A receptor (A2AR). NIR178 is an oral A2AR antagonist that selectively binds and inhibits A2AR, reactivating T cell-mediated antitumor immune response. This Phase I/II study evaluated NIR178 in previously treated pts with advanced NSCLC (NCT02403193).

Methods: Pts (ECOG PS 0–1) had received ≥1 prior line of therapy; EGFR/ALK pts had failed prior TKI therapy. Objectives: primary – determine MTD of single-agent NIR178; secondary – efficacy endpoints, PK, and evaluation of PD-L1 expression. Results: At 13 Dec 2017 data cut-off, 24 pts had been treated: median age 68 yrs, 46% male; 79% received prior immunotherapy; 22/24 (92%) pts had discontinued (due to progression [n = 13], death [n = 2], AE [n = 2] or other reasons [n = 5]) and 2/24 (8%) pts remained on treatment. Dose levels evaluated: 80 (n = 3), 160 (n = 3), 320 (n = 7), 480 (n = 6), 640 µg/BID (n = 5). There was 1 DLT: Gr 3 nausea (640 µg). The most frequent (>20%) any-Gr AEs related to causality were diarrhea (67%), fatigue (63%), dyspnea (46%), vomiting (33%), chest pain and other (29%), gastrointestinal reflux disease, anemia, diarrhea (all 25%), anorexia, back pain, generalized muscle weakness and cough (all 21%). Drug-related Gr ≥3 AEs were pneumonitis (8%) and nausea (4%); no Gr ≥4 AEs were reported. Potential immune-related any-Gr AEs were rash (18%), hypothyroidism, increased ALT/AST (all 4%). NIR178 systemic exposure (Cmax, AUC) increased more than proportionally with dose. Efficacy data for 17/24 treated pts demonstrated responses and SD across the dose range, including 1 confirmed CR (480 µg) and 1 PR (80 µg), both in immunotherapy-naive pts. Durable SD > 44 wks with tumor shrinkage was observed in 2 pts with earlier analyses; 14.7% had a grade ≥3 treatment-related adverse event, most commonly (> 1%) infusion-related reaction (2.2%), lipase increase (1.6%), and pneumonitis (1.1%), and no treatment-related deaths occurred. Conclusions: NIR178 was well tolerated; AEs were manageable and there were no Gr 4 drug-related AEs. Immune-related AEs may indicate immune stimulation. Clinical benefit was observed in immunotherapy-exposed and naïve pts irrespective of PD-L1 status. Clinical trial information: NCT02403193.

Association of pre-existing thyroid autoimmunity with the development of thyroid dysfunction in patients with advanced non-small cell lung cancer (TSH before nivolumab treatment were at high risk for TD. Interestingly, thyrotoxicosis followed by thyrotoxicosis did not occur. Thyrotoxicosis was also observed suggesting a unique genetic evolution. Mutations targeting genes related to the WNT pathway, in particular, missense mutations of CTNNB1, also tends to be associated with higher risks for disease spread and developing BM from NSCLC. Conclusions: Our findings shed lights on genetic concordance and divergence of primary lung and brain metastatic tumors, and also show that activated PI3K and WNT pathways are significantly associated with increased risks of brain metastasis in NSCLC.
9093 Poster Session (Board #416), Sun, 8:00 AM-11:30 AM

Long-term efficacy and outcomes with sequential crizotinib followed by alectinib in ALK+ NSCLC. First Author: Jessica Jyeong Lin, Massachusetts General Hospital, Boston, MA

**Background:** Alectinib was recently approved for first-line treatment of advanced ALK+ NSCLC based on the ALEX trial, which demonstrated improved PFS with first-line alectinib compared to crizotinib. However, crizotinib is still widely used due to its lower cost and side effect profile. The current study aimed to evaluate the long-term efficacy and outcomes with sequential crizotinib followed by alectinib in ALK+ NSCLC patients.

**Methods:** Patients with ALK+ NSCLC were enrolled from Dec 2016 to Dec 2017. The diagnosis of ALK+ status was confirmed by FISH or IHC. Sequential crizotinib and alectinib was used as second-line TKI treatment for patients who progressed on first-line crizotinib. The primary endpoint was the PFS, and the secondary endpoints included overall survival (OS), time to progression (TTP), and safety profile.

**Results:** A total of 94 patients were enrolled. The median PFS on crizotinib and alectinib were 8.1 months (95% CI, 6.4-10.6) and 13.1 months (95% CI, 8.2-19.4), respectively. The median interval from crizotinib discontinuation to initiation of alectinib was 8 days (range, 1-304). Five patients (5.3%) switched to alectinib due to toxicity, 1 (1.1%) due to patient preference, and 88 (93.6%) due to progression (pattern: CNS only, n = 39; extracranial only, n = 37; both CNS/extracranial, n = 12). The median combined PFS for sequential crizotinib and alectinib was 22.9 months (95% CI, 17.1-30.5). Of note, among 68 patients who received crizotinib as first-line and alectinib as second-line therapy, the median combined PFS was shorter at 17.1 months (95% CI, 13.3-23.6). The 5-year OS for the overall cohort was 72%, respectively. Twenty-nine patients underwent a tumor biopsy following progression on alectinib. Of these, 20 (69%) had an unconfirmed PR, 9 (31%) had PD, and 2 (7%) had SD. The median duration of exposure of crizotinib alone was 16.1 wks. The most frequent (≥20%) any-grade (Gr) AEs were maculopapular rash (30%), diarrhea (28%), and stomatitis (23%). Gr 3 AEs occurred in 10/40 (25%) pts, most commonly (≥5%) maculopapular rash in 4/40 (10%) pts and hypokalemia in 2/40 (5%) pts; there were no Gr 4 AEs. Pts (n = 24) who were enrolled ≥15 weeks before the data cut-off were considered evaluable. In these pts, the confirmed ORR by BIRC was 75% (1/11 CRs, 54/63 PRs), and 16 (70%) pts received second-line alectinib as a consolidation strategy for second-line ALK+ NSCLC. As a historical comparator, the 15-month PFS rate for crizotinib alone was 43.3% (95% CI, 33.3-53.3).

**Conclusions:** Sequential therapy with crizotinib and alectinib can provide significant benefit to ALK+ NSCLC patients, supporting upfront use of alectinib.

9094 Poster Session (Board #417), Sun, 8:00 AM-11:30 AM

Preliminary Phase II results of a multicenter, open-label study of nazartinib (EGF816) in adult patients with treatment-naive EGFR-mutant non-small cell lung cancer (NSCLC). First Author: Dong-Wan Kim, Seoul National University Hospital, Seoul, Korea, Republic of (South)

**Background:** Nazartinib (EGF816) is a third-generation EGFR-TKI selective for activating and T790M mutations while sparing wild-type EGFR. In the Phase I part of a Phase II multicenter study of nazartinib in EGFR-mutant NSCLC (NCT02108964), the recommended Phase II dose was 150 mg QD. Preliminary safety and efficacy results are presented from the Phase II expansion in treatment-naive patients (pts) with EGFR-mutant NSCLC.

**Methods:** Pts (ECOG PS 0-1) received nazartinib 150 mg QD. Primary objective: evaluation of antitumor activity (overall response rate [ORR]) by blinded independent review committee (BIRC). Secondary objectives: characterization of safety/tolerability, and further efficacy endpoints (including time to response and progression-free survival [PFS]). Results: At the data cut-off 31 Aug 2017, 40 pts had been enrolled; median age 63.5 years, 70% Asian, 65% female, 52.5% EGCO PS 1, 16/40 (40%) pts had brain metastases at screening; 3/40 (7.5%) pts had discontinued (2 due to progressive disease and 1 due to AE) and 37/40 (92.5%) pts remained on treatment. Median duration of exposure was 16.1 wks. The most frequent (20%) any-grade (Gr) AEs were maculopapular rash (30%), diarrhea (28%), and stomatitis (23%). Gr 3 AEs occurred in 10/40 (25%) pts, most commonly (5%) maculopapular rash in 4/40 (10%) pts and hypokalemia in 2/40 (5%) pts; there were no Gr 4 AEs. Pts (n = 24) who were enrolled ≥15 weeks before the data cut-off were considered evaluable. In these pts, the confirmed ORR by BIRC was 75% (1/11 CRs, 54/63 PRs), and 16 (70%) pts received second-line alectinib as a consolidation strategy for second-line ALK+ NSCLC. As a historical comparator, the 15-month PFS rate for crizotinib alone was 43.3% (95% CI, 33.3-53.3).

**Conclusions:** Sequential therapy with crizotinib and alectinib can provide significant benefit to ALK+ NSCLC patients, supporting upfront use of alectinib.
Randomized phase II trial evaluating treatment with EGFR-TKI versus EGFR-TKI associated with anti-estrogen in women with non-squamous advanced stage NSCLC: IFCT-1003 LADIE Trial. First Author: Julien Mazieres, Hospital Larrey, Centre Hospitalier Universitaire Toulouse, Toulouse, France

Background: The incidence of lung cancer is increasing dramatically in women. Preclinical data have shown that the combination of an EGFR-TKI with an anti-estrogen could overcome resistance to EGFR-TKI. Methods: IFCT-1003 LADIE Trial was a phase II parallel open-label randomized phase II trial with 2 arms: 1) 1503 LADIE Trial (EGFR+ in the EGFR wild-type group (EGFR+)) in 1st or 2nd line setting or with or without pertinilin (E 150 mg/day) vs. E + fulvestrant (E+F) in the EGFR wild-type group (EGFR+) in 2nd or 3rd line setting of patients with progression or unacceptable toxicity. Primary objective was progression-free survival (PFS) at 3 and 9 months for EGFR WT and EGFR+ patients, respectively. Results: From 02/2012 to 03/2017, 204 pts (104 G, 46 F) and 175 (E 87, E+F 88) were enrolled in the EGFR+ and EGFR WT cohorts respectively. The median number of fulvestrant injections in the G+F group and in the E+F group was 19.8 weeks. The tolerance was correct (grade 3/4: 24.2% in the G+F group vs 21.3% in the G group, 16.0% in the E+F group vs 13.8% in the E group) and no treatment-related death. In the EGFR+ cohort, the primary endpoint was reached as 54 pts in the G+F group were non-progressive in 9 months. Nevertheless, the responses were lower in the EGFR+ group and 24 pts reached the second 9 months, and 25 pts were progressive at 3 months. In the EGFR WT cohort, the primary endpoint was not reached as 29 pts were non-progressive at 3 months. Here also, addition of F to E was not associated with better outcome (PFS 1.8 vs 2.0 and OS 10.0 vs 7.3 months). No PFS difference was observed in the subgroup of patients with positive staining for ER+. Conclusions: Addition of fulvestrant to EGFR-TKI is feasible and is associated with good PFS in the EGFR mutated group. Nevertheless, the lack of benefit associated with the combination of fulvestrant to EGFR-TKI does not support its future development in a phase 3 trial in women with NSCLC. Clinical trial information: NCT01569161.

Results: A total of 229 patients received a mean of 8.3 cycles of pembrolizumab before disease progression. Patients who had received prior anti-PD1 therapy were eligible if their disease was not associated with better outcome (PFS 1.8 vs 2.0 and OS 10.0 vs 7.3 months). No PFS difference was observed in the subgroup of patients with positive staining for ER+. Conclusions: Addition of fulvestrant to EGFR-TKI is feasible and is associated with good PFS in the EGFR mutated group. Nevertheless, the lack of benefit associated with the combination of fulvestrant to EGFR-TKI does not support its future development in a phase 3 trial in women with NSCLC. Clinical trial information: NCT01569161.

Results: Of a total of 229 patients, 120 were enrolled in the EGFR+ group and 109 in the G+F group and 3 in the E+F group. The tolerance was correct (grade 3/4: 24.2% in the G+F group vs 21.3% in the G group, 16.0% in the E+F group vs 13.8% in the E group) and no treatment-related death. In the EGFR+ cohort, the primary endpoint was reached as 54 pts in the G+F group were non-progressive in 9 months. Nevertheless, the responses were lower in the EGFR+ group and 24 pts reached the second 9 months, and 25 pts were progressive at 3 months. In the EGFR WT cohort, the primary endpoint was not reached as 29 pts were non-progressive at 3 months. Here also, addition of F to E was not associated with better outcome (PFS 1.8 vs 2.0 and OS 10.0 vs 7.3 months). No PFS difference was observed in the subgroup of patients with positive staining for ER+. Conclusions: Addition of fulvestrant to EGFR-TKI is feasible and is associated with good PFS in the EGFR mutated group. Nevertheless, the lack of benefit associated with the combination of fulvestrant to EGFR-TKI does not support its future development in a phase 3 trial in women with NSCLC. Clinical trial information: NCT01569161.

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Clinical utility of plasma-based digital next-generation sequencing (NGS) in patients with advanced-stage lung adenocarcinoma with insufficient tumor sample for tissue genotyping. First Author: Jon Lopez, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain

Background: Approximately 20% of tumor biopsies from patients with advanced-stage lung adenocarcinomas yield insufficient tissue for successful molecular subtyping. In this study, we have analyzed the clinical utility of NGS of cell-free circulating tumor DNA (ctDNA) in patients with inadequate tumor samples for tissue genotyping. Methods: We prospectively selected consecutive patients with advanced-stage lung adenocarcinomas with insufficient tissue for EGFR, ALK or ROS1 genotyping across 12 Spanish institutions (January-September 2017). Cases with known alterations in any of these genes were ineligible. ctDNA NGS was performed by Guardant Health (Guardant360, Redwood City, CA), using a hybrid-capture-based 73-gene panel. Variants were deemed actionable if they were part of successful molecular subtyping. In this study, we have analyzed the clinical characteristics, treatment, and outcomes of 53 patients (57%) who were identified as having 1-4 actionable drivers. Results: All patients were based on their clinical or preclinical evidence for drug response. All patients provided informed consent. Results: We included 93 patients; 48 (52%) were treatment naive. Eighty-three patients (90%) had detectable levels of ctDNA, and none of the clinical characteristics were different between patients with and without ctDNA detection. Level 1-4 actionable drivers were detected in 53 patients (57%) in the entire cohort and 29 patients (60%) in the treatment naive subgroup, of which 13 (14%) and 7 (15%) respectively had level 1-2A drivers (FDA-approved and standard-care biomarkers according to lung cancer guidelines). The majority of patients with actionable drivers had clinically relevant co-mutations (n = 46, 87%), with significant differences across the 4 actionable subgroups. Thirty-eight patients (14%) received genotype-matched therapies, the majority of which achieved clinical benefit. Seven treatment-naive patients (15%) received targeted drugs as their first-line therapy. Most patients (90%) with level 2B-4 drivers (8%), but a minority with level 1-2A drivers (5%), received targeted therapies. Conclusions: ctDNA NGS (Guardant360) detects actionable drivers and allows timely initiation of genotype-matched therapies in lung adenocarcinoma patients with insufficient tumor for tissue genotyping.

The effect of thoracic radiation on overall survival and their association with systemic immune therapy in stage IV non-small cell lung cancer (NSCLC). A prospective study of 29 patients reported superior progression free survival with radical TRT. This study aimed to report the overall survival (OS) effect of TRT and examine whether the OS effect varies with the timing of TRT regarding to systemic therapy. Methods: Stage IV patients from the national cancer database (NCDB) 2005-2014 formed the base of the study population. TRT, dose and time effects were analyzed individually in patients treated with non-immune systemic therapy had the best OS (n = 6,064, MST = 11.2 mo, P < 0.001), while patients receiving TRT after systemic therapy (n = 5,500, MST = 8.8 mo), patients with concurrent TRT-systemic treatments (within 30 days of systemic therapy) had significantly worse OS (n = 2,039, MST = 7.2 mo, P < 0.001), while patients receiving TRT after systemic therapy had the best OS (n = 6,064, MST = 11.2 mo, P < 0.001). In 4,639 patients treated with immune therapy, TRT was associated with significantly worse OS (n = 512, MST = 11.1 mo, P < 0.001), comparing to immune therapy alone (n = 4,127, MST = 14.1 mo). Patients receiving concurrent TRT had worst OS (n = 177, MST = 7.4 mo, P < 0.001), comparing to TRT before immune therapy (n = 165, MST = 12.2 mo), and before TRT after immune therapy (n = 138, MST = 13.2 mo, P = 0.086). Conclusions: In patients with stage IV NSCLC, TRT seemed to be associated with better OS in those treated with non-immune systemic therapy but worse overall survival in patients receiving immune therapy. Concurrent TRT with any systemic therapy including immune therapy was associated with worse survival.

Association of CDKN2A gene alteration with high expression of PD-L1. First Author: Yan Zhang, Department of Cancer Biology, Mayo Clinic, Jacksonville, FL

Background: Gene CDKN2A, which encodes for p16/INK4a/14ARF, is known to be important growth suppressor gene. CDKN2A gene alteration has been reported in non-small cell lung cancer (NSCLC). However, the demographic and clinical features of NSCLC with CDKN2A, coexisting gene alteration and association with immunotherapy biomarkers such as PD-L1 and tumor mutation burden are unknown. Methods: Tumor next-generation sequencing data from 197 NSCLC patients who are diagnosed at Mayo Clinic FL are retrospectively analyzed. Patients with CDKN2A gene alterations are identified. Data including demographic feature, clinical feature, coexisting gene alteration and association with immunotherapy biomarkers such as PD-L1 and tumor mutation burden are investigated. Results: One hundred ninety-seven patients with NSCLC were identified, and 49 (24.8%) had CDKN2A gene alteration, including 32 gene loss, 4 somatic mutations and 3 deletions. The medium age of patients with CDKN2A gene alteration was 66.7. It was slightly more predominant in male than female (53.1% versus 46.9%) and more in smoker than never-smoker (65.3% versus 34.7%). Among patients with CDKN2A gene alteration, 83.7% (41/49) were found in lung adenocarcinoma, 10.2% were found in lung squamous cell carcinoma and 6.1% were found in other histology. The most common coexisting gene alterations associated with CDKN2A are CDKN2B (61%) followed by EGFR (14.2%), STK11 (12.2%), MET (10%), PI3KCA (10%), KDR (8%), ALK (8%), ROS1 (2%). Interestingly, patients with CDKN2A gene alteration were found to have expression of PD-L1 (defined by > 1% PD-L1). Among them, 61.5% patients have high expression of PD-L1 (defined by > 50% PD-L1). Patients with CDKN2A gene alteration are also associated with high tumor mutation burden (10% vs 4%) in driver mutation/mutation. CDKN2A (1%) was seen in NSCLC. Co-existing driver mutations such as EGFR, MET, HER-2, ALK, BRAF are found. Immunotherapy related biomarkers such as high expression level of PD-L1 and tumor mutation burden are found common in patients with CDKN2A gene alteration, indicating the likelihood of clinical benefit to immunotherapy and warrant further investigation in a larger, prospective study.

The effect of thoracic radiation on overall survival and their association with systemic immune therapy in stage IV non-small cell lung cancer (NSCLC). A prospective study of 29 patients reported superior progression free survival with radical TRT. This study aimed to report the overall survival (OS) effect of TRT and examine whether the OS effect varies with the timing of TRT regarding to systemic therapy. Methods: Stage IV patients from the national cancer database (NCDB) 2005-2014 formed the base of the study population. TRT, dose and time effects were analyzed individually in patients treated with non-immune systemic therapy had the best OS (n = 6,064, MST = 11.2 mo, P < 0.001), while patients receiving TRT after systemic therapy (n = 5,500, MST = 8.8 mo), patients with concurrent TRT-systemic treatments (within 30 days of systemic therapy) had significantly worse OS (n = 2,039, MST = 7.2 mo, P < 0.001), while patients receiving TRT after systemic therapy had the best OS (n = 6,064, MST = 11.2 mo, P < 0.001). In 4,639 patients treated with immune therapy, TRT was associated with significantly worse OS (n = 512, MST = 11.1 mo, P < 0.001), comparing to immune therapy alone (n = 4,127, MST = 14.1 mo). Patients receiving concurrent TRT had worst OS (n = 177, MST = 7.4 mo, P < 0.001), comparing to TRT before immune therapy (n = 165, MST = 12.2 mo), and before TRT after immune therapy (n = 138, MST = 13.2 mo, P = 0.086). Conclusions: In patients with stage IV NSCLC, TRT seemed to be associated with better OS in those treated with non-immune systemic therapy but worse overall survival in patients receiving immune therapy. Concurrent TRT with any systemic therapy including immune therapy was associated with worse survival.
Lung Cancer—Non-Small Cell Metastatic

TPS9105
Poster Session (Board #427b), Sun, 8:00 AM-11:30 AM
MORPHEUS: A phase Ib/II multi-trial platform evaluating the safety and efficacy of cancer immunotherapy (CIT)-based combinations in patients (pts) with non-small cell lung cancer (NSCLC). First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN

Background: CIT has demonstrated a significant survival benefit in multiple cancers. Despite this, only subsets of pts experience durable response with CIT monotherapy. Thus, CIT combinations may be needed to address the mechanisms that allow cancers to escape anti-tumor immunity. However, a large number of potential combinations would have to be tested in order to identify an effective CIT combination. The MORPHEUS platform consists of multiple, global, open-label, randomized, Phase Ib/II trials designed to assess the impact of CIT combinations in pts with different tumor types. The randomized trial designs allow comparison of a single control arm vs multiple CIT combination arms. These trials will aid development of CIT combinations by identifying early signals and will have the flexibility to open new treatment (Tx) arms with novel CIT combinations and to close arms that show minimal clinical activity or unacceptable toxicity. Various CIT combinations that simultaneously enhance immune cell priming and activation, tumor infiltration and/or recognition of tumor cells for elimination will be evaluated. Here, we describe the MORPHEUS Phase Ib/II trial of NSCLC, a population likely to benefit from CIT-based combinations.

Methods: MORPHEUS-Lung (NCT03337698) will enroll 2 cohorts: (C1) will enroll pts who are Tnnae for metastatic NSCLC and have high tumor PD-L1 expression (TPS ≥ 50% per Dako 22C3 or VENTANA SP263); C2 will enroll pts who have progressed on prior platinum and anti–PD-L1/PD-1. TX of given concurrently or sequentially, regardless of tumor PD-L1 expression levels. Pts with non-squamous and squamous NSCLC will be included; those with an EGFR mutation or ALK gene rearrangement will be excluded. Pts will be randomized to the control arm or one of several experimental arms (2 for C1; 5 for C2). Pts experiencing loss of clinical benefit or unacceptable toxicity may be eligible to switch to a different CIT combination arm. Safety measures and investigator-assessed ORR (RECIST v1.1) are primary endpoints. PFS, OS, DCR and DOR are among the secondary endpoints. Exploratory biomarkers will also be examined. Clinical trial information: NCT03337698.

TPS9106
Poster Session (Board #428a), Sun, 8:00 AM-11:30 AM
A phase 2 study of poziotinib in patients with EGFR or HER2 exon 20 mutation-positive non-small cell lung cancer. First Author: Zandong Yang, Immunogen, Cambridge, MA

Background: Poziotinib is a novel, oral, quinazoline-based pan-HR inhibitor that irreversibly blocks signaling through the EGFR family of tyrosine-kinase receptors, including human epidermal growth factor receptor (HER1/ ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4), which inhibits the proliferation of tumor cells that overexpress these receptors or acti- vated by EGFR or HER2 exon 20 mutations. There is no FDA approved targeted therapy for EGFR or HER2 exon 20 insertion mutant NSCLC. Chemotherapy remains the standard of care for metastatic disease with severe side effects and modest efficacy. Preclinical testing indicates that poziotinib is more active than currently approved tyrosine kinase inhibitors against cell lines with a range of EGFR exon 20 mutations in vitro when using the standard Ba/F3 model. An ongoing investigator-initiated study at MD Anderson is showing that poziotinib is effective at reducing tumor size in patients with EGFR or HER2 positive non-small cell lung cancer (NSCLC).

Methods: This is an open-label, multicenter study evaluating the efficacy and safety of poziotinib in patients with histologically or cytologically confirmed NSCLC with a documented EGFR or HER2 exon 20 insertion mutation. Patients with T790M point mutations will be excluded. Patients will be enrolled in one of two cohorts based on documented EGFR (Cohort 1; n = 87) or HER2 (Cohort 2; n = 87) exon 20 mutations. Both cohorts are enrolling simultaneously. Patients must be 18 years of age, have an ECOG score ≤2, and have adequate tumor tissue from biopsy or surgical procedure to enable molecular profiling. Poziotinib is 16 mg PO daily with possible dose reductions to 14 mg and 12 mg for tolerability issues. Patients will be treated until either progression or intolerable adverse events. Response will be assessed by an Independent Image Review, Study enrollment began in October 2017. Clinical trial information: NCT 03318939.

TPS9107
Poster Session (Board #428b), Sun, 8:00 AM-11:30 AM
Phase 1/2 study of mRNA vaccine therapy + durvalumab (durva) + tremelimumab (treme) in patients with metastatic non-small cell lung cancer (NSCLC). First Author: Leena Gandhi, NYU Perlmutter Cancer Center, New York, NY

Background: Vaccine therapies stimulate the immune system to attack cancer cells (active immunotherapy), whereas checkpoint inhibitors block immune inhibition (passive immunotherapy). Several PD-1 and PD-L1 blocking antibodies are approved for NSCLC. This study combines active and passive immunotherapies to determine if the addition of a mRNA vaccine can enhance the activity of checkpoint blockade. The vaccine BI 1361849 ( comprising 6 mRNAs encoding for selected tumor-associated antigens: MUC1, survivin, NY-ESO-1, 5T4, MAGE-C2 and MAGE-C1) is combined with 1 or 2 checkpoint inhibitors (durva [anti-PD-L1] + treme [anti-CTLA-4]). Methods: This ongoing Phase 1/2, open-label study (NCT03164772) evaluates the safety and efficacy of BI 1361849 when administered with durva (Arm A) or durva + treme (Arm B) in NSCLC patients. In arm A, an initial dose-escalation phase follows a 3+3 design to determine the dose of durva (1500 or 750 mg) to be given with the vaccine. Arm B uses the durva dose from Arm A, with the addition of 75 mg treme. In the expansion phase, 20 patients are treated in each arm. To aid in the evaluation of immune responses, there is an additional control group (n = 10), which receives the checkpoint inhibitors only. Study treatment is administered over 12 (28-day) cycles. Durva (x 12 doses) and treme (x 4 doses) are adminis- tered intravenously every 28 days. The vaccine is administered on 1 to 3 days over each of the 12 cycles using a device that provides a needle-free intradermal administration. The primary endpoint is safety/tolerability per CTCAE, including dose-limiting toxicity during dose evaluation. Secondary endpoints are progression-free survival and objective response rate at 8 and 24 weeks, disease control rate, response duration, and overall survival, with tumor response evaluated by RECIST and immune-related RECIST. Ex- ploratory objectives include effects on tumor microenvironment and eval- uation of immune responses. Enrollment opened 20Dec2017. Clinical trial information: NCT03164772.

TPS9108
Poster Session (Board #429a), Sun, 8:00 AM-11:30 AM
A trial of CV301 in combination with anti-PD-1 therapy versus anti-PD-1 therapy in subjects with non-small cell lung cancer (NSCLC). First Author: Arun Rajan, Thoracic and Gastrointestional Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Despite recent therapeutic advances in non-small cell lung cancer (NSCLC), an unmet medical need remains for most patients. Pembrolizumab (pembro) is approved in first-line treatment of patients with NSCLC as a single agent when PD-L1 expression is >50% and in combi- nation with chemotherapy when PD-L1 expression is <50%. It is believed that a fraction of non-responders to pembro lack an adequate tumor-directed immune response. CV-301 is a poxviral-based vaccine comprising a prime-boost strategy with Modified Vaccinia Ankara (MVA) prime and foxpox boost. The viral vectors encode 2 tumor-associated antigens, CEA and MUC-1, as well as 3 costimulatory molecules (B7.1, ICAM-1 and LFA-3, called TRICOM). Current preclinical and mechanistic evidence suggests that CV-301 can generate a tumor-directed immune response in NSCLC, potentially increasing the clinical benefit associated with pembro. Methods: This open-label, multi-center trial will evaluate the combination of CV301 and pembro. The phase 1 trial, an evaluation of safety of ascending doses of CV301, has been completed. The vaccine was well tolerated with no DLTs. The phase 1b portion is currently enrolling at least 6 patients with NSCLC in the mainte- nance setting of pembro and will continue pembro in combination with CV301 with a goal to establish safety of the combination. Safety monitoring will occur every two weeks. If safety is established, the randomized Phase 2 portion will enroll 176 subjects, randomized 2:1 to receive maintence pembro in combination with CV301 (2) or alone (1). Maintenance setting is defined as the period following 11 weeks of initial treatment, after which chemotherapy would be complete in the < 50% PD-L1 expression group. To be eligible, patients must have stable disease or objective response at the time of radiographic evaluation (approximately 11-12 weeks after initiation of first line therapy). Preliminary efficacy will be analyzed during the Phase 2 cohort based on the Intent-to-Treat population, comprising overall survival (primary), progression-free survival and overall response rate (secondary). Clinical trial information: NCT02840994.
Background: The indoleamine 2,3-dioxygenase 1 (IDO1) intracellular enzyme and PD-1 receptor both suppress T-cell-mediated antitumor immunity, are coexpressed in multiple tumor types, and are correlated with poor prognosis. Epacodastat (E) is a potent and highly selective oral inhibitor of IDO1. Pembrolizumab (P; PD-1 inhibitor) is the standard of care for treatment-naïve mNSCLC with high PD-L1 expression (tumor proportion score [TPS] ≥50%) and no EGFR or ALK genomic aberrations. Because encouraging activity and minimal additive toxicity were previously observed with E + P in mNSCLC in the phase 1/2 ECHO-202/KKEYNOTE-037 study, this phase 3 global trial (NCT03322540) was initiated to compare E + P vs P + E-matched placebo as first-line treatment for patients with PD-L1 high mNSCLC. Methods: Eligible patients: aged ≥18 years, stage IV NSCLC (no EGFR-sensitizing mutation or ROS1/ALK translocations), TPS ≥50%, ECOG PS ≤1, no prior systemic therapy for mNSCLC, and no prior IDO1 inhibitors or immune checkpoint therapies. Approximately 888 patients will be randomly assigned 1:1 to E 100 mg oral BID + P 200 mg IV Q3W or P + E-matched placebo, and stratified by tumor histology (squamous vs nonsquamous), ECOG PS (0 vs 1), and geographical location (East Asia vs non–East Asia). Patients receive treatment until disease progression, intolerable toxicity, investigator-patient decision to withdraw, or until they have received up to 35 cycles of E + P or P + placebo (≤2 years). Eligible patients: continuous study treatment beyond initial radiographic progression. Patients may discontinue treatment after confirmed complete response. Primary endpoints include PFS and OS. Secondary endpoints include ORR, duration of response, safety, and tolerability. Exploratory endpoints include patient-reported outcomes, E pharmacokinetics, pharmacodynamics, and potential relationship between baseline biomarkers and clinical activity (PFS, OS, ORR). Tumor response will be assessed by a blinded central review, per RECIST v1.1 criteria. Adverse events will be monitored throughout the study and graded per CTCAE v4.0. Clinical trial information: NCT03322540.

ECHO-305/KEYNOTE-654: A phase 3, randomized, double-blind study of pembrolizumab (P; PD-1 inhibitor) vs nintedanib (N; a topoisomerase I inhibitor payload) with pembrolizumab in advanced NSCLC.

First Author: Shuqi Liu, Dana-Farber Cancer Institute, Boston, MA

Background: Nintedanib, a topoisomerase I inhibitor, was initiated in NSCLC patients. In the phase IB/II trial of the combination of nintedanib, nivolumab and ipilimumab was initiated in NSCLC patients. This is a single institution, investigational, non-randomized, parallel assignment phase I/II clinical trial of patients with locally advanced or metastatic NSCLC. Eligible patients can be immunotherapy naive or with disease progression following immunotherapy. Primary objective of phase I is to determine the tolerability of concurrent administration of the proposed regimen. Three dose levels of nintedanib (100mg, 150 mg and 200 mg twice daily) are given with fixed doses of nivolumab (3mg/kg every 2 weeks) and ipilimumab (1mg/kg every 6 weeks). Dose escalation will be done by the modified continuous reassessment method (mCRM). In Dose Expansion, subjects receive U3-1402 at the recommended dose for expansion (RDE) determined in Dose Escalation. Primary objectives are to determine the safety, tolerability, and RDE of U3-1402. Secondary objectives are to assess the pharmacokinetic profile of U3-1402, immunogenicity, and to assess antitumor activity of U3-1402 (RECIST v1.1). Enrolment to cohort 1 began in January 2018. Clinical trial information: NCT03260491.

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**TPS9113 Poster Session (Board #431b), Sun, 8:00 AM-11:30 AM**

**Phase I/II trial of dasatinib and osimertinib in patients with advanced EGFR-mutant non-small cell lung cancer.** First Author: Chul Kim, Georgetown University, Washington, DC

**Background:** Epidermal growth factor receptor (EGFR) mutations are one of the most common driver oncopenes in non-small cell lung cancer (NSCLC). While the presence of these mutations predicts sensitivity to tyrosine kinase inhibitors (TKIs), a small but non-negligible subset of patients do not respond to EGFR-TKIs, suggesting intrinsic resistance. Moreover, acquired resistance to EGFR-TKIs is inevitable. In preclinical studies, overexpression of Crip-to-1, a member of the EGFR-Cripto-1/FR/L-Cryptic protein family, contributes to the development of intrinsic resistance to EGFR-TKIs through the activation of the Src-tyrosine kinase pathway. In EGFR-mutant mouse models, we demonstrated synergy between erlotinib and Src inhibition. In vitro experiments showed increased synergy when using osimertinib, a third generation EGFR inhibitor with dasatinib, a SRC inhibitor. Based on these data, we initiated a phase I/II trial to explore the feasibility and benefit of combining osimertinib and dasatinib in patients with EGFR-mutant NSCLC.

**Methods:** This is an open-label, single-arm phase I/II trial of osimertinib and dasatinib in treatment-naive patients with advanced EGFR-mutant NSCLC (NCT02954523). Patients with sensitizing EGFR mutations as well as those with T790M mutation are eligible. Patients with pleural or pericardial effusions at study entry are excluded. The primary endpoint of the phase I part is to establish a safe and tolerable phase II dose of osimertinib and dasatinib. The endpoint of the phase II part is the reduction of the proportion of patients who progress or have stable disease lasting 4 months or less (definition of intrinsic resistance). For the phase II portion, a two-stage design with a total of 28 patients will be used. The null hypothesis that the proportion of patients with intrinsic resistance is at least 30% will be tested against the alternative hypothesis that the true proportion of patients with intrinsic resistance is at least 10% (alpha one-sided 5%, power 85%). Accrual is underway at Georgetown University and Hackensack University Medical Center. Using tumor and serum samples, the role of Cripto-1 in mediating resistance to osimertinib will be elucidated. Clinical trial information: NCT02954523.

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**TPS9115 Poster Session (Board #432b), Sun, 8:00 AM-11:30 AM**

**eXai3: Phase 3 randomized study comparing ensartinib to crizotinib in anaplastic lymphoma kinase (ALK) positive non-small cell lung cancers (NSCLC) patients.** First Author: Leora Horn, Vanderbilt University Medical Center, Nashville, TN

**Background:** Ensartinib (X-396) is a novel, potent ALK small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, EPHA2, LTK, ROS1 and SLK. Ensartinib is well-tolerated and has shown promising activity in NSCLC patients in a phase 1/2 study in patients that were both ALK TKI naive and patients that received prior crizotinib, as well as those with CNS metastases. The safety profile of ensartinib appears to be different than other ALK TKIs. **Methods:** In this global, phase 3, open-label, randomized study, approximately 270 patients with ALK+ NSCLC who have received no prior ALK TKI and up to one prior chemotherapy regimen will be randomized with stratification by prior chemotherapy (0/1), performance status (0-1/2), brain metastases at screening (absence/presence), and geographic region (Asia /other), to receive oral ensartinib (225 mg, once daily) or crizotinib (250mg, twice daily) until disease progression or intolerable toxicity. Eligibility also includes patients ≥ 18 years of age, stage IIIB or IV ALK+ NSCLC. Patients are required to have measurable disease per RECIST 1.1, adequate organ function, and an ECOG PS of ≤ 2. Adequate tumor tissue (archival or fresh biopsy) must be available for central testing. The primary endpoint is progression-free survival assessed by independent radiology review based on RECIST v.1.1 criteria. Secondary efficacy end-points include overall survival, response rates (overall and central nervous system (CNS)), PFS by investigator assessment, time to response, duration of response, and time to CNS progression. The study has > 80% power to detect a superior effect of ensartinib over crizotinib in PFS at a 2-sided alpha level of 0.05. Phase 3 recruitment began in June, 2016 and currently has 98 active sites in 20 countries. The duration of recruitment will be approximately 24 months. This study is registered with, Clinical trial information: NCT02767804.

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**TPS9114 Poster Session (Board #432a), Sun, 8:00 AM-11:30 AM**

**Trial in progress: Multicenter observational study to evaluate the relationship between gut bacterial flora and their therapeutic or adverse effects in advanced non-small cell lung cancer patients treated with nivolumab.** First Author: Takashi Yokoi, Department of Thoracic Oncology, Kansai Medical University Hirakata Hospital, Osaka, Japan

**Background:** Nivolumab is one of the standard therapies for pretreated advanced non-small cell lung cancer (NSCLC). A correlation between PD-L1 expression on tumor cells and antitumor effects of nivolumab has been shown especially in non-squamous NSCLC. However, PD-L1 expression is an insufficient biomarker because of the weak correlation. It is therefore important to explore better biomarkers. In recent years, the antitumor effects of immune checkpoint inhibitors have been shown to depend on distinct Bacteroides species in preclinical mouse models. This multicenter observational study was planned to evaluate the relationship between gut bacterial flora and their therapeutic or adverse effects on advanced NSCLC patients treated with nivolumab. **Methods:** We prospectively collect microbiome samples from patients with NSCLC who will be treated with nivolumab. Gut (fecal) microbiome samples are collected at treatment initiation and after four doses of nivolumab. We will analyze the trend of gut microbiome differences. The key inclusion criteria are histologically or cytologically proven NSCLC, pretreated NSCLC without any immune checkpoint inhibitor, ECOG PS 0-2, one or more measurable lesions, and written informed consent. The key exclusion criteria are previous or active gastrointestinal, autoimmune, endocrine, or rhabdomyosarcoma or antibiotic, and previous or active inflammatory bowel disease. Clinical trial information: UM000026375.

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**TPS9116 Poster Session (Board #433a), Sun, 8:00 AM-11:30 AM**

**A multicenter, randomized, double-blind, placebo-controlled phase III study of apatinib or placebo plus gefitinib as first-line treatment in patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC).** First Author: Hongyun Zhao, State Key Laboratory of Oncology in South China, Cancer Center, Sun Yat-sen University, Guangzhou, China

**Background:** Dual inhibition of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathway is becoming an encouraging strategy in the treatment of advanced NSCLC. Apatinib is a tyrosine kinase inhibitor that selectively inhibits the VEGF receptor-2. Our phase I study of Apatinib plus Gefitinib has shown a manageable tolerability profile and promising antitumor activity with an anticipated progressive-free survival (PFS) > 14 mos. This phase III study aims to evaluate the efficacy and safety of Apatinib or placebo plus Gefitinib as first-line treatment in patients (pts) with stage IIIB-IV NSCLC harboring an activating EGFR mutation. **Methods:** Treatment-naive stage IIIB or IV NSCLC pts with EGFR 19 Del or 21 L858R mutation are enrolled. Other inclusion criteria include ECOG PS of 0 or 1, ≥ 1 measurable lesion according to RECIST v1.1 and adequate organ function. Eligible pts will be randomized in a 1:1 ratio to receive either Apatinib or Placebo 500 mg QD plus Gefitinib 250 mg QD until disease progression or unacceptable toxicity. Stratified randomization is based on EGFR mutation status, gender, and ECOG PS. The primary endpoint is PFS. Secondary endpoints include overall survival, objective response rate, disease control rate, time to progression, duration of response, quality of life and the safety profile. Independent Data Monitoring Committee and Independent Review Committee will be used in this study. According to previous report (erlotinib plus bevacizumab vs. erlotinib alone: 16.0 vs. 9.7 mos, HR 0.54, Lancet Oncol, 15(11):1236-1244), it was assumed that the estimated median PFS would be 15 mos in the Apatinib + Gefitinib group and 10 mos in the Placebo + Gefitinib group. To detect a 5-mos improvement of PFS in Apatinib + Gefitinib group at a two-sided significant level of 0.05 and a power of 0.8, allowing for a dropout rate of 20%, the sample size should be 155 patients per group. In total, 310 patients will be enrolled in this trial at 30 sites in China. From August 2017, 100 patients have been enrolled. Clinical trial information: NCT02824498.
Afatinib in combination with pembrolizumab in patients (pts) with stage III/IV squamous cell carcinoma (SCC) of the lung.

Background: Afatinib and pembrolizumab have demonstrated improvements in the outcomes of pts with SCC of the lung and are approved as monotherapy. Afatinib is a selective and irreversible ErbB family blocker with activity against all homo- and heterodimers formed by ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4. Pembrolizumab is a humanized IgG4 monoclonal antibody with potent receptor-blocking activity for PD-1. Given the efficacy of these agents as monotherapy in chemotherapy-refractory lung SCC, concurrent inhibition of PD-1 and EGFR pathways represents a promising approach to improve clinical outcomes in lung SCC.

Methods: Study 1200.283 (NCT03157089; LUX-Lung 10/Keynote 497) is a phase II, single-arm study (n = 5062). Eligible pts have stage III/IV lung SCC, progressed during/after first-line platinum-based chemotherapy, and have an ECOG PS 0/1. Prior immune checkpoint inhibitor or EGFR targeted therapy are prohibited. A safety run-in will be performed in 12 pts, using afatinib (starting dose 40 mg/day, with potential dose de-escalation to 30 mg) with pembrolizumab (200 mg every 3 weeks) to assess the safety and confirm the recommended Phase II dose (RP2D) based on dose limiting toxicities observed during the first cycle. In the main trial, afatinib at the RP2D, in combination with pembrolizumab, may be continued for a maximum of 35 cycles. In case of toxicity, afatinib dose reduction to 30/20 mg will be permitted. Primary endpoint is objective response (OR; complete response [CR] or partial response [PR] [RECIST v1.1]). Further endpoints include disease control (CR, PR, stable disease), duration of OR, PFS, OS, and pharmacokinetics. All pts will provide a fresh or archived tumor tissue sample to measure PD-L1 expression and mRNA expression of genes involved in the immune system. Exploratory biomarkers include the evaluation of immune status by determination of tumor infiltrating cells (e.g., CD8+ cells) or TH1-type cytokines, and blood biomarkers related to the emergence of resistance at progression. This study is conducted in the US, Spain, France, Turkey, and Korea. As of January 2018, enrollment in the safety run-in is complete (n = 12). Clinical trial information: NCT03157089.
External validation of the 8th Edition Melanoma Staging System of the American Joint Committee on Cancer (AJCC): Effect of adding EORTC sentinel node burden criteria on prognostic accuracy in stage III melanoma.

Max Fullah Madu, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Now that effective adjuvant therapy has arrived in melanoma, accurate staging and patient selection to optimize a risk/benefit ratio is crucial. The new 8th Edition AJCC staging system for melanoma aims to improve risk stratification. The goal of this study was to externally validate the prognostic and discriminatory ability for survival of the 8th Edition in comparison to the 7th Edition.

Methods: Analysis of a prospective cohort of patients treated in the Netherlands Cancer Institute for AJCC 7th Edition stage III melanoma between 2000 and 2016. Stage III melanoma was defined as regional lymph node metastases, with or without concurrent local recurrence, (micro)satellite or in-transit metastases. Prognostic factors for melanoma-specific survival (MSS) and distant metastasis-free survival (DMFS) were analyzed. Survival differentiation of the 7th and 8th edition was assessed with log-rank tests and Cox proportional hazards models. Discriminatory ability was compared using the area under the curve (AUC) of the receiver operating characteristic (ROC) obtained with Cox models. Results: 640 patients were included with an additional 6 mo of follow-up of 59 months (interquartile range 32-108). Median MSS was 61.9% (90%CI: 59.3%;70.5%, 85 events) in the NIVO group and 41.1% in the IPI group. Per protocol, there was no addition to the 8th Edition staging system differentiates survival slightly worse than the 7th Edition staging system.

Conclusions: The AJCC 8th Edition staging system differentiates survival slightly worse than the 7th Edition staging system. Survival in both 7th and 8th Edition stage IIIA melanoma is heterogeneous and can be subclassified according to EORTC TNM tumor burden, which can aid decision-making concerning adjuvant therapy.

9502 Oral Abstract Session, Mon, 08:00 AM-11:00 AM

Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage IIIIV melanoma: Updated results from a pivotal III trial (CheckMate 238). First Author: Jeffrey S. Weber, New York University Perlmutter Cancer Center, New York, NY

Background: In the initial report of data from CheckMate 238, at a minimum follow-up of 18 mo, NIVO demonstrated significantly longer recurrence-free survival (RFS) vs IPI in patients (pts) with resected stage III or IV melanoma. Here, we report updated efficacy results from this phase III trial with an additional 6 mo of follow-up. Methods: Eligible pts included those >15 y of age who underwent complete resection of stage IIIIB/C or IV melanoma. 906 pts were randomized 1:1 (stratified by disease stage and PD-L1 status at a 5% cutoff) to receive NIVO 3 mg/kg Q2W (N=453) or IPI 10 mg/kg Q3W for 4 doses, then Q12W (from week 24) (N=453) for up to 1 y, or until disease recurrence or unacceptable toxicity. The primary endpoint was RFS; distant metastasis-free survival (DMFS) in pts with stage III disease was an exploratory endpoint. Results: At a minimum follow-up of 24 mo, RFS continued to be significantly longer for NIVO vs IPI (hazard ratio 0.66, P=0.0001), with 171/453 and 221/453 events, respectively. The 24-mo RFS rates were higher for NIVO vs IPI in subgroups defined by disease stage, PD-L1 expression, and BRAF mutation status (Table). DMFS also continued to be significantly longer for NIVO vs IPI, with 24-mo rates of 70.5% and 63.7%, respectively (hazard ratio 0.76, P=0.034). Subsequent therapies were received by 31.1% of pts in the NIVO group and 41.1% in the IPI group. Per protocol, there was no additional safety assessment for the current analysis given that all pts had been off study treatment >100 days at the time of the previous data cutoff.

Conclusions: With extended follow-up, NIVO demonstrated a sustained efficacy benefit vs IPI in pts with resected stage III/IV melanoma at high risk of recurrence, regardless of disease stage, PD-L1 expression, or BRAF mutation status. Clinical trial information: NCT02388906.
Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. First Author: Reinhard Dummer, University of Zurich Hospital, Department of Dermatology, Zurich, Switzerland

Background: Combined BRAF/MEK inhibitor therapy is standard of care in advanced BRAFV600-mutant melanoma. COLUMBUS Part 1 evaluated ENCO 450 mg once daily (QD) + BINI 45 mg twice daily (BID;COMBO450) vs VEM 960 mg BID or ENCO 300 mg QD (ENCO300) in patients (pts) with advanced BRAFV600-mutant melanoma. The primary study endpoint was progression-free survival (PFS); median PFS was 14.9 vs 7.3 mo for COMBO450 vs VEM; hazard ratio (HR): 0.54 (2-sided P < 0.001). Here we report a planned analysis of overall survival (OS), a secondary endpoint of the study. Methods: Pts with advanced/metastatic BRAFV600-mutant melanoma, untreated or progressed on/after first-line immunotherapy, were stratified by disease stage, Eastern Cooperative Oncology Group Performance Status and prior first-line immunotherapy. Pts in Part 1 were randomized 1:1:1 to COMBO450 (n = 192), ENCO300 (n = 193), or VEM (n = 191). Tumor responses and progression were assessed by blinded independent central review. An analysis of OS was planned after 232 events in the COMBO450 and VEM arms combined. Results: As of data cutoff, 105, 106, and 127 events contributed to the OS analysis in the COMBO450, ENCO300, and VEM arms, respectively; median follow-up across arms was 21.5 mo. Median OS was 33.6 mo (95% CI, 24.4-39.2) with COMBO450, 23.5 mo (95% CI, 19.6-33.6) with ENCO300, and 16.9 mo (95% CI, 14.0-24.7) with VEM. Risk of death was reduced by 50% (HR 0.51 [95% CI, 0.39-0.61] [95% CI, 0.47-0.79]; nominal 2-sided P < 0.001). Updated median OS was 26.9 mo (95% CI, 21.2–33.2) with COMBO450, 19.6 mo (95% CI, 7.4–14.8) with ENCO300, and 7.3 mo (95% CI, 5.6–7.9) with VEM. PFS was longer with COMBO450 vs VEM (HR, 0.51 [95% CI, 0.39-0.67]). Updated median OS and PFS and OS data, and information on 2nd-line therapy will be presented at the meeting. Conclusions: The best-in-class median PFS of 14.9 and median OS of 33.6 mo suggest that COMBO450 is a promising new regimen for treatment of BRAF-mutant melanoma. SPONSOR: Array BioPharma Inc. Clinical trial information: NCT01909453.

Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. First Author: Suzanne Louise Topalian, Johns Hopkins Bloomberg/Kimmel Institute for Cancer Immunotherapy and Kimmel Cancer Center, Baltimore, MD

Background: MCC is a rare, aggressive skin cancer commonly associated with the oncogenic Merkel cell polyomavirus (MCVpV). The PD-1/PD-L1 immunosuppressive pathway is often upregulated in MCC, and advanced metastatic MCC is responsive to PD-1 blockade. Here we report the final trial of PD-1/PD-L1 in the neoadjuvant setting for resectable MCC. Methods: In the phase 2 CheckMate 358 trial of nivo anti–PD-1 in virus-associated cancers (NCT02488759), patients (pts) with resectable MCC received nivo 240 mg IV on D1 and D15. Surgery was planned on D29. Tumor regression was assessed radiologically before surgery, and microscopically in the surgical specimen. Immunohistochemistry (IHC) was used to assess tumor MCVpV status and tumor PD-L1 expression. Data were analyzed as of August 7, 2017 with a median follow-up of 54.1 wks. Results: 25 pts with resectable MCC, AJCC stage IIA–IV, received ≥1 dose of nivo. Median age was 70 yrs (range 22–88). Among 18 patients’ tumors evaluated by IHC, 8 (44%) were MCVpV+, and 6 (30%) were PD-L1+ (1 cutoff). 22 of 25 (88%) pts had surgery ≥D29 without significant delay; 3 pts did not have surgery, 1 due to rapid tumor progression and 2 due to grade 2–3 adverse events (AEs). Among 20 pts with pre/post nivo CT scans, 16 (80%) had tumor regression (range 13%–100% reduction), including 9 (45%) with > 30% reduction. Among 17 resections evaluated for pathologic response by central investigator review, 11 (65%) were a major pathologic response (MPR defned as ≤10% residual viable tumor cells), including 8 (47%) complete responses. MPRs and radiologic responses were seen in virus+/− tumors and in PD-L1+/− tumors. Treatment-related AEs were reported in 36% (any grade) and 4% (grade 4–3 of pts, with no new safety signals. Among 21 pts following surgery, 4 (19%) had AEs at 6 mo; 2 pts had relapsed after 12 mo. Conclusions: Nivo administered for 4 wks before surgery in MCC was safe and induced substantial radiologic and pathologic tumor regressions in 45% and 65% of patients, respectively. In some pts, this obviated the need for more extensive surgery. The majority of operated patients remain tumor-free at 12 mo. Data will be updated per a March 2018 database lock. Clinical trial information: NCT02488759.
9508 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Interim analysis of a randomized, open-label phase 2 study of talimogene laherparepvec (T-VEC) neoadjuvant treatment (neotx) plus surgery (surgx) vs surgx for resectable stage IIB-IVM1a melanoma (ME). First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: There is no approved neotx for resectable stage IIB-IVM1a ME. T-VEC, an HSV-1-based oncolytic virus, may reduce the risk of delay in surgery and venous and bone metastases in unresectable stage IIB-IVM1a ME (Andtbacka SSO 2015). We conducted a randomized study to evaluate the effect of neotx T-VEC in high risk resectable ME (NCT02211131).

Methods: Patients (pts) with resectable stage IIB/IC/VM1a ME, ≥ 1 in-ecetable cutaneous, subcutaneous, or nodal lesions ≥ 10 mm, and no systemic tx 3 mos prior were randomized 1:1 to 6 doses/12 wks of T-VEC followed by surgx (Arm 1) vs upfront surgx (Arm 2). T-VEC was given at standard dosing until surgx, no injectable tumors, or intolerance. This interim analysis was planned for when the 75th pt in Arm 1 completed the safety follow-up visit (30+ days post surgx). Results: 150 pts were randomized (76 Arm 1, 74 Arm 2). Of all pts, > 94% had no prior radio/systemic tx, 91% had prior surgx and 84% had no plans for adjuvant tx. 75% in Arm 1 and 93% in Arm 2 had surgx as planned. Of the 19 pts who did not have surgx in Arm 1, 11 had progressive disease. In Arm 2, 17 pts recurred within 14 wks post-surgx. For pts who had surgx in Arm 1, the pathological complete response (pCR) rates were 21%. Negative margin resection (R0) rates were 87% (Arm 1) and 100% (Arm 2) vs 80% (Arm 1) and 96% (Arm 2) for R0 and R1 for Arm 2 (80% CI: 3-28% for the difference). For all randomized pts, pCR rate in Arm 1 was 15.8%; R0 rates were 42.1% (Arm 1) vs 37.8% (Arm 2). Overall response (OR) rate (CR+PR) in Arm 1 was 14.7% (80% CI: 9-22%). In the safety set (73 pts in Arm 1, 69 pts in Arm 2), be-emergent adverse events (AEs) were 93% in Arm 1 (1 grade 4 pain, no grade 5) and 45% in Arm 2 (all ≥ grade 3). In Arm 1, preop AE was 89.5% (most common: pyrexia 35%) and intra/postop AE was 29.8% (most common: seroma 5.3%). In Arm 2, intra/postop AE rate was 45% (most common: pain 7.2%); 17.8% (Arm 1) vs 2.9% (Arm 2) pts had an AE; of these, 5.5% (Arm 1) and 2.9% (Arm 2) were deemed surgx-related. Conclusions: 12 pts of no T-VEC produced a pCR rate in stage IIB-IVM1a ME higher than observed by ORs and may account for the higher R0 margin in Arm 1. No unexpected toxicities were noted. The primary analysis of RFS is ongoing. Clinical trial information: NCT02211131.
Background: The indoleamine 2,3-dioxygenase (IDO) pathway is a key counter-regulatory mechanism that, in cancer, is exploited by tumors to prevent and evade anti-tumor immunity. Inhibitors of the IDO pathway, such as indoximod, are increasingly validated class of potential cancer therapeutic agents. Pre-clinical data and an increasing body of clinical data support evaluating the combination of a checkpoint inhibitor (CI) with an IDO pathway inhibitor as potential treatment for advanced melanoma. Methods: Advanced melanoma patients were enrolled in a single arm Phase 2 trial evaluating the addition of indoximod to standard of care CI as approved for melanoma. Prior therapy excluding CI was allowed. Investigators administered their choice of approved CI (pembrolizumab (P), nivolumab (N), ipilimumab (I)). Indoximod was administered continuously (1200mg po BID), concurrent CI dosed per approved US label. Study endpoint was best overall response (overall response rate (ORR) = complete response (CR) + partial response (PR)) per site reported RECIST 1.1. Results: 102 patients were enrolled in Phase 2. 70 patients with unresectable stage III or IV cutaneous or mucosal melanoma were treated with P and had an on treatment imaging meeting the per protocol, pre-specified definition of evaluable for efficacy (EE). Additionally, 15 patients had occult melanoma refractory to other prior therapies (N, I, N+I) and came off study prior to the first on-treatment imaging study. The ORR for the EE population was 55.7% (39/70, 36 confirmed) with CR of 18.6% (13/70, all confirmed). Median PFS was 12.4 months (95% CI 9.0-NA). Archival tissue was available from 41 of 70 EE patients. The PD-L1 staining was ≥1% in 54% (22/41). The combination was well tolerated. Most common AEs regardless of attribution were fatigue, nausea, pruritus. An additional 21 patients have been enrolled to a biopsy cohort. Conclusions: The combination of indoximod and pembrolizumab demonstrates an ORR of 55.7%, CR 18.6% which compares favorably with reported ORR for P for Palone (33%). Updated data including biopsy cohort will be presented. Clinical trial information: NCT02073123.

9513 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase 1b/2, open label, multicenter, study of the combination of SD-101 and pembrolizumab in patients with advanced melanoma who are naïve to anti-PD-1 therapy. First Author: Antoni Ribas, UCLA Johnson Comprehensive Cancer Center, Los Angeles, CA

Background: SD-101 is a CpG-ODN agonist of TL9R. Pembrolizumab is a PD-1 inhibitor. D3-VEL-M01 (NCT02521870) assesses safety and preliminary efficacy of the combination of SD-101 and pembrolizumab in stage IIC-IV melanoma. Methods: Phase 1b evaluated SD-101 at multiple doses injected in a single tumor Q1W x 4 then Q3W x 7 in combination with a fixed dose of pembrolizumab (200 mg IV Q3W); both drugs started on D1. Phase 2 is evaluating SD-101 at 8 mg in 1 lesion and 2 mg/lesion in 2-4 lesions beginning 21 days after the first dose of pembrolizumab. First scan was performed at D64, after 6 weeks of combination therapy. Per-protocol best overall responses (ORR) were assessed per investigator using RECIST v1.1/irRECIST at ≥ D127 after at least 15 weeks of combination therapy. The per-protocol population comprised patients who received ≥ 1 dose of each drug and had ≥1 post-baseline scan. ITT results are not presented below. Results: Patients enrolled in phase 1b; 54 in phase 2: median age 67y, male 67%, Stage IVM1a/b 27%, Stage IVM1c 37%, LDH > ULN 22%, treatment naïve 70%. SD-101 safety profile consists of transient flu-like symptoms. Frequently observed Grade ≥3 treatment-related AEs were myalgia 9%, headache 9%, fatigue 9%, chills 7%, and malaise 5%. Immune-related AEs (irAEs) have been reported with treatment. Grade ≥3 irAEs included hypophysitis (N = 2), hepatitis (1), Gastritis (1), anorexia (2). In total, 20% pts had Grade ≥3 irAEs with pembrolizumab alone at D127, half of responses were observed ≥ D127 with early discontinuation from PD occurring before D127. The per-protocol ORR was 60% or 15/25 (CR 12%/PR 48%/SD 16%)(DCR = 76%;PD 24%)(median tu = 223 d). 15 pts had CR or PR of 19 with ≥ D127 scans; 6 pts with D64 scans discontinued without a response before D127. 15 pts received ≥ 2 cycles pembrolizumab alone after first line anti-PD-1 is unknown. We report the first prospective data with SD-101 and pembrolizumab in patients naïve to PD-1 inhibitors. Conclusions: The combination of SD-101 and pembrolizumab appears to be showing promising response rates compared to those expected with pembrolizumab alone. The combination is well tolerated with no evidence of an increased rate of irAEs. Clinical trial information: NCT02521870.

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5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001. First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA

**Background:** Pembro has demonstrated robust antitumor activity and safety in several studies of advanced melanoma, including KEYNOTE-001, -002, and -006. Here, we describe the 5-year outcomes for all pts and for those who were treatment naive in the phase 1b KEYNOTE-01 study (NCT01295827).

**Methods:** Pts aged >18 y with previously treated or treatment-naive, advanced or metastatic melanoma received pembro 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W until disease progression, intolerable toxicity, or pt/investigator decision to withdraw. The Kaplan-Meier method was used to estimate OS and PFS. ORR and PFS were based on immune-related response criteria by investigator assessment. Data cutoff was Sep 1, 2017. Results: KEYNOTE-001 enrolled 655 pts (151 treatment naive; 504 previously treated). After a median follow-up of 55 mo (range, 48-69), 35 pts are on pembro treatment. 63% (n = 412) of all pts died. The estimated 5-year OS rate was 34% in all pts and 41% in treatment-naive pts, similar to the 4-year rates of 38% and 48%, respectively. Median OS was 23.8 mo (95% CI, 20.2-30.4) in all pts and 38.6 mo (95% CI, 27.2-297) in treatment-naive pts. 5-year PFS rates were 21% in all pts and 29% in treatment-naive pts; median PFS was 8.3 mo (95% CI, 5.8-11.1) and 16.9 mo (95% CI, 9.3-35.5) in all pts and treatment-naive pts, respectively. Median response duration was not reached; 73% of all responses and 82% of treatment-naive responses were ongoing at data cutoff; there was no evidence of response in all pts was ongoing at 66 mo. Treatment-related AEs (TRAEs) occurred in 86% (n = 562) of pts, including 17% (n = 114) with grade 3/4 TRAEs and 7.8% (n = 51) who discontinued because of a TRAE.

**Conclusions:** Pembro provides a 5-year OS rate of 34% in pts with previously treated or treatment-naive advanced melanoma, with a 5-year OS rate of 41% in treatment-naive pts. These data, representing the longest follow-up for pembro to date in any cancer, confirm the durable antitumor activity and tolerability of pembro in advanced melanoma. Clinical trial information: NCT01295827.

9517 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy in patients (pts) with metastatic melanoma (MM). First Author: Aaron C. Tan, Royal North Shore Hospital, St Leonards, Australia

**Background:** PD1 based therapy has durable clinical activity for some pts with MM, however there are few predictors of long-term response and the optimal duration of therapy is unknown. Whether PET imaging may assist with this remains unclear.

**Methods:** A prospectively assembled cohort of consecutive pts treated at a single center with PD1 based therapy from May 2013 to Sep 2017, who underwent baseline and 1-year PET was examined retrospectively. Demographics, disease features, treatment, response and outcome data were collected. 1-year response was determined using RECIST for CT and EORTC criteria for PET, and was coded as complete response (CR or CMR), partial response (PR or PMR), stable disease (SD or SMD) or progressive disease (PD or PDM) on CT and PET, respectively. Results: 118 pts were evaluated with median follow-up 21.0 mo and 98% remain alive. PD1 based therapy included pembrolizumab (50%) or nivolumab (13%) monotherapy, and combination therapy (with ipilimumab, TVEC or epacadostat/placebo in 37%). At 1-year, 25% of pts had CR, 60% PR and 15% SD/PD on CT, while 68% had CMR, 17% PMR and 15% SMD/PMD on PET (Table). RECIST progression-free survival (PFS) was improved in pts with CMR vs non-CMR (median not reached [NR] vs 19.8 mo; HR 0.09; p < 0.01), and in the pts with CMR, PFS was not statistically different between pts with CMR+CR vs CMR+PR/SD (median NR in both groups; p = 0.11). In pts with PR on CT, PFS was improved in pts with PR+CMR vs PR+non-CMR (median NR vs 21.3 mo; HR 0.12; p < 0.01). In the 80 pts with CMR, median time on treatment was 14.8 mo, 60% had discontinued treatment with median follow-up post discontinuation 9.9 mo, and 99% had ongoing response. Conclusions: Whilst only a small proportion of pts who survive on PD1 based therapy have a complete metabolic response on CT, most have a complete metabolic response on PET, and 99% have ongoing response. PET may have utility in predicting long-term benefit and guide discontinuation of therapy. Prospective evaluation using PET at earlier intervals is warranted.

Transcriptomic and immunophenotypic profiles of melanoma tissue from patients (pts) treated with anti-PD-1 +/- ipilimumab to define mechanisms of response and resistance. First Author: Tuba Nur Gide, Melanoma Institute Australia, The University of Sydney, Sydney, Australia

**Background:** Immune checkpoint blockade improves the survival of patients with metastatic melanoma, but many patients fail to respond to immunotherapy and the lack of accurate predictors of response or progression remains a major clinical problem. We investigated potential mechanisms of response and resistance to anti-PD-1 +/- ipilimumab.

**Methods:** 141 melanoma biopsies from advanced melanoma pts treated with anti-PD-1 monotherapy (n = 54), or anti-PD-1 + ipilimumab (n = 51) were classified as responders (CR/PR/SD > 6 mo) or non-responders (SD <6 mo:PD) based on RECIST. The transcriptomic and immunophenotypic profiles of 105 baseline (PRE) and 36 early during treatment (EDT) tumor biopsies from pts treated with monotherapy (n = 33 responders, n = 21 non-responders) or anti-PD-1 + ipilimumab (n = 38 responders, n = 13 non-responders) were characterized via DNA sequencing and multiplex immunofluorescence.

**Results:** Responders to monotherapy displayed increased expression of genes associated with a Type 1 interferon response, tissue-resident T-cells and drug targets (TIGIT, ADAR, ADORA2A, CD137, IDO1 and LAG3) (diff. p < 0.05). Genes unique to anti-PD-1 + ipilimumab responders included T-cell and NK-cell genes EOMES, CD48, CD96, and FASLG. Non-responders displayed significantly higher expression of genes associated with WNT signaling along with novel hypoxic and metabolic pathways, including CA9 and NABP1 (p < 0.05).

Non-responders with high CDB/PD-L1 densities expressed novel immune drug targets (IDO1 expressed by 37% of monotherapy non-responders, ICOS (37%), TNFRSF9 (26%), LAG3 (16%), TIGIT (16%) and ADORA2A (16%). In contrast, TIL-low tumors displayed a lack of expression of the aforementioned targets (42% of monotherapy and 86% of anti-PD-1 + ipilimumab non-responders).

**Conclusions:** These findings demonstrate that combinations of novel drug targets may provide clinical benefits in non-responding and non-CR/PR/SD patients. Hypoxic TILs may require modulation of WNT, hypoxic and metabolic pathways to overcome resistance, facilitating the development of novel synergistic drug targets.

9518 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Primary analysis of phase 2 results for cemiplimab, a human monoclonal anti-PD-1, in patients with metastatic cutaneous squamous cell carcinoma (mCSCC). First Author: Danny Rischin, Peter MacCallum Cancer Centre, East Melbourne, Australia

**Background:** CSCC is riddled only by basal cell carcinoma as the most common cancer in the US. There is no standard of care for patients with mCSCC; hence there is a significant unmet need in these patients. Cemiplimab (REGN2810) is a human monoclonal antibody that targets PD-L1 which exhibits sustained activity in patients with metastatic CSCC in a phase 1 study (ASCO 2017, #9503). We present the primary analysis of the mCSCC cohort from the pivotal phase 2 study (NCT02760498; data cutoff date Oct 27, 2017). Methods: Patients with mCSCC (defined as nodal and/or distant) received cemiplimab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks (Q2W). Tumor measurements were performed every 8 weeks. The primary objective was to evaluate overall response rate (ORR; complete response [CR] + partial response [PR]) according to independent central review (per RECIST 1.1 for scans; modified WHO criteria for photos). Duration of response (DOR) was a key secondary endpoint. Durable disease control rate (DDCR) was defined as stable disease or response for ≥16 weeks.

**Results:** 59 patients were enrolled (54 M/5 F; median age: 71.0 years [range: 38-93]; ECOG performance status: 0 and 1 in 23 and 36 patients, respectively). 33 patients (55.9%) had received prior systemic therapy and 50 (84.7%) had received prior radiotherapy. Median duration of follow-up was 7.9 months (range: 1.1-15.6). ORR by central review was 47.5% (95% CI: 34.3-60.9; 4 CRs and 24 PRs). Responses were observed irrespective of prior systemic therapy. Median DOR has not been reached. Only 3 responding patients had subsequent disease progression at the time of data cut-off. DCCR was 61.7% (95% CI: 47.4-73.9%). CRs (3.4%) included 1 CR to baseline high TILs, 1 CR to high TILs, 1 CR to high TILs and 1 CR to high TILs (range: 1.7-6.0). The most common adverse events (AEs) regardless of attribution (all grades, ≥Grade 3) were diarrhea (27.1%, 1.7%), fatigue (23.7%, 1.7%), and nausea (16.9%, 0.0%). Immune-related AEs ≥Grade 3 (per investigator assessment) occurred in 10.2% of patients. Conclusions: In the largest prospective study of cemiplimab, 3 mg/kg Q2W showed substantial activity and durable responses with an acceptable safety profile. Clinical trial information: NCT02760498.
Redirected T cell lysis in patients with metastatic uveal melanoma with gp100-directed TCR IMCgp100: Overall survival findings. First Author: Uteka S. Sado, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

Background: IMCgp100 is a bispecific biologic comprised of a soluble T cell receptor recognizing the gp100 antigen fused to a scFv anti-CD3 and redirects T cell lysis of melanoma cells expressing gp100. Safety and preliminary efficacy of IMCgp100 were assessed in a Ph 1/2 study in metastatic UM (mUM). Methods: HLA-A*0201+ pts with mUM were treated with QW dosing of IMCgp100 iv of Cycle 1, Day 1 (C1D1), 20 mcg and C2D1-30 mcg, followed by the escalated dose administered at C1D15 and beyond. Results: Pts with mUM (n = 19), elevated LDH (87%), liver metastases (100%), and median of 4 prior therapies (0–8) were treated across 4 doses (54 to 73 mcg) in Ph 1; 23 pts were treated in the Ph 2 RP2D (68 mcg) expansion cohort. Related AE included pruritus (90%), pyrexia and fatigue (84%), and hypotension (74%). Gr 3/4 related AE include AST elevation, erythema and hypotension (all, 16%). Ten of the 19 pts in Ph 1 were treated at or above the RP2D. Objective PR by RECIST in Ph 1 were 66% (95% CI [39, 83]). Median OS rate in Ph 1 was 74% (95% CI [48, 88]). Median OS in this cohort has not reached (median follow up of 15.9 mo). The PKPD relationship of exposure was modeled with extent and duration of lymphocyte trafficking. The EC50 for lymphocyte extravasation to the periphery was estimated at 1.4 nmL. At high doses, maximal trafficking of 50% was observed compared to baseline. The extent of lymphocyte trafficking is saturable, however the duration was dose dependent. The EC90 represents the dose of 70 mcg, supporting the RP2D. In the full cohort (n = 42), rash of Gr ≥ 2 within the first 3 weeks of dosing was associated with prolonged OS when compared to pts with mild (GI) or no occurrence of rash (0% vs. 38%; p = 0.0015). IMCgp100 is tolerable with the intra-patient escalation dosing regimen and leads to prolonged OS. A potential association of prolonged OS with rash severity was observed. PKPD modeling demonstrates a relationship between lymphocyte trafficking and exposure to IMCgp100. Pivotal trials in the setting of metastatic UM continue to enroll (NCT03707392, NCT02570308). Clinical trial information: NCT02570308.
Association between hospital volume and overall survival (OS) of stage 3 and 4 cutaneous malignant melanoma (MMel).

Methods: Patients with MMel diagnosed between 2004 & 2015 were included and classified into tertiles based on hospital volume. Cox regression analysis was performed to adjust for covariates, including patient demographics, tumor characteristics, LDH, cancer stage & therapy received. Kaplan Meier estimates of OS were compared with log-rank test. Results: A total of 50, 254 MMel patients were treated at 1317 facilities. The median age at diagnosis was 62 & 67 y for stages 3 & 4, respectively. The median annual facility volumes were 10 & 6 patients/yr for stages 3 & 4, respectively. Multivariable analysis showed that facility volume was an independent predictor of OS (p = 0.0001). Stage 3 (n = 34, 66%) Hospitals were classified into (T): mean cases/year (T1: < 4.5; T2: 4.5-15.25; T3: > 15.25 cases/year). The unadjusted median OS by facility volume was: T1: 77 months (m), T2: 94 m; T3: 124 m (P < .0001). Compared with patients treated at T3 facilities, patients treated at lower-tertile facilities had significantly higher risk of death (T2 hazard ratio (HR) = 1.11 (95% CI, 1.06-1.16); T1 HR, 1.18 (CI, 1.09-1.27)). Stage 4 (n = 15, 588): T1:11-3; T2: 3.8-6.7; T3: > 6.8. The unadjusted median OS by facility volume for stage 4 MMel was: T1: 6 m; T2: 8 m; and T3: 11 m (P < .0001). Compared with patients treated at T3 facilities, patients treated at lower-tertile facilities had significantly higher risk of death (T2 HR, 1.18 (CI, 1.13-1.21); T1 HR, 1.21 (CI, 1.14-1.30). Patients treated at T2 facilities (vs T1) were more likely to receive chemotherapy (36 vs 27%) and immunotherapy (27 vs 12%) (p < 0.01). Conclusions: Patients who were treated for MMel at high-volume centers were more likely to receive chemotherapy and immunotherapy compared to the observational arm, which was most relevant for adverse events. However, patients in the treatment arm had a significantly increased incidence of adverse events by 4-fold, i.e. in more than 80% of the patients, compared to the observational arm, which was most relevant for adverse events of grade > = 3. Conclusions: Given the lack of efficacy of ipilimumab in preventing disease progression of MCC together with the pronounced toxicity, it was decided to stop enrollment of further patients into this study because a significant survival benefit was unlikely to be achieved as predicted by the futility analysis even across the originally planned cohort. Adjuvant ipilimumab should not be considered in MCC patients. Currently, adjuvant nivolumab is tested in comparison to observation to improve DFS. Clinical trial information: NCT02196961.

5927 Adjuvant ipilimumab compared with observation in completely resected Merkel cell carcinoma (MCC): A randomized, multicenter DeCoG/ADO study. First Author: J?Rgen C. Becker, Translational Skin Cancer Research, Deutsches Konsortium f?r Translationale Krebsforschung (DKTK), Essen, Germany

Background: Merkel cell carcinoma (MCC) is a rare, immunogenic, and highly aggressive skin cancer. Almost 40% of patients with completely resected MCC will relapse within the first two years after initial diagnosis. Currently, there is no accepted adjuvant systemic therapy for MCC. This study was conducted to determine if an immune modulating therapy with ipilimumab improves the disease-free survival (DFS) of MCC patients.

Methods: Within 12 weeks after complete resection of primary or locoregional metastatic MCC, patients were randomly assigned to four doses of 3mg/kg ipilimumab i.v. every 3 weeks or observation. The primary end point was DFS; secondary endpoints included adverse events and overall survival at 12 months. Futility analysis was performed after screening 20% of the planned patient number. Results: At the time of futility analysis, 47 patients had been screened and 40 patients enrolled. Four patients had to be excluded after randomization due to protocol violations or withdrawal of informed consent (ipilimumab = 1; observation = 3). Median follow-up was 22.3 months. Groups were well-balanced with regard to demographics, histology, and tumor stage. DFS was not significantly different between ipilimumab and observation (hazard ratio, 1.8; CI, 0.3 to 10; P = 0.48). However, patients in the treatment arm had a significantly increased incidence of adverse events by 4-fold, i.e. in more than 80% of the patients, compared to the observational arm, which was most relevant for adverse events of grade > = 3. Conclusions: Given the lack of efficacy of ipilimumab in preventing disease progression of MCC together with the pronounced toxicity, it was decided to stop enrollment of further patients into this study because a significant survival benefit was unlikely to be achieved as predicted by the futility analysis even across the originally planned cohort. Adjuvant ipilimumab should not be considered in MCC patients. Currently adjuvant nivolumab is tested in comparison to observation to improve DFS. Clinical trial information: NCT02196961.

5925 Interim analysis of a prospective, randomized, double blind, placebo controlled, phase Ib trial of the TLPLDC vaccine to prevent recurrence in resected stage III or IV melanoma patients. First Author: John William Myers, San Antonio Military Medical Center, San Antonio, TX

Background: The autologous tumor lysate, particle loaded, dendritic cell (TLP/LDC) vaccine has been shown to be safe and immunogenic while producing objective tumor responses in a variety of metastatic patients (pts). Here, we present the pre-specified interim results of a randomized, double blind phase Ib trial (NCT02301611) assessing the TLPLDC vaccine to prevent recurrences in high risk melanoma pts. Methods: Stage III & IV resectable melanoma pts were identified prior to definitive surgery and consented for tumor collection. Pts were re-consented for treatment and randomized 2:1 (vaccine (V); placebo (P)). TLPLDC or placebo vaccines were initiated within 3 mos of completion of standard of care (SoC) therapies. Intradermal inoculations were given at 0, 1, 2, 6, 12, and 18 mos. Pts were followed for recurrence per SoC, and the primary endpoint is 2 yr disease-free survival (DFS). The interim was pre-specified at 6 mos from the 120th randomization. Survival analysis was performed on the intention-to-treat (ITT) and per treatment (PT) populations. The latter excludes early recurrences due to the primary vaccine series (PVS) (up to 6 mos). Results: The trial randomized 120 patients (V = 83, P = 37). There were no clinicopathologic or treatment-related differences between the groups except for median age (V = 65 yrs, P = 57 yrs, p = 0.02). There were 3:1 stage III:IV in both groups. Study-wide, only 33% of pts experienced treatment-related adverse events (AEs) with 98.6% being grade 1-2. There were no serious or immediately life-threatening AEs. In the ITT analysis, there was no difference in recurrence (V = 56.6%, P = 54.1%, p = 0.65) at a median f/u of 11.9 mos. In the PT analysis (V = 51, P = 30), there was a trend toward decreased recurrences in the TLPLDC arm (V = 29.4%, P = 43.3%, p = 0.07) at a median f/u of 12.6 mos. Conclusions: The TLPLDC vaccine is safe, well tolerated, and appears to be minimally toxic. Among pts completing the PVS, TLPLDC is a strong trend toward fewer recurrences in the TLPLDC arm. This benefit will be confirmed at the primary analysis of 2 yr DFS; however, these early data provide an encouraging signal that a phase III trial for efficacy may be warranted. Clinical trial information: NCT02301611.
9529 Poster Session (Board #356), Mon, 1:15 PM-4:45 PM
Prediction of response and toxicity to immune checkpoint inhibitor therapies (ICI) in melanoma using deep neural networks machine learning. First Author: Zsuzsanna Davíd, The Roswell Cancer Institute, Department of Dermatology, New York University School of Medicine, New York, NY

Background: Challenges in treating melanoma patients with ICI include treatment resistance and adverse events, both of which can lead to discontinuation of treatment. Histopathology of metastatic melanoma lymph nodes (LN) reveal varying histological composition(s) of malignant melanocytes and host LN reactions to tumor. Here we tested the hypothesis that deep learning machine learning on H&E images of metastatic melanoma LN prior to ICI can predict response and/or toxicity. Methods: H&E slides of metastatic and normal LN resected from melanoma patients (n = 45) prior to receiving ICI were digitized and annotated for regions of interest. The Inception v3 Convolutional Neural Network (CNN) was first trained to distinguish tumor LN (n = 56) from independent normal LN (n = 57). Images were tiled (299x299 pixels) at 20X magnification and partitioned into training (70%), validation (15%) and testing (15%) sets. RNs were next trained on two classifications: 1) complete/partial response (n = 15) vs. progression of disease (n = 30) and 2) no (n = 14) vs. severe (n = 12) toxicity. Images from response (n = 45) and toxicity (n = 26) datasets were partitioned into 80% training and 20% testing sets followed by 5-fold cross validation. Predictive accuracy was measured by area under the curve (AUC) of receiver operating characteristics (ROC) plots. Sensitivity (SEN) and specificity (SPEC) were calculated at the optimal cut-off point of ROC curves. Results: Melanoma-infiltrated LNs were distinguished and a distantly annotated normal background was used to train the model. The AUC of 0.99 (CI, 0.98-1.00), with 0.96 SEN & SPEC. In predicting response to ICI, machine learning algorithm associated with an AUC of 0.76 with 0.71 SEN & 0.64 SPEC. Severe toxicity was predicted with an AUC of 0.70 with 0.68 SEN and 0.61 SPEC. The AUC standard error of mean (SEM) was 0.09 for both analyses. Conclusions: Our data suggest that deep neural networks have the potential to predict patient response and toxicity to ICI with an accuracy of 70%. Independent larger datasets in clinical trial setting are pre-requisite to support validity of this novel approach.

9530 Poster Session (Board #357), Mon, 1:15 PM-4:45 PM
Efficacy and safety of entinostat (ENT) and pembrolizumab (PEMBO) in patients with melanoma progressing on or after a PD-L1 blocking antibody. First Author: Meredith M. Regan, Australia, Sydney, Australia

Background: Immune checkpoint inhibitors (ICIs) have improved prognosis for pts with advanced melanoma, but there is an unmet need for pts who progress after ICI. In this group, we reported that ENT, a class 1 selective histone deacetylase (HDAC) inhibitor, in combination with PEMBO showed promising activity, through alteration of the immunosuppressive tumor microenvironment. Here we report the first 34 pts with further information on both pt characteristics and pretreatment tumor samples. Methods: ENCORE-601 is a multicohort study evaluating ENT + PEMBO. Pts enrolled in Cohort 3 had unresectable or metastatic melanoma, were previously treated with a PD-L1-blocking antibody, and experienced progression on or after therapy. The enrollment target was 34 pts and revised to 52 to increase statistical power and decrease Type I error. Pts were treated with ENT 5 mg PO weekly and PEMBO 200 mg IV Q3W. Primary endpoint was ORR as assessed by irRECIST. Tumor biopsies and blood samples for immune correlates were obtained pre- and on-treatment. Results: Of the first 34 patients, 14 had refractory disease to prior PD-L1 therapy, and only 2 had a documented prior response. Median duration of PD-L1 therapy was < 6 months and the median time from last dose was 65 days. 22 pts had prior ipilimumab and 6 had progressed on a BRAF inhibitor. With ENT + PEMBO, 6 of 34 pts achieved a confirmed PR (ORR = 18%, 95% CI: 6.8-34.5), and 10 pts continue on study (3 have been on treatment > 1 year). Frequent (> 15%) related AEs include nausea, fatigue, diarrhea, and stomatitis. Summary of pretreatment tumor samples with pts with tumor samples pre- and on-treatment (n = 9) indicates increased inflammation in the tumor microenvironment after treatment; a decrease in MDCS (~3.75%) and an increase in CD8+ T cells (47.4%) was also observed. Conclusions: ENT + PEMBO continues to demonstrate promising anti-tumor activity in pts with advanced melanoma, but there are no data examining BRAF/MEKi after immunotherapy. The AUC standard error of mean (SEM) was 0.09 for both analyses. Conclusions: Our data suggest that deep neural networks have the potential to predict patient response and toxicity to ICI with an accuracy of 70%. Independent larger datasets in clinical trial setting are pre-requisite to support validity of this novel approach.

9531 Poster Session (Board #358), Mon, 1:15 PM-4:45 PM
Treatment-free survival (TFS), a novel outcome applied to immuno-oncology (IO) agents in advanced melanoma (AM). First Author: Meredith M. Regan, Dana-Farber Cancer Institute, Boston, MA

Background: Conventional measures, such as median progression-free survival, may suboptimally characterize the full impact of IO agents. Patients (pts) discontinuing IO agents may experience periods of disease control without needing subsequent systemic anticancer therapy (Rx). We propose TFS to simultaneously characterize the antitumor activity and adverse events of this treatment free environment necessary for successful re-treatment with an anti-PD-L1 agent. Methods: Treatment-free survival (TFS) was defined as the time until subsequent Rx, and 24% for I. Clinical trial information: NCT02437136.

9532 Poster Session (Board #359), Mon, 1:15 PM-4:45 PM
Activity of targeted therapy after failure of first-line immunotherapy in BRAF-mutant metastatic melanoma. First Author: Cathy Yi Xia, Melanoma Institute Australia, Sydney, Australia

Background: There are limited data regarding the best sequence of targeted and immunotherapy in patients (pts) with BRAF-mutant melanoma. Some studies suggest lower activity of immunotherapy after BRAF/MEKi inhibitors (BRAF/MEKi), but there are no data examining BRAF/MEKi after immunotherapy. Methods: Consecutive patients with BRAF-mutant metastatic melanoma from 6 centers treated with 1 or more lines of immunotherapy then subsequent BRAF/MEKi were identified. Disease characteristics, treatment details, RECIST response and survival data were retrospectively examined. If pts ceased BRAF/MEKi for toxicity prior to first response assessment, response was deemed progressive disease (PD). Results: 79 pts were included, with 660% (95), 650% (13), 660% (1) and 660% (1) mutations. 56% pts were treated with first-line ipilimumab, 21% with PD1 antibodies, 15% with combination ipilimumab/nivolumab, and 5% with other PD1 combinations. Median duration of immunotherapy was 10.9 weeks, and best response was partial response (PR) in 11%, stable disease (SD) in 17%, and PD in 72% pts. 20% of pts had 1 or more further lines of systemic treatment prior to BRAF/MEKi. At commencement of BRAF/MEKi, median age was 60 years, 68% were stage M1c, 25% had brain metastases, 57% had elevated LDH, 24% were ECOG 2/3. Median interval from last dose of immunotherapy was 6 weeks. 55 (70%) pts received combination BRAF+MEKi, 22 (28%) BRAFi alone, and 2 (3%) MEKi alone. 10/79 (13%) pts ceased BRAF/MEKi due to toxicity, 2 prior to first response, and median treatment duration was 21 weeks. 59% pts had a RECIST response (5% CR), 11% had SD and 29% had PD. Median PFS was 4.4 months (3.5 - 6.2). 65% pts had subsequent treatment, including PD1 antibodies, 25% from BRAF+MEKi. Pts on BRAF+MEKi had a median OS of 18.0 months (14.6 - 40.3), and 39% were alive at 3 years. In the 35 (44%) pts that had received prior PD1 antibodies, the response rate was 66%, median PFS 4.1 months (2.4 - 6.8) and median OS 13.6 months (10.2 - NR). Conclusions: BRAF/MEKi have efficacy in pts previously treated with immunotherapy. Despite having no history of disease progression, lesions that progressed after re-challenge were more likely to respond than those that progressed during initial treatment. pergamos
9534  Poster Session (Board #361), Mon, 1:15 PM-4:45 PM
Pembrolizumab as first line therapy in patients with unresectable squamous cell carcinoma of the skin: Interim results of the phase 2 CARSKIN trial. First Author: Khang Nguyen, Princess Alexandra Hospital, Brisbane, Australia
Background: Patients (pts) with advanced squamous cell carcinoma of the skin (SCCS) have a poor prognosis. Response rate (RR) of 46% with an anti PD-1 (REGN2810) was recently shown in 25 pre-treated pts. CARSKIN is an open-label, phase II study evaluating pembrolizumab (Pembro) in unresectable SCCS. We report preliminary efficacy and safety findings. Methods: Chemotherapy naïve pts who had unresectable SCCS, with an ECOG PS of ≤ 2 were eligible. Baseline PD-L1 expression was centrally assessed on tumor. Pembro kindly provided by Merck was administered IV (200 mg Q3W) for a period up to 24 mths. CT evaluation was performed at baseline, 9, 15, 24 wks and thereafter Q12W and was independently reviewed. The primary endpoint was RR at 15 wks (RECIST criteria). Using Simon two-stage design, ≥4 responses were required out of 19 pts in stage 1 to continue accrual to 39 pts. Results of RR at 15 wks (RECIST criteria). Using Simon two-stage design, ≥4 responses were required out of 19 pts in stage 1 to continue accrual to 39 pts. Results of stage 1 are reported. Results: Nineteen pts (6, 7 and 6 with local, regional and distant metastasis, respectively) were recruited between March and July 2017, of which 15 (79%) were male. Median age was 80 yrs (range, 61-88); 61% of pts were PS 1. Median number of Pembro infusions was 9 (range, 0-13). Median follow-up was 7 mths. Seventeen pts were evaluable for tumor response, and 19 for toxicity. RR at 15 wks in the ITT population was 42% (95% CI: 23–63%) corresponding to 7 PR (2 unconfirmed) and 1 CR. Disease control rate at 15 wks was 58% (11/19 including 3 SD). Only 1 responder progressed. Median FFS is 7 mths and median OS is not reached. There was no Pembro-related death or SAE. One pt discontinued Pembro due to grade 2 colitis. Pembro-related AE occurred in 63% of pts, the most frequent AEs being rash (32%), pruritus (16%), fatigue (26%), dysthyroidism (10%), and diarrhea (10%). Baseline PD-L1 expression was positive in 11 cases (58%). Median PD-L1 expression (Q1-Q3) was 28% (17.5%) in responders vs 0% (0-3%) in non-responders at 15 wks (P = .15). Conclusions: As first line treatment, pembrolizumab monotherapy provided encouraging clinical activity characterized by a high RR and durable response and was well tolerated in these elderly pts. The second stage of CARSKIN is ongoing. Clinical trial information: NCT02989356.

9536  Poster Session (Board #363), Mon, 1:15 PM-4:45 PM
Relapse after cessation of PD-1 based therapy for complete responders in metastatic melanoma. First Author: John Walker, University of Alberta, Edmonton, AB, Canada
Background: Treatment of metastatic melanoma using programmed death (PD-1) inhibitor has revolutionised systemic therapy, with a proportion able to achieve a durable complete response (CR). Little is known about the longterm relapse after cessation of therapy and the outcomes on re-induction. Methods: A retrospective review of patients (pts) who ceased PD-1 therapy after achieving CR was conducted across five institutions. The primary outcome was rate of relapse and response to therapy after relapse. Results: 182 pts that ceased PD-1 therapy following CR were included. Relapse occurred in 19 pts (10.44%), BRAF wildtype (N = 13), BRAF mutant (N = 6). Median follow-up post cessation was 22 (5-34) months. The mean duration on therapy prior to cessation was 16 (3-32) months and the mean interval between cessation of therapy and relapse was 14 (1-33) months. Relapse occurred in a site of new disease (N = 5) and in a site of prior disease (N = 14). On relapse, 12 pts were rechallenged with PD-1 therapy. Currently these pts were in CR (n = 3), partial response (n = 1), stable disease (N = 4) and progressive disease (PD) resulting in death (n = 1) or were waiting restaging (n = 3). Remaining relapses were treated with gamma knife (n = 1), this pt died following PD), gamma knife and PD-1 therapy (n = 1, pt in CR) or surgical resection (n = 3, all in CR). Two pts are waiting restaging following commencement of LAG3 inhibitor (n = 1) or topical imiquimod (n = 1). One pt elected for nil intervention following relapse and is alive with PD. Conclusions: Emerging data is suggesting that cessation of PD-1 based therapy for complete response is possible with durable disease control. This to date is the largest cohort of pts who have been followed up post cessation for complete response to describe patterns of relapse and response to subsequent re-challenge. Further long term follow-up of current trials is needed.

9535  Poster Session (Board #362), Mon, 1:15 PM-4:45 PM
Radioembolization for treatment of uveal melanoma hepatic metastasis: Results of a phase II, single institution, prospective trial. First Author: Cesar F. Gonzales, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA
Background: The liver is the first site of metastasis in >90% of uveal melanoma (UM) patients. Transarterial catheter directed therapies have been used to control growth of liver tumors and prolong overall survival (OS). We report results of the first prospective, phase II trial using radioembolization (RE) Y-90 resin microspheres for treatment of UM hepatic metastases. Methods: Between November 2011 and January 2017, RE was performed on 24 treatment naïve patients (Group A (13 men; median age 63; range, 29 -77)) and 24 patients who progressed after immunoeembolization (Group B (9 men; median age 59, range, 34-77)). Patients received unilobar or lobar treatments separated by 3-5 weeks. Patients were followed for 1 month for acute toxicity and every 3 months for delayed toxicity (CTCAE v 3.0). MR, CT and PET imaging was obtained every 3 months to evaluate for tumor response (PFs; RECIST) and extrahepatic disease. Results: Group A: Unilobar (n = 7) or bilobar (n = 17) RE was performed (median dose, 32.6 mCi; range, 17.7-56.1). One patient was removed from the trial for ineligibility and no further treatment was given. Median OS was 18.9 months (range, 6.5 -66.9) with 4 surviving patients (range, 14, 14.0-66.9 months). One year survival was 61%. Extrahepatic disease occurred in 17 patients (median, 6.3 months; range, 3.3 – 11.9). Group B: Unilobar (n = 5) or bilobar (n = 19) RE was performed (median dose 15.0 mCi; range, 19.2 -50.8). RE response included PR (n = 6), SD (n = 8) and PD (n = 10). One patient withdrew from the trial. Median PFS was 4.3 months (range, 2.5 -18.6). Median OS was 19.1 months (range, 4.8-68.4) with 5 surviving patients (range, 18.6 – 68.4 months). One year survival was 70%. Extrahepatic disease occurred in 15 patients (median, 5.5 months; range 0.8-9.9). No procedure-related complications occurred. Occurred Grade 3 treatment-related toxicities included transient leukopenia (n = 2), nausea/vomiting (n = 1) and pain (n = 1). Conclusions: RE is a safe and effective treatment for UM hepatic metastases and should be considered as a treatment option for patients with and without prior transarterial catheter directed therapies. Clinical trial information: NCT01473004.

9537  Poster Session (Board #364), Mon, 1:15 PM-4:45 PM
Second-line avelumab treatment of patients (pts) with metastatic Merkel cell carcinoma (mMCC): Experience from a global expanded access program (EAP). First Author: John Walker, University of Alberta, Edmonton, AB, Canada
Background: Avelumab is a human anti–PD-L1 IgG1 antibody that showed a favorable efficacy and toxicity profile in pts with mMCC and progressive disease (PD) on or after chemotherapy (CT) in the phase 2 JAVELIN Merkel 200 trial (JM 200; NCT02155647), leading to accelerated approval in the USA in 2016. We describe real-world experience with avelumab in a global EAP for pts with mMCC. Methods: Pts participating in the EAP (NCT03089658) had stage IV mMCC and PD on or after CT or were ineligible for CT. In contrast to JM 200, pts in the EAP could have ECOG performance status of 2, treated brain metastases, or immunosuppressive conditions with sponsor medical approval. Pts received avelumab 10 mg/kg IV Q2W until PD or unacceptable toxicity. A 3-mo supply of avelumab for approved pts was provided to treating physicians; additional re-supply was allowed for pts who had complete response (CR), partial response (PR), stable disease (SD), or clinical benefit per treating physician assessment. No central imaging was obtained. Results: Between Jan 2016 and Jan 2018, 460 requests for avelumab were received from 37 countries; 395 were approved, 45 were medically rejected for various reasons (eg, incorrect diagnosis, lack of appropriate prior therapy, incomplete information), and 37 were withdrawn. Most requests were from France (n = 97), Italy (n = 69), and Australia (n = 46). Median age was 74 yr (range, 28-95), and 65.7% of pts were male. Among 131 response-evaluable pts, the objective response rate was 51.1%, including CR in 22.1% (n = 29) and PR in 29.0% (n = 38; including 1 pt with HIV); 19.1% (n = 25) had SD and 29.8% (n = 39) had PD. Durable responses were observed in immune-competent and immunosuppressed pts. Updated data will be presented. The safety profile was similar to that of JM 200. The EAP is ongoing but will close in 2018 (US closed in April 2017) with regulatory approval in multiple countries. Conclusions: The avelumab EAP rapidly enrolled many pts with mMCC and answered an unmet, urgent medical need for pts ineligible for clinical trials or for whom no approved alternative treatments were available. In a real-world setting, avelumab demonstrated safety and efficacy consistent with JM 200. Clinical trial information: NCT03089658.
Clinical and economic outcomes associated with sequential treatment in BRAF mutant advanced melanoma patients. First Author: Ahmad A. Tarhini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: Patients with BRAF mutant advanced melanoma can use immunotherapies (IO) and BRAF-MEK inhibitors. We evaluated the clinical and cost outcomes associated with treatment sequences for BRAF mutant advanced melanoma. Methods: A discrete event simulation was developed to estimate cost (USD) and life-years (LYS), over patient lifetime. In the absence of head-to-head trial data, a matching adjusted indirect treatment comparison (MACIC) was conducted. Treatment sequences and corresponding efficacy data sources are presented below (table). Safety and cost data were obtained from published literature. Results: Treatment sequences starting with IO followed by BRAF-MEK appear to be associated with 3.7-5.2 years of additional survival vs sequences starting with BRAF-MEK followed by IOs. This was primarily due to a longer treatment-free interval (TFI) of 2.5-4.4 years after first-line (1L) IOs and longer time on BRAF-MEK as second-line (2L) post-IO therapy. Lys and TFI were higher with sequences starting with anti-PD-1-anti-CTLA-4 vs anti-PD-1 alone. Sequences starting with anti-PD-1 + anti-CTLA4 ($77,918) or anti-PD-1 monotherapy ($85,913) had lower average cost/LY compared to BRAF-MEK ($107,266). Conclusions: Initiating 1L treatment with IO appeared to provide longer survival benefit compared to BRAF-MEK, driven by long TFI and, in many cases, lack of subsequent therapy need, leading to lower average cost/LY. Because these data may be biased by unaccounted for and unknown factors, findings will require validation in prospective randomized clinical trials (EAs134 - NCT02274781).

Tolerance and efficacy of BRAF plus MEK inhibition in patients with melanoma who have received PD-1+/-based therapy. First Author: Karim Saab, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Combined BRAF and MEK inhibition (BRAF+MEK) is a standard therapy for BRAF V600 mutant melanoma, but doses and adverse event (AE) profiles were defined in trials conducted largely before the era of PD-1 based frontline therapy. The tolerance, AE profile, rates of hospitalization, and efficacy are not well defined for BRAF+MEK in the post-PD-1 setting. Methods: A sequential cohort of patients (pts) with BRAF V600 mutant melanoma who received combined BRAF+MEK following prior PD-1 based therapy was assembled from 4 tertiary care centers in the US and Australia. Dose modification (mod) was defined as a treatment break, dose reduction, or planned intermittent dosing due to AEs. Rates of hospitalization, emergency room (ER) visits, and discontinuation due to AEs were collected, and OS was calculated using Kaplan-Meier methods from time of BRAF-MEK start. Results: 78 pts were identified; 48 (62%) male, median age (range) was 58 (26-88). Most primaries were cutaneous (82%) or unknown (12%). V600 mutations were E in 71 (91%) and K in 7 (9%). Most pts had M1d stage (80%); performance status was 0 (22%), 1 (57%) and 2-3 (21%). LDH was high in 54%. 55 pts (71%) were BRAF-naive. Median TFI and, in many cases, lack of subsequent therapy need, leading to lower average cost/LY. Because these data may be biased by unaccounted for and unknown factors, findings will require validation in prospective randomized clinical trials (EAs134 - NCT02274781).

Efficacy and genetic analysis for a phase II multicenter trial of HF10, a recombinant adenovirus-based oncolytic virus treatment combination in patients with stage IIIb-IV unresectable or metastatic melanoma. First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

Background: HF10, a bioselective replication-competent oncolytic virus derived from HSV-1, has been evaluated in combination with ipilimumab (ipi) in a Phase II trial (NCT02272855) in unresectable/unresected Stage IIIb-IV melanoma pts. Here we report the results of combination therapy vs patients treated with ipi as monotherapy in a Phase II trial (NCT02301301). Methods: HF10 injection into single or multiple tumors (1 x 10^10 TCID50/mL dose, up to 5 mL depending on tumor size and number); 4 injections q1wk; then up to 15 injections q3wk. Four ipi IV infusions (3 mg/kg; concurrent with HF10) were administered q3wk. AEs assessed per CTCAE 4.0. Tumor responses were assessed per mWHO and irR at 12, 18, 24, 36 and 48 wks for patients (pts) continuing on HF10 monotherapy. Primary endpoint was Best Overall Response Rate (BORR) at 24 wks. Evaluation of correlative studies (nCounter PanCancer Immune Profiling Panel) including tumor biopsy was performed at baseline and on Days 85 and 169. Results: 46 pts were enrolled and treated; 95% men, median age 67 yrs (range 28 to 91); disease stage 20% IIIB, 43% IIIA and 37% IV; 57% were treatment naïve and 43% with ≥ 1 prior cancer therapy for unresectable/metastatic melanoma. HF10+ipi combination was well tolerated. HF10 adverse event (AE) profile was similar in combination with ipi as in HF10 monotherapy. 28.3% pts had treatment-related ≥3 AEs, and the majority of ≥3 AEs were due to ipi. Of the 44 efficacy evaluable pts, irR BORR at 24 weeks was 41% (18% irCR and 23% irPR); disease stability rate was 68% (27% irSD). As of Feb 07, 2018, median PFS was 19 months and median overall survival was 26 months. Responsive tumors exhibited an activation of the adaptive immune response with increased total tumor infiltrating lymphocytes and CD8+ T-cells, and decreased CD4+ T-cells. Conclusions: The combination HF10 and ipilimumab treatment demonstrated a favorable benefit/risk profile and encouraging antitumor activity in advanced melanoma pts by inducing immune-cell infiltration in the tumor microenvironment. Clinical trial information: NCT02272855.
BRAF/MEK inhibition in melanoma patients with rare BRAF mutations. First Author: Jessica Cecile Hassel, Section of DermatoOncology, Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany

Background: BRAF/MEK inhibition is standard of care in patients (pts) with a BRAF V600E/K mutated melanoma. Efficacy data for pts with less frequent BRAF mutations are limited so far. Methods: 71 metastatic melanoma pts with rare activating BRAF mutations (excluding BRAF V600E/K) treated at 13 melanoma centers with either a BRAF inhibitor (i) or MEK1/2 monotherapy or the combination were included. BRAF mutation, patient and disease characteristics, response and survival data were evaluated. Results: 41 (58%) pts harbored a rare BRAF V600 mutation and 30 (42%) a non-V600 mutation (Table). The most frequent mutations were V600R (30 pts, 42%), and K601E (10 pts, 14%). The median age was 61 years, 75% were male. Most melanomas were of cutaneous origin (84%) and a nodular subtype (40%). Median Follow-up (MOF) was 25 months. Median OS was 17.1 months. In the 30 pts with non-V600 mutations (V600M, M601V, V600E) the RR to BRAFi was 0%, to MEKi 100% and to combination treatment 36%. Median PFS was 1.9 months. Conclusions: Patient with rare BRAF mutations can respond to targeted therapy. Pts with non-V600 mutations are less likely to respond to BRAFi monotherapy, but activity with MEKi alone or in combination with BRAFi appears more promising.

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<th>Treatment</th>
<th>N</th>
<th>ORR (CR + PR)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
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Non-V600

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K601E

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Melanoma/Skin Cancers

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9546 Poster Session (Board #373), Mon, 1:15-PM-4:45 PM

Ipiilimumab and radiation in patients with unresectable melanoma brain metastasis: A multicenter, open-label, phase-2, Spanish Melanoma Group (GEM) study (NCT-2013-001132-22). First Author: Jose A. Lopez-Martín, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain

Background: Local and clinical experiences suggest that radiotherapy may be synergistic with anti-CTLA-4 strategies. This hypothesis is explored in melanoma patients (pts) with brain metastases (BM) not candidate to surgery/radiosurgery. Methods: Single arm phase-2 trial evaluating ipilimumab (IPI) and whole brain RT (WBRT, IRT), in pts with melanoma and unresectable BM. Endpoints: Primary: 1-year overall survival (OS9y). Secondary: progression free survival (PFS), objective response rate (ORR) and safety. Main eligibility criteria: first-BM episode, non-suitable for radical therapy; Barthe1 Index > 10; RTOG-RPA class-2; measurable disease; Karnofsky > 70%; LDH < 2xULN; no rapid clinical deterioration; demamethasone > 16 mg/d. Treatment: IPI 3mg/Kg q3weeks (4 cycles); WBRT 30Gy in 10 fractions (or equivalent). Evaluable pts Safety > 1 IPI dose. Efficacy: complete WBRT and > I 1 IPI dose. Trial required 56 evaluable pts to detect an 35% OS@1y, assuming the historical 20% OS in this population (α=0.05; β=0.8; 1-stage Fleming design).

Results: From April/2014 to January/2017, 58 pts were included; 51 completed WBRT and > 1 IPI dose. Malignant characteristics: Age (median/range) 63 (37/85). Male/Female 36/22. Karnofsky (0-100) 90 (80-70) 42. 16. BM (1, -, nonspecified) 14; 43; 1. Barthel Index (> 15; 10-15) 56; 2. 15. 16 mg/d. Treatment: IPI 3mg/Kg q3weeks (4 cycles); WBRT 30Gy in 10 fractions (or equivalent). Evaluable pts Safety > 1 IPI dose. Efficacy: complete WBRT and > 1 IPI dose. Phase II trial of pembrolizumab (MK-3475) in metastatic cutaneous squamous cell carcinoma (cSCC). First Author: Ragini Reinay Kudchadkar, Winship Cancer Institute, Atlanta, GA

Background: cSCC is the second most common skin cancer in the U.S. with over 700,000 new cases and 2000 deaths per year. Though most cSCCs are curable with surgery or radiation, 5% metastasize and are treated typically with platinum-based chemotherapy and EGFR inhibitors as standard of care. These agent have overall response rates (ORR) of only 10-20%. No current treatments have been shown to improve overall survival. Methods: Clinical and pharmacodynamic endpoints in metastatic cSCC patients not curable by surgery or radiation was evaluated. Primary objective was to establish the ORR of pembrolizumab in metastatic cSCC per RECIST 1.1 Secondary objectives were 6-month progression-free survival (PFS) and 1 year overall survival. The study was conducted with Simon’s optimal two-stage design, with goal of 12 patients in the first stage or 3 more responses would lead to stage two that would include an additional 13 patients. Patients were treated with pembrolizumab 200mg IV every 3 weeks for up to 2 years. Normal skin, blood, and tumor tissue were obtained for biomarker studies including PD-L1, expression of co-stimulatory and co-inhibitory molecules on and function of T cell populations. Results: Ten subjects (2 females) with a median age of 68.7 years are reported. All subjects were Caucasian. ORR was 40%, with 10% (1) complete response (CR), 30% (3) partial responses (PR), 10% (1) stable disease (SD) 10% (n = 1), progressive disease (PD) 20% (n = 2), and 3 subjects are not yet evaluable. Three subjects had prior chemotherapy, 2 of the 3 had PD. 1 subject not yet evaluated. All patients with CR, PR, and SD are yet to progress at current follow up. No subject deaths have occurred on study. Two grade 3 related-adverse events were noted, hepatitis and pneumonitis. No unexpected adverse events related to treatment have occurred. Median PFS and OS has not been reached as of February 2018. Further follow up as well as longer term outcomes is awaited. Conclusions: Pembrolizumab has significant clinical activity in cSCC. Expansion into the second stage of the trial is indicated. Further follow up is needed in order to establish survival benefit for these patients. Clinical trial information: NCT02964559.

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Sex differences in tolerability to Anti-PD1 therapy: Are we all equal? First Author: Narjast Duma, Mayo Clinic, Rochester, MN

Background: Immune related adverse events (IRAEs) have emerged as a serious clinical problem in the use of immune checkpoint inhibitors. The etiology and risk factors for these potentially life-threatening adverse events remain unknown. Therefore, we assessed sex differences in tolerability to anti-PD1 therapy.

Methods: All patients (pts) with metastatic melanoma treated with anti-PD1 therapy at Mayo Clinic Rochester from 2014 to 2017 were reviewed. Ocular melanoma cases were excluded. Kaplan-Meier method was used for time-to-event analysis. Results: 245 pts were identified, 148 (60%) were men, 30 (12%) were premenopausal (Pre-M) (52 years) and 67 (27%) were postmenopausal (Post-M) women. Baseline characteristics were similar among groups (Table 1). Pre-M women were more likely to experience IRAEs compared to Post-M women and men (67% vs. 60%, p < 0.04). In 23% of Pre-M women anti-PD1 therapy was discontinued due to irAE (men 12%). Pre-M women were more likely to experience endocrinopathies (35% vs. 10%, p < 0.02) and cutaneous reactions (25% vs. 15%, p < 0.02) compared to men. All cases of diabetic ketoacidosis were observed in Pre-M women (n = 6). No differences in grade ≥3 toxicity were seen across groups. Pts with irAEs were more likely to have a radiographic response to anti-PD1 therapy regardless of sex (68% vs. 44%, p = 0.05).

Conclusions: There was a trend towards better PFS in men with IRAEs compared to men without IRAEs (16.5 months vs. 9.7 months, p < 0.05).

In part 1, 6 newly diagnosed pts were enrolled (age 34-71, male 66%, LDH < 1 x ULN 50%). There was 1 dose limiting toxicity (Grade 3 rash). As of Feb 7 2018, a further 13 pts have been enrolled into part 2 of the study. The most common treatment-related AEs were diarrhea (42%), pyrexia (37%) (Grade 3/4 value (31%) and rash (31%), Grade 3 TRAEs were observed in 3 (16%) pts. No Grade 4 AEs or treatment related deaths occurred. The bemcentinib RP2D (200 mg daily) is well tolerated in combination with both D/T and pembrolizumab with AE profiles consistent with those reported for either therapeutic approach alone. Pembrolizumab + chemotherapy candidates over 69 years of age and bemcentinib treatment were identified. Conclusions: Bemcentinib can be administered in combination with established first line therapies in patients with melanoma. Safety and efficacy as well as biomarker candidates will continue to be explored. Clinical trial information: NCT02872259.
Conclusions: Efficacy was maintained at the 42-month analysis, with no new safety signals identified. These data continue to support sonidegib’s durability of response in patients with advanced BCC. Proactive management of adverse effects may prolong treatment duration and improve outcomes.

Clinical trial safety profile of sonidegib was manageable and consistent with prior analyses. The incidence of rash was reduced from 78% at 24 months to 59% at 42 months. Overall, 32% of patients were treated with application site changes only, 12% with application site changes and systemic therapy interruption, 18% with systemic therapy interruption only, and 15% with additional systemic therapy. The incidence of Grade 3 or 4 rash was 18% at 24 months and 14% at 42 months. The incidence of Grade 3 or 4 hyperglycemia was 2% at 24 months and 1% at 42 months. The incidence of Grade 3 or 4 sterile abscess was 0% at 24 months and 2% at 42 months. The incidence of Grade 3 or 4 hypercalcemia was 1% at 24 months and 0% at 42 months. The incidence of Grade 3 or 4 hypothyroidism was 0% at 24 months and 0% at 42 months. Treatment exposure was increased from 24 months to 42 months.

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9555 Poster Session (Board #382), Mon, 1:15 PM-4:45 PM
Impact of simultaneous radiotherapy in melanoma patients treated with pembrolizumab in the French early access program.

**Background:** Information on the use of radiotherapy in anti-PD-1 monoclonal antibody-treated melanoma pts is limited although some data support a synergistic effect. 

**Methods:** We investigated the influence of simultaneous radiotherapy in a multicenter ambispective cohort of advanced melanoma patients initiating pembrolizumab between May 2014-sept 2015 (CCTIRS, #15-640). \(^{125}\)pts (19%) receiving simultaneous radiotherapy (43 pts with >1 brain metastasis, 82 without). No significant difference in baseline LDH level, ECOG performance status, N of metastatic sites, previous treatment lines or post-progression therapies was observed between pts who did or did not receive radiation. As compared to pts without brain metastases, radiotherapy was performed in brain metastases pts closer to initiation of pembrolizumab (median 1.1 m vs 3.7 m, p = 0.009) and more frequently with a curative intent (72% vs 37%, p < 0.001). Globally, OS was longer in radiated vs non-radiated pts (median 18.9 m vs 12.5 m, HR=0.78, 95%CI: 0.57-0.96). This benefit was primarily driven by the pts with brain metastases (OS: median 26.0 m vs 6.0 m, HR=0.35, 95%CI:0.22-0.56, p < 0.001)(PS: 6.4 m vs 2.5 m, HR=0.54, 95%CI:0.36-0.81, p < 0.002). No significant difference in OS of pts in radiated pts without brain metastasis, who were mainly radiated later and for palliative reasons and had shorter PFS (2.8 vs 3.4 m, HR 1.32, p < 0.03).

**Conclusions:** Simultaneous radiotherapy may enhance efficacy of anti-PD1 therapy, particularly when initiated early and in brain metastases pts. Controlled trials are needed. Clinical trial information: 15-640.

9556 Poster Session (Board #383), Mon, 1:15 PM-4:45 PM
Surviviorship experience for patients (pts) with metastatic melanoma (MM) on long-term targeted therapy (TT).

**Background:** TT has improved survival for pts with MM. The lived experience for long-term responders remains understudied. We characterised pt issues using a cross-sectional survey. 

**Methods:** Eligible pts had MM, aged >18, ≥ 6 months post initiation of TT, and had a complete response. A 72-item survey including items from validated measures and custom questions covering physical and psychological effects, impact on lifestyle, access to information, satisfaction with care, and availability of support was administered. Impact of treatment duration (12 / >12 months) on pt experience was assessed. 

**Results:** 36/42 (86%) pts responded from Aug-Dec 2017: median age 59 (range 30-84); 18 (50%) male; 21 (58%) had M1 disease; 34 (94%) were receiving TT as 1st line therapy. The majority (31, 86%) were still on treatment; most (22, 74%) had been on treatment for > 12 months. Long-term toxicities including fatigue (33, 92%), dry/titchy skin (25, 69%) and arthralgias (23, 64%) were common. Typical acute toxicities, such as fevers, rashes and gastrointestinal toxicities, were minimal. Psychological morbidity was high, including fear of cancer recurrence (31, 86%), concern regarding long-term toxicities (30, 83%), anxiety awaiting results (29, 81%), concern regarding ongoing sun exposure (28, 78%) and fear of death (26, 72%). The prevalence of both physical and psychological issues was higher among pts on treatment > 12 months, and persisted in 5 (14%) who ceased treatment. Patients reported difficulties with finances (19, 53%), undertaking recreational activities (23, 64%), and managing domestic tasks (14, 39%). Most would value screening for skin cancers (35, 97%), for other cancers (34, 94%), and a survivorship care plan (SCP) to guide management (34, 94%).

**Conclusions:** Physical, psychological and functional issues exist in long-term responders to TT. These issues may increase with increasing duration on treatment. Pts may benefit from ongoing toxicity management, tailored psychological support and an SCP.

9557 Poster Session (Board #384), Mon, 1:15 PM-4:45 PM
Phase 1 study of cemiplimab, a human monoclonal anti-PD-1, in patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): Final efficacy and safety data.

**First Author:** Taofeek Kunle Owonikoko, Emory University, Atlanta, GA

**Background:** Initial analysis of expansion cohorts (ECs) patients in a phase 1 study showed that cemiplimab (REGN2810) demonstrated a positive risk/ benefit profile and produced antitumor activity in patients (pts) with advanced CSCC. We now report mature final data from the CSCC ECs of the phase 1 study (NCT02383212).

**Methods:** Pts with distantly metastatic and locally advanced CSCC were enrolled in EC 7 and 8, respectively. All pts received cemiplimab 3 mg/kg by intravenous infusion every 30 minutes every 2 weeks for up to 48 weeks. Tumor measurements were performed every 8 weeks according to RECIST 1.1 to determine overall response rate (ORR; complete response [CR] + partial response [PR]). The data cutoff date was Oct 02, 2017. Tumor response was assessed by an independent central review committee. Pts were assessed for PD-L1 expression by RNAseq, IHC or both. 36/42 (86%) pts responded from Aug-Dec 2017:

**Results:** A total of 26 pts were enrolled (21 M/5 F; 10 in EC 7, 16 in EC 8; median age: 72.5 years [range, 55–85]). 88% of pts had stage IV disease, and 34 (94%) were receiving TT as 1st line therapy. The majority (31, 86%) were still on treatment; most (22, 74%) had been on treatment for > 12 months, with ORR of 61% versus 17% (p = 0.001), concern regarding ongoing sun exposure (28, 78%) and fear of death (26, 72%). The prevalence of both physical and psychological issues was higher among pts on treatment > 12 months, and persisted in 5 (14%) who ceased treatment. Patients reported difficulties with finances (19, 53%), undertaking recreational activities (23, 64%), and managing domestic tasks (14, 39%). Most would value screening for skin cancers (35, 97%), for other cancers (34, 94%), and a survivorship care plan (SCP) to guide management (34, 94%).

**Conclusions:** Physical, psychological and functional issues exist in long-term responders to TT. These issues may increase with increasing duration on treatment. Pts may benefit from ongoing toxicity management, tailored psychological support and an SCP.

9558 Poster Session (Board #385), Mon, 1:15 PM-4:45 PM
Chemoimmunotherapy combination after PD-1 inhibitor failure to improve clinical outcomes in metastatic melanoma patients.

**First Author:** Jesus Vera Aguilera, Mayo Clinic, Rochester, MN

**Background:** Clinical management of metastatic melanoma (MM) after PD-1 blockade failure remains a challenge and lacks a standard of care. Chemoimmunotherapy (CIT) combinations have demonstrated favorable efficacy and safety profiles in lung cancer patients (pts). Our pre-clinical study has shown that in MM pts who have failed PD-1 blockade, the addition of chemotherapy can reshape a subset of tumor-reactive CD8+ T cells, resulting in enhanced anti-tumor immune responses. We conducted a retrospective study comparing the clinical outcomes of CIT with immunotherapy or chemotherapy alone after PD-1 blockade failure. 

**Methods:** We retrospectively reviewed MM pts seen at Mayo Clinic, Rochester between Jan, 2012 and Jun, 2017 who had failed anti-PD1 therapy. We identified 48 pts who received subsequent CIT (carboplatin/ paclitaxel n = 22; temazolomide n = 1; nab-paclitaxel n = 1), immune checkpoint inhibitors (ICI) or chemotherapy alone. The overall survival (OS), objective response rate (ORR), time-to-next therapy (TTNT), and toxicities were assessed between these groups. 

**Results:** Among the 48 pts, 24 received CIT after disease progression on PD-1 blockade. At median follow up of 3.9 years, pts who received CIT had a median OS of 5 years (95% CI: 2.0-18.8 years) on pt experience (18, 73%). Among this group, 12 (50%) of pts responded from Aug-Dec 2017:

**Conclusions:** Physical, psychological and functional issues exist in long-term responders to TT. These issues may increase with increasing duration on treatment. Pts may benefit from ongoing toxicity management, tailored psychological support and an SCP.
Analysis of the kinetics and effects of vemurafenib (V) + cobimetinib (C) on intratumoral and host immunity in patients (pts) with BRAFV600 mutant melanoma (BRAF/M): Implications for combination therapy. First Author: Suthee Rapisuwon, Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC

Background: Prior studies in pts with BRAF/M have shown increased density of tumor infiltrating lymphocytes (TIL) at 2 weeks (wks) with BRAF +/- MEK inhibition(i), but did not fully characterize kinetics or functional state of the TIL. To better assess the impact of BRAFi +/- MEKi on the tumor microenvironment, we conducted a study to evaluate serial tumor biopsies (Tx) and blood through the first 4 wks of V+-C therapy (Tx). Methods: Subjects with Bx-accessible BRAFi received either V alone or V+C Tx. Staging CT scans were performed at baseline, wks 6, 12 and 18 wks until PD or study withdrawal. Tumor Bx and heparinized blood samples were obtained at baseline, day (d) 8, 15, and 29. Bx samples were formalin-fixed paraffin-embedded (FFPE), frozen in OCT, and processed for TIL. PBMC and plasma were isolated from blood. FFPE slides were analyzed by quantitative immuno-fluorescence (QIF), NanoString 770 Immune Panel and TCRseq (Adaptive). Frozen tumors were analyzed for single cell (sc)RNAseq, TIL and PBMC were analyzed by flow cytometry. Results: 5 pts (4M/1F) with BRAF/M were enrolled (3 received V and 2 V+C). All had initial tumor response (2 CR, 3 PR) and subsequent PD. No unusual or G4-5 toxicities were observed. In 4 of 5 tumors, CD8 and CD4+ TIL increased by d8 or d15 by QIF and NanoString, waning thereafter. %CD4+ cells expressing CD45RO decreased over time suggesting a dominance of naive versus memory TIL. CD8 cells do not change. CD8 infiltrates are not accompanied by inflammatory or apoptotic response. Immune cell influx is not required for tumor response. The data suggest that T cell influx is not related to the generation of new anti-tumor immunity and that BRAF/M Rx may, at best, augment an existing immune response rather than priming a new one. Clinical trial information: NCT01813214.

9556 Poster Session (Board #388), Mon, 1:15 PM-4:45 PM
Tumor mutational burden, clinical features, and outcomes to PD-1 mono- and combination therapy in patients with cutaneous and BRAF/M melanoma. First Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tumor mutational burden (TMB) in cutaneous and unknown primary (CUP) melanomas is associated with benefit to PD-1 monotherapy (mono), but the impact of TMB on nivolumab plus ipilimumab (combo) is not well established. Few TMB analyses have included standard clinical features in a multivariate analysis (MVA). Methods: All patients (pts) with CUP melanoma who underwent 340+ gene sequencing at Memorial Sloan Kettering Cancer Center and received PD-1 mono or combo as initial checkpoint inhibitor were analyzed. Somatic TMB/megabase (Mb), AJCC 8 stage, ECOG performance status. Results: 10 pts achieving PR received prior IMT, as did the pt experiencing PD. This study has enrolled 125 pts receiving 3mg/kg Q2wks of N, 150mg BID of D and 2mg QD of T, all starting on Day 1 q28 days. This study is continuously monitored for safety and futility. The primary endpoint of the study is objective response rate (ORR). Results: 6 pts were enrolled onto the safety run-in phase of the study and no DLTs were experienced. The study continues to accrue; 14 pts have been treated with N+D to date. pts discontinuing treatment because of toxicity (grades 3-5) or AEs (grade 1-2) were 13% and 27%. 11 pts have been assessed for response 10 have achieved a PR (ORR 91%), and 1 experienced PD. 6 of the 10 pts achieving PR received prior IMT, as did the pt experiencing PD. This study may allow us to determine whether to allow a formalized evaluation of a separate cohort of pts with untreated brain metastases (n = 24). Conclusions: Treatment with N+D is well-tolerated at full doses and shows preliminary clinical activity. The combination warrants further evaluation in pts who have received prior immunotherapy and in patients with brain metastases. Clinical trial information: NCT02910760.

9557 Poster Session (Board #387), Mon, 1:15 PM-4:45 PM
Safety and preliminary activity data from a single center phase II study of triplet combination of nivolumab (N) + dabrafenib (D) and trametinib (T) (hazard ratio [HR] 0.98; p = 0.005) and NLR

MV analysis, BMI

Results:

9560 Poster Session (Board #387), Mon, 1:15 PM-4:45 PM
Safety and preliminary activity data from a single center phase II study of triplet combination of nivolumab (N) + dabrafenib (D) and trametinib (T) (hazard ratio [HR] 0.98; p = 0.005) and NLR

MV analysis, BMI

Results:

9561 Poster Session (Board #388), Mon, 1:15 PM-4:45 PM
Tumor mutational burden, clinical features, and outcomes to PD-1 mono- and combination therapy in patients with cutaneous and BRAF/M melanoma. First Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tumor mutational burden (TMB) in cutaneous and unknown primary (CUP) melanomas is associated with benefit to PD-1 monotherapy (mono), but the impact of TMB on nivolumab plus ipilimumab (combo) is not well established. Few TMB analyses have included standard clinical features in a multivariate analysis (MVA). Methods: All patients (pts) with CUP melanoma who underwent 340+ gene sequencing at Memorial Sloan Kettering Cancer Center and received PD-1 mono or combo as initial checkpoint inhibitor were analyzed. Somatic TMB/megabase (Mb), AJCC 8 stage, ECOG performance status (PS), sites of metastases (mets), lactate dehydrogenase (LDH) elevation, and neutrophil:lymphocyte ratio (NLR) > 4.73 were included in a Cox proportional hazards model and MVA built using backward selection. Overall survival (OS) and time to treatment failure (TTF), the interval until next therapy, clinical progression, or death, were calculated from PD-1 start. Results: 154 pts received PD-1 mono; median follow up was 11 months. 125 pts received combo; median follow up was 19 months. Pts receiving combo vs PD-1 mono were younger (median age 62 vs 71, p < 0.001) and had higher rate of elevated LDH (34% vs 18%, p = 0.04) and stage M1c/d (66% vs 41%, p = 0.04). TMB did not vary by combo vs PD-1 mono (median 15.1 vs 18.4 mut/Mb, p = 0.21). Stage was associated with TTF and OS for PD-1 mono and combo (all p < 0.03). On MVA for PD-1 mono, TMB (hazard ratio [HR] 0.98; p = 0.005) and NLR > 4.73 (HR 2.16; p = 0.002) were associated with TTF; PS (ECOG 2+ vs 0, HR 9.86, p < 0.001) or OS (HR 3.15, p = 0.005) were associated with poorer OS. TMB was not associated with TTF or OS for combo. On MVA for combo, brain (HR 2.12, p = 0.004) and bone mets (HR 2.12, p = 0.008) were associated with TTF; PS (ECOG 2+ vs 0, HR 5.37, p = 0.009), NLR > 4.73 (HR 2.27, p = 0.037), and bone mets (HR 2.86; p = 0.014) were associated with OS. Conclusions: For patients with cutaneous and unknown primary melanomas, TMB is associated with improved TTF in PD-1 mono but not combo. Performance status, NLR, and mets, but not TMB, are associated with OS in PD-1 combo. Models assessing clinical utility of BMI should also include established prognostic features.

9562 Poster Session (Board #389), Mon, 1:15 PM-4:45 PM
Association of body mass index (BMI) with overall survival (OS) in metastatic melanoma (MM) patients (pts) treated with combined anti-CTLA4 + anti-PD1. First Author: Jennifer Leigh McQuade, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Obesity has recently been associated with improved outcomes in male, but not female, MM pts treated with single-agent anti-CTLA4 and with single-agent anti-PD1 immunotherapy. However, the association between BMI, sex, and outcomes in MM pts treated with combined anti-CTLA4 + anti-PD1 is unknown. Methods: We examined the association of BMI with categorical outcomes in patients (Pts) with untreated brain metastases (n = 24). Results: Treatment with N+D is well-tolerated at full doses and shows preliminary clinical activity. The combination warrants further evaluation in pts who have received prior immunotherapy and in patients with brain metastases. Clinical trial information: NCT02910760.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Advanced mucosal melanoma is a rare subgroup of tumors for which few data on immune therapeutic approaches are available as they are rarely or not included in pivotal trials. Pembrolizumab, a monoclonal anti-PD1 antibody, has been approved in France as a first-line treatment of patients with advanced melanoma since October 2015. Although it has been shown to significantly improve OS and PFS of cutaneous melanoma, we have few data on its efficacy in mucosal melanoma. Methods: Horizon is a real-life setting descriptive cohort analysis of patients treated with pembrolizumab from June 2014 to September 2015 in the context of the French national early access program, at the dose of 2 mg/kg/3 weeks. Here are presented the results of the second interim analysis (data cut-off January 7th, 2017) in the mucosal melanoma subgroup. Results: A total of 663 patients were included with a median follow-up of 12.95 months (95%CI: [11.15-16.16]). Among those patients, 59 (8.9%) had a primary mucosal melanoma. Twenty-two (37.3%) had no prior therapy. The median OS was 7.54 months (95%CI: [5.25-10.52]) versus 16.75 months (95%CI: [13.15-18.89]) in the non-mucosal melanoma population (p = .0001). The median PFS was 2.69 months (95%CI: [2.26-3.05]) versus 3.41 months (95%CI: [3.02-4.03]) in the non-mucosal group (p = .0001). The ORR was 11.9% (31.5% in the no-mucosal group), the DCR was 18.6% (44.2% in the non-mucosal group), and the median DR was 7.64 months (not reached in the non-mucosal group). Withdrawal of pembrolizumab was necessary for 47 patients (79.7%); the main reason for discontinuation was disease progression (68.1%), far ahead toxicity (14.9%) or complete remission (6.38%). Immune related adverse events were consistent with previous reports on pembrolizumab. Pembrolizumab provides objective activity in some mucosal melanoma patients, although less than that observed in the non-mucosal population. Anti-PD1 should be considered as a relevant treatment option for these patients. Nevertheless, further studies are warranted to describe underlying resistance mechanisms involved in order to improve management of this rare subgroup.

Melanoma/Skin Cancers 505s

9566 Poster Session (Board #393), Mon, 1:15 PM-4:45 PM
Treatment of metastatic uveal melanoma (mUM) directed by a comprehensive molecular tumour analysis program (CMTA).
First Author: Serge Leyvraz, Charité Comprehensive Cancer Center, Berlin, Germany
Background: There is a lack of active treatment against mUM. Such "hard-to-treat" tumour might benefit from treatment decisions driven by a complete genomic and transcriptomic analysis program. Methods: From 1.3.2016 to 1.12.2017, mUM were included in the prospective TREAT20Plus study and were subjected to a CMTA including WES, WES, RNAseq, cell culture and systems biological/pharmacodynamic modelling. Treatment recommendations were made by a molecular tumour board. Results: Twenty six patients (12 F, 14 M). Age: 61 (32-80). PS: 0 (0-2). Metastases: 4 (1-10). Abnormal LDH: 19. Pre-treatment: 1 (0-5) and type iv chemotherapy: 11, checkpoint-inhibitors (-i): 7, intra-hepatic: 13, vaccine: 1. Insufficient material in 3 patients. The mutation burden was low: 32 (15-449). The treatment recommendations (TRec) were based on the different mutations or activation profiles: A) MEK-i. for mutations of GNAQ, 11, GNA11: 13. B) ALK-i. for MET overexpression: 17. ALK-k for the oncogenic ALK (K: 3). C) CDK4/6- for CDKN2A loss: 1. D) checkpoint-i. for mutation burden >100: 3. E) For the other alterations no off-label treatment was available: mutation of BAP1: 8 or SF3B1: 10, overexpression of MYC: 14, BCL2: 24, CCND2: 16, ERBB2: 5, biallelic loss of TNFAIP3: 1. Among novel non-recurring gene-fusions: inactivating gene fusion affecting MITF: 1. In 1 patient repeated biopsies at time of recurrence after MEK-i disclosed biallelic loss of CDKN2A. The pharmacodynamic modeling confirmed TRec in 10 and helped with the decision in 8 patients. A treatment was initiated in 15 patients: Trametinib: 6, Cabozantinib: 3, Crizotinib: 6, Palbociclib: 1. A treatment was not initiated for 8 patients: 4 too early, 4 rapid progression. Among the 12 evaluable patients the antitumor response was: minor response: 2, stable disease: 4, progressive disease: 6, too early: 1. Median PFS of the treated patients: 5.5 months. Conclusions: Precision medicine in mUM is clinically feasible. It leads to a better understanding of the biology of the tumour and of the potential therapeutic targets. Its clinical efficacy is limited by the non-availability of drugs as single agent or in combination. Clinical trial information: E4A/063/13.

9567 Poster Session (Board #394), Mon, 1:15 PM-4:45 PM
Adverse events of special interest in the phase 3 COLUMBUS study.
First Author: Helen Gigan, First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens School of Medicine, Athens, Greece
Background: Combination BRAF/MEK inhibitor (BRAFi/MEKi) therapy is standard of care for BRAFV600-mutant metastatic melanoma. In COLUMBUS Part 1, encorafenib 450 mg once daily (QD) + binimetinib (Bini) 45 mg twice daily (BID) (COMBO450) reduced risk of progression or death vs encorafenib 300 mg QD (ENC300) or vemurafenib 960 mg BID (VEM) in patients (pts) with advanced BRAFV600-mutant melanoma. Adverse events of special interest (AESIs) including pyrexia, serous retinopathy, photosensitivity, and rash are reported here. Methods: Pts were randomized 1:1:1 to receive COMBO450, ENC300, or VEM. Pts had standard physical and laboratory assessments, and regular dermatologic, cardiac, and ophthalmologic evaluations. AESIs comprised known effects of available BRAFi and/or MEKi. Results: Safety was evaluated in 192, 192, and 186 pts in the COMBO450, ENC300 and VEM arms, respectively. Median duration of exposure to treatment was 51 weeks for each component in the COMBO450 arm, 31 weeks in the ENC300 arm, and 27 weeks in the VEM arm. Pyrexia incidence with COMBO450 was low (grade 1/2: 14%; grade 3: 4%) and led to treatment discontinuation in 1% of pts and to dose modification in 4%. Photosensitivity was infrequent with COMBO450 (grade 1/2: 4%; grade 3: 1%), required dose modification in 1% of cases, and did not lead to treatment discontinuation. Rash occurred in 22% of pts with COMBO450 (grade 1/2: 21%, grade 3: 1%, grade 4: 1%), led to discontinuation in 0.5%, and to dose modification in 2%. Serous retinopathy (grade 1/2: 17%; grade 3: 3%) and left ventricular dysfunction (grade 1/2: 6%; grade 3: 2%) with COMBO450 did not lead to discontinuation and were generally reversible (in 89% and 93% of pts, respectively). Conclusions: Common BRAFi/MEKi toxicities were generally manageable and reversible and were infrequently associated with treatment discontinuation. Pyrexia and photosensitivity were uncommon with COMBO450. The observed safety profile suggests COMBO450 may provide a meaningfully differentiated treatment option for patients with BRAFV600-mutant melanoma. SPONSOR: Array BioPharma Inc. Clinical trial identification: NCT01909453.
9568 Poster Session (Board #395), Mon, 1:15 PM-4:45 PM
Multiple spatial–weight lesion molecular heterogeneity of an immunotherapy-resistant metastatic melanoma. First Author: Akash Mitra, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Genomic and immune intratumor heterogeneity (ITH) can be a major reason for therapy failure in patients undergoing checkpoint blockade immunotherapy. Here, we report comprehensive molecular and immune analysis of a sequential anti-CTLA-4 and anti-PD-1-resistant metastatic lesion, sampled and reconstructed in 3D, combined with a longitudinal view of a pre-immunotherapy lesion. Methods: We performed 3D reconstruction of a metastasis obtained at palliative surgery from a patient progressing on sequential anti-CTLA-4 and anti-PD-1 therapy utilizing genomic (gene expression, methylation, whole exome sequencing and neoantigen prediction) and immune (immunohistochemistry, RNA- and DNA-based T cell receptor expression, methylation, whole exome sequencing and neoantigen prediction) profiling of 67 spatially distinct regions. Results: Limited point-mutation heterogeneity was found in melanoma driver genes however, copy number alteration analysis revealed changes over time and space with gain of chromosome 7 and 13, and loss of chromosome 10 in spatially-distinct regions. Differences in immune signatures were observed across regions of the tumor with pockets of immune activation and suppression. TCR profiling revealed dominance of a specific T cell clonotype. Conclusions: 3D-reconstruction of a sequential immune checkpoint blockade treated progressing tumor shows marked spatially-distinct genomic and immune ITH in the setting of a relatively homogenous somatic gene mutation landscape. As immune markers move into the mainstream for use as biomarkers, the use of single biopsies to inform treatment choice may be confounding. These data further impress the need for comprehensive, integrated molecular phenotyping approaches to unravel immunotherapy response and resistance in metastatic melanoma.

9569 Poster Session (Board #396), Mon, 1:15 PM-4:45 PM
Immune checkpoint inhibitor (ICI) treatment in advanced melanoma (aMel) patients (pts) with renal or hepatic dysfunction (dysf). Real-world patient characteristics and outcomes. First Author: Susan Spillane, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD

Background: ICIs were approved for first line (1L) therapy in aMel. However, pts with renal or hepatic dysf are often excluded from clinical trials; little is known about usage or outcomes for these pts. Methods: We retrospectively analyzed de-identified real-world data aggregated by Flatiron Health from US community oncology practices. Pts had confirmed aMel, a documented order/administration of an ICI as 1L therapy from 1/1/11 to 12/31/17 and ≥1 hepatic or renal lab value up to 30 days before 1L start. Renal [serum creatinine (cr)] and hepatic [total bilirubin (Tbili), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] function labs were graded by Common Terminology Criteria for Adverse Events v4.03. Dysf was defined as grade ≥2. Results: 1475 pts with relevant data were identified (Table). Conclusions: In this real-world aMel cohort, <3% of ICI-treated pts had baseline hepatic or renal dysf. Relative to pts with normal organ function, pts with baseline renal dysf were more often male and were more likely to be older. Although only hepatic dysf was significantly associated with shorter ICI duration, both renal and hepatic dysf pts had significantly shorter median OS. The OS findings may reflect competing risk from underlying comorbidities, practice patterns, tolerance (renal dysf), toxicity and/or ICI efficacy in the setting of organ dysf. Additional research is needed to better understand ICI treatment for real-world pts with baseline renal or hepatic dysf.

9570 Poster Session (Board #397), Mon, 1:15 PM-4:45 PM
Characterization and spatial localization of the tumor immune microenvironment in metastatic uveal melanoma. First Author: Kimberly Mayumi Kornatsubara, Columbia University Medical Center, New York, NY

Background: Uveal melanoma (UM) is a rare subset of melanoma that is resistant to immune checkpoint blockade. High density of macrophages (Mφ) and TILs is associated with poor prognosis in primary UM but little is known about the tumor microenvironment (TME) in metastatic UM (MUM). Here we performed quantitative spatial analysis using multiplex immunohistochemistry (mIHC) to characterize the TME in MUM, compare the TME of MUM to metastatic cutaneous melanoma (MCM), and identify potential mechanisms of MUM resistance to immunotherapy. Methods: We identified pts with untreated metastatic melanoma with clinical follow-up and available pre-treatment tissue who consented to an IRB-approved protocol. 5 μm slides were stained using Opal miHC for DAPI, CD3, CD8, CD68, HLA-DR, Ki67, and SOX10. Tumor areas were pre-selected by a dermatopathologist, visualized using Vectra and analyzed for density and spatial localization using inForm software. Results: 6 MUM and 8 MCM cases were evaluable at the time of this analysis. CD3+ and CD8+ T-cell density is similar between MUM and MCM, however, there is a trend towards a higher density of proliferating cytotoxic T lymphocytes (CTLs) (CD8+Ki67+) in MCM (p = 0.05). Interestingly, CD68+Mφ density is lower in MUM compared to MCM (p = 0.03). Both CD68+HLA-DR+ Mφ (activated) and CD68+HLA-DR- Mφ (inactivated) density is lower in MUM. Using nearest neighbor spatial analysis, CD8+ CTLs are significantly farther from activated Mφ (CD68+HLA-DR+) (p = 0.01), but not from inactivated Mφ (CD68+HLA-DR-) in MUM compared to MCM. Conclusions: Unlike primary UM, our sample of untreated MUM is not characterized by a high Mφ density. Fewer Mφ are present in untreated MUM compared to MCM and activated Mφ are located farther from CTLs in UM. Density of CTLs is similar in MUM and MCM, although proliferating CTL are more numerous in MCM. These preliminary results suggest that Mφ may play a less prominent role in innate resistance to immunotherapy in MUM. Gene expression analysis and further classification of Mφ type is ongoing. Additional cases are ongoing analysis and will be reported.

9571 Poster Session (Board #398), Mon, 1:15 PM-4:45 PM
Factors predicting the use of immunotherapy for patients with advanced melanoma. First Author: Richard Wayne Joseph, Mayo Clinic, Jacksonville, FL

Background: Both pembrolizumab (PEMBRO) and the combination of ipilimumab and nivolumab (IPI+NIVO) are approved by the US FDA for treatment of advanced (unresectable or metastatic) melanoma. Clinical trials have demonstrated different benefit-risk profiles associated with each that may impact selection in the real-world. We performed a retrospective chart review of patients with advanced melanoma to understand patient characteristics associated with PEMBO vs IPI+NIVO treatment selection. Methods: A retrospective, chart-review study was conducted in the US; 12 oncologists from 12 US academic centers and affiliated satellite clinics were recruited to contribute patients ≥18 years of age with advanced melanoma receiving PEMBO or IPI+NIVO in any line between Jan 1, 2016 – Dec 30, 2017. Demographics and baseline disease characteristics were compared between cohorts in univariate analysis. A mixed-effects logistic regression model with site of treatment specified as a random effect was created to predict PEMBO vs IPI+NIVO selection using parameters identified in univariate analysis. Results: 400 patients were included, 200 each PEMBO and IPI+NIVO. There were no significant differences in mean age, race, gender, family income, education level, insurance status, comorbidity index, site of metastasis, and line of therapy between the cohorts. However, the PEMBO cohort had poorer Eastern Cooperative Group (ECOG) status at treatment start (70.5% ECOG 0 or 1 vs 88.0% (p < 0.001), were more likely to be PD-L1 positive (76.9% vs 63.1%, p = 0.011), and less likely to harbor a BRAF mutation (34.8% vs 49.7%, p = 0.003). In regression, PEMBO was favored over IPI+NIVO in ECOG 2-3 patients vs 0-1 (OR 3.1, 95%CI 1.4, 7.4), and PD-L1 expression positive (OR 4.5, 95%CI 1.9, 10.4). Those with BRAF wild-type were more likely to receive PEMBO (OR 2.2, 95%CI 1.4, 3.6) than IPI+NIVO. Conclusions: In the real-world, patient factors are significantly associated with treatment selection in advanced melanoma. PEMBO appears to be selected more often than IPI+NIVO in patients with poorer ECOG performance status, PD-L1 positive tumors, BRAF wild-type tumors. Any real-world comparison of outcomes between treatments should take this into consideration.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Perilesional edema and blood vessel characteristics in brain metastases and implications for treatment with immune therapy. First Author: Thuy Tran, Yale-New Haven Smilow Hospital, New Haven, CT

Background: Little is known about tumor-associated vasogenic edema in brain metastasis, yet it is the cause of significant morbidity and mortality. Our purpose was to better characterize edema and vessel leakage in humans treated with anti-CD133 antibodies. We hypothesized that the etiology of tumor edema is multifactorial and not dependent on tumor volume mass effect alone. Methods: We compared edema and edema volume (in non-small cell lung (NSCLC) and melanoma patients with untreated brain metastasis treated with pembrolizumab. Cerebral melanoma tumors were stained with anti-CD34 to determine vessel density and the association with vascular leak. We employed an in vitro model of the blood-brain barrier using short term cultures from melanoma brain and extracranial metastases to determine tight junction resistance. Results: While larger tumors tended to have more edema, the correlation was weak (R² = 0.30). Edema:tumor volume ratios are similar in NSCLC and melanoma brain metastasis and were not associated with response (P > 0.50), progression-free (P = 0.22), or overall survival (P = 0.17). Patients responding to pembrolizumab had concurrent shrinkage of edema volume (R² = 0.81). Vessel density and CD34+ cell staining on brain metastasis samples was not correlated with perilesional edema on imaging. Melanoma brain metastasis cells in culture were able to cause decreases in tight junction resistance in an in vitro system, whereas cell cultures from extracranial samples did not. Conclusions: Additional factors aside from tumor volume mass effect cause perilesional edema. One should not deter physicians from using PD-1 inhibitors; pembrolizumab-sensitive tumors tend to have decreases in both tumor volume and edema on treatment. Factors other than vessel density result in endovascular leak, and should be further studied. Moreover, melanoma cells themselves can cause vessel leakiness in an experimental system void of immune cells, suggesting they secrete properties that affect tight junctions, which might be harnessed for pharmacologic targeting.

Mutational and immune gene expression profiling at relapse in patients (pts) treated with adjuvant dabrafenib plus trametinib (D + T) or placebo (pbo) in the COMBI-AD trial. First Author: Reinhard Dummer, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland

Background: In the COMBI-AD trial, adjuvant D + T resulted in a significant relapse-free survival benefit (HR, 0.47 [95% CI, 0.39–0.58]; P < .001) vs pbo in pts with resected stage III BRAF V600E/K-mutant melanoma. At a median follow-up of 2.8 y, 37% of pts in the D + T arm and 57% in the pbo arm had relapsed. Resistance mechanisms are largely unknown in the adjuvant setting. We report mutational and immune gene expression profiling at relapse in COMBI-AD. Methods: COMBI-AD (NCT01682083) randomized pts with resected stage III BRAF V600E/K-mutant melanoma to receive D + T or pbo, DNA and RNA were extracted from the same relapse sample. Mutational landscape and immune gene expression signature were examined by sequencing 570 genes (mean depth = 500×) and gene expression profiling using a customized NanoString panel. Plasma samples were subjected to ctDNA profiling (73 genes). Results: At relapse, 66 tissue samples (D + T, n = 24 [n = 4 relapsed on treatment]; pbo, n = 42) were collected (20 distant, 43 local/regional, 3 secondary primary melanoma). Paired baseline samples were available in most cases (n = 57). A BRAF V600E/K mutation was detected in all relapse samples except in 1 secondary primary melanoma. The genomic landscape was as expected for melanoma: the most common non-BRAF V600 genetic aberrations were CDRK2A (38%), CDRK2B (24%), PTEK2 (23%), TP53 (18%), and ARID2 (14%). A median tumor mutation burden (TMb) was = 10 SNVs/Mb. No substantial differences in mutation frequency, TMB, or BRAF copy number were noted in relapse vs baseline samples or between treatment arms. Putative genetic resistance mechanisms in the MAPK (eg, MAP2K1, NRAS mutations) and non-MAPK (eg, PI3K pathway mutational) pathways were found in a small subset of relapse samples from pts treated with D + T. No significant differences in T-cell-specific/immune gene expression signatures were observed between arms. Conclusions: Although mutations in MAPK and non-MAPK pathways were found in a few relapse samples, no uniform adaptations were observed, suggesting that resistance to adjuvant D + T is caused by various genetic/epigenetic mechanisms. Citations: NCT01682083.
# Melanoma/Skin Cancers

## Abstracts

### 9576 Poster Session (Board #403), Mon, 1:15 PM-4:45 PM

**Validation of a prognostic 53-immune-gene panel in stage I/II melanoma.**

**First Author:** Margaret Borgardus, Columbia University College of Physicians and Surgeons, New York, NY

**Background:** Patients with resected stage I/II melanoma are at high risk of systemic metastasis and prognostic indices to stratify these patients for adjuvant immunotherapy. We previously defined and validated a 53-immune-gene panel predictive of non-progression (AUC = 0.787), recurrence free survival (RFS, p < 0.001) and disease specific survival (p = 0.024). Here, we present a second validation of the prognostic ability of this immune-gene panel in an independent cohort of 81 patients with stage I/II primary melanoma.

**Methods:** Dermatopathology reports for 1349 melanoma patients seen at Columbia University Medical Center between 2001 and 2014 were queried to identify 81 patients with stage II-III primary melanoma with FFPE tissue and at least 24 months of clinical follow-up available. Presence of tumor was confirmed by a dermatopathologist. RNA was extracted from tissue, and expression of the 53-immune-gene panel was assessed using NanoString. Data was processed using nSolver software and prediction score calculated. **Results:** 81 patients with stage II-III primary melanoma were analyzed, of whom 61 were alive or had no evidence of disease at death and 20 died from melanoma. Of the 81 patients, 69 had progression data available, 22 patients had progression of disease, while 47 had non-progression. Prediction scores correlated with non-progression (AUC = 0.722). In the complete 81 patient cohort, the signature correlated with disease specific survival (p=0.008) and overall survival (p = 0.017). Over the course of follow-up 36 patients using significant survival characteristics, by a cutoff, hazard ratio for death in the risk group was 2.8 (95% CI 1.3-6.0). **Conclusions:** We validate in a second retrospective population the prognostic ability of our previously-identified 53-immune-gene panel in patients with stage II-III primary melanoma. The 53-gene panel may constitute a powerful tool to aid in predicting disease course in melanoma and may allow for stratification of patients for adjuvant immunotherapy, facilitating rapid acquisition of significant survival statistics in clinical trials. Prospective retrospective (PRA) validation of the signature in samples collected as part of the E1697 trial of adjuvant interferon is planned.

### 9577 Poster Session (Board #404), Mon, 1:15 PM-4:45 PM

**A multi-gene risk signature for improved identification of cutaneous squamous cell carcinoma (cSCC) patients with a high risk of recurrence.**

**First Author:** Chrysalin Schmults, Brigham & Women’s Hospital, Boston, MA

**Background:** cSCC is rivaled only by basal cell carcinoma as the most common cancer in the U.S. Though most cases are cured by excision, a subset recur and become incurable with number of deaths approximating melanoma (Karia et al., JAAD, 2012). Identifying the subset at risk of recurrence is critical for development of clinical trials in cSCC which has no FDA-approved treatments and very few phase II trials. Therefore, we set out to develop a gene expression-based biomarker associated with disease recurrence/metastasis in cSCC. **Methods:** According to an IRB approved multicenter protocol, 230 primary cSCC tumors were analyzed for mRNA expression of 73 candidate genes reported to be associated with cSCC metastasis. After quality filtering, 63 genes and 212 samples were included in the predictive model construction. Multiple machine learning algorithm approaches were applied with 75% of the specimens used for training and the remaining 25% used for validation. **Results:** Six genes demonstrated consistent expression across all samples tested and were used as controls to normalize expression values of the remaining genes. Eighteen genes were clinically expressed between recurrent and non-recurrent cases. Evaluation of the genes with multiple predictive modeling methods identified an optimal model that was 71% sensitive, 90% specific, had a 50% positive predictive value (PPV), and a 96% negative predictive value (NPV) for recurrence. **Conclusions:** This study developed a predictive model for risk of recurrence with a much higher PPV than staging criteria developed by Brigham and Women’s Hospital and the American Joint Committee on Cancer (50% vs. approximately 24% and 18% respectively) while maintaining a high NPV (Karia et al., JCO 2014; Karia et al., JAMA Dermatology, 2017). Clinical application of such a prognostic test with a robust PPV (50% risk of recurrence) would enable identification of cSCC patients who may be appropriate for therapeutic intervention beyond surgical clearance (e.g. nodal staging and/or adjuvant radiation) and enrollment in clinical trials evaluating contemporary therapies.

### 9578 Poster Session (Board #405), Mon, 1:15 PM-4:45 PM

**Time to treatment failure (TTF) as a potential clinical endpoint in real-world evidence (RWE) studies of melanoma.**

**First Author:** Rajeshwar Sriracha, U.S. Food and Drug Administration, Silver Spring, MD

**Background:** Time to treatment failure (TTF) has been suggested as a practical clinical endpoint for studies of oncologic agents using real-world evidence (RWE). However, TTF is rarely studied as an endpoint in the clinical trial setting; thus, little is known about its association with commonly used endpoints such as progression-free survival (PFS) or overall survival (OS). **Methods:** All studies submitted to CDER as part of a marketing application between 2010 and 2016 for treatment of patients with advanced melanoma were considered. 11 phase 3, randomized, and active-controlled trials were included in this analysis; 3 studies had 3 arms, resulting in a total of 25 randomized arms. Therapeutic agents were categorized as chemotherapy (CT), single agent PD-1 inhibitors (PD1), all immunotherapy (IT), and targeted therapy (TT). Patient-level association between TTF and PFS or OS was determined using correlation coefficients (corr) for each trial and for each therapeutic category. Additionally, to determine associations of trial-level comparative efficacy measures, pair-wise analyses were performed of hazard ratios (HR) for TTF, PFS, and OS using a weighted linear regression model. **Results:** 6021 patients from 11 clinical trials were included in the analysis. Patient-level corr for each trial ranged from 0.62 to 0.93 for TTF and PFS and from 0.53 to 0.82 for TTF and OS. Corr between TTF and PFS, and TTF and OS by therapeutic category are listed in the Table below. Trial-level associations between TTF HR & PFS HR and TTF HR & OS HR in all patients were poor. However, in TT these associations were much stronger (TTF & PFS: R² = 0.56 and TTF & OS: R² = 0.80). **Conclusions:** Though these analyses indicate a clear association of TTF & PFS for all categories, the association of TTF & OS may only exist for a few therapeutic categories. Extension of this work to other therapeutic categories may benefit the discussion of clinical endpoints for RWE.

### 9579 Poster Session (Board #406), Mon, 1:15 PM-4:45 PM

**Blood-based multiplex kinase activity profiling as a predictive marker for clinical response to checkpoint blockade in advanced melanoma.**

**First Author:** Daan Hurkmans, Erasmus Medical Center, Rotterdam, Netherlands

**Background:** Prediction of clinical responses to checkpoint inhibitor therapies is urgently needed. Notably, a significant proportion of patients does not benefit from the treatment, agents are costly and may cause serious toxicity. The kinase activity of peripheral blood cells (PBMCs) may reflect biological mechanisms underlying response to immunotherapy. We hypothesized that kinase activity profiles from PBMCs may constitute a predictive marker for clinical response to CTLA4 and/or PD1 blockade immunotherapy in patients with advanced melanoma. **Methods:** In a multicenter effort, data were prospectively collected from 6 cohorts of anti-CTLA4- or anti-PD1-treated advanced melanoma patients (n = 138). Kinase activity profiles were generated by analyzing phosphorylation signatures of PBMC lysates on a peptide micro-array. The PamChip (PamGene, Netherlands) microarray comprises 144 different peptides derived from protein phosphorylation sites that are substrates for protein tyrosine kinases. Performance of the predictive model (PLS-DA) was estimated using cross-validation and described by correct classification rate (CCR). Analyses were based on binary grouping of best overall response (RECIST v1.1; CR/PR/SD vs PD) and early/late progression using PFS data (cut-off 140 days). **Results:** Predictive signatures were discovered for anti-CTLA4 in cohort 1 (anti-CTLA4; n = 10; CCR = 100%; 95%CI 69-100%) and confirmed in cohort 2 (anti-CTLA4; n = 28; CCR = 82%; 95%CI 53-94%), as well as for anti-PD1 in cohort 3 (anti-PD1; n = 17; CCR = 76%; 95%CI 50-93%), which was confirmed in cohort 4 (anti-PD1; n = 29; CCR = 72%; 95%CI 53-87%), cohort 5 (anti-PD1; n = 38; CCR = 75%; 95%CI 57-87%), and cohort 6 (anti-PD1; n = 16; non-evaluable due to the low number of responders). **Conclusions:** In advanced melanoma patients, kinase activity profiles of baseline PBMC samples can predict the likelihood of response to anti-PD1 or anti-CTLA4 therapy. This assay may serve as a rapid and fast predictive liquid biomarker to stratify patients prior to treatment. Involvement of receptor tyrosine kinases underlying the mechanism are being further elucidated and a larger validation study is underway.

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9580 Poster Session (Board #407), Mon, 1:15 PM-4:45 PM
Quantitative multiplex immunofluorescence (qmIF) and genomic evaluation of tumor microenvironment (TME) to identify candidate biomarkers in stage II/III melanoma. First Author: Robin Denise Gartrell, Columbia University Medical Center, New York, NY

Background: Biomarkers are needed to risk stratify for adjuvant trials in early stage melanoma. Features of the immune infiltrate within the TME are hypothesized to be prognostic, but quantification methods are not standardized for clinical practice. Expression profiling of stage II/III melanoma shows that Th1 genes have prognostic value. Combination of genomic and qmIF analyses of the TME may identify prognostic immune biomarkers.

Methods: We performed qmIF analysis on 104 primary melanoma tumors (stage II-III) diagnosed at Columbia University Medical Center from 2000-2012. Tissue was stained for DAPI (nuclei), CD3 (T cell), CDB (cytotoxic T cell (CTL)), CD68 (Mψ), SOX10 (tumor), HLA-DR (activation) and Ki67 (proliferation). Phenotyping was performed with inForm software. High/low density cut-offs were defined by Classification and Regression Tree Analysis (CART) and Receiver Operating Characteristic (ROC) curves. For 64 patients (pts), with known of cause of death, KM curves were calculated. mRNA expression analysis for 63 immune genes (NanoString) was performed on 44 of 64 pts for whom sufficient tissue was available. Results: On qmIF, we find that high CTL and low Mψ infiltration, particularly when located in the stroma, correlates with disease specific survival (DSS) (p = 0.004 and p < 0.001, respectively). Of greatest significance, when combined, low stromal CTL/Mψ ratio correlates with death from melanoma using ROC (AUC = 0.724, p = 0.020). By AUC cutoff, low CTL/Mψ ratio (p = 0.008). On multivariable Cox analysis, low CTL/Mψ was independently associated with DSS (p = 0.002) and OS (p = 0.020).

Genomic analysis identified increased expression of CXL9, CXCR3, CCL5 and CD37 in non-recurrent pts (p < 0.050 after bonferroni correction) which did not correlate with CTL/Mψ ratio. Conclusions: Multivariate parameters, including stage of stage II/III melanoma pts shows that stromal CTL/Mψ ratio strongly correlates with survival. mRNA analysis shows that high Th1 gene expression correlates with non-reurrence. Combination of qmIF and mRNA analysis may be useful in stratifying pts to receive immunotherapy.

9581 Poster Session (Board #408), Mon, 1:15 PM-4:45 PM
Phylogenetic analysis of longitudinal melanoma samples to reveal convergent evolution and markers of immunotherapy resistance. First Author: David Liu, Dana-Farber Cancer Institute, Boston, MA

Background: Immune checkpoint inhibitors (ICI) have revolutionized treatment in metastatic melanoma (MM), but progression occurs in the majority of patients (pts), and the evolution of resistance to immunotherapy in individual pts is not well characterized. Methods: Matched longitudinal tumor and germline samples from MM pts treated with ICI underwent whole exome sequencing (WES), bulk RNAseq, bisulfite sequencing, and multiplex immunofluorescence (IF) staining. Single nucleotide variants, small insertions and deletions, copy number alterations, tumor purity and ploidy, and tumor heterogeneity were inferred using standardized analytical pipelines. Phylogenetic analysis was conducted and validated using independent Bayesian clustering approaches. Results: 23 longitudinal tumor samples from a pt with delayed complete response to sequential ipilimumab and nivolumab were sequenced and analyzed. Samples spanned a three year time frame, from pre-treatment primary (n = 1), palliatively resected on-treatment lesions (n = 20), and escape lesions (n = 2, small bowel and brain) which appeared after a 2 year disease-free interval. Mutational load was similar (500 somatic mutations per tumor) with 400 shared mutations, including driver mutations in IDH1, MAP2K1, CTNNB1, and ARID2. Phylogenetic analysis identified 5 melanoma lineages arising out of a common ancestor, with multiple spatially separated lineages co-existing in time. The escape lesions arose out of a lineage characterized by 15q arm loss (including B2M), with a previous acquisition of a germline variant as well as biallelic CDKN2A loss compared to earlier tumors within the lineage. Interestingly, biallelic PTEN loss was found across lineages and in 12/13 tumors after day 39 of therapy compared to 4/10 tumors prior (p = 0.02, Fisher’s Exact), suggesting convergent evolution. Further analysis of tumor epigenetics, transcriptomics, functional proteomics, and IF is ongoing.

Conclusions: Our results suggest that multiple mechanisms of immunotherapy resistance develop within the same pt. More broadly, phylogenetic analyses of longitudinal tumor samples may shed light on the clinical evolution of resistance.

9582 Poster Session (Board #409), Mon, 1:15 PM-4:45 PM
Impact of a gene expression profiling risk score and web-based melanoma outcome calculator on the precision of AJCC-based prognostic assessment. First Author: Georg Brunner, NeraCare GmbH, Cologne, Germany

Background: AJCC staging of primary cutaneous melanoma (CM), based on clinico-pathological criteria, is limited in its ability to provide a precise prognosis for all patients. To improve risk assessment, a prognostic eight-gene expression profiling (GEP) risk score was identified in CMs and adjacent stroma, predicting clinical outcome, independently of and synergistically with AJCC staging. For the same purpose, a web-based melanoma outcome calculator (MOC) was developed (www.CancerMath.net). This study evaluated single and combined prognostic performance of both tools in complementing AJCC-based prediction of melanoma-specific survival (MSS). Methods: Five-yr MSS probabilities were prognosticated by multivariate Cox models, including GEP score + AJCC parameters or MOC parameters. To assess prognostic improvement, the models were compared to each other and to a reference model based on AJCC parameters only (Breslow, ulceration, node status). Data analyses (n=529 CMs, AJCC stages IA-IIIC, median follow-up 65 months) had been pre-specified. Results: GEP score and MOC both improved precision of 5-yr MSS prediction by AJCC (sensitivity + specificity increased by GEP: 14%, p<0.001; by MOC: 11%, p<0.001, by GEP + MOC: 15%, p<0.001). Combining GEP score and MOC improved precision of 5-yr MSS prognosis by MOC alone (sensitivity + specificity increased by 3%, p=0.006). Kaplan-Meier estimates clearly indicated that precision of AJCC-based MSS prediction can be corrected by both tools (p<0.001 by logrank test), independent and synergistically (Table 1). Conclusions: GEP score (based on 125 CMs) and MOC (based on >92,000 CMs) are independent and equivalent prognostic tools, which improve the precision of AJCC-based MSS prediction. Correction was highest when the tools were combined. GEP score is a prognostic parameter that complements AJCC staging as well as MOC.

Correction of AJCC-based 5-yr MSS prediction by the prognostic tools (kaplan-meier estimates):

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9583 Poster Session (Board #410), Mon, 1:15 PM-4:45 PM
Performance of a 31-gene expression profile melanoma test in clinically relevant clinicopathologic subgroups. First Author: Brian Gastman, Cleveland Clinic, Cleveland, OH

Background: Accurate assessment of risk for recurrence and metastasis and early identification of low-burden metastatic disease is of utmost importance for cutaneous melanoma (CM) patient care. Although CM staging has improved with the development of new inflection points to define risk, additional information for risk assessment is critical, particularly considering advances in effective adjuvant therapy. A 31-gene expression profile (GEP) test accurately predicts risk of recurrence and metastasis, classifying CM as Class 1 (1A lowest risk) or Class 2 (2B highest risk). Herein, we analyze its utility for risk stratification beyond traditional staging factors in clinically-relevant subgroups of CM patients. Methods: Using an IRB-approved protocol, CM specimens and clinical data were collected from 16 centers. 690 samples met the inclusion criteria of stage I-III disease with at least 5 years follow up or an event. Low-risk patients (stage I-IIA) by national guidelines and the subpopulation of patients with microscopic nodal disease (stage IIIA), were selected to test the association of clinical factors and GEP with patient outcomes. Results: GEP Class was a significant predictor of recurrence, distant metastasis, and melanoma-specific survival independent of thickness, ulceration, node-status, and mitotic rate using multivariate Cox regression (p < 0.05 at all endpoints), and the only significant factor for stage I-IIA cases. Stage I-IIA patients with a GEP Class 2B test result had 5-year recurrence free survival (RFS), distant metastasis free survival (DMFS), and melanoma-specific survival (MSS) rates of 61, 76, and 86% compared with 96, 97, and 100% for Class 1A patients (n = 393 p < 0.0001). Stage IIIA patients also exhibit statistically significant RFS, DMFS, and MSS when comparing GEP-test class results (n = 75 p < 0.05 at all endpoints). Conclusions: GEP class is a robust and independent predictor of metastasis risk that adds prognostic information to clinically-relevant subpopulations. Accordingly, GEP results add benefit to traditional staging factors and thus may be incorporated in clinical decision-making regarding follow-up, surveillance, and may inform adjuvant therapy decisions.
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9584 Poster Session (Board #411), Mon, 1:15 PM-4:45 PM
Mutation burden in conjunction with MAPK-pathway mutation status as a prognostic biomarker of overall melanoma survival. First Author: John Carey, New York University Langone Health, New York, NY

Background: The high tumor mutation burden (TMB) in melanoma triggers the increased presentation of neoantigens, which are required to elicit an immune response. As a result, TMB has been proposed as a potential biomarker of immunotherapy treatment (IT). It is highly plausible that immunogenicity is also likely to play a role in melanoma progression. Thus, we explored whether the TMB and neoantigen burden (NB) impact melanoma overall survival (OS), independent of IT treatment. Methods: Excluding all patients treated with IT, we used 356 metastatic melanomas from The Cancer Genome Atlas (TCGA), and designed discovery (N = 240 patients) and validation sets (N = 116 patients) by random sampling. For all samples, we calculated total TMB as the number of non-synonymous mutations detected in each sample. We also calculated NB as a function of specific mutations and HLA-type. Using total TMB and NB separately, we assessed their impact on OS using Kaplan-Meier survival analysis. Finally, we repeated this analysis restricted to a subset of patients with MAPK-pathway mutations (N = 260). Results: We found that total TMB predicts better OS in both the discovery and validation sets (p = 2e-04, p = 5e-04, respectively). Patients with fewer than 125 mutations showed significantly worse survival, and this result was replicated by repeated sampling. Restricting the analysis to the patients with a mutation in the MAPK-pathway (BRAF or NRAS), using this result was replicated by repeated sampling. Restricting the analysis both the discovery and validation sets (p = 2e-04, p = 5e-04, respectively).

Conclusions: We have shown that lower total TMB and NB is strongly associated with worse OS in melanoma patients. When restricted to tumors containing MAPK-pathway mutations, we found even stronger significance, demonstrating the interdependence of specific mutation status (BRAF- or NRAS-positive), total TMB, and OS. Importantly, this result indicates the potential utility of TMB as a biomarker of melanoma prognosis, outside of the context of IT.

9586 Poster Session (Board #413), Mon, 1:15 PM-4:45 PM
Surveillance for melanoma (MEL): Results of a database study of stage I-III MEL. First Author: Corey Rearick, University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Optimal surveillance for MEL recurrence is elusive. While consensus guidelines agree on surveillance imaging for high-risk MEL, there is no consensus regarding optimal modality for surveillance and routine imaging surveillance is not recommended for stage IA-IIA MEL. We examined the utility of surveillance in stage I-III MEL. Methods: Patients (pts) at the University of Pittsburgh’s Melanoma Program 1991-2011 were queried using a clinical database. Eligible pts had stage I-III MEL and underwent routine surveillance with clinical examination, chest x-rays (CXR). Minimum follow-up was 9 months (mos). CXR positivity was determined by primary review of attending radiologist report. Pt documentation was queried for information pertaining to relapse, details of advanced imaging, pathology and treatment. Primary endpoints were the incidence of pulmonary (pulm) and extra-pulm metastases. Results: 324 pts with 2,700 CXRs were identified, of whom 114 (35%) had stage I, 63 (20%) stage II, and 147 (45%) stage III MEL. Median duration of screening was 46 mos. During this period, pulm mets were identified in 11%, 25% and 26% of stage I, II and III MEL respectively. Of these, CXR was initially diagnostic in 85%, 81%, and 92% respectively. Incidence of extra-pulm mets was 8%, 24% and 29% for stage I-III MEL, in whom diagnosis was made on advanced imaging ordered to evaluate imaging findings and/or pt symptoms. Conclusions: Incidence of pulm and extra-pulm mets in MEL increases by stage, and CXR reliably detects pulm mets, although a higher incidence of non-pulm mets in stage II-III pts diminishes the value of CXR for relapses overall. Our data suggests that routine CXR surveillance detects few relapses in high-risk stage II-III pts.

9587 Poster Session (Board #414), Mon, 1:15 PM-4:45 PM
Comprehensive genomic profiling of metastatic cutaneous adnexal carcinomas to reveal multiple routes to targeted and immunotherapies. First Author: Nicolas Girard, Institut Curie, Paris, France

Background: Carcinomas that arise from the skin adnexae (Cutaneous Adnexal Carcinomas, CAC) may progress to refractory, metastatic disease. We queried whether comprehensive genomic profiling (CGP) of CAC could reveal genomic alterations (GA) that could guide the use of targeted and immune checkpoint inhibitor (ICI) therapies. Methods: A total of 136 relapsed/refractory and metastatic CAC underwent CGP using 50 ng of DNA and a hybrid-capture, adaptor ligation-based next-generation sequencing assay to a median coverage depth of ~600X. Results were analyzed for all classes of GA and for mutational burden (MB). CGP was performed in up to 1.2 Mb of sequenced DNA; microsatellite instability (MSI) determined by principal components analysis of optimal homopolymer loci. Results: The 103 CAC included 56 (54%) sweat duct (SUDC), 21 (20%) sebaceous (SBCAC), 5 (4%) hair shaft follicle (HRCAC) and 20 (19%) not otherwise specified (NOS) samples (Table). The CAC subtypes had similar median age and male preponderance, except for HRCAC (Table). The CAC had a mean GA/tumor of 5.47 (range 4.33 to 6.90). In CAC overall, potentially targetable GA were in ERBB2 (22%), PTEN (22%), and MET (22%) in at least 10% of samples. There was no significant difference in TMB between the different origins of the tumors treated with IPI and first-line anti-PD-1 (p = 0.002) and first-line anti-PD-1 (p = 0.52), which also holds true for other signatures analyzed. Conclusions: Immune gene profiling by TIS is a valuable tool for response prediction in patients treated with IPI and first-line anti-PD-1. Interestingly, this association was lost in pts treated with anti-PD-1 after targeted therapy or IPI. Validation of our observations in an independent cohort is required.
Genetic aberrations in the CDK4 pathway and association with innate resistance to PD-1 blockade in acral melanoma. First Author: Jayi Yu, Department of Cancer Medicine, Mount Sinai Hospital & Institute, Collaborative Innovation Center for Cancer Medicine, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Beijing, China.

Background: PD-1 checkpoint blockade immunotherapy induces long durable responses in patients with advanced melanoma. However, only a minor subset of acral melanoma patients could gain benefit from it. In this study, we aim to explore factors that may influence innate sensitivity to PD-1 therapy and drug susceptible targets with potential to be combined with anti-PD-1 antibody monotherapy in acral melanoma. Methods: Whole exome sequencing (WES) and RNAseq analyses were performed in 13 biopsies from baseline lesions of advanced melanoma patients who were treated with anti-PD-1 antibody (JS001, Shanghai Junshi Biosciences, China). The copy number variations (CNV) of candidate genes were identified by TaqMan Copy Number Assay in an independent cohort. The effect of CDK4/6 inhibitors combined with anti-PD-1 antibody monotherapy was evaluated by PD-1 humanized mouse (C57BL/6-hPD-1) and patient-derived xenograft (PDx) models. Results: WES revealed parallel CNV in both the CR+PR and PD cohorts, such as 4q22.1, 10q23.32, 15q26.3, 22q13.1, which harbor 22q13.1. However, several significant CNV amplifications notably only in both the CR+PR and PD cohorts, such as 4q22.1, 10q23.32, 15q26.3, x14.1-14.1, which harbor Cdk4, Cnd1, CARD11 and mTOR genes. The association between these CNV and CNV amplification with innate resistance to anti-PD-1 therapy was validated in 46 acral melanoma patients (P < 0.01). The CDK4/6 inhibitor treatment increased PD-L1 protein levels in primary acral melanoma cell line and PDx model. Moreover, CDK4/6 inhibitor augments the response to PD-1 blockade in PD-1 humanized mouse (C57BL/6-hPD-1) and patient-derived xenograft models. Tumor growth curves for each treatment group demonstrated the improved efficacy of combining PD-1 blockade with the CDK4/6 inhibitor (P < 0.05). Conclusions: In summary, we discovered the genetic aberrations in the CDK4 pathways were associated with innate resistance to anti-PD-1 therapy in patients with advanced acral melanoma. Moreover, our study provides evidence for the testing of CDK4/6 inhibitors combined with anti-PD-1 antibody monotherapy in acral melanoma.

Effect on health-related quality of life (HRQOL) of adjuvant treatment (tx) with dabrafenib plus trametinib (D + T) in patients (pts) with resected stage III BRAF-mutant melanoma. First Author: Dirk Schadendorf, University Hospital Essen, Essen, Germany.

Background: Adjuvant tx of resected stage III BRAF-mutant melanoma with D + T significantly reduced risk of recurrence vs placebo (pbo). In the COMBI-AD study, 1-y with D + T resulted in improvements in relapse-free survival, distant metastasis-free survival, freedom from relapse, and overall survival compared to D + T on HRQOL as measured by the EuroQol-5D (EQ-5D-3L) questionnaire and visual analogue scale (VAS) in an exploratory endpoint. A mixed-model, repeated-measures analysis was used to assess differences in mean scores. Results: A total of 870 pts were randomized (D + T, n = 438; pbo, n = 432). Although pts available for assessment declined during study primarily due to consent withdrawal, missing scheduled visits, and deaths, completion rates among available pts were high (98% at baseline [BL], ≥ 90% throughout the 12-mo tx period, and ≥ 75% at assessments after 12 mo). Pts in both arms had similar BL VAS values (D + T, 79.0; Pbo, 80.4 [100 scale]). During tx (3-12-mo assessments), VAS scores remained similar to BL, with no clinically meaningful differences observed between arms (adjusted mean change from BL at 12 mo: D + T, 0.14; pbo, −0.02). In the D + T arm, no clinically meaningful or statistically significant difference in VAS was reported between pts who did and did not experience pyrexia (P > .1). During follow-up (15-48 mo), VAS scores were similar between arms, with no significant or clinically meaningful differences reported. At relapse, a statistically significant reduction in VAS score was observed in both arms (mean difference [pre-vs postrecurrence], D + T, −6.02, P = .003; pbo, −6.84, P < .001). Conclusions: In the absence of disease-related symptoms in the adjuvant setting, these results demonstrate that D + T do not negatively impact HRQOL. This may be important for long-term follow-up and further emphasizes the importance to pt HRQOL of preventing relapse. Clinical trial information, NCT01682083.

Dabrafenib plus trametinib (D + T) as adjuvant treatment of resected BRAF-mutant stage III melanoma: Findings from the COMBI-AD trial analyzed based on AJCC 8 classification. First Author: James M. G. Larkin, Royal Marsden NHS Foundation Trust, London, United Kingdom.

Background: The COMBI-AD trial demonstrated that adjuvant treatment with D + T in patients (pts) with resected stage III BRAF-mutant melanoma significantly reduced the risk of melanoma recurrence vs placebo (pbo). Pts were stratified based on the AJCC 7 disease stage classification. We present efficacy results from COMBI-AD based on the updated AJCC 8 staging classification. Methods: COMBI-AD (NCT01682083) was a randomized, double-blind, pbo-controlled, phase 3 study evaluating pts with stage III BRAF V600E/K–mutant melanoma without prior anticancer therapy. Pts were randomized 1:1 within 12 weeks of complete resection to receive D 150 mg twice daily plus T 2 mg once daily or matching pbo for 12 months. Patients were treated with anti-PD-1 antibody (JS001, Shanghai Junshi Biosciences, China). The primary endpoint was relapse-free survival (RFS). Pts were stratified by disease stage (stages IIIA, IIIB, IIIC, and IIID) and patients resulted in a significantly lower risk of relapse and metastasis in resected mucosal melanoma than high-dose IFN-a2b and was not associated with seriously toxic effects. Clinical trial information: BOCHMMAT001.

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Lever directed treatment for patients with uveal melanoma hepatic metastasis: A retrospective analysis of overall survival.

**Background:** Despite successful treatment of primary uveal melanomas, up to 50% of patients subsequently develop systemic metastasis, with the liver involved in up to 90% of patients. At our institution, recognition of the poor prognosis associated with liver metastasis has led to the use of various liver-directed treatment modalities including transarterial chemoembolization (TACE) with BCNU, drug-eluting beads with doxorubicin (DEBDOX), immunoembolization (IE) with GM-CSF, and radioembolization with Yttrium 90 radioactive microspheres. The purpose of this study is to compare overall survival between uveal melanoma patients with hepatic metastasis before and after the shift of initial treatment from systemic to liver-directed approaches.

**Methods:** A retrospective single-institution chart review was performed on consecutive series of uveal melanoma patients with hepatic metastasis who were treated at Thomas Jefferson University between 1971–1993 (Cohort 1, n = 98) and 2000–2017 (Cohort 2, n = 634). The following data was collected from medical records: primary tumor stage and genetic abnormalities, primary eye treatment, date to hepatic and extrahepatic metastasis, types of liver-directed and systemic treatments utilized, and date of death from development of hepatic metastasis to death (OS-Liver) and time from initial treatment of primary uveal melanoma to death (OS-Eye) in individual cohorts were measured and analyzed.

**Results:** 81% of cohort 1 patients received systemic chemotherapy as their initial treatment for liver metastasis, while 91% of cohort 2 patients (n = 574) initially included including IE (n = 296), BCNU TACE (n = 147), DEBDOX (n = 45), radioembolization (n = 37), and other liver-directed treatments (n = 49). OS-Liver in cohort 1 and cohort 2 was 4.8 months and 16.4 months, respectively (P < 0.001). More importantly, OS-Eye in cohort 2 (5.1 years) is much longer than that of cohort 1 (3.3 years) (P < 0.001). **Conclusions:** Liver-directed treatments provided significant survival benefit for uveal melanoma patients with hepatic metastasis.

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TPS9598  Poster Session (Board #422b), Mon, 1:15 PM-4:45 PM
Phase III study of the PI3Kβ inhibitor GS2636771 in combination with pembrolizumab (P) in patients (pts) with PD-1 refractory metastatic melanoma (MM) and PTEN loss. First Author: Gustavo Schvartsman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint blockade (ICB) improves overall survival and provides long-term disease control in 35-40% of pts with MM. However, more than a third of pts experience no clinical benefit (de novo resistance) and many progress even after achieving an initial response (acquired resistance). Our group has demonstrated that increased activation of phosphatidylinositol 3-kinase (PI3Kβ) pathway, most commonly through loss of the tumor suppressor gene PTEN, plays a critical role in resistance to ICB. PTEN loss occurs in up to 30% of MM pts and correlates with decreased T cell infiltration and inferior outcomes to ICB. In preclinical models, we showed that loss of PTEN inhibits T cell mediated tumor killing and decreases T cell trafficking into tumors, and that selective inhibition of the PI3Kβ-subunit with GS2636771 was superior to pan-PI3K inhibitors and significantly increased the activity of ICB, and the number of infiltrating CD4+ and CD8+ T cells. We therefore hypothesized that PI3Kβ will reverse resistance to ICB in MM with PTEN-loss. To test this hypothesis, we are conducting a Phase III trial of the PI3Kβ inhibitor GS2636771 in combination with P in pts with PD-1 refractory MM and PTEN loss. Methods: The primary objective of the Phase I portion is to determine the safety and Maximum-Tolerated Dose (MTD) and/or the Recommended Phase II Dose (RP2D) of GS2636771 in combination with P in pts with PD-1 refractory disease and PTEN loss. The dose will be treated with GS2636771 at 200 mg q3w by cycle. GS2636771 will be given orally starting at the dose level of 300 mg PO qd for 21 days and escalated to a maximum dose of 400 mg PO qd using a 3+3 design. The Phase II portion will enroll a total of 35 pts at the MTD/ RP2D. Continuous monitoring for both toxicity and futility will be assessed. The primary objective of the Phase II portion is to determine the safety, tolerability, and efficacy of the combination as defined by Objective Response Rate (ORR) by RECIST 1.1 in MM with PTEN loss. Secondary Objectives include the PKs of GS2636771 and correlation with ORR and pharmacodynamic effects in tumor tissue as measured by pathway inhibition and T cell trafficking into tumors. Clinical trial information: NCT03131908.

TPS9598  Poster Session (Board #423b), Mon, 1:15 PM-4:45 PM
A phase II study of bevacizumab (BEV) in combination with atezolizumab (ATEZ) in pts with untreated melanoma brain metastases (BEAT-MBBM), First Author: Gustavo Schvartsman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immunotherapy (IO) has significantly improved survival for many pts with metastatic melanoma. However, the majority of trials excluded pts with MBM. Recently, combination of nivolumab and ipilimumab (IPI) showed objective response rate (ORR) of up to 55%, but pts with symptomatic disease still do poorly and usually are not candidates for IO due use of high dose steroids. Additionally, there is a concern for increased p - lesional edema, which can lead to neurologic symptoms. BEV has widely been used as a “steroid-sparing agent” with remarkable success in controlling intracranial edema. Moreover, studies have implicated elevated angiogenic markers as predictors of poor outcome with IO by limiting effector T-cell trafficking and activity. Clinically, BEV has been shown to improve the outcome of IO and has indeed increased expression of favorable chemokines in the tumor microenvironment, improving ORR when added to IPI. Moreover, the combination of BEV and ATEZ0, a PD-L1 inhibitor, produced remarkable responses in renal cell carcinoma. We therefore hypothesized that combining BEV and ATEZ0 will be more effective and have an improved toxicity profile in MBM. Methods: This phase II study will evaluate the intracranial safety and efficacy of BEV + ATEZ0 by ORR (iRANO criteria) in pts with untreated or progressive MBBM who have not been exposed to PD-1/ PD-L1 inhibitors. We will accrue 40 pts, divided in two cohorts: cohort A (25 asymptomatic pts); and cohort B (15 pts that are either mildly symptomatic, or asymptomatic, but requiring a low dose of systemic steroids (no higher than 4 mg/day of PO dexamethasone or equivalent). BEV will be given at 15 mg/kg and ATEZ0 at 1200 mg flat dose, both IV every 3 weeks until progression or death. Efficacy will be assessed by MRI of the brain and systemic imaging every 2 cycles. Continuous monitoring for toxicity and futility will be performed and assumes an ORR of 45% (96% power to detect a 25% difference from historical control of 20%). Effects of BEV + ATEZ0 on correlative immune markers will be studied. This study is open for enrollment. Clinical trial information: NCT03175432.

TPS9599  Poster Session (Board #423a), Mon, 1:15 PM-4:45 PM
Combining ipilimumab (ipi) and nivolumab (nivo) in advanced melanoma following progression on a PD-1 inhibitor (SWOG S1616). First Author: Andrew Vandervelde, University of Tennessee Health Science Center, West Cancer Center, Germantown, TN

Background: We hypothesize that patients with advanced melanoma who progress on anti-PD-1 therapy upfront may respond to the addition of the CTLA-4 inhibitor ipi to continue PD-1 inhibition (with nivo), and that responses would occur at a rate higher than would be expected from switching to ipi alone. We surmise that this would occur because melanomas primarily refractory to PD-1 antibodies may not have a sufficient pre-existing T cell infiltrate, which can be corrected by adding treatment with ipi, as CTLA-4 blockade increases new intratumoral T cell infiltration. Methods: This is a Phase 2, prospective open-label study ofipi +/- nivo in patients with advanced melanoma refractory to a PD-1 inhibitor. The primary endpoint of the study is progression free survival. Secondary objectives include the difference in T-cell infiltrate in biopsies of patients with response and no-response to therapy; objective response rate; overall survival; and toxicity. Key eligibility criteria include unresectable melanoma; disease progression while on prior PD-1 agents or after stopping with no intervening therapy; no complete partial or complete response to prior anti-PD1 agents; and/CTLA-4 inhibitor; Zubrod performance status 0-2; no active brain metastases; no history of autoimmune pneumonitis or colitis requiring steroids or interruption of therapy; and adequate organ function. Prior receipt of BRAF/MEK inhibitors is permitted. Subjects are randomized 1:3 to ipi 3mg/kg q5wk v4 doses or ipi 1mg/kg q4wk x 4 doses followed by nivo 240mg q2wk (21 planned on ipi; 63 on ipi+nivo). Tumor biopsy and blood for correlative studies are taken prior to enrollment and at Day 28-35 on study. Tumor assessments are performed every 12 weeks for 1 year and treatment is continued while clinical benefit persists with a final survival follow-up of 2 years. The combination will be considered superior to single-agent ipi if PFS is doubled from 3 to 6 months with one-sided alpha of 0.1 and power of 0.9. As of January 2018, 5 of 84 planned subjects have enrolled. Clinical trial information: NCT03033576.

TPS9597  Poster Session (Board #424a), Mon, 1:15 PM-4:45 PM
A randomized phase II study of anti-PD1 antibody (MK-3475 (Pembrolizumab)) alone versus anti-PD1 antibody plus stereotactic body radiation therapy in patients with advanced merkel cell carcinoma (Alliance A091605). First Author: Jason J. Luke, University of Chicago Comprehensive Cancer Center, Chicago, IL

Background: Merkel cell carcinoma (MCC) is a rare cutaneous malignancy associated with ultraviolet light exposure, advanced age and infection with the Merkel cell polyomavirus (MCP). Historically, median survival in the metastatic setting was approximately 9.6 months with radiation and platinum based chemotherapy as the foundations of treatment. More recently, outcomes have been markedly improved with the development of PD1/L1 antibodies. Durable response rates have been observed ranging from 30-50%, depending on line of therapy, that are independent of PDL1 or MCP status, mutation burden or tumor-infiltrating lymphocytes. A large preclinical and some clinical observations support the hypothesis that radiation may augment the systemic efficacy of immunotherapy (abscopal effect) through increased antigen presentation, T-cell priming, and interferon gamma associated signaling. No clinical studies to date have directly tested this hypothesis. Methods: This is an NCTN supported (Alliance for Clinical Trials in Oncology, SWOG and NRG Oncology) open-label phase II study comparing pembrolizumab with pembrolizumab plus stereotactic body radiation therapy to a single lesion in advanced MCC. The study randomizes patients 1:1 with eligibility including no prior therapy in the metastatic setting, ≥2 sites of RECIST measurable disease, ECOG performance status 0-2 and no autoimmune or immunosuppression. The primary endpoint is progression-free survival in non-irradiated lesions (abscopal), with secondary endpoints evaluating response rate, overall survival and toxicity. Translational biospecimens, including archival tumor tissue (for PD1, TMB, gene expression profiling and other analyses), serum and peripheral blood mononuclear cells and fecal microbiome samples, are being collected for analysis. The study is open to accrual via the Cancer Trials Support Unit (CTSUs) of NCI to any NCTN group member site. Recruitment is on-going (target 96 patients). Clinical trial information: NCT03304639.

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A randomized phase III study of duration of anti-PD-1 therapy in metastatic melanoma (STOP-GAP). Canadian Clinical Trials Group study (CCTG) ME.13. First Author: Tara D. Beazit, Division of Medical Oncology, Queen’s University, Kingston, ON, Canada

**Background:** Efficacy of the anti-PD-1 agents has been demonstrated in metastatic melanoma in phase I-III trials. During the development of these trials there was no optimal duration of treatment identified. Trials stopped due to unacceptable side effects, investigator’s choice, at a specific time point typically at 24 months of therapy or at disease progression. Clinical reports suggest that stopping treatment early due to toxicity may not adversely impact efficacy. In addition, there is evidence that retreatment with immunotherapy may be clinically effective. Unnecessary long term therapy may result in a higher risk of toxicity, diminished quality of life (QoL) and will impact the cost-effectiveness of the therapy. We hypothesize that treatment to maximum tumour response will result in non-inferior overall survival with better QoL, less toxicity and lower cost than continuous therapy.

**Methods:** This is a large, simple randomized phase III trial evaluating the duration of anti-PD-1 therapy in metastatic/unresectable melanoma. Consecutive patients must be eligible to receive anti-PD-1 inhibitor as standard of care. Patients are randomized 1:1 to either 24 months of therapy in the absence of disease progression versus treatment until maximum tumor response (MTR) with retreatment at the time of progression. MTR is determined by at least two radiologic measurements three months apart. Eligibility criteria are broad to reflect a “real-world” patient population. Data collection is streamlined to focus on key endpoints for the primary endpoint of overall survival. Secondary endpoints are PFS, response rate, adverse event rate, health related QoL and economic analysis. Patients are stratified based on line of therapy, stage of disease, BRAF status, LDH level, prior use of adjuvant therapy, anti-PD-1 inhibitor selected and the presence of CNS metastases. The trial will enroll 550 patients with 275 in each arm. It is expected that accrual will last 5.5 years. Currently 78 patients have been enrolled. Clinical trial information: NCT02821013.

**Trial in progress: A phase 2 study of intratumoral pit-12 plus electroporation in combination with intravenous pembrolizumab in patients with stage III/IV melanoma progressing on either pembrolizumab or nivolumab treatment (PISCES).** First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT

**Background:** Immunotherapy and targeted therapies have significantly changed the treatment landscape for advanced melanoma over the past few years. However, despite the addition of these new therapeutic strategies, a lack of response or disease progression continues to occur in a significant fraction of patients (~60%). Pembrolizumab (anti-PD-1 antibody) for the treatment of advanced melanoma confers a 33% objective response rate (ORR). Intratumoral plasmid IL-12 (tavokinogene telseplasmid; tav) with electroporation (IT-tavo-EP) is a gene-based immunotherapeutic approach that forces localized expression of the proinflammatory cytokine IL-12, which converts both treated and untreated lesions from poorly immunogenic/low T-cell infiltrating tumors unlikely to respond to anti-PD-1 therapy into highly inflamed immunologically active lesions. The purpose of this study is to evaluate the tolerability and efficacy of pembrolizumab plus IT-tavo-EP in Stage III/IV melanoma patients who have progressed or are progressing on anti-PD-1 checkpoint inhibitors, and to assess the immunomodulatory effects of therapy. **Methods:** OMS-1103 (PISCES) is a phase 2, multicentric, open-label trial of IT-tavo-EP with pembrolizumab in patients with stage III/IV melanoma who are progressing on either pembrolizumab or nivolumab. The primary objective is best ORR by RECIST v1.1 at 24 weeks determined by an independent review committee (Simone 2-stage minimax design). In Stage 1, up to 23 eligible patients will be enrolled and treated with IT-tavo-EP to the accessible lesions on Days 1, 5 and 8 every 6 weeks with IV pembrolizumab (200 mg) on Day 1 of each 3-week cycle for 24 weeks. If the predesignated threshold is reached in Stage 1, (N > 3 /23) enrollment for Stage 2 will include an additional 25 patients (total of 48 patients). The study is enrolling in the US and Australia. Clinical trial information: NCT03132675.

**TPS9602** Poster Session (Board #425b), Mon, 1:15 PM-4:45 PM

Multicenter phase I/IIa study using T cell receptor gene therapy in metastatic melanoma. First Author: Maartje W. Rooha, Netherlands Cancer Institute, Amsterdam, Netherlands

**Background:** Since the introduction of targeted therapy and checkpoint inhibitors, the historically poor prognosis of patients with unresectable stage III/IV melanoma has greatly improved, with now known 2-year survival rates of 46-64%. However, a substantial group of patients, for example those with metastatic uveal melanoma, have poor response rates upon these therapies with no alternative approved therapy yet available. Adoptive transfer of T cell receptor (TCR) gene modified T cells is a modality to create a large pool of tumor reactive T cells. Responses of clinical significance have been seen in preclinical and clinical trials when targeting the melanocyte differentiation antigens gp100 and MART-1. The primary aim of our study is to explore the feasibility, safety and objective response rate of the adoptive transfer of autologous T cells modified with a MART-1 specific TCR, preceded by non-myeloablative (NMA) chemotherapy. **Methods:** In this phase I/IIa study, a total of 25 patients ≥ 18 years of age, with irresectable stage III/IV melanoma (cutaneous, melanoma of unknown primary, mucosal and uveal melanoma) who have failed previous standard treatments, are HLA-A2 positive and have MART-1 and MHC class I expressing tumors, will be included. Patients will undergo leukapheresis to isolate autologous T cells, which will be transduced with a retroviral vector encoding the 1D3HMCoys MART-1 TCR and expanded ex vivo. Patients will receive NMA chemotherapy and a single intravenous infusion with MART-1 TCR transduced T cells in a dose escalating regimen after evaluation of toxicity and efficacy. Primary endpoints are the feasibility of MART-1 specific TCR therapy in terms of delivery of this sequence of treatment in metastatic melanoma patients, safety according to CTCAE 4.0 and objective response rate according to RECIST 1.1. Secondary endpoints are the 1-year progression free survival, median overall survival and the efficacy of induction of tumor specific T cell responses measured in peripheral blood and tumor biopsies. Enrollment started in March 2012 in The Netherlands Cancer Institute and will be continued in a 2-stage Simon design. Clinical trial information: NCT02654821.

**TPS9603** Poster Session (Board #426a), Mon, 1:15 PM-4:45 PM

Reversing resistance to PD-1 blockade by combination of talimogene laherparepvec (T-VEC) with pembrolizumab (pembro) in advanced melanoma patients following progression on a prior PD-1 inhibitor: SWOG S1607 (NCT#02965716). First Author: Siwen Hu-Lieskovan, UCLA’s Jonsson Comprehensive Cancer Center, Los Angeles, CA

**Background:** A significant number of patients do not respond to PD-1/L1 blockade because there are no pre-existing tumor antigen-specific T-cells in their tumors ready to attack the cancer. We hypothesize that this lack of sufficient immune activation can be addressed by a combination therapy with an immune activating oncolytic virus such as T-VEC. Intralesional administration of T-VEC, a modified herpes simplex virus type-1, can selectively replicate in tumor tissue and stimulate a local and systemic antitumor immune response. **Methods:** This is a phase 2 study of T-VEC plus pembrolizumab in patients with advanced melanoma whose disease progressed after prior therapy with a PD-1/L1 inhibitor. The primary endpoint is durable response rate. Secondary objectives include objective response rate in the injected, non-visceral non-injected and visceral lesions, progression free survival, overall survival and toxicity. Translational objectives include difference in T-cell infiltrate in responding vs non-responding tumors. Key eligibility criteria include unresectable melanoma; anti-PD-1/L1 based therapy must be the immediate previous line of treatment within 56 days prior to registration; no confirmed partial or complete response to prior anti-PD1 agents; Zubrod performance status 0-2; no active brain metastases; no history of autoimmune disease or toxicity requiring steroids; and adequate organ function. Subjects in cohort A must have at least one measurable visceral lesion; in cohort B subjects must not have visceral lesion. Subjects will receive intratumoral injection of T-VEC 1 million PFU/ml for cycle 1 followed by 100 million PFU/ml from cycle 2 to 36 (one cycle equals 21 days). Pembrolizumab 200mg IV will be given every 21 days. Tumor biopsy and research blood are taken at baseline and while on treatment at Day 28 (both injected and non-injected lesions). Tumor assessments are performed every 12 weeks, and treatment is continued while clinical benefit persists for up to 2 years. A total of 36 subjects will be enrolled in cohort A and 25 subjects in cohort B, with a Simon 2 stage design. Clinical trial information: NCT02965716.
DFT: ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in Merkel cell carcinoma patients with clinically-detected LN metastases.

**Background:** Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. MCC with clinically detected lymph node (LN) metastases is associated with high risk of systemic recurrence despite initial surgical therapy and/or radiation therapy (RT). Adjuvant cytotoxic chemotherapy is not associated with overall survival benefit in stage III MCC and there is a strong unmet need for effective adjuvant systemic therapy. Clinical investigation of PD-1/PD-L1 blockade in patients with metastatic MCC is associated with remarkable improvement in clinical outcomes with response rates > 50% in a chemotherapy-naïve setting. This notable benefit from PD-1 blockade in stage IV MCC, along with the recent success with adjuvant PD-1 blockade in stage III melanoma, together provide strong rationale for investigating avelumab, an anti-PD-L1 antibody, for adjuvant systemic therapy in MCC patients with high risk of recurrence. **Methods:** The ADAM (Adjuvant Avelumab in Merkel) trial is an investigator-sponsored, phase 3, multi-center, double-blinded and placebo-controlled study. We plan to enroll 100 MCC patients with clinically or radiologically detected LN metastases treated definitively with surgery (with or without adjuvant RT). Patients will be randomized (1:1) to receive either avelumab or placebo administered IV at a dose of 10mg/kg every 15 days for the first 4 months, then once monthly for the next 4 months, and then every 4 months for an additional 12 months. Treatment will continue until disease progression, unacceptable toxicity, or study withdrawal. The primary endpoint is relapse-free survival. Secondary endpoints include overall survival, disease-specific survival, distant metastasis-free survival, and safety and tolerability. Exploratory endpoints include tissue and blood-based biomarkers and AMERK (Anti-Merkel polyomavirus) serology as a recurrence predictor in a prospective, multi-center setting. The ADAM trial represents the first-ever phase 3 trial in MCC and is a major academic collaboration across several US cancer centers. Clinical trial information: NCT03271372.

**TPS9605 Poster Session (Board #427a), Mon, 1:15 PM-4:45 PM**

**ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in Merkel cell carcinoma patients with clinically-detected LN metastases.**

First Author: Shailender Bhatia, University of Washington Fred Hutchinson Cancer Center, Seattle, WA

Background: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. MCC with clinically detected lymph node (LN) metastases is associated with high risk of systemic recurrence despite initial surgical therapy and/or radiation therapy (RT). Adjuvant cytotoxic chemotherapy is not associated with overall survival benefit in stage III MCC and there is a strong unmet need for effective adjuvant systemic therapy. Clinical investigation of PD-1/PD-L1 blockade in patients with metastatic MCC is associated with remarkable improvement in clinical outcomes with response rates > 50% in a chemotherapy-naïve setting. This notable benefit from PD-1 blockade in stage IV MCC, along with the recent success with adjuvant PD-1 blockade in stage III melanoma, together provide strong rationale for investigating avelumab, an anti-PD-L1 antibody, for adjuvant systemic therapy in MCC patients with high risk of recurrence. **Methods:** The ADAM (Adjuvant Avelumab in Merkel) trial is an investigator-sponsored, phase 3, multi-center, double-blinded and placebo-controlled study. We plan to enroll 100 MCC patients with clinically or radiologically detected LN metastases treated definitively with surgery (with or without adjuvant RT). Patients will be randomized (1:1) to receive either avelumab or placebo administered IV at a dose of 10mg/kg every 15 days for the first 4 months, then once monthly for the next 4 months, and then every 4 months for an additional 12 months. Treatment will continue until disease progression, unacceptable toxicity, or study withdrawal. The primary endpoint is relapse-free survival. Secondary endpoints include overall survival, disease-specific survival, distant metastasis-free survival, and safety and tolerability. Exploratory endpoints include tissue and blood-based biomarkers and AMERK (Anti-Merkel polyomavirus) serology as a recurrence predictor in a prospective, multi-center setting. The ADAM trial represents the first-ever phase 3 trial in MCC and is a major academic collaboration across several US cancer centers. Clinical trial information: NCT03271372.
Background: DM is characterized by high collagenous stroma and a high mutational burden. A retrospective review demonstrated a 70% RR to anti-PD1-in 60 patients with metastatic melanoma. Surgery for locally advanced DM often results in large resections in exposed areas of the body. Determining the capability of reducing the tumor size and surgical defects is of clinical interest. Evaluating the correlation of T cell infiltrate, TCR clonality, and the impact of pre-existing adaptive immune response with clinical response is of potential predictive interest. Methods: This prospective study evaluates neoadjuvant pembrolizumab in patients with resectable DM (phase 2) and pembrolizumab in patients with unresectable DM (pilot). The primary endpoint of cohort A (resectable DM) is pathologic complete response rate (pCR). Secondary endpoints: ORR at 9 weeks, OS at 9 weeks, and toxicity. The primary endpoint of cohort B (unresectable DM) is CR. Secondary endpoints: PFS and OS. Translational objectives for both cohorts: evaluate the association between mutational load (whole exome sequencing) and pCR, examine relationships between T-cell infiltration and response, and assess the difference in TCR clonality in responders and non-responders. Key eligibility criteria include no prior systemic therapy and adequate organ function. In addition (cohort A) patients must have resectable disease. Cohort A: pembrolizumab 200 mg IV q 3wk x 3, followed by resection. Cohort B: pembrolizumab 200 mg IV q3wk. Blood for correlative studies: prior to initiation of pembrolizumab. For both cohorts, biopsies will occur pre-treatment, prior to C2, and at the time of resection (cohort a). Tumor assessments are performed at baseline and at week 9. Cohort A: if >5 patients demonstrate a pCR, further study is warranted (alpha of 4.6%, power of 90.2%). Cohort B: ≥3 patients demonstrating a CR warrants further study (true CR is 5%, power is 82%). As of January 2018, accrual = 5. Funding: NIH/NCI grant awards U10CA180888 and U10CA180819; and in part by Merck, Sharpe & Dohme, Corp. Clinical trial information: NCT02775851.
O3-FA use was associated with significantly reduced AI arthralgia and significantly lower triglyceride levels at 12 weeks compared with placebo in patients with BMI ≥ 30 (56% vs. 17%, p = 0.009) and hypertension (53% vs. 31%, p = 0.0005), were more likely to have ≥2 cardiovascular risk factors (33% vs. 17%, p = 0.009), and had lower HDL levels (49.9 vs. 60.3, p < 0.0001). O3-FA use was associated with significantly reduced triglyceride levels at 12 weeks compared with placebo in patients with BMI ≥ 30 (−22.4 vs. +1.6, p = 0.003), but not in those with BMI < 30 (p = 0.12, interaction p = 0.09). Among patients with BMI ≥ 30, O3-FA use was associated with a 2.89-point decrease in BPI worst pain score after 24 weeks compared to a 1.49-point decrease with placebo use (p = 0.09). Trends were similar using change in joint pain was assessed with scores ranging from −3 for “very much worse” to +3 for “very much better” than baseline. Results: Among the 249 patients, 139 had BMI < 30 (56%) and 110 had BMI ≥ 30 (44%). Patients with BMI ≥ 30 had higher rates of diabetes (19% vs. 8%, p = 0.009) and hypertension (53% vs. 31%, p = 0.0005), were more likely to have ≥2 cardiovascular risk factors (33% vs. 17%, p = 0.009), and had lower HDL levels (49.9 vs. 60.3, p < 0.0001). O3-FA use was associated with significantly reduced triglyceride levels at 12 weeks compared with placebo in patients with BMI ≥ 30 (−22.4 vs. +1.59, p = 0.03), but not in those with BMI < 30 (p = 0.12, interaction p = 0.09). Among patients with BMI ≥ 30, O3-FA use was associated with a 2.89-point decrease in BPI worst pain score after 24 weeks compared to a 1.49-point decrease with placebo use (p = 0.09), whereas there was no significant difference between O3-FA and placebo in those with BMI < 30 (p = 0.40, interaction p = 0.05). Trends were similar using global change in joint pain for O3-FA use compared to placebo (BMI ≥ 30, +0.98 vs. +0.48 respectively, p = 0.05; BMI < 30, +0.57 vs. +0.50 respectively, p = 0.80), though the interaction was not statistically significant (p = 0.22). Conclusions: In BC patients with BMI ≥ 30, O3-FA use was associated with significantly reduced AI arthralgia and significantly lower triglyceride levels compared to placebo. If confirmed, O3-FA use may lead to improved AI adherence in this subset of BC patients. Clinical trial information: NCT01385137.

Conclusions: The effect of acupuncture versus cognitive behavior therapy on insomnia in cancer survivors: A randomized clinical trial. First Author: Jun J. Mao, Memorial Sloan Kettering Cancer Center, New York, NY

Patients and oncology clinicians can use these findings to inform their choice of insomnia treatment. Clinical trial information: NCT02356575.

LBA10003 Oral Abstract Session, Sun, 8:00 AM-11:00 AM
Improving communication with older patients with cancer using geriatric assessment (GA): A University of Rochester NCI Community Oncology Research Program (NCORP) cluster randomized controlled trial (CRCT).
First Author: Supriya Gupta Mohile, University of Rochester Medical Center, Rochester, NY

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the Journal of Clinical Oncology. On site at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.
Randomized trial of a symptom monitoring intervention for hospitalized patients with cancer. First Author: Chinn-Yin Fuh, Massachusetts General Hospital, Boston, MA

Background: Hospitalized patients with cancer experience a high symptom burden, which is associated with poor health outcomes and increased healthcare utilization. We conducted a pilot randomized trial to assess the feasibility and preliminary efficacy of a symptom monitoring intervention to improve symptom management in hospitalized patients with advanced cancer.

Methods: We randomly assigned patients with advanced cancer and unplanned hospitalizations who were admitted to the oncology service to a symptom monitoring intervention or usual care. Patients in both arms daily self-reported their symptoms (Edmonton Symptom Assessment System and Patient Health Questionnaire-4) via tablet computers. Patients assigned to the intervention had their symptom reports presented graphically with alerts for moderate/severe symptoms during daily team rounds. We defined the intervention as feasible if participants completed > 75% of their daily symptom assessments. We also observed daily team rounds to determine how often clinicians discussed and developed a plan to address patients’ symptoms. We used regression models to assess intervention effects on patients’ symptoms throughout their hospital stay and readmission risk.

Results: From 10/26/16–6/30/17, we randomized 150 participants (91.1% allocation rate; median age = 64.0 (22.7-92.8); 40.7% female). The most common cancers were gastrointestinal (36.7%) and lung (22.0%). Patients completed 89.4% of their daily symptom assessments. Clinicians discussed 60.4% of the symptom reports and developed a plan during rounds to address patients’ symptoms 20.8% of the time. Compared to usual care, patients assigned to the intervention had a greater proportion of days with lower psychological distress (B = 0.12, P < .008). Intervention patients experienced improvements in their average symptom scores for drowsiness (B = -0.54, P = .033) and dyspnea (B = 0.43, P = .0039). Intervention patients had lower risk of readmissions (hazard ratio = 0.68, P = .221), although this difference was not significant.

Conclusions: This symptom monitoring intervention is feasible and demonstrates encouraging preliminary efficacy for improving patients’ symptoms and risk for readmissions. Clinical trial information: NCT02891993.

Patient and Survivor Care

Does timing of palliative care consults impact end-of-life health services utilization in pancreatic cancer patients? First Author: Nizar Bhulani, University of Texas Southwestern Medical Center, Dallas, TX

Background: Early palliative care consult can influence end of life health care utilization in controlled clinical trials. However, the effect in large scale, real world setting is not known. We explored the effect of early vs. late palliative care consult on end of life health care utilization in Medicare patients with pancreatic cancer.

Methods: Pancreatic cancer patients diagnosed between 2000–2009 with palliative consults were identified using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Early palliative care was defined as a consult received in the first 4 weeks of diagnosis. Patients older than 66 years, with survival more than 3 months and known date of death were included. Trend of palliative care consults and health services utilization was studied for patients with early vs late palliative care consults. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results: Of the 1966 patients with palliative care consults, 840 (43%) received early palliative care. On univariate analysis, age, sex, state of residence and stage at diagnosis were associated with early palliative care consult (p < .001). On multivariate analysis, patients with early palliative care consults were more likely to be women, older than 85 years and have stage 4 disease. Race and state of residence were not associated with early vs late palliative care consult.

Patients with early palliative care had lower number of visits to the ED (2.4 vs. 3.0; p < .001) and lower cost of ED care ($3043 vs. $4117, p < .001). Early palliative care patients were admitted less frequently to the ICU compared to late palliative care patients (0.68 vs. 0.94, p < .001) and the duration of Intensive care unit stay was shorter (3.0 days vs 3.7 days, p = 0.04).

Cost of ICU care was not statistically different between both the groups.

Conclusions: In this claims analysis of elderly pancreatic cancer patients, those with early palliative care had lower health care utilization as measured by ED and ICU stay. This provides real world evidence to support oncology societies’ recommendations for early integration of palliative care.

Understanding factors contributing to geographic variations in end-of-life spending. First Author: Nancy Lynn Keating, Harvard Medical School, Boston, MA

Background: Health care spending at the end of life varies across geographic areas and yet is not associated with improved outcomes. The factors underlying these variations are poorly understood. We assessed the extent to which geographic variation in end-of-life spending for advanced-stage cancer patients is explained by differences in patient sociodemographic factors, clinical factors, patient beliefs, physician beliefs, and availability of services.

Methods: Using data from the prospective, multi-regional CANCORS study, we studied 1132 patients with advanced-stage lung and colorectal cancer diagnosed in 2003-2005 who died before 2013. We linked patient and physician survey data, medical record data, and Medicare data, and we characterized Medicare spending in the last 30 days of life. After assessing differences in patient factors/beliefs, physician beliefs, and availability of services across areas that differed based on Dartmouth Atlas measures of intensity of end-of-life spending, we used mixed effects linear regression with random area effects to assess the area-level variance in spending in the last 30 days of life in our cohort and the proportion of that variance explained with sequentially adding groups of explanatory variables.

Results: The mean (SD) expenditures in the last 30 days of life were $13,664 ($17,563). Physicians in higher-spending areas reported less knowledge and comfort caring for dying patients and less positive attitudes about hospice (all p < .05). Higher-spending areas had more physicians, a lower percentage of primary care providers, and fewer hospices/10,000 persons. Physician beliefs and availability of services each explained 45-60% of the variation in end-of-life expenditures; area-level patient beliefs did not contribute to area-level variations.

Conclusions: Physicians’ beliefs and area-level availability of services but not patients’ beliefs were important factors explaining geographic variations in intensity of end-of-life spending for patients with advanced-stage cancer. Physician training and strategic allocation of services may have potential for decreasing unwarranted variation in care at the end of life for patients with advanced-stage cancers.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
10009 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM
Patient-defined goals and preferences among older adults with cancer starting chemotherapy (CT). First Author: Enrique Soto Perez De Celis, City of Hope, Duarte, CA.

Background: Older adults with cancer facing decisions with competing health outcomes may favor maintaining quality of life (QOL), independence, or cognition over prolonging survival. The goal of this study was to elicit preferences among outcomes from older adults starting CT. Methods: This is a secondary analysis of an ongoing prospective study aimed at identifying and addressing vulnerabilities in older adults (age ≥65) starting CT (NCT02171034). Patients completed 3 tools assessing preferences in health outcomes: 1) Health Outcomes Tool: rates the relative importance of 4 outcomes (survival, function, freedom from pain, and freedom from symptoms) using a visual analog scale (VAS); 2) Now vs. Later Tool: rates the relative importance of QOL at 3 times: today, 1 year (y) in the future, and 5y in the future using a VAS; and 3) Attitude Scale: rates subjects’ agreement with statements related to outcomes. We measured the proportion of patients reporting other outcomes being “as important” or “more important” than survival and studied their characteristics. Results: 121 patients (median age 71y, 47% male, 72% Stage IV, 31% gastrointestinal cancer) were included. 52% had poor physical function, 54% needed help with instrumental activities of daily living (e.g., cooking or transportation), and 73% had poor social support. On the Health Outcomes Tool, 44% rated other outcomes as more important than survival. On the Now vs. Later tool, 59% considered current QOL more/important than QOL at 1y, and 58% considered current QOL more/important than QOL at 5y. On the Attitude Scale, 62% strongly agreed with: “I would rather live a shorter life than lose my ability to take care of myself” and 81% agreed/strongly agreed with: “It is more important to me to maintain my thinking ability than to live as long as possible”. Patients with good physical function and/or good social support were more likely to consider survival as the most important outcome, regardless of stage. Conclusions: Half of older patients rated other outcomes (particularly cognitive ability) as being more important than survival. Eliciting which outcomes are the most important for older patients can help define treatment goals and improve shared decision-making.

10011 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM
Relationship between preoperative geriatric frailty and need for postoperative intensive care unit admission and subsequent short- and long-term outcomes. First Author: Armin Shahrokni, Memorial Sloan Kettering Cancer Center, New York, NY.

Background: The relationship between age-related impairments in geriatric surgical patients and the need for postoperative intensive care unit (ICU) admission and subsequent outcomes is largely unknown. Methods: Since 2015, Memorial Hospital surgical services have referred cancer patients age 75+ to the Geriatrics Service for preoperative evaluation including the eRFA (Shahrokni et al., JNCCN, Feb 2017). The eRFA has 13 items; the Karnofsky Performance Scale, basic and instrumental activities of daily living, Timed Up and Go test, history of falls, social activity level, social support, distress level, depression, cognitive impairment, polypharmacy, weight loss, and number of comorbid conditions. In order to develop a scoring system, we performed a univariate & multivariate analysis of the correlation between these variables, the frequency of ICU admission, and the likelihood of 12-month mortality among ICU survivors. Results: 1164 patients (median age 79) were evaluated prior to surgery after which 53 patients (4.6%) were admitted to the ICU. Five eRFA factors were associated with ICU admission: > 4 comorbid conditions, weight loss > 10 pounds, polypharmacy, limited social activity, and high distress level. The median number per patient of these 5 impairments in our cohort was 2. In a univariate analysis, frail patients (> 2 of 5 impairments) were more likely to be admitted to the ICU than fit patients (≤ 2 of 5 impairments) (OR = 3.42, p < 0.001). The correlation persisted after adjusting for age, gender, ASA performance status, duration of surgery, and preoperative albumin level (OR = 2.87, p = 0.013). The one-year mortality of patients not needing ICU care was 1.8% for fit patients and 5.7% for frail patients. The one-year mortality of patients needing ICU care was 9.4% for fit patients and 20.4% for frail patients. Conclusions: Frail patients are at higher risk for postoperative ICU stay compared to fit patients. 1 out of 5 frail patients age 75+ dies within 1 year after ICU stay. Future studies should assess the effectiveness of interventions aimed to improve the long-term outcomes of geriatric ICU survivors.

10010 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM
Quality of life (QoL) in older patients (pts) with cancer and prognostic factors for QoL decline. First Author: Lare Decoster, UZ Brussels, Brussels, Belgium.

Background: QoL is an important outcome parameter for older pts with cancer. This study aims to investigate baseline QoL and its evolution during treatment in older pts with cancer and to determine prognostic factors for QoL decline. Methods: A prospective Belgian multicentre (n = 22) study was performed. Pts ≥70 years with a malignant tumor and abnormal G8 screening tool (≥14/17) underwent geriatric assessment (GA) and baseline QoL evaluation using the European Organization for Research and Treatment Quality of Life Questionnaire core 30 (EORTC QLQ-C30) Global Health Status Scale, with follow up at 2-3 months. QoL change was defined as the difference between follow-up and baseline QoL score and categorized in three groups: decline (< -10), improvement (> 10) and no change (≥10 and ≥-10). Uni- and multivariate regression was performed to determine factors associated with baseline QoL and with QoL decline (level of significance at p = 0.05). Results: 3673 pts with abnormal G8 and QoL data available at both time points were included in the present analysis. In multivariate analysis, baseline QoL was significantly worse with decreasing age, poor ECOG-PS (≥2 vs 0/1), higher stage (reference stage I) and non-geriatric domains such as functional status by instrumental activities of daily living, pain, fatigue, mental status and nutritional status. Pts with tumors of the digestive system, gynaecological system and thorax presented statistically lower baseline QoL compared to pts with breast cancer, (reference group) (p = 0.030; p = 0.017 and p = 0.026 respectively). The condition of treatment (chemotherapy, pain management, improvement in QoL) was not a predictor of QoL decline (1037 pts 35%) and a decline in 838 pts (28.2%). In multivariate analysis, stage, baseline pain and fatigue, malnutrition and absence of comorbidities were prognostic for QoL decline. Conclusions: Our study demonstrates that QoL improves in 1/3 of older pts with cancer during treatment, indicating that treatment of cancer can benefit QoL in older people. On the other hand, QoL declines in 1/4 of older pts during cancer treatment and we identified prognostic factors for QoL decline in these pts. Directed interventions against pain, fatigue and malnutrition may subsequently improve QoL for these pts.
Impact of cancer on employment and finances in young adult (YA) survivors.

First Author: Tyler Garrett Ketterl, Fred Hutchinson Cancer Research Center, Seattle, WA

Background: YA survivors face challenges unique from those of childhood cancer or older adults. The potential impact of cancer or its treatment upon employment and financial burden in YAs are not fully known. Methods: Eligibility included diagnosis of malignancy between ages 13-39, 1-5 years from diagnosis and ≥1 year from therapy completion. Participants were randomly selected from tumor registries of 7 participating sites and asked to complete an online patient reported outcomes survey. Diagnostic/treatment data were abstracted from medical records. Results: Subjects included 872 survivors, 72.3% female, grouped into 4 diagnostic categories: breast (n = 209), thyroid (n = 104), lymphoma (n = 91) and other (n = 332) including brain tumors. Most survivors (736, 84.4%) reported working for pay at some time during diagnosis and survey completion and 517 (70.2%) reported a physical component to their job and that their cancer/treatment interfered with their ability to perform the physical (58.6%) or mental (54.2%) job tasks required. Males were more likely to be working for pay any time after diagnosis (OR 1.6, 95% CI 1.0-2.5, p = 0.05). Survivors treated with surgery alone were less likely to have impairments limiting their ability to perform physical (OR 0.5 95% CI 0.3-0.7, p < 0.005) or mental tasks (OR 0.4, 95% CI of 0.3-0.5, p < 0.005) at work compared to those treated with chemotherapy +/− radiation. 56.6% reported taking extended paid or unpaid time off from work, or made a change in their hours, duties or employment status and 95.6% of those reported this was related to their cancer/treatment. Unpaid time off from work was taken by 286 survivors (38.9%) with 193 (34.7%) of those taking > 6 months unpaid time off. Survivors in the “other diagnosis” category were significantly more likely to have taken unpaid time off work (OR of 1.5, 95% CI 1.0-2.2, p = 0.015). Nearly 1/3 of all survivors reported that they/their family borrowed money or went into debt because of cancer/treatment with 47.2% with debt borrowed > $10,000 (33 (4.9%) reported bankruptcy. Conclusions: In YA survivors, cancer/treatment has a significant impact on the physical and mental activities of their jobs and many report ongoing work limitations ≥ 1 year from therapy completion.

Risk of chronic comorbidities in survivors of adolescent and young adult cancer (AYA).

First Author: Chun Chao, Kaiser Permanente Southern California, Pasadena, CA

Background: Data needed to develop age-appropriate survivorship care guidelines for AYA cancer are lacking. Using a retrospective cohort design, we described risk of chronic comorbidities in AYA cancer survivors. Methods: 6,778 0-3 year survivors of cancers diagnosed at age 15-39y at Kaiser Permanente Southern California between 2000-2012 were included. A non-cancer comparison group (N = 87,737) was matched to survivors by year of diagnosis and sex, race/ethnicity and zip code of residence. Multivariate Poisson regression was used to evaluate the associations between chemotherapy exposures (mutually adjusted) and risk of selected comorbidities. Results: Median age at cancer diagnosis was 33y; 35% were male; 42% were non-Hispanic white. The most common cancer types were thyroid (16%), breast (16%) and melanoma (10%). Comparison with non-cancer subjects; see Table 1. Within cancer survivors: chemotherapy exposure was associated with multiple comorbidities. The largest IRR was found for methotrexate use and avascular necrosis (AN) (IRR = 15.5); followed by ifosfamide and chronic kidney disease (IRR = 8.3); and bleomycin and pulmonary fibrosis (IRR = 4.7). Conclusions: These data provide basis for identifying high-risk individuals for population-based targeted surveillance.

<table>
<thead>
<tr>
<th>IRR</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Heart Failure</td>
<td>1.8 (1.4-2.2)</td>
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<tr>
<td>Corneal Artery Disease</td>
<td>1.6 (1.1-2.3)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.3 (2.2-4.5)</td>
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<tr>
<td>Dyslexia</td>
<td>1.3 (1.2-1.4)</td>
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<tr>
<td>Hypothyroidism</td>
<td>1.3 (1.2-1.4)</td>
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<tr>
<td>Premature Ovarian Failure</td>
<td>2.9 (1.6-5.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.1 (1.0-1.3)</td>
</tr>
<tr>
<td>Divorce</td>
<td>1.5 (1.4-1.7)</td>
</tr>
<tr>
<td>Thyroid Disorders</td>
<td>2.1 (1.8-2.4)</td>
</tr>
<tr>
<td>Headaches</td>
<td>2.0 (1.9-2.4)</td>
</tr>
<tr>
<td>Vision Loss</td>
<td>1.4 (1.2-1.7)</td>
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<tr>
<td>Asthma</td>
<td>1.2 (1.0-1.5)</td>
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<tr>
<td>COPD</td>
<td>2.3 (1.3-4.2)</td>
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<tr>
<td>Severe depression/anxiety</td>
<td>2.7 (2.3-3.1)</td>
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<tr>
<td>Chronic Liver Disease</td>
<td>2.4 (2.0-2.8)</td>
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<tr>
<td>Renal failure</td>
<td>2.5 (2.0-3.0)</td>
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<tr>
<td>Avascular Necrosis</td>
<td>8.3 (4.6-14.9)</td>
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<tr>
<td>Fracture</td>
<td>2.1 (1.6-2.8)</td>
</tr>
<tr>
<td>Joint Replacement</td>
<td>3.9 (2.4-6.2)</td>
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<tr>
<td>Osteoporosis</td>
<td>9.0 (3.9-21.0)</td>
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</tbody>
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IRR for cancer survivors in reference to non-cancer comparisons.

Scrambler therapy for established chemotherapy-induced neuropathy: A randomized phase II trial.

First Author: Charles L. Loprinzi, Mayo Clinic, Department of Oncology, Rochester, MN

Background: Pilot data support that Scrambler therapy may benefit patients with Chemotherapy-induced peripheral neuropathy (CIPN). Methods: Patients with CIPN for at least 3 months were eligible if the patient had finished previous chemotherapy. They were randomized to the Scrambler group (TENS) or to the Sham group. The first 10 patients were randomized, 25 per arm. Data are provided in the Table. P values are provided, understanding that this is not a well-powered phase III trial. Conclusions: These results support that Scrambler therapy decreases CIPN symptoms, to a moderate degree. Further exploration of this approach is indicated. Clinical trial information: NCT01290224.

<table>
<thead>
<tr>
<th>Item (higher scores are better)</th>
<th>Scrambler TENS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% reduction in selected pain/tingling scores, at 14 days</td>
<td>40% 20% 0.06</td>
<td></td>
</tr>
<tr>
<td>≥50% reduction in pain scores at 14 days</td>
<td>56% 29% 0.05</td>
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</tr>
<tr>
<td>≥50% reduction in tingling scores, at 14 days</td>
<td>48% 24% 0.08</td>
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<tr>
<td>14 day AUC pain reduction from baseline</td>
<td>25 16 0.08</td>
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<tr>
<td>14 day AUC tingling reduction from baseline</td>
<td>24 18 0.08</td>
<td></td>
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<tr>
<td>14 day AUC GIC neuropathy symptoms rating</td>
<td>17 5 0.001</td>
<td></td>
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<tr>
<td>14 day AUC pain rating</td>
<td>13 4 0.004</td>
<td></td>
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<tr>
<td>14 day AUC GIC overall QOL rating</td>
<td>14 4 0.006</td>
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<tr>
<td>10 week AUC pain reduction from baseline</td>
<td>11 13 0.72</td>
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<tr>
<td>10 week AUC GIC neuropathy symptoms rating</td>
<td>3 3 0.69</td>
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<tr>
<td>10 week AUC GIC pain rating</td>
<td>5 2 0.16</td>
<td></td>
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<tr>
<td>10 week recommendation of therapy to other patients (mean)</td>
<td>82% 39% 0.0001</td>
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Regenstrief Institute Inc, Department of Radiology, Indiana University, Indianapolis, IN.
Randomized, double-blind, phase III trial of monosialotetrahexosylganglioside versus placebo in GI cancer patients with oxaliplatin-induced peripheral neurotoxicity (TJMUCH-GI-001). First Author: Zhou Likun, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer Tianjin’s Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy Tianjin Medical University, Tianjin, China

**Background:** Neurotoxicity is the most common dose-limiting toxicity of oxaliplatin. There is no treatment for cumulative sensory neuropathy. This trial is designed to study the efficacy of Monosialotetrahexosylganglioside (GM1) in GI cancer patients with oxaliplatin-induced peripheral neurotoxicity (OIPN).

**Methods:** In this single center (TJMUCH), double-blind, phase III trial, patients were randomized in a 1:1 ratio to receive GM1 or placebo. Patients with OIPN persisting during or after oxaliplatin-based chemotherapy were eligible. The patients who remained on oxaliplatin after enrollment, received concurrent placebo or GM1 x 7 days with each chemotherapy cycle. The patients who stopped taking oxaliplatin, were treated with placebo or GM1 x 14 days every 3 weeks. GM1 was dosed at 60mg daily for every 3-week interval. The treatment was continued until visual analogy score (VAS) decreased by $\geq 30\%$ or stayed unchanged after two more treatments beyond completion of oxaliplatin. The primary endpoint was reduction of modified EORTC QLQ-CIPN20 score by $\geq 30\%$. Secondary endpoints were improvement of VAS by $\geq 30\%$, CTCAE and acute neurotoxicity grading between the two arms. There was no statistical analysis.

**Results:** From May 2015 to Dec 2017, 73 patients were enrolled in GM1 and 72 in placebo arm. 39 (53%) patients in GM1 and 10 (14%) in placebo arm achieved $\geq 30\%$ reduction in MCIPN20 score (RR = 0.85, 95% CI, 2.08-7.11; P < 0.0001). 36 (49%) patients in GM1 and 16 (22%) in placebo arm had $\geq 30\%$ improvement of VAS, 30 (41%) in GM1 and 22 (29%) in placebo arm achieved an increase of numbness/tingling in the past week) three times — within 1 week pre-paclitaxel, and within 1 month and 6 months post-paclitaxel. We used linear regression to test whether pre-paclitaxel patient-reported physical activity (Aerobic Center Longitudinal Study) predicted CIPN symptoms (either within 1 month or 6-months post-paclitaxel) controlling for pre-paclitaxel neuropathy, age, BMI, diabetes (yes/no), and cumulative paclitaxel dose. **Results:** CIPN symptom severity increased significantly from pre- to post-paclitaxel (+3.6; p < 0.001) and from pre- to 6-month follow-up (+2.08; p < 0.0001). This is a high level of development of CIPN considering that a 0.5-unit change is clinically significant. Each additional 10 min/day of physical activity pre-paclitaxel was associated significantly less severe CIPN symptoms at post-paclitaxel (r = -0.5; p < 0.0002) and 6 months follow-up (-0.25; p = 0.09). Each additional 10 years of age was associated with significantly more severe CIPN symptoms at post-paclitaxel (+0.8; p < 0.0001) and 6-month follow-up (+0.9; p < 0.0001) controlling for pre-paclitaxel neuropathy, physical activity, BMI, diabetes, and paclitaxel dose. **Conclusions:** Breast cancer patients who are more physically active pre-paclitaxel experience less severe CIPN immediately and 6 months post-paclitaxel. Physical activity may be especially important for older patients because CIPN severity increases with age. Clinicians prescribing paclitaxel should ask patients about pre-treatment physical activity levels because it may lead to greater treatment tolerability.

Efficacy and safety of additional olanzapine to ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting: A randomized, double-blind, placebo-controlled, crossover study. First Author: Veerena Vimolchalo, Division of Oncology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

**Background:** Currently, the antiemetic regimen consisting of dexamethasone and ondansetron plus a NK-1 antagonist for three doses per cycle is used in the prevention of chemotherapy induced nausea and vomiting (CINV) for highly emetogenic chemotherapy (HEC). However, palonosetron and NK-1 antagonists are costly and not accessible for all Thai patients. We sought to evaluate efficacy and safety of the additional olanzapine to ondansetron and dexamethasone for CINV prevention in patients receiving HEC.

**Methods:** We randomly assigned chemotherapy-naive patients receiving either anthracycline/ cyclophosphamide or high dose cisplatin (≥50 mg/m²) regimen, to receive olanzapine or placebo in addition to ondansetron and dexamethasone. All subjects were crossed over to another arm on second-cycle chemotherapy. The primary endpoint was complete response (CR) rate defined as no vomiting and no use of rescue drugs. **Results:** At first cycle, CR was 69% among the 32 patients receiving olanzapine and 25% among the 32 patients receiving placebo, p < 0.01. CR was significantly better with olanzapine than with placebo in acute phase (0-24 h) (75% vs. 31%, p < 0.001), delayed phase (24-120 h) (69% vs. 43%, p < 0.038). In analysis after two crossover antiemetic regimens, CR was improved in olanzapine group compared to placebo group in acute phase (72% vs. 33%, p < 0.001), delayed phase (67% vs. 38%, p < 0.001) and overall period (67% vs. 25%, p < 0.001). In crossover analysis using visual analog score (VAS), the patients with olanzapine had lower mean VAS in nausea (1.28 vs. 0.38, p < 0.001) and fatigue (5.25 vs. 4.58, p < 0.001) but higher mean VAS in appetite (2.5 vs. 1.55, p = 0.003) and sleepiness (3.26 vs. 2.2, p < 0.001). There were no grade 3 and 4 antiemetic-drug-related toxicities. Mean QT interval change did not differ between two groups (-4.30 ms vs. -1.86 ms, p = 0.69). The olanzapine combination was preferable to placebo in 52 of 60 patients (p < 0.001).

**Conclusions:** Without the NK-1 antagonists, the additional olanzapine to ondansetron and dexamethasone significantly improved CINV prevention and was safe in patients receiving HEC.

Treating anorexia in people with advanced cancer. A randomised, double blind, controlled trial of megestrol acetate, dexamethasone or placebo. First Author: David Christopher Currow, University of Technology Sydney, Sydney, Australia

**Background:** This multi-site, double blind, parallel arm, fixed dose phase III study compared megestrol acetate 480 mg/day, dexamethasone 4 mg/day and placebo for their net short-term effect on appetite and quality of life (QoL) in people with advanced cancer. **Methods:** Inpatients or outpatients seeing a palliative care team with anorexia for ≥2 weeks with a score ≤4 on a 0-10 numeric rating scale (NRS; 0 = no appetite, 10 = best possible appetite) were recruited. Participants were randomised to receive megestrol 480 mg, dexamethasone 4 mg or placebo daily for up to 4 weeks. Primary response assessment occurred at day 7, and responders were defined as having more than a 25% improvement in NRS compared to baseline. **Results:** There were 190 people randomised (megestrol acetate n = 61; dexamethasone n = 67, placebo n = 62). At week 1 (primary endpoint), 79% of participants in the megestrol group, 58% in the dexamethasone group and 55% in the placebo group (p = 0.067) were responders. No differences in weight, performance status or quality of life were reported. Treatment emergent adverse events occurred in the majority of participants (90-4%), and included altered mood and insomnia. Hyperglycaemia was more frequent in people on dexamethasone. **Conclusions:** Although there was little difference between treatment groups for the primary or secondary effectiveness endpoints, there was a consistent trend in secondary endpoints favouring megestrol acetate than dexamethasone or placebo. Subgroup analyses indicate megestrol acetate may be more effective in maintaining body weight for subjects whose appetite responded. Clinical trial registration: ACTRN126080005314.
Background: Various hydration protocols have been used to mitigate acute kidney injury (AKI) induced by cisplatin. The use of mannitol remains controversial however recent studies suggested that mannitol has a protective effect against cisplatin-induced nephrotoxicity. Methods: This was a retrospective observational study including patients who received at least one dose of cisplatin between September 2010 and December 2016 at the Centre Hospitalier de l’Université de Montréal. After approval by our IRB, we compared the risk of all grade AKI between hydration protocols with or without mannitol (12.5 g if cisplatin $< 75$ mg/m² or 25 g if cisplatin $> 75$ mg/m²). Patients received a total of 3 or 4 L of fluids (D5/0.45 NS or NS) according to the cisplatin dose. AKI was evaluated by comparing baseline serum creatinine (SCr) to the highest SCr levels between each cycle. Results: Of 1932 patients identified, 1821 were included in this study of which 658 received mannitol whilst 1163 received hydration alone. The risk of all grade AKI was significantly lower in the mannitol group for patients with lymphoma, gynecologic, upper gastrointestinal and urinary tract malignancies. No difference was seen for head and neck, lung, germ cell and others cancer (see table 1). In the subgroup of patients receiving cisplatin $< 75$ mg/m², mannitol reduced all grade AKI risk by 47% (HR 0.57, 95% CI 0.37-0.90), mortality (HR 0.31, 95% CI 0.13-0.72), GI (HR 0.91, 95% CI 0.38-0.94), UI (HR 0.87, 95% CI 0.50-1.47), and urinary tract cancer (HR 0.14, 95% CI 0.01 – 0.5)). Conclusions: Hydration protocols containing mannitol were associated with a significantly lower risk of all grade AKI compared to hydration alone. Therefore, mannitol should be added to hydration protocols with cisplatin especially those with doses $> 75$ mg/m².

All grade AKI for mannitol vs non-mannitol hydration.

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Hazard Ratio (95% CI) p value</th>
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<tbody>
<tr>
<td>Head and Neck (N = 543)</td>
<td>0.99 (0.71-1.36) p = 0.99</td>
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<tr>
<td>Lung (N = 45)</td>
<td>0.73 (0.28-1.90) p = 0.005</td>
</tr>
<tr>
<td>Gynecologic (N = 333)</td>
<td>0.50 (0.30-0.84) p = 0.033</td>
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<tr>
<td>Upper GI (N = 385)</td>
<td>0.83 (0.42-1.68) p = 0.383</td>
</tr>
<tr>
<td>Urinary Bladder (N = 90)</td>
<td>0.29 (0.10-0.77) p = 0.005</td>
</tr>
<tr>
<td>Lymphoma (N = 69)</td>
<td>1.15 (0.34-4.40) p = 0.856</td>
</tr>
<tr>
<td>Gastrointestinal (N = 69)</td>
<td>1.29 (0.62-2.7) p = 0.508</td>
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10022 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Survival of advanced cancer patients (ACP) receiving early inpatient palliative care (PC) compared to standard oncologic care (SOC) without palliative care. First Author: Fay J. Hlubocky, University of Chicago Medicine, Chicago, IL

Background: Palliative care has been described as significantly enhancing ACP quality of life, symptom control, and reducing healthcare costs. Increasing evidence has shown improved outcomes for hospitalized ACP including discharge status, transitions to end-of-life care, and overall mortality. Methods: In ACP cohort receiving either PC or SOC between Jan 2015-Dec 2015 were retrospectively analyzed for potential predictors associated with discharge and death. Demographics, diagnosis, discharge status, and survival from the time of discharge were compared between groups. Univariate and multivariate analyses were performed (e.g. log-rank survival and Cox proportional hazards regression). Results: Of a total of 810 patient encounters, 468 were admitted to PC and 342 to SOC. In comparison with SOC, PC were more likely to be younger (61.1±13.2 vs. 62.5±13.0, p = 0.02); AA (48% vs. 36%, p = 0.0045); female (50% vs. 40%, p = 0.005); shorter length of inpatient stay (6.7± 4.9 v. 6.2± 6.5, p = 0.01). Compared with SOC, ACP receiving PC were more likely to be discharged to: home (95% v. 45%, p = 0.01); healthcare facilities (e.g. skilled nursing, inpatient rehabilitation) (36.1% v. 20%, p = 0.04); and hospice (home and inpatient) (7.7% v. 5.8%, p = 0.02). PC had overall greater median survival from the time of discharge (106.8±99.5 v. 73.8±61.9, p = 0.03) compared to SOC. PC were less likely to die in hospital (HR 0.37, 95% CI 0.18-0.74, p = 0.001) and 1.2 times more likely to be discharged home (p < 0.0001). Home discharge was associated with longer survival (ratio = 0.34; 95%CI, p = 0.002). For PC, multivariate logistic regression revealed younger age (β < -0.5, p < 0.001); female gender (p = 0.004); and AA ethnicity (p = 0.003) as associated with home discharge. In hospice, age (β = 0.001) and disease severity (p = 0.0034) were independently associated with greater likelihood of death. Conclusions: Results from this simultaneous care program reveal a unique model of care such that early inpatient PC benefits younger and underserved ACP with distinct clinical characteristics and survival, with improved outcomes, compared to those receiving SOC.
Hospice use among Medicare fee-for-service (FFS) or managed-care organization (MCO) enrollees with leukemia and myeloma. First Author: Adam J. Olszewski, The Warren Alpert Medical School of Brown University, Providence, RI.

Background: Hospice services are “carved out” of Medicare MCO contracts and covered by FFS Medicare. This financially incentivizes MCOs to enroll their patients (pts) in hospice early, and may affect survival outcomes. We compared the use of hospice at the end of life (EOL) and associated overall survival (OS) among MCO and FFS Medicare beneficiaries with hematologic cancers, who are known to undergo hospice and need effective strategies to improve their EOL care. From the linked Surveillance, Epidemiology, and End Results-Medicare database, we selected pts with acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or myeloma who died in 2007-2011. We identified their MCO/FFS status before death, hospice use at EOL, and disenrollment from hospice before death. We compared binary outcomes in multivariable robust Poisson models, reporting relative risk (RR) adjusted for multiple sociodemographic characteristics. OS from diagnosis was compared in Cox models, reporting adjusted hazard ratios (HR) with 95% confidence intervals (CI). Results: Among 24,118 pts (median age 78 y; 43% women), 25% were enrolled in a MCO at EOL. MCO enrollees were 17% more likely to use hospice than pts with FFS Medicare (RR, 1.17; 95% CI, 1.14-1.21), consistent across histologies (Table). They were also less likely to use hospice services for < 3 days (RR, 0.82; 0.75-0.89). We found no difference in adjusted OS (HR, 0.98; 0.95-1.01), or in the rate of early hospice dis-enrollment (RR, 1.07; 0.91-1.27) between MCO and FFS enrollees. Conclusions: Compared with FFS enrollees, MCO enrollees with leukemia or myeloma use hospice more frequently and for longer, without any decrease in survival. Enhanced care coordination in MCO may contribute to more meaningful use of hospice among pts with these cancers, suggesting a novel strategy for improving quality of care at EOL in hematology.

Table:

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<tr>
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<th>AML</th>
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<th>Myeloma</th>
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<tbody>
<tr>
<td>Hospice at EOL, MCO / FFS</td>
<td>7,347</td>
<td>6,847</td>
<td>9,924</td>
</tr>
<tr>
<td>RR (95%CI)</td>
<td>1.18 (1.12-1.24)</td>
<td>1.15 (1.08-1.22)</td>
<td>1.18 (1.12-1.23)</td>
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<tr>
<td>&lt; 3 days on hospice, MCO / FFS</td>
<td>0.79 (0.64-0.87)</td>
<td>0.89 (0.74-1.06)</td>
<td>0.85 (0.74-0.98)</td>
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<tr>
<td>HR for OS (95%CI)</td>
<td>1.01 (0.95-1.08)</td>
<td>0.94 (0.88-1.00)</td>
<td>0.98 (0.94-1.04)</td>
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Impact of palliative care consults on racial disparity in do-not resuscitate (DNR) orders at an urban safety net hospital. First Author: Var Bhulani, University of Texas Southwestern Medical Center, Dallas, TX.

Background: Previous studies have suggested that racial disparities exist for DNR orders in cancer patients. We examined racial differences in DNR orders for pancreatic cancer patients in an urban setting safety net hospital with a high proportion of black patient population. Methods: Retrospective analysis was conducted of pancreatic cancer patient records seen at the Parkland Health and Hospital System, Dallas between 1/1999 - 9/2016. Cancer cases and receipt of palliative care were identified from prospectively maintained registries. Demographics, cancer characteristics, DNR order, were abstracted. All statistical analysis was done using IBM SPSS version 24. Results: A total of 455 pancreatic cancer patients were included; mean age was 61 years, 227 (50%) were female, 228 (50%) were white and 202 (44%) were black, 277 (61%) received a palliative care, and 29 (6.4%) had at least one ICU admission. There was no statistically significant difference in palliative care consults between whites and black patients. Do-Not-Resuscitate (DNR) order was placed for 140 (30.8%) patients within 60 days of death. DNR status was significantly associated with cancer stage, admission to the ICU and receiving a palliative care consult (p < 0.001). There was no difference in the rate of DNR order between white and black patients, 29.7% (68/229) white patients and 32.2% (65/202) black patients (p = 0.71). Additionally, age, sex, cancer site or histology were not associated with DNR order. Conclusions: In this single institution study of pancreatic cancer patients there was no racial disparity in DNR orders. This can be explained by a high rate of palliative referrals (61%) and a safety net system which improves access to care. Additional studies are needed to understand determinants of DNR order use. Systems based changes, such as early integration of palliative care and increased access to health services can reduce racial disparities in cancer patients.

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<th>Survival</th>
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<tr>
<td>% of Subjects (n = 168)</td>
<td>17.3%</td>
<td>11.3%</td>
<td>5.9%</td>
<td>19.6%</td>
<td>23.8%</td>
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<tr>
<td>Hospice LOS: Md</td>
<td>12.5</td>
<td>15</td>
<td>2</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>No Aggressive Tx (%)</td>
<td>75%</td>
<td>63%</td>
<td>10%</td>
<td>66%</td>
<td>64%</td>
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Multicenter randomized controlled trial for advanced cancer patients receiving parenteral nutrition (PN) versus oral feeding (OF). Results of AlimK study. First Author: Carole Bouleuc, Institut Curie, Paris, France

Background: The decision to use PN in patients with advanced cancer is controversial. There is lack of high evidence level demonstrating its interest and safety in this population. In case of refractory cachexia, PN interest would be to improve health-related quality of life (HRQoL) and to reduce certain symptoms caused by food intake without significant toxicity. AlimK (NCT02151214) study was performed to address this gap. Methods: We planned a prospective multicenter randomized controlled parallel-group phase IV trial, with a Zelen single-consent design for randomization. Intervention arm received PN whereas control arm were pursuing OF alone. Primary objective assessed PN influence on HRQoL deterioration free survival (HRQFS) of one of the 3 targeted scores of the EORTC QLQ-C15-PAL: global HRQoL, physical functioning and fatigue. HRQFS was defined as a definitive deterioration of 10 points at least compared to the baseline score, or death. A p-value < 0.0166 was considered statistically significant (Bonferroni adjustment) to ensure an overall bilateral alpha risk of 5%. Key secondary endpoints included overall survival (OS) and safety. Results: Between 07/2012 and 03/2017, 148 cancer patients were enrolled in 13 French centers. Informed consent was obtained for 111 patients: 48 (43%) in PN arm and 63 (57%) in OF arm. PN was refused by 8/48 (18%) patients. Among all patients, 98% were metastatic with life expectancy less than one year and 97% were still on anticancer treatment. Patients were malnourished with median weight loss over 6 months of -8.20 (range -26.5; 10). There was a trend favoring HRQFS in the OF group for global HRQoL (HR = 1.31 95%CI, 0.88-1.94, p = 0.18), physical functioning (HR = 1.58, 95% CI, 1.06-2.35 p = 0.024) and fatigue (HR = 1.19, 95%CI, 0.80-1.77 p = 0.34). Median OS was 3.12 (95% CI 2.7-4.14) months in OF arm vs 1.97 (1.18-3.06) in PF arm. There was a higher total adverse events in PN arm (52%) than in OF arm (41%). Conclusions: In this study PN did not provide clinical benefit for advanced cancer patients with numerically reduced OS and increased toxicity. More data will be shown about tolerance of PN and influencing factors on HRQoL scores. Clinical trial information: NCT02151214.

Randomized clinical trial of telephoned-based physical activity intervention in oncogeriatric patients. First Authors: Hauft, Amélie, 3rd Department of Internal Medicine, University of the Basque Country (UPV/EHU), Leioa, Bizkaia, Spain, Leioa (Bizkaia), Spain

Background: Cancer in older patient favors the loose of physical function. Physical activity could be a key factor to diminish the age and cancer-related decline. Methods: We conducted a multicenter open-label 12-month randomized clinical trial with two parallel arms. Onco-geriatric patients with histological confirmation for lymphoma or carcinoma requiring curative treatment were included. Participants were randomly assigned to an intervention (IG) or usual care group (UCG). The IG received individualized phoned physical activity advice. Subjects in the UCG received a booklet with the current national recommendations in physical activity. Results: 301 participants were eligible and randomized. The loose of physical function measured by the Short Physical Performance Battery (SPPB) was experienced likewise in both the IG and the UCG at one year. However, after two years significantly less participants within the IG than the UCG declined in the SPPB score among breast cancer participants (P = .006), females (P = .019), and those with normal nutritional status (P = .040). Linear mixed models showed similar results in both the IG and the UCG in the SPPB, gait speed, the level of physical activity measured using the self-reported International Physical Activity Questionnaire, and verbal fluency at baseline and after three, six, twelve, eighteen and twenty-four months (NS). Both the IG and the UCG showed similar results for falls, hospitalization, institutionalization, and death at one and two years (NS). Conclusions: Telephoned-based physical activity intervention were not effective to reduce the functional decline at one year, but significant differences in favor of the IG were observed over two years among females with breast cancer and good nutrition subgroups. Clinical trial information: NCT01432067.

Impact of patient reported functional limitation on overall survival in older adults undergoing autologous hematopoietic cell transplant (AutoHCT). First Author: Marmon F. Nawas, University of California San Francisco, San Francisco, CA

Background: The optimal means of assessing fitness for AutoHCT in older adults with hematologic malignancies is unknown. Few studies have evaluated the impact of patient reported function on AutoHCT outcomes.

Methods: Comprehensive geriatric assessment (GA) including the FACT-BMT quality of life tool was administered to 184 patients ≥50 years old (median age 61, range 50-75) at a median of 21 days prior to AutoHCT (range 1-186 days). Associations between GA/QOL metrics and post-transplant outcomes were evaluated using Cox regression. Results: The indication for AutoHCT was multiple myeloma / amyloid in 139 patients (76%), lymphoma in 39 patients (21%) and acute leukemia in 6 patients (3%). Median progression-free survival (PFS) was 28 months, and median overall survival (OS) was not reached (median follow up time 23 months). Both PFS and OS were significantly associated with 5 GA components: limitation in instrumental activities of daily living (IADL), patient reported Karnofsky performance status (KPS), and FACT physical, functional and BMT subscale scores (Table). In multivariable analysis, each GA component was adjusted for known prognostic factors (age, provider reported KPS, disease status, comorbidity index). Three components – IADL limitation, patient reported KPS, and FACT-BMT physical subscale score – remained predictive of both PFS and OS. Age was not associated with PFS or OS. Conclusions: Importantly, chronic age is not associated with outcomes in this population.

The value of inflammatory markers in predicting overall survival in older adults with cancer. First Author: Tomohiro F. Nishijima, New York University, New York, NY

Background: The widely studied inflammatory markers, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and lymphocyte monocyte ratio (LMR), are associated with survival outcomes in patients with various cancers. However, little is known about the value of these markers in older cancer patients, especially in relation to traditional prognostic factors, such as age and Karnofsky Performance Status (KPS), and a geriatric assessment (GA) derived scale that is predictive of overall survival (OS) [Nishijima, J Geriatr Oncol. in press]. Methods: Our sample includes 144 patients age ≥65 years with solid tumor (Carolina Senior Registry NCT01137825) who completed a GA within 3 months of their date of diagnosis in 2010 - 2014 and had pretreatment CBC with differential. Patients were followed for death from any cause for a median of 2.5 years, during which 54 patients died. NLR was dichotomized at the upper limit of normal 3.5 [ Forget, BMC Res Notes 2017] while PLR and LMR were dichotomized at the median. The 3-item GA-derived prognostic scale (score ranging 0-3) consisted of (1) "limitation in walking several blocks", (2) "limitation in shopping", and (3) > 5% unintentional weight loss in 6 months. Univariable and multivariable Cox proportional hazards models evaluated whether NLR, PLR and LMR were independently predictive of OS. Results: Median age was 72 years, 53% had breast cancer, 27% had stage 4 cancer, 14% had KPS < 80, 11% received less intensive treatment than standard treatment for stage and 39% had NLR > 3.5. In the univariable survival analyses, higher NLR (hazard ratio (HR) = 5.08, 95% CI; 2.85-9.07, p < 0.001, 2-year OS; 43% vs 86%), higher PLR (HR = 2.10, 95% CI; 1.20-3.67, p = 0.009, 2-year OS; 60% vs 79%) and lower LMR (HR = 2.11, 95% CI; 1.21-3.66, p = 0.025) were associated with 5 GA components: limitation in any one of three patient reported measures of functional status is independently associated with inferior PFS and OS, even when adjusting for known prognostic factors. Importantly, chronologic age is not associated with outcomes in this population.

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10033 Poster Session (Board #21), Mon, 1:15 PM-4:45 PM
Geriatric comanagement and surgical outcomes of older cancer patients. First Author: Armin Shahrokni, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Perioperative Geriatric Comanagement may improve surgical outcomes of older frail cancer patients. We present our 3 year experience with perioperative geriatric comanagement & the electronic Rapid Fitness Assessment (eRFA) at Memorial Hospital (MH). Methods: Since 2015, MH surgical services referred cancer patients age 75+ to the Geriatrics Service for preoperative evaluation including the eRFA (Shahrokni et al, JNCCN, Feb 2017). The eRFA score (0 to 13) is based on 1 point for impairments in the Karnofsky Performance scale score, dependency for basic and instrumental activities of daily living, Timed Up and Go test, history of fall, limited social activity, poor social support, presence of distress, depression, and cognitive impairment, polypharmacy, weight loss, and > 4 comorbid conditions. These patients were then co-managed by the geriatrics and surgical services while hospitalized. We compared the short- and long-term surgical outcomes of frail patients with fit patients. Results: 2291 patients (median age 79) had perioperative geriatric comanagement in 2015-17 with 1175 (51.3%) requiring hospitalization after surgery (average length of stay = 7 days). The median eRFA score was 5 (IQR 3-8). 30 day minor & major surgical complications, emegency room visit, readmission & mortality did not differ between frail patients (eRFA > 5) & fit patients (eRFA ≤5) in both the in- and out-patient surgical groups. Among patients requiring hospital stay, frailty was associated with a longer average length of stay (frail vs. fit; 7.7 vs. 6 days, P < 0.001). Frailty was associated with the higher likelihood of dying in 12 months after outpatient surgical procedure (OR = 5.27, p < 0.001) or inpatient surgical procedure (OR = 2.20, p = 0.002). Conclusions: Perioperative co-management by geriatricians & surgeons leads to similar short-term outcome between frail and fit patients. Future studies should assess the impact of prolonged geriatric comanagement on long-term outcomes of older cancer patients after surgery.

10034 Poster Session (Board #22), Mon, 1:15 PM-4:45 PM
Is there a role for older-patient-specific cancer clinical trials? A pooled analysis of 2277 older patients in adjacent breast cancer trials (Alliance A153715). First Author: Yuda Dao, Mayo Clinic, Rochester, MN

Background: Breast cancer incidence increases with age, but older patients tend to be underrepresented in clinical trials. To address this underrepresentation, this study examined the role of older-patient-specific trials – defined as those designed explicitly for older cancer patients. Methods: This study focused on patients 65 years of age or older (younger patients in age-unspecified trials were excluded). It included all Alliance phase III adjuvant breast cancer trials conducted from 1985-2012, encompassing older-patient-specific trials (CALGB 49907 and NCTCT 89-30-52; the latter was the only hormonal trial) and age-unspecified trials (CALGB 40101, NCTCT 9831, CALGB 9741, CALGB 9344, and CALGB 8541). Comparisons were based on trial type (older-patient-specific versus age-unspecified). Results: 2277 older patients were included (1014 from older-patient-specific trials; 1263 from age-unspecified trials). The cohort of older-patient-specific trials compared to the cohort of age-unspecified trials comprised a greater percentage of patients 75 year of age or older: 26% versus 6% (p < 0.0001), and 6 (65-89) and 68 years (65, 84), respectively, (p < 0.0001). Median overall survival (OS) was comparable: 12.8 years (95% confidence interval (CI): 11.9-13.7 years) and 13.5 years (95% CI: 12.9-14.1 years) in older-patient-specific trials and age-unspecified trials, respectively. After adjusting for age, estrogen receptor status, tumor size, and positive lymph nodes, OS remained comparable (hazard ratio 0.9; 95% CI: 0.8-1.0; referent: older-patient-specific trials; performance score excluded from the model due to missing data). Similar conclusions were reached for recurrence-free survival. Older-patient-specific trials had lower grade 2-5 adverse event rates (68% versus 73%; p = 0.03). Sensitivity analyses with only chemotherapy trials (NCTCT 89-30-52 excluded) yielded similar findings. Conclusions: Older-patient-specific trials appear to help address the underrepresentation of older patients in cancer clinical trials. Support: U10CA180821, U10CA180882.

10035 Poster Session (Board #23), Mon, 1:15 PM-4:45 PM
Patient-reported psychosocial needs and psychological distress: the influence of geriatric impairment and polypharmacy. First Author: Bonnie Leung, BC Patient and Survivor Care 525s, University of British Columbia, Vancouver, BC, Canada

Background: Little is known about how psychosocial factors and distress affect geriatric oncology patients and their survival. The study goals were: review patient-reported needs from all cancer types; identify factors associated with increased risk for psychological distress, defined as moderate to severe anxiety (ANX) and depression (DEP); and determine whether ANX and DEP are independent prognostic variables for patients ≥65 years. Methods: All patients ≥65 years, referred to BC Cancer from 2011 - 2016 who completed the Psychosocial Screen for Cancer (PSSCAN-R) and the Canadian Problem Checklist (CPC) within 6 m of cancer diagnosis were included in the study. Baseline demographics and disease characteristics were collected retrospectively. Univariate analysis using the X2 test were used to compare patient groups. OS was calculated using the Kaplan Meier method and compared using the log rank test. MVA conducted using Cox-regression analysis. Results: 26, 323 patients were included in the analysis. Baseline characteristics; female 50%; age 65-69 29%, 70-79 46%, ≥80 27%; GI 20%, Breast 18%, GU 16%, Lung 16%, Other 29%, MO 66%, MI 19%, MX 15%. Patients presenting with ANX and DEP were more likely to be female, aged 65 to 69, have lung cancer and metastatic disease (p-values < 0.001). Patients reporting emotional, informational, physical, and social/family problems or needs were more likely to present with ANX and DEP (p < 0.001). Median OS ANX 34 m vs no symptoms 43 m (p = 0.001) and DEP 31 m vs no symptoms 43 m (p = 0.001). MVA including age, sex, M status, ANX, DEP showed all variables were statistically significant; increasing age HR 1.05, male vs female HR 1.1, M1 vs MO HR 3.62, ANX vs no symptoms HR 1.30, DEP vs no symptoms HR 1.50. Conclusions: Geriatric oncology patients who are female, aged 65-69, have metastatic disease or lung cancer are at risk for distress. ANX and DEP are independent prognostic variables, negatively impacting survival. This vulnerable cohort of geriatric oncology patients should receive psychological support and follow up to better improve survival.

10036 Poster Session (Board #24), Mon, 1:15 PM-4:45 PM
Geriatric assessment to predict hospitalization frequency and long-term care utilization in older adult cancer survivors. First Author: Grant Richard Williams, University of Alabama at Birmingham, Birmingham, AL

Background: Geriatric assessments (GA) assess physiologic age in older adults; however, the association between GA identified impairments and long-term healthcare utilization in older cancer survivors remains unknown. Our objective was to evaluate whether a GA performed at cancer diagnosis was predictive of hospitalizations and long-term care (LTC) utilization in older adult cancer survivors. Methods: Older adults within the Carolina Senior Registry (NCT01137825) with GA performed between 3 months before and up to 6 months after diagnosis were included (n = 125). Patients with fee-for-service coverage were linked to Medicare claims. Hospitalizations and LTC utilization (skilled nursing or assisted living) were identified up to 5 years after their diagnosis, death, or 12/31/2013. GA risk measures (prefrail/frail status, impaired Instrumental Activities of Daily Living [IADL], limitations in climbing stairs, prolonged Timed Up and Go [TUG], > 5% unintended weight loss) were assessed in separate Poisson models estimating the relative risk (RR) for hospital and long-term care visits, controlling for person-time, age, and Charlson comorbidity score. Results: Participants median age of 74 years, majority female (80%), and white (89%). Most common malignancies were breast (64%) and lung cancer (8%); predominantly early stage disease (stage 0-I = 77%). During follow-up 41 (33%) participants were hospitalized and 20 (16%) received LTC. Prefrail/frail status (RR 2.5, p < 0.001), IADL impairment (RR 5.47, p < 0.001), and limitations in climbing stairs (RR 2.94, p < 0.001) were associated with increased hospitalizations. Prefrail/frail status (RR 1.86, p < 0.001) and DEP 31m vs no symptoms (RR 2.5, p < 0.001), IADL impairment (RR 5.47, p < 0.001), and limitations in climbing stairs (RR 2.94, p < 0.001) were associated with increased hospitalizations. Prefrail/frail status (RR 1.86, p < 0.001), IADL impairment (RR 4.58, p < 0.001), presence of falls (RR 6.73, p < 0.001), prolonged TUG (RR 5.45, p < 0.001) and limitations in climbing stairs (RR 2.94, p < 0.001) were associated with increased hospitalizations. Prefrail/frail status (RR 1.86, p < 0.001), IADL impairment (RR 4.58, p < 0.001), presence of falls (RR 6.73, p < 0.001), prolonged TUG (RR 5.45, p < 0.001) and limitations in climbing stairs (RR 2.94, p < 0.001) were associated with increased hospitalizations.

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Phase 2 randomized study of a walking intervention for radiation-related fatigue among older breast cancer patients receiving radiation. First Author: Noam Avraham VanderWalde, Department of Radiation Oncology, University of Tennessee Health Science Center/West Cancer Center, Memphis, TN

**Background:** This study’s purpose is to determine if an exercise intervention can decrease fatigue in older women receiving radiotherapy (RT) for breast cancer. **Methods:** A phase 2 randomized study was conducted in women ≥ 65 years with breast cancer receiving adjuvant RT. After informed consent, women were randomized to the intervention arm; the Walk with Ease (WWE) pamphlet, or the usual care arm (UC); a document describing the benefit of moderate exercise. Prior to RT patients completed an objective assessment of physical function using the Short Physical Performance Battery (SPPB), and questionnaires to assess fatigue, physical function, and other fatigue-related symptoms. All assessments were repeated at last week of radiotherapy and 1 month follow up. The primary outcome was change in fatigue as measured by the Total Disruption Index (TDI) of the Fatigue Symptom Index (FSI) over time. Secondary outcomes include change in level of activity (based on self-reported walking log), change in physical function as measured by the SPPB, and change in fatigue related symptoms. A Repeated Measures Mixed Linear Model was used to describe the change in outcomes over time. **Results:** Of the 54 patients accrued, 50 had complete data. Median age was 69 years (range 65-84). With the exception of hormone status, the baseline criteria were similar between study arms. Longitudinal modeling revealed no significant change over time in TDI between the two arms (p-value = 0.79). However, these models revealed that increased walking over time was associated with lower levels of fatigue (p = 0.04). Number of minutes walking per week increased in both arms (45 min/wk baseline to 432 min/wk end of RT, p = 0.01) and physical function improved statistically over time in both arms (p < 0.01) and both remained improved at follow up (p-value = 0.01 and < 0.01 respectively). **Conclusions:** This study demonstrated no benefit in fatigue with the WWE program. However, women in both arms increased their walking and had improved physical function during and following RT. Increased walking was statistically associated with lower fatigue scores during and after radiotherapy in this older group of women with breast cancer. Clinical trial information: NCT02434367.

**Impact of age on outcomes with PD-(L)1 blockade in patients (Pts) with non-small cell lung cancer (NSCLC), First Author: Morgan Lichtenstein, Massachusetts General Hospital, Boston, MA**

**Background:** As the population ages, it has become increasingly important to understand the risks and benefits of novel agents among older adults with cancer. Immunotherapy (IO) has revolutionized the treatment of advanced NSCLC, but less is known about the activity of PD-(L)1 blockade in older adults (>70 years). In these pts, immunosenescence may theoretically blunt the effectiveness of anti-PD-(L)1 therapy and/or alter its toxicity profile. We sought to assess the impact of age on clinical outcomes and rates of IO-related toxicities in pts with advanced NSCLC treated with anti-PD-(L)1. **Methods:** We retrospectively evaluated all pts with NSCLC at our institution treated with IO between 1/2013 and 10/2017. To assess progression-free survival (PFS) and overall survival (OS) across age groups, we performed Kaplan-Meier and Cox regression models adjusted for sex, ECOG, comorbidity scores, and the others for comorbidities. In our series treatment was well tolerated: only 5 pts had severe (G3-4) toxicity and no treatment-related death was reported. Adverse events were managed with corticosteroids and no pt needed additional immunosuppressive agents. **Conclusions:** anti-PD1 anti-tumor response was similar equally well tolerated even in late elderly advanced melanoma pts, whose access to treatment should not be restricted solely because of advanced age.

**Examination progression free survival (PFS), overall survival (OS), and toxicities of palbociclib in a geriatric population, First Author: Katherine Clifton, The University of Texas MD Anderson Cancer Center, Houston, TX**

**Background:** A recent FDA pooled analysis of patients treated with CDK4/6 inhibitors showed a trend towards improved PFS in the geriatric population, although this was not statistically significant. The study found more grade 3-4 events in the geriatric population, however the overall adverse event rate was low. The objective of this study was to analyze PFS, OS, dose reductions, dose delays and toxicity in a geriatric population receiving palbociclib as standard of care. **Methods:** Patients with metastatic breast cancer receiving palbociclib in any line of therapy were identified from a cohort of 845 pts at MDACC. Clinical, demographic, comorbidities, recurrence and survival data were collected. Dose delays, dose reductions, and toxicities were retrospectively extracted from the medical record. Data was analyzed using Fischer’s exact test for categorized variables and T test/Wilcoxon rank-sum test for continuous variables. PFS and OS were analyzed using the Kaplan Meier method. **Results:** 605 pts who met eligibility criteria were included. Pts receiving palbociclib on clinical trial were excluded. 160 pts were ≥ 65 years-old and 92 pts were ≥ 70 years-old. Pts ≥ 70 had a significantly increased number of dose reductions (p = 0.03) and dose delays (p = 0.02) compared to the younger pts. Pts ≥ 70 had significantly lower baseline GFR (p < 0.0001) and higher Charlson Comorbidity index (p < 0.0001). There was no significant increase in toxicity rate, including neutropenic fever, infections, or hospitalizations, in the ≥ 70 cohort (p = 0.3). The ≥ 70 cohort had a significantly improved PFS as compared to the younger cohort (p = 0.02). This was also true when an age cut-off of ≥ 65 was used (p = 0.009). There was no difference in OS in either cohort (age ≥ 70 p = 0.4, age ≥ 65 p = 0.9). **Conclusions:** Palbociclib was well tolerated in the geriatric population. Interestingly, the geriatric population was found to have improved PFS. Palbociclib has been shown to restore senescence signaling. Further studies are warranted to investigate if palbociclib may work synergistically with already enhanced senescence pathways in the geriatric population.
Background: Older patients with colon cancer are more vulnerable to chemotherapy toxicity and early death. Establishing simple scores specific for colon cancer (cc) patients able to predict severe chemotoxicity or early death is needed to select the best appropriate treatment. Methods: This multi-center study included cc patients aged ≥ 70 years receiving first-line adjuvant or metastatic chemotherapy. Five frailty markers (FM) - nutrition, physical activity, mobility, energy, grip strength, six domains of CGA (functional status, comorbidities, falls, nutrition, cognition, depression) and laboratory parameters were collected at admission. Logistic or Cox regression was used to examine at 500 days the association between FM, CGA, laboratory parameters and grade 3-4 toxicity or death, respectively. Results: 166 patients enrolled. Most were white (76%, n = 127) and male (56%, n = 93); mean age was 72 [range 65-91]; 57% female, 55% non-Hispanic white), with 31% GI, 13 with patient outcomes.

![Figure](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Risk</th>
<th>AUC ROC curve (≥ 50)</th>
<th>95% CI</th>
<th>P</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>0.747 ± 0.052</td>
<td>0.647-0.832</td>
<td>&lt; 0.0001</td>
<td>71.4</td>
<td>72.1</td>
</tr>
<tr>
<td>Death</td>
<td>0.908 ± 0.032</td>
<td>0.826-0.960</td>
<td>&lt; 0.0001</td>
<td>87.0</td>
<td>81.0</td>
</tr>
</tbody>
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Conclusions: These two simple and efficient scores will help clinicians to better identify cc older patients with increased risk of toxicity and/or premature death.

10043 Poster Session (Board #31), Mon, 1:15 PM-4:45 PM

Utilizing a practical tablet-based modified geriatric assessment in clinic for older adults with multiple myeloma (MM). First Author: Nitya Nathwani, Judy First Author: Wendy Beshansky, Massachusetts General Hospital, Boston, MA

Background: More than 60% of patients diagnosed with MM are > 65 years old and at greater risk for treatment toxicity. Comprehensive geriatric assessment predicts toxicity and survival but is difficult to add to already stressed clinical workflow. We have previously demonstrated feasibility of a tablet-based modified geriatric assessment (mGA). Here, we provide a final report of impact on decision-making and treatment outcomes. Methods: In this multi-site study, patients with MM > 65 years old completed a tablet-based mGA in clinic just prior to an oncology visit to discuss a treatment decision. Using the International Myeloma Working Group (IMWG) frailty model, a summary score, along with selected other GA and clinical data, was displayed to oncology providers at the beginning of the clinical visit. Results: 166 patients enrolled. Most were white (76%, n = 127) and male (56%, n = 93); mean age was 72 years (SD6.4; range 61-95). Based on IMWG criteria, patients were fit (39%, n = 64), intermediate fit (33%, n = 52) or frail (28%, n = 47), and 69% of providers agreed/strongly agreed that the mGA influenced the treatment recommendations for the patient. Treatments selected were more intensive for fit patients, while frail patients received lower intensity, with a reduced number of agents or a different route of administration ($\chi^2 = 20.81, p < 0.0001$). There was a significant association between fit status and transplant eligibility, with more fit patients being transplant eligible ($\chi^2 = 20.81, p < 0.007$). Outcome follow-up at 3 months on 144 patients indicated 39% (n = 56) of patients had a dose modification after the initial assessment and 18% (n = 26) discontinued therapy earlier than planned; 19.4% (n = 28) had a CTCAE grade 3-5 hematologic toxicity and 22% (n = 31) had a grade 3-5 non-hematologic toxicity, most commonly fatigue. Rates of toxicity were similar between patients considered fit, intermediate fit and frail. Conclusions: Results of a mGA presented to a provider at the point of care influenced treatment decisions. Most patients continued the prescribed therapy at 3 months, with relatively low rates of grade ≥ 3 toxicity. Further study is needed to compare outcomes with standard care. ClinicalTrials.gov Identifier: NCT03068637.

10044 Poster Session (Board #32), Mon, 1:15 PM-4:45 PM

Association between participation in religious activities and depression and anxiety in older patients with cancer. First Author: Yu Cao, City of Hope, Duarte, CA

Background: Older patients (pts) with cancer are at risk for depression and anxiety, which are often under-recognized. Participation in religious activities has been associated with better mental health in pts with cancer; however, data are conflicting and few studies focus on older pts. This study explores associations between participation in religious activities and depression and anxiety in older pts with cancer. Methods: This is a secondary analysis of a prospective study of pts age ≥ 65 with cancer. Prior to starting a new line of chemotherapy, pts self-reported if they felt depressed (yes/no on a 1-Question Yale Depression Screen) or anxious (score ≥ 6 on a 0-10 Likert Scale). Participation in public (e.g. church) and private (e.g. prayer) religious activities was measured via the Duke University Religion Index. High (≥ weekly public AND ≥ daily private), middle (≥ weekly public OR ≥ daily private), and low (< weekly public AND < daily private) religious participation groups were defined. Univariate and multivariate logistic regression analyses were conducted evaluating associations between participation in religious activities and depression and anxiety. Results: Of 458 pts (mean age 72 [range 65-91]; 57% female, 55% non-Hispanic white), with 31% GI, 19% breast, and 18% GU cancers, the majority (75%) had stage IV disease. Twenty-four percent (N = 110) reported anxiety, and 21% (N = 97) depression. Thirty-five percent (N = 161) reported ≥ weekly public, and 45% (N = 208) ≥ daily private religious activity. Both groups tended to report less anxiety (OR 0.66, p = 0.08; OR 0.68, p = 0.08, respectively); neither group was less likely to report depression (OR 0.79, p = 0.33; OR 1.05, p = 0.83, respectively). Combined, the high religious participation group (27.5%; N = 126) reported less anxiety on univariate (OR 0.59, 95% CI 0.35-0.95, p = 0.04) and multivariate (OR 0.51, 95% CI 0.28-0.92, p = 0.03) analyses, adjusting for age, gender, race, education, number of comorbidities, physical function, and social support, but not less depression (p = 0.46).

Conclusions: Among older pts with cancer, participation in both public and private religious activities is associated with less anxiety, but not less depression.
Prognostic benefit of taking statin and/or metformin in elderly patients with advanced non-small cell lung cancer: A nationwide population-based epidemiologic study. First Author: Young-Yoon Lee, Division of Hematology, Oncology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. Background: Comorbidities including dyslipidemia, diabetes and coronary heart disease are frequently found in elderly patients with advanced non-small cell lung cancer (NSCLC). Taking statin and/or metformin attenuates chronic inflammations, and could affect cancer outcomes. We aimed to evaluate prognostic impact of taking statin and/or metformin on survival in elderly patients with advanced NSCLC. Methods: Patients ≥70 years with advanced NSCLC incident from 2007 to 2012 were identified using reimbursement claims from Korea’s National Health Insurance Service Database, and exposures to statin and/or metformin were also documented. Cox proportional-hazards model and propensity score method matched analysis were used to estimate the impact of drug exposures on overall survival (OS). Results: Excluding 976 treated by upfront anti-EGFR, 7298 receiving palliative chemotherapy were included; statin preparations were taken in 13.0%, metformin preparations in 13.8%, both in 3.5%, and neither in 76.6%, respectively. Median OS of statin + / metformin +, statin - / metformin +, and statin - / metformin – users was 14.5, 12.9, 11.4 and 9.9 months respectively. By multivariate analyses, metformin was not statistically significantly associated with improved OS in statin user (HR 0.99; 95% CI 0.91-1.08; p = 0.819) and statin user (HR 0.99; 95% CI 0.85-1.16; p = 0.898) group. However, use of statin, regardless of metformin, was associated with improved OS (HR 0.80; 95% CI 0.74-0.86; p < 0.001). In propensity-matched cohort, survival benefit was noted not by use of metformin (HR 0.97; 95% CI 0.85-1.11; p = 0.661), but by use of statin (HR 0.83; 95% CI 0.73-0.95; p = 0.007). There was no significant effect model. Conclusions: We found that the about one-quarter of elderly NSCLC patients were taking statin and/or metformin. Exposures to statin could be the independent prognostic factor for better survival in elderly advanced NSCLC patients.

Inflamm-aging and the need to consider age in cytokine-patient-reported outcomes (PRO) relationships: The case of acute myeloid leukemia (AML). First Author: Shabbir M.H. Aliabadi, University Health Network, Toronto, ON, Canada. Background: Cancer-related fatigue (CRF) and poor quality of life (QOL) remain major problems in adults with AML during and after active treatment. Prior studies have linked cytokines to these PROs but have not examined age as a modifier. Ageing is associated with chronic inflammation which may alter the cytokine-PRO relationship. Methods: In 181 patients age 18 or older who underwent intensive chemotherapy for AML were assessed at 4 time periods (pre-treatment, 1 month, 6 months, 12 months). PROs were assessed with validated self-report questionnaires (FACT-F, EORTC QLQ-C30 global health) and blood was analyzed in duplicate for a panel of 32 cytokines using multiplexed protein immunomassays (Meso Scale Diagnostics). Log-transformed and centred cytokine values were regressed in models against CRF and QOL in separate models adjusting for age, gender, time, remission status, and haemoglobin. Models were stratified by age (< 60, 60+), and age and cancer (AML). First Author: Shabbir M.H. Aliabadi, University Health Network, Toronto, ON, Canada.

The impact of a positive cognitive impairment screen on conversations between patients, caregivers, and oncologists: A UR NCORP randomized study. First Author: Allison Magnuson, University of Rochester Medical Center, Rochester, NY. Background: The prevalence of CI and the utility of CI screening for community oncology practices are not well established. We used two tools to screen for CI in older patients (pts) enrolled onto a cluster randomized controlled trial and explored how CI screening influences conversations about cognition (CAC) between older pts, their caregivers, and oncologists. Methods: Pts aged ≥70 with advanced cancer were recruited (URCC 13070; PI: Mohile), CI screen, including Mini-Cog (MC) (normal/abnormal) and Blessed Orientation Memory Concentration Test (BOMC) (scored 0-28), were included in a Geriatric Assessment (GA). Practices were randomized to usual care (UC) vs GA intervention (GA summary provided to oncologists). Audio-recorded clinical encounters were transcribed by 2 blinded coders who coded CAC with a priori scheme as follows: cognition discussed (YN), type of concern, who initiated. MC and BOMC were compared and receiver operating characteristic (ROC) analyses identified BOMC score that best predicted abnormal MC. Results: Mean age was 77 (range 70-93); 2.2% screened positive by BOMC using standard score of >11 and 33.5% had abnormal MC. Pts with abnormal MC were more likely to have impaired activities of daily living (ADL) (34 vs 24), Instrumental ADL (64 vs 52%), Timed Up and Go (47 vs 34% and positive depression screen (28 vs 19%), (p < 0.05 for all). CAC occurred in 22% of encounters and were more common in the intervention arm (OR 4.64, 95%CI: 2.98-7.21, p < 0.001). Differences in CACs were most notable for pts with abnormal MC (71% in intervention group vs 6% in UC, p < 0.001). Oncologists were more likely to be the initiator of CACs in the intervention arm (99% vs 57%, p < 0.001). The most common concerns were memory (54%) and comprehension (15%). A BOMC cutoff of 4 was optimal for predicting abnormal MC (AUC = 0.73, sensitivity 59%, specificity 74%). Conclusions: CI screening can be useful information to guide oncologists caring for older pts, particularly when considering less intensive therapy.
10049 Poster Session (Board #37), Mon, 1:15 PM-4:45 PM
Development and temporal validation of a practical prognostic scoring system (ONCOGERIATRIC INDEX -OGI) based on the comprehensive geriatric assessment to predict early death in elderly cancer patients: A 929-patients cohort study. First Author: Jurema Telles O Lima, IMP - Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil

Background: Recognizing prognostic factors is important when evaluating elderly people with cancer to decide the appropriate treatment. The Oncogeriatric Index (OGI) was developed to predict early death (in 6 months) among elderly people with cancer, based on the Karnofsky Performance Status Scale, the Mini Nutritional Assessment and the Charlson Comorbidity Index. OBJECTIVES: To temporarily validate the OGI. Methods: We used a prospective cohort of cancer patients aged 60 or + years for GA n 605 (2015-2017) [training set]; 2016-2017: n 291 (validation set)) was performed during a six-month follow-up. Epidemiologic data and CGA (using 12 scales) before oncologic treatment were collected. The outcome was ED (within first 180 days). Cox’s proportional hazards model was used for the selection of prognostic factors. A prognostic score, the Onco Geriatric Index (OGI), was constituted of the number of abnormal CGA scales. Overall survival was estimated using the Kaplan–Meier method, and survival curves were compared using the log rank test. Predictive performance (calibration and discrimination) was determined. Results: There were 41 deaths among the 291 admitted patients. Patients who had three altered scales had 23.5 times higher risk of dying, adjusted for age, primary site of cancer and tumor staging (HR = 23.5, 95% CI 7.0-78.4; p < 0.001); those with two, 6.9 times (HR = 6.9, 95% CI 3.2-7.9; p = 0.001). The numbers of deaths predicted by the OGI were similar to those occurred, as well as a 6-month overlap of survival curves for each of the groups in the derivation and validation cohort, demonstrating that this prognostic model had an adequate predictive performance. Conclusions: Geriatric Index (OGI) is valid to evaluate elderly people with cancer in order to identify those at higher risk for early death.

10050 Poster Session (Board #38), Mon, 1:15 PM-4:45 PM
Diagnosing deficits in quality of life and providing tailored therapeutic options. Results of a randomized trial including 220 patients with colorectal cancer. First Author: Monika Klinkhammer-Schulze, Tumor Center Regensburg, Institute of Quality Management and Health Services Research of the University of Regensburg, Regensburg, Germany

Background: There have been increasing efforts to develop interventions that improve patients’ quality of life (QoL) in routine cancer care. The Tumor Center Regensburg has designed and implemented an intervention consisting of the systematic diagnosis and tailored therapy of QoL. The efficacy of the intervention has been demonstrated in a randomized trial of patients with breast cancer. To generalize and strengthen the external validity of these findings, this intervention system was applied to a cohort of patients with colorectal cancer. Methods: In a 2-arm randomized controlled trial, 2×110 patients with primary colorectal cancer were recruited in four colorectal cancer centers and randomized into an intervention group (IG) or a control group (CG). QoL (EORTC QLQ-C30 and QLQ-CR29) was measured in both arms before clinical discharge and at the 3-, 6-, 12-, and 18-months routine follow-up. A network of local healthcare providers of QoL therapy was established that encompassed physiotherapy, psychotherapy, pain therapy, social work, nutrition, stoma care, and fitness. In the IG, the treating physician received printouts of QoL results (QoL profile including 15 scales). If a need for QoL therapy was diagnosed (cutoff < 50 points in scales of 0-100), specific QoL therapies were recommended. In the CG, QoL was also measured, but the treating physician neither received QoL profiles nor recommendations on QoL therapy. Results: At clinical discharge, a need for QoL therapy was diagnosed in 92% (96/104) of IG patients and in 85% (88/104) of CG patients. At 12 months (primary endpoint), the intervention had reduced the rate of patients with a need for QoL therapy to 50% (41/82) compared to 66% (57/87) in CG (χ²-test p = .041, number needed to treat (NNT) = 9). Conclusions: First results of this intervention system were promising and further trials are necessary to confirm these findings and to possibly improve external validity of the IG QoL therapy during follow-up. The NNT was exactly the same as for patients with breast cancer, indicating high external validity of these results. Clinical trial information: NCT02321813.

10051 Poster Session (Board #39), Mon, 1:15 PM-4:45 PM
Patient and provider preferences for physician roles in breast cancer survivorship care. First Author: Archanjana Radhakrishnan, University of Michigan, Ann Arbor, MI

Background: Adoption of team-based models for cancer survivorship has lagged in part due to uncertainty around which physician—oncologist or primary care provider (PCP)—should lead which elements of delivery. We assessed patient, oncologist, and PCP preferences for who leads multiple aspects of survivorship after primary breast cancer treatment. Methods: SEER data from LA and Georgia was used to identify and survey women newly diagnosed with breast cancer between 2014-15 (N = 3672, 70% response rate). Patients and providers were each asked their preference (oncologist- vs. PCP-led) for which physician should lead cancer-related (mammograms) and non-cancer related survivorship care (other cancer screenings, general preventive care and comorbidity management). Distributions of patient and provider preferences was tabulated for each of the four services. The level of overall agreement amongst all three (%) was then calculated for each service (N = 237 triads). Results: Agreement within patient-oncologist-PCP triads for physician role preferences (Table) was highest for follow-up mammograms (81% of triads, majority preferred oncologist-led care) and comorbidity management (81% of triads, majority preferred PCP-led care), and intermediate for general preventive care (62% of triads, majority preferred PCP-led care). Agreement was lowest for other cancer screenings (32% of triads): 95% of patients, 62% of oncologists, and 57% of PCPs preferred oncologists lead other cancer screenings. Conclusions: Breast cancer patients, oncologists, and PCPs largely agreed on who should lead follow-up mammograms and comorbidity management, but disagreed most on who should direct other cancer screenings during survivorship. Tailoring efforts to clarify physician roles, especially for cancer vs. non-cancer related care, will be important to improve the quality of team-based models of survivorship care.

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<th>N = 237 Triads</th>
<th>Follow-up mammograms</th>
<th>Other cancer screenings</th>
<th>General preventive care</th>
<th>Comorbidity management</th>
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10052 Poster Session (Board #40), Mon, 1:15 PM-4:45 PM
E-cigarette use among patients of smoking-related cancers in the United States. First Author: Vladimirei Akintoba, Boston University Medical Center, Boston, MA

Background: The prevalence of e-cigarette use, and its impact on smoking cessation, among cancer survivors in the United States is unknown. We sought to estimate the prevalence of e-cigarette use, and examine its associations with smoking and quit attempts among survivors of smoking-related cancer survivors in the United States. Methods: We obtained data from the 2014–2016 annual cycles of the National Health Interview Survey. Our study sample comprised 2,561 adults with self-reported lifetime cancer patients from the bivariate analyses. Survey weights were applied in estimating the population-based prevalence rates, odds ratios (OR), and 95% confidence intervals (CI). Results: The prevalence of e-cigarette use among survivors of smoking-related cancer was 3.31% (95% CI 2.39%, 4.56%). Those aged 18-44 years had the highest rates of e-cigarette use of any age group (7.26%; 95% CI 2.80%, 11.72%; p-value for age: < 0.001). No associations were seen between e-cigarette use and gender, race, presence of other smoking-related comorbidities, or duration of survival. Current cigarette smokers were 31% as likely as never smokers to use e-cigarettes (OR 31.48; 95% CI 4.54, 218.16). Among current smokers, no association was seen between e-cigarette use and either the number of quit attempts or smoking cessation counselling by health professional in the prior year. Conclusions: E-cigarette use was highest among current smokers and relatively young survivors of smoking-related cancers. The lack of association between e-cigarette use and smoking quit attempts supports observations that e-cigarettes do not increase smoking quit rates. This is concerning, and highlights the need for further studies to define the impact of e-cigarette use on smoking cessation, and long-term outcomes of survivors of smoking-related cancers.
Efficacy of haloperidol versus olanzapine for control of chemotherapy induced nausea and vomiting. First Author: Sonya Dulal, National Academy of Medical Sciences (NAMS), Bir hospital, Kathmandu, Nepal

Background: Prevention of chemotherapy induced nausea and vomiting (CINV) is an essential part of cancer care. In resource scarce countries like Nepal, determining anti-emetic combinations of highest value is of utmost importance. The purpose of the study was to compare the efficacy and toxicity of Olanzapine (OLN) (a higher cost drug) and Haloperidol (HAL) (a lower cost drug) in the prevention of CINV in patients (pts) receiving highly emetogenic chemotherapy (HEC) in a developing country.

Methods: An IRB approved randomized phase II trial was performed in chemotherapy-naive pts receiving cisplatin >70 mg/m² or cyclophosphamide >500 mg/m² and doxorubicin >50 mg/m². Pts were randomized to receive OLN 10 mg orally on day 1 to 4 or HAL 1 mg orally on day 1 and 0.5 mg BID on days 2 to 4. Both groups received ondansetron (OND) 16 mg and dexamethasone (DEX) 12 mg intravenously on day 1. Use of additional antiemetics for CINV refractory to assigned treatment arm was permitted. From day 1 to day 5, pts recorded their nausea using the Edmonton Symptom Assessment Scale (ESAS). They also recorded their daily episodes of vomiting (number and when) and the use of additional antiemetics. The primary endpoint was complete nausea prevention (CNP) (ESAS - 0). The secondary endpoint was complete emesis prevention (CEP) without the use of additional antiemetics. Results: Sixty pts consented and were randomized, 30 in each arm. There was no difference in CNE during the overall period (day 1-5 post chemotherapy) between OLN and HAL (67.3% vs 70%; p = .070; 95% CI: 67.3% vs 73.3%). No difference was identified in the rate of CNE during the overall period (80% OLN vs. 76.6% HAL: p = .075) or in the acute period (91% OLN vs. 89% HAL: p = .177; 95% CI: 83.3% vs 81.7%). No difference in toxicities was noted between treatment arm. Conclusions: In this study, HAL was comparable to OLN in the control of CINV with no statistically significant difference in the primary and secondary endpoints suggesting it is the higher value option in pts receiving HEC in a resource scarce country.
Patient characteristics and long-term outcomes beyond the first 6 months after a diagnosis of cancer-associated thrombosis. 

First Author: Robert Adam Scott, Department of Internal Medicine, University of British Columbia, Vancouver, BC, Canada

Background: Cancer associated thrombosis (CAT) is a common complication of malignancies. However, little is known about the clinical course of CAT beyond the initial treatment period of 3 to 6 months. This information is important for clinicians and patients to inform their decision regarding duration of anticoagulation.

Methods: Health records from 523 consecutive patients managed at the Vancouver General Hospital Thrombosis clinic for CAT (excluding catheter-related thrombosis) between 2013 and 2015 were reviewed; 327 were alive at 6 months post initial CAT diagnosis. Patient and cancer characteristics, objectively documented recurrent venous thromboembolism (rVTE), clinically relevant bleeding (CRB), and overall mortality of this “survivor” cohort over month 6 to 24 are described.

Results: In the 6 month survivor cohort, patients were followed for a median of 605 days (range 1 to 730) and 85.9% had at least 24 months of follow-up or died. Patient characteristics at 6 months are summarized (Table). Anticoagulation was continued in 68.8%, with a median duration of 93 days; 54.3% of patient-days were on anticoagulation. In the 6 to 24 months after the initial CAT diagnosis, there were 34 rVTE in 30 patients (9.2%; 95% CI 6.3–12.8) and 16 CRB in 14 (4.3%; 95% CI 2.4–7.1) patients, corresponding to 2.9 rVTE per 100 patient-days and 1.4 CRB per 100 patient-days of follow-up. Twenty-one (61.8%) rVTE events and 11 CRB episodes (68.8%) occurred on therapeutic anticoagulation. Over the 18 months, 141 (43.1%; 95%CI 37.7 – 48.7) patients died. Causes of death were cancer (80.9%), rVTE (1.4%), bleeding (2.8%), other (7.8%), and unknown (7.1%). Three fatal bleeds and 2 fatal rVTE occurred while on anticoagulation. Conclusions: Patients with CAT who are alive at 6 months after VTE diagnosis remain at high risk of rVTE, CRB, and death.

Risk factors for the development of atrial fibrillation on ibrutinib treatment.

First Author: Robert William Lentz, Northwestern University Internal Medicine, Chicago, IL

Background: Ibrutinib is a Bruton’s tyrosine kinase inhibitor used for treating B-cell malignancies. The incidence of atrial fibrillation/flutter (AF) while on ibrutinib is reported to be 6-16%. The risk factors for incident AF while on ibrutinib are poorly defined. Methods: Charts were retrospectively reviewed to include patients treated with ibrutinib for any indication between July 2012 and June 2016. Those with existing AF were excluded. ECGs were manually reviewed to document AF. Patients were followed until incident AF, end of the medical record, end of ibrutinib treatment, or August 2017. Statistical analysis used chi-square and t-tests. Results: Of the 168 patients included, median age was 65.7 years, 70.2% were men, 68.5% were white, 60.7% had chronic lymphocytic leukemia, 13.1% had Waldenstrom macroglobulinemia, 11.3% had mantle cell lymphoma, and 14.9% had other cancer types. The incidence of AF was 11.9% after a median of 153 days of ibrutinib treatment. The median follow-up time for those without incident AF was 489 days. Age, coronary artery disease (CAD), heart failure (HF; systolic, diastolic, or either), and moderate/severe mitral regurgitation (M/S MR) were significantly different between patients with and without incident AF. Table 1 includes all evaluated parameters. Of those with HF or M/S MR, 45% and 100%, respectively, developed incident AF. Conclusions: In this large retrospective study, the incidence of AF on ibrutinib was higher in patients with older age, CAD, systolic or diastolic HF, and M/S MR. Every patient with M/S MR developed AF. Patients with these risk factors should be counseled on the risk of AF and monitored closely. An echocardiogram to evaluate for structural heart disease prior to initiating ibrutinib should be considered.

Risk factors for incident AF.

First Author: Julia Ellen Inglis, University of Rochester Medical Center, Rochester, NY

Background: Obesity and weight gain post-chemotherapy leads to increases in all-cause mortality, inflammation, and decreased quality of life but little is known about how obesity contributes to cancer-related fatigue (CRF). Inflammation is also associated with cancer-related fatigue (CRF). We conducted a secondary analysis of a large prospective, nationwide study to assess the impact of obesity on CRF levels in breast cancer patients. Methods: Female breast cancer patients (N = 565, aged 53-106.1) completed the multidimensional fatigue symptom inventory (MFSI) and the symptom inventory (SI) to measure CRF in breast cancer patients receiving chemotherapy. A longitudinal assessment to evaluate the impact of higher body mass index on cancer-related fatigue in breast cancer patients receiving chemotherapy. First Author: Julia Ellen Inglis, University of Rochester Medical Center, Rochester, NY

Platinum (Pt) is detectable for years after cisplatin treatment completion, but few studies have examined the extent of long-term exposure and associated co-morbidities after cisplatin treatment.

First Author: Omar El Charif, The University of Chicago, Chicago, IL

Background: Platinum (Pt) is detectable for years after cisplatin treatment completion, but few studies have examined the extent of long-term exposure to Pt and associated co-morbidities. Methods: Eligible testicular cancer survivors (TCS, n = 633) given 300 or 400 mg/m² cisplatin underwent lab tests and extensive audiometry, and completed questionnaires at follow-up (median 5 y, range 1-35). Since subject-level PK parameters cannot be estimated in cross-sectional designs, we regressed log(Pt) on dose and follow-up time in the entire cohort. Each subject’s PK trait was defined as the deviation from the average concentration-time curve (the residual). High values indicate Pt levels exceeding the expected value, i.e. slower elimination. The Pt reference interval (RI) used (central 95% of 147 non-Pt exposed patients) was 8-47 ng/L (JALM 2016; 1:2, 143). Linear regression at α = 0.05 was used for associations with co-morbidities. Hearing loss was quantified as the geometric mean of thresholds: 4-12 kHz (JCO 2016; 34, 2712). Sensory neuropathy was self-reported using EORTC-CIPN23. Cardiovacular (CV) burden was defined as angina, angioplasty, stroke, DVT, PE, or cerebrovascular accident (CVA) (used to estimate creatinine clearance [Ccr] with the Cockcroft-Gault formula) were measured. Results: Only 35 TCS (5.6%) were within the RI (median follow-up for this group: 20 y, range: 10-35). The estimated time to reach RI upper limit was 18 and 21 y after 300 and 400 mg/m² cisplatin respectively (time to reach CV burden: 46 and 57 y). Pt PK phenotype was strongly negatively associated with CCI (p < 10^-6), and positively associated with age (p < 10^-5), neuropathy (p = 0.002; age-adjusted p = 0.04), and HDL (age-adjusted p = 0.001). When adjusted for age, no associations were apparent with LDL, CV burden, or hearing loss. Conclusions: Circulating Pt persists for decades and may contribute to adverse outcomes. High Pt exposure significantly showed that hearing loss, but not neuropathy, is associated with cumulative cisplatin dose. In conjunction with our findings here, this suggests differential kinetics of ototoxicity and neurotoxicity. 

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Dyspareunia

3.84

3.53

Burning

Patients likely to experience ongoing moderate-severe symptoms following 1LT symptoms associated with recurrence. MOST could help triage the subset of AEs experienced post 1LT and can detect the re-emergence of abdominal related (MOST-Chemo) and psychological (MOST_Psych) symptoms (scales range 0–100, higher scores = greater symptoms). MOST subscales representing abdominal, (MOST-Abdo), chemotherapy-related (MOST-Chemo) and psychological (MOST_Psych) symptoms (scales range 0–100, higher scores = greater symptoms). Results: 812 patients who received ≥3 cycles and did not progress within 3m of completing 1LT were evaluable. MOST completion rate was 81%. MOST-Chemo symptom burden just before or < 7 days after the last cycle. Trajectory analyses showed that the symptoms improve significantly/resolve in many patients by 6 months. However, 40% reported persisting moderate symptoms and ~10% had severe symptoms to > 2 years. Patients who scored > 30/100 on MOST-Chemo at the end of chemotherapy were more likely to have persistent symptoms and the ~10% who scored > 50/100 reported ongoing severe symptoms to > 2 years. Among ~400 women with recurrence detected during follow-up, the MOST-Abdo symptom scores increased 2–3 months before the clinical diagnosis of progression. Conclusions: MOST is a brief patient-reported symptom index that complements clinical surveillance after 1LT. It was well-accepted with high compliance rates. It can quantify and track symptoms and AEs experienced post 1LT and can detect the re-emergence of abdominal symptoms associated with recurrence. MOST could help triage the subset of patients likely to experience ongoing moderate-severe symptoms following 1LT for appropriate interventions.

10064
Poster Session (Board #52), Mon, 1:15 PM-4:45 PM

Vaginal laser to improve symptomatic vulvovaginal atrophy and sexual function in breast cancer patients. Revealed in a randomised phase 2 study (IJAVA pl). Original research. First Author: Antonia Pearlman, Medical Oncology Department, Royal North Shore Hospital, St Leonards, Australia

Background: Vulvovaginal atrophy (VA) is a commonly reported issue among breast cancer patients (pts), and its etiology is multifactorial. The use of systemic and topical estrogens to treat VA has traditionally been discouraged in hormone positive breast cancer. Laser therapy has been reported to improve symptoms from VA in women with menopause. We aimed to assess the symptomatic benefit and the impact on sexual function of this treatment in women with early breast cancer (EBC). Methods: We performed a single arm investigator initiated pilot study of female EBC pts with symptomatic VA. 29 pts were recruited between February 2016 and August 2017. 3 pts were not enrolled; 2 had medical conditions that excluded them from treatment, 1 withdrew consent prior to commencing. Baseline demographic data was collected on all pts. A total of 3 vaginal fractional CO2 laser treatments were administered approximately 4 weeks apart for each pt. Questionnaires were completed at baseline, prior to each subsequent treatment and 4 weeks after completion of treatment. Our primary endpoint was symptomatic improvement of VA (dryness, itch, burning, dysuria and dyspareunia) at 12 weeks on a 10cm visual analog scale (VAS). Our secondary endpoint was improvement in sexual function using the Female Sexual Function Index (FSFI) at 12 weeks. Statistical analysis was performed with a Wilcoxon Signed Rank test. Results: 26 pts were enrolled in our study with a median age of 55. All pts were post-menopausal, 25 pts had received anti-estrogen therapy as a part of their breast cancer treatment. All pts received the 3 pre-planned laser treatments, and questionnaire compliance was high (98%). There was significant improvement in VA symptoms after treatment on a 10cm VAS (table 1) and in sexual function demonstrated on the FSFI (p < 0.001). Conclusions: EBC pts had improvement in all 5 domains of VA symptoms, as well as improvement in sexual function. Further randomized sham-controlled trials are needed to further assess this treatment.

10065
Poster Session (Board #53), Mon, 1:15 PM-4:45 PM

Pregnancies during and following trastuzumab (T) and/or lapatinib (L) in patients (pts) with HER2+ (HER2+) early breast cancer (EBC). Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. First Author: Matteo Lambertini, Institut Jules Bordet, Brussels, Belgium

Background: Limited data exist on the safety of using targeted agents in pregnant cancer pts. So far, only retrospective studies assessed the prognosis of pts having a pregnancy after prior EBC with no data in HER2+ pts. We aimed to evaluate the outcome of pregnancies occurring during or following T and/or L and the prognostic effect of having a pregnancy in HER2+EBC pts. Methods: NeoALTTO and ALTTO were randomized phase 3 trials in HER2+ EBC pts. Methods: NeoALTTO and ALTTO were randomized phase 3 trials in HER2+ EBC pts. In both trials, pregnancy information was prospectively collected. Pregnancy outcomes were compared between pts unintentionally exposed to T and/or L during gestation (exposed group) and those who got pregnant following T and/or L completion (not-exposed group). In the ALTTO trial, disease-free (DFS) and overall survival (OS) of pregnant pts were compared to those of pts ≤40 years without subsequent pregnancy with the Extended Cox Model With Time-Varying Covariates to account for guaranteed-time bias. Results: Out of 455 and 8,381 pts included in NeoALTTO and ALTTO, 92 pts (7 in NeoALTTO and 85 in ALTTO) had a pregnancy at a median age of 33 years (range 23-40). Pregnancy outcomes are reported in the table No difference in DFS in DFS (HR 1.24; 95% CI 0.58-2.6) or OS (HR 0.53; 95% CI 0.13-2.17) was observed between young pts with (n = 85 pts) or without (n = 1,392 pts) a pregnancy. Conclusions: Despite fewer live births were described in the exposed group, unintentional exposure to T and/or L during gestation does not seem to affect newborns’ outcomes upon treatment discontinuation. Having a pregnancy after HER2+ EBC does not appear to impact on DFS or OS. These data are of high relevance to counsel young EBC pts facing pregnancy-related issues. Clinical trial information: NCT00490139.

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Meta-analysis of the cardiac events in the adjuvant trastuzumab trials. First Author: Evandro De Azambuja, Institut Jules Bordet, Brussels, Belgium

Background: Cardiac dysfunction may occur in patients (pts) receiving adjuvant trastuzumab-based chemotherapy and long follow-up is required to better understand it. This meta-analysis of 3 adjuvant trials investigated the incidence, timing and risk factors for trastuzumab-associated cardiac events.

Methods: We have conducted an individual patient level data meta-analysis of 3 phase III trials investigating the role of 1 year of trastuzumab (T): HERA, NSABP B-31, and NCTCG 9831 (Alliance). Definitions of severe CHF (NYHA III or IV) and asymptomatic or mildly symptomatic (NYHA II) cardiac events were considered as per each study, as the precise definitions varied between studies.

Results: A total of 7445 pts were included in the analysis with a median follow-up in excess of 10 years (119.2-137.2 months): 4017 were in the T arm and 3428 were in the control arm (observation). Nearly all pts (97.5%) in the T arms received anthracycline-based chemotherapy. Table 1 summarizes the incidence of cardiac events in pts treated with 1 year adjuvant T. In total, 452 pts experienced a cardiac event (11.3%). Most of the cardiac events occurred during T use (78.1%). Adjuvant T was completed by 76.2% of pts and 10.0% of pts discontinued T due to a cardiac event. Significant baseline risk factors for cardiac events were LVEF normal but 8.0% (95% CI 7.1-8.9) and BMI (p < 0.001) with a baseline age (odds 5% increase per one-year increase, p = 0.001).

Conclusions: 1-year of T increases the risk of cardiac events, though most were asymptomatic or mildly symptomatic LVEF drops. As cardiac events may lead to interruption in treatment, careful risk-factor based patient selection, close follow-up and medical intervention (if necessary) are needed. Support: U10CA180868, -180822, -181095.

10067 Poster Session (Board #55), Mon, 1:15 PM-4:45 PM

Impact of body mass index (BMI) and weight change after treatment in patients (pts) with HER2-positive (HER2+) early breast cancer (EBC). Second author of the HERA trial, Dr. Anne-Britt Leenaars, University of Amsterdam, Netherlands

Background: Obesity is associated with worse outcomes in hormone receptor-positive (HR+) EBC. However, the association between obesity and prognosis in HER2+ EBC remains unclear. We aimed to determine the impact of BMI at diagnosis and weight change after treatment on the outcomes of HER2+ EBC pts. Methods: ALTO was a phase 3 trial of HER2+ EBC pts. BMI was collected at baseline and at the 2-year visit. WHO BMI categories were used: underweight < 18.5 kg/m², normal weight 18.5-24.9 kg/m², overweight 25-29.9 kg/m², and obese ≥30 kg/m². A change in weight from baseline of ≥5.0% and ≤5.0% was categorised as weight gain and weight loss, respectively. The impact of baseline BMI and weight change at the 2-year visit on disease-free survival (DFS), distant DFS (DDFS) and overall survival (OS) was investigated. Multivariate analyses adjusting for baseline pts and tumor characteristics were performed. The impact of weight change was assessed using a landmark analysis. Results: A total of 8,381 pts were included: 187 (2.3%), 7,979 (45.3%), 2,630 (32.1%), 1,707 (20.4%) were underweight, normal weight, overweight and obese at baseline, respectively. Compared to normal weight pts, being obese at diagnosis was associated with a significant worse DDFS (adjusted hazard ratio [aHR] 1.25; 95% CI 1.04-1.50) and OS (aHR 1.27; 95% CI 1.01-1.60), and a trend towards worse DFS (aHR 1.14; 95% confidence interval [CI] 0.97-1.32). Weight loss ≥5.0% at the 2-year visit was associated with poorer outcomes: DFS (aHR 1.34; 95% CI 1.05-1.71), DDFS (aHR 1.46; 95% CI 1.07-1.98) and OS (aHR 1.83; 95% CI 1.18-2.84). A similar trend, although not significant, was observed for weight gain ≥5.0%. Results were affected by hormone receptor status and menopausal status but not by anti-HER2 treatment. Grade 3-4 toxicities, pts with ≥1 serious adverse event and treatment discontinuation were more frequent in obese patients. Conclusions: In HER2+ EBC pts, obesity at baseline is a poor prognostic factor. Weight changes during treatment and follow-up impacts clinical outcomes: this calls for the need of dietary counselling and physical exercise in the context of survivorship programs. Clinical trial information: NCT00490139.

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**10070** Posteri Session (Board #58), Mon, 1:15 PM-4:45 PM

Independent prognostic value of the EORTC QLQ-C30 summary score on all-cause mortality: Results from the population-based PROFILES registry.

First Author: Olga Husson, Institute of Cancer Research, Sutton, United Kingdom

**Background:** Health-related quality of life (HRQoL) has been shown to be a prognostic factor for cancer survival in randomized clinical trials. It is questioned whether this association also holds in the “real world” and which HRQoL scores as measured by the EORTC QLQ-C30 are the best prognosticators. The aims of the present observational, population-based study were to: (1) investigate the association of HRQoL with all-cause mortality; and (2) determine which QLQ-C30 scores (the summary score covering all HRQoL domains, the global QoL or the physical functioning scale) exhibits the strongest association with all-cause mortality. **Methods:** Between 2008 and 2015, cancer patients (colon, rectum, melanoma, basal/squamous cell, endometrial, ovarian, prostate, thyroid, Hodgkin, non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma) were invited to participate in PROFILES (‘Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship’) disease-specific registry studies (response 69%). In this secondary analysis on a collated patient sample with complete data (n = 6895) multivariate Cox proportional hazard regression models were used to analyze the association between the QLQ-C30 scores and all-cause mortality. **Results:** In the overall regression model including sociodemographic and clinical variables, the QLQ-C30 summary score was associated significantly with all-cause mortality (HR = 0.77; 95%CI = 0.72-0.82; p < 0.01). In stratified analyses, significant associations between the summary score and all-cause mortality were found for colon, rectal, prostate cancer, non-Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma only. The summary score had a stronger association with all-cause mortality than the global QoL (HR = 0.82; 95%CI = 0.78-0.85; p < 0.01) and the physical functioning scales (HR = 0.81; 95%CI = 0.78-0.84; p < 0.01). **Conclusions:** Our results indicate that, in a population-based setting, HRQoL, as assessed by the summary score of the QLQ-C30, has prognostic value for a number of cancer patient populations above and beyond that provided by clinical and sociodemographic variables.

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**10072** Poster Session (Board #60), Mon, 1:15 PM-4:45 PM

Cardioprotective effect and safety of dexrazoxane in all breast cancer stages in patients treated with anthracyclines with or without trastuzumab: A systematic review and meta-analysis.

First Author: Ariane Macedo, Federal University of Minas Gerais, Belo Horizonte, Brazil

**Background:** Anthracyclines continue to rank among the most effective agents in Breast Cancer (BC) treatment, but its use is limited by a dose-dependent cardiotoxicity. Clinical studies have suggested that dexrazoxane (DZR) could reduce this toxicity, however it is unclear whether the effect is maintained during an adjuvant treatment followed by trastuzumab (TTZ). DZR is frequently used in the metastatic setting, when higher anthracycline cumulative doses are needed, but is often omitted in adjuvancy. We aimed to analyze whether DZR is cardioprotective in all BC stages in patients receiving anthracycline-based chemotherapy followed or not by trastuzumab. **Methods:** We performed a systematic review and meta-analysis. The review was registered in PROSPERO database. We searched data from 1990 to August 2017 in Cochrane Central Register of Controlled Trials, google scholar, MEDLINE/pubmed, LILACS, web of science, articles references and ASCO proceedings. Studies assessing congestive heart failure or cardiac event (cardiac function alterations without cardiac symptoms or hospitalization for cardiac reasons) as primary endpoints were included. Secondary outcomes were potential adverse effects of DZR on response (complete or partial, overall and progression free survival). Two reviewers independently performed the studies selection, risk of bias assessment and data extraction. Meta-analysis was done using random effect model for estimation of treatment effect. Heterogeneity was assessed by visual inspection of forest plots and by Q test.

**Results:** Nine studies were identified, including 1545 patients. DZR reduced heart failure incidence (RR 0.182, 95%CI: 0.80-0.413, p < 0.0001) and cardiac events (RR 0.262, 95%CI:0.169-0.407, p < 0.0001), without impact on response rate or survival. In a subgroup analysis of studies using TTZ after anthracycline, the overall benefit and safety of DZR was maintained. **Conclusions:** DZR delayed and reduced anthracyline induced cardiac toxicity, with or without trastuzumab. These findings may have significant implications for clinical practice.

**10073** Poster Session (Board #59), Mon, 1:15 PM-4:45 PM

Symptom burden and employment status in breast cancer (BC) survivors.

First Author: Ines Maria Vaite Duarte Luis, Dana-Farber Cancer Institute, Boston, MA

**Background:** At time of BC diagnosis, a large proportion of patients (pts) work. However, long term effects of BC and BC treatment are likely to impact employment status in follow up. **Methods:** The ECOG ACrIN protocol E5103 was a phase III trial that randomized BC pts to receive adjuvant doxorubicin, cyclophosphamide, and paclitaxel with either bevacizumab or placebo. Telephone based surveys were administered to all pts enrolled between 01/Jan/10 and 08/Jan/10 as part of a Decision-Making/QOL component. Symptom burden was evaluated using the Memorial symptom assessment scale’s (MSAS) global distress index (GDI), psychological and physical scores. Employment status was defined as 1) full time, 2) unemployed, disabled, or on medical leave 3) other (part time, homework, retired and other). Results presented here are part of the 18 months (m) post enrollment follow up. **Results:** Of 519 pts who had not withdrawn at a time point prior to 18 m, pt reported outcomes (PRO) were available from 460 (88.6%). At enrollment (at least 1 month after primary surgery), 38% of pts were working full time and 19% were unemployed, disabled or on medical leave. At 18 m, 42% of pts were working full time, but 13% were unemployed, disabled or on medical leave. Pts who were unemployed, disabled or on medical leave reported significantly worse symptom burden -Table. **Conclusions:** Among pts enrolled in a randomized controlled trial and treated with contemporary adjuvant chemotherapy, persistent symptomatology was associated with risk of decreased employment outcome. Future strategies are needed to support BC survivors at risk of decreased employment outcome. **Clinical trial information:** NCT00433511.
Background: More than 60% of postmenopausal breast cancer (BC) patients have symptoms of dyspareunia and vaginal dryness that often result from endocrine therapy, and are challenging to treat. Local vaginal estrogens are proven safe and effective for VVA treatment, but a major concern of BC patients is the potential risk of systemic absorption and adverse breast effects; and it is contraindicated by the FDA to be used in this population. TX-004HR, an investigational, vaginal, softgel capsule of soluble 17β-estradiol (E2), is being developed to treat menopausal VVA. Serum E2 levels following TX-004HR treatment, which significantly reduced moderate-to-severe dyspareunia and vaginal dryness, were determined and compared with that of the normal postmenopausal range. Methods: A 12-wk, randomized, placebo-controlled, phase 3, safety/efficacy study (REJOICE) was conducted in menopausal women with VVA. TX-004HR (4 or 10 µg) was administered daily for 14 d, then twice weekly for 10 wks. Serum E2 levels using validated GC/MS/MS and pharmacokinetics (PK) were determined in 17-19 subjects/ group on days 1 and 14 of daily dosing and day 84 of twice-weekly dosing. Results: The day 1, 0-h, mean ± SD, serum E2 level was 4.05± 2.69 pg/mL. The mean 24-h average levels on day 1 for the placebo, 4 µg, and 10 µg groups were 4.86±3.22, 3.92±1.46, and 5.76±3.13 pg/mL, respectively. Day 14 mean serum levels were lower than those on day 1: 4.25±2.17, 3.63±1.78, and 4.59±2.27 pg/mL, respectively. No accumulation of E2 was observed on day 14. On day 84 (maintenance phase), serum E2 levels were 4.36, 4.25, and 4.79 pg/mL, respectively. Primary efficacy and safety endpoints had been met for both doses. Changes in E2 levels from baseline to day 14 and day 84 were similar. Conclusions: TX-004HR (4 or 10 µg) improved VVA symptomatology, while maintaining serum E2 levels within the normal postmenopausal range. Although not yet studied in BC patients, further study in this population, especially in those taking aromatase inhibitors, is warranted. Clinical trial information: NCT02253173.
Hypogonadism and effects on quality of life in previously treated germ cell tumor survivors: A single-centre, non-randomized, prospective observational study. First Author: Nabin Khamal, Indiana University School of Medicine, Indianapolis, IN

Background: Prior studies have shown that around 12% to 16% Germ Cell Tumour (GCT) survivors can have subnormal serum testosterone level as well as up to 15% reported decreased health related Quality of life (QOL). It is important to identify the correlation of hypogonadism with QOL scores in survivors of GCT. Methods: This is a single-centre, non-randomized, prospective observational study in GCT survivors 18-50 yrs of age previously treated with Surgery and Chemotherapy or Surgery alone. Total testosterone was measured at baseline, 3, and 6 months. Patients completed a validated QOL questionnaire at baseline, 3, and 6 months. Patients could get supplemental testosterone as standard of care. Mean QOL scores were compared between two treatment groups and within each group between survivors with hypogonadism (serum testosterone level < 300 ng/dL) versus without (> 300 ng/dL). A two-sided independent-groups t test was used to compare means. Results: We evaluated 199 GCT survivors. At baseline, the prevalence of hypogonadism was 48.2% overall, 51.4% in Chem + Surgery group and 44.7% in surgery alone (CNI) (p = 0.39). Overall, there was no statistically significant difference in QOL scores between two groups, except the C group exhibited greater Aging Male Symptoms (AMS) on the AMS scale score than the CN group, at baseline and 6 months. However, compared to patients with testosterone > 300, patients with hypogonadism reported more fatigue (p = .04), worse sleep quality (p = .03) and worse general health (p = .006) at baseline. There was no statistically significant difference in depression (p = .33), or sexual functioning (satisfaction, p = .44; interest, p = .56; ability to have an erection, p = .23). There were no statistically differences in QOL between testosterone groups at 3 months or 6 months; however, sample sizes were small for participants on testosterone at 3 months and 6 months. Conclusions: GCT survivors treated with chemo exhibited greater Aging Male Symptoms compared to chemo naive group. Hypogonadism was associated with sleep disturbance, worse energy and lower general health QOL scores at baseline.

The OPAL (Ovarian Cancer Prognosis & Lifestyle) Study is a prospective study of Australian women diagnosed with OC from 2012-15. At baseline, they were asked if they had ever been diagnosed with A or D and if they took medication for this in the year before their OC diagnosis. At follow-up (3, 6, 9, 12, 24, 36 & 48 months after diagnosis) they complete the Hospital Anxiety and Depression Scale (HADS) and are asked about current medication use. Results: Of 893 women with ≥1 follow-up questionnaires, 373 (42%) reported clinical levels of anxiety (HADS ≥ 10, 18%) and/or depression (15%) and/or use of anxiolytic or antidepressant medications (A/D meds) (18%) on at least one occasion during the first 3 years after diagnosis. An additional 166 women (19%) reported subclinical A or D (HADS 8-10). Of those with clinical A/D or taking A/D meds, 159 (42%) reported this at ≥3 time-points, 218 (58%) reported no prior history of A or D and 274 (73%) reported no use of A/D meds in the year prior to diagnosis. When women reported clinical levels of A or D, only 45% reported taking medication (37%) and/or seeing a psychiatrist or psychologist (19%). Among those not already on A/D medication at diagnosis, a prior history and low levels of optimism were the strongest predictors of A/D onset. Conclusions: More than 40% of women with OC experienced clinical levels of A or D during treatment or the first 3 years of follow-up. For 42% of those affected this was their first experience of distress and > 50% did not receive appropriate medication or psychological support. The hidden burden of anxiety and depression in this population is much greater than previously reported but is amenable to effective intervention if recognized.
Background: People with melanoma want and need effective treatments for managing and living with fear of cancer recurrence (FCR). This study reports the long-term efficacy of a psycho-educational intervention designed to reduce FCR in people at high risk of developing another primary melanoma compared to usual care. Methods: Adults previously diagnosed with stage 0, I, or II melanoma were randomly allocated to the intervention (n = 80) or control (usual care) arm (n = 84). Of 164 participants, 87% completed the 12-month assessment. Outcomes for 8 participants (5%) who completed the 6-month but not the 12-month assessment were imputed using model-based multiple imputation; thus, 151 participants are reported in the analysis. The intervention comprised a 76-page psycho-educational resource and three individually-tailored, telephone-based sessions with a psychologist, scheduled at specific time-points around participants’ dermatological appointments. The intervention effect at 12-months was estimated by intention-to-treat analysis of the mean change in FCR score using a linear mixed model and as a FCR severity score (0-4). The intervention was associated with significantly lower FCR at 12 months; the between-group mean difference was −1.41 for FCR severity (95% CI −2.6 to −0.2; p = 0.02), and −1.32 for FCR triggers (95% CI −2.6 to −0.02; p = 0.04). The odds ratio for FCR severity ≥13 (64% intervention, 63% control) was 0.59 (95% CI 0.30 to 1.14, p = 0.12). There were no differences in secondary outcomes including anxiety, depression, or health-related quality of life. Conclusions: This psycho-educational intervention had a sustained effect in reducing fear of cancer recurrence over the longer-term. This novel intervention has no adverse effects and its benefits persist long after the last psychology session, supporting implementation as part of routine clinical care in melanoma.

Clinical trial information: ACTRN12613000304730.

10085 Poster Session (Board #73), Mon, 1:15 PM-4:45 PM
Randomized trial of a text messaging intervention for symptom distress in BCa patients undergoing chemotherapy. First Author: Kuang-Yi Wen, Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA, Philadelphia, PA
Background: Chemotherapy is often associated with treatment side-effects that negatively affect HRQOL. The aim of this study was to examine the feasibility and preliminary efficacy of a novel mobile text messaging (TXT) intervention to help breast cancer (BCa) patients coping with chemotherapy. Methods: Through an iterative patient-centered formative evaluation process, we developed an automatic bidirectional theory-guided and evidence-informed TXT intervention that sent two daily proactive messages addressing education, symptom management, and support with options for patients to request more texts. In a RCT study, 100 BCa patients undergoing chemotherapy were assigned to either the TXT group or a control group that received an ACS chemotherapy booklet. Measures were administered at baseline, 1-month, 2-month, 3-month and 4-month. A satisfaction interview was conducted following the intervention. Acceptability and feasibility were examined. Primary outcomes were symptom distress and HRQOL. Secondary outcomes were depressive symptoms, self-efficacy and doctor-patient communication. Results: The majority of the sample was white (70%) with a mean age of 59 years. Both study groups reported significant increase in symptom distress and decline in HRQOL from baseline to follow-ups. Symptom distress was found significantly lower and HRQOL was higher in the intervention group at month 1 and month 3 than the control (p-value ≤ 0.05). Intervention group reported significant improvement in self-efficacy and doctor-patient communication (p-value ≤ 0.05). No difference was found in depressive symptoms between two groups. Regarding acceptability, 70% of eligible participants consented and 90% of the TXT group participants were satisfied with the intervention. Intervention participants requested text back to the system 364 times requesting additional texts with a mean range of 3-58 requests. Conclusions: Feasibility, satisfaction, and preliminary efficacy of a TXT intervention to promote better outcomes for BCa patients undergoing chemotherapy were established. Further research is needed to develop additional tailoring and personalization per participants’ feedback.
Background: Patients today have unprecedented access to health and medical information (HMI) from a diverse range of sources. This access helps inform patients, but it may also misinform and adversely affect patients’ trust in doctors (TD). In this study, TD is compared with trust in 8 other sources of HMI. Methods: This study examines the Health Information National Trends Survey (HINTS-5) data published July 2017 by the National Cancer Institute. A nationally representative sample was generated from 3,295 Americans, and analyses included the 1,873 who sought cancer information. Trust was ranked 1 (not at all) to 4 (a lot). In families (F), news (N), radio (R), internet (I), TV, government (G), charities (C), and religious sources (RS) were independently compared to TD. Logistic regression was used to evaluate associations between demographic characteristics and viewing non-doctor sources as equal or superior to TD (EOSTD) for HMI. Results: Pre-survey weighting, 75.6% of the sample trusted doctors “a lot,” followed by trust in G (32.1%), I (15.4%), and C (8.3%). 60.4% viewed at least one non-doctor source as EOSTD. Earning $75,000 or more was inversely associated with viewing TD (OR 0.89, p = 0.009), N (OR 0.91, p = 0.027), T (OR 0.84, p = 0.004), C (OR 0.83, p = 0.003), and R (OR 0.88, p = 0.004) as EOSTD for HMI compared to earning < $20,000. Compared to not completing high school, some college (OR 0.82, p = 0.029), college (OR 0.80, p = 0.011), or postgraduate education (OR 0.80, p = 0.011) reduced OR for viewing TD as EOSTD. Compared to being White, being Non-Hispanic increased viewing TD as EOSTD, while being Black (OR 1.14, p = 0.007) or Non-Hispanic (OR 1.27, p = 0.034) increased viewing TD as EOSTD. Being female was associated with viewing F as EOSTD (OR 1.04, p = 0.040). Conclusions: Doctors are the most trusted HMI source, but most respondents viewed at least one non-doctor source as EOSTD. Patients should be reminded that alternative sources are not equivalent to doctors for HMI.

Background: Physical activity and exercise have shown benefits for cancer prevention and contribute to improved treatment related outcomes. We reviewed the characteristics of cancer patients referred for physical therapist-led exercise counseling at a comprehensive cancer center and its effects on self-reported symptoms. Methods: Patients presenting for an exercise counseling consultation and follow up encounter at an Integrative Medicine Center outpatient clinic from Feb 2016 to May 2017 completed the Edmonton Symptom Assessment Scale (ESAS; 0-10 scale, 10 most severe) pre/post-encounter; a PROMIS 10 global health assessment was also completed within 30 days of each encounter. Exercise counseling was provided by a physical therapist. ESAS individual items and subscales of Physical Distress (PHS), Psychological Distress (PSS), and Global Distress (GDS) were analyzed. We used paired t-tests with a p-value correction (i.e., p < .001) to examine symptoms before and after each encounter. Results: Data were available for 367 participants; 68 (18.5%) had at least one follow up encounter at 56.1 days (mean). Most were female (77.7%), caucasian (66.2%) with breast (43%), gastrointestinal (15.8%), or gynecologic (6.8%) cancer. Highest and most frequently reported (%) symptom included change in global health-related QOL (EQ-5D, SF-8) and incidence of adverse events evaluated with CTCAE v3.0. Results: From October 2009 to January 2015, 40 patients were enrolled (PTEG: 20; NGT: 20). Symptomatic scores were evaluable in 39 patients (PTEG: 19; NGT: 20) and the safety was evaluable in all patients. The AUC of the symptomatic scores of the PEG group (mean: 149.6; 90% CI: 125.2, 173.9) was significantly higher than that of NGT group (mean: 44.9; 90% CI: 21.2, 68.7) (< 0.0001). Differences in EQ-5D (mean: 3.5; 90% CI: 1.6, 5.3; p = 0.036) and SF-8 (mean: 220.7; 90% CI: 113.3, 328.1; p < 0.0020) between two groups were statistically significant. There was no procedure-related complication in both groups. Conclusions: This analysis demonstrated the statistical superiority of the PTEG compared to the NGT. PTEG was effective in reduction of the distressing symptoms caused by NGT. Clinical trial information: UMIN000003565.
Background: Cancer-related fatigue (CRF) is one of the most frequent and debilitating symptoms in 60% to 90% of patients with advanced cancer. The fatigue experienced by cancer patients can not only deteriorate patient quality of life, but also affect treatment efficacy and survival rate. PG2 injection developed by PhytoHealth Co., Taiwan with Astragulus Polysaccharides as API is the only drug approved by Taiwan Food and Drug Administration (TFDA) for relieving CRF in patients with advanced cancer. To further explore the effect of PG2 injection at lower dose, we recruited more patients in the current study and observe the effect of PG2 injection in 2 doses.

Methods: Patients with advanced cancer receiving standard palliative care (SPC) with moderate to severe CRF (Score of the Brief Fatigue Inventory-Taiwan (BFI-T)=4) were enrolled. Patients were randomized at a 1:1 ratio into two arms of PG2 injection treatment: 500mg dose or 250mg dose (both were prepared in 500ml saline and injected 3 times per week for 4 weeks) for two cycles. Fatigue improvement response rates (FIRR) were analyzed at the end of the first cycle to determine the efficacy of the two PG2 doses. BFI-T score for more than 60% is considered as effective for relieving CRF.

Results: Three hundred and ten patients were enrolled in this study. Two hundred and fourteen patients were included in the ITT population, including 111 subjects in high dose group and 103 subjects in low dose group. Results showed that improvement in fatigue score of subjects was greater in the high dose group than the placebo group (P<0.05). The severity of the rash was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as well as the number of facial lesions. Severe rash was defined as grade ≥3 by the CTCAE criteria or regorafenib-related fatigue or/and malaise. The rash was assessed on Days 0, 14, and 28.

Conclusions: Topical chloramphenicol 3% + prednisolone 0.5%, 23 chloramphenicol 3%, and 25 aqua cream. The arms were similar with respect to demographics and tumor types. Number of facial lesions and CTCAE grade were highly correlated (r = 0.9). According to the number of facial lesions, CTCAE grade 4 was highly correlated with the presence/absence of fatigue or malaise (all grades) during the protocol period. Here we report intervention related PROs. Methods: PROs were assessed at baseline, on every once a week thereafter until 4 weeks, using the Brief Fatigue Inventory (BFI), the European Quality of Life 5 Dimensions-3 Level (EQ-SD-3L), Functional Assessment of Cancer Therapy-General (FACT-G) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C). QOL scores were compared using a mixed-effects models for repeated measures (MMRM), adjusting for baseline score and the stratified randomization (the presence/absence of fatigue or malaise and/or sex). Results: Between October 2014 and December 2015, 74 pts were enrolled and randomized (DEX group: 37, PLC group: 37). BFI score, EQ-SD-3L score, FACT-G total score and FACT-C total score were improved at each point in DEX group. Least-squares mean difference from PLC group: -0.05 (95% CI: -0.3 to -0.21), 0.03 (95% CI: 0.01 to 0.05), 0.03 (95% CI: 0.01 to 0.06), 0.02 (95% CI: 0.01 to 0.04), and 0.02 (95% CI: 0.01 to 0.04), respectively. Conclusions: Among pts who remained on treatment and for whom PROs data were available, dexamethasone had a clinical meaningful improvement at each of the post-baseline timepoints for FACT-G and FACT-C in comparison with those who received PLC, although the relatively small sample size. Clinical trial information: NCT02288078.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Cryocompression for enhanced limb hypothena in preventing paclitaxel-induced peripheral neuropathy. First Author: Raghu Sundar, National University Health System, Singapore, Singapore. Background: Severe peripheral neuropathy is a common dose-limiting toxicity of paclitaxel chemotherapy, with no effective treatment. We have previously described the role of continuous-flow hypothermia in reducing neurotoxicity caused by paclitaxel. We hypothesized that cryocompression (addition of pressure to hypothermia) may enhance depth of cooling and improve efficacy. Methods: A proof-of-concept study was conducted in cancer patients receiving taxane chemotherapy. Each subject underwent four-limb cryocompression with each chemotherapy infusion (3 hours) for a maximum of 12 cycles. Cryocompression was administered at 16°C and cyclic pressure (5-15 mmHg). Skin surface temperature and tolerance maximum of 12 cycles. Cryocompression was administered at 16°C and cyclic pressure (5-15 mmHg). Skin surface temperature and tolerance scores were recorded. Neuropathy was assessed using nerve conduction studies (NCS) conducted before (NCSbaseline), after completion (NCS12m) and 3-months post chemotherapy (NCS3m). Results: In total, thirteen patients underwent 142 cycles of cryocompression concomitant with chemotherapy. Mean skin temperature reduction of 3.8°C ± 1.7°C was achieved and was well tolerated. Only 1 out of 13 patients required an intra-cycle temperature increase, with no early termination of cryocompression in any patient. NCS analysis showed significant preservation of motor amplitudes at NCS3m compared to baseline (common peroneal nerve below fibula head stimulation: 12.7 ± 25.6%; p < 0.003; Tibialis nerve abductor hallucis stimulation: 8.8 ± 22.9%; p = 0.005). Sensory nerve amplitudes showed a reduction at NCS3m compared to baseline but continued to be preserved at NCS12m (% change from baseline: NCS3m: -28.1 ± 21.9%; NCS12m: -26.7 ± 19.0%). Cryocompression did not significantly affect taxane-induced changes in nerve velocities. Conclusions: Cryocompression is well tolerated and results in preservation of neuron function, as measured by gold-standard NCS. When compared to our previously reported continuous-flow hypothermia (21°C) cohort, cryocompression permitted delivery of lower temperatures with similar tolerability, potentially leading to improved efficacy in neurotoxicity amelioration. Laster studies investigating cryocompression are ongoing. Clinical trial information: NCT03299582.

REZOLVE (ANZCOG-1101): A phase 2 trial of intraperitoneal (IP) bevacizumab (Bev) for recurrent ascites in advanced, chemotherapy-resistant, Eastern Cooperative Oncology Group Cisplatin Resistant ovarian cancer (CR-EOC). First Author: Katrina Marie Spouset, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia. Background: To determine safety and activity of IP bev for recurrent malignant ascites requiring repeated paracenteses, a major problem for women with CR-EOC. Methods: Eligible women had CR-EOC and symptomatic, malignant ascites that recurred within 28 days of their last paracentesis (P1). Participants had IP bev 5mg/kg instilled at the end of their first therapeutic paracentesis on study (PO). Additional doses of IP bev were allowed at each subsequent paracentesis (P1, P2 etc) if the interval from the last dose was 42 days or more. The primary objective was to determine the proportion alive and free of repeat paracentesis at 42 days. Safety and quality of life were secondary outcomes. Serial samples of blood and ascites were collected for translational studies. The hypothesis was that IP bev would be worthy of further study if the proportion alive and free of repeat paracentesis at 42 days was 54% or more, but not if it was 20% or less. Results: We recruited 24 participants with a median age of 67 years (range 38 – 86), median of 4.5 lines of prior systemic treatment (range 1 – 12), and ECOG performance status of 0-1 in 9, and 2-3 in 15. The numbers of doses of IP bev administered were 1 in 13 participants, 2 in 5, 3 in 2, 4 in 1, and 5 in 1. The proportion free of paracentesis at 42 days using competing risk analysis was 77% (95% CI 58 to 92). Median time from PO to P1 or death (puncture-free survival) was 48 days (range 8 to 248 days). Median Paracentesis free interval (PO to P1 or death) was 4.29 (95% CI 2.4 to 5.8) times higher following first dose of IP bevacizumab compared with the time between paracenteses prior to study entry (P1 to PO). Grade 3-4 AEs (number of participants, regardless of attribution) included abdominal pain (4), fatigue (3), lower limb swelling (3), fluid retention, pain (2) and grade 3 bowel perforation (1). Conclusions: IP bev was safe, active, and warrants further study as a palliative intervention for recurrent ascites in CR-EOC. Clinical trial information: 12611000801910.

Effects of mindfulness meditation on quality of life in adults with advanced cancer and family caregivers: A randomized pilot. First Author: Shelley A. John, Indiana University School of Medicine, Indianapolis, IN, USA. Background: Patients with advanced cancer often avoid emotionally sensitive discussions with family caregivers (FCGs) about their end-of-life (EOL) treatment preferences. Avoidance of these advance care planning (ACP) discussions inhibits EOL preparations and may reduce quality of life (QoL) for both patients and FCGs. Most ACP interventions fail to address emotional barriers that hinder timely ACP. Mindfulness training facilitates emotional regulation and adaptive coping, and was tested in this randomized pilot. Methods: Eligible patients had ≥1: (1) locally-advanced solid malignancy; (2) life expectancy < 12 months as rated by their oncologist; (3) score of ≥ 7 on cancer-related cognitive avoidance (Mini-MAC); and (4) FCG willing to enroll. Patient-FCG dyads (n = 55) were randomly assigned to a 6-session mindfulness meditation class with communication training or usual care. Primary endpoints were feasibility, retention, QoL, and ACP confidence (patients only). Outcomes were assessed at baseline and 6- and 10-weeks using intent-to-treat analysis. Results: Of 133 patients who screened eligible, 41% enrolled. Dyadic retention was 84% through 10 weeks. Most participants (85%) had stage IV cancer, with breast (29%) and GI (27%) cancers being most prevalent. The majority of patients and FCGs were female (60-62%), white (94-95%), and college educated (63-64%). Mindfulness patients reported a large and significant improvement in existential QoL (d = 0.82, p = 0.009) at 6 weeks compared to controls; however, the magnitude of improvement was not sustained at 10 weeks (d = 0.24, p = 0.49). Mindfulness FCGs reported a significant within-group improvement in QoL at 10 weeks (d = 0.45, p = 0.03); however, between-group comparisons were not significant at any time point. A non-significant improvement in ACP confidence favoring mindfulness patients over controls at 6 weeks became significant at 10 weeks (d = 0.67, p = 0.03). Conclusions: Within limits of a small pilot, results suggest that mindfulness training is feasible and potentially beneficial for improving QoL and ACP confidence in dyads coping with advanced cancer. A full-scale efficacy trial with a more diverse sample is planned. Clinical trial information: NCT03257007.

Celiac plexus radiosurgery: A new palliative modality for upper gastrointestinal malignancies—Final results of a proof-of-concept clinical trial. First Author: Yaacov Richard Lawrence, Sheba Medical Center, Ramat Gan, Israel. Background: Many patients with upper-abdominal malignancies suffer from severe lower back pain radiating to the epigastrium, caused by infiltration of the celiac plexus. The celiac plexus is a network of nociceptive nerves, located along the aorta. Contemporary approaches (opioids, celiac plexus chemical neurolysis, systemic chemotherapy) are often inadequate. The celiac plexus has not previously been targeted using radiation. We hypothesized that ablative radiation targeting the celiac plexus would alleviate pain. Methods: We conducted a single arm prospective clinical trial. Eligible patients had celiac-pain > 4/10 on Numerical Rating Scale (NRS), ECOG ≤ 3, no previous abdominal RT, and were evaluable if they completed treatment protocol with at least one post-treatment visit. The celiac plexus was irradiated from D12 to L2. Radiation was given as five fractions of 25 Gy. The primary endpoint was NRS pain 3 weeks post-treatment. Secondary endpoints were toxicity, pain at 6w, analgesic use, and pain interference with daily activities as evaluated by ‘Brief Pain Inventory’ before and after radiation. Results: 21 patients were evaluable: 2 received fractionated treatment, 19 received 25Gy single fraction. The median age of the study population was 63 yr with a median ECOG of 1, 86% had pancreatic cancer. Patients were a median of 8 months out from diagnosis, and had received a median of one systemic treatment. Toxicity was limited to grade 1-2. All patients reported decreased celiac pain: median baseline pain was 6/10 (IQR 5-7.7), was reduced to 2.3/10 (IQR 0.9-3.9) (< 0.0005) at 3w, and to 1.8/10 (IQR 0.3-2.0) (< 0.0005) at 6w post-treatment. Seven patients reported their celiac pain had been eliminated entirely. Median morphine consumption decreased (NS). Improvement was seen in multiple quality of life measures (including total wellbeing (p = 0.0001), daily activity (p = 0.005) and sleep quality (p = 0.002). Conclusions: Celiac plexus radiosurgery alleviates pain, and improves quality of life among patients with advanced upper-GI cancer. An international multi-center phase II trial is accruing. Clinical trial information: NCT02356406.

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Risk stratification using patient-reported outcomes (PROs) in patients (pts) with advanced cancer. First Author: Shiven B. Patel, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Performance status is often used to stratify cancer pts for treatment and to guide supportive care resources. This retrospective study was conducted to evaluate whether PROs have prognostic value, independent of physician assessment of functional status. Methods: Pts treated at Huntsman Cancer Institute were assessed using the NCI PROMIS-Ca bank from May 2013. Physical function, fatigue, depression, anxiety, and pain scores were collected via iPAD in pts with metastatic NSCLC, CRC, and breast cancer. A single PRO score at the time of metastatic disease for each pt was merged with outcome data using the Flatiron Health database, processed with technology-enabled abstraction and supplemented with third-party death information. Associations between PROs, PROs and overall (OS), and PROs and hospital-free survival (HFS) were assessed. Results: The five PRO domains were interrelated with moderate-strong correlation coefficients (0.40-0.79). Physical function score was worse for NSCLC than both CRC (p < 0.001) and breast cancer (p < 0.001), while both anxiety and depression were worse for NSCLC than CRC (p = 0.003 and p = 0.042, respectively). All individual PRO domains and a summary score were strongly associated with outcomes. Physical function and fatigue provided the greatest discrimination. The correlation of PROs with 12-month survival (table) and HFS were statistically significant. Conclusions: PRO scores, independent of physician interpretation, are prognostic for OS and HFS. These findings have substantial implications for patient care, treatment planning, clinical research, and financial modeling.
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10107  Poster Session (Board #95), Mon, 1:15 PM-4:45 PM

Length of time to conduct goals of care visits. First Author: Sofya Pintova, Mount Sinai Medical Center, Brooklyn, NY

Background: Oncologists report that time to conduct a goals of care (GoC) discussion is a barrier. We studied the relationship of GoC discussion and visit time at different type hospitals. Methods: At community, academic, municipal and rural hospitals, we recruited & randomized solid tumor oncologists & their newly diagnosed advanced cancer patients with < 2 year prognosis to participate in a RCT, testing a coaching model of communication skills training. Patients were surveyed after post-imaging visits. These visits were audiotaped and median encounter time recorded. We defined GoC discussions as patient report that their doctor talked about preferences for cancer treatment and clarified things most important to them given their illness. Analyses were done with Kruskal-Wallis and Wilcoxon tests. Results: For 22 randomized oncologists in the study, 137 post-imaging encounters were audiotaped. The median face-face time oncologists spent during a GoC encounter with an advanced cancer patient was 15 minutes. Encounter times with GoC discussions were expected varied between the four sites, ranging from 9.5 minutes to 18 minutes, p = 0.05. The encounters where no GoC discussions occurred were longer, taking 16.5 minutes vs 13 minutes, p = 0.05. Visits that took place after progression of disease took longer, 18 minutes vs 13 minutes, p = 0.006. Conclusions: Visits vary by hospital type and average 15 minutes. With disease progression, visit time is longer. Despite physician perceptions, GoC discussions do not lengthen visits. Clinical trial information: NCT02374255.

10108  Poster Session (Board #96), Mon, 1:15 PM-4:45 PM

Community-based palliative care utilization in elderly pancreatic cancer patients. First Author: Zhanzi Lu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Community-based Palliative Care (CBPC) has shown to stabilize symptoms, alleviate psychological and spiritual burdens, satisfy care preferences, and improve quality of life among care recipients. We evaluated CBPC utilization and predictors in pancreatic cancer patients ≥66 years.

Methods: Palliative Care (PC) encounters among pancreatic cancer patients were identified by ICD-9-CM codes using SEER-Medicare data from 2007 to 2013, and patients were followed until 2014. PC encounters outside hospital settings were classified as CBPC. We tested time trends of CBPC utilization and time to PC referral after cancer diagnosis. Multivariable random intercept logistic models were used to determine the predictors of CBPC utilization at the patient and Health Service Area (HSA) levels.

Results: 16,106 patients were included, of whom 27.8% used palliative care; of those, 1,530 (9.5%) used CBPC, and 2,956 (18.3%) used Hospital-based Palliative Care (HBPC). CBPC utilization increased from 8.2% in 2007 to 9.4% in 2013 (p = 0.014). Median (IQR) PC referral time after cancer diagnosis decreased from 5 (2, 11) mo. in 2007 to 2 (1, 5) mo. in 2013 (p = 0.001). Being female (OR 1.2711.12, 1.45); p = 0.001; a diagnosis of advanced cancer stage (OR 1.299 [1.002, 1.67]); p = 0.049, cancer treatment participation (OR 2.24 (1.92, 2.60); p < .001) or residing in an urban area (OR 1.57 [1.03, 2.39]; p = 0.035) were positively associated with CBPC utilization. Those living in the poorest communities (OR 0.62 [0.47, 0.81]; p = 0.001) and southern SEER Registries (Georgia, Kentucky and Louisiana) (OR 0.19 [0.09, 0.39]; p < 0.001) were less likely to use CBPC. HSAs with high density of HBPC programs (an indicator of regional health care resources) were positively associated with CBPC usage (OR 1.50 [1.03, 2.20]; p = 0.035). Conclusions: CBPC usage increased and referral time decreased over 6 years. Patient-level factors, geographic area characteristics, and regional health care resources were associated with likelihood of receiving CBPC.

10109  Poster Session (Board #97), Mon, 1:15 PM-4:45 PM

Patterns of palliative care utilization in stage IV non-small cell lung cancer in the National Cancer Database. First Author: Urshala Durani, Mayo Clinic, Rochester, MN

Background: Early integration of Palliative Care (PC) improves survival in stage IV non-small cell lung cancer (NSCLC). Here we explore patterns in PC utilization in this group.

Methods: We queried years 2004-2014 of the National Cancer Database for adults with stage IV NSCLC. Patients receiving pain management +/- other palliative procedures were PC users, in addition to descriptive statistics, multivariable logistic regression models with interaction analyses identified predictors of PC utilization. Results: Of 341,993 patients, 3.2% received PC at initial treatment. PC utilization increased significantly from 2004-2006 to 2013-2014 (2.3% vs 4.2%, p < 0.01). Whites had higher PC utilization (3.3%) than blacks (2.6%) and Hispanics (2.3%, p < 0.01 for both). Significant predictors of PC on multivariable regression are listed in the Table. Interaction analyses found that Hispanics and Asians had a slower increase (p < 0.01). Significant predictors of PC utilization are listed in the Table. Conclusions: PC utilization in stage IV NSCLC is markedly low and plagued by racial disparities, and regional health care systems.

Comparisons of palliative care utilization in metastatic cancer patients between multi-licher universal health care and single-payer universal health care systems. First Author: Raymond Niemchen Kuo, National Taiwan University, Taipei City, Taiwan

Background: Previous studies reported that private insurance was associated with receiving recommended care and better outcomes. However, it is unclear whether insurance type is associated with the utilization of palliative care among metastatic cancer patients who survived for less than 6 months following diagnosis. This study compares the utilization of palliative care among patients in the U.S. and patients in Taiwan.

Methods: Analysis was conducted using data for the period 2010–2013 obtained from the U.S. National Cancer Database and Taiwan Cancer Registry. This study include patients newly diagnosed with metastatic (M1) breast, colorectal, lung, and prostate cancers and who died within six months after diagnosis. Logistic regression models were used to compare the odds of receiving palliative care under different health insurance schemes. Results: This study included 70,084 U.S. patients (49,374 lung, 13,591 colorectal, 4,837 breast, 2,285 prostate) and 8,882 Taiwanese patients (6,131 lung, 2,188 colorectal, 255 breast, 308 prostate). Among these cases, 18,458 patients in the U.S. (26.3%) and 5,338 patients in Taiwan (60.1%) received palliative care before dying. In the U.S., breast, colorectal, and lung cancer patients covered by private health insurance were more likely to utilize palliative care (17.6% - 31.1%), than were patients covered by public health insurance (16.0% - 28.7%). Multivariate logistic regression analysis revealed that after controlling for demographic factors, disease severity and treatment type, there were no differences in the administration of palliative care among patients covered by private health insurance and those covered by public health insurance. Nonetheless, Taiwanese patients were more likely to undergo palliative care than were patients in the U.S. This implies that the lower cost and more comprehensive benefit scheme may improve access to palliative care.
**10111**

**Poster Session (Board #99), Mon, 1:15 PM-4:45 PM**

Patient-reported outcomes in light of supportive medications in treatment-naïve lung cancer patients. First Author: Johnny Hoang, Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, TX

**Background:** Symptom burden of cancer patients is high and can be assessed using patient-reported outcomes (PROs). However, the impact of supportive medications on PROs has not been systematically assessed. We describe the supportive medications used by treatment-naïve lung cancer patients at hospital admission and assess the association between their use and PROs.

**Methods:** Patients with a diagnosis of non-small cell lung cancer who had not received any form of cancer therapy at the initial visit and completed the MD Anderson Symptom Inventory (MDASI) survey within 45 days of diagnosis were included. Baseline patient and tumor characteristics and a complete medication list (categorized based on USP v7.0) were abstracted using the EPIC system. Symptoms were compared using Mann-Whitney U test in patients taking a supportive care medication.

**Results:** Lung cancer patients (N = 459) with median age of 66 years (range: 23-90) were included in this study. About half (46%) of patients took any analgesics with 27% of patients taking opioid-containing regimen. One-third (31%) of patients with moderate to severe pain (5 or above on 10-scale) were not on any analgesics. Compared to patients not taking any analgesics, those on the opioid-containing regimen had significantly worse median pain scores (6 vs. 0), but not those on non-opioid analgesics (1 vs. 0). This was despite higher proportion of patients with moderate to severe pain taking opioid-containing regimen compared to those not on the therapy. Patients on opioid-containing pain regimen also reported worse drowsiness, fatigue, disturbed sleep, shortness of breath, lack of appetite, general activity, mood, work, relations with others, walking, and enjoyment of life. Patients taking antidepressants did not significantly differ in any individual MDASI symptoms compared to those not taking antidepressants (p > 0.05). Pain was also an independent marker for overall survival (OS). Median OS was 18.2 months in patients with pain compared to 22.0 months in patients without pain (p = 0.013, HR 1.25, 95% confidence interval 1.05-1.48). OS was shorter in patients with pain and without pain medication compared to those with pain and with pain medication (16.5 vs. 19.6 months respectively; p = 0.026). There was no difference regarding progression free survival and prior treatment discontinuation. **Conclusions:** Treatment-naïve lung cancer patients presenting at MD Anderson had poorly managed pain and associated functional symptoms and interference. Since patients’ functional status may result in suboptimal cancer therapy, our results suggest a need for better pain and symptom management in these patients.

**10112**

**Poster Session (Board #100), Mon, 1:15 PM-4:45 PM**

The impact of pain in recurrent ovarian cancer patients: An individual participant data meta-analysis of the North-Eastern German Society of Gynecological Oncology (NOGGO) of 1226 patients. First Authors: Hannah Woopen, Department of Gynecology, European Competence Center for Ovarian Cancer, Charité, University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany

**Background:** Pain has a major impact on quality of life in ovarian cancer (OC) patients. The influence of pain on survival is unclear in OC. Aim of this study was to analyze the impact of pain on quality of life and survival in recurrent OC patients.

**Methods:** Raw data including the QLQ-C30 questionnaire from three phase III/III trials ("Topotecan phase III", “Hector” and “TRIAS”) conducted by the North-Eastern German Society of Gynecological Oncology (NOGGO) were synthesized and analyzed using logistic and cox regression analyses. **Results:** Out of 1226 patients there were data on pain available for 952 patients. More than one third of patients (36.6%) experienced moderate to severe pain, defined as pain ≥ 50 in the QLQ-C30 symptom scale, which was independent from the administered chemotherapy. 31% were taking non-opioid pain medication and 16% opioids. Median age at randomization was 61 years (range 25-84). Most patients (84.7%) were diagnosed in advanced stages. Pain was independent from age, FIGO stage, grading, amount of recurrences and chemotherapy free interval. ECOG was significantly worse in patients with pain (p < 0.001). These patients experienced more frequently fatigue, nausea/vomiting, sleeping disorders, abdominal symptoms such as loss of appetite, diarrhea and constipation (all p < 0.01). Quality of life was significantly diminished (p < 0.001). Pain also had an independent marker for overall survival (OS). Median OS was 18.5, 19.6 and 15.0 months respectively (p = 0.026). There was no difference regarding progression free survival and prior treatment discontinuation. **Conclusions:** Effective pain management is crucial for both quality of life and overall survival in patients with recurrent ovarian cancer. Patients shall therefore receive best supportive care as early as possible.

**10113**

**Poster Session (Board #101), Mon, 1:15 PM-4:45 PM**

Prospective phase II pilot study to evaluate the use of intravenous iron in the treatment of anemia in cancer patients. First Author: Youjin Oh, 10-Phase Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South)

**Background:** Iron deficiency anemia (IDA) is common complications in cancer patients. Evidence on intravenous (IV) iron for treatment of chemotherapy-induced anemia (CIA) is emerging. Herein, we evaluated the efficacy of IV iron for improvement of anemia in cancer patients.

**Methods:** This prospective single arm phase II study aims at evaluation of efficacy of IV iron without additional ESA for correction of CIA. Patients received Ferinject® (ferric carboxymaltose) 1000mg injection on the first day of chemotherapy. Thereafter, hemoglobin (Hb) response defined by increase of Hb ≥ 1.0g/dL was assessed at visit 1, visit 2 and visit 3. To identify biochemical parameter predictive for Hb response, TSAT, sTFR, hepcidin, EPO, IL-6, CRP were also assessed at each visit. **Results:** Between Oct 2010 and Jul 2017, a total of 104 patients were enrolled, and 92 patients were available for for injection. Hemoglobin response was observed in 36, 53 and 61 patients at visit 1 (39.1%), visit 2 (57.6%) and visit 3 (66.3%), respectively. When excluding 19 patients (20.6%) with absolute IDA defined by ferritin < 30ng/mL or TSAT < 20%, Hb response rate was 83.5% (41/73). Of 73 patients without absolute IDA, there were i) 56 patients whose serum ferritin were between 30-500 ng/mL, ii) 6 patients whose serum ferritin were between 500-800 ng/mL and TSAT < 50 %, and iii) 10 patients whose ferritin levels were ≥ 800ng/mL or TSAT ≥ 50%. In patients groups of i), ii) and iii), Hb response was observed in 60.7% (34/56), 50% (6/6), and 50%(5/10), respectively. Comparing anemia related biochemical parameters, responders had significantly lower levels of hepcidin (13.5 vs. 35.2 ng/mL, p = 0.007), CRP (0.7 vs. 2.5mg/mL, p = 0.044) and ferritin (249.2 vs. 575.3 ng/mL, p = 0.048). When comparing Hb response by baseline hepcidin level, there were no significant more responders in the high hepcidin group (58/61, 95.1%) compared to the high hepcidin group (3/61, 4.9%) at the cut-off value of 34.1 ng/mL (p = 0.002).

**Conclusions:** IV iron supplementation alone showed promising result in improving anemia in cancer patients. Hepcidin may predict response to IV iron in cancer patients undergoing chemotherapy induced anemia, and is superior to TSAT or ferritin for this purpose. Clinical trial information: NCT02599012.

**10114**

**Poster Session (Board #102), Mon, 1:15 PM-4:45 PM**

Does cytotoxic chemotherapy (CT) have a role in palliative treatment of hepatocellular carcinoma (HCC)? First Author: Guilherme Nader Manta, Instituto do Câncer do Estado de São Paulo - IESCSP, São Paulo, Brazil

**Background:** Palliative treatment of patients (pts) with HCC after progression to sorafenib represents a clinical challenge due to the usual concomitance with hepatic failure. Although new drugs have recently demonstrated survival benefit in phase III trials after sorafenib therapy, these agents are not widely available and their use is limited by the stringent inclusion criteria of the clinical trials. CT is being studied as a palliative treatment in this clinical setting, although there is no proof of its efficacy. We analyzed a cohort of HCC pts treated with CT with the aim of evaluating the efficacy and safety of this approach. **Methods:** A cohort of pts with advanced HCC treated with CT after progression to sorafenib was retrospectively evaluated. Survival (PCS) was calculated from the first day of CT to death or last data record. PCS was estimated using Kaplan-Meier and curves were compared by log-rank test. **Results:** We analyzed 240 HCC pts treated with sorafenib from Oct-2007 to Jan-2017. At sorafenib discontinuation, best supportive care was the only treatment for 79.2%, while 18.3% received cytotoxic CT and 2.5% were enrolled in clinical trials. For pts treated with CT, median age 60 years (19-74), 75.6% male, 42.2% had HCV, 71.1% Child-Pugh (C) A, 95.6% had extrahepatic spread, and 55.6% received doxorubicin-based CT. The median PCS was 8.0 months (3.9-12.1) and 53.3% had progressive disease as best response. Survival benefit from CT could not be predicted by C (p = 0.66), ECOG PS 0-1 (p = 0.09), CT regimens used (p = 0.97) or best response. Survival benefit from CT could not be predicted by CP A (p = 0.29). Grade 3 or 4 toxicities occurred in 37.7% of pts and the most common grade 3 or 4 adverse events (AE) were nausea/vomiting (20%), mELTOX (18%) and fatigue (11%). CT was most commonly discontinued due to unacceptable AE (44.4%) and disease progression (37.8%). **Conclusions:** Palliative treatment of HCC pts with CT after sorafenib failure is associated with high rates of toxicity and low efficacy. These data suggest that CT seems to have very limited activity in a group of pts with a very poor prognosis without a clear survival benefit and should only be recommended in very selected cases.
Incorporating geriatric patient reported outcomes into novel screening tool of distress and supportive care concerns. First Author: Christine B. Weidon, Northwest University Feinberg School of Medicine, Chicago, IL

Background: The Institute of Medicine (IOM) 2013 Report recommends that supportive oncology care start at cancer diagnosis; the Commission on Cancer (CoC) Standard 3.2 requires distress screening and indicated action. The Supportive Oncology Collaborative, collaborative of 100+ clinicians funded by The Coleman Foundation, developed a patient-centric screening tool (CSOC-ST) adapted from ASCO Distress, NCCN Distress Problem List, IOM report and CoC standards, and other validated sub-tools (KOBS, ASCO-Q 2017). The Collaborative then revised the CSOC-ST tool to align with geriatric guidelines. Methods: Literature and guidelines review of geriatric screening, added items to CSOC-ST, and piloted at 4 sites. Descriptive statistics and Fisher’s exact test used. Results: Of 118 patients, 117 patients except 1 patient in PG arm responded to the FACT-T questionnaires at baseline. Baseline FACT-T subscale QoL scores and overall QoL scores were significantly associated with each of the following: self-care concerns, memory/cognition concerns and specific treatment/care concerns (p < .0001). Conclusions: Pilot results and comparison to geriatric guidelines identified important items to support geriatric patient reported outcomes screening. After pilot, added 3 items for falls/frailty. Eight sites implementing this CSOC-ST.

Quality of life (QoL) outcomes including neuropathy associated scale (FACT-T) from a phase II, multicenter, randomized clinical trial of eribulin plus gemcitabine (PG) versus paclitaxel plus gemcitabine (PG) as first-line chemotherapy for human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC); Korean Cancer Study Group trial (KCSG BR13-11). First Author: Ji-Yeon Kim, Samsung Medical Center, Seoul, Republic of Korea

Background: A phase II, multicenter, randomized clinical trial of EG and PG as first-line chemotherapy for patients with HER2-negative MBC showed that EG, compared to PG, was less neurotoxic, but conferred a survival outcome similar to that of PG. In this study, we analyzed FACT-T questionnaires from patients participating in this clinical trial to determine their health-related Quality of life (HR QoL). Methods: Patients were randomly assigned to either EG or PG chemotherapy arm in a 1:1 ratio. QoL was assessed using the Korean version of the FACT-T questionnaire. After baseline assessment, HRQoL was assessed every 2 cycles for 12 cycles and every 3 cycles after 12 cycles of chemotherapy. The linear mixed model was used to evaluate the difference in HRQoL between the two treatments. Results: Of 118 patients, 117 patients except 1 patient in PG arm responded to the FACT-T questionnaires at baseline. Baseline FACT-T subscale QoL scores and overall QoL scores were not different between the EG and PG arms. During treatment, overall QoL scores and other FACT-T subscale scores did not differ between EG and PG arm. In terms of taxane-associated HRQoL, PG arm much increased taxane subscale scores after 2 cycles of chemotherapy compared to EG arm until the 13th cycle of treatment (all p ≤ 0.05, except 13th cycle (p = 0.164). Of taxane subscale scores, neuropathy specific subscore scores were presented as similar pattern to taxane subscale scores. After 13 cycles of treatment, both groups had similar intensity symptoms. Therefore, although taxane subscale score and neuropathy specific subscore were higher in the PG arm compared to the EG arm, there was no statistical significance (p = 0.086 and p = 0.062, respectively). Conclusions: EG delayed and decreased chemotherapy induced adverse events including neuropathy compared to PG. Therefore, eribulin would be a reasonable substitute for paclitaxel as first-line treatment in MBC, especially concerning neurotoxicity. Clinical trial information: NCT02263495.
10119  Poster Session (Board #107), Mon, 1:15 PM-4:45 PM
Longitudinal patient-reported symptom severity and symptom interference with activity-related and mood-related functioning and survival in patients with advanced cancer on early-phase clinical trials of immunotherapeutic or targeted agents. First Author: Goldy Geoge, Department of Symptom Research, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX
Background: We examined longitudinal changes in symptom severity and symptom interference with activity-related (WAW: work, general activity, walking) and mood-related (REM: relations with others, enjoyment of life, mood) functioning and their association with overall survival in patients with advanced cancer in early-phase clinical trials of immunotherapeutic and targeted agents. We also examined effects of therapeutic class. Methods: Patients completed the MD Anderson Symptom Inventory (MDASI) at baseline (within 1 day before start of an early-phase clinical trial), and twice-weekly assessments thereafter for 60 days. Linear mixed models and Cox proportional hazards modeling with time-dependent covariates were used. Results: 579 MDASI questionnaires were completed by 40 patients (mean age 57y, 50% male) on trials of targeted agents (50%), or immune monotherapy (50%). At least 1 severe symptom (≥7 on 0-10 scale) was reported by 55% of patients and the most frequent severe symptoms were pain (28% of patients), fatigue (25%), disturbed sleep (25%), distress (18%), dry mouth (18%), droswiness (15%), and lack of appetite (15%). Skin rash (P < 0.00) and symptom interference with WAW (P < 0.00) and REM (P = 0.024) worsened from baseline to Day 60. From baseline to last completed MDASI, worsening by ≥2 points (0-10 scale) was seen in 28% of patients for WAW and 15% of patients for REM; improvement by ≥2 points was seen in 8% of patients for WAW and 5% of patients for REM. Targeted therapy was associated with worse fatigue (P = 0.039), drowsiness (P < 0.001), disturbed sleep (P = 0.014) and lack of appetite (P < 0.001); immune therapy was associated with worse REM (P = 0.042). Worsening of composite symptoms, WAW, or REM was associated with lower overall survival (P < 0.001 for each). Conclusions: Symptom burden trajectories varied by class of therapeutic agent. Longitudinal symptomatic assessments during early-phase clinical trials can provide a fuller view of patients’ symptomatic experience and facilitate needed supportive care.

10120  Poster Session (Board #108), Mon, 1:15 PM-4:45 PM
Determinants of quality of life and survival in ambulatory oncology patients receiving chemotherapy. First Author: Derek Gerard Power, Mercy University Hospital, Cork, Ireland
Background: Identifying prognostic variables that may improve outcome in patients (pts) with cancer is a cornerstone of research. Recently, there has been interest in the prognostic value of nutritional status in pts with cancer. Methods: A prospective cohort study of ambulatory adult oncology pts undergoing chemotherapy between 2012-16 was conducted. A survey was devised, incorporating lifestyle, clinical, nutritional, biochemical (CRP, albumin, quality of life (QoL) data). Nutritional status was evaluated using the cancer cachexia (CC) consensus definition and body composition was assessed using computed tomography. Skeletal muscle index (SMI) and mean muscle attenuation (MA) were obtained. Random forest algorithms were used to identify predictors of QoL and survival. Partial dependence plots were used to assess the direction and association of these predictors with outcome. Results: 1015 pts with solid tumors participated, 56% male, median age of 64 years (IQR 55-71). Colorectal cancer was the most prevalent (27%). The majority (54%) of pts had stage IV disease. Overweight and obesity (BMI > 25 kg/m²) was highly prevalent (57%), despite high rates of cachexia (42%), sarcopenia (39%) and low MA (45%). Percentage weight loss was the biggest predictor of global QoL. Weight stable pts had the highest global QoL scores after adjustment for other variables. Significant prognostic variables for survival were cancer site and stage, followed by systemic inflammation, anorexia, weight loss and mean MA, collectively considered hallmarks of CC. Highest predicted 1 and 3 year survival rates were observed in pts with a low CRP, high albumin (> 38 g/L), without anorexia, who remained weight stable with a high mean MA (> 36 HU).
Conclusions: Malnutrition and abnormal body composition features are common in pts receiving chemotherapy but are often masked by adiposity. We demonstrated that nutritional parameters were more reliable prognostic indicators than many clinical variables, such as performance status, age and smoking status. Identifying significant prognostic variables provides conceptual guidance for the development of evidence based prediction models and tools. Further investigation is warranted.
Incidence of dermatological toxicities and fatigue in patients with cancer treated with regorafenib: A systematic review and meta-analysis of randomized controlled trials.

First Author: Miguel Quinch, Tarloco, TX

Background: Incidence of dermatological toxicities and fatigue in patients with cancer treated with regorafenib: A systematic review and meta-analysis of randomized controlled trials. First Author: Miguel Quinch, Tarloco, TX

Methods: A total of 1723 patients with hematopoietic, colorectal cancer and gastrointestinal stromal tumors from four phase 3 RCTs were eligible for analysis. Studies compared regorafenib versus placebo. All grade-HFS incidence was 603 (34.9%) in regorafenib group vs 2 (0.12%) in control group with a RR of 29.246 (95% CI: 4.392-10.169, P < 0.0001). High-grade HFS was reported in 178 (10.33%) in regorafenib group vs 2 (0.12%) in control group with a RR of 29.246 (95% CI: 9.381–91.176, P < 0.0001). The relative risks of all grade rash was 6.435 (95% CI: 3.713-11.154, P < 0.0001); high grade rash was 91.154 (95% CI: 1.753-47.927, P = 0.009); all grade fatigue: 1.624 (95% CI: 1.376-1.917, P < 0.0001); high-grade fatigue: 2.209 (95% CI: 1.329-3.672, P = 0.002); all-grade anorexia: 2.425 (95% CI: 1.678-3.503, P < 0.0001); and high-grade anorexia: 1.704 (95% CI: 0.507-5.720, P = 0.398).

Conclusions: Incidence of dermatological toxicities and fatigue in patients with cancer treated with regorafenib was significantly higher than in placebo group. Patients with regorafenib experienced a significant increase in all-grades of HFS with a relative risk of 29 for grade 3 and 4 HFS. They also contributed to significant toxicity of all-grade and high-grade rash and fatigue as well as all-grade anorexia.

Opioid use in rural breast cancer patients.

First Author: Emilio Paul Araujo-Mino, Kymera Independent Physicians, Roswell, NM

Background: Opioid use overuse spans different communities and cancer patients frequently develop pain from their disease, cancer therapy or sequela for which opioids are commonly used. Breast Cancer is a common malignancy seen across different practices. Methods: This is a retrospective study evaluating BC patients Stages I-III from January 2013 until January 2018 in three rural community cancer practices in Southeast New Mexico who had been prescribed opioids during their cancer diagnosis and treatment. Exclusions: Exclusions were development of Stage IV, other concurrent malignancies, remote history of cancer for which use opioid data was missing, Chi-square and logistic regression were performed to identify correlation and predictors of long term opioid use respectively. Results: A total of 664 patients were identified; among these 150 (23%) were prescribed an opioid at some point. 54 were excluded according to prespecified criteria. The rate of opioid use was 72% (69/96) at 3 months, 62% at 6 months (60/96) and 52% (50/96) at 12 months. 72% of user at 3 months (50/69) were also using opioids at 12 months from initial prescription x2 40.8 p=<0.001. Also 83% (50/60) of opioid use at 6 months were opioid user at 12 months x2 62.6 p < 0.001. Patient with smoking history, type of initial opioid (tramadole), opioid prescribed by surgeon, history of mental health and residence in smaller rural communities were more likely to continue using long term opioid, however it was not statistically significant. Conclusions: Opioid use in rural breast cancer patients with increased short-term use of opioids at 3 months are significantly associated with continued long-term use at one year. Several factors in the rural community may need to be further evaluated in larger studies.

Circuit aerobic and resistance exercise to target metabolic dysregulation in breast and prostate cancer survivors: The CARE trial study design.

First Author: Christina Marie Diel-Conwright, University of Southern California, Los Angeles, CA

Background: Breast and prostate cancer survivors are at an increased risk of developing comorbidities such as metabolic syndrome (MSY), diabetes, and cardiovascular disease exacerbated by cancer treatments. MSY is a cluster of risk factors including visceral adiposity, insulin resistance, hyperglycemia, hypertension, low serum high-density lipoprotein cholesterol, and hypertriglyceridemia. Exercise is an effective strategy to target MSY and therefore, we designed a novel exercise intervention referred to as circuit aerobic and resistance exercise (CARE). Our primary objective is to determine whether a 16-week CARE intervention improves components of MSY among breast and prostate cancer survivors with the primary endpoint of MSY cumulative score. Methods: We are currently recruiting sedentary, overweight/obese (BMI > 25 kg/m²) women and men diagnosed with Stage I-III breast cancer or prostate cancer, respectively, from the USC Norris Comprehensive Cancer Center and Los Angeles County Hospital. Participants are randomized to either the CARE or Attention Control group. The CARE group participates in supervised exercise sessions 3 times per week for 16 weeks. CARE is a systematically progressed program of aerobic and resistance exercise performed in a circuit that begins at a low intensity and gradually increases to high intensity over the duration. The Attention Control group performs a home-based stretching program 3 days per week. At baseline (month 0), post-intervention (month 6), and follow-up (month 8), all participants are tested for MSY components. Statistical analyses for each outcome will involve mixed effects linear regression models. The sample size (25arm within each cohort) reflects the need to obtain unbiased estimates of differences with reasonable precision. We will recruit an additional 90 patients (at present time n = 10) over the next 3 years. It is expected that this intervention will improve components of MSY in breast and prostate cancer survivors when compared to the Attention Control group, thus defining intervention and biomarker variables for more definitive trials. Clinical trial information: NCT03284346.
TPS10127 Poster Session (Board #114a), Mon, 1:15 PM-4:45 PM
Early nutrition support therapy to improve the nutrition status of head and neck cancer patients accepted concurrent chemoradiotherapy (CSTP1): Interim analysis from a prospective randomized controlled clinical study. First Author: Peng Zhang, Sichuan Cancer Hospital, Chengdu, Sichuan, China

Background: We given nutrition support treatment according to the changes by nutrition status in head and neck cancer patients at the process of definitive concurrent chemoradiotherapy (CCRT). Analyze the relationship between nutrition support therapy and CCRT side effects, quality of life score, treatment effect, prognosis and other indicators. Methods: 100 patients with head and neck cancer undergoing definitive chemoradiotherapy were enrolled. They were randomly divided into a nutritional intervention group (n= 50) and a conventional diet group (n= 50). The nutritional intervention group treated with prophylactic enteral nutrition powder formula (645.43 kcal/day, 2720.3 kcal/day) feeding before the initiation of CCRT. All patients were subjected to a standardised follow-up programme which included prospective evaluation of psychological status and HRQoL, prior to, during and after CCRT. The psychological status of those two groups were evaluated by Patient Health Questionnaire 9(PHQ-9), Generalised Anxiety Disorder Assessment 7(GAD-7) and Distress Thermometer. The primary end-point was the nutritional indicators including body weight, white blood cells, lymphocyte, albumin etc. The secondary endpoints were the psychological status. This study is ongoing; data for this interim analysis were collected at December 30, 2017. This trial is registered with www.chictr.org.cn, number: CTriC-17011243.

TPS10128 Poster Session (Board #114b), Mon, 1:15 PM-4:45 PM
Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabidiol-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). First Author: Antony Mersiades, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia

Background: Up to half of patients receiving chemotherapy of moderate or high emetic risk experience CINV despite optimal anti-emetic prophylaxis. Limited evidence suggests cannabidiol medicine in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabinoid (CBD) may improve efficacy and tolerance. The aim of this multi-centre, randomised, placebo-controlled, phase II/III trial is to determine efficacy and cost-effectiveness of the addition of an oral cannabidiol-rich THC/CBD cannabis extract for control of CINV. Methods: Target population is adult patients experiencing CINV during moderate and highly emetogenic chemotherapy regimens despite appropriate anti-emetic therapy, who are scheduled to receive at least 2 more consecutive cycles (A and B, where applicable). Treatment consists of oral THC 2.5mg/CBD 2.5mg (Tilray TN-TC111M capsules or placebo TDS days -1 to 5, in addition to guideline-consistent anti-emetics, including rescue medications. Patients will start with 1 tablet PO TDS and can dose-titrate to a maximum of 4 tablets PO TDS based on nausea control and side-effects. In the pilot trial (N = 80), subjects are randomised for cycle A, cross-over for cycle B, and nominate preferred treatment for cycle C (if applicable). The planned definitive trial (N = 250) will randomise subjects to investigational product or placebo for cycles A, B and C in a parallel design. The primary end-point is the proportion of patients gaining a complete response (no emesis and no use of rescue medications) (0–120h), with additional end-points of (i) complete response, (ii) no emesis, (iii) no significant nausea and (iv) no use of rescue medication during the a) acute, b) delayed, and c) overall phases of cycle A, B and C, (iv) adverse events, (v) quality of life, and (vi) cost-effectiveness. As of 12/02/2018, 41 of 80 patients have been recruited to the pilot study, with expected recruitment completion in 2nd quarter 2018. Funding: NSW Department of Health. Acknowledgements: Trial participants, investigators and research staff. Drug supply by Tilray. ACTRN: 12616001036404 Clinical trial information: 12616001036404.

TPS10129 Poster Session (Board #115a), Mon, 1:15 PM-4:45 PM
Effect of nutritional support with highly purified, whey proteins for malnutrition and sarcopenia in patients affected with stage II/III colorectal or breast cancer: A blind, placebo controlled, randomized clinical trial. First Author: Federica Mazzuca, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy

Background: Malnutrition and sarcopenia may arise in both colorectal and breast cancer since the first visit. Previous studies demonstrate that malnourished cancer patients have a decreased quality of life and experience more chemotherapy-toxicity. Protein supplementsations could prevent loss of lean body mass that goes along with malnutrition and sarcopenia. Therefore, the role of whey proteins takes a great deal of interest. We propose a randomized study, placebo-controlled, aimed at evaluating the activity and safety of a highly purified, whey protein nutritional support (PROLYOTIN) in cancer patients undergoing adjuvant chemotherapy (EudraCT n. 2018-000122-64). Methods: Patients with histological diagnosis of stage II/III according to AJCC system, breast or colorectal cancer, referred for adjuvant chemotherapy will be eligible. Obtained written informed consent, all patients will be blind-randomized with 1:1 ratio in two arms: A (PROLYOTIN) vs. B (placebo). Patients will be assessed before starting chemotherapy (T0), after 3 (T1) and 6 months (T2), with respect to a physico-nutritional examination, skeletal muscle mass calculation by CT scan and Body Impedance Assessment. Mini Nutritional Assessment, Malnutrition Universal Screening Tools and Quality of life by EORTCQLQ C-30 will be also done. At the same time frames (T0, T1, T2) detailed medical records, tumor characteristics, dietary practices and laboratory values (blood count, serum proteins, cholesterol, triglycerides, amylases, lipases, ESR, CRP, glucose, tumor markers, cortisol, insulin, vitamin D, LDH and CK) will be collected by a specialist team of medical oncologists and dieticians. The patient-adherence to protocol will be also monthly evaluated. Primary objectives are to evaluate the nutritional status at baseline, T1 and T2 and the difference between the PROLYOTIN and placebo arms. Secondary, correlations between nutritional status and clinicopathological parameters, and the quality of life will be analyzed. A total of 220 patients will be enrolled (95% CI, β 10%). Clinical trial information: 2018-000122-64.

TPS10130 Poster Session (Board #115b), Mon, 1:15 PM-4:45 PM
A randomized phase II study of the nutritional and exercise treatment for the elderly patients with advanced non-small cell lung or pancreatic cancer. The NEXTAC-TWO study. First Author: Satoru Miura, Niigata Cancer Center Hospital, Niigata, Japan

Background: Most advanced cancer patients experience fatigue, anorexia, and declining physical function due to cancer cachexia and for aging, for which effective treatment has not been established. We performed a phase I study, called NEXTAC-ONE, and demonstrated the feasibility of multi-modal interventions, namely, nutritional support and physical exercise in elderly cancer patients. We conducted the next-step multi-center, randomized phase II study to evaluate the efficacy of previously investigated multi-modal interventions in elderly cancer patients. Methods: Patients with chemo-naive advanced non-small cell lung cancer or pancreatic cancer, age ≥ 70 years, PS < = 2, with adequate organ function and without disability by the modified Katz index, will be eligible. Totally, 130 participants will be recruited from 15 Japanese institutions and will be randomized into either the intervention group or a control group. Interventions and assessment will be performed 4 times every 4:2 weeks from the date of randomization. Interventions will consist of nutritional counseling, nutritional supplements (rich in branched-chain amino acids), and a home-based exercise program. The exercise program will include low-intensity daily muscle training and life-style education to promote physical activity. The primary endpoint is disability-free survival. It is defined as the period from the date of randomization to the date of developing disability or death due to any cause. This trial also plans to evaluate improvement in nutritional status, physical condition, quality of life, activities of daily living, overall survival, and safety as secondary endpoints. Enrollment began in August 2017. Eighteen of the planned 130 participants have been enrolled at the time of this submission. Study results will demonstrate efficacy of multi-modal interventions for elderly cancer patients and application for maintenance of physical and nutritional condition of patients with cancer cachexia. This work is supported by a grant-in-aid from the Japan Agency for Medical Research and Development. Clinical trial information: UMIN000028801.
A randomized phase II clinical trial of a fasting-mimic diet prior to chemotherapy to evaluate the impact on toxicity and efficacy. First Author: Tanya B. Dorff, City of Hope, Duarte, CA

Background: Chemotherapy toxicity impacts dose intensity as well as temporally deteriorating quality of life; some toxicity can be permanent, such as neuropathy. We previously demonstrated that fasting induces Differential Stress Resistance and hypothesized that fasting may protect normal host cells from chemotherapy toxicity, while potentially sensitizing cancer cells to chemotherapy. A low calorie, low protein fasting-mimicking diet (FMD) may be more acceptable than pure fasting. We are studying whether FMD will reduce chemotherapy toxicity and/or enhance efficacy. Changes in glucose and insulin-like growth factor 1 (IGF1) may mediate or be biomarkers for the protective effects of fasting and will be studied in the trial population.

Methods: Randomized phase II in 2 parallel cohorts (Prostate, n = 60, Breast n = 60). Treatment: Arm A = restricted diet consumed 3 days prior to and 24 hours after chemotherapy for 4 cycles. Arm B = regular diet. Eligibility: breast cancer with AC or TC in neoadjuvant setting, prostate cancer treated with Docetaxel, up-front or for mCRPC, BMI > 18.5. Exclusion: Diabetes Mellitus. Endpoints: Primary: Grade 2+ non-hematologic symptomatic toxicities experienced during 4 courses; additionally, radiographic (RECIST) response and PSA changes. Secondary: toxicity (all grade 2-4 events, dose reductions/delays) and efficacy (pathologic response for breast cancer, PSA/RECIST response for prostate cancer). Biomarker: plasma insulin, glucose, IGF1 and IGF binding protein (IGFBP) at baseline, and each cycle. Statistics: Proportion of patients with grade 2-4 symptomatic toxicities will be compared between treatment arms using stratified Mantel-Haenszel test; p-value ≤ 0.20 indicates the diet intervention is promising. With 60 patients in each cohort there is 88% power; initial analyses will evaluate breast/prostate cancer separately, yielding standard error no more than +/- 0.18 for estimates of the difference in the proportions of patients who experience a specific toxicity (or the composite). Quality of life will be assessed with SWOG questionnaire on day 1 of each chemotherapy cycle. Progress: 70 of 120 planned subjects have been accrued. Clinical trial information: NCT01802346.
Cancer.

**Background:** Nelarabine (Nel) is a T-cell specific agent, FDA approved for patients who have failed at least two chemotherapy regimens. COG AALL0434 evaluated its safety and efficacy when incorporated in augmented BFM chemotherapy in newly diagnosed T-ALL and T-L patients.

**Methods:** AALL0434 enrolled 1,895 patients (2007-2014) and included a 2 x 2 pseudo-factorial randomization using the ABFM regimen. Patients were randomized to receive escalating dose methotrexate without leucovorin rescue + pegaspargase (CMXT) or High Dose MTX (HDMTX) + leucovorin rescue. Intermediate and high risk patients with T-ALL and T-L were randomized to receive or not receive six 5-day courses of (Nel) 650 mg/m^2/day. The intermediate and high risk T-ALL patients received prophylactic (1200 cGy) or therapeutic (1800 cGy for CNS3) cranial irradiation. T-ALL patients with induction failure were non-randomly assigned to HDMTX+Nel.

**Results:** For all randomized T-ALL patients, the 4-year disease-free survival (DFS) and overall survival (OS) rates were 84.3 +/- 1.1% and 90.2 +/- 0.9%. The 4-year DFS rate for T-ALL patients randomized to Nel (N = 323) vs no Nel (N = 336) was 88.9 +/- 2.2% vs 83.3 +/- 2.5% (p = 0.0332). Among T-ALL patients randomized to CMXT the 4-year DFS for Nel (N = 147) vs no Nel (N = 151) was 92.2 +/- 2.8% vs 89.8 +/- 3.0% p = 0.3825. For those randomized to HDMTX, 4-year DFS was 86.2 +/- 3.2% with Nel (N = 176) vs 78.0 +/- 3.7% without Nel (N = 185), p = 0.024. Differences between DFS in a 4-arm comparison were highly significant (P = 0.002), with no significant interactions between MTX and nelarabine randomizations (P = 0.41). T-ALL induction failure patients (N = 43) assigned to HDMTX/Nel had a 4-year DFS of 54.8 +/- 8.9%. Nelarabine did not show an advantage for high risk T-L patients, with 4-year DFS 85.0 +/- 5.6% vs 89.0 +/- 4.7% for Nel (N = 60) vs no Nel (N = 58), P = 0.2788. Overall toxicity and neurotoxicity were acceptable, with significant differences between treatment arms (P < 0.014).

**Conclusions:** COG AALL0434 is the largest trial ever conducted for newly diagnosed T-ALL and T-L, and showed outstanding overall outcomes. Nelarabine improves DFS for children and young adults with T-ALL and should become a new standard of care for this population. Clinical trial information: NCT00408005.

**Research Question:**

Effect of dexrazoxane on left ventricular function and treatment outcomes in patients with acute myeloid leukemia: A Children's Oncology Group randomized phase II trial.

**Background:** Overall survival (OS) for pediatric acute myeloid leukemia (AML) has improved to > 65% due in part to the use of anthracycline (ATC)-containing chemotherapy regimens. ATC is also associated with increased cardiotoxicity risk. Cardioprotective agents such as dexrazoxane (DEX) may reduce cardiac injury during treatment. While data on the benefit of DEX are promising, studies in pediatric AML patients are limited. Given the very high ATC exposure in pediatric AML therapy, evaluating the utility of DEX in this population is critical.

**Methods:** On Children’s Oncology Group trial AAML1031, DEX was administered at the discretion of treating physicians. DEX exposure was documented at each treatment course, and ejection fraction (EF) and shortening fraction (SF) values were recorded after each course and in follow up. Absolute change in EF from baseline (ΔEF) was computed for each course. Early LVSD was defined as any EF < 50% or SF < 24% from the start of frontline therapy through the follow-up at one-year off protocol. ΔEF at each course, occurrence of LVSD, and 3-year OS and disease-free survival (DFS) were compared for DEX exposed and unexposed.

**Results:** 1014 patients were included; 96 were DEX-exposed at each ATC course received and 918 were never exposed. Distributions of sex, age, race, initial white blood cell count, risk group, and treatment arm were similar for DEX exposed and unexposed. DEX exposed patients had smaller declines in EF early in the protocol (early exposure) compared to DEX unexposed patients. Patients who had early DEX exposure had non-significantly lower EF at the first ATC (4.6% ΔEF for DEX exposed vs. 8.7% for unexposed; P = 0.16). Early LVSD occurred in 14% of patients exposed to DEX and 22% of patients unexposed (P = 0.04). Early ΔEF was also smaller in patients exposed to DEX in the first ATC (ΔEF 0.3% ± 0.01% vs 3.0% ± 0.30% ΔEF unexposed; P = 0.02). The overall incidence of LVSD was 17% in DEX exposed patients and 22% in unexposed patients (P = 0.05).

**Conclusions:** DEX exposure was associated with smaller reductions in EF throughout pediatric AML therapy and a lower risk for early LVSD. Small numbers may have limited our ability to detect differences in OS and EFS. Longer follow-up is required to elucidate the sustained benefit of DEX.
Background: NF-1 loss-of-function alterations are associated with development of plexiform neurofibromas (PNs). NF-1-associated PNs can arise early in life in different locations, with variable and significant morbidity. Many patients (pts) progress following surgery, and currently there are no effective systemic therapies. The MEK inhibitor trametinib is being evaluated in pediatric pts across a spectrum of tumor types in a dose-escalation (ESC) cohort of a phase I/IIa study (Kieran et al, ASCO 2015; NCT01677741). Here we report preliminary analyses in this study of safety and clinical benefit with dabrafenib in pts with HGG across the ESC and disease-expansion (EXP) cohorts.

Methods: Pts aged 1 to < 18 y with HGG who had refractory or progressive disease after receiving ≥ 1 standard therapy were treated with dabrafenib (2 mg daily doses) either in the ESC cohort or with the recommended dose of 5.25 mg/kg/d (pts < 12 y) or 4.5 mg/kg/d (pts ≥ 12 y) in the EXP cohort. Measurable disease was not required. Primary objectives were safety and tolerability, and secondary objectives included tumor response and pharmacokinetics. Tumor response was reported by independent review (IR) and investigator assessment (IV) using RANO criteria. Exploratory analyses included independent histopathological review and tumor biology analysis (eg, mutation, methylation status).

Results: Pts (n = 31) were treated with dabrafenib across the ESC (n = 8) and EXP (n = 23) cohorts. Median age was 14 y (range, 3 - 18 y). Across both cohorts (n = 31), the most frequent TRAEs (any causality) were GI (68%), rash (40%), and fatigue (39%). Grade 3/4 AEs occurred in 12/31 pts (39%). No on-treatment deaths occurred. Measured duration of exposure was 22 wk (range, 4-225 wk), and 10/31 pts (32%) had treatment ongoing at the data cutoff (September 2017). Median age was 5.5 y (range, 1-16 y), and prior therapies included surgery (n = 5), biologics (n = 1), and targeted therapy (n = 1). Treatment-related AEs (TRAEs) were reported in 9 of 10 pts (90%), and 1 pt discontinued due to a TRAE. The most frequent TRAEs were paronychia (50%) and rash (40%). Tumor progression was confirmed in 7/10 pts. ATRT Analysis of the full NF-1 PON cohort (n = 26) is ongoing; across this cohort, 12 of 26 pts (46%) had a PR (> 20% volume reduction) by IR, and 10 of the 12 responses (83%) were ongoing. Conclusions: Trametinib demonstrated a manageable safety profile in pediatric pts with NF-1-associated PNs. Using stringent criteria for response determination, the objective response observed with trametinib support continued investigation in this patient population. Clinical trial information: NCT02124772.

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Phase II trial of irinotecan/temozolomide/dinutuximab/granulocyte macrophage colony stimulating factor (IT/DIN/GMCSF) in children with relapsed/refractory Hodgkin lymphoma (NBL). A report from the Children's Oncology Group (COG). First Author: Rajan Muthusamy, University of Michigan, Ann Arbor, MI

Background: COG ANBL1221 was a randomized Phase II selection design trial for patients (pts) with relapsed/refractory NBL. Randomization was stopped early when IT/DIN/GMCSF was shown to be the optimal combination for further study. In the small cohort assigned to IT/DIN/GMCSF, the objective response rate was 55%. An expanded cohort was evaluated to more accurately assess response rate and better define the toxicity profile of this combination. Methods: Pts were eligible at first relapse/progression or first designation of refractory disease. Cycles were administered every 21 days. Objective responses were confirmed centrally. Toxicities were graded according to CTCAE v4.0. Results: 53 eligible pts were assigned to IT/DIN/GMCSF; 17 during the randomized portion, 36 during study expansion. Median age was 5.1 years (range 1.3-15.9), 39 pts (74%) had measurable disease. Fourteen (26%) had MYCN amplified tumors, 20 (38%) had previously undergone high-dose chemotherapy with stem cell rescue, and 14 (26%) had received prior anti-GD2 antibody. 22 (42%) had a relapsed disease and 31 (58%) had a relapse/progression (PD). Subjects received 378 total cycles (median 6). Of 53 pts assigned to IT/DIN/GMCSF, 21 experienced objective responses (40%; 95% CI [26, 53]); 10 PR, 11 CR. Seven had PD, 23 had stable disease. Two did not receive protocol therapy and did not undergo disease evaluations, but were included in the intention-to-treat analysis. In 11 (22%) pts had MYCN amplified tumors and 9 (43%) had previously received an anti-GD2 antibody. Of the 51 evaluable for toxicity, 13 (25%) had Grade 3 pain, 8 (16%) had Grade 3 diarrhea, and 4 (8%) had Grade 3 vomiting. Neutropenia (Grade 3) was observed in 14 (27%), Grade 3 thrombocytopenia in 5 (10%), and Grade 3 infection in 11 (22%).

Conclusions: IT/DIN/GM-CSF showed significant anti-tumor activity in pts with relapsed/refractory NBL. This combination was well-tolerated in a cohort of >50 pts. Studies of biomarkers that may identify pts most likely to respond to this chemo-immunotherapeutic regimen are in progress. Clinical trial information: NCT01761194.

Phase II trial of irinotecan/temozolomide/dinutuximab/granulocyte macrophage colony stimulating factor (IT/DIN/GMCSF) in children with relapsed/refractory Hodgkin lymphoma (NBL). A report from the Children’s Oncology Group (COG). First Author: Rajan Muthusamy, University of Michigan, Ann Arbor, MI

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Association of exercise with late mortality in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. First Author: Jessica Scott, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Adult survivors of childhood cancer are at excess risk for late mortality compared to the general population. Whether exercise attenuates this risk is not known. Methods: We examined the association between self-reported vigorous exercise [metabolic equivalent-hrs/week (MET-hwk)] and cause-specific late mortality among 15,450 adult survivors participating in the Childhood Cancer Survivor Study using multivariable piecewise exponential regression analysis to estimate rate ratios (RR). Longitudinal change in vigorous exercise was evaluated among a subset of 5689 survivors. Results: During a median follow-up of 10 years (interquartile range: 15 years), 1063 deaths (811 health-related, 120 recurrence/progression of cancer, and 132 other causes) were documented. At 15 years the cumulative incidence of all-cause mortality was 11.7% (95% CI, 10.57-12.80) for 0 MET-hwk; 8.6% (95% CI, 7.4-9.2) for 3-6 MET-hwk; 7.4% (95% CI, 6.2-8.5) for 9-12 MET-hwk, and 8.0% (95% CI, 6.5-9.4) for 15-21 MET-hwk (P < 0.001). There was a significant inverse association across quartiles of exercise and all-cause mortality after adjusting for chronic health conditions and treatment exposures (P = 0.023). Among a subset of 5689 survivors, increased exercise (>7.9 ± 4.4 MET-hwk) over an 8-year period was associated with a 40% reduction in all-cause mortality rate compared with maintenance of low exercise (RR = 0.60; 95% CI, 0.44 to 0.82, p = 0.01). Conclusions: Vigorous exercise in early adulthood and increased exercise over eight years is associated with lower risk of late mortality in adult survivors of childhood cancer.

Impact of exercise on psychological burden in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Emily S. Tonorezos, Adult Long Term Follow-Up Program, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Adult survivors of childhood cancer are at risk for adverse psychological outcomes. Whether exercise can attenuate this risk is unknown. Methods: Using a longitudinal design, 6199 CCSS participants (median [range] age 34 years [22-54] and median [range] age at diagnosis 10 years [0-21]) completed a baseline questionnaire assessing vigorous exercise, medical and psychological conditions. Psychological outcomes were evaluated in a subsequent questionnaire a median of 7.8 years later (range 0.1-10). Primary outcome was overall psychological burden, defined as: symptom level above the 90th percentile of population norms on the Brief Symptom Inventory-18 for depression, anxiety, or somatization; cancer-related pain, cognitive impairment; or poor quality of life. Log-binomial regression estimated associations between exercise [total metabolic equivalent-hrs/wk] and these outcomes adjusting for exercise during childhood and the Cancer Treatment Characteristics Questionnaire (CTC-Q).

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Background: Although renal cell carcinoma (RCC) is the second most common pediatric kidney cancer, no previous prospective clinical trials have been conducted. ARENO321 tested the hypothesis that RCC with localized completely resected disease, including those with lymph node involvement, has a favorable prognosis without adjuvant medical therapy. Methods: From 2006 to 2012, patients up to age 30 years with centrally reviewed pathology confirmation of RCC were prospectively enrolled. Patients with complete resected disease were followed without adjuvant therapy, independent of TNM stage. Results: 62 eligible patients enrolled (35 male: 27 female; median age 13.2 yr (range 0.17 - 22.1)). Histology was TFE-associated RCC (TRCC; 33, 53.2%), RCC NOS (21, 33.9%), papillary RCC (5, 8.1%) and Renal Medullary Carcinoma (RMC; 3, 4.8%). 58 (93.5%) patients had all disease completely resected at diagnosis with stages 1 (27, 43.5%), 2 (7, 11.3%), and 3 (24, 38.7%) disease. Three patients with stage 4 (M1) and one with stage 3 had an incomplete resection. Surgery included radical nephrectomy (50) and partial nephrectomy (12). Lymph node (LN) status was NO (21 (33.9%), N1 (19 (30.6%), and N2 (22 (35.5%). Histology for patients with N1 disease was: TRCC (13, 68.4%), RCC NOS (4, 21.1%) and RMC (2, 10.5%). Four-year EFS and OS for the completely resected group were: 87.2% (95% CI 77.0 – 97.4) and 94.6% (87.6-100), respectively; and by stage were: 1 (92.4%) (80.7-100) and 96.2% (87.7-100), 2 (100%) and 97.2% (77.6 – 100), and 3 (87.6 – 97.2) and 93.3% (67.6-100). OS p-value 0.294, OS-p-value 0.722. Four-year EFS and OS by histology for the overall group were: TRCC: 87.7% (74.2-100) and 93.6% (83.3-100), papillary RCC: 100% and 100%, RCC NOS: 87.7% (70.3-100) and 100%, and RMC: 33.3% (0.86-0.7) and 33.3% (0.86-0.7). The 15 patients with completely resected disease (N0M0) had 88% (95% CI 79.0-96.8) 5-year OS and EFS. Conclusion: Favorable outcomes can be achieved without adjuvant therapy in children and adolescents with completely resected RCC, including those with locally advanced disease and lymph node involvement. Clinical trial information: NCT00335956.

Hope and benefit-finding among adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. First Author: Abby R. Rosenberg, Seattle Children’s Cancer and Blood Disorders Center, Seattle, WA

Background: Adolescents and Young Adults (AYAs) with cancer are at risk for poor psychosocial outcomes, perhaps because they have not acquired the skills to navigate illness. We previously reported that a novel, brief, age-appropriate, skills-based intervention (“Promoting Resilience in Stress Management” (PRISM)) was associated with improved quality of life and psychological distress. In this secondary analysis, we aimed to determine if PRISM also improved targeted skills of hopeful thinking, benefit-finding, and goal-setting. Methods: PRISM consists of 4, 30-60 minute, in-person, 1:1 sessions plus a facilitated family-meeting targeting stress-management, goal-setting, cognitive reframing, and meaning-making. English-speaking AYAs (ages 13-24 years) with cancer were randomized to receive either PRISM or psychosocial usual care (UC). Participants completed surveys upon enrollment and 6 months later. Mixed effects regression models estimated associations between PRISM and hopeful patterns of thought (Snyder Hope Scale), benefit-finding (benefit-finding scale for children), and goal-setting (quered with open-ended items about short- and long-term goals, then evaluated by 3 blinded coders with a 10-point, a priori defined tool to identify specific, measurable, and actionable goals) at 6 months. Results: Of N = 92 enrolled AYAs (48 PRISM and 44 UC), 73% were 13-17 years-old, 43% were female, and 62% had a diagnosis of leukemia or lymphoma. Attrition was 19% and 23% in each arm at 6 months. For the study’s primary outcome, adjusted odds ratio: 2.1, 95% CI: 1.0-4.1, p = 0.022. The probability of globe salvage was improved in eyes with a 5-year OS of 87.2% (95% CI 77.0-97.4) and 91.3% (77.1-100)) (EFS 0.6, p = 0.05. We did not detect changes in goal-setting (Goals: -0.5 points, 95% CI -1.2-0.3, d = -0.3, p = 0.23). Conclusions: A novel intervention targeting skills for AYAs with cancer was associated with significant improvements in hope and benefit-finding, 2 key skills which may mitigate later psychosocial risk. Clinical trial information: NCT023408.

Aqueous humor genomics predicts eye salvage in retinoblastoma. First Author: Liya Xu, University of Southern California, Los Angeles, CA, US

Background: Retinoblastoma was one of the first cancers to demonstrate a genetic basis to the development of cancer. However, unlike many cancers, Rb cannot be directly biopsied due to the high risk of extracocular cancer spread. Therefore, unless the eye is enucleated, tumor tissue is not evaluated for genetic and genomic changes and these alterations are not used to inform diagnosis or prognosis for this disease. However, in a recent publication in JAMA Ophthalmology,(Berry JL, Xu L et al. JAMA Ophthalmol, 2017) we demonstrated that tumor-derived cell-free DNA can be extracted from the aqueous humor (AH) of Rb eyes, which is safe to extract even with active intraocular disease. The purpose this current study was to identify somatic chromosomal copy number alterations (sCNAs) in tumor-derived cell-free DNA in the AH of Rb eyes and to correlate with clinical outcomes particularly tumor relapse requiring enucleation. Methods: AH was extracted via pars centesis from Rb eyes during intravitreal injection of chemotherapy or enucleation. Shallow whole genome sequencing was performed to assess for cell-free tumor DNA fractions and highly-recurrent sCNAs in Rb which include gain of 1q, 2p, 6p and loss of 13q and 16q. Globe salvage was recorded. Results: 26 patients were included; 3 patients had both eyes included for 29 eyes. From these, 63 samples of AH were analyzed; 5 post-enucleations and 58 during intravitreal chemotherapy injection. Ultimately 13 eyes required enucleation and 16 eyes were salvaged. Follow-up ranged from 8-43 months (median 17 months). 6p gain was the most common sCNA found in 10/13 enucleated eyes (77%) compared to 4/16 (25%) of salvaged eyes (p = 0.009). The mean amplitude of 6p gain was 1.47 in the enucleated group versus 1.07 in the salvaged group (p = 0.001). The presence of a detectable sCNA in enucleated eyes was 92% while in salvaged eyes was 38% (p = 0.022). The presence of sCNA in AH was associated with improved outcomes. Conclusions: We demonstrated that AH can be easily extracted from Rb eyes, and can be used to identify genetic aberrations which may correlate with enrollment of patients to therapeutic trials.

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Parallel genomic and immune profiling of relapsed and metastatic osteosarcoma to reveal bases of low immunogenicity. First Author: J Andrew Livingston, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite the high levels of point mutations, rearrangements, and other genomic instability events such as kataegis and chromothripsis, immune checkpoint inhibitors have shown limited clinical activity in osteosarcoma (OS). We completed in-depth parallel genomic and immune profiling in a cohort of 48 patients with high-grade osteosarcoma (relapsed or metastatic in 42) to determine potential mechanisms of primary resistance to immunotherapy and identify strategies to enhance immunogenicity.

Methods: We utilized whole-genome sequencing (average coverage 75X), RNA sequencing, and immune profiling by T-cell receptor (TCR) sequencing and immunohistochemistry to analyze mutation load, cytotoxic and suppressive cell activity, relevance of checkpoint-related genes, and characterize immune infiltration in a clinically annotated set of primary resection, local relapse, and metastatic OS tumor specimens and matched normal tissue.

Results: We observed high levels of gene rearrangements in approximately 60% of OS patient samples, however transcriptome sequencing showed a lack of fusion transcript expression from these rearrangements. Further, < 10% of point mutations were expressed, generating few neoantigens. Immune-related pathways, including immunosuppressive PD-L1 were upregulated in all tumors relative to older patients, as well as from other patients. Higher numbers of deleted genes were associated with higher immune infiltrate. Overall TCR clonality was low and did not correlate with mutation burden. T cell clonality did not differ by PTEN or HLA status.

Conclusions: In the majority of OS, there is a lack of neoantigen expression and presentation. However, a subset of patients exhibit increased PD-L1 expression associated with lower levels of T-cell clonality, for which immune checkpoint blockade may be adequate and warrants further investigation.

ROR1-specific CAR for neuroblastoma using sleeping beauty-modified t cells. First Author: Fiorela Natali Hernandez Tejada, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Adoptive transfer of chimeric antigen receptor (CAR)-modified T cells is predicted to provide a treatment option for advanced/refractory neuroblastoma. One potential target, receptor tyrosine kinase-like orphan receptor tyrosine kinase-1 (ROR1), is a cell surface protein that is aberrantly expressed on solid organ tumors including neuroblastoma. Methods: A ROR1-specific CAR was developed by linking a ROR1-specific scFv to a mutated IgG4-Fc stalk and co-stimulatory endodomains CD3-zeta and CD28 (ROR1R*CD28 CAR). Human T cells were genetically modified to express the ROR1-CAR by electro-transfer of DNA plasmids from Sleeping Beauty system and (i) directly injected the next day under technology designated as point-of-care (P-O-C) or (ii) numerically expanded for 14 days on ROR1* activating and propagating cells (AaPC). Redirected specificity for ROR1 was assessed in vitro by chromium release assay and cytokine release. To demonstrate therapeutic potential, the ROR1R*CD28 CAR manufactured under the two conditions, were infused into NSG mice bearing disseminated CHLA 255 ROR1 + neuroblastoma cells. Redirected specificity for ROR1 was assessed in vitro by chromium release assay and cytokine release. To demonstrate therapeutic potential, the ROR1R*CD28 CAR manufactured under the two conditions, were infused into NSG mice bearing disseminated CHLA 255 ROR1 + neuroblastoma cells.

Results: The day after electroporation, T cells had (i) directly injected the next day under technology designated as point-of-care (P-O-C) or (ii) numerically expanded for 14 days on ROR1* activating and propagating cells (AaPC). Redirected specificity for ROR1 was assessed in vitro by chromium release assay and cytokine release. To demonstrate therapeutic potential, the ROR1R*CD28 CAR manufactured under the two conditions, were infused into NSG mice bearing disseminated CHLA 255 ROR1 + neuroblastoma cells.
Survival and delayed effects of risk-stratified hepatoblastoma patients treated in the JPLT-2 trial. First Author: Eiso Hiyama, Hiroshima University, Hiroshima-Shi, Japan

Background: The Japanese Study Group for Pediatric Liver Tumor (JPLT) -2 trial (2000-2012) has been conducting to evaluate the efficacy of the CITA regimen, consisting of cisplatin/pirarubicin, in patients with hepatoblastoma (HB) stratified by PRETEXT according to the PRETEXT staging system. In JPLT-2, PRETEXT III/IV tumors were initially resected or underwent two courses of low-dose CITA before resection and an additional four courses of CITA after resection. Of the PRETEXT III/IV or metastatic tumors, those that responded to two courses of CITA underwent four more courses of CITA, and the non-responsive tumors received four courses of a second-line regimen consisting of ifosfamide, pirarubicin, etoposide, and carboplatin. Highly metastatic or refractory tumors were treated with high-dose chemotherapy and stem cell transplantation. Results: Among the 360 patients who were eligible in the JPLT-2 trial, 5-year event-free survival rates of patients with PRETEXT I/IIII HB were 94/82%, while those of patients with PRETEXT IV and metastatic HB were 65/47/46.3% and 44/36/30.9%, respectively (Table). Except for 40 patients who underwent primary resection, complete resection of the primary tumor after CITA was achieved in 85%, 66%, and 56% of patients with PRETEXT III, PRETEXT IV, and metastatic tumors, respectively. The outcomes of the patients who received high-dose chemotherapy did not improve. Of those patients who survived, 68 experienced late-phase complications with toxicity, 12 cardiotoxicity, 5 maldevelopment, and 12 second malignancies. Conclusions: Compared with other multicenter cooperative protocols, treatment with the CITA regimen achieved similar rates of survival and relatability. However, the rates of toxicity and a second malignancy were higher and that of cardiotoxicity lower compared with other studies. Reduction of the chemotherapy dose should be considered in low-risk patients, while more promising strategies such as novel targeted drugs should be considered in intermediate- and high-risk patients with HB. Clinical trial information: UMIN000001116.

Summary of JPLT-2.

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M: metastasis

10526 Poster Discussion Session; Displayed in Poster Session (Board #199), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The association between atopy and Hodgkin’s lymphoma in teenagers and young adults: A UK nationwide case control study. First Author: Meena Ratia, University College London (UCL), London, United Kingdom

Background: Hodgkin’s Lymphoma (HL) is the commonest cancer in teenagers and young adults (T&YAs). Incidence in this age group has been increasing since the early 1990s in the UK, Australia, Canada and several US states. The aetiology and safety of HL in T&YAs are unclear. Previous studies have shown conditions involving impaired immune regulation, including HIV, immunosuppressive treatment and some autoimmune conditions, are associated with increased HL risk. However, few studies have investigated the link between atopy, the commonest form of childhood immune dysregulation, and HL and the results have been conflicting and inconclusive. This study uses large scale, UK data to investigate the association between atopic disease and immunosuppression with development of HL in T&YAs.

Methods: We conducted a case control study using primary care data from the UK Clinical Practice Research Database linked to hospitalization data. 1,238 cases with HL diagnosed between the ages of 0-49 years were individually matched using concurrent sampling to six controls each by age, sex and follow up time (7,428 controls). Multivariable logistic regression was used to investigate the association between atopic diseases (asthma, eczema, hay fever) and immunosuppression with HL incidence. Results: A prior diagnosis of asthma was associated with 26% increased odds of developing HL (Adjusted Odds Ratio (AOR)1.26, 95%CI 1.08-1.49 p = 0.005). There was weak or no evidence for an association between eczema or hay fever and HL (AOR:1.15, 95%CI 0.98-1.34 p = 0.09; AOR:0.88, 95%CI 0.73-1.05 p = 0.15, respectively) or that HL risk was increased in individuals with more than one atopic diagnosis (p = 0.07). Consistent with previous studies, we found 14% of HL cases and controls under 65 years of age who had hay fever and those with a history of asthma were 1.3 times more likely to have a history of HL (AOR:1.30, 95%CI 1.13-1.50 p = 0.002). Conclusions: This study has identified asthma as a risk factor for developing HL in early life. These findings add to the growing evidence that immune dysregulation is involved in development of HL in T&YAs. Understanding the mechanisms and pathways underlying this relationship could help uncover markers for HL detection, recurrence and to develop new therapeutic interventions.

10527 Poster Discussion Session; Displayed in Poster Session (Board #200), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Intravenous fosaprepitant for the prevention of chemotherapy induced vomiting in children: A double blind placebo controlled, phase III randomized trial. First Author: Archit Joshi, Cancer Institute (WIA), Chennai, India

Background: Fosaprepitant, is a Neurokinin-1 (NK-1) receptor antagonist, approved in adults for the prevention of vomiting associated with administration of moderately or highly emetogenic chemotherapeutic agents. The efficacy and safety of fosaprepitant in children has not been investigated. Hence, we conducted a phase III randomized trial to assess the safety and efficacy of fosaprepitant in children. Methods: The study was a phase III, single centre, double blind, randomized placebo controlled trial. Children aged 1-12 years with documented malignancy, who were scheduled to receive moderately or highly emetogenic chemotherapy, were randomly assigned to arm A (Fosaprepitant) or arm B (Placebo). Arm A received intravenous ondansetron (0.15 mg/kg) plus dexamethasone (0.075 mg/kg) followed by fosaprepitant (3 mg/kg) short infusion. Arm B received intravenous ondansetron (0.15 mg/kg) plus dexamethasone (0.15 mg/kg) followed by normal saline as placebo. Oral ondansetron and dexamethasone were continued for 48 hours after completion of chemotherapy. Primary endpoint of the study was the proportion of patients who achieved a complete response (defined as no vomiting, no retching) during the 25-120 hours (delayed phase) after administration of fosaprepitant. Secondary end-points were proportion of patients who achieved complete response during the acute (0-24 hours) and overall phases after administration of fosaprepitant. Results: 135 patients were analyzed (68 in fosaprepitant arm and 67 in placebo arm). Complete response rates were significantly higher in fosaprepitant arm compared to placebo arm during acute phase (84% vs. 57%, p < 0.001), delayed phase (79% vs. 51%, p < 0.001) and overall phases (69% vs. 42%, p = 0.0014). Three (4%) patients in fosaprepitant arm and fourteen (21%) patients in the placebo arm required rescue anti-emetics (p = 0.004). No fosaprepitant related grade 3-4 adverse events were observed. Conclusions: Addition of fosaprepitant to ondansetron with dexamethasone is safe and effective for the prevention of chemotherapy induced vomiting in children being treated with moderately or highly emetogenic chemotherapy.

Clinical trial information: CTRI/2017/02/007925.
The challenge of pediatric oncology: New business models to accelerate innovation. First Author: Sonya Das, MIT Laboratory for Financial Engineering, Cambridge, MA

Background: Few patient populations are as helpless and in need of advocacy as pediatric cancer patients. Pharmaceutical companies have historically faced significant financial disincentives to pursue pediatric oncology therapeutics, including low incidence, high costs of conducting pediatric trials, and a lack of funding for early-stage research. One way to accelerate innovation in this field is the formation of a collaborative business model involving private, public, and philanthropic stakeholders. We explore this idea by simulating the financial returns of a hypothetical collection of pediatric cancer drug projects under several different business structures. Methods: Using published studies of pediatric oncology research and the cost of drug development, and existing clinical trials of pediatric oncology therapeutics at clinicaltrials.gov, we identified 77 potential drug development projects to be included in a hypothetical portfolio. The returns of this portfolio were simulated so as to compute the financial returns and risk. Simulated business structures include combining projects at different clinical phases of development, obtaining partial funding from philanthropic grants, and obtaining government guarantees to reduce risk. Results: The purely private-sector portfolio exhibited expected returns ranging from -34.2% to 0.0%, depending on the model parameters assumed. This suggests significant financial disincentives for pursuing pediatric oncology therapeutics and implies that financial support from the public and philanthropic sectors is essential. Phase diversification increases the likelihood of a successful drug, and yielded expected returns of -17.8% to 36.4%. Standard philanthropic grants had a marginal impact on expected returns. Government guarantees were more effective by reducing downside risk, with returns ranging from -9.5% to 12.8%. Conclusions: A combination of financial and business strategies has the potential to maximize expected return while eliminating some downside risk—in certain cases enabling expected returns upwards of 36.4%—which can overcome current financial disincentives and accelerate the development of pediatric oncology therapeutics.

Association of regulatory- and helper-T- cells with inferior survival of neuroblastoma patients treated with low-dose infusions of ch14.18 combined with interleukin-2. First Author: Holger N. Lode, University Medicine Greifswald, Greifswald, Germany

Background: Long-term infusion (LTI) of the anti-GD2 antibody (Ab) ch14.18/CHO in combination with interleukin-2 (IL-2) prolongs survival in patients (pts) with high-risk neuroblastoma compared to historical controls. We investigated a correlation between lymphocyte subunits, functional immune parameters and survival in treated patients. Methods: 53 pts received 5 cycles (35 days (d)) of 6x10^6 IU/m^2 subcutaneous IL-2 (d1-5; 8-12), LTI of 100 mg/m^2 ch14.18/CHO (d8-18) and 160 mg/m^2/d oral 13-cis RA (d22-35) in a closed single center program (APN311-303). The counts of cytotoxic NK cells (CD16 ^+ CD56 ^+ ), helper T cells (CD3 ^+ CD4 ^+ ), cytotoxic T cells (CD3 ^+ CD8 ^+ ), regulatory T cells (Treg; CD4 ^+ CD25 ^+ CD127 ^- ) and granulocytes (CD64 ^+ ) were determined by flow cytometry (cycle 1; d1, 8 and 15). Ab-dependent cellular cytotoxicity (ADCC) was determined and correlated between cell counts and progression-free survival (PFS) was analyzed. Results: IL-2 treatment resulted in a strong increase of cytotoxic NK cells, cytotoxic- and helper T cells and Treg on d8 compared to baseline (d1) (2.4-, 3.9- and 15.0-fold increase, respectively). Subsequent combined treatment with IL-2 and ch14.18/CHO did not further increase lymphocyte counts on d15. In contrast, elevation of granulocytes occurred during the combined treatment. We did not observe any correlation between cell counts and ADCC on d15 as well as between cytotoxic NK and cytotoxic T cells and PFS. Similar observations were made for granulocytes. In contrast, pts with low Treg (≤ 138 cells/μl) on d15 (n = 11) showed a better PFS compared to high Treg pts (n = 31; P = 0.072). The 5-year PFS was 44% (95% CI (0.13, 0.74)) and 19% (95% CI (0.05, 0.33)) for low and high Treg counts, respectively. On d15, pts with low helper T cells (n = 11, < 365 cells/μl) also showed an improved PFS compared to those who had high helper T cells (n = 31; P = 0.013). The 5-year PFS was 53% (95% CI (0.23, 0.83)) and 16% (95% CI (0.03, 0.29)) for low and high helper T cell count, respectively. Conclusions: IL-2-dependent elevation of helper T- and Treg-cells may negatively affect efficacy of ch14.18/CHO combined with IL-2.

Evaluation of pegaspargase (PEG-ASP) adverse events among adolescents and young adults (AYAs) and younger patients with lymphoid malignancies (LM) at the Children's Hospital of Eastern Ontario (CHEO). First Author: Nicole Mathies, University of Ottawa, Ottawa, ON, Canada

Background: PEG-ASP is a common component of the chemotherapy regime for LM, but with significant side effects. The aim of this study was to determine the prevalence of major adverse events: allergic reactions, pancreatitis and thrombosis/hemorrhage among pediatric patients treated with PEG-ASP, and whether there is an association between age and a specific adverse event. Methods: Patients aged 0-18 years diagnosed with LM from January 1, 2007 to June 30, 2017 at CHEO, a tertiary care pediatric hospital, were eligible for this retrospective cohort study. A stratified, discrete-time, multivariable Cox regression model was fitted to elucidate the relationship between age at diagnosis and risk to adverse event. Model covariates included sex, body mass index and route of PEG-ASP administration (intravenous versus intramuscular). Results: Among 186 eligible patients, the median duration of follow-up was 2.0 years (IQR: 1.0-3.0). There were 34 allergic reactions, 8 cases of pancreatitis, and 32 cases of thrombosis/hemorrhage were observed. Estimates of 4-year cumulative incidence were 18.9% [95%CI:13.9, 25.4], 4.5% [95%CI:2.3, 8.7], and 19.4% [95%CI: 13.8, 26.9] for the three adverse events, respectively. Cox regression revealed a significant association between age at diagnosis and risk of allergic reaction (adjusted Hazards ratio (HR) = 2.18 [95%CI:1.45, 3.28], p < .001 for a 5-year increase in age) and risk of pancreatitis (adjusted HR = 1.93 [95%CI:1.02, 3.63], p = 0.04 for a 5-year increase in age), but not the risk of thrombosis/hemorrhage (adjusted HR = 1.25 [95%CI: 0.84, 1.85], p = 0.28, for a 5-year increase in age). The Cox model concordance index was 0.58. Conclusions: Evidence of an association between age at diagnosis and 2 of 3 adverse events (allergic reaction and pancreatitis) was revealed among pediatric patients treated with PEG-ASP. In light of the study results, cautious observation is further warranted when administering PEG-ASP particularly to AYAs with lymphoid malignancies.
Predictors of differential response to induction chemotherapy in high-risk neuroblastoma: A report from the Children’s Oncology Group (COG). First Author: Kevin R. Pinto, Seattle Children’s Hospital, Seattle, WA

Background: Induction chemotherapy plays an important role in the management of patients with high-risk neuroblastoma. Predictors of response to induction therapy itself are largely lacking. We sought to describe clinical and biological features associated with differential response to induction.

Methods: Patients from the following COG high-risk trials with at least one disease evaluation during Induction were included: A3973; ANBL02P1; ANBL0532; and ANBL12P1. Response at end-Induction was evaluated by the 1993 International Neuroblastoma Response Criteria. The primary endpoint was partial response (PR) or better. A series of univariate analyses (Fisher’s exact or chi-squared tests) were performed to compare response as a function of clinical or biologic predictor variables. For each predictor variable, the Holm-Bonferroni method was used to correct for multiple testing, using an overall α=0.05. A multivariate logistic regression model using significant predictors from univariate analyses was constructed to model PR or better. Results: The analytic cohort included 1,242 patients (79.8% with PR or better; 20.8% with CR; 9.1% with PD). Baseline factors significantly associated with a PR or better included age <18 months (87.4% with PR or better vs. 78.7% if older; p=0.0103), age <5 years (82.0% vs. 76.6% if older; p<0.0001), INSS Stage 4 (89.0% vs. 78.4% if Stage 4; p=0.0016), MYCN amplification (85.5% vs. 77.1% if non-amplified; p=0.0006), 1p loss of heterozygosity (LOH; 85.6% vs. 76.0% if no 1p LOH; p=0.0088), 1q LOH (94.9% vs. 81.7% if no 1q LOH; p=0.0004), and high mitosis-karyorrhexis index (MKI); 84.5% vs. 77.5% if low-intermediate MKI; p=0.0098). On multivariate analysis (n=407), the absence of 1q LOH was the only factor that remained significantly associated with PR or better (odds ratio: 1.962 compared to 1q LOH; 95% confidence interval 1.04-3.487; p=0.0216). Conclusions: Clinical and biological factors are associated with differential response to induction chemotherapy. These findings may further improve our ability to predict treatment response.

Rhabdomyosarcoma in the first year of life: outcome data from five trials and one cohort of the Cooperative Weichteilsarkom Studiengruppe (CWS). First Author: Monika Sparker-Sauer, Klinikum Stuttgart - Olgaospital, Stuttgart Cancer Center, Zentrum für Kinder-, Jugend- und Frauenmedizin, Pediatrics 5 (Onkology, Hematology, Immunology), Stuttgart, Germany

Background: Infantile soft tissue sarcoma (STS) has been associated with worse survival than STS in older children. Age, histology, molecular phenotype and treatment adjustment according to age may affect the outcome of patients with rhabdomyosarcoma (RMS) diagnosed during the first year of life.

Methods: The records of 5 trials and one registry, conducted by the Cooperative Studiengruppe (CWS) between 1981–2016, were reviewed to identify children diagnosed with RMS during the first year of life. Patient characteristics, treatment data and outcome were evaluated. Results: A total of 155 infants ≤12 months with histological diagnosis of RMS were identified, including 115 cases of embryonal RMS (RME), 38 cases of alveolar RMS (21/25 PAX7/3:FOXO1-positive (PF+)), 1 case of botryoid RMS, 144 infants presented with localized disease of whom 11 achieved complete response (CR), 41 had partial response (PR), 82 had stable disease (SD), 1 had progressive disease (PD) and 5 of 34 had 2nd malignancy. 11% of 107 infants with histological high grade RMS and best resection (R 0/R1/R2) were in grade 3-4 and 11% of 96 infants in grade 1-2. 7.55 years [0.24-30], the 5-year overall survival (OS) and event-free survival (EFS) for patients with RMS were 79.8% and 72.0% respectively compared to 72% and 64% for patients with RME. Conclusions: RMS of a solid tumor, lymphoma, or leukemia.

The addition of cycles of irinotecan/temozolomide (i/T) to cycles of vincristine, doxorubicin, cyclophosphamide (VDC) and cycles of ifosfamide, etoposide (IE) for the treatment of Ewing sarcoma (ES). First Author: Paul A. Meyers, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Treatment for ES in North America has evolved to include cycles of VDC and IE. A regimen including these 5 agents with interval dose compression has achieved 5 year EFS of 73% for localized ES. At Memorial Sloan Kettering (MSK) we have instead used the strategy of increasing doses of alkylating agents to achieve dose intensification and reported similar results. The combination of i/T given as irinotecan 20 mg/m2/day for 10 days with temozolomide 100 mg/m2/day for 5 days has achieved objective responses for patients who recur after initial therapy with the 5 drug combination. Our prospective protocol incorporates cycles of i/T with cycles of VDC and IE for the treatment of newly diagnosed patients with ES.

Methods: We have enrolled patients with and without clinically detectable metastatic disease at initial presentation. For patients with localized ES we administer high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T. For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agents. Results: We have enrolled 22 patients with localized and 16 patients with metastatic ES. With a median followup of 14 (3-51) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95%. With a median followup of 20 (8-51) months, patients with metastatic ES have achieved a 3 year EFS of 55% and OS of 70%. Conclusions: The addition of cycles of temozolomide 100 mg/m2/day. 3 patients with histological high grade glioma and one with metastatic ES and 4 patients with non-metastatic ES achieved responses for patients who recur after initial therapy with the 5 drug combination. For patients with localized ES we administered high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T. For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agents. Results: We have enrolled 22 patients with localized and 16 patients with metastatic ES. With a median followup of 14 (3-51) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95%. With a median followup of 20 (8-51) months, patients with metastatic ES have achieved a 3 year EFS of 55% and OS of 70%.

Phase 1/2 intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma, or leukemia. First Author: Cornelis Martinus van Tilburg, KiTZ Clinical Trial Unit, Hop Henners Children’s Cancer Center at the NCT Heidelberg (KiTZ), German Cancer Research Center (DKFZ) and Heidelberg University Hospital, Heidelberg, Germany

Background: In preclinical pediatric cancer models, the HDAC inhibitor vorinostat showed significant activity only at higher concentrations compared with those achieved with currently recommended dosing regimens. The aim of this trial was to intra-individually dose escalate to an individual maximum tolerated dose (MTD) in order to increase the likelihood of response whilst keeping toxicity acceptable.

Methods: Children 3–18 years old with relapsed or therapy-refractory solid tumor, lymphoma or leukemia were eligible. In phase 1 an intra-patient dose (de)escalation was performed until the MTD was reached. After identification of MTD, patients did continue treatment in phase 2 at their individual MTD until progression.

Results: Fifty-two patients were enrolled and 50 received treatment. 27/50 patients completed the intra-patient (de)escalation phase 1 part and entered phase 2. A safe starting dose of 130mg/m2/day with weekly increments of 50mg/m2 was determined (maximum: 580mg/m2/day). 46/50 (92%) patients experienced treatment related AE, in 17 patients (63%) $>$ CTCAE grade 3. Of the patients who reached phase 2, 24/27 patients (89%) experienced treatment related AEs, in 17 patients (63%) $>$ grade 3. Of the grade 3-4 AEs were reversible hematologic toxicity (mostly thrombocytopenia), fatigue, nutrition and gastrointestinal disorders and weight loss. The median MTD was 280mg/m2/day (range 130 - 580mg/m2/day). Overall response rate (CR + PR + SD) in the phase 2 was 6/27 (22%). 5 patients stayed on treatment for $>$ 12 months receiving doses of 280 – 580mg/m2/day. 3 patients with histological high grade glioma and one with metastasized SETTLE tumor showed prolonged SD. 1 patient was on drug for $>$ 4 years. Conclusions: A safe starting dose of 130mg/m2/day for individual dose escalation with weekly increments of 50mg/m2 was identified. This resulted in higher drug exposure associated with responses and long-term disease stabilization confirming that activity can only be expected at doses higher than currently recommended. The toxicity profile was compatible with published adult and pediatric safety data. PK, PD and biomarker analysis are ongoing. Conventional clinical trial information: NCT01864109.
**Background:** Entektinib (RXDX-101) inhibits TRK/A/B, ROS1, and ALK tyrosine kinases with IC50 < 2 nM. In vivo, entektinib is active in several fusion-driven solid tumor and TRKB-expressing neuroblastoma (NB) models. Central nervous system (CNS) penetration enables targeting of CNS metastases and primary tumors. Entektinib has clinical activity in adults with malignancies harboring NTRK1/2/3, ROS1, or ALK gene fusions (DSP-2017).

**Methods:** Patients (age 2-21 years) with recurrent or refractory extracranial solid tumors were eligible for this multicenter Phase 1 study. 4 doses levels (250, 400, 550, 750 mg/m2) were evaluated using a 3+3 design to determine the recommended phase 2 dose (RP2D). Entektinib capsules were administered orally, once daily, on continuous 4-week cycles. Adverse events were graded using CTCAE v4.03; response assessed by RECISTv1.1 and detailed pharmacokinetic sampling was completed.

**Results:** 16 patients enrolled; 15 were evaluable (9 male, 6 female) with median (range) age 10 (4-20) years. Diagnoses included NB (n = 10), inflammatory myofibroblastic tumor (IMT, n = 2), salivary gland adenocarcinoma (n = 1), synovial sarcoma (n = 1), and infantile fibrosarcoma (IFS, n = 1). Somatic target gene fusions were identified in IMTs (DCTN1-ALK, TFG-ROS1) and IFS (ETV6-NTRK3). Dose-limiting toxicities included grade (G) 2 creatinine increase (> 7 days in 1/6 patients receiving 550 mg/m2 and 1 patient each with G2 dyspnea, G2 > 7 days and G3 hyperbilirubinemia when patients receiving 750 mg/m2, thus confirming the pediatric RP2D as 550 mg/m2. Overall toxicity profile and drug exposure were comparable to the adult RP2D. 4 patients (2 IMT, 1 IFS, 1 NB) continue protocol therapy. All 3 fusion-positive patients have experienced an objective response. Conclusions: The RP2D in children with advanced adult patients with solid tumors is 550 mg/m2 daily. Preliminary antitumor activity has been seen in gene-fusion-positive patients. Entektinib continues to be investigated in expansion cohorts of patients with primary CNS tumors, extracranial solid tumors harboring NTRK, ROS1, or ALK fusions, and patients with NB. Clinical trial information: NCT02650401.

**Background:** G_d as a circulating tumor biomarker (CTB) for neuroblastoma (NBL). First Author: Frank M. Balis, Children’s Hospital of Philadelphia, Philadelphia, PA

**G_d as a circulating tumor biomarker (CTB) for neuroblastoma (NBL).**

**Background:** CTBs that reflect tumor burden or viability can improve the accuracy and sensitivity of assessing tumor response in phase 2 trials and substantially shorten the timeline of phase 3 trials if they are predictive of response or survival. G_d is a ganglioside present in the plasma membrane of NBL tumor cells, is measurable in the serum of patients with high-risk NBL, and lipoforms that differ in the chain length of the fatty acid moiety (C18 and C20) are predominant circulating form of G_d in controls and in patients with NBL. The median concentration of the C18 lipoform in children with high-risk NBL at diagnosis was 156 nM (range, 4-1060 nM), which was > 25-fold higher than the median concentration (5.6 nM) in controls. G_d was not measurable (< 2.4 nm) in 16 of 40 controls, and the highest concentration in controls was 15 nM. G_d was not elevated in children with 10 other childhood cancers. The most abundant circulating form of G_d in controls and in patients with NBL. The median concentration of the C18 lipoform in children with high-risk NBL at diagnosis was 156 nM (range, 4-1060 nM), which was > 25-fold higher than the median concentration (5.6 nM) in controls. G_d was not measurable (< 2.4 nm) in 16 of 40 controls, and the highest concentration in controls was 15 nM. G_d was not elevated in children with 10 other childhood cancers except for medulloblastoma (median, 34 nM; range, 6-111 nM). MYCN amplification (p = 0.0001), high-risk disease (p = 0.0001), and INSS stage 4 (p = 0.0001) were associated with higher G_d concentration. Median G_d concentration in non-high-risk NBL was 9.9 nM. Conclusions: These preliminary data indicate that G_d may be a sensitive and specific CTB for high-risk NBL. G_d will be studied prospectively and longitudinally in new COG trials of patients given (5y-EFS if yes: 50% 6 MC at diagnosis (6% vs 3% (IP vs CP) and in CEM-treated patients (p = 0.0107; MNA localised disease vs 3% vs 35% for patients on the HR-NBL1 trial. Clinical trial information: NCT02124772.

**Immunotherapy with anti-GD2 antibody ch14.18/CHO – IL2 with the HR-NBL1/SIOPEN trial to improve outcome of high-risk neuroblastoma patients compared to historical controls.** First Author: Ruth Lydia Ladenstein, St. Anna Children’s Hospital and Department of Paediatrics, Medical University, Vienna, Austria

**Background:** Randomization of immunotherapy versus standard was not possible in the HR-NBL1/SIOPEN trial. In order to explore an impact of immunotherapy on outcome, we used trial patients prior to availability of ch14.18/CHO as control. Methods: Patients received rapid COJEC, two courses of TVID if needed, surgery, HDT/SCT (BuMel or CEM) and chemotherapy. MNA treated patients (n = 12) were enrolled. MNA localised disease (844) were randomised. Patients with MNA localised disease or disseminated disease were randomised to receive or not receive ch14.18/CHO as control. Results: The control population achieved a major improvement in outcomes compared to historical controls. Immune response (IP) and clinical improvement (CP) were compared to historical controls. Immune response (IP) and clinical improvement (CP) were compared to historical controls. Immune response (IP) and clinical improvement (CP) were compared to historical controls. Immune response (IP) and clinical improvement (CP) were compared to historical controls.
Phase I multicenter trial of CUDC-907 in children and young adults with relapsed/refractory solid tumors, CNS tumors, and lymphomas. 
First Author: David Stephen Shulman, Dana-Farber Cancer Institute/Boston Children’s Hospital, Boston, MA

Background: CUDC-907 is a first-in-class small molecule inhibitor of histone deacetylases and phosphatidylinositol-3-kinases. Data from pediatric preclinical models, and adult clinical studies suggest that CUDC-907 can downregulate Myc/Mycn, providing a potential therapeutic strategy for Myc/Mycn-driven pediatric tumors. Methods: Using a 3+3 dose escalation design, CUDC-907 was administered at 3 dose levels to patients 1-21 years of age with relapsed/refractory solid tumors, brain tumors and lymphomas (NCT02909777). Primary objectives were to determine the pediatric recommended phase II dose (RP2D), describe toxicities, and describe PK parameters. Other endpoints included antitumor activity and pharmacodynamic effects. Patients received CUDC-907 orally on a 5 days on / 2 days off (“5/2”) schedule in 28-day cycles, with a pediatric mini-tab formulation for children who could not swallow pills. Results: As of 11/16/2017, 15 patients enrolled, with a median age of 15 (4.6-20.9) years. Diagnoses included: osteosarcoma (n=4); alveolar rhabdomyosarcoma (n=3); DIPG (n=2); ependymoma (n=2); Ewing sarcoma (n=2); CNS germ cell tumor (n=2). Median age at diagnosis was 15 years (4.6-20.9). Baseline performance status were included. Autologous MSCs were collected from a patients with advanced relapsed/refractory solid tumors, adequate organ function and carrying an oncolytic adenovirus are presented. Methods: Patients (1-18 yrs) with advanced relapsed/refractory solid tumors, adequate organ function and performance status were included. Autologous MSCs were collected from a bone marrow aspirate (BMA). Celyvir was manufactured within 6 weeks from BMA and then given IV weekly for 6 weeks at doses from 2x10^6 cells/Kg and 2x10^6 viral particles (vp) per cell. Dose was based in a previous compassionate use program (Melen et al, 2016;371:161). Primary objective was to determine safety and efficacy. Secondary objective was to obtain responses in the pediatric population.

Celyvir, the combination of MSCs and oncolytic virus administered to patients, minimizing toxicities and avoiding the need for new therapies. Immunotherapy with oncolytic viruses show great promise in adult cancers but have scarcely been explored in children. The results of a first-in, first-in-child trial (NCT02909777) using Celyvir in children with advanced relapsed/refractory solid tumors is dis...

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Various checkpoint proteins, and tumor infiltrating lymphocytes in common pediatric solid tumors: Possibilities for novel immunotherapy. First Author: Kazuo Mochizuki, Fukushima Medical University, Fukushima, Japan

**Background:** Despite the significant improvements of long-term survival rates for pediatric cancers, prognosis of refractory/relapsed solid tumors are extremely poor, and novel strategies are desired. Recently, tumor immunotherapies such as anti-PD-1/PD-L1 antibodies have been recognized as an effective option for many intractable cancers. However, there are still a substantial number of patients who do not show objective responses to the PD-1/PD-L1 blockade. On the other hand, like PD-1/PD-L1, other immune checkpoint pathways such as TIM3/GAL9, LAG3/MHC-II, and CTLA4/HVEM have been reported to regulate immune responses in tumor microenvironment. Although these pathways could be alternative targets for novel immunotherapies, almost no information is available whether pediatric solid tumors express these molecules. Herein, we characterized the expression of various checkpoint proteins, and tumor infiltrating lymphocytes (TILs) in tumor specimens from untreated children with common pediatric solid tumors. **Methods:** Sections cut from formalin-fixed, paraffin-embedded tissue blocks were processed and evaluated for GAL9, MHC-II, and HVEM on tumor cells, and TIM3, LAG3, and CTLA4 on TILs by immunohistochemistry. **Results:** Specimens from 65 patients, including 16 neuroblastomas, 11 rhabdomyosarcomas, 12 osteosarcomas, 10 hepatoblastomas, 10 Wilm's tumors, and 6 Ewing sarcomas were evaluated. Although in neuroblastoma and Ewing sarcoma, checkpoint proteins on the tumor were rarely detected, 64% of the patients with rhabdomyosarcomas, 83% with osteosarcoma expressed moderate to high levels of HVEM. TILs were detected in all tumor types among which CD8 positive T cells were the most dominant population following CD4 positive T cells. Interestingly, in rhabdomyosarcoma, and osteosarcoma, more than 70% of the TILs expressed moderate to high levels of CTLA4. **Conclusions:** A subset of pediatric solid tumors demonstrated tumor associated checkpoint expressions, and TILs also expressed corresponding ligands of the checkpoints, which suggested immunogenic environments may be created, and the checkpoint blockades could induce favorable immune responses.

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Visceral primary non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in patients ≥30 years of age: Findings of Children’s Oncology Group (COG) study ARST0332. First Author: Meena Kadapakkam, Stanford University School of Medicine, Stanford, CA

**Background:** Little is known about the clinical features, optimal management, and prognosis of young patients with primary visceral NRSTS. **Methods:** We analyzed clinical features, treatment, and outcomes of patients with visceral tumors (defined as intrathoracic, intraperitoneal, retroperitoneal, pelvic and penile) enrolled in COG ARST0332, which evaluated a risk-based treatment strategy for NRSTS patients aged <30 years (surgery +/- radiotherapy +/- chemotherapy based on tumor size, grade, extent of surgery, and extent of metastases). Variables analyzed included gender, age, race, ethnicity, tumor grade/size/invasiveness, extent of metastases, age, gender, and high-risk patients was 96.7%, 78%, and 25.4%, respectively, and was not statistically significantly different than for non-extremity tumors. Older patients had more high-risk features. Risk group was the most important predictor of outcome. Clinical trial information: NCT00346164.
Background: Retrospective reports of poor outcomes of ependymoma (EPN) subgroups, posterior fossa A (PF-EPN-A) and supratentorial C11orf95-RELA (ST-EPN-RELA), need confirmation in prospective trials. Methods: Fifty-four children (median age 1.6 y, range 0.4–3.1) with newly diagnosed EPN (WHO grade II/III) were treated (2008–2016) with maximal safe surgical resection + chemotherapy (high-dose methotrexate, vincristine, cisplatin and cyclophosphamide), consolidation using focal conformal radiation therapy (RT) to 54Gy (MO) or additional cyclophosphamide/topotecan with no RT (M4) and 6 months of oral maintenance chemotherapy. DNA methylation was performed using Infinium MethylationEPIC BeadChip and profiled on the DPKFZ MN2.0 classifier. Fluorescent in-situ hybridization was used to determine tumor 1q status. Results: No participant had imaging evidence of metastatic disease at diagnosis (MO = 40, M1 = 1, CSF not obtained = 13). At a median follow-up of 3.6 y (range, 1.0–9.3), 49 patients (91%) were alive with a 4-y PFS = 77.0% ± 7.5% and OS = 91.3% ± 5.2%. There was no significant difference in outcomes by subgroup [4-y PFS: PF-EPN-A (n = 42), 74.3% ± 8.2%; ST-EPN-RELA (n = 8), 80.0% ± 20.7%; ST-EPN-AP (n = 4), 100%; p = 0.42]. Five patients with PF-EPN-A had 1q gain but no difference in outcome (p = 0.59 for OS and p = 0.15 for PFS). For 6 patients with subtotal resection (STR) prior to RT, outcome was inferior to those of the 48 with gross-total or near-total resection (4-y PFS = 27.8% ± 16.7% vs 81.7% ± 7.3%, p = 0.047). Fourteen patients experienced progression at a median time of 28 mos (range, 1.7m–7.3y). Recurrence was distant (n = 7), local (n = 6), or combined (n = 1), 3/4 recurred at 6 (n = 2) and 7 years post diagnosis. Conclusions: In a uniformly treated, prospective EPN cohort, we found no significant difference in PFS or OS by molecular subgroup; however, the number of ST-EPN-RELA was small. In our data, 1q was not associated with outcome in PF-EPN-A, though only 5 subjects had 1q gain. Patients with STR prior to RT had inferior outcomes. Close surveillance and follow-up beyond 5 years is warranted due to risk of metastasis and late progression. Clinical trial information: NCT00602667.

**10549**  
**Poster Session (Board #222), Sat, 8:00 AM-11:30 AM**  
Final results of the phase II, single arm trial of irinotecan and cisplatin in children with high-risk glial tumors. First Author: Oselia Cruz, Hospital Sant Joan de Déu, Esplugues Llobregat-Barcelona, Spain

Background: We conducted an open label, single arm phase II clinical trial with irinotecan and cisplatin (IC) for pediatric patients with glial tumors (EudraCT:2009-010742-59). Methods: Patients diagnosed with high-risk (HR) gliomas at diagnosis (HGG, Ependymomas, DIPG, or HR-LGG) received sixteen weekly outpatient iv courses of Cisplatin (30mg/m2) and irinotecan (65mg/m2). Malignant gliomas received radiation upon progression. Objective response was evaluated by MRI volumetric analysis. Clinical and neurological changes were assessed. Results: From November 2009 until December 2012 39 patients aged 7m to 17y (mean 84 months) diagnosed with DIPG (n = 7); HGG (n = 5); Ependymoma (n = 6); atypical neurocytoma (n = 1); LGG (n = 22); pilocytic Astrocytoma (n = 1); Astrocytoma NOS (n = 5); Ganglioglioma (n = 2); and NF1 related LGG (n = 3) were included. Most frequent events were nausea/vomiting (5/39 grade ≥ 2); 17 patients (43.6%) with grade-1 diarrhea. Three of 31 (9.7%) evaluable patients developed hypoaacusis, all grade 1. Five (45.5%) patients with HGG, 1 relapsed HGG (100%), 7 DIPG (100%) and 3 LGG (15%) progressed during treatment. Objective response rate (ORR) at the end of therapy (week 21) is 54.4% for HGG; 0% for DIPG; and 85% for HR-LGG. After a median follow-up of 67.5 months OS/EFS for relapsed HGG and DIPG is 0%/0%; for high-grade glial tumors 62%/23%; and 95%/43% for HR-LGG. Radiation was avoided in 19 of 20 HR-LGG patients. Conclusions: The IC regimen was well tolerated and showed anti-tumor activity and clinical benefit for children with HR-LGG. Clinical trial information: NCT01574092.

**10550**  
**Poster Session (Board #223), Sat, 8:00 AM-11:30 AM**  
Risk prediction based on post induction bone marrow response and genomic profile: A new way to stratify stage M neuroblastoma patients? First Author: Stefan Fiedler, St. Anna Kinderspital, Vienna, Austria

Background: So far, and apart from minor adaptations, high-risk neuroblas-toma patients have been treated uniformly by not taking biological features of the tumor into consideration. To mend this oversight and address the lack of biological information: NCT00602667.

Methods: Diagnostic/post-induction bone marrow (BM) samples from 115 (83 fulfilled all criteria) stage M patients with subtotal resection (STR) prior to RT, outcome was inferior to those of the 48 with gross-total or near-total resection (4-y PFS = 27.8% ± 16.7% vs 81.7% ± 7.3%, p = 0.047). Fourteen patients experienced progression at a median time of 28 mos (range, 1.7m–7.3y). Recurrence was distant (n = 7), local (n = 6), or combined (n = 1), 3/4 recurred at 6 (n = 2) and 7 years post diagnosis. Conclusions: In a uniformly treated, prospective EPN cohort, we found no significant difference in PFS or OS by molecular subgroup; however, the number of ST-EPN-RELA was small. In our data, 1q was not associated with outcome in PF-EPN-A, though only 5 subjects had 1q gain. Patients with STR prior to RT had inferior outcomes. Close surveillance and follow-up beyond 5 years is warranted due to risk of metastasis and late progression. Clinical trial information: NCT00602667.

**10551**  
**Poster Session (Board #224), Sat, 8:00 AM-11:30 AM**  
Pediatric preclinical testing consortium evaluation of the EZH2 inhibitor tazemetostat in orthotopic PDOX models of pediatric brain tumors. First Author: Xiao-Nan Li, Laboratory of Molecular Neuro-Oncology, Program of Preclinical Neuro-Oncology Research, Texas Children’s Cancer Center, Baylor College of Medicine, Houston, TX

Background: Tazemetostat (EPZ-6438) is an EZH2 inhibitor that has entered clinical trials both in pediatric and adult patients. Over-expression of EZH2, the catalytic subunit of Polycomb Repressive Complex 2 that catalyzes H3K27me3, has been detected in a series of pediatric malignant brain tumors. Methods: Expression of EZH2 mRNA was examined in 23 patient derived orthotopic xenograft (PDOX) mouse models (10 GBMs, 11 medulloblastomas and 1 ATRT) with comparison to normal tissue levels. H3K27me3 was evaluated with immunohistochemical staining and Western blotting. Tazemetostat (250 mg/kg and 400 mg/kg) was tested in 4 PDOX models (1 GBM, 2 medulloblastomas and 1 ATRT) both as a single agent and in combination with cisplatin (5mg/kg days 8 and 11) and/or radiation (2 Gy/day x 5 days). Kaplan-Meier estimate of median time-to-event, ratio in median time-to-event between the treated and control groups (EFS T/C), and EFS p values were calculated and compared between the treatment groups. Results: Over-expression of EZH2 mRNA was detected in all GBM models (34.6% ± 12.7) and medulloblastoma models (6.2±1.7 in group 3, 6.0±0.24 in group 4) ac- companied by increased H3K27me3. INI1 mutation was confirmed in the ATRT model. In 3/4 models, tazemetostat at 250 mg/kg caused significant extension of median survival times (P<0.05), with EFS T/C ranging from 1.32 to 1.39. Increasing drug dose from 250mg/kg to 400mg/kg resulted in sig- nificant EFS prolongation only for the ATRT model (EFS T/C 1.39 vs 2.01). When compared with cisplatin and radiation used alone, tazemetostat was not significantly more active. When combined with cisplatin and/or radiation, tazemetostat did not significantly prolong survival compared to the standard therapy used alone. A group 3 medulloblastoma was not responsive to any treatment tested. Conclusions: Tazemetostat prolonged survival times in 3/4 PDOX models tested, with the greatest treatment effect observed in the INI1 mutant ATRT model at the higher 400 mg/kg dose. These data are consistent with the BBB in these PDOX models not preventing anti-tumor activity of tazemetostat. The addition of tazemetostat to standard therapies did not lead to improved survival.
Background: Malignant rhabdoid tumors (MRTs) are rare, aggressive pediatric solid tumors characterized by a 22q11 chromosome rearrangement that inactivates the SMARCB1 gene. Outcomes remain poor despite multi-modality treatment. MRTs are among the most genomically stable cancers and lack therapeutically targetable genetic mutations. We used the Virtual Inference of Protein-activity by Enriched Regulon analysis (VIPER) algorithm to computationally infer protein activity from MRT whole transcriptomic data available in the TARGET database to identify candidate non-genetically encoded vulnerabilities. This approach identified markedly aberrant activation of the nuclear export protein Exportin-1 (XPO1) in MRTs compared to other tumor types. We hypothesized that MRTs may be dependent on high XPO1 activity and this dependence can be co-opted as a novel non-oncogene directed therapeutic approach using the XPO1 inhibitor selinexor.

Methods: A panel of 6 MRT and 3 atypical teratoid/rhabdoid tumor (ATRT) cell lines were used for in vitro studies. Two patient-derived xenograft (PDx) mouse models of MRT were treated with selinexor to determine anti-tumor effects. Results: All MRT cell lines demonstrated marked baseline activation of XPO1. The median IC50 following 72 hour selinexor treatment was 200 nM (IQR 175-435 nM) for MRT, 460 nM (IQR 400 nM-1.4 μM) for ATRT and 1.1 μM (IQR 580 nM-1.4 μM) for 5 non-MRT cell lines. There was a correlation between inferred XPO1 activity and IC50 with cell lines with the highest inferred activity being the most sensitive to selinexor. Treatment with selinexor in vitro led to cell cycle arrest and induction of apoptosis in MRT cell lines. Post-perturbation RNAseq of selinexor treated cell lines with VIPER dynamic protein activity inference demonstrated decreased activity of XPO1, SWI/SNF complex proteins, kelch proteins and cell cycle regulators. In vivo treatment of two MRT PDx with oral selinexor for 15 days significantly inhibited tumor growth in both models (p < 0.0001 and p = 0.0002). Conclusions: Selinexor demonstrates efficacy in preclinical models of MRT. This results supports further investigation of selinexor in a phase II study in children with MRT.

Background: Plasma cell-free DNA (cfDNA) allows real-time molecular analysis of solid tumors. Neuroblastoma, the most common extracranial pediatric solid tumor, is known to have a higher mutational burden at relapse. In this study, we use the gene expression signature derived from the training set was strongly associated with the molecular subtypes of neuroblastoma. The 24-gene expression signature was validated in 8 WNT, 61 SHH, 62 Group 3 and 227 Group 4 samples. With the 24-gene expression signature, 8 samples were classified as WNT, 63 as SHH, 73 as Group 3 and 214 as Group 4. The gene expression-based assignments reached a 95.5% overall agreement with the reference diagnoses (342 of 358; 95% CI: 0.928 to 0.974), Sensitivity ranged from 94% to 100%, while specificity ranged from 96% to 100%. The full gene set enrichment analysis showed that 24 genes were significantly associated with signal transduction and WNT signaling pathway. Conclusions: A 24-gene expression signature that could accurately discriminate molecular subtypes of neuroblastoma was identified in this study. Our results may prompt further development of this gene expression signature into a molecular assay amenable to routine clinical practice.
ADVL1513: Results of a phase 1 trial of entinostat, an oral histone deacetylase inhibitor, in pediatric patients with recurrent or refractory solid tumors. First Author: Suman Malempati, Oregon Health and Science University, Portland, OR

Background: Histone modification plays a key role in oncogenesis and progression of malignancy. Histone deacetylase (HDAC) inhibition has shown promise as anti-cancer therapy. Entinostat is an oral small molecule inhibitor of class I and IV HDACs that has not previously been evaluated in pediatric patients. We report the results of a phase 1 study of entinostat in children and adolescents with solid tumors. Methods: Children and adolescents (age £ 21 years) with relapsed or refractory solid tumors, including CNS tumors were eligible. Body-surface area was required. Entinostat (1 or 5 mg tablets) was administered orally, once daily, in 4-week cycles. A rolling 6 design was used to evaluate two dose levels of 3 or 4 mg/m2. A pharmacokinetic (PK) cohort was enrolled at the recommended dose. Results: Twenty eligible patients (10 male, 10 female), median age 14.4 (8 - 20) years were enrolled. Diagnoses included patients with CNS tumors (n = 11), sarcomas (n = 6) or other solid tumors (n = 3). Twelve patients were evaluable for DLT. Eight patients were not evaluable due to progression of disease prior to receiving the required percent of protocol-prescribed therapy. No DLTs were observed at 3 mg/m2 (n = 3) or among 9 patients (6 in dose escalation and 3 in the PK cohort) at the 4 mg/m2 dose level. Grade 3 toxicities included neutropenia (n = 4), lymphopenia (n = 1), and leukenia (n = 1). Most common non-hematologic toxicities (all grade £ 2) were evaluated AST, fatigue, and hypophosphatemia (n = 4 each) and elevated ALT, hypalbinemia, and vomiting (n = 3 each). Pharmacokinetics of entinostat were evaluated and will be reported. Conclusions: Entinostat was well-tolerated with no DLTs observed. The recommended phase 2 dose in pediatric patients with solid tumors is 4 mg/m2. Evaluation of entinostat in combination with other agents is planned. Clinical trial information: NCT02778094.

NANT 2012-01: Phase 1 study of DFMO and celecoxib with cyclophosphamide and topotecan for relapsed or refractory high-risk neuroblastoma. First Author: Araz Marachelian, Children’s Hosp Los Angeles, Los Angeles, CA

Background: MYC drives polyamine expansion to support its oncogenic functions. Omithine decarboxylase (ODC) is a direct MYC target that is rate-limiting for polyamine synthesis, and is itself amplified in a poor-outcome subset of NB. Difluoromethylmethione (DFMO) is an ODC inhibitor with preclinical activity via protein translation and immunomodulatory effects. We studied dose-escalated DFMO added to celecoxib (polyamine export inducer), CycloTopo. Methods: Patients 2-30 years with RR HR NB were eligible. DFMO was studied at four dose levels (DL1-3,000; DL2/2A-4,500; DL3A-6,750; and DL4A-9,000mg/m2/day po daily) with celecoxib (500mg/m2/day), Cyclo (250mg/m2/day) and Topo (0.75mg/m2/day) IV for 5 days, with G-CSF. DFMO pharmacokinetics and biomarkers of ODC regulation (promoter SNP) and polyamine depletion were performed. Results: Twenty-four patients enrolled; median age 6.8 years. Patients received 124 total cycles (range, 1-17). DL1 and 2 used 212 cycles (DFMO given 14/21). Due to delayed platelet recovery, DL 2A-4A used 282 cycles (DFMO given 21/280). Toxicities were predominantly hematologic/fever-related. There were three cycle-1 DLTs (hematologic; anorexia; transaminitis) and two DLTs in later cycles (cycle-2 hematuria; cycle-1 hypertension). Eight patients stopped therapy by choice; two due to DLT; 9 due to PD; 3 completed therapy (CR = 1, PR = 2); all at dose-levels ≥4500 mg/m2/day (DFMO); and 2 remain on therapy. Median time-to-progression was 19.8 months. Dose-level 4A exceeded tolerability (2/6 with DLT). Dose-level 3A (6,750mg/m2/day) is the RP2D. Steady-state Cmax for DFMO increased by dose-level with median Cmin of 125mm at DL3A, equivalent to DFMO concentrations achieved in preclinical murine studies in water, and above the exposure needed to inhibit protein translation. Conclusions: DFMO and celecoxib added to Cyclo/Topo is tolerable in heavily pretreated NB patients, with a RP2D of 6,750mg/m2/day. Achievable DFMO concentrations at this dose have demonstrable bioactivity using in vitro and in vivo preclinical models. Further testing with DFMO in combination with chemotherapy in this population is warranted. Clinical trial information: NCT02030964.
Impact of survivorship care plans (SCPs) on adherence to surveillance for second malignant neoplasms (SMNs) and cardiac dysfunction in childhood cancer survivors (CCSS). First Author: Adam Paul Yan, The Hospital for Sick Children, Toronto, ON, Canada

Background: Since specific treatments increase the risk of SMN and cardiac dysfunction in childhood cancer survivors, the Children’s Oncology Group (COG) has published guidelines for SMN and cardiac surveillance. In 2006, the Institute of Medicine recommended that survivors receive a SCP documenting their required surveillance in order to maximize their adherence. The impact of this recommendation on adherence is not known. Methods: A survey conducted between 2014-2016 by 10,791 survivors in the CCSS ascertained adherence to COG guidelines among those for whom surveillance for breast cancer (N = 657; mammogram/MRI), colorectal cancer (N = 951; colonoscopy), skin cancer (N = 5468; skin exam) and cardiac dysfunction (N = 4310; echocardiogram) was recommended. We estimated adherence rates and identified factors associated with adherence using multivariable logistic regression. Results: Median age at diagnosis was 7 years (range 0-21) and time from primary cancer diagnosis was 36 years (16-66). Adherence to recommended breast, colorectal, skin and cardiac surveillance was 45.7% (95% CI 41.9-49.5%), 38.2% (CI 35.1-41.3%), 22.6% (CI 21.6-23.7%) and 42.3% (CI 41.0-43.6), respectively. 26.9% of survivors and 19.8% of primary care providers (PCPs) had a copy of the SCP. Providing the PCP with a SCP was associated with increased skin cancer surveillance (OR 1.4, CI 1.1-1.7) only. Survivors’ having a SCP was associated with increased cardiac surveillance (OR 1.8, CI 1.5-2.2) only. Visiting a specialized cancer survivor clinic in the last year (vs. never) was associated with increased breast (OR 2.0, 95% CI 1.1-3.8), skin (OR 1.3, CI 1.1-1.7) and cardiac (OR 8.9, CI 6.4-12.7) surveillance. Conclusions: Less than half of survivors at high risk for SMN or cardiac dysfunction adhere to surveillance guidelines. Few survivors and PCPs have SCPs, which has limited the impact of SCPs on cardiac surveillance. Adherence was most strongly associated with attending a specialized survivor clinic. New initiatives to improve adherence must be developed and tested.

Cardiac outcomes in childhood cancer survivors (CCS): A population-based study. First Author: Ashna Khanna, University of Toronto, Toronto, ON, CA

Background: CCS are at an elevated risk for cardiac morbidity due to cancer treatments such as anthracycline chemotherapy and thoracic radiation. Morbidities include congestive heart failure, arrhythmias, valve abnormalities, pericarditis, and coronary artery disease (CAD). However, cohort-based studies have focused primarily on CHF. We conducted a population-based study to determine the incidence of all types of cardiac disease in CCS. Methods: Using a provincial pediatric cancer registry, we identified all children <18 years of age at cancer diagnosis who were treated at a pediatric cancer center in Ontario, Canada between 1987-2010, and who survived ≥5 years from diagnosis. Each CCS was matched to population controls in a 1:5 ratio by age, sex, and geographic region. The index date was 5 years after cancer diagnosis. Administrative health datasets were linked to determine the incidence of CHF, arrhythmias, valve disorders, pericardial disease, CAD (including myocardial infarction), and cardiac-related death using established algorithms. Cumulative incidence of cardiac events was calculated in both cohorts, accounting for competing risks of non-cardiac death and adult cancer events. Results: We studied 7,354 CCS (median diagnosis age 6 years, IQR 2-12) and 36,647 matched controls. The median follow-up of 11 years (IQR 5-17) from index, 2.5% of survivors vs. 0.8% of controls experienced ≥1 cardiac event. At 15 years from index, the cumulative incidence of any cardiac disease was 3.7% (95% CI 3.4-4.3%) in survivors and 1.2% (95% CI 1.1-1.4%) in controls (HR 3.1, 95% CI 2.8-3.9, p < 0.0001). Among survivors, the 15-year cumulative incidence of morbidities was: CHF (2.0%, CI 1.6-2.4%), arrhythmias (1.5%, CI 1.2-1.9%), valve disorders (0.5%, CI 0.3-0.7%), pericardial disease (0.5%, CI 0.3-0.7%), and CAD (0.2%, 95% CI 0.1-0.4%). The 10-year incidence of cardiac-related death was 0.1% (CI 0.0-0.2%) vs. < 0.1% (CI 0.0-0.3%) in controls. Conclusions: CCS are at increased risk for multiple types of cardiovascular disease. Their absolute risk at 15-year follow-up is low, but is expected to increase as they age. Follow-up care of CCS should assess and manage general cardiovascular risk rather than limiting to CHF.
Radiation dose and volume to the pancreas and subsequent risk of diabetes mellitus: A report from the Childhood Cancer Survivor study. First Author: Danielle Novotsky Friedman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Childhood cancer survivors exposed to abdominal radiotherapy (abdRT) are at increased risk for diabetes mellitus (DM). We examined the association between DM risk and pancreatic radiation dose and dose-volume metrics. Methods: Participants included 4,527 5-year survivors (median age 35 years, range 10–58; median follow-up 21 years, range 2–34) diagnosed 1970–1999 and treated with abdRT, excluding total body irradiation. We estimated maximum radiation dose to the abdomen, whole pancreas, pancreatic head, body and tail, and volume of the pancreas absorbing ≥10, 20, and 30 Gy (V10, V20, V30). Prevalence of DM, defined by DM medication use, was compared to 4,853 siblings and 15,944 survivors without a history of abdRT using a GEE model with a Poisson distribution adjusted for attained age. Results: Survivors exposed to abdRT were 2.9 times more likely than siblings (95% confidence interval [CI] 2.0–4.3) and 1.6 times more likely than survivors not exposed to abdRT (95% CI 1.3–2.1) to have DM. Among those treated with abdRT, the prevalence of DM was 2.9% for survivors aged 31–40 years and 4.7% for those over 40. In multivariable analysis of survivors treated with abdRT, attained age (RR = 1.09, 95% CI 1.06–1.11, p < 0.001); body mass index (< 18.5: RR = 1.1, 95% CI 0.4–2.7; 18.5–24.9: reference); 25–29.9: RR = 2.7, 95% CI 1.6–4.6; ≥30: RR = 7.7, 95% CI 4.8–12.4, p < 0.001); and pancreatic tail dose (0.1–9.9 Gy: reference; 10–19.9: RR = 6.3, 95% CI 2.1–18.8; 20–29.9 Gy: RR = 4.7, 95% CI 1.4–16.3; ≥30 Gy: RR = 11.4, 95% CI 3.6–36.3, p < 0.001) were associated with increased DM risk. An interaction was noted between age at diagnosis and pancreatic tail dose (p < 0.001), with the largest differences between tail doses found among those diagnosed at age < 10. Radiation to other regions of the pancreas, by dose or volume, as well as exposure to cranial irradiation, alkylating agents, and corticosteroids, were not associated with DM risk. Conclusions: Among survivors treated with abdRT, DM risk is associated with higher pancreatic tail dose, but not with other dosimetric or volumetric factors. Research is needed to identify interventions to decrease cardiometabolic risk in survivors treated with abdRT.

Exercise intolerance among survivors of childhood cancer exposed to cardiotoxic therapy: Identification of survivors at increased risk through myocardial strain and ejection fraction. First Author: Kristen K. Nasa, St. Jude Children's Research Hospital, Memphis, TN

Background: Exercise intolerance is an established risk factor for heart failure and death in the general population. Exercise capacity and factors associated with intolerance have not been extensively studied in adult survivors of childhood cancer exposed to cardiotoxic therapy. Methods: Survivors exposed to cardiotoxic therapies, without clinical heart failure (N = 577, 52% male, mean age 34.4 ± 10.0 years) completed maximal cardiopulmonary exercise testing to determine exercise capacity (pkVO2, intolerance defined as < 20% of tile of age- and sex-specific predicted values) and echocardiography for EF and global longitudinal strain (GLS). EF < 50% and GLS ≥ 2 SD above age and sex normative values were evaluated for associations with exercise intolerance among survivors in models adjusted for race, pulmonary function, neuropathy, strength, physical activity and smoking. Results: Exercise intolerance (93.7%) and abnormal EF (7.6%) and GLS (27.6%) were common among survivors, differing significantly from controls: lower mean pkVO2 (25.8 ± 8.0 vs. 39.2 ± 9.4, p = 0.001) and EF (57.6 ± 5.5 vs. 60.3 ± 5.5, p < 0.001) and higher GLS (-19.6 ± 2.6 vs. -20.4 ± 3.2, p < 0.001). Conclusions: Survivors exposed to cardiotoxic agents have dose dependent impairment in exercise capacity. Abnormal GLS, but not EF, is associated with exercise intolerance among survivors, and should be considered in screening guidelines for survivors.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Chronic pain and disability in long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Cynthia Karlson, University of Mississippi Medical Center, Jackson, MS

Background: Chronic pain has not been well characterized in survivors of pediatric cancer. The current study is the first to examine prevalence and predictors of chronic pain and pain-related disability in this population.

Methods: Participants included 10,012 adult survivors (48.7% female; median age 31 years; M time since diagnosis 15.3 years) from the CCSS. Participants completed the Short-Form 36 and Brief Symptom Inventory-18 on two occasions between 2002 and 2011. Chronic pain was defined as self-report of moderate to severe pain at both time points. Pain-related disability was defined as pain that interferes with normal work at either time point. Covariates included sex, age, time since diagnosis, treatment, and grade 3-4 chronic health conditions. Multinomial logistic regression estimated relative risk (RR) and 95% confidence intervals (CI) for predictors. Structural equation models examined associations between pain, depression, anxiety, and vitality.

Results: 29% of survivors reported moderate to severe pain at either time point, 32% reported moderate to severe pain-related disability, and 10% reported chronic pain. Compared to survivors of leukemia, survivors of sarcoma (RR 1.33, CI 1.32-1.34) and solid tumors (RR 1.04, CI 1.03 1.06) reported more chronic pain. Survivors with a history of amputation (RR 1.54, CI 1.52-1.56) and, in separate models, those with chronic health conditions (RR 1.57, CI 1.56-1.59) were more likely to report chronic pain. Survivors with symptoms of depression (RR 1.11, CI 1.09-1.12) and anxiety (RR 1.11, CI 1.24-1.27) were also more likely to report chronic pain. Similar patterns were observed for pain-related disability. Controlling for demographics, treatment, and chronic health conditions, vitality mediated the effects of depression and anxiety on chronic pain (RMSEA 0.011) and pain-related disability (RMSEA 0.000).

Conclusions: Adult survivors of childhood cancer experience chronic pain and pain-related disability that is associated with amputation, chronic health conditions, depression, anxiety, and poor vitality. Increased screening and comprehensive treatment of pain is warranted, particularly for these risk factors.

Neurologic morbidities, psychological distress, and functional independence in adult survivors of childhood cancer treated with CNS-directed therapy: A report from the Childhood Cancer Survivor Study. First Author: Stefanie C. Vuotto, St. Jude Children’s Research Hospital, Memphis, TN

Background: Survivors of childhood cancer who received CNS-directed therapies are at risk for neurologic sequelae, which may adversely impact psychological functioning and independence in adulthood. Methods: Participants included 7,942 survivors of childhood cancer treated from 1970-99 with cranial radiation, intrathecal methotrexate or cytarabine (55% leukemia; 27% CNS tumor; 11% non-Hodgkin; 3% other; mean(SD) age = 25.5(5.8) yrs, time since diagnosis = 17.7(4.6) yrs). Self-reported neurologic conditions included stroke, seizure, sensory deficits, focal neurologic dysfunction, and severe headaches. Emotional distress symptoms (BSI-18) included anxiety, depression, and suicide ideation (SI). Functional independence was assessed using latent class analysis with six indicators (independent living, assistance with routine needs, assistance with instrumental activities of daily living, care of personal needs, mobility, and cognition). Results: Prevalence of neurologic conditions was: 3% stroke; 11% seizure; 25% sensory deficits; 29% focal neurologic dysfunction; 31% severe headaches. In multivariable models, risk of emotional distress was associated with focal neurologic dysfunction (anxiety: RR 1.6, 95% CI 1.3-2.1; depression: RR 1.4, CI 1.2-1.7), sensory deficits (anxiety: RR 1.3, CI 1.0-1.6; depression: RR 1.3, CI 1.1-1.5; SI: RR 1.3, CI 1.0-1.6), and severe headaches (anxiety: RR 1.5, CI 1.2-1.9; depression: RR 1.6; CI 1.4-2.0; SI: RR 1.5; CI 1.2-1.8). Stroke (OR 0.3, CI 0.2-0.5), seizure (OR 0.2, CI 0.2-0.3), and focal neurologic deficits (OR 0.26, CI 0.2-0.3) were associated with decreased likelihood of functional independence.

Conclusions: Childhood cancer survivors who develop neurologic morbidities are at-risk of emotional distress symptoms, particularly for these risk factors, and failure to attain independence in adulthood.
**Background:** After the introduction of pre-emptive therapy, the incidence of CMV disease dramatically decreased in HSCT recipients, while indirect effects of CMV infection (CMVI) are still under investigation.

**Methods:** We retrospectively analyzed children (< 18 years) who underwent allogeneic HSCT for malignancies at our institution between 01/2003 and 12/2016. CMVI was defined as the presence of pp65 or DNA in any body fluid. Patients were stratified according to their CMVI status. 5-year probabilities of OS, DFS, GVHD-free survival (GRFS) and infections were estimated using Kaplan-Meier method and log-rank test. Cumulative incidence and Gray’s test were used to assess differences in relapse, NRM, aGVHD grades 2-4, extensive cGVHD, neutrophils and platelets engraftment. Cox regression was performed to identify possible correlations. Major endpoints are reported in Table 1 with standard errors (SE).

**Results:** 92 HSCT were included (CMVI+ N = 40). Groups were homogeneous for age, sex, diagnosis, donors, HSC source and graft composition with the exception of lower median cellularularity in UCBU. No significant differences were reported for OS, DFS, infections, GRFS, relapse, NRM, and both neutrophils and platelets engraftment (p > 0.05). The mean day of CMVI diagnosis was 39.6 (28.2-51.0). Although statistically nonsignificant aGVHD grade 2-4 was higher in CMVI+, suggesting a possible association. Noticeable, aGVHD has often preceded CMVI (N = 7 vs N = 1). In contrast, e-cGVHD was less frequent in CMVI+ patients. Remarkably, infections were slightly higher in the early period in CMVI+...**Conclusions:** Despite variations in HSCT procedures and the limited sample size, pre-emptive therapy determined a dramatic decrease in CMV indirect effects. Moreover, aGVHD is a possible risk factor for CMVI but not vice versa. Further evaluations are needed to enlighten the role of CMVI in the modern era of pediatric HSCT.

### Endpoints (SE) CMVI CMV- p

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<th>Timepoint</th>
<th>OS (%)</th>
<th>DFS (%)</th>
<th>Relapse (%)</th>
<th>NRM (%)</th>
<th>aGVHD (%)</th>
<th>e-cGVHD (%)</th>
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<td>6.3 (0.04)</td>
<td>35.0 (0.08)</td>
<td>58.3 (0.09)</td>
</tr>
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</table>

**Conclusions:** Despite variations in HSCT procedures and the limited sample size, pre-emptive therapy determined a dramatic decrease in CMV indirect effects. Moreover, aGVHD is a possible risk factor for CMVI but not vice versa. Further evaluations are needed to enlighten the role of CMVI in the modern era of pediatric HSCT.

**TPS10575 Poster Session (Board #248a), Sat, 8:00 AM-11:30 AM**

**Open-label, dose-escalation, phase 1 study of venetoclax in combination with navitoclax and chemotherapy in patients with relapsed acute lymphoblastic leukemia.** First Author: Thomas Alexander, Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC

**Background:** Acute lymphoblastic leukemia (ALL) relapse in children and adults is associated with poor prognosis. Venetoclax (VEN) is a potent, highly selective BCL-2 inhibitor, and navitoclax (NAV) inhibits various BCL family proteins, including BCL-2, BCL-W, and BCL-X. VEN and NAV have shown activity in a variety of ALL cell lines and xenografts, and their combination resulted in synergistic antitumor effect in most ALL xenografts (Khaw et al. Blood 2016;128:1382-95). This trial evaluates VEN in combination with NAV and chemotherapy in patients with relapsed ALL. Methods: This is an open-label, multicenter phase 1 dose-escalation trial (NCT03181126) in patients ≥4–45 years old with relapsed or refractory ALL. Patients receive daily oral VEN, weight-adjusted to match the adult-equivalent exposure of 400 mg. Daily oral NAV administration starts on day 3. Based on the patients’ weight, up to 3 dose levels (25, 50, and 100 mg) will be explored. Chemotherapy consists of peg-asparaginase (1,250 IU/m² intravenous [IV] on days 9 and 22), vincristine (1.5 mg/m² IV on days 9, 15, 22, and 29), and dexamethasone (20 mg/m²/day orally on days 9–13 and 22–26). At the investigator’s discretion, chemotherapy may be delayed, not administered, or repeated for a second cycle. Dose escalation is guided by a Bayesian optimal interval design. For each weight group (< 45 kg and ≥45 kg), the initial cohort at each dose level enrolls ≥3 dose-limiting toxicity (DLT)- evaluable patients, and additional cohorts ≥2 DLTs are assessed during the first 42 days. In the absence of progressive disease, patients may receive VEN + NAV for up to 9 months; thereafter, therapy may be continued for those with ongoing benefit. Primary endpoints are safety and DLTs of VEN + NAV and chemotherapy, and safety and pharmacokinetics of VEN + NAV. Secondary objectives include assessments of antitumor activity and number of patients who proceed to stem cell transplantation. BH3 profiling and comprehensive genomic analysis will be performed to explore biomarkers of disease response. Approximately 42 patients are planned to be enrolled. As of Jan 5, 2018, 3 patients were enrolled at dose level one. Clinical trial registration: NCT03181126.
Phase 1 multicenter trial to assess the maximum tolerated dose, safety, pharmacokinetics, and pharmacodynamics of pazopanib in combination with irinotecan and temozolomide (PAZIT) for children and young adults with advanced sarcoma. First Author: Kieuhoa Tran Vo, University of California San Francisco, San Francisco, CA

Background: Sarcomas express pro-angiogenic factors that may represent therapeutic targets. Pazopanib, an oral multi-kinase inhibitor of VEGFR-(1-3), c-kit, and PDGFR, is FDA-approved for the treatment of advanced soft tissue sarcomas. In a phase 1 study of single-agent pazopanib in children with recurrent or refractory solid tumors, this agent was well tolerated and the clinical activity was encouraging in this heavily pre-treated population. Preclinical studies have demonstrated a potential additive or synergistic interaction between anti-angiogenic agents and cytotoxic chemotherapy. The combination of irinotecan and temozolomide is well tolerated and provides a modest degree of antitumor activity in heavily pre-treated sarcoma patients, thus making it a useful platform onto which new compounds may be tested. Methods: This is a phase 1, open-label, multicenter trial of pazopanib in combination with irinotecan and temozolomide (PAZIT) in children and young adults ages 6-30 years with relapsed or refractory sarcomas (NCT03139331). The primary objectives are to determine the recommended phase 2 dose, describe toxicities, and describe pharmacokinetic parameters in this population. Secondary and exploratory objectives include evaluation of disease response and exploration of pharmacodynamic effects of PAZIT. Pazopanib is administered orally on days 1-21 of 21-day cycles according to assigned dose level. All patients receive fixed doses of irinotecan IV (50 mg/m²/day) or PO (90 mg/m²/day) and temozolomide 100 mg/m²/day PO on days 1-5. Oral cephalosporin diarrhea prophylaxis is required. Dose escalation follows a standard 3+3 design evaluating up to three pazopanib dose levels. Following dose escalation, up to 10 additional patients will be enrolled to the dose expansion cohort to obtain additional toxicity and efficacy data. Correlative studies include changes in plasma angiogenic factors and circulating tumor DNA. Enrollment began in May 2017 and is ongoing. Clinical trial information: NCT03139331.
11000 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM
Addressing the burden of cancer in East Africa through cascaded training and education by local doctors. First Author: Jennifer Eastin, Royal College of Physicians of London, RCP, London, United Kingdom

Background: Development of cancer services in low and middle income countries (LMIC) is a challenge. The Medical Education, Training and Fellowship (METAF) program aims to improve early detection, research and treatment of cancer in East Africa (EA). Through clinical training courses, participating physicians will be better equipped to diagnose, triage and manage cancer within local hospitals. Methods: The EADB, which is responsible for the development of infrastructure in EA, through the British Council, appointed the RCP as the technical partner in this 4-year project. During Year 1, a needs assessment was carried out in Kampala with oncologists from Kenya, Tanzania, Uganda and Rwanda. Course conveners were recruited, curricula developed and two intensive “training of trainers” (TOT) courses delivered with RCP volunteers teaching alongside local faculty. In Year 2, 5 training courses were delivered, including the first round of ‘cascaded’ courses, facilitated by trainers who participated in the previous TOT workshops, supported by a member of local faculty and an RCP volunteer. Quantitative feedback to evaluate learning was gathered using multiple choice tests at the beginning and end of training. Qualitative feedback was gathered from written evaluations at the end of each course. Course content is continually amended based on country specific needs and participant and faculty feedback. Results: Since the launch of the program in 2016, 7 clinical training activities have been delivered; 3 oncology TOT workshops and 4 oncology cascaded training courses. During Years 1 and 2 the total number of doctors trained across East Africa as part of the METAF programme was 137. Participant feedback suggests that over 935 clinical staff will benefit from the knowledge gained on the clinical courses through mentoring by course participants at home facilities. Conclusions: The TOT solution to the need for a rapid cascade of knowledge has been well received and demonstrated to be effective in this multinational program. The methodology may be applicable to similar needs in LMIC settings. Lessons learned to date will be implemented during Years 3 & 4.

11002 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM
The teaching of multi-disciplinary cancer care: A flipped classroom approach. First Author: Helen Sarah Winter, University of Oxford, Huntingdon, Cambridge, United Kingdom

Background: Multi-disciplinary team (MDT) cancer care was introduced to improve cancer outcomes in UK. Teaching of MDTs involves observation from the ‘back of the room’. A flipped classroom approach was used as a tool for experiential learning of participation in a meeting. Team dynamics, shared decision-making and representing patient views are important in MDTs. Methods: Four true-to-life cancer cases requiring a multi-modality approach were developed. A flipped classroom was developed following feedback from students. Participants were given cases; individual roles with specialty-specific information; links to cancer resources and guidelines for case discussions. Following preparation facilitators set the scene and supported the groups to run the case discussion. Observers gave feedback on the decision-making, team dynamics and how the patient’s views were voiced. Participants gave feedback on their participation within the team, reflections on their role, and their learning of cancer care. Results: Eighty 4th year medical students each participated in two cases, with on average of 10 participants per case. Students compared their learning with their observational experiences of attending MDTs. Students rated this experience highly as a learning experience. Attendance was high, although not all students had prepared their roles. Feedback on the sessions was positive with the majority of students preferring this as a method for learning about MDTs. Results included reflections on how it felt to be a member of the team with a different opinion, how group dynamics affected decision-making and suggestions for improvements for the flipped classroom approach. Conclusions: A flipped classroom approach to teaching cancer management was rated highly by students. This approach offers a flexible, learning tool that stimulates knowledge application and conceptual understanding. Other professional skills were developed by chairing, presenting evidence from prior preparation and considering the patient’s wishes and values. The evaluation of a new innovative way to teach cancer care was well-supported by the students who overwhelmingly had advised to implement the pilot fully into the undergraduate clinical course.

11003 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM
Professional development improves geriatric focused oncology activities in settings across the nation. First Author: Denice Economou, City of Hope, Duarte, CA

Background: Although older adults represent the majority of patients with cancer, oncology nurses receive little training in the care of older patients. In an effort to bridge this knowledge gap, an NCI-funded R25 grant supported the development and implementation of an educational curriculum in geriatrics for oncology nurses. Methods: Competitively chosen 3-person nursing teams (manager, educator, and clinical provider) from cancer settings across the nation participated in a 2 1/2 day course in geriatrics for oncology nurses. Teams developed 3 goals aimed to improve geriatric oncology care in their settings. Goals were coded into detailed subcategories by PI and Co-Is. Code categories included: research-focused, clinical care, education, geriatric assessment, symptom focused, caregiver-related, infrastructure/team building, and other. Progress in implementing the goals was tracked at 6, 12, and 18 months post course. Goal completion rate over time was analyzed using generalized estimating equation for repeated measures. Results: 99 nurses (34 teams) participated in the 1st conference. A single goal may have had 2-3 codes applied and therefore 3 goals per 34 teams yielded a total of 181 codes. The most common goals focused on improving geriatric oncology clinical care (23%; N = 41 codes), professional education (23%; N = 41), geriatric assessment (9%; N = 16), infrastructure/team building (8%; N = 14) and resource development (7%; N = 13). Overall goal achievement at 6, 12, and 18 months was categorized as never started (29%, 7%, 4%), stopped (2%, 10%, 15%), stalled (9%, 20%, 13%), in process (48%, 38%, 30%) and completed (13%, 25%, 37%). Seventeen (8%) of the 41 clinical care goals and 8 (4%) of the education goals had stopped or stalled. Four teams had goals that were not started by 18 months. Goal completion rate increased significantly from 6 to 18 months (P < .0001). By 18 months, 67% of the goals were either in process or completed. Conclusions: An education curriculum in geriatrics for oncology nurses was implemented. Over the subsequent 18 months, nurses enacted goals to improve geriatric oncology care in their institutions. Continued follow-up and support is needed post course to foster goal completion.

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11004 Poster Session (Board #1), Mon, 8:00 AM-11:30 AM
Quantitative assessment of learning behaviors for oncology providers. First Author: Marie Wood, University of Vermont, Burlington, VT

Background: Understanding how different types of providers choose topics and activities for learning is key to meeting their needs. We sought to identify these needs in a diverse group of oncology providers. Methods: An online focus group study was conducted between November 2015 and August 2016. Participants included international, domestic, academic, and private practice providers as well as physicians and advanced practitioners (AP). Providers were asked monthly to journal their learning needs and explain how they identified that need. They were then asked what learning activity they chose to meet that need and what informed their choice. Results: 201 journal entries from 32 providers were reviewed; 47% from academic settings, 9% APs, and 41% international. Individuals provided an average 6 entries (range 1 to 17). Learning needs were associated with practice setting and professional role, with a significant association between practice setting and making a choice based on a self-identified knowledge gap (p = .005). Colleague recommendation impacted learning needs for APs (p < .001), and patient cases drove > 50% of identified learning needs across groups. Preference for learning activity type, formal versus informal, was associated with practice setting (p = .02). The choice of learning activity was associated with practice setting, professional role, and geographic location, with international providers more likely to consider cost versus informal, was associated with practice setting (p = .02). Over 75% of learner responses identify convenience and quality of content as factors in choosing an activity. Conclusions: To our knowledge, this study represents the first quantitative assessment of learning behaviors for oncology providers and shows that identification of learning needs and activity selection differ across them. Our cohort is small and may impact the generalizability of our findings. Future research should focus on educational needs of different members of the oncology care team and rank priorities for learning.

11007 Poster Session (Board #4), Mon, 8:00 AM-11:30 AM
Creation of a high-fidelity simulation tool to teach competency in radiation oncology treatment plan evaluation. First Author: Jerna Adelman, Radiation Medicine Program Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Although treatment plan evaluation (TPE) is a core competency for radiation oncology residents, gaps in teaching exist. The purpose was to create an interactive TPE case bank for residents to improve competency. Methods: A needs assessment informed case bank development. Residents assessed their confidence in TPE using a 10-point Likert scale (1 = least, 10 = most confident). A list of clinically unacceptable plans were compiled and categorized by clinical site, reason for rejection and relevance. An online web-based DICOM-RT tool was used to query and interact with the case bank database. A companion software tool, acting as an interactive simulation platform, was created allowing user interaction. Results: Twenty-three participants (70%) responded to the needs assessment: 6 junior, 7 senior and 10 former residents. Opportunities for improving TPE were identified; the mean confidence scores were: target coverage assessment (6.3 ± 2.7), doses to normal tissue (6.2 ± 2.5), conformity (5.5 ± 2.6), plan acceptability (5.4 ± 2.5) and ability to suggest improvements (4.8 ± 2.3). Extracted themes for case bank development included incorporating diverse clinical sites, target coverage/normal tissue assessment, conformity and provision of feedback. Of the 677 clinically unacceptable plans, a final list of 50 were selected for inclusion. They were categorized, anonymized and imported. Additional (un)acceptable plans were generated to augment the case bank where required. The companion simulation software platform describes each clinical scenario and allows residents to enter their assessment and suggested corrective action (if applicable). The platform then provides immediate feedback, including error description and correction strategy. Conclusions: An innovative TPE case bank has been created to address a learning gap in radiation oncology training. The high fidelity simulation format allows case interactivity and feedback with the goal of improving TPE competency. This platform can be leveraged for teaching/assessment in competency based medical education. Future work will evaluate resident satisfaction with and effectiveness of the case bank as a learning tool.

11008 Poster Session (Board #5), Mon, 8:00 AM-11:30 AM
Implementation of a model for training and career development in the emerging academic field of global oncology. First Author: Rebecca Deboer, University of California, San Francisco, San Francisco, CA

Background: As interest in global oncology increases, the need to support early career investigators is a priority, as advocated by the ASCO Global Oncology Leadership Task Force. The Global Cancer Program (GCP) at UCSF strives to implement a novel multifaceted strategy to support trainees from UCSF and our partner institutions in low and middle-income countries in pursuing careers focused on global cancer research and capacity-building. Methods: In 2017, the GCP launched a Global Cancer Fellowship (GCF) for post-doctoral trainees, Future Global Cancer Leaders (FGCL) monthly seminar, and quarterly Global Cancer Lecture Series. GCF protects research time, provides mentorship, and lends credibility to an unprecedented career track in this emerging field. FGCL is a multi-disciplinary group of students, residents, fellows, and others who convene to share experiences, present works-in-progress (WIPs), and interact with faculty mentors and visiting experts. In 2018, GCP developed a feasibility and adoption of this strategy and measured early indicators of effectiveness with an anonymous survey administered to FGCL members. Results: The Global Cancer Program Princess Margaret Cancer Centre, Toronto, ON, Canada

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Use of medical simulation for cancer education in Nigeria. *First Author:* Kelechi Ngezi Eguzu, University of Saskatchewan, Saskatoon, SK, Canada

**Background:** Among the many limitations of cancer control in Nigeria are lower awareness/competence and poorer training of healthcare professionals (HCPs). These manifest as deficiencies in advocacy, screening/diagnostic practices, and patient management. Medical simulation (MS) using models is an effective approach for sustainably improving the competence of HCP, especially regarding clinical breast examination (CBE), pelvic examination (PE) and digital rectal examination (DRE). Pre-training surveys showed non-significant differences in practices patterns; 71% (22/35) of respondents regarding clinical breast examination (CBE), 81% (28/35) regarding pelvic examination (PE) and 77% (27/35) regarding digital rectal examination (DRE). Study evaluates the effect of MS during a Nigerian training course focusing on CBE, PE and DRE. It answers the question: what are the perspectives of HCP on use of MS for cancer education?

**Methods:** Participants included a convenience sample of Nigerian physicians and nurses who attended the ASCO-sponsored Multidisciplinary Cancer Management Course. Intervention was MS using high-fidelity models. The models demonstrated normal anatomic and common pathologic features of the breast, cervical and prostate. Pre- and post-training surveys with comments evaluating self-reported comfort levels were basis for comparison. Data analysis included descriptive statistics. Wilcoxon signed rank test, chi-square and thematic analysis.

**Results:** Of the 92 course participants (physicians 36, nurses 56), 51 completed the course evaluation forms (response rate = 55.4%; 51/92), and average number of years in practice was 8 (±5.2 years). Pre-training survey showed non-significant differences in practices patterns; 71% (22/35) of physicians rarely performed PE (p = 0.92), and 93% (14/16) of nurses rarely performed DRE (p = 0.07). According to some participants, “the use of simulation is quite commendable as it gives room for improvement before using a human; “it is the best method of learning I have ever enjoyed.”

**Conclusions:** MS-based training significantly improved the comfort levels of participants regarding CBE, PE, and DRE, as well as their likelihood to perform CBE, PE and DRE. Participants recommend widespread use of MS for medical education and undergraduate training.

<table>
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<th>Comfort levels</th>
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11013 Poster Session (Board #10), Mon, 8:00 AM-11:30 AM
Impact of closed Facebook group participation on women hematology/oncology physicians. First Author: Julia Lee Close, University of Florida, Gainesville, FL

Background: Making meaningful connections is an important aspect of career satisfaction. The Hematology Oncology Women Physician Group (HOWPG) is a private Facebook (FB) group of 936 women who practice within the hematology and oncology (H/O) field. We hypothesized that HOWPG adds value to the education, emotional wellness, and practice of oncology for its membership. A survey was conducted within HOWPG to define the impact this group has on members. Methods: A voluntary anonymous 12-question online survey was distributed to members of HOWPG by sharing the survey link in the FB group 4 times between 11/16/2017-1/03/2018. Participants were surveyed regarding demographic data, general FB use vs. exclusive use of HOWPG, and opinions regarding HOWPG value and impact. Survey was approved by University of Florida institutional review board. Results: Of the 936 members of the site, between 1, and 169 completed the survey; 9% were females, 65% in practice <10 years, 26% >10 years. 62% were less than 40 years of age and 35% between the ages of 40-49, 85% practice adult H/O, and the remainder divided between pediatric H/O, radiation oncology, surgical specialty and palliative care. 90% use FB at least daily, with 82% accessing the HOWPG group at least daily, 16% using less than daily but at least twice per week. The most common uses for the site included education (65%-89%), advice on complex cases (65%), emotional support (65%), and networking (55%). On a scale of 1-10, learning from clinical cases (6), knowledge in cancer patient management (6), and support (6.5) were rated the most beneficial aspects. The aspects of the group rated most important were: membership limited to women, physicians, in the H/O field, secret group. Results: The HOWPG FB group has provided an opportunity for education, clinical and emotional support. Social media can be an effective venue to educate physicians, augment patient care via advice, foster networking, reduce burnout, and improve career satisfaction amongst women physicians in the field of hematology and oncology.

11014 Poster Session (Board #11), Mon, 8:00 AM-11:30 AM
Oncology education for family medicine (FM) residents and family physicians (FPs): A needs assessment survey. First Author: Steven Yip, BC Cancer Agency Vancouver Cancer Centre, Vancouver, BC, Canada

Background: Cancer care demands in FM continue to grow. This study aimed to determine the current state of oncology education in FM and examine opinions regarding optimal FM oncology education. Methods: A survey was designed to evaluate ideal and current oncology teaching, topics and objectives in FM post graduate medical education (PGME) and continuing medical education (CME). The survey was pilot-tested and sent to FM residents (n = 30) and FM program directors (PDs) across Canada and FP Cancer Committee members of the College of Family Physicians of Canada. Results: From May 1 - August 31, 2017, 131 FM residents and 15 FM PDs affiliated with 16 of 17 Canadian medical schools and 42 FP completed the surveys. The PGME survey results are in Table 1. Residents reported that the best way to learn oncology is through clinical experiences alone. PDs stated that case-based and didactic teaching are also important. Residents and PDs agreed that the most important topics are cancer prevention, cancer screening, breaking bad news, and palliative care. These topics were taught to 89-100% of residents. Yet, the other important topics of appropriate care, referrals, managing cancer complications and post-treatment surveillance were only taught to 52%, 40% and 36% of residents, respectively. According to 40% of FP s, the amount of oncology CME completed was inadequate; 21% reported that CME inadequately updates their knowledge in cancer patient management. Conclusions: Current FM PGME oncology education is sub-optimal across Canada, although the degree of difference varies. However, differences in the opinions of the residents and PDs. Sub-optimal oncology teaching is also likely for FM CME. FM oncology education can be improved using suggestions generated from this survey.

11015 Poster Session (Board #12), Mon, 8:00 AM-11:30 AM
Utilization of a web-based supportive oncology training curriculum for healthcare professionals (HCPs). First Author: Shelly S. Lo, Loyola University Medical Center, Maywood, IL

Background: A challenge in supportive oncology, is training the HCP workforce. A collaborative funded by The Coleman Foundation of 30+ clinicians and organizations designed to evaluate current and ideal oncology teaching, topics and objectives in FM post graduate medical education (PGME) and continuing medical education (CME). The survey was pilot-tested and sent to FM residents (n = 30) and FM program directors (PDs) across Canada and FP Cancer Committee members of the College of Family Physicians of Canada. Results: From May 1 - August 31, 2017, 131 FM residents and 15 FM PDs affiliated with 16 of 17 Canadian medical schools and 42 FP completed the surveys. The PGME survey results are in Table 1. Residents reported that the best way to learn oncology is through clinical experiences alone. PDs stated that case-based and didactic teaching are also important. Residents and PDs agreed that the most important topics are cancer prevention, cancer screening, breaking bad news, and palliative care. These topics were taught to 89-100% of residents. Yet, the other important topics of appropriate care, referrals, managing cancer complications and post-treatment surveillance were only taught to 52%, 40% and 36% of residents, respectively. According to 40% of FPs, the amount of oncology CME completed was inadequate; 21% reported that CME inadequately updates their knowledge in cancer patient management. Conclusions: Current FM PGME oncology education is sub-optimal across Canada, although the degree of difference varies. However, differences in the opinions of the residents and PDs. Sub-optimal oncology teaching is also likely for FM CME. FM oncology education can be improved using suggestions generated from this survey.

11016 Poster Session (Board #13), Mon, 8:00 AM-11:30 AM
Gender differences in faculty rank amongst radiation oncologists in United States: A cross-sectional study. First Author: Irbaz Bin Riaz, Mayo Clinic, Rochester, MN

Background: Female faculty in academic medicine is underrepresented in leadership positions and reportedly has fewer publications, lower h-indices and grant funding. However, there is a lack of evidence examining whether this gender disparity persists after adjusting for scholarly productivity and clinical experience among academic radiation oncologist. Methods: We used the Fellowship and Residency Electronic Interactive Database (FREIDA) to identify faculty members of radiation oncology residency training programs in the US. Faculty rank (assistant, associate and full professor) was obtained by review of program website. Data on physician gender, clinical experience in years, number of publications, h-index, clinical trial investigator, advance degree and rank of medical school was collected using program websites, Doximity and Scopus databases. Primary outcome of the study was a binary outcome odds of professorship versus assistant plus associate professorship. We used a multivariable logistic regression model to estimate the gender difference in full professorship after adjusting for these factors. Results: A total of 906 radiation oncologists were included in the final analysis. 70.2% (n = 636) were men and 29.8% (n = 270) women. Women had less clinical experience (median of 10 years vs 14 years, p < 0.0004), fewer publications (median of 17 vs 32 publications, p < 0.0001), less h-index (median of 7 vs 12, p < 0.0001), less likely to be clinical trials investigator (41% vs 48%, p = 0.05), less likely holding advance degree (22% vs 28%, p = 0.067) but were more likely to be graduate of top 20 medical schools in research (27% vs 25%, p = 0.66). Women were under represented at higher faculty rank with 43 out of 270 (15.9%) were full professors compared to 194 out of 636 (30.5%) men with the absolute difference of 14.6% (p < 0.001). Moreover, women were found less likely to be full professors compared to men (odds ratio, 0.55; 95% confidence interval, 0.32-0.94; p = 0.029) in adjusted logistic regression analysis. Conclusions: Among radiation oncology faculty gender disparity exists at higher faculty ranks even after accounting for academically relevant factors influencing the academic progress.
Prostate cancer treatment: an update on targeted therapy

Background: Drug resistance is typically associated with primary tumors, but little is known about the presence of drug resistance in metastatic prostate cancer. The objective of this study was to examine the presence of drug resistance in metastatic prostate cancer samples.

Methods: We examined the presence of drug resistance in a cohort of metastatic prostate cancer samples. We used a panel of 16 commonly used drugs to screen for drug resistance. We also performed a panel of next-generation sequencing (NGS) to identify mutations associated with drug resistance.

Results: We identified a high prevalence of drug resistance in metastatic prostate cancer samples. The most common mutations identified were in the androgen receptor (AR) gene, which is commonly associated with drug resistance. We also identified mutations in the PI3K and PIK3CA genes, which are associated with drug resistance in other cancer types.

Conclusions: Drug resistance is a common feature of metastatic prostate cancer. Identifying mutations associated with drug resistance will be essential for developing personalized treatment plans.

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Establishment of a medical student elective on the oncology consult service using the seven principles of teaching. First Author: Hari Anant Deshpande, Yale Cancer Center, New Haven, CT

**Background:** A busy academic oncology consult service has challenges for effective student teaching. The aim of this research is to establish an academic oncology elective through signature pedagogies - learning in the practice setting.

**Methods:** The Seven Principles of teaching and learning will be used to develop an effective teaching model for the Inpatient Oncology Consult service. 1 Prior knowledge is the key to learning 2 Prior knowledge must be activated 3 Learners must be actively involved in constructing personal meaning (i.e.: understanding) – the links are more important than the elements 4 Making more and stronger links requires time 5 Context provides important cues for storing and retrieving information 6 - A Intrinsic motivation is associated with deep approaches to learning; B Extrinsic motivation and anxiety are associated with surface approaches to learning 7 - Teaching should be geared toward making the teacher increasingly unnecessary; that means the development of learner autonomy as well as intellect To address these principles: 1 - A short 10 question quiz to ascertain prior knowledge of general oncology 2 - Activate prior knowledge by asking about experiences or planting concepts at the beginning of the discussion. This should reflect the students’ interests: e.g., focusing on the disease, the social aspects, financial aspects, symptom management or end of life care. 3 - Encourage teachers to be guides, coaches or co-inquirers more than a source of knowledge during rounds to encourage deep and holistic rather than surface discussions. 4 - Allow students time to elaborate their knowledge base – make links between subjects as well as between theory and practice to focus on intrinsic motivation. Limit the size of the teaching service. 5 - Teach in the context from which they eventually use their knowledge. Observe patient encounters and critique their presentations. 6 - A flipped curriculum where the student studies an aspect that then can be discussed in more detail; this becomes the basis for constructing a management plan. 7 - A feedback session to stay within the students’ zone of proximal development and maintain in the course. Development of a smartphone app for assessment.
Phase III, randomized, double-blind, placebo-controlled trial of sorafenib in desmoid tumors (Alliance A091105). First Author: Mininal M. Gounder, Memorial Sloan Kettering Cancer Center, New York, NY

Background: DT is a rare cancer of connective tissue affecting young patients (pts), arising in any location, with a wide natural histories. DT are a group of locally aggressive tumors of fibroblastic origin within a 6-months interval. Pts were randomly assigned to receive PZ 800 mg/d PO x 22 wks (Part 1). Pts completing Part 1 could continue on P (p = 0.3); 1-yRFS: 43%-P, 87%-S; Med PFS: 9.4 mo (95% CI 5.7-NE) for P, not reached (med f/u 26 mo): PD 69% (22/32) P, 16% (7/43) S, 1 death (S); Durable responses (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 17 (37%) and SD in 21 (45.7%)...
Background: Oral multikinase inhibitor REG has shown activity in GIST and non-adipocytic soft tissue sarcomas. We designed REGBONE as a non-comparative phase II, double-blind, PL-controlled trial to evaluate the efficacy and safety of REG for pts with metastatic osseous osteosarcoma (metOS), on behalf of the French Sarcoma Group (FSG) and Unicancer. First Author: Florence Duffaud, La Timone University Hospital, Marseille, France

Results: Forty-eight subjects were enrolled with 47 (27 M: 20 F) eligible for efficacy analysis. Of 38 efficacy-evaluable pts (12 in PL arm and 26 in REG arm), 24 were men, median age was 33 (18-74) years, 28 (74%) had 1 previous CT regimen. 17 pts (65.4%; one-sided CI95% = [47.4%-]) were non-progressive at 8 weeks in the REG arm vs. 0 in the PL arm. Common grade 3-4 AEs included: grade 3 abdominal pain (13%), hypertension (13%), rash (13%), diarrhea (7.9%). One PR was observed in P. Median OS was NR (4.2-NR) for R vs 8.1 (2.9-16.0) months for P, stratified p-value = 0.13. No new safety signals were observed. Clinical trial information: NCT01861951.

Outcome of primary and key secondary endpoints

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<td>Progression-free survival</td>
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Conclusions: REG demonstrates very promising activity, with acceptable toxicity, in metOS after failure of conventional chemotherapy, justifying confirmatory trials.

Clinical trial information: NCT02389244.

Background: Pazopanib, a multi-targeted tyrosine kinase inhibitor, has shown activity in various soft tissue sarcomas. Activity in liposarcoma, however, is limited. Regorafenib is a multi-kinase inhibitor with antiangiogenic properties similar to pazopanib. We conducted a randomized, phase II study of regorafenib (R) vs. placebo (P) in refractory liposarcoma patients (pts). Methods: Pts with advanced/metastatic, treatment-refractory liposarcoma were randomized 1:1 to receive regorafenib 160 mg daily or placebo (3 weeks on/1 week off). Pts with well-differentiated liposarcoma only were excluded. Crossover for placebo pts was allowed upon progression. The primary objective was progression-free survival (PFS) for R vs P. Stratification factors included prior lines of therapy (1 vs 2+) and WHO performance status (0 vs 1-2). The study was powered to detect a difference of ≥3 months in median PFS.

Results: Eighty-four subjects were enrolled with 47 (27 M: 20 F) in the REG arm and 37 (19 M: 18 F) in the PL arm. Median age was 71 years (range: 60-88). In the PP population, DOX vs. PAZ achieved a median OS of 8.0-27.3 vs. 8.0-27.3 months. PFS of 5.3 vs. 4.4 mos was observed. DOX 75 mg/m2 every 21 days were administered. The Cox regression analysis ANCOVA and Kaplan-Meier curves were applied to analyze the data (NCT01861951).

Background: DOX is still the standard in metastatic STS. We assessed the efficacy and safety of oral TRO. Methods: This is a randomized phase 2 trial at 15 german and 1 french centers. We included pts with metastatic high-grade STS, older than 60 yrs of age, with an ECOG of 0-1. They were randomly (1:1) assigned to either (A) DOX 60 mg/m2 s.i. on day 1, q 22 d or 6 cycles) or arm B (oral TRO, 300 mg, d1-7, then 150mg daily continuously p.o.) as first-line b. Randomisation was stratified by presence of liver mets, and PS (0 vs 1). Pts were treated until PD or unacceptable toxicity. Primary aim was a 6-months (mos) PFS rate of at least 20 % in Arm B; secondary: safety, ORR, survival. Results: Between 8/4 and 10/12 pts were randomly assigned to arm A and 80 to Arm B, median age 70 yrs (60-89). Median duration of f/u of surviving patients was 18.4 mos (range, 3.8-94.7). Median treatment duration was 2.8 mos (0.4-6.4) in A and 2.8 mos (0.4-4.1) in B. No difference in terms of ORR with 7.7% (1.6-20.9) in arm A and 6.7% (2.2-14.9%) in arm B (p = 0.99); disease control rate (including disease stabilization) (53.8% (95%-CI, 37.2-69.9%) vs. 41.3% (95%-CI, 30.1-53.3%) p = 0.23), FFS (4.3 mos; 95%-CI, 2.2-5.9 vs. 2.8 mos; 95%-CI, 1.6-3.5), p = 0.09) and OS (9.6 mos; 95%-CI, 6.4-11.6 vs. 12.1 mos; 95%-CI, 9.5-16.0), p = 0.59) were seen, without difference in ITT- and per-protocol populations. Duration of response lasted 5.0 mos in arm A (range, 1.3-8.0) and 4.0 mos (0.46-6.0) in Arm B; however, in pts achieving a CR or PR duration was longer in favor of cohort B (0 vs. 27.7 mos resp. 4.3 vs. 8.2 mos). Primary study endpoint (6-mos PFR) was 27.6% in Arm B (95%-CI, 18.0-39.1). Safety analyses in 115 pts showed that at least one side effect in 97.4% (95%-CI, 96.1-98.9) of pts was noted; of side effects 43% were lower in favor of Arm B (59% vs. 30.3%; p = 0.005). TRO caused more frequent dyspnoe, fatigue (but only minor degree); DOX leukocyto- and neutropenia as well as mucositis, G1-4. Discontinuation rate other than PD was 15.4% vs. 7.9. Conclusions: In an elderly population of pts who received either standard dox or oral TRO, similar efficacy and less side effects were achieved. TRO associated with a more favorable toxicity profile. Clinical trial information: NCT0204568.
35x619]stratified by L-STS (lipo-leiomyosarcoma) and non L-STS and with a WHO # of age with histologically proven ASTS who progressed after at least 1 Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.

Results of a prospective randomized phase III T-SAR trial comparing Sarcoma France unacceptable toxicity, or patient's request. Pts allocated to BSC could cross over to T at PD. The primary endpoint was progression-free survival (PFS). Results: Between January to November 2015, 103 pts (median 65 yrs (range 22-84), grade 3 ASTS in 57% of cases, median number of 1 prior CT lines) were enrolled by 16 FSG centers, 52 in the T arm and 51 the BSC arm. Pts with L-STS and non L-STS represented 60% and 40% of pts, respectively. Two pts refused to be allocated in the BSC arm and received other CT. The objective response rate (ORR) in the T arm was 11.8%, all observed in the L-STS group (ORR: 18.8% in L-STS). 23% of pts in the T arm received more than 5 cycles of CT and median PFS of the L-STS arm 3.1m and 3.1m in the T arm (HR: 0.39, p < 0.0001). In the L-STS cohort, the median PFS were 1.4m and 5.1m in the BSC and T arm (HR: 0.29, p < 0.0001), respectively, whereas in the non L-STS group they were 1.5m and 1.8m (p = 0.16). A cross-over was performed in 92% of pts included in the trial. By After reaching the median follow-up time, 19 pts had stopped due to PK plateau; the RP2D was 1000 mg QD. In P2, no DLTs were observed at the doses studied. PK of PLX9486 was not affected by prior therapy. Conclusions: This study met its first endpoint as a preplanned PFS analysis showed a significant improvement in median PFS with T over BSC in pts with pretreated ASTS of multiple histologies. L-STS pts benefit the most from T therapy in terms of prolonged tumor control. Clinical trial information: NCT02675257.

Phase Ib study of rapid alternation of sunitinib (SU) and sorafenib (RE) in patients (pts) with advanced gastrointestinal stromal tumor (GIST). First Author: Cesar Serrano, Vall d’Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain

Background: Polyclonal emergence of KIT secondary mutations (muts) is the main mechanism of imatinib (IM) progression in GIST. Although approved KIT inhibitor, IM is only infrequently effective in IM-resistant patients. Sunitinib (SU) and sorafenib (RE) have shown complementary activity in GIST models and clinical trial correlates. Preclinical evidence suggests that rapid alternation of SU and RE broadens the spectrum of IM-resistant subclones targeted, compared to either agent as monotherapy. Methods: This phase Ib study of rapid alternation of SU and RE was performed in pts with IM-resistant advanced GIST. A standard 3+3 dosing schema was utilized to determine the recommended phase II dose (RP2D). Pts received continuous treatment with cycles of 3 days of SU followed by 4 days of RE. Plasma samples for pharmacokinetics and ctDNA studies (deep next generation sequencing and ddPCR) were collected at several timepoints. Results: Fourteen pts were enrolled, and 13 received treatment. Median age 64 (range 42-78), 43% female, median prior therapy 4 (range 3-7), all pts had ≥ 3 prior therapies. SU 37.5mg daily 3 days followed by RE 120mg daily 4 days was established as the RP2D. Two dose limiting toxicities (DLTs) occurred at DL2 (asymptomatic G3 hypophosphatemia). Non-DLT G3/4 toxicities were hypertension (1/13 pts) and hand-foot syndrome (2/13 pts). 8/13 patients experienced dose modification, delay, or both. No unexpected toxicities were observed. Of the 13 pts with evaluable CT scans, stable disease (SD) was the best response observed in 4 pts by RECIST. Median progression free survival was 10.2 weeks (95% CI of 6.6-11.5 weeks). SU and RE did not reach the steady state, although pts with SD had higher median drug concentration than progressing pts. ctDNA studies show that GIST has low ctDNA shedding and remains KIT-driven even at late stages of disease, with a predominance for activation-loop secondary mutations. Conclusions: Rapid alternation of drugs with complementary activity is a tolerable treatment option for pts with evaluable tumor ctDNA and effectively specific subpopulations. Although GIST sheds low ctDNA in this heavily pretreated population, identifying KIT muts in plasma is feasible. Clinical trial information: NCT02164240.

Phase II dose (RP2D). Pts received continuous treatment with cycles of SU and RE was performed in pts with IM-resistant advanced GIST. A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of PLX9486 alone and in combination (combo) with the KIT inhibitors pexidartinib (pexi) or sunitinib (su) in patients (Pts) with advanced solid tumors and gastrointestinal stromal tumor (GIST). First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA

Background: Most metastatic GISTS have primary (1st) mut in KIT exons (ex) 9 or 11, which confer sensitivity to imatinib and other agents. Tumors develop clonal secondary (2nd) resistance mut, typically in ex 13, 14, 17, and 18. PLX9486 inhibits KIT 1st mut and ex 17 and 18 2nd mut. Pexi (PLX3397) and su inhibit 1st mut and ex 13 and 14 2nd mut. Combo of PLX9486 with pexi or su may have activity against a broader spectrum of mutations. Methods: 3 + 3 dose escalation study in pts with solid tumors and GIST who had progressed on imatinib and other TKI. Safety, efficacy, PK of RE, and PK were assessed. Ct DNA was assessed as a biomarker. Patient (P) 1: single agent PLX9486 dose escalation once (QD) and twice daily (BID). P2: combos of PLX9486 500 mg QD with pexi 600 mg QD fed and fasted or su 25 mg QD with food. Results: As of January 8, 2018, 36 pts (31 GIST; Par 1-20 pts, part 2-11 pts) were enrolled; median age was 63 years (range 49-82). GIST pts had a median of 4 prior therapies (range 1-7), and all on imatinib. Most pts had tumors with ex 11 and 17 mut. QD dosing of PLX9486 had saturable absorption at steady state with a half-life of 71.4 hrs. No PK advantage to BID dosing and no food effect. One DLT of Grade (G) 3 anemia with reticulocytosis median PFS of the 100 mg QD arm and 3.1m in the T arm (HR: 0.39, p < 0.0001), respectively, whereas in the non-L-STS group they were 1.5m and 1.8m (p = 0.16). A cross-over was performed in 92% of pts included in the trial. By After reaching the median follow-up time, 19 pts had stopped due to PK plateau; the RP2D was 1000 mg QD. In P2, no DLTs were observed at the doses studied. PK of PLX9486 was not affected by pexi. Pexi food effect was observed. Adverse events (AEs) in P1 in ≥ 20% pts (N = 24) were diarrhea, nausea, increased AST (29% each) and fatigue (21%). AEs in P2 ≥ 20% pts (N = 12) were hair color changes (42%), anemia (25%), nausea (25%), and anorexia (25%). Majority were G1 or 2. No ≥ G3 LFT changes in P1 or P2. In P1, 2 partial responses (PR) were seen with PLX9486 1000 mg and PFS was ≥ 24 weeks. In P2, 1 pt had a PR in the pexi/PLX9486 combo, and the median PFS has not been reached. Conclusions: PLX9486 alone and in combination was tolerated well with evidence of activity in KIT 1st and 2nd mut-resistant GIST. Combos with su and pexi, agents with complementary activity against KIT 2nd resistance mut in GIST, are accruing. Clinical trial information: NCT02401815.

Mutation profile of drug resistant gastrointestinal stromal tumor (GIST) patients (pts) enrolled in the phase 1 study of DCC-2618. First Author: Suzanne George, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA

Background: GIST is driven by primary and secondary driver mutations in KIT/PDGFRα and cell-free tumor (ct) DNA may provide the opportunity to arm pts to therapy while measuring disease activity. A phase 1b dose-escalation control inhibitor DCC-2618 has demonstrated durable disease control in heavily pre-treated GIST pts in the ongoing Phase 1 study (NCT02571036). Methods: Pts with advanced GIST were treated in either the escalation stage or in expansion cohorts of the Phase 1 study with oral DCC-2618. Tissue and liquid biopsies were performed and tested via next generation sequencing (NGS) of tumor tissue and/or plasma ctDNA. Results: A total of 136 GIST pts enrolled in the first 4 cycles of treatment with DCC-2618 will be presented. 76% of 136 pts are still on treatment. In 99 GIST pts with > 1 on-study tumor assessment, the best response rate (ORR) was 16%. Conclusions: Identification of ctDNA by NGS in the majority of patients in this cohort was feasible. The mutation profile of GIST in both tumor and plasma suggests the need for a pan-KIT inhibitor across various lines of therapy. DCC-2618 is being tested in a pivotal, randomized phase 3 study, INVICTUS, (NCT03353753) in the 1st line setting. DCC-2618 was tested in a phase 1b study in a heavily pretreated line GIST. ctDNA in this patient population deserves further study as a non-invasive marker of disease heterogeneity and response assessment. Clinical trial information: NCT02571036.
Phase 2 results of selinexor in advanced de-differentiated (DDLS) liposarcoma (SEAL) A phase 2/3, randomized, double blind, placebo controlled cross-over study. First Author: Mininal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Locally advanced DDLS is incurable with an overall survival of 11–20 mo with palliative therapies. Ideal imaging criteria for efficacy is currently undefined. Selinexor (S) is an oral, selective inhibitor of nuclear export that specifically blocks export 1, leading to the nuclear accumulation and reactivation of tumor suppressor proteins. S demonstrated anti-tumor activity against DDLS in preclinical studies and a Ph 1b study in patients (pts) with soft tissue sarcomas. Methods: Eligible pts had DDLS and progressive disease (PD) with ≥ 1 prior systemic therapy. Pts were randomized 1:1 to receive blinded S (60 mg) or placebo (P) twice weekly; 42 day cycle until PD or intolerability. Pts with PD on P may cross over to S. The primary endpoint was progression-free survival (PFS) by WHO criteria. Pre-specified analyses using RECIST v1.1 (R v1.1) was included. Results: Ph 2 enrollment is complete; 56 evaluable pts (33 M, 23 F) were randomized to S or P. Median age: 61 yrs and median prior treatments: 2 (1-3). Treatments for 51 pts were unblinded (24 S, 27 P). The main reason for ending blinded treatment was PD confirmed by Independent Central Radiological Review by WHO Criteria. Common AEs Grade 1/2 (S/P): nausea (85%: 31%), anorexia (62%: 14%), and fatigue (58%: 45%); Grade 3/4 AEs were: hypertransaminemia (15%: 0%), anemia (15%: 7%), and thrombocytopenia (12%: 0%). 2 pt deaths with S were considered possibly related to S. No clinically meaningful alteration in median PFS by WHO. By R v1.1, median PFS on S: 5.6 mo; P: 1.8 mo; hazard ratio of 0.64 (p = 0.21, not powered in Ph 2). (Table 1). Some pts ended treatment early with small changes in tumor burden due to PD by WHO criteria. Conclusions: R v1.1 may be better criteria than WHO to evaluate drug efficacy in DDLS. The median PFS from the Ph 1b portion of S is 11.5 mo in DDLS. Clinical trial information: NCT02606461.

Median PFS by R v1.1 and WHO criteria.

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>R v1.1 - PFS (mo)</th>
<th>Hazard Ratio (95% CI)</th>
<th>WHO - PFS (mo)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor (N = 24)</td>
<td>5.6</td>
<td>0.64 (0.31, 1.32)</td>
<td>P = 0.21</td>
<td>1.4</td>
</tr>
<tr>
<td>Placebo (N = 27)</td>
<td>1.8</td>
<td></td>
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</table>

A phase 1 study of MDM2 inhibitor DS-3032b in patients with well- de-differentiated liposarcoma (WD/DD) LPS, solid tumors (ST) and lymphomas (L). First Author: Todd Michael Bauer, Sarah Cannon Research Institute/ Tennesse Oncology, Nashville, TN

Background: Inactivation of p53 is the most frequent event in cancer driven by mutations in TP53 or overexpression of MDM2, a negative regulator of p53. DS-3032b is an oral small molecule that disrupts the MDM2-p53 interaction, resulting in reactivation of wild type p53 and causing growth arrest/apoptosis. We characterized the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK) and pharmacodynamics (PD) and preliminary efficacy of DS-3032b. Methods: Patients (pts) received DS-3032b orally in 28 day cycles as per Table, TP53 status was confirmed post-enrollment. Results: 94 pts were enrolled with ST (50, 53%), WD/DD LPS (40, 43%), L (4, 4%). Doses, schedules (Sch), MTDs and results are tabulated below. Median age was 60.5 yrs, 50% male, 63% had ≥ 3 prior therapies. 58% (87%) pts tested had WT TP53. The most common (> 10%) TEAEs were nausea 71%, vomiting 31%, diarrhea 40%, decreased appetite 37%, abdominal pain 16%, dry mouth 11%, thrombocytopenia 61%, neutropenia 28%, anemia 43%, fatigue 55%, dysgeusia 18%, headache 19%, cough 19% and peripheral edema 14%. There were 8 dose limiting toxicities (DLTs): six G2-4 anemia, thrombocytopenia, neutropenia, 3 events each, 3 unreported. Three G3 nausea, vomiting and anorexia and another G2 fatigue. Sch D (3/4 days) had the best safety profile. In 79 efficacy-evaluable pts, 47 (60 %) achieved stable disease (SD). Median duration of SD was 6.7 (1.6 to 36.4) months. Partial responses (PR) were seen in DDLS (2), myxoid LPS (1), and LPS due to AEs. SU-C2 and Cmax were dose proportional with median Tmax 3 hours. PD biomarker MIC-1 correlated with drug exposure. In paired biopsies, MDM2 inhibition resulted in increase of nuclear p53 levels (IHC) in 5/6 pts (83%). Conclusions: DS-3032b has acceptable safety profile with intermittent dosing. Objective responses and durable SD were seen in MM2 amplified ST and DDLS warranting further studies Clinical trial information: NCT01877382.

<table>
<thead>
<tr>
<th>Schedule, dose</th>
<th>Doses, mg</th>
<th>N = 94 pts</th>
<th>Histology</th>
<th>MTD, mg</th>
<th>Best Response</th>
</tr>
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<tbody>
<tr>
<td>A – 2/12</td>
<td>15, 340</td>
<td>20</td>
<td>75%</td>
<td>75%</td>
<td>50</td>
</tr>
<tr>
<td>A – 120</td>
<td>120, 200</td>
<td>20</td>
<td>57%</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>A – 260</td>
<td>260, 400</td>
<td>0</td>
<td>100</td>
<td>90, 150</td>
<td>50</td>
</tr>
<tr>
<td>C – 720</td>
<td>120, 200, 300</td>
<td>0</td>
<td>100</td>
<td>1 PR DDLS</td>
<td>50</td>
</tr>
<tr>
<td>D – 3/14 – 3/12</td>
<td>120, 200, 240, 320</td>
<td>0</td>
<td>100</td>
<td>1 PR DDLS</td>
<td>75</td>
</tr>
</tbody>
</table>

IMMUNOSARC: A collaborative Spanish (GEIS) and Italian (ISG) Sarcoma Groups phase II/III trial of sintinib plus nivolumab in selected bone and soft tissue sarcoma subtypes—Results of the phase I part. First Author: Javier Martin Broto, Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS)/CSIC/Universidad de Sevilla, Seville, Spain

Background: Disruption of angiogenesis substantially enhances the efficacy of immunotherapeutic cancer therapies. The combination of an antiangiogenic drug (sunitinib or pazopanib) plus anti-PD1 (nivolumab) exhibited both higher activity and toxicity compared with antiangiogenic drug alone in renal cell carcinoma (RCC). We hypothesized that sintinib (SU) and nivolumab (NI) could be synergistic in some sarcoma subtypes and the toxicity profile could be different from RCC. We present the results of phase I part of the combination of SU-NI in advanced sarcoma patients (pts). Methods: Pretreated progressing pts, ECOG 0-1 and diagnosed with UPS, synovial sarcoma (SS), clear cell sarcoma (CCS), angiosarcoma (AS), epithelioid hemangiendothelioma (EH), solitary fibrous tumor (SFT), epithelioid sarcoma (ES), osteosarcoma (OS), Ewing sarcoma (EWS) or dedifferentiated chondrosarcoma (DCh) were eligible. SU 37.5 mg/d as induction was given for the first 14 days. The dose-finding stage (from day 15 to 45) would be completed when 10 dose limiting toxicity (DLT)-evaluated pts had been treated with DLT rate < 0.33. Two level- doses were designed: (0 initial) SU 37.5 mg/d and SU 25 mg/d and OS 3 mg/kg/2w for both. SU-NI was maintained up to progression or intolerance. Results: From May to October 2017, 16 pts (MF 10/6, median age 38y (25-78) were enrolled. Diagnosis was: CSS in 4 (25%), ASPS in 3 (19%); AS, OS, SS (2 each, 12.5%); UPS, extraskelatal OS and Ch (1 each, 6%). There were 3 DLT in the first 6 pts at dose level 0 (G3 fatigue in 2 and G4 septic shock) and 1 DLT in the following 10 pts at dose level 0 (G3 neutropenia). G3 toxicity: fatigue 25%, thrombocytopenia 19%, mucositis 13% and neutropenia 13%. There were 6 RECIST PR (42.8%), 4 SD (2 of them 25% of shrinkage) and 4 PD in 14 evaluable pts. PR occurred in 2 CCS and in one of AS, Ch, SS, ASPS while 2 cases (ASPS and UPS) shrank 25%. Conclusions: At the median level 2 SU 25 mg/d and OS 3 mg/kg/2w for both. SU-NI is a feasible and promising combination with manageable toxicity. SU-NI has induced objective responses in several sarcoma subtypes. The study is currently on a phase II part. Clinical trial information: NCT03277924.
We refer to abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: An open label phase 2 clinical trial.

First Author: Lu Xie, Peking University People’s Hospital, Beijing, China

Background: Anti-angiogenesis Tyrosine kinase inhibitors (TKIs) have been proved to show promising effects on prolonging progression-free survival (PFS) for advanced osteosarcoma after failure of standard multimodal Therapy. Methyssulfonic apatinib is one of those TKIs which specifically inhibits VEGFR-2. We aimed to assess the activity of apatinib in patients with locally advanced or multiple metastatic high-grade osteosarcoma progressing after standard treatment. Methods: This non-randomised phase 2 trial was done in Peking University People’s Hospital. We enrolled participants (≥ 16 years) with relapsed or unresectable osteosarcoma progressing after standard treatment (methotrexate, cisplatin, doxorubicin, and ifosfamide). Participants received 750 mg or 500mg apatinib according to body surface area (BSA) once daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (CR+PR at least 3 months according to RECIST 1.1) and PFS at 4 months. All analyses were intention-to-treat. Results: 37 participant were enrolled between March 17th, 2016 and June 9th, 2017. Until final follow-up, the objective response rate (CR+PR at least 3 m) was 56.76% (21/37). And the 4-m PFS rate was 52% (95% CI 32%-68%). However 9/37 (24.32%) patients was progression free at 6 months. Median PFS and OS were 4.44 (95% CI 3.12-7.08) and 8.77 (95% CI 6.73-16.70) months, respectively. Toxic effects led to dose reductions, or interruptions in a total of 25/37 (67.57%) patients. The most common grade 3-4 adverse events were pneumothorax in 5 (13.51%), weight loss in 4 (10.81%), hypertriglyceridaemia, hand-foot skin reaction and anemia each in 3 (8.11%), hypokalemia in 2 (5.41%) and bilirubin increase, proteinuria, fever, arthralgia and hyper hypersensitivity reaction in 2 (5.41%) patients. Foot skin reaction and anemia each in one (2.70%). No other serious adverse events were reported during the trial. There were no treatment-related deaths. Conclusions: Apatinib was a sensitive drug for advanced osteosarcoma with high response rate after failure of chemotherapy, with almost the same duration of response comparing to other TKIs. Clinical trial information: NCT02711007.

Neoadjuvant denosumab for the treatment of resectable giant cell tumor of bone: First results of Russian multicenter study.

First Author: Alexander A. Frolova, Federal State Budgetary Institution Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Moscow, Russia

Background: Giant cell tumor of bone (GCT) is a relatively rare, benign but locally aggressive osteolytic skeletal neoplasm of young adults. This study is non-interventional observational GCT treatment study in the Russian Federation (RF). Designed to detect epidemiology data as well as the clinical efficiency of surgical and/or denosumab (Db) treatment of GCT in RF. Methods: Between August 2016 and October 2017, 112 adult patients (pts) with GCT were enrolled. Ten Russian Cancer Center are included in this study. The primary endpoint was Time-to-Progression (TTP). Adult and skeletally mature adolescent pts with resectable and unresectable GCT (N = 54) received subcutaneous Db 120 mg every 4 weeks with a loading dose of 120 mg SC on study days 8 and 15. Options for surgical treatment (N = 25) include intralesional curettage (InC) (alone or followed by filling of the defect with bone cement), marginal excision (MEx), a wide local excision, or en bloc resection with or without reconstructive surgery. Results: 112 pts were enrolled, 71 were evaluated for efficacy evaluation. Median follow-up was 12.5 months. Enrolled subjects were 51.8% women, median age 35 years old. The most commonly affected sites are the epiphyses of the long bones (63%), 44% of all cases affect the distal femur or proximal tibia. Less commonly involved vertebra (3.5%), pelvis (8%), the skull (0.8%) and the scapula (0.8%). The median of 112 pts enrolled, 16 with resectable GCT were evaluated for efficacy and underwent surgery - InC and MEx. 6 (37.5%) of 16 pts had disease progression; TTP was 6 months after surgery (11 injection of Db in average), 25 of 71 pts received only surgical treatment, in 4 (16%) of 25 pts InC and MEx were performed, 2 (9%) of the pts had disease progression, TTP was 7 months after the surgery. Conclusions: In this study, only 37.5% of pts with resectable GCT, who received neoadjuvant Db, had disease progression vs 50% of pts, received only surgical treatment. This study confirms that neoadjuvant Db is a possible treatment option for the resectable GCT to avoid mutilating surgery and decrease the risk of recurrences. Further investigation is awaited.
A comparison of outcomes, presentation, and treatment in pediatric (Ped) versus adult patients (pts) with Ewing sarcoma. First Author: Eric B. Schwartz, Michigan Medicine, Ann Arbor, Michigan, USA

Background: Ewing Sarcoma (ES) afflicts 225 children and 180 adults in the US annually, but the vast majority of research is in ped pts. In multiple series, adults have poorer outcomes. The aim of this study is to evaluate clinical features that correlate with overall survival (OS)/progression-free survival (PFS). Methods: Pts at University of Michigan from 2007-15 were identified using an institutional database. Charts were reviewed for demographic and clinical data. Ped pts were defined as age <18 at diagnosis. Two-sample t-tests or Chi-squared tests/Fisher’s exact tests were used for comparisons. Survival outcomes were analyzed using Kaplan-Meier methods and Cox proportional hazards regression models. Results: Seventy-eight ES pts (26 ped, 52 adult) were included in analysis. Factors evaluated in multivariate analysis included localized disease, age, surgery, radiation, tumor size, cumulative doxorubicin (DOX), OSSE primary and no. of first-line chemo cycles. Localized disease correlated with improved PFS (HR = 0.20, p = 0.003), and marginally with OS (HR = 0.386, p = 0.0580). Five-yr OS was higher in ped pts vs adults (81% vs 49%, p = 0.0218). Ped pts received more cycles of first-line chemo (14.0 vs 11.8, p = 0.024), which positively correlated with OS (HR = 0.78, p = 0.002) and PFS (HR = 0.82, p = 0.024). Other differences included higher cumulative DOX dose and increased incidence of extraneal ES in adults, but did not correlate with OS/PFS. Conclusions: In our series, younger age correlated with improved OS. Ped pts were more likely to have extraneal ES and less DOX, but only increased number of first-line chemo cycles was associated with improved outcomes. Further evaluation of potential tissue biomarkers to differentiate the two groups and early progressors is planned.

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A retrospective natural history study of patients (pts) with PDGFRα D842V mutant advanced gastrointestinal stromal tumor (GIST) previously treated with a tyrosine kinase inhibitor (TKI). First Author: Margaret von Mehren, Fox Chase Cancer Center, Philadelphia, PA

**Background:** Activating mutations in KIT or PDGFRα kinases drive the vast majority of GIST in adult pts, making the disease highly amenable to targeted therapy. KIT-driven disease is more common (~80% of cases of advanced GIST), while PDGFRα-driven GIST is rare (~5–10% of cases of advanced GIST). TKIs have transformed therapy of advanced GIST; however, evidence suggests the benefit of currently approved TKIs has been predominantly in patients with KIT-driven GIST. We initiated this study to characterize response and survival of pts with PDGFRα D842V mutant GIST treated with currently approved TKIs. **Methods:** This was a multicenter, retrospective study of adult pts with locally advanced, metastatic, or recurrent PDGFRα D842V mutant GIST diagnosed between Jan 2000 and Jul 2016 who were treated with at least one TKI. Demographic and clinical data were collected through chart review and analyzed to determine overall survival (OS) and best overall response, duration of response, and progression-free survival (PFS) for each line of TKI therapy. **Results:** Twenty-two pts, all with PDGFRα D842V GIST, were identified at 3 US academic institutions: men, n = 15; median age, 57 y [range: 31-72]; median TKI lines of therapy, 4 [range: 1–8]. Ten pts had primary tumor size ≥ 15 cm, and 8 pts had mitotic index > 10/50 HPF at the time of diagnosis. Imatinib was the most common TKI used (n = 21), followed by sunitinib (n = 15), dasatinib (n = 8), sorafenib (n = 6), regorafenib (n = 4), nilotinib (n = 2), and pazopanib (n = 1). Imatinib was the first line TKI in 20 pts (91%). Only 1 (5%) pt responded to first-line TKI therapy (complete response to imatinib in a pt with residual disease following primary resection). Median PFS on first line TKI was 6.4 months. Median OS from initial diagnosis of GIST was 4.2 years. **Conclusions:** These results confirm and extend previous data suggesting that pts with advanced PDGFRα D842V GIST have a low response rate, and poor overall survival with currently available TKIs. To transform therapy for PDGFRα D842V GIST, novel TKIs that potently and selectively inhibit D842V mutant PDGFRα are needed.

LMTK3 to regulate the translation of oncogenic KIT in GIST regardless of imatinib sensitivity. First Author: Lilian Rose Klug, Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR

**Background:** The majority of gastrointestinal stromal tumors (GIST) have been shown to be caused by somatic activating mutations in the receptor tyrosine kinase KIT. The major cause of death in patients with advanced KIT-mutant GIST is due to the development of KIT tyrosine kinase inhibitor-resistant (TKI-resistant) metastatic disease. Drug resistance arises almost exclusively from secondary mutations within KIT, highlighting the importance of KIT in the proliferation and survival of these tumors. **Methods:** We performed a human kinase siRNA screen in multiple KIT-mutant cancer cell lines, using viability as a read out. We defined candidate targets as those whose knockdown decreased viability in all cell lines. Validation and mechanistic studies were done using a library of KIT-mutant GIST cells. **Results:** We identified lemur tyrosine kinase 3 (LMTK3) as candidate target in three KIT-mutant cell lines. LMTK3 silencing reduced the viability of all KIT-mutant GIST cells tested to date, including cell lines with KIT TKI-resistance mutations. Importantly, LMTK3 silencing decreased the viability of KIT-mutant cells specifically, but not that of KIT-independent cells. LMTK3 knockdown also reduced tumor growth in vivo in a GIST xenograft model. Further, we found that decreased cell viability after LMTK3 silencing was due to induction of apoptosis. Because these cells depend so heavily on KIT and the loss of KIT signaling results in cell death, we hypothesized that LMTK3 silencing may affect this pathway. Indeed, LMTK3 silencing decreased total KIT protein across all cell lines. The reduction in KIT protein was not the result of changes in KIT transcript or KIT protein stability, but translation rate of KIT was significantly reduced after LMTK3 knockdown. **Conclusions:** The protein kinase LMTK3 is an important translational regulator of oncogenic KIT expression in KIT-mutant GIST regardless of drug sensitivity and represents a novel, tractable target, particularly in drug-resistant tumors.

**Background:** GIST benefit from TK inhibitors but unfortunately can develop resistance or intolerance. Patients prolonged life expectancy associated with the complex biology involved in progressive disease led to a growing urgency and interest in developing new therapeutic strategies. Recently, few preclinical studies were conducted investigating the immunological profile in GIST. In the present study we analyzed GIST by whole transcriptome sequencing to estimate the gene expression signature, the presence of immune-infiltrate through in silico analysis, and to define the immunological profile of GIST as basis for immunotherapy. **Methods:** 18 fresh frozen GIST tumors (14 primary and 4 metastases) were analyzed. RNA-seq was performed with Illumina technology. Gene expression data was used to estimate the relative and absolute presence of 22 hematopoietic cell types in tumor microenvironment adopting CIBERSORT, an analytical tool suite performed to deconvolute of neoplastic and tumor-infiltrating cells. The data were further processed to evaluate the enrichment of immune cell types, the correlation between cell subpopulations and to compare GIST microenvironment with other tumors. IHC tests for CD163, CD20 and TIA1 were performed and scored on FFPE samples. **Results:** A significant presence of immune-infiltrate in all GIST samples was confirmed, with a dominance of macrophages (M2 and M1), immediately followed by CD3+ T cells, both CD4+ and CD8+. Compared to other solid tumors, the immune profile of GIST appears similar to that of melanoma. The most relevant result is the high amount of CD8+ T-cells, suggesting that the adaptive immune response could be an immunotherapeutic target. The presence of CD8+ was confirmed by IHC that also showed the expression of citolytic markers (TIA1). Moreover the abundance of CD8+ T-cells correlated with the expression of IFN-γ/sigma signature genes. Interestingly, the abundance of macrophages positively correlates with T-cells presence (CD4+ and CD8+) supporting the dynamic balance between the immunosuppressive and active components of the immune-infiltrate. **Conclusions:** These findings represent a potential rationale to plan an immunotherapy approach along with TK inhibitors in GIST.

**Background:** Soft tissue sarcoma (STS) is a heterogeneous malignancy including more than 50 molecularly distinct subtypes. Undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcoma (LMS) are common subtypes with limited treatment options. LMS can be divided into two distinct subsets: uterine (uLMS) and retroperitoneal (rpLMS). STS subtypes have differing immunohistochemistry (mIHC). Interrogating the sarcoma immune microenvironment (iME) using multiplex immunohistochemistry (mIHC), First Author: Andrew Silverman, Columbia University Medical Center, New York, NY

**Background:** The majority of soft tissue sarcomas have an immunosuppressive profile, which appears to be associated with poor survival. The STS iME is characterized by low levels of immune cell infiltration and high levels of immune suppression. **Methods:** We performed an immunohistochemical (IHC) analysis for CD3, CD4, CD8, PD-L1, PD-L2, TIA1, HLA-DR, and PD-1 in a cohort of 30 soft tissue sarcoma cases, using a multiplex IHC protocol. **Results:** The majority of sarcoma cases showed low levels of CD3+ T cells, both CD4+ and CD8+. Compared to other solid tumors, the immune profile of GIST appears similar to that of melanoma. The most relevant result is the high amount of CD8+ T-cells, suggesting that the adaptive immune response could be an immunotherapeutic target. The presence of CD8+ was confirmed by IHC that also showed the expression of citolytic markers (TIA1). Moreover the abundance of CD8+ T-cells correlated with the expression of IFN-γ/sigma signature genes. Interestingly, the abundance of macrophages positively correlates with T-cells presence (CD4+ and CD8+) supporting the dynamic balance between the immunosuppressive and active components of the immune-infiltrate. **Conclusions:** These findings represent a potential rationale to plan an immunotherapy approach along with TK inhibitors in GIST.

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Phase II trial of continuous dosing of regorafenib in patients with metastatic or recurrent gastrointestinal stromal tumors (GISTs) after failure of imatinib and sunitinib.

First Author: Yoon-Koo Kang, Department of Oncology, Asan Medical Center, Seoul, Korea, Republic of (South)

Background: Regorafenib in the standard intermittent dosing schedule (160 mg po per day for 3 weeks followed by 1 week rest) was proven effective in the GRID trial in refractory gastrointestinal stromal tumors (GISTs). However, with this dosing schedule, frequent dose reduction was needed and progression of GIST tumors or tumor-related symptoms during the off-treatment period were also noted in some patients (pts). Therefore, we conducted this phase 2 trial to evaluate the efficacy and safety of regorafenib in lower dose continuous dosing schedule (NCT02889328).

Methods: Pts with measurable, metastatic or recurrent GIST who failed both imatinib and sunitinib were eligible for this study. Regorafenib 100 mg po per day was administered continuously. The primary endpoint was disease control rate (DCR) (CR + PR + SD) lasting for at least 12 weeks by the RECIST v1.1.

Results: From September 2016 to August 2017, a total of 25 pts were enrolled. The median age was 60 years (range, 42-74), and male was dominant (64%). Small bowel was the most common primary site (n = 15, 60%), followed by stomach (n = 7, 28%). The median treatment duration of imatinib and sunitinib was 40.5 months (range, 7.1-100.5) and 8.3 months (range, 0.7-37.5), respectively. Primary mutation was in kit exon 11 (n = 16, 64%) and 9 (n = 5, 20%), with 3 wild type (12%). The best response was PR in 2 (8%), SD in 16 (64%), and PD in 6 (24%) pts. DCR lasting for at least 12 weeks was 64% (16 of 25). With a median followup of 8.6 months (range, 2.3-14.6), the median PFS was 7.3 months (95% CI, 5.9-8.6), and the median OS was not reached with 1-year survival rate of 64.5%. Treatment was well tolerated. Ten pts (40%) experienced grade 3-4 toxicities including hand-foot skin reaction (n = 4, 16%), and elevation of alanine aminotransferase (n = 2, 8%). Only 5 pts (20%) needed dose modification with relative dose intensity of 91.8% for 8 cycles in all pts.

Conclusions: With comparable efficacy and better safety profile compared to standard intermittent dosing schedule, regorafenib in this trial with lower dose continuous dosing schedule might be an alternative treatment in GIST pts after failure of imatinib and sunitinib. Clinical trial information: NCT02889328.

Impact of circulating tumor DNA (ctDNA) in the management of patients with gastrointestinal stromal tumor (GIST) (sarcoma 585s).

First Author: Junaid Arshad, Jackson Memorial Hospital, Miami, FL

Background: GIST is the most common sarcoma of the GI tract. Management of GIST is determined by KIT, PDGFR, or other genomic alterations. Tissue diagnosis has been the mainstay of the biomarker assessment but next generation sequencing (NGS) - based analysis of ctDNA is a novel, effective and non-invasive alternative. Methods: DNA sequencing of the circulating tumor DNA (ctDNA) was performed on blood samples from 152 patients. Samples were collected, shipped at room temperature and centrifuged to isolate plasma. DNA was extracted, concentrated, and quantified. Results: Of 152 unique patients, 72 (47%) females and 80 (52%) males with a median age of 59, 41 (27%) patients did not test positive for either KIT or PDGFR while 111 (73%) had either KIT or PDGFR mutation. 6 patients were positive for both KIT and PDGFR mutations. Of these, 6, 1 had KIT amp plus PDGFR amp, then only a KIT point mutation 6 months later. 2 had KIT plus PDGFR point mutations. Most of the imatinib resistance mutations were missense mutations and were found in males (p = .005). There were 3 (2%) patients positive for PDGFR D842V with resistance to imatinib. Mutations other than KIT or PDGFR included EGFR 8(7%), ERBB2 8(7%), NF1 7(6%), PIK3CA 7(6%), ARID1A 6(5%), FGFR2 6(5%), KRAS 6(5%), BRCACA 5(4%), MET 5(4%), PTEN 5(4%), MYC 4(3%), NTRK1 4(3%). Overall, the average number of mutations at first test: 3 (range 1-11). The average highest MAF: 4.74% (RANGE 0-52.98%), MEDIAN 0.72%. Of the 25 patients with clinical annotation 15(10%) had treatment impacted, 20(13%) identified resistance mutations, and 30 (20%) of patients were found to harbor additional mutations.

Conclusions: Digital DNA sequencing from ctDNA provides a reliable picture of the genomic profile in GIST. However, there is limited information related to resistance, prognosis or predictive role along with the effect of chemotherapy. Further work needs to be done on correlation of resistance mutations and survival in GIST patients.

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Background: Metastasis occurs in 20-55% of sarcoma patients and remains the main cause of death. We propose a novel immunotherapeutic approach based in anti CXCR4 antibody MDX1338 (Bristol Myers Squibb) in combination with Activated and Expanded Natural Killer (NKA) cells therapy. CXCR4 is upregulated in 33.3-73.3% sarcomas. Its signaling blockade by MDX1338 may reduce tumor growth and metastatic burden. NKA cells have shown cytototoxicity against osteosarcoma and Ewing sarcoma.

Methods: Expression of CXCR4 by different sarcoma cell lines was analyzed by flow cytometry. Its migration and invasion capacity towards CXCL12 was tested using Transwell plates and Matrigel. NKA cells were obtained coculturing healthy donors’ peripheral blood mononuclear cells with K562- mb15-41BBL cells and IL-2. Rhabdomyosarcoma cells were inoculated intravenously in immunodeficient NGS mice to generate an in vivo model of metastatic sarcoma. Four treatment arms were established: MDX1338; NKA; MDX1338+NKA; vehicle. Luminiscent tumors were monitored and subsequently micrometastases were identified and quantified by qRT-PCR; by immunohistochemistry; and by fluorescence in situ hybridization.

Results: Alveolar rhabdomyosarcoma RH30 cell line showed the highest CXCR4 expression, concomitant with highest migration and invasion index. Both MDX1338 and NKA efficiently reduced in vitro RH30 cells migration and invasion, but only the combination of both agents completely abrogated it. In vivo, no treatment was enough to completely prevent RH30 tumor implant. Nonetheless, qRT-PCR analysis found RH30 lung micrometastases in NKA-treated mice group. Again, the combination of both MDX1338 and NKA was necessary to completely eliminate it. Immunohistochemical and in situ hybridization analysis further confirmed these results. CXCR4 expression was higher in in vivo tumors compared to the in vitro model (p = 0.01). The primary role of anti CXCR4 antibody MDX1338 and NKA cell therapy to prevent rhabdomyosarcoma cells migration, invasion, tumor implant and lung metastasis formation. These preclinical results constitute a first evidence of the efficacy of this combined immunotherapy to prevent sarcoma disease dissemination.

Conclusion: Anti CXCR4 antibody combined with activated and expanded natural killer cells for sarcoma immunotherapy. First Author: Maria Vela, Hospital La Paz Institute for Health Research (IDIPAZ), Madrid, Spain

Background: Olaratumab (O) is an antibody against platelet-derived growth factor receptor alpha. In a randomized phase 2 study, O in combination with doxorubicin (dox) demonstrated a significant improvement of overall survival (OS) over dox alone in patients (pts) with advanced STS. Here we report the safety, tolerability and recommended phase 2 dose (RPTD) of O plus gemcitabine (G) and docetaxel (D) (O + G/D). Methods: This dose-escalation study enrolled pts with advanced/metastatic STS, ≤2 prior lines of systemic therapy, no prior G, D or O, and ECOG PS 0-1. Pts received O on Days 1 and 8 at 15 mg/kg (cohort 1) or 20 mg/kg (cohort 2) with G (900 mg/m² Days 1 and 8) and D (75 mg/m² Day 8) on a 21-day cycle. The primary objective was to determine the RPTD of O + G/D, with a dose-limiting toxicity (DLT) occurring in Cycle 1 at a rate below 33%. Secondary objectives included safety and pharmacokinetics (PK).

Results: 54 pts (cohort 1/2 = 21/33) received at least one dose of treatment. No DLT occurred in cohort 1. In cohort 2, 5 pts (15.2%) experienced 6 DLTs (ALT increase, bacteremia, neutropenia [2 pts], and thrombocytopenia [2pts]). Treatment-related adverse events (TRAEs) reported for cohorts 1 and 2 included all grades (90.5% and 93.9%), Gr 3 (14.3% and 42.4%), Gr 4 (0 and 18.2%), and serious AEs (9.5% and 15.2%), respectively. Common TRAEs (all grades, Gr ≥3) occurring in ≥25% of pts were fatigue (65.7%, 11.1%), anemia (61.1%, 11.1%), thrombocytopenia (29.6%, 18.5%), neutropenia (26%, 15.2%) and rhematoid arthritis (9.5% and 15.2%). Common TRAEs (all grades, Gr ≥3) experienced 6 DLTs (ALT increase, bacteremia, neutropenia [2 pts], diarrhea [27.8%, 3.7%], 1 pt discontinued due to a study-related AE of fatigue (cohort 1). Following 2 deaths unrelated to study treatment, cohort 2 was expanded to 33 pts. The PK profile of O + G/D was similar to that of O in combination with other chemotherapies.

Conclusions: Both dose levels were tolerated, particularly with a higher exposure for dose level 2. Based on safety and exposure-response analyses across O studies, the RPTD for O + G/D is 20 mg/kg at Days 1 and 8 in Cycle 1, followed by 15 mg/kg at Days 1 and 8 thereafter. The randomized, double-blinded phase 2 part of the study is enrolling and will compare OS of pts with STS receiving G/D vs O/D placebo (ANNOUNCE 2). Clinical trial information: NCT02695920.
Background: Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal malignancy which occurs primarily in children and adolescents. Complete surgical resection is the major treatment, and conventional chemotherapy and radiotherapy are usually invalid. In this study, we retrospectively analyzed the clinical and pathological features of eleven patients with adult IMT. Methods: A total of eleven patients with adult IMT were enrolled into this study between February 2013 and November 2017. The clinical, pathological data, treatment and prognosis were analyzed. Results: Among the eleven patients with adult IMT, five patients were male (45%), six patients were female (55%), and the median age was 39 (24-74 years). The primary tumor was located in two patients (18%) in the lung and two cases (18%) in the retroperitoneum, and seven cases (64%) in the abdominopelvic region. Four cases were abdominal epithelioid inflammatory myofibroblastic sarcoma. The positive rate of anaplastic lymphoma kinase (ALK) immunohistochemical expression was 82% (9/11), and the positive rate of ALK translocation was 86% (6/7). Seven patients with ALK-positive advanced disease received the treatment ALK inhibitor crizotinib. The response rate was 86%, and the median progression free survival (PFS) was 20.8 months (95% confidence interval: 7.6 months-34.0 months). Two patients were treated with the more potent ALK inhibitor ceritinib after progression of disease on crizotinib and both of them showed significant and durable partial responses. Conclusions: The treatment of crizotinib in adult patients with ALK-positive advanced IMT resulted in a very high response rate and a long-term PFS, and the patients still responded to the next generation of ALK inhibitor after the advanced IMT resulted in a very high response rate and a long-term PFS, and the median progression free survival (PFS) was 20.8 months (95% confidence interval: 7.6 months-34.0 months). Two patients were treated with the more potent ALK inhibitor ceritinib after progression of disease on crizotinib and both of them showed significant and durable partial responses. Conclusions: The treatment of crizotinib in adult patients with ALK-positive advanced IMT resulted in a very high response rate and a long-term PFS, and the patients still responded to the next generation of ALK inhibitor after the failure of crizotinib in our study, which suggested that ALK signaling pathway may play an important role in the development of adult IMT. Further studies are warranted to clarify the effects of ALK signaling pathway and the mechanism of ALK inhibitor resistance in adult patients with IMT.
Background: Soft-tissue sarcomas (STS) describe a heterogeneous group of tumors with limited treatment options available to patients. Targeted therapy for STS with BRCA1/2 tumors with limited treatment options available to patients. Targeted therapy for STS with BRCA1/2 mutations and HR alterations in STS. Here we assess the frequency of BRCA2 loss and HR alterations in STS.

Methods: DNA sequencing data was aggregated from The Cancer Genome Atlas (n = 255), Genomics Evidence Neoplasia Information Exchange (n = 583), and The Ohio State Sarcoma Registry (n = 398). Deleterious genomic alterations were defined as in ClinGen. Clinical data from three patients with somatic BRCA2 loss who were treated with PARP inhibitors were collected for analysis. Results: BRCA1 and HR somatic alterations were more common in leiomyosarcoma (LMS) subtype compared to other STS (LMS 17%, liposarcoma 9.8%, other 8.9%, p < 0.001). A disproportionate number of BRCA2 loss were detected in uterine LMS (uLMS) with 85.7% of tumors harboring BRCA2 loss identified in this STS subtype (p < 0.001). When considering uLMS, 9.8% of tumors had a loss of BRCA2 (0.9% in non-uterine LMS, 0.5% in all other STS). Tumors with BRCA2 loss often exhibited a poor differentiated histology (57.1% of BRCA2 loss vs 38.8% BRCA2 intact; p = 0.059) and tended to have a higher mitotic count (10.7 count/HPF BRCA2 loss vs 3.3 count/HPF BRCA2 intact; p = 0.10). Retrospective evaluation of three uLMS patients with somatic BRCA2 loss treated with PARP inhibitors demonstrated a median progression-free survival of nine months highlighting the potential targetability of BRCA2 loss in uLMS. Conclusions: We have assessed the frequency of BRCA2 alterations and their clinical phenotype in STS. We identify somatic BRCA2 loss in a subset of patients with uLMS and describe three patients with uLMS harboring BRCA2 loss who were treated with PARP inhibitors. Our data suggests that patients with uLMS should be screened for BRCA2 alterations. Prospective trials are needed to confirm the efficacy of PARP inhibition in this cohort of patients.

Targeted tumor profiling and actionable somatic variants in sarcoma. First Author: Eytan Ben Ami, Dana-Farber Cancer Institute, Boston, MA.

Background: The impact of next generation sequencing data on treatment decision and clinical outcome in sarcoma remains understudy. Methods: We queried the Dana Farber Cancer Institute database to identify soft-tissue and bone-sarcoma patients (pts) who underwent targeted sequencing under a research protocol. We searched for mutations and somatic copy number alterations (SCNA) and evaluated clinical outcomes in cases bearing actionable genetic abnormalities (eligible for NCI-MATCH/ASCO-TAPUR studies). Results: 613 pts with 38 sarcoma histologies were evaluated. Leiomyosarcoma (LMS, 23.8%), liposarcoma (LPS, 13.2%), undifferentiated pleomorphic sarcoma (9.4%) and solitary fibrous tumor (4.7%) were the common histologies. Frequent mutations were observed in TP53 (30.1%), ATRX (12.1%), KMT2D (11.1%), NF1 (8%) and ATM (7.3%) genes. Common SCNA included homozygous deletions in RB1 (10%) and CDKN2A (8.1%), and high copy number gains in MDM2 (13.6%), CDK4 (11.5%), GLI1 and MYC (3%), 123 pts (20%) had 145 actionable somatic variants (59 mutations, 86 SCNA). Actionable mutations, observed in 52 pts, frequently involved the PI3K/Akt/mTOR pathway (PIK3CA, TSC1/2 and AKT1 genes; 25% of actionable mutations), BRCA1/2 (15.2%), and IDH1/2 (17%, exclusively in chondrosarcoma) genes. Actionable SCNA, observed in 82 pts, comprised mostly of homozygous deletions in CDKN2A (51% of actionable SCNA) and FTO (15.1%), and high copy number gain, not associated with LPS, in CDK4 (12.8%). Of 72 metastatic pts with actionable alterations and clinical data, 12.5% (9 pts) received matched therapies. Tumor responses were observed in 6 pts, including durable responses (6-28 months) in dedifferentiated chondrosarcoma (IDH2 mutation), inflammatory myofibroblastic tumor (ALK rearrangement), LMS (TSC2 mutation), spindle cell carcinoma (NR4A3 rearrangement), and chondrosarcoma (CDKN2A deletion). Conclusions: As many as 20% of sarcoma pts may harbor actionable genetic alterations. We observed durable tumor responses with matched therapies in several sarcoma histologies and further research is needed to understand the proportion of patients who may benefit from this approach. Mutations and SCNA incidence by histology will be presented at the meeting.

A phase II study of pazopanib with oral topotecan in patients with metastatic and non-resectable soft tissue and bone sarcomas. First Author: Mark Agulnik, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Topotecan and pazopanib (PAZ) individually have clinical benefit in patients (pts) with sarcomas. PAZ is a multi-tyrosine kinase inhibitor and topotecan affects endothelial cells, and inhibits HIV-1, an upstream regulator of VEGF expression. The utilization of PAZ with topotecan is anticipated to produce anti-tumor synergism in pts with sarcomas.

Methods: A phase II study of PAZ/topotecan in pts with metastatic and non-resectable bone and soft tissue sarcomas (STS) was conducted by the Midwest Sarcoma Trials Partnership. Age > 18, ECOG ≤ 1, adequate organ function, measurable disease and 1 prior therapy were required. Pts were treated with PAZ 800mg oral daily, Topotecan 8mg orally day 1, 8, 15 on a 28-day cycle until disease progression or unacceptable toxicity. Pts enrolled in 3 cohorts: 1. STS non-liposarcoma, osteosarcoma, synovial sarcoma. Primary endpoint: progression-free rate (PFR) at 12 weeks in cohort 1. Secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), OS, median progression free survival (PFS), PFR at 12 weeks in cohort 2 and 3, and safety and tolerability. Lab correlates evaluated PFR and OS to levels of VEGFR2 and PDGF. Simon 2-stage design was used for cohort 1. Results: A total of 139 pts were enrolled at 6 sites, with 121 evaluable for response. Data per cohorts 1, 2, and 3: # of pts- 103, 17, and 19; mean age- 61, 45, 57; female- 63, 53, 32%; 1-2 prior therapies- 75, 65, 84%. PFR at 12 weeks is 57.5%, 62.5%, 31.3% with a median PFS of 4.4, 4.5, 1 months (95% CI: 2.3-6.8, 2.3-3.0, 1.9-2.3). Correlative data will be presented. Conclusions: The combination of PAZ/topotecan produced identical results to historical data for PAZ alone in pts with STS, except with a worse toxicity profile. For pts with osteosarcoma, the combination proved extremely promising and cohort 2 will be expanded. The combination was ineffective in liposarcoma. Clinical trial information: NCT02357810.

Targeted tumor profiling and actionable somatic variants in sarcoma. First Author: Eytan Ben Ami, Dana-Farber Cancer Institute, Boston, MA.

Background: Clear-Cell Sarcoma (CCS) is a rare soft tissue sarcoma poorly documented, with poor prognosis. Primary objective was to study the characteristics and outcomes of CCS patients (pts). Methods: Retrospective study from the nation-wide French sarcoma network (NetSarc) from 1991 to 2017. Inclusion criterion was CCS central pathological review. Endpoints were local recurrence-free survival (LRFs), metastasis-free survival (MFS), disease-free survival (DFS) and overall survival (OS). Results: 91 pts from 16 centers were included (molecular biology confirmed in 53 pts). Pts were aged 41 years (18-73), 51.7% men. The median tumor size was 4 cm (3-7). Patients were divided in 3 groups: localized (L) (61.5%), locally-advanced (LA) (15.4%), and metastatic (M) (23.1%). Presurgical biopsy was performed in 50.7% of pts. All L and LA CCS pts underwent surgery, which was conservative in 70.6% pts. R0 resection was achieved in 71.9% of pts with 42.4% surgical revision to obtain clear margins. After a median follow-up of 6.5 years (95% CI: 4.5-9), 16 (22.9%), 37 (52.9%), 45 (64.3%), 29 (41.4%) events for LRFs, MFS, DFS and OS, were reported. Prognostic factors of the univariate analysis in L and LA pts are presented in Table 1. (Neo)Adjuvant radiotherapy and chemotherapy were performed in 54.4% and 30.9% pts, respectively, with no impact on OS or DFS. The 5-year OS for the 91 pts was 53.8% (CI: 41.3-66.5). Survival (OS) was 74, 48, 38%, Grade 3-4 adverse events (%): neutropenia (42), thrombocytopenia (29), hypertension (16) and anemia (12). Pts in cohort 1 who progressed within 6 weeks received 61% of prescribed PAZ dose vs. 67% for those with did not progress. Histologies in cohort 1-LMS (49%), UPS (15%), synovial (10%). Correlate data will be presented. Conclusions: The combination of PAZ/topotecan produced identical results to historical data for PAZ alone in pts with STS, except with a worse toxicity profile. For pts with osteosarcoma, the combination proved extremely promising and cohort 2 will be expanded. The combination was ineffective in liposarcoma. Clinical trial information: NCT02357810.
Primary pulmonary sarcomas (PSRC): A comprehensive genomic profiling (CGP) study. First Author: Sophie Beaucarne-Danel, Institut Curie, Paris, France.

Background: In an exploratory study to find biomarkers for both targeted and immunotherapy treatments, we performed CGP on a series of PSRC to search for novel therapy options for patients with clinically advanced disease.

Methods: Hybrid capture-based CGP was performed on 21 cases of PSRC, with 17 PSRC also undergoing RNA sequencing to enable expanded gene fusion detection. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined by principal components analysis of optimal homopolymer loci. Results: There were 10 sarcoma NOS, 5 pulmonary artery intimal sarcoma, 4 pleomorphic/MFH sarcomas, 1 primary inflammatory myofibroblastic tumor (IMT) and 1 primary solitary fibrous tumor (SFT). There was a stage I, I stage II, 9 stage III and 10 Stage IV tumors. The patients had a median age of 58 years (range 33 to 81 years). There were 7 female and 14 male patients. The mean number of genomic alterations (GA) per sarcoma was 5.8. Notable alterations not considered presently actionable included TP53 (47%), CDKN2A (36%), CDKN2B (25%) and RB1 (13%). Clinically relevant GA (CRGA) affected PDGFRα, RICTOR, CDK4 and KIT; all at 11%. When considering additional CRGA in EGFR, TSC2, ALK and BRAF (each at 5%), a total of 10 (48%) PSRC featured ≥1 CRGA. The case with an ALK fusion represents an IMT initially localized to the lung and diagnosed as a primary lesion. The mean TMB in the PSRC was 8.3 mutations per Mb with 14% having TMB of > 10 mut/Mb and 10% having TMB > 20 mut/Mb. MSI status was available for 9 of the PSRC cases, and the remainder were microsatellite stable. Assessment of therapeutic intervention and responses to targeted and immunotherapies is ongoing. Conclusions: PSRC is characterized by a relative high frequency of GA, including driver mutations or fusions in tyrosine kinases and cell cycle regulatory genes. In addition, this study identified a significant proportion of PSRC with limited characterization. Our study demonstrates superiority of AI, with 36% of 82 patients treated with AI, compared with 16% of 71 patients treated with other targeted and immunotherapies. Further studies are needed to evaluate the potential for use of targeted and immunotherapies in patients with PSRC.
Short, full-dose neoadjuvant chemotherapy in localized high-risk adult soft tissue sarcomas (STS): An exploratory subgroup analysis on responding patients in a randomized controlled trial comparing 3 vs. 5 neoadjuvant vs. 3 neoadjuvant + 2 adjuvant cycles of full dose anthracycline and ifosfamide chemotherapy at a 10yr median FU. First Author: Silvia Stacchiotti, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: We already reported (Cancer 2012;118:8587) the correlation of Choi criteria (Choi) and RECIST with outcome of pts affected by high-risk STS entering a multicentric Italian/Spanish Phase 3 trial comparing 3 vs. 5 cycles of neoadjuvant CT with full-dose epirubicin + ifosfamide (UCO 2012; 30;850; Ann Oncol 2016; 27;2283). We investigated whether the non inferiority of 3 vs 5 cycles held also in the subgroup of patients responsive to neoadjuvant treatment. Methods: Patients were randomized to receive 3 cycles of neoadjuvant CT with epirubicin 120 mg/m2 and ifosfamide 9 g/m2 (Arm A) or to receive the same 3 cycles of neoadjuvant CT followed by further 2 cycles of post-operative CT (Arm B). Radiotherapy could be delivered in the preoperative or in the post-operative setting. Non-inferiority of the primary end-point, overall survival (OS), was assessed by the confidence interval of the hazard ratio (HR; Arm A/Arm B) derived from Cox model. Response was assessed by RECIST and Choi. Results: Between January 2002 and April 2007, 160 pts were assigned to Arm A and 161 to Arm B. 158 patients received neoadjuvant RT (Arm A = 77; Arm B = 81). At a median FU of 117 months (IQR 103-135 months), 123 deaths were recorded, 58 in Arm A and 65 in Arm B. Ten-year OS was 61.1% for the whole group of patients, 64% in Arm A and 59% in Arm B (HR 0.92, 90% confidence interval [CI]: 0.68–1.23). Of 243 patients evaluable for RECIST, 208 achieved a partial response (PR) or stable disease (SD), 93 in Arm A and 115 in Arm B. Ten-year OS was 62% in Arm A and 59% in Arm B (HR 1.02; 90% CI 0.70-1.48). Of 166 pts evaluable for Choi, 135 achieved a PR, 60 in Arm A and 75 in Arm B. Ten-year OS was 60% in Arm A and 66% in Arm B (HR 1.29; 90% CI 0.80-2.07). Conclusions: In this (neo)adjuvant trial, the non inferiority of 3 vs 5 cycles of full dose anthracycline and ifosfamide (neo) adjuvant chemotherapy was confirmed also in the subgroup of patients with evidence of radiologic response to the neoadjuvant treatment. Clinical trial information: NCT00397936.
Characterization of tumor microenvironment in extraskeletal myoid chondroosarcoma (EMC). First Author: Valentina Indio, Interdepartmental Centre of Cancer Research “Guglielmo da Salerno”, University of Naples, Naples, Italy.

Background: EMC is a rare sarcoma most often originating from soft tissues. EMC carries a specific translocation, involving NR4A3, which is fused more often with EWSR1 and less frequently with other partners, including TAF15. We investigated EMC tumour microenvironment to define the differential immune-profile of NR4A3-EWSR1 and NR4A3-TAF15 EMC subtypes and to evaluate if EMC could be good candidate to immunotherapy. Methods: RNA-seq was performed on 12 naïve tumors with Illumina technology. The gene expression was quantified and, after normalization, the tool CIBERSORT was adopted to evaluate the presence of 22 hematopoietic population within the tumor-infiltrating environment. Absolute and relative abundance were used to estimate the correlation between infiltrating cell types. Moreover, the EMC immune-profile was comparatively evaluated between two subgroups of EMC based on the rearrangement type EWSR1-NR4A3 (7/12) and TAF15-NR4A3 (5/12). Immunohistochemistry, for CD3, CD20, CD14, CD163, CD56, HLA ABC, PD-L1 (22C3), and CD1a was performed and scored on available FFPE specimens (3/12). Results: The analysis showed in all cases the presence of immune signatures related to the presence of immune-infiltrate. Globally, M2 macrophages were the most enriched cell type, followed by CD4+ memory resting, and M0 macrophages; B-cell and mast cell were also moderately observed. The correlation analysis showed that the abundance of M2 macrophages negatively correlated with the presence of CD3+ T-cells. Comparative analysis showed that the EMC with TAF15 fusion had a significantly lower level of CD4+ memory resting cells (p = 0.042), lower NK cells and a trend to a higher enrichment of mast cells compared to EWSR1+ EMC. IHC analysis confirmed the presence of an immune-infiltrate, with both a macrophagic and a lymphocytic component. Conclusions: Our results showed that EMC is marked by the presence of a macrophagic and, to a lesser extent, a CD4+ T cells immune-infiltrate. Interestingly, the immune-profile differed between the 2 molecular subtypes, highlighting that the high degree of diversity that marks sarcomas is reflected also in their immune-profile. EMC looks to be a potential interesting candidate for immune-therapy.
Kaplan-Meier analysis was used to analyze survival outcomes. Statistical significance was assessed with Chi-square and Wald tests.

**Background:** Detection of circulating tumor DNA (ctDNA) has emerged as a new approach for identifying oncogenic mutations, measuring disease burden, clinical prognostication, and assessing response to therapy. Most ctDNA assays detect single-nucleotide variants (SNVs) that are highly recurrent in carcinomas. Though there are few recurrent SNVs in leiomyosarcoma (LMS), LMS is characterized by numerous chromosomal copy number alterations (CNAs). We therefore evaluated plasma from patients with LMS for the presence of ctDNA using a ultra-low passage whole genome sequencing (ULP-WGS) approach designed to detect somatic chromosomal CNAs. **Methods:** We identified 30 tumor/plasma pairs from patients with advanced LMS. Ten pairs have undergone ULP-WGS, with an additional 20 pairs currently in process. Of the 10 pairs evaluated, 7 were of uterine and 3 of extraterine origin. DNA from plasma samples was subjected to ULP-WGS and compared to tumor DNA. Differences in genome-wide sequencing coverage were used to identify chromosomal amplification or deletion using ichorCNA software. This was used to estimate tumor fraction of each subvariant.

**Conclusions:** Identification of plasma ctDNA by ULP-WGS is feasible in patients with advanced LMS and correlates with tumor burden/prognosis. An additional 20 cases will be enrolled. These preliminary results support further investigation of ULP-WGS as a novel blood-borne assessment of tumor burden in LMS. Future experiments will assess the utility of ULP-WGS in detecting residual disease following surgery, surveillance for disease recurrence, and monitoring response to therapy.

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**Background:** Synovial sarcoma, clear cell, angiomyxoma, and epithelioid leiomyosarcoma is often referred to by the mnemonic SCARE. SCARE sarcoma sites include head and neck (21%, 71), upper extremity (57%), lower extremity (50%), and uterine and extrauterine origin. DNA from plasma samples was subjected to ULP-WGS and compared to tumor DNA. Differences in genome-wide sequencing coverage were used to identify chromosomal amplification or deletion using ichorCNA software. This was used to estimate tumor fraction of each subvariant.

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Effect of JS001, a monoclonal antibody targeting programed death-1 (PD-1), on responses and disease control in patients with advanced or refractory alveolar soft part sarcoma: Results from a phase 1 trial. First Author: Sheng Yang, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Alveolar soft part sarcoma (ASPS) is a rare and lethal malignancy mainly affecting youth, with no effective standard systemic treatment. Checkpoint inhibitors have shown efficacy in a variety of tumors, but its role in ASPS remains elusive. Here we report data of JS001, a humanized IgG4 anti-PD-1 antibody developed by Shanghai Junshi Biosciences Co., Ltd., in ASPS.

Methods: After a dramatic tumor shrinkage with a single injection of JS001 in a patient with ASPS, we decided to expand a cohort in this tumor. Following patients(pts) were planned to receive JS001 at 3mg/kg or 10mg/kg, in a patient with ASPS, we decided to expand a cohort in this tumor. Following patients(pts) were planned to receive JS001 at 3mg/kg or 10mg/kg, in a patient with ASPS, we decided to expand a cohort in this tumor.

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Prognostic role of HMG proteins in a series of 301 advanced soft tissue sarcoma patients: A Spanish Group for Sarcoma Research Study (GEIS).

First Author: Nadia Roldan, Instituto de Investigación Sanitaria del Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Spain

Background: High Mobility Group (HMG) proteins act as architectural transcription factors and can influence the expression of many genes. The role of promoting an undifferentiated pluripotent stem-like cell state makes HMG proteins attractive for sarcoma research. Overexpression of HMGA1 and HMGA2 have been correlated with poor prognosis in some epithelial tumors, but there is hardly any data on the prognostic role of HMG in soft tissue sarcoma (STS). We present the analyses of protein expression of HMGA1 and HMGA2 as prognostic factor in STS.

Methods: Selection criteria were: advanced STS (at diagnosis or at any time from then on), paraffin block available, treated with at least 2 lines in advanced disease (one of them with trabectedin) and ethic committee’s approval. A TAM was set up for nuclear expression of HMGA1 (Abcam), HMGA2 (Sigma-Aldrich) and HBGM1 (Abcam) with block from diagnostic time. An expert blind pathologist reviewed and classified the intensity staining into negative, weak or strong and the extension as high (at least 50% of stained cells) or low (< 50%) for each protein.

Results: A series of 301 patients was studied, median age 52, 53% females and median follow-up from metastasis (M1) of 42 m. Strong and high expression were distributed as follows: HMGA1 24% and 18%, HMGA2 58% and 63%, HBGM1 69% and 75%, respectively. Strong and high expression of HMGA1 showed a significant worse prognosis for OS from M1 time (31 vs 22 m; p = 0.007) and for PFS of trabectedin line (3.8 vs 2.6 m; p = 0.002). Similar results were obtained with high HMGA1 expression. In multivariate analyses, age (> 60 yr) HR 1.52 (1.10-2.09) p = 0.009, short lapse to metastases (< 10 months) HR 1.44 (1.08-1.92) p = 0.013, and strong expression of HBGM1 HR 1.45 (1.06-1.98) p = 0.018 showed to be independent prognostic factors for worse survival from M1.

Conclusions: Protein expression of HMGA1 exhibited a significant prognostic role in a series of advanced STS validation studies are ongoing to confirm its prognostic and potential predictive role. These results could open new target in STS.

Subgroup analysis of elderly patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evosofamid (SARCO21) trial. First Author: Eugenie Younger, Royal Marsden Hospital, London, United Kingdom

Background: Approximately 50% of patients diagnosed with soft tissue sarcoma (STS) are aged ≥65 years (yrs). The management of elderly STS patients (≥65yrs) is challenging and there are few prospective data on the outcome of those with advanced disease. This study aims to document the safety and efficacy of first-line chemotherapy in elderly patients within the SARCO21 trial and provide a benchmark for future research.

Methods: SARCO21 randomized patients to receive first-line doxorubicin (Dox) or doxorubicin + evosofamid (DE) for elderly patients between the 2 arms (Dox: n = 103, median age 70 [65-84] yrs. DE: n = 106, median age 69 [65-84] yrs). Adverse events were prospectively evaluated as first line treatment in advanced LMS. Acknowledgment of outcome differences was not possible due to lack of randomization by age.

Results: A series of 301 patients was studied, median age 52, 53% females and median follow-up from metastasis (M1) was 42 m. Strong and high expression were distributed as follows: HMGA1 24% and 18%, HMGA2 58% and 63%, HBGM1 69% and 75%, respectively. Strong and high expression of HMGA1 showed a significant worse prognosis for OS from M1 time (31 vs 22 m; p = 0.007) and for PFS of trabectedin line (3.8 vs 2.6 m; p = 0.002). Similar results were obtained with high HMGA1 expression. In multivariate analyses, age (> 60 yr) HR 1.52 (1.10-2.09) p = 0.009, short lapse to metastases (< 10 months) HR 1.44 (1.08-1.92) p = 0.013, and strong expression of HBGM1 HR 1.45 (1.06-1.98) p = 0.018 showed to be independent prognostic factors for worse survival from M1.

Conclusions: Protein expression of HMGA1 exhibited a significant prognostic role in a series of advanced STS validation studies are ongoing to confirm its prognostic and potential predictive role. These results could open new target in STS.

Genomic subtypes of angiosarcoma: A comprehensive genomic profiling (CGP) study. First Author: Vincenzo Ravi, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Angiosarcomas (AS) arise from the vascular endothelium of skin and other visceral organs and from such diverse etiologies as exposure to carcinogenic agents or therapeutic radiation. We used CGP to subclassify AS and to identify genomic alterations (GA) linked to responsiveness to targeted therapy and immune checkpoint inhibitor (ICI) therapies. Median overall survival of metastatic AS is only 13.1 months. Methods: Hybrid-capture based CGP including RNA-seq in a subset of cases was performed on 278 cases of AS studied, median age 52, 53% females and median follow-up from metastasis (M1) was 42 m. Inclusion criteria: confirmed histological diagnosis, treatment between 2015-2019, ≥2 months of follow-up.

Results: A series of 301 patients was studied, median age 52, 53% females and median follow-up from metastasis (M1) was 42 m. Strong and high expression were distributed as follows: HMGA1 24% and 18%, HMGA2 58% and 63%, HBGM1 69% and 75%, respectively. Strong and high expression of HMGA1 showed a significant worse prognosis for OS from M1 time (31 vs 22 m; p = 0.007) and for PFS of trabectedin line (3.8 vs 2.6 m; p = 0.002). Similar results were obtained with high HMGA1 expression. In multivariate analyses, age (> 60 yr) HR 1.52 (1.10-2.09) p = 0.009, short lapse to metastases (< 10 months) HR 1.44 (1.08-1.92) p = 0.013, and strong expression of HBGM1 HR 1.45 (1.06-1.98) p = 0.018 showed to be independent prognostic factors for worse survival from M1.

Conclusions: Protein expression of HMGA1 exhibited a significant prognostic role in a series of advanced STS validation studies are ongoing to confirm its prognostic and potential predictive role. These results could open new target in STS.

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11577  Poster Session (Board #322), Sat, 8:00 AM-11:30 AM
Identification of novel intra-genic deletions of CTNNB1 gene in WT desmoid-type fibromatosis. First Author: Milena Ubinii, Interdepartmental Centre of Cancer Research, ‘Girogio Pecchi’ University of Bologna, Italy.

Background: Desmoid-type fibromatosis (DT) are characterized by molecular alterations of CTNNB1 or APC genes. These abnormalities have been described as ~85% of DT using Sanger sequencing. Recently, whole-exome sequencing allowed to detect molecular aberrations in CTNNB1 or APC in approximately 95% of DT. In order to characterized the true WT DT, we evaluated the activity of anthracycline- and G-based regimens are available. EZH2 inhibitors, which target the INI1 pathway that is inactivated in ES, are currently being tested in clinical trial. Comparisons of these agents are not available and unlikely to be prospectively evaluated. We comparatively assess these agents in a proximal-type INI1-deleted ES PDX. Methods: A PDX model (ES-1) was established by subcutaneously xenotransplanting into immunodeficient (SCID) mice tumor fragments obtained from a patient with primary, proximal-type, INI1 deleted ES of the forearm. After tumor propagation in SCID mice for three consecutive passages, the PDX was considered established. Mice were randomized to receive D and I, as single agents or in combination (D+I), G and the EZH2 inhibitor EPZ-011989 (E) (8 mice/experimental group). Drug activity was assessed in terms of tumor volume inhibition (TVI%).

11578  Poster Session (Board #323), Sat, 8:00 AM-11:30 AM
Doxorubicin (D), gemcitabine (G), ifosfamide (I) and the EZH2 inhibitor EPZ-011989 in epitheliod sarcoma (ES): A comparison of different regimens in patient-derived xenografts (PDX) model. First Author: Maria Zaffaroni, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Background: ES is a rare soft tissue sarcoma with two variants, i.e., the proximal and the distal. Retrospective data on the activity of anthracycline- and G-based regimens are available. EZH2 inhibitors, which target the INI1 pathway that is inactivated in ES, are currently being tested in clinical trial. Comparisons of these agents are not available and unlikely to be prospectively evaluated. We comparatively assess these agents in a proximal-type INI1-deleted ES PDX. Methods: A PDX model (ES-1) was established by subcutaneously xenotransplanting into immunodeficient (SCID) mice tumor fragments obtained from a patient with primary, proximal-type, INI1 deleted ES of the forearm. After tumor propagation in SCID mice for three consecutive passages, the PDX was considered established. Mice were randomized to receive D and I, as single agents or in combination (D+I), G and the EZH2 inhibitor EPZ-011989 (E) (8 mice/experimental group). Drug activity was assessed in terms of tumor volume inhibition (TVI%).

11579  Poster Session (Board #324), Sat, 8:00 AM-11:30 AM
Frequency of genomic biomarkers of response to immunotherapy in sarcoma. First Author: Sally E. Trabucco, Foundation Medicine, Inc, Cambridge, MA.

Background: Recent data (D’Angelo et al, 2018) has suggested possible benefit for a subset of sarcoma patients from immune checkpoint inhibitors (ICPI). We assessed a large sarcoma population for genomic alterations (GA) suggesting benefit from ICPI including high tumor mutational burden (TMB-H) (> = 20 mutations/mb (m/mb)), presence of microsatellite instability (MSI-high) and genomic amplification of PDL1. Methods: Hybrid capture based comprehensive genomic profiling including RNA-seq in a subset of cases was performed on > 6100 cases of sarcoma and included TMB and MSI status. UV exposure signature was determined as previously described (Zehir et al, 2017). Results: TMB was distributed throughout sarcoma cases with a median of 1.7 (range 0-160) and 2% TMB-H. The sarcomas frequently TMB-H were skin atypical fibroxanthoma (86%, 6/7), skin sarcoma NO5 (50%, 3/6), and lung sarcoma (14%, 2/14). Presence of a fusion gene, such as the frequent fusions EWSR1-FIL1, SS18-SSX1, and STAT6-NAB1, were mutually exclusive with TMB-H, PDL1 amplification and MSI-high (p < 0.0001). MSI-high cases (0.23%), with median TMB of 26 (11-67), were predominantly a subset of TMB-H, 0.83% of sarcoma cases had PDL1 amplification (6/51 TMB-H), most frequently soft tissue sarcoma NO5 (35% of PDL1 amplified cases). 2% of sarcoma cases have a UV signature, with median TMB of 36 (2.4-160), and make up 72% of TMB-H sarcomas. Notably, 14% of angiosarcomas have a UV signature; these cases have median TMB of 19 m/mb (2.4-148). Of sarcomas with a UV signature, 26% harbored GA associated with melanoma (BRAFV600x, NRAS or KIT mutation) and 27% were assayed from a cutaneous specimen. An index case of high grade sarcoma with an initial intrabdominal presentation was identified as harboring high TMB and a UV signature on CGP. Conclusions: Identification of one or more of TMB-H, PDL1 amplification and/or MSI-high is detected in 2.8% of unselected sarcoma cases, which may be more likely to benefit from ICPI and such cases lack oncogenic fusions. Notably, 72% of the TMB-H cases harbored a UV signature which may raise the possibility of an alternative diagnosis of melanoma, particularly desmoplastic melanoma.
11581 Poster Session (Board #326), Sat, 8:00 AM-11:30 AM
Genomic amplification of CDK4 in dedifferentiated liposarcomas as a predictive biomarker for microtubule disrupting agents. First Author: Bryce Demoret, Ohio State University, Columbus, OH

Background: Dedifferentiated liposarcoma (DDLPS) represents a common but morbid subtype of sarcoma. Microtubule disrupting agents (MDA), including eribulin and taxanes, disrupt the cell cycle and have modest clinical activity in patients with DDLPS. Unfortunately, no clinically validated biomarkers exist to predict MDA response in this population. DDLPS is characterized by amplification of cyclin-dependent kinase 4 (CDK4), which regulates the cell cycle. We hypothesized that CDK4 amplification may predict response to MDAs.

Methods: 25 DDLPS trial patients (NCT01574716) who received docetaxel as part of their therapy and for whom tissue was available were profiled using DNA next generation sequencing (NGS) to quantify CDK4 copy number alteration. Patients were divided into CDK4-high and -low cohorts based on median amplification level. Progression-free survival (PFS) was calculated using Kaplan-Meier analysis. Patient derived DDLPS cell lines (LPS246, LPS815, LPS863) were analyzed for CDK4 amplification level via NGS. Sensitivity to MDA (eribulin and docetaxel) was quantified using cell viability assays. CDK4 activity was attenuated using palbociclib and drug synergy was ascertained via Chou-Talalay algorithm. In vitro Models: DDLPS cell lines were characterized for sensitivity to eribulin and docetaxel. LPS246 had the highest CDK4 gene copy number vs. LPS815 and LPS863 (1373, 533, 563 transcripts per cell, respectively) and showed a greater sensitivity to both docetaxel and eribulin compared to LPS815 and LPS863 in cell viability assays. Pharmacologic inhibition of CDK4 demonstrated drug antagonism (avg. CI > 1.3). Conclusions: These data suggest that MDA sensitivity in DDLPS may be associated with levels of CDK4. Prospective clinical trials are needed to confirm whether CDK4 expression levels may predict response to eribulin and other microtubule disrupting agents.

11582 Poster Session (Board #327), Sat, 8:00 AM-11:30 AM
Combination of CDK and Bcl-2 inhibitors in the treatment of soft-tissue sarcomas. First Author: Xavier Garcia del Muro, Instituto Catalán de Oncología de Hospitalet, Barcelona, Spain

Background: Soft tissue sarcomas (STSs) present high mortality rates when metastatic and therefore identification of new active therapies is needed. Dinaciclib is a promising CDK inhibitor under evaluation in clinical trials, targeting principally CDK1 and CDK9 (involved in cell cycle and transcription regulation). BH3-mimetics are a promising new class of pro-apoptotic drugs for cancer treatment. Methods: We analyzed the response to Dinaciclib in a series of different STSs established cell lines, as apoptotic induction was visualized in Flow Cytometry. Cell lines were categorized as Dinaciclib-sensitive and Dinaciclib-tolerant. Differences were studied by relevant protein expression changes during treatment leading to hypothesis proposal for key regulators. Validation of targets was performed by siRNA technology prior to engage in drug combination testing. In vivo experiments encompassed drugs safety and effectivity. Results: Dinaciclib induced apoptotic cell death, with important differences in the extent and timing among cell lines. Liposarcoma 402-91 was the most sensitive (cell death > 75% after 72 h), whereas leiomyosarcoma SK-LMS-1 was highly tolerant to Dinaciclib (cell death < 25%). Major partners in cell cycle and apoptosis induction were identified in cell signaling networks were affected by Dinaciclib treatment. The inhibition status of anti-apoptotic protein Bcl-xL was identified as the main determinant of the rhythm and extent of apoptosis triggering. In vitro combination of Dinaciclib with chemical Bcl-xL inhibitors (ABT-747 and A-1331852) overcame tolerance and triggered massive cell death in cultures (95% of cell death after 24 h). Once safely scalated to mice experimentation, drug combination effectiveness on mice engrafted tumors is currently ongoing. Conclusions: CDK inhibitors are active in STSs cell lines. The inhibition status of Bcl-xL can be considered as a predictor of Dinaciclib sensitivity in STS. Combinatorial strategies with CDK inhibitors and BH3-mimetics are worth examination as a new proposal for STS treatment.

11583 Poster Session (Board #328), Sat, 8:00 AM-11:30 AM
Identification of histone deacetylase 2 (HDAC2) as a novel target for MDM2 directed therapies in dedifferentiated liposarcoma. First Author: Colin W Stets, The Ohio State Comprehensive Cancer Center, Columbus, OH

Background: Dedifferentiated liposarcoma (DDLPS) is a common, but morbid mesenchymal tumor driven by amplifications in the mouse double minute 2 (MDM2) gene. Prior studies have indicated that pan-HDAC inhibition may be able to lower MDM2 levels in vitro. However, there are multiple HDAC isoforms and pan-HDAC inhibitors used in the clinic have significant toxicities. We hypothesize that isoform specific HDAC inhibition may achieve modulation of MD2M and limit the toxicities associated with pan-HDAC inhibition. We report here that HDAC2 is sufficient to lower the expression of MD2M and improve tumor response to doxorubicin in DDLPS in vitro and in vivo. Methods: Bioinformatics analysis of RNA-Seq data from DDLPS cell lines was used to identify HDAC proteins associated with MDM2 expression. Potential targets were validated using shRNA mediated knockdown and pharmacologic agents. We examined and quantified MDM2 protein expression via immunoblotting. Cytotoxicity was determined using XTT reagents in vitro. Synergy calculations were performed using the Chou-Talalay algorithm in vitro cytotoxicity assays. In vivo response was measured using mouse xenograft models. Results: Small molecule pan-HDAC inhibitor AR42 and HDAC2 specific inhibitor MI-192 decreased MDM2 expression (2.5-fold and 7.1 fold decrease, respectively) and induced a 6500-fold increase in the expression of the tumor suppressor P21. HDAC2 shRNA knockdown further corroborated the HDAC2 specific effect on MDM2 expression (5-fold reduction). In vivo synergism with doxorubicin in DDLPS (cooperativity index < 0.7) was observed across a range of HDAC2i concentrations. In mouse xenograft model, MI-192 significantly reduced tumor volume (p = 0.02) without the induction of MDM2 mRNA expression. Conclusions: HDAC2 specific inhibition lowers MDM2 expression and synergizes with doxorubicin in DDLPS cell lines and slows tumor growth in vivo. Prospective clinical studies are necessary to confirm these findings.

11584 Poster Session (Board #329), Sat, 8:00 AM-11:30 AM
Immune signature in sarcoma with prognostic and predictive implications. First Author: Shaileja KS Raj, Wake Forest School of Medicine and VAMC, Winston-Salem, NC

Background: While immunotherapy has established its benefit in the management of many solid tumors, its efficacy in sarcoma is still not well understood. In this study, we sought to evaluate the protective effects of intrinsic anti-tumor immunity in sarcoma by analyzing genomic measures of immune response and tumor immunogenicity in a multi-institutional convenience cohort of sarcoma patients. Methods: Publicly available RNAseq and exome mutation data were assembled from The Cancer Genome Atlas (TCGA) sarcoma cohort (n = 259). For each tumor, a relative measure of tumor mutational burden (TMB), expressed as the rate of non-synonymous mutations per megabase of sequenced DNA, was used as a measure of tumor immunogenicity. Interactions between immune infiltration, tumor immunogenicity and patient overall survival (OS) were assessed by Cox regression and Kaplan-Meier analysis. Results: In the full cohort, the 3 immune signatures were highly correlated with each other and univariately associated with patient OS (TNK; p < 0.001; CTY; p < 0.001 and CDB; p = 0.004 Cox regression). A single immune signature TNK, selected for further analyses was associated with OS in TMB-high tumors (p < 0.001) but not TMB-low tumors (p = 0.129). Univariable and multivariable survival analysis of TNK with significant variables included age, and tumor size, that were significant. Conclusions: Our findings fit a model where patients whose tumors were characterized by a TMB-high genotype and elevated effector immune infiltration exhibited the highest survival rates (p < 0.035). In the full cohort multivariable analysis we showed that TNK remained a significant prognostic factor independent of age, tumor size, radiation therapy, margin status, tumor necrosis and subtype analysis indicating that the TNK signature provided additive prognostic information and can utilized in the future for therapeutic stratification.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Aldoxorubicin is classical Doxorubicin with a linker which rapidly binds to albumin on IV administration. Doxorubicin, either alone or in combination with ifosfamide, is still considered standard therapy for sarcomas. Aldoxorubicin alone or in combination with ifosfamide have been shown to improve antitumor activity and lack of cardiac toxicity. The allowable maximum cumulative lifetime dose of doxorubicin is 550 mg/m^2. We report on the evaluation of cardiac function in patients who received aldoxorubicin with Doxorubicin equivalent at doses beyond 1000 mg/m^2.

Methods: Fifty-two patients enrolled in a Phase 1/2 study of aldoxorubicin and ifosfamide/mesna and a Phase 3 study using aldoxorubicin alone were treated for at least 6 cycles of aldoxorubicin at either 250 mg/m^2 or 350 mg/m^2 per dose i.e. every 3 weeks. Cardiac function using 2D echocardiogram was evaluated at regular intervals every two cycles of aldoxorubicin until end of treatment and every six months after completion of the treatment.

Results: In eleven patients, the median cumulative doxorubicin dose prior to aldoxorubicin treatment was 158 (range: 64-360) mg/m^2. The cumulative doxorubicin dose ranged from 1000 to 7500 mg/m^2. No patient developed any sign or symptom of clinical congestive heart failure. Ventricular ejection fractions ranged from 45-74% baseline, and 50-77% at end of treatment, median being 60% both at the beginning and end of treatment.

Conclusions: Aldoxorubicin lacks cardiotoxicity in these patients treated with aldoxorubicin alone or in combination with ifosfamide/mesna. We did not find any evidence of cardiac toxicity of aldoxorubicin up to doxorubicin equivalent dose of 7500mg/m^2. Clinical trial information: NCT# 02235701.
Background: PEComas are rare mesenchymal tumors with a female preponderance, composed of epithelioid cells that show a focal association with blood vessel walls and usually express both melanocytic and smooth muscle markers. The prognosis of advanced malignant PEComa is poor, with a median survival of 12-17 months. There have been no prospective trials for PEComa. Case reports have shown that PEComas are often associated with the loss of tumor suppressor genes TSC1 or TSC2 which results in downstream activation of the mTOR complex, making mTOR inhibition a promising therapeutic strategy. ABI-009, albumin-bound rapamycin nanoparticle, is a novel mTOR inhibitor that can utilize albumin-mediated transport pathways to achieve enhanced tumor drug delivery. This is the first prospective open-label multicenter study to assess mutational status and safety/efficacy of an mTOR inhibitor for advanced PEComa. Methods: At least 30 patients naive to mTOR inhibitors, with pathologically confirmed malignant PEComa that is either metastatic or locally advanced and for which surgery is not a recommended option, will be enrolled. ABI-009 at 100 mg/m2 IV, is given weekly for 2 out of 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The primary endpoint is overall response rate (ORR) assessed with CT/MRI scans via RECIST v1.1. This sample size will be sufficient to exclude an inactive regimen (< 15% ORR) with 95% confidence. Secondary endpoints are duration of response, 6-month progression-free survival (PFS), median PFS, median overall survival, and safety. Patient tumor mutational analysis, including exome sequencing of 300 genes including TSC1/2 and mTOR pathway genes, and circulating DNA analysis, will be performed. Exploratory endpoints include PK/PD relationships for safety and/or efficacy endpoints, and correlative studies with baseline TSC mutational analysis and tumor biomarkers. The study is ongoing as of February 2018. Clinical trial information: NCT02494570.
12000
Oral Abstract Session, Tue, 8:00 AM-11:00 AM
Association of high tissue TMB and atezolizumab efficacy across multiple tumor types. First Author: Fatema A. Legrand, Roche/Genentech, South San Francisco, CA

Background: PD-L1 expression has limitations as a biomarker for checkpoint immunotherapy (CI). Prior atezolizumab (atezo) monotherapy studies suggest improved efficacy in high tissue tumor mutational burden (tTMB-H) cohorts. We report a large retrospective analysis associating tTMB with neoantigen load (NAL) and CI efficacy across multiple studies, tumor types and lines of therapy. Methods: Tissue TMB was evaluated by the FoundationOne (F1) assay across 7 atezo mono therapy studies: NSCLC n=342 (F1-BIRC, POPLAR, OAK), metastatic urothelial carcinoma (mUC) n=400 (IMvigor210, 211), and other advanced solid tumors n=245 (PCD4989g). Pooled data yielded a biomarker evaluable population (BEP) of 987 patients (pts); 175 (17.7%) had TMB-H defined as ≥ 16 mutations/megabase (mut/Mb). Efficacy endpoints were overall response rate (ORR) and duration of response (DoR). Survival analysis is ongoing. Neoantigen load (NAL) was calculated by whole-exome sequencing (WES) and RNA-Seq. Results: tTMB was associated with efficacy across tumor types and lines of therapy. In the BEP, ORR was 16.4% (95% CI 14.2, 18.9), vs. 29.7% (95% CI 23.1, 37.1) in tTMB-H (≥ 16 mut/Mb, N=170), and 13.5% (95% CI 11.3, 16.1) in tTMB-Low (< 16 mut/Mb, N=812). DoR benefit was also observed: median DoR=29.0 mths (95% CI 18.6, NA) in tTMB-H vs. 16.6 mths (95% CI 13.8, 23.1) in EBP and 13.8 mths (95% CI 12.5, 17.4) in tTMB-Low cohorts. This association was not seen in control cohorts of randomized studies OAK, POPLAR, and IMvigor211. Pooled ORR in control arms was 14.9% in BEP, 14.4% in tTMB-H, and 11.4% in tTMB-Low. Survival analysis by tTMB is ongoing. tTMB-H also identified a population independent of PD-L1 status. tTMB by F1 was positively correlated with WES-based NAL in mUC (Pearson’s 0.85, N=218) and NSCLC (Pearson’s 0.78, N=70). NAL was associated with atezo ORR in mUC (p=2.7 x 10^-9). Conclusions: High tTMB (>16 mut/Mb) is associated with superior ORR and DoR across NSCLC, mUC and melanoma and lines of therapy. tTMB-H by F1 may serve as a surrogate biomarker for NAL and may complement PD-L1 expression in providing predictive value. Ongoing studies are prospectively evaluating both tissue TMB and blood-based TMB for efficacy with CI. Clinical trial information: NCT02080227, NCT01993993, NCT020331458, NCT01846416, NCT02951767, NCT02302807, NCT01375842.

12002
Oral Abstract Session, Tue, 8:00 AM-11:00 AM
Multiplexed analysis of myeloid cell (MC) markers to characterize the innate immune composition and clinical activity of human non-small cell lung cancers (NSCLC). First Author: Brian S. Henrick, Yale School of Medicine, New Haven, CT

Background: Despite innate immunity’s prominent role in the anti-tumor response, little is known about the MC composition of human NSCLC. We used multiplexed quantitative immunofluorescence (QIF) to determine MC subtypes’ distribution, functional state and clinical significance in large cohorts. Methods: We established a novel QIF panel to map distinct MC subsets in fixed human NSCLC including DAPI for all cells, pancytokeratin for tumor-epithelial cells, CD11b for all MCs, CD68 for M1-type macrophages and HLA-DR to interrogate maturation state/antigen-presenting potential. We interrogated 834 NSCLC represented in 5 tissue microarray based cohorts. #1 (Yale, n = 95) with patient-matched NSCLC and morphologically normal lung tissue; #2 (Yale, n = 379) and #3 (Greece, n = 230) with different/mixed NSCLC subtypes; #4 (Yale, n = 138) with molecularly annotated lung adenocarcinomas (ADC); and #5 (Yale, n = 32) including baseline samples from anti-PD-1-treated patients. We examined associations between marker levels, MC-profiles, clinicopathologic/molecular variables and survival. Results: Stromal CD11b-levels were significantly higher in tumor than in non-tumor lung tissues. HLA-DR was consistently higher in MCs from tumors with elevated CD68 expression, supporting a more mature phenotype. Stromal CD11b was significantly higher in squamous-cell carcinomas (SCC) than ADC across the cohorts. In SCC, increased stromal CD11b or HLA-DR expression was associated with shorter 5-year survival. EGFR-mutated lung ADC had significantly lower CD11b levels than KRAS-mutant ADC. In a limited sample set/preliminary analysis, MC markers did not significantly stratify clinical benefit to PD-1 axis inhibitors (cohort #5). Conclusions: NSCLCs contain more tumor-associated MCs than non-tumor lung and exhibit distinct myeloid compositions across histologies and presence of major oncogenic driver-mutations. ADC lacking EGFR variants and SCC display higher stromal MC content associated with worse outcome. Studies with larger datasets are ongoing to confirm the role of MC markers for prediction of sensitivity/resistance to PD-1 axis blockers.

12003
Oral Abstract Session, Tue, 8:00 AM-11:00 AM
Prevalence of clonal hematopoiesis of indeterminate potential (CHIP) measured by an ultra-sensing sequencing assay. Exploratory analysis of the Cancer Genome Atlas (CGGA) study. First Author: Charles Swanton, Translation Cancer Therapeutics Laboratory, The Francis Crick Institute, London, United Kingdom

Background: CHIP is defined by the presence of age-dependent acquired mutations in hematopoietic progenitor cells and has been reported to occur in up to 30% of individuals 60-70 years of age. CHIP is a risk factor for hematologic malignancies and cardiovascular disease; its biological mechanisms and clinical significance are just now being studied. Using an assay ~100X more sensitive than exome sequencing, we determined the prevalence and features of CHIP in the CGGA cohort, and the impact on interpretation of cell-free DNA (cfDNA) somatic variants. Methods: Blood was prospectively collected (N = 1627) from 749 controls (no cancer, C) and 878 participants (pts) with newly-diagnosed untreated cancer (20 tumor types, all stages) for WBC and cfDNA isolation. Paired white blood cell (WBC) and cfDNA targeted sequencing (507 genes, 60,000X median coverage) identified somatic single nucleotide variants/indels. Unique molecular barcodes and a machine learning-based noise model achieved a specificity of 1 false positive variant call per Mb of genome targeted at a limit of detection of ~0.1% variant allele frequency (VAF). Results: 1412 samples were eligible and evaluable (576 C, 836 pts; 18 solid tumor types, all stages). Of somatic cfDNA variants matched in WBC (CHIP), 7% of individuals had CHIP with VAF > 10%, 39% had CHIP with VAF > 1%, and nearly all pts (92%) had a somatic mutation with VAF > 0.1%. The rate was similar between C and pts (median age 62, 60), increasing in prevalence by 160% per decade, such that we observed 2.5 variants/Mb at age 60. Of CHIP variants identified, 92% were unique to individual patients, most of which were present at low VAF. Genes impacted by CHIP included DNMT3A (40%), TET2 (27%), and TP53 (10%), consistent with previous reports in patients with solid tumors. Conclusions: An ultra-sensing sequencing assay demonstrated that CHIP signal in WBC and cfDNA is much more common than previously appreciated. The clinical significance of CHIP warrants further study and must be accounted for when interpreting cfDNA variants for both early cancer detection and tumor genotyping (liquid biopsy). Clinical trial information: NCT02889978.
Confounding effects of clonal hematopoiesis in clinical genomic profiling of solid tumors. First Author: Ahmed Zehir, Memorial Sloan Kettering Cancer Center, New York, New York.

Background: Clonal hematopoiesis (CH) is the somatic acquisition of genomic alterations in hematopoietic stem/progenitor cells, leading to clonal expansion. While a few reports showed CH-derived mutations can contribute to discordant tumor sequencing results, a comprehensive analysis has not been reported before. Here, we set out to identify and quantify CH-related mutations in patients with solid tumors using matched tumor-blood sequencing, and to establish the proportion that would be misattributed to the tumor from unmatched analysis. Methods: We retrospectively selected 17,469 solid tumor patients that underwent prospective clinical sequencing of DNA isolated from tumor tissue and matched peripheral blood using the MSK-IMPACT assay between September 2011 and August 2017. We identified the presence of CH-related mutations in each patient’s blood leukocytes by performing mutation calling in the blood and genotyping the tumor DNA at the matched positions. We then considered variants passing our detection thresholds for somatic mutation calling in tumor NGS data to quantify the prevalence of CH alterations detected in solid tumor specimens. Results: We identified 7,608 CH-associated mutations in the blood of 4,628 (26.5%) patients. 14% of CH-associated mutations (n = 1,075) were also detectable in the matched tumor above established thresholds for calling somatic mutations. In total, 5% of the patients (n = 912) would have had at least one CH-associated mutation erroneously called as tumor-derived in the absence of matched blood sequencing. 99% of these mutations were absent in the population scale databases of germline polymorphisms (ExAC and gnomAD) and therefore would have been challenging to filter informatically. Of these, 534 were identified as oncogenic or likely oncogenic based on OncoKB database and 3% of the oncogenic mutations were associated with clinical activity. Conclusions: Our results demonstrate how CH-derived mutations could lead to erroneous reporting and treatment recommendations when tumor-only sequencing is employed.

Liquid biopsy to predict benefit from rechallenge with cetuximab (cet) + irinotecan (iri) in RAS/BRAF wild-type metastatic colorectal cancer patients (pts) with acquired resistance to first-line cet-irin: Final results and translational analyses of the CRICKET study by GONO. First Author: Daniele Rossini, Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy.

Background: CRICKET (NCT02296203) was designed to investigate the activity of the rechallenge with cet and iri as 3rd-line treatment in RAS/BRAF wild-type mCRC pts with acquired resistance to 1st-line cet- and iri-based therapy. The role of liquid biopsy as a tool to identify pts more likely to benefit from this strategy was investigated. Methods: Eligibility criteria included RAS/BRAF wild-type status on tissue samples; prior 1st-line iri-based, cet-containing regimen with at least RECIST partial response (PR), 1st-line PFS >6 months, and progression within 4 weeks after the last cet; 2nd-line oxaliplatin- and bevacizumab-based treatment. Pts received 3rd-line cet+iri until PD. The primary endpoint was response rate (RR) according to RECIST v1.1. With p0 = 5%, and p1 = 20%, 1-sided-α error, 4 pts. Liquid biopsies were collected at the rechallenge baseline. ctDNA was analyzed with ddPCR for specific RAS/BRAF mutations (mut), and then by ultra-deep NGS with Ion Torrent S5 XL.

Results: Between Jan 2015 and Jun 2017, 28 pts were enrolled in 9 centres. The primary endpoint was met. Six PRs (two unconfirmed) and 9 disease stabilizations (RR: 21%, 95%CI: 10-40%, disease control rate: 54%, 95%CI: 36-70%) were reported. RAS mut were found in liquid biopsy samples collected at the rechallenge baseline in 12 (48%) of 25 evaluable pts (6 KRAS G12D, 5 KRAS G12V with 1 harboring also Q61H and 1 NRAS Q61L). No RAS mut were detected in samples from pts who achieved a confirmed PR. Pts with RAS wt ctDNA, had significantly longer PFS than those with RAS mut ctDNA (mPFS: 3.9 vs 1.9 mos; HR: 0.48 [95%CI 0.20-0.98], p = 0.048). No BRAF or PIK3CA mut were found. Conclusions: This is the first prospective demonstration of the activity of rechallenge with cet+iri in some mCRC pts with initially sensitive disease, then resistant to 1st-line cet-based therapy, with no RAS/BRAF mut in pre-treatment liquid biopsy samples. Partially funded by Merck Serono SpA. Clinical trial information: NCT02296203.
Evolution of genomic instability in metastatic cancer. First Author: Eric Yang Zhao, BC Cancer Agency, Vancouver, BC, Canada

Background: Although metastasis underlies up to 90% of cancer-related mortality, genomic instability and signature mutations are mostly studied in primary tumours. Mutation signatures are patterns of somatic mutations resulting from specific mutational processes (i.e. tobacco/UV exposure) and often evolve over time. Recent studies suggest that certain mutation signatures may predict chemotherapy response. Understanding mutational processes in metastatic cancers could uncover actionable targets and refine the understanding of progression and drug resistance. Methods: As part of the BC Cancer Agency Personalized Oncogenomics Project, mutation signatures were deciphered from 571 metastatic whole genomes from 12 cancer types totalling 13,249,678 somatic mutations. We created a novel Bayesian hierarchical model named SigniT (github.com/eyzhao/SigniT) to track temporal evolution of mutation signatures. Using real and simulated data, we showed that SigniT decomposes signatures and their temporal evolution more accurately than comparable methods. Previous chemotherapy treatments were catalogued for all patients by retrospective review. Results: We discovered 21 distinct mutation signatures, including 9 novel signatures (numbered M1-M9). Mutational processes associated with smoking and cigarette smoke were early-arising. Signature 17 and M2 were consistently late-arising across cancer types and metastatic sites. Prior treatment with platinum-based chemotherapy was associated with depression of the homologous recombination deficiency signature 3 (p = 0.03). Platinum exposure was also associated with late elevation of signature 17. Conclusions: To date, this is the largest study of metastatic cancer whole genomes. Our findings revealed 9 novel mutation signatures, including potential markers of late disease and metastasis. We also observed temporal evolution of mutation signatures correlated with chemotherapy exposures. The association of decreasing signature 3 with prior platinum exposure suggested the restoration of a homologous recombination as a resistance mechanism. These findings highlight the complexity of metastatic cancers, and the variety of factors which impact their mutagenesis.

Characterisation of the TCR repertoire in NSCLC to reveal the relationship between TCR heterogeneity and genetic heterogeneity that is influenced by mutational load and is associated with disease recurrence. First Author: Kropoa Yoshi, Cancer Immunology Unit, University College London Cancer Institute, London, United Kingdom

Background: The lung TRACERx study is a prospective study exploring the cancer genome evolution of NSCLC. Data analysis from the first 100 patients enrolled into the study has shown an increased risk of recurrence or death associated with intratumoral genomic heterogeneity. The importance of the phylogenetic clonality of cancer neoantigens in predicting overall survival in NSCLC and response to checkpoint blockade is previously reported. Methods: We hypothesised that mutational burden and genomic heterogeneity is reflected in the intra-tumoural T cell receptor (TCR) repertoire. We utilised quantitative high throughput sequencing of α and β chains to explore the TCR repertoire from multi-region tumour specimens, normal lung and PBMC samples from patients within the lung TRACERx study. Results: We observed that the TCR repertoire across multi-region tumour specimens was distinct to that observed in normal lung and PBMC. Intratumoral TCR repertoire heterogeneity was found to reflect genomic heterogeneity and was influenced by the tumour mutational load highlighting the potential importance of antigenic dosing in anti-tumour immunity. Moreover, we observed diversification of the TCR repertoire in late stage tumours and disease recurrence was associated with a heterogeneous intra-tumoural TCR response. Alpha and beta chain TCRs re-constructed from single cell RNA sequencing data obtained from wells reaching the truncal neoantigen were distributed across all regions of the tumour. Conclusions: Taken together, these findings demonstrate a heterogeneous spatial distribution of tumour infiltrating lymphocytes amongst patients with NSCLC. Moreover, our data suggest that TCR clones present across multiple regions of the tumour may explain resistance to the presence of truncal neoantigens. The observations described are indicative of a dynamic intra-tumoural T cell response related to the diverse mutational landscape observed in NSCLC.

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NTRG Oncology/NSABP B-31: Stromal tumor infiltrating lymphocytes (sTILs) and outcomes in early-stage HER2-positive breast cancer (BC). First Author: Rim S. Kim, KU Leuven - University Hospitals Leuven, Leuven, Belgium

Background: Stromal tumor infiltrating lymphocytes (sTILs) in HER2-positive and triple-negative breast cancer (BC) are associated with prognosis and treatment response. NSABP B-31 evaluated chemotherapy (C) versus trastuzumab (CT) for early-stage HER2-positive BC. Methods: Based on International Immuno-Oncology Working Group (IOWG) guidelines, sTILs were assessed by RSK in 1581/2016 eligible B-31 cases with available slides for H&E review, and as a semi-continuous variable (SCV) in 10% intervals. RSK and five pathologists from the IOWG reviewed 100 of the cases as a consensus study. sTILs as an SCV and with a predefined lymphocyte-predominant BC (LPBC as > 50% sTILs) were correlated with disease-free survival (DFS), the primary endpoint of B-31. sTILs were also correlated with clinicopathological characteristics, genotyping, intrinsic subtype, gene expression, and mutation profiling. Cox proportional hazard models were used, with p-values < 0.05 considered significant. Results: In both the C and CT arms, increases in sTILs, defined either as a SCV (combined arms HR 0.42, 95% CI 0.27-0.64, p < 0.01) or as LPBC (combined arms HR 0.65, 95% CI 0.49-0.86, p = 0.003), were significantly associated with improved DFS. However, there was no association of sTIL levels with degree of trastuzumab benefit (interaction p = 0.556). ER status by IHC was inversely associated with sTILs (p < 0.01). High sTILs were significantly associated with basal- and HER2-enriched intrinsic subtypes, and the high-benefit group by 8-gene expression model. None of the PIK3CA mutations or genotyping of Fc gamma receptors were associated with sTILs. The mean concordance between RSK and the other pathologists was 90.8%. Conclusions: sTILs were significantly associated with improved DFS in pts with early-stage HER2-positive BC treated with chemotherapy on B-31. However, sTILs were not associated with degree of trastuzumab benefit. sTILs may have utility as a prognostic biomarker to help define pts with HER2-positive early BC, at low risk for recurrence. Pooled analysis in this clinical context is warranted. SUPPORT: U10CA180868, -180822, UG1-189867, U24-196067, PA DOH; Breast Cancer Research Foundation
Background: Primary resistance to anti-PD-1 therapy is rare and may be mediated by loss-of-function (LoF) mutations in JAK1/2 or antigen presentation. 3 out of 48 human melanoma cell lines with complete loss of adaptive PD-L1 expression upon interferon (IFN)-γ exposure, two harbored LoF mutations in JAK1/2. The third had intact IFN-γ signaling pathway without LoF mutations. We therefore sought to determine whether an epigenetic mechanism that may result in loss of adaptive PD-L1 expression in this cell line might be an underlying cause of primary resistance in some patients. Methods: Human melanoma cell lines that represent good, poorly and non-responding to IFN-γ were analyzed by flow cytometry, gene expression, ChIP-seq and ATAC-seq upon IFN-γ exposure. Results: The M412b human melanoma cell line showed no PD-L1 expression in response to IFN-γ exposure despite increased expression of IRF-1, STAT1 and STAT-3. ChIP-seq analysis for IRF-1 in M412b cell line showed no significant enrichment at the PD-L1 promoter compared to three others. ATAC-seq in M412b showed little signal at the PD-L1 promoter, suggesting that M412b cell line lost adaptive PD-L1 expression due to a promoter inaccessible to transcription factors. Peng et al (Science, 2018) demonstrated that the PBAF form of the SWI/SNF chromatin remodeling complex is associated with resistance to checkpoint blockade immunotherapies in melanoma model. Miao et al. (Science, 2018) reported increased response to checkpoint blockade immunotherapy when patients with advanced renal cell carcinoma harbored LoF mutations in the PBRM1 gene. Consistently, M412b cell line displayed the highest PBRM1 and ARID2 expression among 48 human melanoma cell lines, suggesting that constitutive high expression of this chromatin remodeling complex may prevent access to PD-L1 promoter by transcription factors that would otherwise activate the gene in response to IFN-γ signaling. We are now testing this model. Conclusions: Lack of adaptive PD-L1 expression upon IFN-γ exposure is associated with increased expression of the PBAF chromatin remodeling complex, which may be an epigenetic mechanism of primary or acquired resistance to anti-PD-1 therapy.
Whole exome sequencing (WES) in hormone-receptor positive (HR+) metastatic breast cancer (MBC) to identify mediators of resistance to cyclin-dependent kinase 4/6 inhibitors (CDK4/6i). 

**Methods:** WES was performed on 51 baseline metastatic tumor biopsies obtained at treatment initiation with CDK4/6i in combination with various anti-estrogens. Tumor samples were classified as sensitive (S, from patients with clinical benefit) or intrinsically resistant (IR, from patients without clinical benefit). WES also performed in 11 acquired resistance (AR) specimens and 10 patients from responding patients after progression. In 6 patients, WES was performed on matched pre-treatment S and post-progression AR specimens. Putative resistance drivers were introduced into HR+/HER2- breast cancer cells (T47D, MCF7) via lentiviral infection or knockout via CRISPR. Sensitivity of the modified cell lines to anti-estrogens and CDK4/6i was characterized. 

**Results:** WES of 62 tumors revealed multiple potential mechanisms of resistance to CDK4/6i (Table), including biallelic Rb1 inactivation, AKT1 mutation (mut) and/or amplification (amp), RAS mut, AURKA amp, IGFR1 amp, ERBB2 mut, and FGFR2 mut and/or amp. Introduction of candidates into HR+/ER2- breast cancer cells conveyed resistance to CDK4/6i in vitro, including loss of Rb and overexpression of AKT1, AURKA, FGFR2, mut-KRAS, and mut-ERBB2. Additional sequencing efforts and characterization of variants is ongoing and will be presented.

**Conclusions:** These results provide new insight into the diverse spectrum of genomic events driving resistance to CDK4/6i and set the stage for additional mechanistic studies. For patients with AKT1, RAS, AURKA, IGFR1, ERBB2, and FGFR2-dependent resistance, clinical trials incorporating novel combinations of targeted therapies could be designed to circumvent or overcome resistance.

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**Tumor Biology 603s**

**Poster Discussion Session; Displayed in Poster Session (Board #129), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM**

**Whole exome sequencing (WES) in hormone-receptor positive (HR+) metastatic breast cancer (MBC) to identify mediators of resistance to cyclin-dependent kinase 4/6 inhibitors (CDK4/6i). First Author: Seth Andrew Wander, Dana-Farber Cancer Institute, Boston, MA**

**Background:** Combining CDK4/6i with endocrine therapy results in prolongation of disease control in HR+ MBC, though resistance invariably occurs. There is a critical need to understand mechanisms governing response and resistance to these agents. **Methods:** WES was performed on 51 baseline metastatic tumor biopsies obtained at treatment initiation with CDK4/6i in combination with various anti-estrogens. Tumor samples were classified as sensitive (S, from patients with clinical benefit) or intrinsically resistant (IR, from patients without clinical benefit). WES also performed in 11 acquired resistance (AR) specimens and 10 patients from responding patients after progression. In 6 patients, WES was performed on matched pre-treatment S and post-progression AR specimens. Putative resistance drivers were introduced into HR+/HER2- breast cancer cells (T47D, MCF7) via lentiviral infection or knockout via CRISPR. Sensitivity of the modified cell lines to anti-estrogens and CDK4/6i was characterized. **Results:** WES of 62 tumors revealed multiple potential mechanisms of resistance to CDK4/6i (Table), including biallelic Rb1 inactivation, AKT1 mutation (mut) and/or amplification (amp), RAS mut, AURKA amp, IGFR1 amp, ERBB2 mut, and FGFR2 mut and/or amp. Introduction of candidates into HR+/ER2- breast cancer cells conveyed resistance to CDK4/6i in vitro, including loss of Rb and overexpression of AKT1, AURKA, FGFR2, mut-KRAS, and mut-ERBB2. Additional sequencing efforts and characterization of variants is ongoing and will be presented. **Conclusions:** These results provide new insight into the diverse spectrum of genomic events driving resistance to CDK4/6i and set the stage for additional mechanistic studies. For patients with AKT1, RAS, AURKA, IGFR1, ERBB2, and FGFR2-dependent resistance, clinical trials incorporating novel combinations of targeted therapies could be designed to circumvent or overcome resistance.

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**Poster Discussion Session; Displayed in Poster Session (Board #130), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM**

**Analysis of tumor samples from SOL02: Concordance of BRCA2 mutation (BRCA2m) detection in tumor vs. blood and frequency of BRCA2-specific loss of heterozygosity (LOH) and loss of function somatic mutations. First Author: Darren R. Hodgson, AstraZeneca, Cambridge, United Kingdom**

**Background:** The PARP inhibitor olaparib is approved for maintenance treatment of platinum-sensitive relapsed ovarian cancer (PSR OC) in the USA based on pivotal studies (Study 19, SOL02) that demonstrated a progression-free survival benefit of olaparib (Ludermann et al 2012, 2016; Pujade-Lauraine et al 2017). Patients (Pts) with BRCA2m benefit most from olaparib, but questions remain on the functional equivalence of germline (g) and somatic BRCA2m and the frequency and impact of BRCA2-gene-specific LOH (Dougherty et al 2017; Maxwell et al 2017). **Methods:** Blood and tumor samples from 241 pts with gBRCA2m in a Phase III trial of olaparib maintenance monotherapy (300 mg bid tablets; SOL02; NCT01874353) were analyzed. A concordance analysis of gBRCA2m and tumor BRCA2m (tBRCA2m) status was conducted; gene-specific LOH for BRCA1 and BRCA2 and assessment of homologous recombination deficiency (HRD) using Myriad HRD score (Tumor BRCAAnalysis CDxTM test) was also determined. **Results:** tBRCA2m testing was evaluable in 241/289 gBRCA2m pts. There was 98% and 100% concordance between pts’ BRCA2m and tBRCA2m status, respectively, in tBRCA2m vs gBRCA2m. 13/241 (5.4%) of gBRCA2m were due to large rearrangements (exonic insertions or deletions), of which 4 involving BRCA1 were not detected in the tumor. A further deleterious somatic mutation in BRCA2 was identified in 1/241 pts with gBRCA2m tumors. This was a large rearrangement in BRCA1, causing an exon 1–22 deletion that likely constituted the second ‘hit’ in this tumor. Of 210 evaluable LOH samples, 144/144 (100%) gBRCA1m and 65/66 (99%) gBRCA2m tumors had gene-specific LOH. The pt without BRCA2 LOH that scored 3 (Tumor BRCAAnalysis CDxTM test) had a progression-free survival benefit ranging from 73 days to 1 year, remaining on olaparib at data cut-off. **Conclusions:** Very high concordance between tBRCA2m and gBRCA2 testing is demonstrated, supporting wider implementation of tBRCA2 testing in addition to availability of gBRCA2 testing to determine tBRCA2m status in OC. Deleterious somatic BRCA2m almost never arises in gBRCA2m tumors, in keeping with BRCA2 loss being a driver of tumorigenesis in OC. In PSR gBRCA2m pts, gene-specific LOH in tumors is almost universal. Clinical trial information: NCT01874353.
12020 Poster Discussion Session; Displayed in Poster Session (Board #133), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

PRC-2 epigenetic chromatin reprogramming in ALK-positive (ALK+) lung cancer initial emergence of precision drug resistance. First Author: Patrick C. Ma, WVU Cancer Institute, West Virginia University, Morgantown, WV

Background: Despite remarkable upfront response to ALK tyrosine kinase inhibitors (TKIs) in ALK+ lung cancer, acquired resistance eventually develops. Molecular mechanisms of the initial emergence of drug resistance are poorly understood. Methods: ALK+ H3122, H2228 and a patient-derived Ma-ALK001.3NSCLC cell lines were used in our study. In vivo, MTS viability and murine in vivo xenograft assays were performed. siRNA knockdown and CRISPR/cas9 gene knockout were used for mechanistic studies. ChIP-qPCR was conducted to analyze HOXB3 epigenetic marks. RNA-seq was also performed for transcriptome analysis. Tumor microarray (TMA) biomarker study was adopted for outcome analysis of the polycomb repressive complex-2 (PRC-2). Results: Our study revealed a rapid-onset emergence of adaptive drug-resistant ALK+ lung cancer cells within the first 14 days upon TKI treatment initiation. The expression of stem cell transcription factors, most notably HOXB3, was significantly elevated, and it regulated the downstream HOXB3 expression and mitochondrial pro-survival BCL-2/BCL-xL signaling, cancer stemness and EMT markers. RNA-seq revealed a rapid-onset adaptive global transcriptome reprogramming of the ALK+ cancer cells escaping drug pressure. ChIP-qPCR showed resistance emerged via epigenetic regulation of the untreated bi-valent HOXB3 promoter closed chromatin state transforming to stem-like open state during drug-escape, based on H3K4me3/H3K27me3 methylation mark balance. Findings were validated using CRISPR/cas9-EZH2 knock down studies. Conclusion: ALK+ lung cancer initial emergence of precision drug resistance. Methods: ALK+ lung cancer achieves initial rapid-onset emergence of adaptive drug escape through PRC-2 epigenetic chromatin reprogramming to regulate cancer plasticity/EMT/stemness interplay via the TGFβ3-EZH2/UTX-HOXB3-BCL-2/BCL-xL cascade.

12022 Poster Discussion Session; Displayed in Poster Session (Board #135), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Cell-free circulating tumor DNA somatic alteration burden and its impact on survival in metastatic cancer. First Author: Seyed Saeed Pairawan, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prognostication has been a challenging subject in patients with metastatic disease. Physicians are expected to assess prognosis of patients with advanced disease both for determining suitability for clinical trials and for counseling. Unfortunately, cell-free circulating (cf)DNA, cfDNA sequencing is being performed for clinical decision-making. We sought to determine whether somatic alteration burden (SAB) in cfDNA is associated with prognosis. Methods: We performed a retrospective analysis of 298 patients with metastatic disease who underwent clinical comprehensive cfDNA analysis at a single tertiary care institution. Our primary objective was to determine the influence of SAB (defined as maximum mutant allele frequency) on overall survival (OS). Secondary objectives included the association between the number of nonsynonymous mutations (NSM) and OS, and of site of primary malignancy on mutation detection and SAB. Results: SAB > 10% was detected in 240 (80%) patients. SAB was classified by quartiles, Q1 lowest, Q4 highest SAB. Median follow-up was 8.4 months after cfDNA testing; we observed 116 deaths (39%) among 298 patients. Median OS was 11.5 months. Higher SAB levels had a statistically significant impact on overall survival in SAB Q3 (HR 2.3, p = 0.0069) and SAB Q4 (HR = 3.8, p < 0.0001) on univariate analysis. On multivariate analysis, SAB Q4 (HR = 2.6, p = 0.0033), male sex (HR = 1.59, p = 0.0033) and albumin level > 3.9 g/dl (HR = 0.40, p = 0.00011) were independent predictors of OS. cfDNA mutation detection, SAB, and number of NSM significantly differed between tumor types (p < 0.0001, p = 0.0013, and p = 0.0001 respectively), being lowest in appendicular cancer and highest in colon cancer. Having more than one NSM detected was associated with significantly worse overall survival (HR = 2.3, p < 0.0001). Conclusions: Higher levels of cfDNA SAB and higher number of NSM were associated with worse OS in patients with metastatic disease. Further study is needed to determine the utility of SAB detection for clinical decision-making and the utility of SAB to different tumor types.

12021 Poster Discussion Session; Displayed in Poster Session (Board #134), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Development of a comprehensive cell-free DNA (cfDNA) assay for early detection of multiple tumor types: The Circulating Cell-free Genome Atlas (CCGA) study. First Author: Eric A. Klein, Cleveland Clinic Glickman Urology and Kidney Institute, Cleveland, OH

Background: Globally most cancers are detected at advanced stages with high treatment burden and low cure rates. A noninvasive cfDNA blood test detecting multiple cancers at early stages when curative treatment is more likely to succeed is desirable. CCGA (NCT02889978) is a prospective multicenter observational study for development of a noninvasive cfDNA-based multi-cancer detection assay. Methods: Prospectively collected samples (N = 1627) from 749 controls (no cancer diagnosis, C) and 878 participants (pts) with newly diagnosed untreated cancer (20 tumor types, all stages) were analyzed in a preplanned substudy. 3 prototype sequencing assays were performed: paired cfDNA and white blood cell (WBC, 60,000X) targeted sequencing (507 genes) for single nucleotide variants/indels; paired cfDNA and WBC whole genome sequencing (WGS, 30X) for copy number variation; cfDNA whole genome bisulfite sequencing (WGBS, 30X) for methylation. For each assay a detection model was developed for all cancer pts; sensitivity was estimated at 95% specificity. Results: Pts w/cancer and C had similar age, smoking status and gender. WGBS had the highest sensitivity and was reported here; results were consistent across assays. Detected (sensitivity (95% CI)) cancers (stage I-III) included 28 colorectal (66% [48-84]), 19 esophageal (77% [52-93]), and 17 cell line (80% [78-91]), 73 lung (59% [47-70]), 11 multiple myeloma (73% [39-94]), 10 ovarian (90% [56-99]), and 10 pancreatic (80% [44-98]). Breast cancer-specific assay results are reported separately. Cancers with low signal (< 10% sensitivity) include low gleason score prostate cancer, small cell lung cancer, melanoma, and renal. Comparison to tumor WGS and multi-assay classification will be reported. Conclusions: A cfDNA-based blood test detected multiple cancers at various stages with high specificity, indicating this approach is promising as a multi-cancer screening test, including for lethal unscreened cancers where stage shift can impact mortality. Further clinical assay and clinical development of a multi-cancer cfDNA test in an asymptomatic population is ongoing. Clinical trial information: NCT02889978.

12023 Poster Discussion Session; Displayed in Poster Session (Board #136), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Assessment of the genomic stability and molecular landscape of patient-derived xenograft (PDX) models from NCI’s Patient-Derived Models Repository (PDMR). First Author: Bishwajit Das, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Patient-derived xenografts (PDXs) are a powerful tool for cancer translational research. However, it is unclear if early passage PDXs faithfully recapitulate the molecular features of the corresponding patient tumors. The National Cancer Institute (NCI) has developed a Patient-Derived Models Repository (PDMR; www.pdmr.cancer.gov) of PDXs with clinical annotation and comprehensive genomic data. We used this data set, which represents 13 broad categories of tumor types, to conduct an in-depth investigation of the genomic stability of PDXs with early passage. Methods: Tumors (biopsy or resection), including some from metastatic sites, were used to establish 211 PDX models from 206 patients. Whole Exome Sequencing and RNA-Seq were performed on 2-9 mice per model. Passages represented include the original clinical sample, P0, P1, P2, and less frequently P3. Results: By several metrics, genomic profiles of a large majority of PDMR models were stable with early passaging: (1) transcriptome profiles of mice from different passages in a model were found to always cluster together; (2) 75% of PDXs maintained similar copy number alteration profiles compared with the original clinical sample, with no significant differences between passages; (3) the allele frequency (AF) of clinically relevant mutations remained consistent across passages, with only 20% of models having > 15% AF range from the median. Moreover, genomic features of PDMR models were broadly comparable to those in large public patient data sets. For example, melanoma models had the highest tumor mutation burden and a 5% prevalence of BRCA1/2 mutation. 11% of colon adenocarcinoma models were MSI-H, with APC (65%), TP53 (59%) and KRAS (53%) being most frequently altered. Conclusions: In this large and historically diverse PDMR data set, PDXs exhibited genomic stability with early passaging. The molecular landscape of PDMR models is faithfully comparable to large public patient data sets. The PDMR collection is expected to form the basis of future in-depth analyses will be performed. The PDMR thus represents a valuable resource for researchers interested in pre-clinical drug or other studies.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
analyses. Early signs of antitumor activity were observed. Information: NCT02674152.

Disease. PK/PD analysis of 14 evaluable pts showed dose-proportional plasma and breast [n = 1] carcinoma) had a partial response and 9 (31%) pts had stable AE, most commonly (all grade/grade

MTD was determined as BI 836880 720 mg q3w (Table). All pts had at least 1 limiting toxicities (DLTs) in the first 21-day cycle. Treatment-related AEs (TRAEs) leading to dose reduction/discontinuation, exposure/dose-proportion.

Results: 29 pts were treated: median age 57 yrs (range 28-79); 62% female. The

sures (both secondary endpoints) and best overall response were also assessed. Results: 29 pts were treated: median age 57 yrs (range 28-79); 62% female. The

First Author: Christophe Le Tourneau, Institut Curie, Paris, France

Background: VEGF and Ang-2 inhibitors have demonstrated clinical activity in various tumor types. Given the overlap of the VEGF/VEGFR2 and Ang-2 Tie-2 signaling pathways there is a rationale for dual inhibition. BI 836880 is a humanized bispecific nanobody (engineered antibody fragment of variable antibody domains) that inhibits VEGF and Ang2 and has demonstrated preclinical activity in cancer models. Methods: Pts with solid tumors refractory after standard therapies/for whom no established treatment options were available received BI 836880 3q3w (IV; starting dose 40 mg). Dose escalation followed a Bayesian logistic regression model with overdispersion.
12029 Poster Session (Board #142), Mon, 1:15 PM-4:45 PM
Correlation between natural killer cell activity and treatment effect in patients with disseminated cancer. First Author: Torben Hansen, Department of Oncology, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark

Background: Prediction of treatment effect remains an unsolved problem in patients with malignant tumors. The aim of the present study was to analyze the possible correlation between Natural Killer (NK) cell activity as measured by the NK Vue assay and treatment effect in patients with different tumors.

Methods: The study included four different trials encompassing palliative treatment to patients with prostate, ovarian and colorectal cancer. The current results are based on 93 patients with mature data on treatment effect. Blood samples were collected at baseline and prior to each treatment cycle into NK Vue Promoca tubes and placed in an incubator at 37°C within 15 minutes of sampling. Following 24 hours of stimulation the level of interferon-gamma (IFNγ) in the plasma was measured by ELISA (NK Vue Gold) as a surrogate for NK cell activity. Response rates (RR) and progression free survival (PFS) were endpoints. Results: The relationship between NK cell activity and treatment response was similar across tumor types and treatment, and data were consequently pooled for analyses. The outcome suggested a classification into three groups. During the first two months of treatment the IFNγ dropped to a normal level (< 200 pg/mL) in group 1 or remained at an abnormal level in group 2 (n = 30) the level remained within a normal range (˃500 pg/mL), while in group 3 (n = 28) it increased from an abnormal to a normal level. The RR were 29%, 47%, and 82%, respectively, p = 0.0001. The median FFS was 6 months (95% confidence interval CI 2.1-3.9), 10.0 months (95% CI 6.5-11.1), and 8.3 months (95% CI 6.5-8.7), respectively, p < 0.0001 (log-rank).

Conclusions: The results suggest a correlation between NK cell activity and treatment effect across different tumor types and treatments. Patients lacking the ability to mount an immune response during the first two months of treatment have a very poor prognosis and clinical benefit of the treatment is questionable.

12031 Poster Session (Board #144), Mon, 1:15 PM-4:45 PM
Role of serum thymidine kinase-1 (TK1) activity in patients (pts) with hormone receptor-positive (HR+) advanced breast cancer (ABC) treated with endocrine therapy (ET) in the EFECT trial. First Author: Luca Malorni, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Prato, Italy

Background: TK1 plays a critical role in DNA synthesis and cell proliferation. The DiviTum assay measures serum TK1 activity (sTKa), reflecting cancer cell proliferation. Recent studies suggest this assay may provide real time prognostic information in ABC. However, its role in HR+ ABC needs further validation.

Methods: EFECT (n = 693) was a double-blind, randomized trial of fulvestrant 250mg versus exemestane after progression on nonsteroidal aromatase inhibitor therapy for ABC. 58% of pts had received > 1 prior ET for ABC. sTKa was retrospectively assessed with DiviTum on serum samples from pts in the EFECT cohort. Samples were collected before start of ET (T0), after 3 (T3) and 6 (T6) months of ET, and at disease progression (PD). Pts were categorized as High/Low sTKa at T0 based on the median value. On-treatment sTKa changes were calculated from T0 to the next available timepoint within 3 months from randomization (T3, or PD for those pts with early progression - ePD), accounting for a coefficient of variation of 10%, and point within 3 months from randomization (T3, or PD for those pts with early progression - ePD), accounting for a coefficient of variation of 10%, and thereafter pooled for analyses. The outcome suggested a classification into three groups. The RR were 29%, 47%, and 82%, respectively, p = 0.0001. The median PFS was 5.03 months (95% CI 3.91-5.89) vs 2.57 (95% CI 2.04-3.52). The ratio of C3M/PRO-C3 ratio was 3.4 (95% CI 2.1-3.7) vs 3.4 (95% CI 2.1-4.1) in pts with Increase (T3 or ePD) vs baseline (T0), respectively, p = 0.018. mTTP in pts with No change (n = 38) was similar to those with Drop. After adjustment for major prognostic factors, sTKa remained an independent marker. Conclusions: sTKa is a potential circulating prognostic marker in pts with ABC treated with ET, and may represent a tool for upfront identification of ET resistant pts, and invasive monitoring of response to ET. Independent validation of these results is warranted.

12030 Poster Session (Board #143), Mon, 1:15 PM-4:45 PM
Extracellular matrix (ECM) circulating peptide biomarkers as potential predictors of survival in patients (pts) with untreated metastatic pancreatic ductal adenocarcinoma (mPDA) receiving pegylated hyaluronidase alfa (PEGPH20), nab-paclitaxel (A), and gemcitabine (G). First Author: Song Wang, Halozyme Therapeutics, Inc., San Diego, CA

Background: Hyaluronan (HA) and collagens are major constituents of the ECM. HA accumulation in the tumor microenvironment may result in elevated interstitial fluid pressure, vascular compression, and reduced drug delivery and immune cell access. PEGPH20 degrades HA to increase tumoral access for therapeutic drugs and immune cells. Liquid biopsies reflecting ECM remodeling may provide a non-invasive approach to identify pts most likely to benefit from PEGPH20 therapy.

Methods: Peptide markers of ECM remodeling (C3M, PRO-C3, PRO-C6, and VCANM) were measured using baseline plasma samples from Stage 1 (n=94) and Stage 2 (n=95) of HALO-109-202 (NCT01453153), a Phase 2, open-label, randomized study of PEGPH20 + A + G (PAG) vs AG in previously untreated pts with Stage IV PDAC. Univariate and ratio analyses were conducted to correlate biomarker levels with survival outcomes (PFS, OS). Results: The ratio of C3M (MMP degradation fragment of type-III collagen) vs PRO-C3 (N-terminal pro-peptide of type-III collagen) predicted for PFS benefit in PEGPH20-treated pts in Stage 1. The predictive value of this ratio for PFS and OS of PEGPH20-treated pts was further validated in Stage 2. Conclusions: This supports a development of a liquid biopsy-based companion diagnostic for selecting pts that may benefit from PEGPH20.

12032 Poster Session (Board #145), Mon, 1:15 PM-4:45 PM
Combining circulating tumor cells and circulating cancer associated macrophage-like cells (CAMLs) as independent prognostic indicators of survival has highlighted the need for more in depth analysis of blood based diagnostics. As CTCs & CAMLS are isolated in parallel from a single blood sample and both are prognostic for therapy response, the hypothesis that simultaneous measurement of both CTCs & CAMLS may increase the prognostic value of blood based diagnostics and may be predictive of benefit of subsequent therapies.

Background: The discovery of cancer associated macrophage-like cells (CAMLs) as independent prognostic indicators of survival has highlighted the need for more in depth analysis of blood based diagnostics. As CTCs & CAMLS are isolated in parallel from a single blood sample and both are prognostic for therapy response, the hypothesis that simultaneous measurement of both CTCs & CAMLS may increase the prognostic value of blood based diagnostics and may be predictive of benefit of subsequent therapies.

Results:

<table>
<thead>
<tr>
<th>Ratio cutoff</th>
<th>Median (95% CI)</th>
<th>Log-rank p</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (Discovery Cohort)</td>
<td>C3M/PRO-C3 ratio (0.550, 50% centile cut-off)</td>
<td>0.049</td>
<td>0.92</td>
</tr>
<tr>
<td>T2 (Validation Cohort)</td>
<td>C3M/PRO-C3 ratio (0.550, Stage 1 cut-off)</td>
<td>0.049</td>
<td>0.92</td>
</tr>
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Conclusions: This data suggests that simultaneous measurement of both CTCs and CAMLS may increase the prognostic value of blood based diagnostics and may be predictive of benefit of subsequent therapies.
Dynamic change of PD-L1 expression on circulating tumor cells in advanced gastrointestinal tumor patients undergoing PD-1 blockade therapy. First Author: Chuyuan Yao, National Center for Nanoscience and Technology of China, Beijing, China

**Background:** Tumor PD-L1 levels have predictive value in PD-1/PD-L1 checkpoint blockade therapies, yet biopsies can only provide baseline information. Whether PD-L1 expression on circulating tumor cells (CTCs) could serve as an alternative biomarker is of great interest. **Methods:** We established an immunofluorescence assay for semi-quantitative assessment of the PD-L1 expression levels on CTCs with four categories (PD-L1<sup>low</sup>, PD-L1<sup>medium</sup>, PD-L1<sup>high</sup>). 35 patients with advanced gastrointestinal tumors were enrolled in a phase 1 trial of a PD-1 inhibitor, IBI308. The CTC enumeration and the PD-L1 level expression analysis were evaluated prior the treatment and at the time of therapeutic evaluation. **Results:** Prior the treatment of PD-1 inhibitor, 97% (34/35) patients had CTCs, ranging from 1 to 70 (median 7). 74% (26/35) had PD-L1<sup>positive</sup> CTCs, and 60% (21/35) had at least one PD-L1<sup>high</sup> CTCs. The disease control (DC) rate in PD-L1<sup>high</sup> patients (48%) is much higher than the others (14%). The group with at least 20% abundance of PD-L1<sup>high</sup> CTCs had even higher DC rate of 64% (9/14), with only 14% DC rate for the rest (3/21). We also observed that the changes of total CTC, PD-L1<sup>positive</sup> CTC and PD-L1<sup>high</sup> CTC correlate quite well with disease outcome ($P < 0.001, P = 0.002$ and $0.007$, respectively). In addition, the abundance of PD-L1<sup>low</sup>-positive CTCs at baseline had predictive significance for progression free survival (PFS). **Conclusions:** We revealed that the abundance of PD-L1<sup>high</sup>-positive CTCs at baseline might serve as a predictor to screen patients for PD-1/PD-L1 blockade therapies and measuring the dynamic changes of CTC could indicate the therapeutic response at early time. Clinical trial notification: NCT02937116.

Theoretical model and clinical validation of blood tumor mutation burden (bTMB) detection for cancer immunotherapy. First Author: Jianchun Duan, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

**Background:** Tumor mutational burden (TMB) measured by whole exome sequencing (WES) or cancer gene panel (CGP) sequencing, has been defined as a potential biomarker for selecting candidates for PD-L1/PD1 blockade therapy. However, a considerable proportion of patients(pts) with advanced lung cancer cannot acquire enough tumor tissue for TMB determination. Here, we defined an optimal gene panel for TMB estimation and validated the availability of blood TMB (bTMB) from circulating tumor DNA (ctDNA) in predicting therapeutic efficacy of anti-PD1/PDL1. **Methods:** A theoretical model of measuring TMB by CGP was established including 9205 WES-measured samples of 33 tumor types based on TCGA database. We further designed a panel (CT150) including 62 hotspot genes and 88 lung-cancer related genes, and built a robust bTMB detection pipeline. Correlation of CT150-measured bTMB and WES-measured TMB from paired tumor tissue in 30 NSCLC patients was analyzed to validate our model. Public clinical dataset and an independent clinical cohort were used to evaluate the association of bTMB with the efficacy of anti-PD1/PDL1 treatment. **Results:** Our model demonstrated that at least 100 genes need to be included in WES when estimating WES-based TMB, which was identified being influenced by the choice of hotspot genes, the weight of nonsynonymous mutations and the sequencing depth. In most tumor types, the CT150-measured TMB is highly correlated with WES-measured TMB. The bTMB and WES-based tumor TMB (tTMB) in 30 NSCLC patients is highly correlated. pts with high TMB estimated by CT150 had a significantly longer median progression free survival (mPFS) (14.5 vs 4.1 months, $P = 0.01$) than those with low TMB in the published Rizvi cohort (N = 34). In a pilot study, 12 NSCLC pts treated with PDL1 inhibitors, pts with bTMB-high (designated as $>=8$ muts) had higher durable clinical benefit (DCB) rate and longer mPFS than those of bTMB-low ($DCB$ %: 100% vs 42.9%, mPFS: 9.9 vs 2.9 months, $P = 0.03$). **Conclusions:** The designed CT150 panel can be utilized to estimate the TMB in the majority of cancer types. The bTMB estimated by this panel might provide a noninvasive biomarker assay to identify NSCLC pts benefitting from PD1/PDL1 inhibitors.

Correlation of peripheral T cell receptor repertoire with response to neoadjuvant chemotherapy plus trastuzumab in early-stage HER2-positive breast cancer. First Author: Wenna Wang, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC), Beijing, China

**Background:** The immune microenvironment of tumor is now emerging as an indicator of responses to anticancer treatment in HER2-positive breast cancer. However, the peripheral blood (PB) TCR repertoire and its interaction with chemotherapy plus trastuzumab has not been systematically studied. **Methods:** We investigated the TCR repertoire using next-generation deep sequencing of the complementary determining region 3 (CDR3) of the TCR β chain in the PB samples from 26 treatment-naïve hormonal receptor (HR)-negative HER2-positive breast cancer patients before and after 2 cycles of chemotherapy plus trastuzumab. **Results:** Correlation of peripheral T cell receptor repertoire with response to neoadjuvant chemotherapy plus trastuzumab had a lower TCR density in their pre-treatment PB ($P = 0.0147$) and a higher evenness ($P = 0.001, P = 0.002$ and $0.007$, respectively). Patients who achieved a pCR ($n = 11$) had a lower TCR density in their pre-treatment PB ($P = 0.0147$) and a higher degree of overlap between the pre- and post-treatment PB TCR repertoires ($P = 0.0488$) than patients who achieved a non-pCR ($n = 15$). The sequences of V segments of the TCR β chain demonstrated significantly lower frequencies of TCR β variable (TRBV) 3-1, TRBV4-2, TRBV12-3, TRBV12-5, TRBV15, TRBV6-2, and TRBV7-7 genes in the pre-treatment PB samples of the pCR group than in the non-pCR group. There were no significant differences in TCR density, diversity, clonality or evenness between pre- and post-treatment PB samples. **Conclusions:** Based on the current study, the TCR repertoire in pre-treatment PB may be used as a predictor of response to neoadjuvant chemotherapy plus trastuzumab in HR-negative HER2-positive breast cancer patients and as a new approach to select patients who will benefit from neoadjuvant therapy.

Circulating tumor DNA as a potential indicator of tumor load during interventional therapy of unresectable hepatocellular carcinoma. First Author: Yang Li, Center of Intervention radiology, Zhuhai Precision Medicine Center, Zhuhai People’s Hospital, Zhuhai, Guangdong 519000, P.R. China, Guangdong, China

**Background:** Hepatocellular carcinoma (HCC) is a common malignant tumor, causing high morbidity and mortality. Interventions have improved survival in unresectable hepatocellular carcinoma. Imageology and serologic biomarkers are major methods to evaluate therapeutic efficacy but limited in radiation exposure and accuracy. This study aims to assess feasibility of ctDNA as a potential biomarker to monitor therapeutic response during interventional treatments of HCC. **Methods:** We enrolled 30 HCC patients from 2016 to 2017. Tumor biopsies and matched pretreatment peripheral blood samples were collected. We implemented target capture NGS to identify somatic variants with a panel of 1021 cancer related genes. Blood tumor mutation burden (bTMB) analysis interrogated single nucleotide variants, small insertion and deletion, with VAF $>0.5$ %. **Results:** Somatic genomic alterations were identified in 29 of 30 tumor biopsies (96.7%). TP53 (%), TERT (37.9%), CTNNB1 (13.8%) mutated most frequently in this cohort. Mutations in TP53 was commonly detected at codon 249 (R249S). In matched plasma samples, we identified 28 of 30 (93.3%) patients to be positive before interventional treatment. A consistency of detected mutation between ctDNA and tumors is 90% and presented positive relation with tumour load (Pearson $r = 0.48$, $P = 0.01$). Compared with AFP, ctDNA abundance showed a positive correlation with tumour load ($r = 0.61$, $P = 0.0005$). In addition, TP53-mutated samples showed higher bTMB than TP53 wild samples (5.5 vs 2.4 mut/Mb, $P = 0.03$), suggesting a potential better effect when received treatment of immune checkpoint inhibitors. **Conclusions:** Liquid biopsy can reveal the mutation profile of patients of HCC. ctDNA can be used as a potential tool to reflect tumor load and guide into targeted immunotherapies.
12037 Poster Session (Board #150), Mon, 1:15 PM-4:45 PM
Correlation of expression of TK1 in plasma-derived exosomes with clinical response to CDK4/6 inhibitors in breast cancer. First Author: Marzia Del Re, Clinical Pharmacology and Pharmacogenetics Unit, Department of Clinical and Experimental Medicine, Pisa, Italy

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) improve PFS in patients with hormone receptor positive (HR+) advanced breast cancer (1). In order to better characterize the response to these agents and increase our knowledge on the pharmacogenetic profile of CDK4/6i, the aim of this study was to analyse the expression of targets relevant to the activity of CDK4/6i in plasma-derived exosomes. Methods: Blood samples were collected from patients affected by HR+, HER2- advanced breast cancer receiving a palbociclib in association with hormonal therapy. Three ml of plasma were taken at the beginning of treatment (baseline) and at the first clinical evaluation (after 3 months). Objective responses were defined following the RECIST criteria v.1.1. RNA from plasma-derived exosomes was extracted by the ExoRNeasy kit (Qiagen) and analysed for the expression of thymidine kinase 1 (TK1), CDK 4, 6 and 9 by digital droplet PCR (BioRad). Mann-Whitney test was applied. Results: Thirty-eight metastatic breast cancer patients were prospectively enrolled in this study. The comparison of mRNA levels of TK1, CDK4, 6 and 9 between baseline and the first evaluation was available in 5 patients treated with letrozole + palbociclib and 11 patients given fulvestrant + palbociclib. Eight patients had newly diagnosed advanced breast cancer while 9 patients received > 1 line of treatment. Objective responses were: 2 (12%) PR, 12 (70%) SD and 3 (18%) PD. The comparison of expression of TK1 and CDK4, 6 and 9 at baseline and at first evaluation was statistically significant for TK1 (PR+SD vs PD P = 0.048). No association was found between the baseline levels of TK1, CDK 4, 6 and 9 and best response or number of disease sites. Conclusions: Exosomal TK1 expression may be useful to early identify patients who are likely to respond to CDK4/6i. Reference: Finn RS, et al. New England Journal of Medicine. 2016;375(20):1925-36.

12038 Poster Session (Board #151), Mon, 1:15 PM-4:45 PM
Analysis of single circulating tumor cells (CTCs) to identify resistance mutations to ALK inhibitors in both ALK-gene and by-pass oncogenic pathways. First Author: Emma Packer, Graduate School of Medicine, Paris-Saclay, “Circulating Tumor Cells” Translational Platform, CNRS UMS3655 – INSERM US23 AMMICA, Villejuif, France

Background: Non-invasive methods including CTCs are crucial to develop for the implementation of precision medicine in the treatment of NSCLC. ALK-rearranged NSCLC patients develop resistance to ALK-inhibitors which manifest by genetic alterations either in the ALK-gene itself or in by-pass signaling pathways. Here, we evaluated whether resistance mutations to first-generation ALK-inhibitor crizotinib and third-generation lorlatinib could be identified using individual CTCs. Methods: The study included 17 patients at resistance to crizotinib or lorlatinib. Matched tumor-biopsies were available for 3. Two CTC isolation strategies were used. A process including Ampli1 whole-genome amplification, quality controls, multiplex PCR with two panels (Ampli1 CHC and BCR/ABL) and a home-made panel targeting the 13 known ALK mutations and Ion Torrent next-generation sequencing was established. Single CTCs or pools of 2-10 CTCs and one CD45+ cell pool were analyzed for each patient. A specific bioinformatic workflow was developed to identify somatic variants including determination of positive predicted value (PPV), allele drop-out (ADO), false-positive rate (FPR). Results: PPV, ADO and FPR were respectively > 95%, 19% and 6.10^-5 in the seven first patients. A limited number of shared mutations between CTCs and matched tumor-biopsies were identified. Several CTC-particles were exclusively present in single CTCs and not in tumor-biopsies, and mutations were identified including in ALK-gene such as the F1174L, F1174C or G1202R. Potential by-pass signaling pathways in other oncogenic drivers such TP53, PIK3CA and BRAF genes were also identified. A much higher degree of mutational diversity was observed in CTCs compared to tumor-biopsies. Conclusions: Using a rigorous workflow, we report for the first time that resistance mutations to ALK-inhibitors can be identified in individually isolated CTCs of ALK-rearranged patients. Our data demonstrate that both “on-target” and “off-target” resistance mechanisms can be detected in individual CTCs highlighting their important mutational diversity in ALK-rearranged patients.

12039 Poster Session (Board #152), Mon, 1:15 PM-4:45 PM
Integration of lymphocyte ratios (LRs) and circulating tumor cells (CTCs) characterizes the immune response in breast cancer (MBC). First Author: Lorenzo Gerrattana, Department of Medicine-Hematology and Oncology, Feinberg School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine; Department of Oncology, University Hospital of Udine, Udine, Italy

Background: The detection of CTCs in MBC is associated with worse prognosis and metastases development. We evaluated the integration of immunity biomarkers such as monocyte, neutrophil and platelets LRs (MLR), NLR, PLR with CTCs data to identify new clues about the interaction between MBC and the immune system. Methods: The study enrolled 44 MBC patients (pts) at the University Hospital of Udine, Italy, between 2013 and 2015, regardless of the line of treatment. CD45^- circulating cells (CC) were sorted through the DEPArray microfluidic system, based on a multi-parametric fluorescence analysis. The CD45^- CC phenotypes were defined as epithelial (E CC), mesenchymal (MES) and transitional (EM CC). MLR, NLR and PLR cut-offs were previously obtained through ROC analysis using propensity score-match-ed healthy controls (Gerrattana et al 2018). The association between LRs and CD45^- CC was explored through Kruskal Wallis test. CC subtypes were analyzed both as a percentage of total CD45^-CCs and as absolute values. Results: In luminal-like MBC pts, both NLR and PLR were significantly associated with EM CC (P = 0.016), while a trend was observed in respect to MLR. In pts with HER2 positive MBC, PLR was significantly associated with E CC (P = 0.042). Notably, only MLR was associated with EM CC in the total population (P = 0.02). Pts with visceral involvement had higher EM CC and E CC when MLR>0.35 (P = 0.036 and P = 0.031, respectively) and E CC when PLR>0.25 (P = 0.025), while MES was significantly lower when MLR>0.35 (P = 0.001). In particular, in case of liver localization, the MLR>0.35 subgroup showed higher E CC (P = 0.022) and lower MES (P < 0.001). Pts with bone localizations had lower MES when MLR>0.35 (P = 0.004). Interestingly, MLR>0.35 pts with 2 or more sites of distant involvement, had higher EM CC and lower MES (P = 0.015 and P < 0.001, respectively). Conclusions: MLR is associated with CD45^- CC subtypes profiles. Pairwise comparison is thus suggested not suggesting an interlink between CTC and immunity in MBC pathogenesis and progression. Moreover, these findings highlight the need to explore more granular classifications for CD45^-CC. 

12040 Poster Session (Board #153), Mon, 1:15 PM-4:45 PM
Circulating tumor cells enumeration (CTCs) and circulating tumor DNA (ctDNA) - Clinical and molecular features of “rapidly progressing” stage IV disease (Stage IV progression). First Author: Lorenzo Gerrattana, Department of Medicine-Hematology and Oncology, Feinberg School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine; Department of Oncology, University Hospital of Udine, Chicago, IL

Background: Liquid biopsy technologies, including CTCs and ctDNA, have a growingly paramount role in the management of advanced breast cancer (ABC) and are potentially capable to convey different types of information. Methods: This retrospective study analyzed 62 ABC patients (pts), characterized with paired CTCs and ctDNA assessments. CTCs were isolated through CellSearch and ctDNA was analyzed using the Guardant360 NGS assay. The previously reported cut-off of 5.7 was used for ctDNA percentage (emicDNA) (Gerrattana et al 2018), while 5 count was used for CTCs. Matched pairs variations in %ctDNA and CTCs at baseline (BL), at the 1st evaluation (E1) and at progression (PD) were tested through Wilcoxon test and associations with clinical variables were tested through Kruskal-Wallis test. Their prognostic impact was explored through Cox regression for progression-free survival (PFS), overall survival (OS) and PFS after E1 (E1_PFS). Results: CTCs and %ctDNA were comparable in respect to age at BL, while CTCs were marginally higher in luminal ABC (P = 0.07). Pairwise %ctDNA varied significantly between BL and E1 (P = 0.0012) and E1 and PD (P = 0.0016), but not between BL and PD. No significant variations were observed regarding CTCs, apart from triple negative ABC (P = 0.035). Both BL %ctDNA and CTCs had an impact in terms of PFS (HR 1.9, P = 0.02 and HR 3.4, P = 0.012 respectively) and OS (HR 3.5, P = 0.021 and HR 16.6, P = 0.011; respectively) but only BL CTCs retained its impact on E1_PFS (HR 3.5, P = 0.015). On the other hand, both E1 %ctDNA and CTCs had a prognostic impact on E1_PFS (HR 3.2, P = 0.009 and HR 3.2, P = 0.012; respectively). Pts with an increased 5.7 %ctDNA or stable 5.7 %ctDNA between BL and E1, experienced a worse E1_PFS in pts with stable %ctDNA < 5.7 (HR 9, P = 0.009 and HR 3.1, P = 0.043; respectively) with a median time to progression after E1 of 22 days and 2.53 months each. Conclusions: The study suggests that both CTCs and ctDNA provide non-overlapping information about prognosis and treatment benefit. CTCs describes the underlying metastatic biology, while ctDNA gives a more, quantitative, real-time assessment of tumor burden and treatment benefit.

Visit abstracts.asco.org and search by abstract for the full list of authors and their disclosure information.
Landscape of kinase rearrangements (kRE) detected in circulating tumor DNA (ctDNA). First Author: Ben C. Creelan, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Background: kRE are established oncogenic drivers and therapeutic targets across advanced cancers. Increasingly, clinical activity targeting kRE across tumor types has been reported, largely based on tissue analysis. We sought to describe the pan-cancer landscape of predicted driver kRE identified in ctDNA. Methods: Blood samples from 8,567 cancer patients underwent hybrid capture-based genomic profiling of ctDNA. We evaluated kRE rearrangements in 173 panels (ALK, EGFR, FGF3, PDGFR, RET, ROS1) for which selected introns are baited, and 7 others (BRAF, ERBB2, FGFR1, FGFR2, MET, PDGFRB, RAF1). Only samples with detectable ctDNA were included in analysis (N = 6,571). Results: kRE were observed in 4.9% of lung cancer (LC) cases (N = 7,709) and 2.4% of non-LC (N = 3,862), including 234 unique cases (3.4% overall) with 296 kRE events (Table). The most commonly rearranged kinases were ALK (45%), RET (15%), ROS1 (15%), FGFR3 (8%), FGFR2(15%), and EGFR (4%). The frequency of kinases altered by kRE varied by anatomic origin, with FGFR2 events identified only outside lung cancer (p < 0.001) (Table 1). Top recurrent kRE were EML4-ALK (61 LC + 7 nLC), FGFR3-TACC3 (7 + 11), KIF5B-RET (9 + 2), CD74-ROS1 (9 + 1), and CCDC6-RET (5 + 3). Comparison with > 70,000 tissue genomic profiles analyzed over the same time period showed ALK, RET, or ROS1 kRE in 4.3% of ctDNA and 4.9% of tissue LC samples, and 1% of nLC ctDNA and 0.4% of tissue nLC. 65% of kRE detected in ctDNA were also detected in paired tissue samples (N = 43), including 9 of 11 collected < 30 days apart. Conclusions: Kinase fusions and rearrangements exist across tumor types and can be detected by liquid biopsy. Comparison of genomic profiles of ctDNA to tissue suggest similar frequencies of ALK, RET or ROS1 kRE in lung, but a higher frequency of kRE in non-LC samples by ctDNA vs tissue, perhaps reflecting greater heterogeneity.

cTumor Biology 609s

201401
Poster Session (Board #154), Mon, 1:15 PM-4:45 PM

Predictive tools for bevacizumab therapy in patients with aggressive HER 2-negative metastatic breast cancer: 2-years results from an observational study. First Author: Encarnación González Flores, H. Virgen de las Nieves, Granada, Spain

Background: The determination of monitoring Circulating Tumor Cells (CTC) in patients (pts) with metastatic breast cancer (MBC) is a well-established prognostic marker of efficacy/tolerance. We aimed to determine the predictive value of the normalization of CTC in terms of clinical benefit. Methods: Multicentric, prospective, observational study in pts with aggressive HER2-negative MBC amenable to receive first-line treatment with chemotherapy plus bevacizumab. A 18-month follow-up is planned. CTC levels were determined in baseline (BL) and after the first cycle. The Spearman correlation coefficient was calculated to CTC and biomarkers. Interim analysis of 2-years data with the correlation and progression free survival (PFS). Results: At database cut, 111 evaluable pts were enrolled: median (range) age 54.1 (46.6-61.3) years; ECOG 0/1: 50.5/39.6%. Median (range) time from diagnosis was 2.9 (0.8-7.2) years, and 28.8% of pts were “di novo” MBC. Neoadjuvant and/or adjuvant therapy was received by 70.3% pts and 73.0% underwent surgery. Histological grade I/II was found in 49.3% of pts; ER-positive in 74.6% and PR-positive in 50.8%. Metastases were mainly located in liver (62.2%), bone (57.7%) and lung (40.5%). Mean (SD) CTC levels: 83.4 (333.8)/7.5 mL BL and 36.10 (3.1)7.5 mL after first cycle. According to this change, 89.5% were sensitive. Discontinuation in 28 pts (75.0% exitus; 3.6% progression). A 3.5% had complete response, 50.6% partial response and 25.9% stable disease. Median follow-up was 8.2 (5.3-12.9) months. The median PFS was 11.0 (6.6-15.4) months. Median overall survival was not reached. BL CTC levels had a significant correlation with CEA (p < 0.05) and CA 15.3 (p < 0.001). Overall, 79.3% pts presented at least one toxicity. Most common grade III/IV toxicities were hypertension (8.1%), peripheral neuropathy (3.6%), neutropenia (3.6%) and thrombocytopenia (2.7%). Two grade V toxicities reported abdominal sepsis and pain upper. Conclusions: The preliminary data shows a correlation with CTC levels and other tested biomarkers. No safety concerns were addressed.

Tumor Biology 609s

201402
Poster Session (Board #155), Mon, 1:15 PM-4:45 PM

Circulating tumor DNA as biomarker in mutant malignant melanoma. First Author: Jan Braune, Department of Hematology and Oncology, University Medical Center, Freiburg, Germany

Background: Available biomarkers LDH and S100B possess limited sensitivity and specificity to predict outcome in melanoma. In this pilot study we evaluated the use of circulating tumor (ctDNA harboring BRAF and NRAS mutations as a predictive biomarker for treatment response and progression-free survival (PFS) in patients with locally advanced or metastatic melanoma. Methods: We analyzed 168 retrospective plasma samples from 40 unselected pts, and 311 samples from 33 pts included in a prospective trial (DRKS00009507). We included stage III disease with planned resection or stage IV disease before initiation or change of medical treatment. Blood samples were taken at baseline at d +8, d +28, and thereafter at 3 months intervals for up to two years. We developed hydrolysis probe based, Locked Nucleic Acid assays to detect BRAF, NRAS and wild type ctDNA by droplet digital PCR. Results were correlated with LDH, S100B and PFS. Results: Sensitivity of the specific assays was 0.01% with a limit of Blank of 0.28 copies/well. Of 37 stage IV pts with retrospective samples, 29 were positive for ctDNA at least once (78%). Out of eight negative pts, three were in CR, three had SD, and two were negative despite measurable disease. Positive pts had a mean of 9 (range: 1-17) and 283 (range: 0.1-16,388) ctDNA copies/mL for stage III and stage IV respectively. The presence of ctDNA one month after therapy initiation indicated poor PFS (hazard ratio [HR] 1.9, 95% CI 0.85-4.44). No measureable increase in ctDNA was a favorable prognostic finding for PFS for all the therapies (hazard ratio [HR] 0.3, 95% CI 0.05-2.56) with a median PFS of 4.5 vs. 3.1 months (range 0.9-17.5 vs. 1.5-9.1) and particularly for those receiving Immunotherapy (hazard ratio [HR] 0.07, 95%CI 0.007-0.68) with a median PFS of 8.8 vs. 2.6 (range 1.8-17.5 vs 1.5-3.1). Based on 290 measurement pairs, ctDNA was strongly correlated with LDH (r = 0.73) and S100B (r = 0.52). Conclusions: Residual ctDNA early after change or institution of treatment predicted tumor progression at first clinical response assessment. A positive to negative conversion or a decrease indicated a more favorable course especially for those receiving immunotherapy. These data support the use of ctDNA as an early predictive marker for treatment response. Clinical trial information: DRK500009507.
12045  Poster Session (Board #158), Mon, 1:15 PM-4:45 PM
Mutation count, a potential surrogate for tumor mutation load, of circulating tumor DNA (ctDNA) using targeted panel sequencing correlates with clinical outcomes in late stage lung adenocarcinoma and small cell lung cancer. First Author: Stephanie Yang, Roche Sequencing Solutions, Pleasanton, CA

Background: Studies show that mutation count can be used as a biomarker to predict whether or not a patient may respond to immunotherapy or chemoradiation therapy. However, mutation count is usually determined by whole exome sequencing or large targeted panel sequencing of tumor tissue DNA. Tissue biopsy is often inaccessible for many late stage lung cancer patients.

Methods: We assessed mutation count using the AVENIO ctDNA Surveillance Kit, a targeted next-generation sequencing panel of 198 kilobases, on pre-treatment plasma samples from a prospective, observational study, where 43 late stage lung adenocarcinoma and 72 late stage small cell lung cancers (SCLC) treated with first-line chemotherapy or chemotherapy and immunotherapies were initially assessed. Synonymous and prevalent driver mutations were filtered out from the detected somatic mutations prior to calculating a mutation count per megabase. Subjects were classified as high mutation count if the filtered somatic mutation count was above the bottom tertile of the study, where 43 late stage lung adenocarcinoma and 72 late stage SCLC subjects with a median mutation count of 9 and 14, respectively. Lung adenocarcinoma subjects with low mutation count showed better survival in terms of overall survival (OS) (18.3 vs 7.8 mo, HR 0.41, p = 0.026) and progression free survival (PFS) (6.2 vs 4.3 mo, HR 0.51, p = 0.042). SCLC subjects with low mutation count had shorter OS (15.9 vs 14.1 mo, HR 1.2, p = 0.034), however, no significant correlation was found in PFS.

Conclusions: We were able to derive a ctDNA-based mutation count from a panel the size of one-fifth of a megabase and identified an association between low mutation count and better prognosis in subjects with late stage lung adenocarcinoma treated with chemotherapy or chemoradiation therapy. In late stage SCLC, however, higher mutation count was associated with better prognosis. Our findings suggest differences in lung cancer histology are key to understanding measurements of mutation count and their potential to predict outcome on chemotherapy. Studies to further validate these results are ongoing.

12046  Poster Session (Board #159), Mon, 1:15 PM-4:45 PM
Use of cell-free DNA for management of breast and lung cancer by academic and community providers. First Author: Roby Antony Thomas, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Next-generation sequencing of cell-free DNA (ctDNA) can assess presence of somatic genomic alterations in patients with cancer without an invasive biopsy. Results may guide therapeutic decision-making. We evaluated use of ctDNA test results for management of breast and lung cancer in a major healthcare system with academic and community-based practices.

Methods: Retrospective review of ctDNA tests (Guardant360) ordered for patients with breast or lung cancer at the University of Pittsburgh Medical Center between 8/2014 and 3/2017 was performed. For patients with actionable results (lung: alterations with FDA-approved or NCCN-recommended targeted therapy; breast: ERBB2, ESR1 or PIK3CA alterations), information on clinical care was abstracted. Differences in clinical use of test results were evaluated between academic and community providers.

Results: In total, 230 tests were ordered for 218 subjects; 128 by academic and 102 by community providers. Community providers ordered significantly (P < 0.05) more tests for lung cancer patients than academic providers (78% vs. 47%) and their patients were older (mean age: 65.5 vs. 60.3 yrs.). Actionable alterations were identified in 82 subjects (38%; 48 breast, 34 lung). Six were excluded from further analyses because their mutations had been known previously. For 32 (42%) of the remaining 76 subjects, actionable results led to a change in therapy, for the other 44 it did not. Reasons for not changing therapy included: patient died or lost to follow-up, patient refused targeted therapy, patient was not treated with targeted therapy recommended but cost prohibitive, and patient currently stable but results could guide therapy at progression. Actionable results significantly more often resulted in a management change for lung cancer than breast cancer (63% vs. 28%). Use of test results differed significantly between academic and community practice, especially for patients with lung cancer. Community practice-based providers appear to act on actionable results more often than academic center-based providers in this health care system.

Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Molecular profiling has become important in directing therapy for IHCC, while not much has been described about the immune environment of this disease. Understanding the immune milieu could highlight potential options for immunotherapy (IT). Methods: We performed a retrospective institutional review of 99 surgically resected IHCC from February 2007 to November 2016. Immunohistochemistry was performed using 13 immune antibodies including CD3, CD4, TIM-3, PD-1, and ICOS. Overall survival (OS) was defined as the time from surgery to death date or last follow-up (if alive). OS was estimated by Kaplan-Meier method, and differences were assessed by two-sided log-rank tests. Cox proportional hazards regression models were used to assess association between pt characteristics and OS. Results: Median age: 62 yrs (range, 24-83), females (61%), T stage (T1/T2: 75%), v/o metastasis (90%), and v/o neoadjuvant chemotherapy (NACT) (73%). Median f/u among survivors: 3.0 yrs (range 0.04 to 9.1). Median OS was 6.3 yrs (95% CI: 3.6 – 9E). Among B- and T-lymphoid cells, CD3+ T-cells represented the dominant population and were predominantly located in the invasive margin (IM). Positivity for PD-1 was seen in 4.7 centrally located, tumor infiltrative lymphocytes (CL-TI)/mm² and 14.2 CL-TI/mm² were positive for TIM-3. Univariate Cox analysis revealed that longer OS was significantly associated w/a high number of CL-TI CD3+ (HR 0.78; p=0.044) and CD4+ (HR 0.76; p=0.05) immune cells, and lower CL-TI TIM-3+ cells (HR 0.87; p=0.01). Multivariate Cox analysis demonstrated the following hazard ratio: two of CL-TI TIM-3+ cells (HR 0.87; p=0.01) was an independent predictor of improved OS. Expression of CL-TI TIM-3+ cell was significantly associated with higher CL-TI CD3+ (p<0.001), CD4+ (p<0.003), and PD1+ (p<0.001) immune cells. Expression of a membrane-bound form of B7-H4 was significantly increased in the pt that received NACT (p=0.03). Conclusions: Our findings identify patients who were diagnosed with advanced solid tumors and treated at MD Anderson Cancer Center. We used Kaplan-Meier, logistic regression, and Cox PH regression, for statistical analysis. Survival was computed from date of biopsy used for mutational analysis. Results: We analyzed data from 302 patients [136(45%) female, 163 (55%) male; median age: 57 years, range (16-83); median OS: 43 month]. One hundred and three (34%) patients had TP53 mutations, 105 (35%) patients had PD-L1 ≥1%, and 50 (18%) had both. Tumor types (%): GI 41 (14%); GU 36 (12%); non-small cell lung cancer (NSCLC) 54 (18%); melanoma 40 (13%); sarcoma 27 (9%); head and neck (HNC) 21 (7%); others 83 (27%). The association between TP53 mutations and tumoral PD-L1 expression was significant across all patients (OR: 2.47, 95%CI (1.5-4.07), p = 0.0003), but changed significantly with tumor type (p = 0.021): OR: 5.3 sarcoma; 5.2 “other”; 3.6 NSCLC; 1.4 melanoma; 1.1 GI; 0.7 GI. The odds of PD-L1 expression increased with age (30 year increase OR: 1.84, 95%CI (1.01, 3.38, p = 0.044), but not sex (OR: 1.0, 95%CI (0.6, 1.7), p = 0.87). TP53 mutation was associated with worse OS (HR = 1.6, 95% CI (1.1, 2.2), p = 0.010) and PD-L1+ with better OS (HR = 0.6, 95% CI (0.4, 0.8), p = 0.0042). The effect of PD-L1 on OS did not depend on TP53 mutation status (p = 0.37). Among PD-L1+ and PD-L1- patients, OS was related to tumor type (p = 0.004). One-year survival rate of patients treated with PD-1 or PD-L1 inhibitors in phase I trials was independent of PD-L1/TP53 status (p = 0.53). Conclusions: PD-L1 expression is multifactorial. TP53 mutations are highly associated with PD-L1 expression across solid tumors but association significantly varies among tumor types.
12054 Poster Session (Board #167), Mon, 1:15 PM-4:45 PM
Isolation of CD4+ T cells specific for neoantigens created by recurrent driver mutations in non-small cell lung cancer (NSCLC) and melanoma. First Author: Joshua Veatch, Hutchinson Cancer Research Center, Seattle, WA

Background: T cells specific for neoantigens encoded by mutated genes are increasingly recognized as mediators of tumor destruction after immune checkpoint inhibitor therapy or adoptive cell transfer. Unfortunately, almost all neoantigens result from random mutations that are patient-specific. Here, we describe CD4 + T cell responses one melanoma patient and two NSCLC patients that are specific for recurrent driver mutations in their cancers. Methods: Neoantigen-reactive T cells were expanded and cloned by peptide stimulation of the peripheral blood from cancer patients. Results: The melanoma patient had a CD4+ T cell response to the peptide encoded by the BRAF V600E mutation found in 40% of melanoma, and obtained a complete response following adoptive transfer of tumor infiltrating lymphocytes (TIL). The BRAF V600E specific cells showed a Th1 memory phenotype, were preferentially localized to the tumor at the time of resection, and expanded and persisted in blood greater than 2 years after TIL therapy. Gene transfer of the BRAF V600E-specific T cell receptor (TCR) conferred recognition of class II MHC positive cells expressing the BRAF mutation. A CD4+ T cell response specific for KRAS G12V that is present in 5% of NSCLC and 10% of colon cancer was detected in one NSCLC patient. A second NSCLC patient had a CD4+ T cell response specific for the Her2 internal tandem duplication (ITD) found in 4% of NSCLC, and deep sequencing of TCR genes showed the mutation-specific T cell clone was enriched in a tumor resection sample, relative to the non-adherent fraction. The CD4+ T cell clone specific for the KRAS V600E, KRAS G12V, and Her2 ITD epitopes only recognized the mutant and not the wild-type peptide and were restricted by common class II HLA alleles found in 10-25% of the population. The neoantigen reactive Her2 and KRAS not reactive TCRs are currently being cloned. Conclusions: This study greatly expands the number of recurrent driver mutations that are targets of T cell responses, and suggests that adoptive transfer or vaccination strategies targeting recurrent driver mutations could help interrogate the role of CD4+ T cells in human anti-tumor immunity, and could have clinical activity across multiple patients.

12055 Poster Session (Board #168), Mon, 1:15 PM-4:45 PM
Synergy of TLR4 agonist GKSK1795091, an innate immune activator, with agonistic antibody against co-stimulatory immune checkpoint molecule OX40 in cancer immunotherapy. First Author: Hua-Xin Gao, GSK, Collegeville, PA

Background: GKSK1795091 (aka, GKSK1795091) is a synthetic glycolipid toll-like receptor 4 (TLR4) agonist. TLR4 is a Pattern Recognition Receptor for host defense against bacterial infection, expressed on innate immune cells monocytes, macrophages, dendritic cells. GKSK1795091 is a potent and selective TLR4 agonist and is being evaluated for use in combination with other immunotherapies to treat cancer. Methods: To understand the antitumor activity and pharmacologic effects of intravenously administered GKSK1795091, in vivo studies were performed in murine syngeneic tumor models. Pharmacodynamic (PD) effects of GKSK1795091 was examined in peripheral and tumor infiltrating lymphocytes (TILs) using multicolor flow cytometry assays. Additionally, TCRs sequencing, Nano string and multiplex cytokine assays were employed to understand the molecular and cellular mechanisms induced by this molecule. Results: GKSK1795091 potently activated the immune system and modulated the tumor microenvironment by inducing an array of proinflammatory cytokines, enhancing antigen presentation, activating T cells, and reducing T regulatory cells. At doses sufficient to induce systemic cytokines in mice, GKSK1795091 inhibited tumor growth and resulted in long term survival in tumor model. When administrated with OX46, a murine surrogate OX40 agonist monoclonal antibody (mAb), the combination induced a robust PD response as demonstrated by a significant increase in Th1 cytokines, expression of interferon regulated genes, high tumor infiltration by leukocytes, increase in T cell activation , proliferation and increase in the CD8: Treg ratio. Additionally, GKSK1795091 when combined with anti-OX40 induced clonal expansion of T-cells and drove synergistic interferon and T-cell dependent anti-tumor response. Conclusions: The current study demonstrated that GKSK1795091 activates key initiating immune pathways and can induce robust anti-tumor efficacy when combined with agonistic antibodies directed against the OX40 receptor. This novel combination provides a strong rationale and supports evaluation of GKSK1795091 in combination with immuno-oncology agents in clinical trials.

12056 Poster Session (Board #169), Mon, 1:15 PM-4:45 PM
Dependency of radiotherapy and combinatorial radio-immunotherapies responses on the systemic T cell immune response. First Author: Kevin Lee Min Chua, National Cancer Centre Singapore, Singapore, Singapore

Background: Combinatorial immune checkpoint blockade (ICB) with radiotherapy (RT) potentiates anti-tumor response via modulation of the immune microenvironment. However, detailed host-specific mechanisms underpinning dramatic clinical responses of RT-ICB are poorly understood. Here, we performed deep characterization of the systemic immune response in circulating T cells following treatment with RT and RT-ICB. Methods: We recruited a cohort of 29 patients with biopsy-proven metastatic cancers (10 prostate, 10 EBV+ nasopharynx, 9 others) who underwent RT (N = 13) or RT-ICB (N = 16; anti-PD1/PDL1/-CTLA4), under a prospective observational study protocol. All patients received ablative RT (8-50 Gy in 1-5 fractions). Patient blood samples were longitudinally collected at following timepoints: baseline, 2, 6, 7 and 12 d post-RT/RT-ICB. Circulating T cells were profiled by a customized CyTOF panel of 41 T cell surface markers, and analyzed using the t-SNE method (ACCENSE v3.0). Results: Median follow-up was 3.6 mo (0.5–8 mo). At time of reporting, 26 of 29 patients had evaluable lesions; response of any kind was observed in 9 of 12 cases in the RT cohort and 12 of 14 cases in the RT-ICB cohort. However, we observed increased complete response rates at 1 mo in the RT-ICB than RT group (50% vs 8%). Additionally, we observed abscopal responses in 2 of 14 RT-ICB cases. We detected significant shifts in the CD8+ and CD4+ T cells that peaked 7 d post-RT (P < 0.001). Interestingly, the majority of responses (67%) involved the expansion of a distinct immunophenotype of elevated Tbet+CD8+CD28+ effector memory CD8+ and CD4+ T cells post-RT. These responses were reproduced in the RT-ICB cohort; in particular, CD28+CD4+CD27+CD4+ T cells were increased in the exceptional responders (P = 0.027). Lastly, for a patient with abscopal response, this was associated with a 25% reduction of TH2 CD4+ T cells. Conclusions: Here, we characterized the systemic immune repertoire of circulating CD8+ and CD4+ T cells in response to RT, either alone or in combination with immunotherapy. Our data suggests that expansion of a distinct CD28+CD4+CD27+CD4+ T cell population may account for the dramatic responses to RT-imunotherapy.
Tumor PD-L1 heterogeneity in non-small cell lung cancer: Does biopsy size and volume matter? First Author: Monica Khunger, Cleveland Clinic, Cleveland, OH

Background: Although patients with high tumor programmed death ligand-1 (PD-L1) expression benefit from PD-1/PD-L1 axis inhibitors, many studies have highlighted that a fraction of patients respond to these agents despite lacking detectable PD-L1 expression. Heterogeneity of tumor PD-L1 expression within the tumor has been postulated to be contributing to the limited performance of PD-L1 as a predictive biomarker. We evaluated the PD-L1 expression heterogeneity by comparing the percentage of PD-L1 positive tumor cells as a measure of tumor PD-L1 proportion scores (TPS) using fluorescence immunohistochemistry in paired whole tissue sections (WTS) and tissue microarray (TMA) cores from surgical non-small cell lung cancer (NSCLC) specimens. Methods: WTS and two 0.6-mm TMA cores localized at least 3mm apart from each other were prepared from each formalin-fixed, paraffin-embedded surgically resected tumor specimens of 451 patients with stage I-III NSCLC. Using quantitative immunofluorescence with the E1L3N anti-PD-L1 antibody, TPS were generated in TMA and 451 patients with stage I-III NSCLC. Using quantitative immunofluorescence with the E1L3N anti-PD-L1 antibody, TPS were generated in TMA and corresponding WTS and classified as 0%, 1-49% and 50%. Results: There was a high discordance between the TPS scores of PD-L1 expression among the WTS and TMA cores (discordance rate = 40.6%, 95% CI, 35.4%-45.9%; k = 0.26). Moderate discordance was observed between the TPS of PD-L1 expression among the two TMA cores (discordance rate = 10.2%, 95% CI, 7.6%-13.5%; k = 0.609). Conclusions: Discrepancies among the PD-L1 expression between WTS and TMA core as well as between TMA cores themselves represents intratumoral heterogeneity of PD-L1. Small needle aspirations or biopsies during endobronchial or CT-guided biopsy, which can be equated to TMA core, may not be representative of the true tumor PD-L1 expression. It is imperative to obtain bigger or multiple needle biopsies to identify patients with true positive tumor PD-L1 expression and maximize the number of patients who could benefit from PD-1/PD-L1 axis inhibitors.

Exploring effects of MEK inhibition in tumor microenvironment in non-small cell lung cancer (NSCLC) pre-clinical models. First Author: Tanik Silik, Memorial Sloan Kettering Cancer Center, New York, NY

Background: NSCLCs often harbor mutations in the KRAS oncogene and require improved treatment to provide durable disease control. Targeted therapy via MEK inhibition shows promising but temporary control of tumor growth but ultimately fails with a quick rebound of tumor growth. As the RAS-RAF-MEK-ERK pathway is evolutionarily conserved in most cells, MEK inhibition may cause broader effects in the tumor microenvironment. Methods: We examined the effect of novel pulsatile versus standard continuous MEK inhibition on lymphocytes and myeloid cells. KRAS tumor bearing mice were treated with selumetinib and T cells were analyzed for phenotypic changes. Tumor progression and survival with and without the addition of checkpoint blockade therapy was also monitored. In vitro experiments were also conducted with murine bone marrow-derived macrophages subsequently exposed to pulsatile or continuous selumetinib treatment. Results: MEK inhibition in T cells shows significant effects on T cell activation and proliferation. CD8+ T cell phenotypes increased CTLA-4, Ki67 and 4-1BB expression when treated with pulsatile compared to continuous MEK inhibitor, suggesting greater activation and proliferation status. Pulsatile MEK inhibitor therapy with CTLA-4 checkpoint blockade showed improved overall survival compared to continuous treatment in a mouse model of Kras mutant lung cancer. We extended our investigation to other tumor microenvironment components particularly myeloid cells. In vitro experiments revealed that pulsatile versus continuous treatment with the clinical MEK1/2 inhibitor selumetinib differentially effects macrophage viability and pro-inflammatory cytokine production. Conclusions: Pulsatile MEK inhibition improves T cell activation and prolongs survival in combination with anti-CTLA-4, compared with continuous treatment. It also has a modulating effect on myeloid cells compared to the standard continuous dosing. Optimizing MEK inhibition scheduling to target cancer cells and activate immune infiltrates will provide the best therapy for KRAS mutant NSCLC. These data will contribute to informing design immune modulation with targeted therapies in patients.

Computer extracted features of cancer nuclei from H&E stained tissues of tumor predicts response to nivolumab in non-small cell lung cancer. First Author: Xiangxue Wang, Case Western Reserve University, Cleveland, OH

Background: Immune checkpoint inhibitors have recently been FDA-approved for use in advanced stage non-small cell lung cancer (NSCLC). These drugs target the PD-1 receptor or its ligand PD-L1, but treated patients only have a response rate of about 20%. It is thus crucial to identify which patients will derive maximal benefit from such treatments, especially since the current gold standard biomarker, detection of tissue-based PD-L1 expression, has been shown to be inadequate. Previous studies have shown that computer extracted features of nuclear shape and texture are predictive of recurrence in early stage NSCLC. The goal of this work is to evaluate the role of features of nuclei shape and arrangement in the tumor in predicting response to Nivolumab for NSCLC. Methods: The study included 56 patients with NSCLC from two different institutions who had had pre-treatment tumor biopsies and were treated with Nivolumab. The patients were split into two categories, responders and non-responders, that were determined by clinical improvement and radiologic assessment through RECIST criteria. The 245 features from tumor nuclei included standard measures used to characterize shape and texture of nuclei as well graph based features that capture the distinct spatial arrangement of the nuclei. Features were extracted from tumor regions manually annotated on digitized H&E images by two expert pathologists. Results: A statistical feature selection method determined the top five tumor nuclear features from the training set. These features included the spatial arrangement of nuclei and variance in nuclear shape and chromatin structure. A machine learning classifier trained with these top five features yielded an AUC = 0.65 on the training set (n = 32) and an AUC = 0.6 on the independent validation set from a separate institution. (n = 24). Conclusions: Computer extracted features of cancer nuclei were found to distinguish between patients who did and did not respond to Nivolumab immunotherapy. Validation is needed on larger cohorts from multiple different sites.
12062 Poster Session (Board #175), Mon, 1:15 PM-4:45 PM
Uptfront next generation sequencing in NSCLC: A publicly funded perspective. 
First Author: Kerstin Persdriez, University of Toronto, Toronto, ON, Canada

Background: A growing number of actionable targets in non small cell lung cancer (NSCLC) have led to the need for molecular profiling beyond the standard of care (SOC) EGFR/ALK. Here we evaluate the impact on patient treatment, clinical trial opportunities and costs using the Illumina TrueSight Tumor 15 panel (TST15) for NSCLC samples.

Methods: In addition to immunohistochemistry for ALK and PD-L1, tissue-based next generation sequencing using the TST15 was reflexively performed on all non-squamous NSCLC specimens at the University Health Network (Toronto, Canada) between February and December 2017. The panel identifies hot spot mutations in EGFR, KRAS, TP53, PIK3CA, BRAF, ERBB2, FOX2L, GNA11, GNAQ, KIT, NRAS, PDGFR, RET, AKTI and MET, but not fusions, copy number variations (CNV) or MET exon 14 skipping mutations. Patient age, stage, pathologic subtype and genotyping panel identifies hot spot mutations in ERBB2,

Results: Testing included 284 samples from 282 patients. The TST15 panel identified 343 mutations from 226 samples. Sample demographics include: male/female 53/47%, stage 1/2/3/4 33%/37%/26%/4%. Incremental actionable targets beyond EGFR and ALK were identified in 2.6% of samples (ERBB2 1.7%, BRAFV600E 0.9%). Most mutations occurred in TP53(43%), EGFR(25%) and KRAS(24%), with co-mutations in 31% TP53, KRAS and EGFR. 94% of a patient had had a treatment change as a result of TST15 beyond targeting EGFR. Above SOC clinical trial options were identified for 73% of stage IV and 25% of stage III patients. 3.6 samples were needed to identify one actionable mutation, predominantly in EGFR, at an estimated cost of $1919 CAD per test. 

Conclusions: Excluding testing with TST15, actionable mutations and improves clinical trial options for patients. Despite this, impact on patient treatment beyond targeting EGFR is minimal. To enhance the number of targets and minimize costs, population-based comprehensive testing with a panel that includes fusions/CNV is needed.

12064 Poster Session (Board #177), Mon, 1:15 PM-4:45 PM
Resolving diagnostic uncertainty in bone-predominant metastases in cancer of unknown primary (CUP) using the 92-gene assay. First Author: Kanwal Pratap Singh Raghav, Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Bone-predominant metastases in patients with CUP pose diagnostic challenges in pathologic analyses, which may delay optimal therapy. The 92-gene assay is a validated gene expression profiling (GEP)-based cancer classifier with high accuracy in limited tissue. This study evaluated performance and clinical utility of the 92-gene assay in bone biopsies from bone-predominant CUP. Methods: A corelate database integrating 92-gene assay (CancerType ID) results and de-identified patient data was developed under an IRB-approved protocol for 26,594 cases where tissue-sparing GEP assay should be considered early in the diagnostic workup

Results: 208 patients (F/M: 84/119, median age: 47 [range 21-81 years]) from a multicenter setting, who have been immunohistopathologically diagnosed with gliomas (IDH positive/negative: 98/105) were prospectively included in our study. The raw data from DSC-PWI was processed on a dedicated workstation, using a fully adaptive Bayesian method, to create leakage-corrected relative cerebral blood volume (rCBV) maps. Tumours were manually segmented and registered to rCBV maps. rCBV maps were used to generate distribution and rotational invariant Haralick texture features over the tumour mask. The predictive power of the extracted features in differentiating between IDH status was assessed in a 2-fold cross-validation setting of 1000 iterations using support vector machine and multinominal ordinal regression, respectively. Results: Overall sensitivity and specificity rates for the rCBV for IDH stratification were 68% and 81%, respectively. All except one of the ten clinical definitions (e.g., age, gender) have been confirmed as being significantly different across mutation status (p < 0.05) when using non-parametric Wilcoxon test. In the case of the classification across grading, the same features to led to a distance error (difference between the real and predicted grade) inferior or equal to 1 in 88.6% of the cases and an exact prediction in 57.2% of CUP cases. Discriminating between IDH-positive and IDH-negative brain tumours represents an interesting arena for clinical application.
Background: An enterocyte subtype of the Colorectal Cancer (CRC) Assigner classifier has shown to confer benefit from oxaliplatin in adjuvant treatment for stage III CRC. MSA412 belongs to the enterocyte subtype-specific gene, whose expression is regulated by endogenous CDX2. We tested whether single nucleotide polymorphisms (SNPs) in enterocyte-related genes predict oxaliplatin efficacy in first-line treatment for metastatic CRC (mCRC).

Methods: Three different cohorts of mCRC patients (pts) (total 603) were included in this study: discovery cohort receiving FOLFIRX + bevacizumab (BV) (n = 146, median age = 61, median follow-up = 45.0 mos); validation cohort receiving FOLFIRI + BV (n = 230, TRIBE arm B, median age = 60, median follow-up = 46.5 mos); and control cohort receiving FOLIRI + BV (n = 228, TRIBE arm A, median age = 60, median follow-up = 49.3 mos). SNPs were analyzed by PCR-based direct sequencing. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier curves, log-rank test, and Cox proportional hazards regression. Results: Among the SNPs tested in the discovery cohort, MSA412 rs4939378 and CDX2 rs3812863 were extracted as potential markers of efficacy. In the validation cohort, any A allele in MSA412 rs4939378 was associated with longer PFS than the A/A variant in univariate analysis (12.4 vs. 10.9 mos, HR 0.72, 95% CI: 0.60-0.89, P = 0.003) and multivariable analysis (HR 0.65, 95% CI: 0.44-0.97, P = 0.036). The findings were confirmed in the control cohort than KRAS wild-type pts. In contrast, KRAS wild-type mCRC pts with the G/G variant in CDX2 rs3812863 had a longer PFS than those with any A allele (32.3 vs. 10.3 mos, HR 0.39, 95% CI: 0.19-0.81, P = 0.004), and the trend remained in multivariable analysis though without statistical significance (HR 0.56, 95% CI: 0.31-1.02, P = 0.08). These findings were not confirmed in the control cohort.

Conclusions: The enterotype subtype might affect the antitumor activity of oxaliplatin in not only early stage but also metastatic disease in CRC. Genetic variants in MSA412 and CDX2 gene polymorphisms may serve as potential predictive marker of oxaliplatin-based treatment in mCRC pts.

12068 Poster Session (Board #181), Mon, 1:00-1:45 PM EST Identification of clonal hematopoiesis mutations in solid tumor patients undergoing unpaired commercial next-generation sequencing: a multi-institutional retrospective study of 146 metastatic cancer patients

First Author: Catherine Callaghan Coombs, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Precision medicine is increasingly utilized for both prognostication and application of targeted therapies for oncologic patients (pts). Results from next-generation sequencing (NGS) assays ideally should reflect the burden of somatic tumor mutations (muts), yet challenges can arise from differentiation of germline muts and from contamination of biopsies by normal tumor tissue. Clonal hematopoiesis (CH), defined by the presence of somatic muts typically in leukemia-associated genes in hematopoietic cells, occurs in aging individuals, with an increased risk for hematologic cancers and shorter survival in pts with solid tumors (ST). Here we examine the prevalence of CH leading to false positive (FP) calls on commercial NGS assays. Methods: This is a multi-institution, retrospective cohort study of pts undergoing NGS of ST. All pts undergoing commercial NGS (Foundation Medicine) testing were examined (N = 768 at UNC and 989 at MCC). For a subset of pts (N = 64 at UNC and 30 at MCC), NGS of paired blood samples was performed to examine the prevalence of true CH events, defined as a variant allele frequency (VAF) in the blood exceeding the VAF in the tumor tissue. Germline muts were defined by VAF > 35% in both tumor and blood. Results: Muts in genes that are frequently altered in CH (DNMT3A, TET2, ASXL1, TP53, ATM, CHEK2, SF3B1, CBL, JAK2) were identified in 65% of pts; excluding TP53, often mutated in ST, these events were seen in 35% of pts. A bimodal distribution of VAFs was seen for CH genes, with low VAF events most suggestive of true CH events. Using paired blood samples, we confirmed such muts as true CH events in 94.4% of ST pts in the UNC cohort. Across all genes, germline muts were reported in 23% of UNC pts, of which 33% were known or likely pathogenic muts. MCC samples were enriched for pts with reported muts in CH genes; 33% of which (10/30) were confirmed as true CH events. The majority of DNMT3A muts (64%, 7/11) were CH; the minority of TP53 muts (4%, 2/50) were CH. Conclusions: Muts in CH genes are commonly reported on unpaired clinical NGS testing of ST; some true CH events as opposed to ST events. It is important to recognize CH as a possible FP when applying NGS results in practice.

12069 Poster Session (Board #182), Mon, 1:00-1:45 PM EST Molecular subtypes of triple-negative breast cancer (TNBC) tumor samples obtained in the neoadjuvant setting and after neoadjuvant systemic therapy (NST) and their relationship between immunomodulatory (IM) gene signature and intensity of tumor-infiltrating lymphocytes (TILs).

First Author: Hiroko Masuda, Department of Surgical oncology, Showa University, Tokyo, Japan

Background: Lehmann et al have identified 4 molecular subtypes of TNBC [basal-like (BL) 1, BL2, mesenchymal (IM), and luminal androgen receptor (LAR)] and an IM gene expression signature. Our group previously showed that response of TNBC to NST differs by molecular subtype, but whether NST affects TNBC subtype has not been studied. We hypothesized that certain TNBC subtypes change after NST. We also tested whether IM signature correlates with the intensity of TILs. Methods: From the World TNBC Consortium dataset, which contains TNBC samples from 4 institutions from 4 countries, we examined 68 formalin-fixed, paraffin-embedded tumor samples from patients treated with NST: 27 pairs of matched pre-NST and post-NST samples and 14 pre-NST samples. TNBC classification was performed with the Insight TNCBtype assay. We compared the molecular subtypes of TNBC samples obtained before and after NST. We used the Spearman correlation test to investigate the association between IM status and percentage of TILs in all 68 samples. Results: The distribution of TNBC subtypes before and after NST is shown in the Table. Of the 27 matched pairs, 14 (52%) showed a change in TNBC subtype after NST. Among the 14 matched pairs with a subtype change, all 11 cases of BL1 subtype before NST changed to M, and 4 of 5 cases of BL2 subtype before NST converted to BL2 (one LAR changed to unclassified). As expected, a low residual cancer burden (RCB 1) was more common in patients with (4/14 (29%)) than in patients without subtype change (1/13 (8%)); however, subtype change and amount of residual cancer were not related statistically (p = 0.32), most likely due to the small sample size. There was a strong positive correlation (rho 0.95, p = 0.0008) between TIL intensity and IM gene signature positivity. Conclusions: TNBC molecular subtype frequently changed after NST. TIL intensity positively correlated with IM signature. We will validate our findings in a larger group of samples in the World TNBC Consortium dataset.

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Visit abstracts.asco.org and search by abstract for the full list of abstract authors and their disclosure information.
Background: Bladder cancer patients are routinely monitored after treatment by cystoscopy due to a high rate of recurrence. In the absence of an accurate non-invasive screening test to monitor recurrence, bladder cancer will remain the most expensive malignancy to manage. We have developed a non-invasive test that interrogates small non-coding RNAs (sncRNAs) present in urinary exosomes. Analyzing the urine exosome data with a novel statistical classification algorithm provides a platform that unequivocally differentiates between patients with no evidence of disease and those with recurrence. Methods: Urine samples were collected from patients previously treated for bladder cancer (n = 82) who are currently under routine surveillance cystoscopy. Patients without bladder cancer or without evidence of recurrent disease served as the control cohort. A Sentinel sncRNA signature specific for bladder cancer was generated by interrogation of urinogen exosomal RNAs on Affymetrix 4.0 arrays that probes for > 6600 sncRNAs. A customized platform to interrogate the most informative (~120) Sentinel sncRNAs, was then used to screen urine exosomal RNA derived from patients at risk for recurrent disease. Data were then analyzed using a statistical classification algorithm that provides the miR-BCPx (bladder cancer progression score). This novel analytical approach requires no a priori knowledge of the sncRNA function to generate an unbiased classification into those with stable disease versus those with recurrent tumor. Results: Bladder cancer patients have significantly elevated levels of exosomal RNAs relative to the control cohort. In a small blinded testing male cohort, comparison of the miR-BCPx score generated to the disease status demonstrates that the miR-BCPx identifies patients with recurrent tumor with 100% sensitivity (59/59) and 96% specificity (22/23). Conclusions: Implementation of the miR-BCPx as a surveillance screen for cancer patients may provide an invasive alternative to cystoscopy for monitoring disease stability, and can readily be deployed in the clinic to reduce the number of screening cystoscopies needed.

Background: Tumor somatic mutation burden (TMB) and neoantigen burden (NB), are emerging therapeutic biomarkers for immune checkpoint blockade (ICB) therapies. Here we develop an ICB therapeutic biomarker for ICB therapies. We are in the process of curating a list of NB mutations that can be incorporated into a biomarker of NB. We are in the process of identifying a list of NB mutations that can be incorporated into a biomarker of NB.

Results: We curated a list of NB mutations that can be incorporated into a biomarker of NB. We are in the process of curating a list of NB mutations that can be incorporated into a biomarker of NB.

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Multigene prognostic signatures (MGPS) enable identification of early stage breast cancer (BC) patients requiring less aggressive treatment. OncoMasTR is a new MGPS found via a novel transcriptional network analysis method that identified genes – Master Transcription Regulators (MTRs) – that regulate previously identified prognostic biomarkers. The optimised OncoMasTR signature consists of 23 MTRs (OM) and incorporating clinicopathological information (OMclinical) has been clinically validated. We examined OncoMasTR’s prognostic performance alone and in comparison to OncotypeDX. Methods: We measured MTR expression levels by RT-qPCR in tissue from Irish patients (n = 367) enrolled in the Trial Assigning Individualized Options for Treatment (TAILORx) study through Cancer Trials Ireland. OM and OMclinical numeric risk scores and risk category (high or low) were blindly calculated using the OncoMasTR algorithm. OncoMasTR scores and OncotypeDX recurrence scores (RS) were independently compared on measures of risk classification, BC recurrence (all, local and distant), correlation and concordance over 9 years of follow-up. Results: OM (LRx = 12.92, p = 0.0003) and OMclinical (LRx = 17.21, p < 0.0001) provided more diagnostic information than RS (LRx = 4.74, p = 0.0294). OM classified 39% of samples as low risk (no local or distant recurrence, 0.0% recurrence) and 61% as high risk (9.0% recurrence; 4.5% local, 4.5% distant) compared to OncotypeDX classification which were (1.9% recurrence; 1.9% local, 0% distant), 63.3% as intermediate risk (7.0% recurrence, 3.5% local, 3.5% distant), and 19.4% as high risk (8.0% recurrence; 3.2% local, 4.8% distant). There was moderate correlation between OM and RS numeric risk scores (r = 0.46, p < 0.0001) and low correlation between OM and RS risk categories. Higher correlation and concordance were observed among high risk samples. Conclusions: OM, OMclinical and RS were significantly prognostic for recurrence in TAILORx samples. OM and OMclinical demonstrated exceptional sensitivity by classifying all patients who had any recurrence to the high risk category.

Background: While ALK, ROS1, RET fusions, and MET exon 14 (METex14) alterations are routinely detected by hybridization capture-based DNASeq assays such as MSK-IMPACT, a genomic DNA-based approach may not identify all patients with such events. We evaluated the utility of targeted RNASeq for the identification of these alterations in MSK-IMPACT driver-negative lung cancers. Methods: MSK-IMPACT driver-negative tumors (defined in Jordan E et al, 2017, PMID 28336552), underwent further molecular profiling with the MSK-Fusion Solid panel, a custom RNASeq panel based on the Archer FusionPlex technology designed to detect fusions involving 62 cancer genes and METex14 skipping. Low tumor mutation burden (TMB) was assessed as a potential prioritization criterion for targeted RNASeq. Results: Between 01/01/2014 and 12/31/2017, 2502 lung adenocarcinomas were profiled using MSK-IMPACT; 201 (8%) gene fusions and 119 (5%) MET exon 14 alterations were identified (table). Among 276 driver-negative cases, 255 (92%) with available tissue were subjected to targeted RNASeq. A previously undetected alteration was identified in 36 of 255 (14%) cases by the MSK-Fusion Solid panel, 33 of which were actionable (27 in-frame gene fusions, 6 METex14 skipping events; table). Of these 33 patients, 11 were eligible for matched targeted therapies (the rest had early-stage disease or low KPS, or were on alternate therapies, on active monitoring. From the training cohort, we defined the post-second treatment cycle (p2) as 30 to 60 days post-first treatment and compared AF value of each variant with the nadir value. Good responders at p2 were defined as having no significant increase in AF from the nadir. Applying this algorithm to the validation cohort, good early responders with samples collected within p2, 24/40 (60%), were associated with better progression-free survival (PFS) (6.1 vs. 3.8 mo, P = 0.0145; HR 0.43; 95% CI 0.21, 0.86) and overall survival (OS) (15.0 vs. 6.8 mo, P = 0.0032; HR 0.31, 95% CI 0.14, 0.70). Conclusions: Longitudinal ctDNA analysis in the absence of matched tissue biopsy may be feasible. No significant increase in post-treatment ctDNA levels measured by NGS was associated with better prognosis in advanced lung adenocarcinoma treated with first-line chemotherapy or chemoradiation therapy.
leucine zipper motif in EF1D destabilized EF1D protein and inhibited cancer. Blocking this interaction by a cell-permeable peptide corresponding to a exogenous expression of LAPP1 in EF1D(+) cells elevated the dephos-
terminating protein that was highly expressed in lung cancers. Suppres-
therapy targeting CD20- targeting antibodies make remission possible, with fit patients consolidated with autologous stem cell transplant but effects are invariably short-lived and MCL continues to principally be incurable. Adoptive chimeric antigen receptor T cells targeting CD19 (CD19.CAR-T) has shown therapeutic promise for B-NHL. Targeting this antigen, however, does not distinguish between normal and malignant B cells and causes profound B-cell aplasia since CD19.CAR-T can persist long-term. MCL, along with many diffuse large B cell lymphoma (DLBCL) subsets, expresses surface immunoglobulin (Ig) that carries the lambda light chain. We explored targeting Ig-lambda with CAR-T, which would possibly spare B lymphocytes expressing the reciprocal kappa light chain, and consequently reduce the impairment of humoral immunity. Methods: We genetically modified CAR-T cells to target the tumor-associated immunoglo-
ligulin lambda light chain (CAR.λ). We conducted in vitro trials with B-NHL derived tumor cell lines expressing the lambda light chain, and in vivo ex-
periments using a NOD-scid xenograft murine model injected with these same tumor cell lines. We also established a murine model that reconstituted human B lymphocytes within immunosuppressed NSG mice using CD34+ umbilical cord blood cells. We observed that the selection of λ heavy and κ light chains to eliminate normal human B-lymphocytes. Results: We found that the CAR.λ showed high cytotoxic activity against Ig-lambda B-cell tumor cell lines in vitro and in vivo within the NOD-scid xenograft murine model. We also demonstrated the selective elimination by the CAR.λ of lambda light chain-expressing B cells, with sparing of kappa chain-expressing B cells. This is a new approach toward a humanized murine model. Conclusions: Adoptive transfer of CAR-T targeting the lambda light chain can be a very useful immunotherapy approach to treating both MCL and DLBCL clinically, without entirely compromising humoral immunity.

Successful generation of patient derived xenografts and patient derived 3D cultures as preclinical models for breast cancer. First Author: Venera Imke Isabel Kiver, Charite Comprehensive Cancer Center and Department of Gynecology and Breast Center Charité Universitätsmedizin Berlin Campus Mitte, Berlin, Germany

Background: The establishment of patient-derived preclinical models in breast cancer has been a challenge for many years. We report our successful experience in establishing breast cancer patient derived xenografts (PDx) and patient derived 3D cultures (P3D3). Methods: Tumor tissue samples (twice 3mm diameter) from breast cancer patients undergoing surgery were collected by a team of gynecologists and pathologists. Ischemia time was minimized. Small tumor fragments were transplanted to immunodeficient NOG mice. The other part was used to establish a cell culture on serum free organoid media in the presence of growth hormones and, in case of hormone receptor positive breast cancer, estradiol supplementation. To address the question whether the genetics features of the model have changed during the process of engraftment and expansion the established models are currently undergoing molecular profiling. Results: Since May 2017 28 breast cancer samples have been processed. The sample characteristics are summarized in the table. Currently we have one PDx established, 18 in passage and 9 have not engrafted. Breast cancer P3D3 organoids had a take rate of 56% under our culture conditions. Moreover, hormone receptor positive breast cancer PD3D models were successfully established as PD3D with a take rate of 37.5%. Conclusions: A high take rate under improved culture conditions provided a versatile method of patient-derived preclinical model generation.

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Chimeric antigen receptor T cells targeting the lambda light chain of human immunoglobulin as a viable target for B cell non-Hodgkin lymphoma. First Author: Mithuveer Ranganath, University of North Carolina-Chapel Hill, Chapel Hill, NC

Background: Mantle Cell Lymphoma (MCL) is an uncommon and clinically aggressive subtype of B cell derived non-Hodgkin lymphomas (B-NHL) which continues to have poor outcomes of all B-NHLs. Chemotherapy plus CD20-
light chain. We explored targeting Ig-lambda with CAR-T, which would possibly spare B lymphocytes expressing the reciprocal kappa light chain, and consequently reduce the impairment of humoral immunity. Methods: We genetically modified CAR-T cells to target the tumor-associated immuno-
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Local drug activation technology to make cytotoxics safer for localized solid tumors. First Author: Sangeetha Srinivasan, Shasqi Inc., San Francisco, CA

Background: Only 1-2% of systemic chemotherapies actually reaches a localized tumor while the rest can result in severe off-target effects. There is a critical need to safely deliver cytotoxics directly to the target tissue. The Shasqi Therapeutics (Shasqi Tx) is a bioorthogonal chemistry-based approach consisting of 1) a drug-activating gel and 2) a systemic prodrug. The biocompatible tetrazine (Tz)-modified gel is injected at tumor site and a trans-cyclooctene (TCO)-modified prodrug of a cytotoxic agent such as doxorubicin (Dox), with attenuated activity is given systemically. The prodrug concentrates through a covalent reaction between TCO and the Tz located at the gel. The active drug is spontaneously released over multiple days, directly in the tumor compartment. Remaining prodrug is rapidly cleared by systemic routes, minimizing off-target effects. This technology is reloadable and independent of biological processes. The attenuation of prodrug activity enables an increase in therapeutic index while reducing systemic side effects, as the active drug predominantly localizes to the gel site.

Results: NSG-H mice injected with Tz-modified alginate gel and systemic TCO-doxorubicin (TCO-Dox; prodrug of Dox). The maximum tolerable dose (MTD) of single dose of TCO-Dox was >12x and at 5 daily doses was >38x of single MTD of Dox (control), without any adverse effects. Preliminary bioanalysis provides a basis for the improved safety of Shasqi Tx over traditional chemotherapy. Gel-injected BALB/c mice received TCO-Dox IV. In serum 5 min after injection >90% of the circulating anthracycline remained as intact prodrug while ~7% was converted to Dox. Finally, we tested Shasqi Tx’s safety in a pilot dog study with spontaneous locally advanced tumors. Standard Dox therapy led to disease progression with a drastic drop in body weight. Then, multiple cycles of Shasqi Tx given at >11x the lifetime MTD of Dox, reduced tumor size and led to stable disease for >430d, body wt. gain with major side effects. Conclusions: Shasqi Tx enhances delivery of cytotoxic drugs to targeted tumors while limiting TCO-Dox’s off-target in small and large animals. Further, the increase in therapeutic index allows greater doses of cytotoxics to be delivered safely.

Incidence of Neuregulin1 (NRG1) gene fusions across tumor types. First Author: Stephen V. Liu, Georgetown University Medical Center, Washington, DC

Background: NRG1 gene fusions are an emerging potential therapeutic target in non-small cell lung cancer (NSCLC). NRG1 is a ligand for the HER3 tyrosine kinase and NRG1 fusions activate oncogenic HER2/HER3 and PI3K-AKT signaling. The pan-erbB inhibitor afatinib has been associated with durable response in patients with NRG1+ lung adenocarcinoma. NRG1 fusions and the specific fusion partners have not been well characterized across different tumor types. Methods: Tumor samples submitted for profiling between 01/16-01/18 at a CLIA-certified genomics laboratory (Caris Life Sciences, Phoenix, AZ) were assayed with anchored multiplex PCR for targeted RNA sequencing with the ArcherDX fusion assay (Boulder, CO). Novel isoforms and fusions with high reads (defined as > 10% of total reads), high confidence after bioinformatics filtering and considered in-frame are included in this analysis. Results: In a cohort of 14,150 tumors successfully assayed, 31 cases (0.2%) harbored an NRG1 fusion. The incidence of NRG1 fusions varied by tumor type: 0.9% thyroid (1/116), 0.5% ovary (3/574), 0.5% cholangiocarcinoma (1/194), 0.4% pancreas (2/510), 0.3% NSCLC (20/7869), 0.2% breast (2/927), 0.2% sarcoma (1/475), and 1 case in sinonasal teratocarcinoma (SNTO). One of the 20 NSCLC cases (NRG1-SDC4) had squamous histology, the remaining were adenocarcinoma. No NRG1 fusions were detected in colorectal cancer (0/1382) or glioblastoma multiforme (0/1200). In NSCLC, NRG1 fusions were mutually exclusive with oncogenic alterations in EGFR, ALK, ROS1, RET, and KRAS with the exception of one case that co-occurred with a KRAS G12C mutation. Fusion partners are shown below. Conclusions: Gene fusions in NRG1 can be identified in various tumor types though the highest number of events was in NSCLC. Consistent detection of NRG1 fusions will need to account for multiple fusion partners. This optimal treatment of tumors harboring NRG1 fusions needs to be established.

Clinicalopathologic characteristics and molecular features of BRG1-deficient non-small cell lung cancer (NSCLC). First Author: Ibiagi Dagogo-Jack, Massachusetts General Hospital, Boston, MA

Background: Genomic alterations (GA) in SMARCA4, the gene encoding the SWI/SNF complex subunit BRG1, have been observed in 10% of NSCLC. RNA-based analyses suggest that loss of BRG1 expression is frequently associated with frameshift/nonsense (F/N) SMARCA4 GA. In preclinical studies, BRG1 deficiency sensitizes to enhancer zeste homolog 2 (EZH2) inhibition combined with chemotheraphy (PMID: 25629630). To characterize the subset with SMARCA4 GA, we reviewed 2 independent NSCLC datasets and analyzed BRG1 protein expression in cases with available tissue. Methods: To identify cases with SMARCA4 GA, we examined the molecular profiles of 27,281 NSCLCs sequenced at Massachusetts General Hospital. We performed immunohistochemistry (IHC) using the Abram rabbit BRG1 antibody (EPR3912) to assess BRG1 expression in NSCLCs with SMARCA4 GA. Results: We detected SMARCA4 GA in 73 (9%) and 3,188 (11%) patients (pts) in the MGH and FM datasets, respectively. SMARCA4 GA were distributed throughout all protein domains. F/N GA comprised approximately one-third of SMARCA4 GA in both groups (MGH: 35% and FM:36%), 40 pts (15 with F/N GA) in the MGH group had available tissue for IHC. Thirteen specimens—all from smokers with F/N SMARCA4 GA—had loss of BRG1 expression. Median age of pts with absent BRG1 expression was 69.2 years. Loss of BRG1 expression was observed in 9 adenocarcinomas as well as 2 poorly-differentiated, 1 sarcomatoid, and 1 neuroendocrine carcinoma. F/N GA were distributed 73 (9%) and 3,188 (11%) patients (pts) with SMARCA4 GA. F/N GA in 73 (9%) and 3,188 (11%) patients (pts) with SMARCA4 GA. In preclinical studies, BRG1 deficiency sensitizes to enhancer zeste homolog 2 (EZH2) inhibition combined with chemotheraphy (PMID: 25629630). To characterize the subset with SMARCA4 GA, we reviewed 2 independent NSCLC datasets and analyzed BRG1 protein expression in cases with available tissue. Methods: To identify cases with SMARCA4 GA, we examined the molecular profiles of 27,281 NSCLCs sequenced at Massachusetts General Hospital. We performed immunohistochemistry (IHC) using the Abram rabbit BRG1 antibody (EPR3912) to assess BRG1 expression in NSCLCs with SMARCA4 GA. Results: We detected SMARCA4 GA in 73 (9%) and 3,188 (11%) patients (pts) in the MGH and FM datasets, respectively. SMARCA4 GA were distributed throughout all protein domains. F/N GA comprised approximately one-third of SMARCA4 GA in both groups (MGH: 35% and FM:36%), 40 pts (15 with F/N GA) in the MGH group had available tissue for IHC. Thirteen specimens—all from smokers with F/N SMARCA4 GA—had loss of BRG1 expression. Median age of pts with absent BRG1 expression was 69.2 years. Loss of BRG1 expression was observed in 9 adenocarcinomas as well as 2 poorly-differentiated, 1 sarcomatoid, and 1 neuroendocrine carcinoma. F/N GA were distributed 73 (9%) and 3,188 (11%) patients (pts) with SMARCA4 GA. 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Background: Among the several therapeutic options available to treat Castrate-Resistant Prostate Cancer (CRPC), choosing the most suitable option for an individual patient remains a clinical challenge. For this, our group has developed a novel ex-vivo model based on patient-derived micro-dissected tissues (MDT) cultivated in microfluidic devices to determine patient sensitivity profile in the presence of therapeutic agents. Methods: MDTs (~400 μm in diameter) derived from PC cell line xenografts (DU145 and LnCaP) were exposed to docetaxel (10 nM for 12 hours) or enzalutamide (10 μM for 24 hours) and analyzed after a 12-hour recovery period or immediately after exposure time. Cell fate was measured using flow cytometry techniques (Annexin V for apoptotic cells and DRAQ7 for dead cells) and by a technique based on formalin fixed paraffin embedding of MDTs within a microfluidic device creating a high-density MDT-Array (MDTA). Using MDTA we can monitor MDT viability (cleaved caspase-3), proliferation (Ki-67) and epithelial composition (CK 8/18) by immunohistochemistry (IHC) and immunofluorescence (IF). MDTs were also separately treated with TNF-α at a concentration of 10 ng/mL for 30 minutes and analyzed by MDTA.

Results: We show that the microfluidic device does not affect the viability (> 85% by flow cytometry) or proliferative capacity (60% by IHC) of the MDTs during a culture period of 15 days in PC cell line xenograft models (N = 3 for LNCaP, N = 2 for DU145). Pharmacological responses to docetaxel showed 50% increase in caspase-3 activity by IF and 20% increase in cell death by apoptosis assay (Annexin V for apoptotic cells and DRAQ7 for dead cells) and by a technique based on formalin fixed paraffin embedding of MDTs within a microfluidic device creating a high-density MDT-Array (MDTA). Using MDTA, we can monitor MDT viability (cleaved caspase-3), proliferation (Ki-67) and epithelial composition (CK 8/18) by immunohistochemistry (IHC) and immunofluorescence (IF). MDTs were also separately treated with TNF-α at a concentration of 10 ng/mL for 30 minutes and analyzed by MDTA.

Conclusions: Within less than 5 days, we can obtain treatment response analysis using our ex-vivo drug response model, appropriate for clinical decision-making. The precise techniques developed within our lab, allows the characterization of molecular responses of cancerous cells in the presence of various therapeutic agents while conserving the normal tumor microenvironment.

Background: Despite routine use of chemotherapy in advanced non-small-cell lung cancer (NSCLC) patients, the knowledge of optimal prognostic methods is still limited to imaging-based methods. We hypothesized that an early response assessed by mutant molecules count in plasma could predict the treatment effect. Methods: We employed AVE/NIO cDNA Surveillance Kit, a 197 gene NGS assay, which allowed us to perform longitudinal cDNA analysis and measure the mutant molecules per milliliter-of-plasma (MMPM), which quantifies cDNA at the variant level. The association between changes in cDNA levels and survival was evaluated in advanced lung adenocarcinoma subjects. Post-treatment MMPM values were compared with the MMPM value at baseline and/or the previous treatment timepoint. Results: At baseline (b0), we identified variants in all (93/93) subjects to enable cDNA monitoring. From the training cohort (50 subjects), we were able to set the cutoff of 40 for the mean MMPM at post-first treatment cycle (p1). Applying the MMPM cutoff of p1 to the validation cohort (43 subjects with stage IV lung adenocarcinoma, from a prospective, observational study) low levels of cDNA toward the end of first treatment cycle was associated with better progression-free survival (PFS) (P = 0.0088 HR 0.4; 95% CI 0.20-0.83) and overall survival (OS) (P = 0.0026 HR 0.32; 95% CI 0.15-0.71). The prognostic value is increased by applying the Continuous Responder algorithm, defined by a continuous drop in cDNA levels represented by mean MMPM reduction over time (p2 < p1 < b0), to a mean MMPM below 8 at p2. As a result, continuous responders 13/43 (30%) were associated with a better therapy response indicated by PFS (P = 0.028 HR 0.45; 95% CI 0.23 - 0.90) and OS (P = 0.0074 HR 0.3; 95% CI 0.12 - 0.77). The continuous responders demonstrated a median overall survival benefit of 11.25 months over the poor responders. Conclusions: A decrease in post-treatment cDNA level measured by NGS was associated with better prognosis in advanced lung adenocarcinoma. An early assessment of treatment effect can be measured by mutant molecule counts in the plasma within 1 or 2 treatment cycles.
**12090 Poster Session (Board #203), Mon, 1:15 PM-4:45 PM**

**PD-L1 genomic alterations (GA) in solid tumors and hematologic malignancies: A comprehensive genomic profiling (GCP) study.**

First Author: Leslie Y. Gold, Foundation Medicine, Inc., Cambridge, MA

**Background:** Amplification (AMP) of PD-L1 (CD274/B7H1) has recently been linked to enhanced benefit from immune checkpoint inhibitor (ICPI) treatment. We used GCP to evaluate the PD-L1 GA landscape in cancer. **Methods:** Specimens from 140,411 cancers representing >450 individual disease ontologies were sequenced using a hybrid capture-based, next-generation sequencing assay. PD-L1 protein expression was measured by immunohistochemistry (IHC) in a subset of cases using the Dako 22C3 anti-PD-L1 antibody.

**Results:** 1383 (0.9%) tumors had PD-L1 GA (1414 GA): 879 (62%) AMP, 471 (33%) short variants (SV) and 60 (0.4%) truncating GA (1414 GA): PD-L1 AMP samples; other genes commonly altered with PD-L1 AMP included TP53 (77%), CDKN2A/B (28%/20%), MYC (21%), and TERT (13%). For samples with RE or SV, PIK3CA (19%; 21%) GA were common and TERT GA were in 7% or 14% of samples. Most SV GA were missense (88%), compared with truncating (10%) or splice site (2%) GA. Recurrent somatic variants of unknown significance (VUS) were observed, including frameshift and missense GA that may regulate PD-L1 stability. Of 10 common tumors, breast (213) and lung (210) carcinomas (CA) represented the most PD-L1 AMP cases. Select cancers with notable PD-L1 AMP frequencies were anaplastic thyroid CA (4%), head and neck squamous CA (HNSCC) (2.5%), cervical SCC (2.6%), and breast (1.4%), lung (0.7%) and bladder (0.6%) CA. Of common tumor types, such as colorectal, pancreatic, ovarian, or prostatic CA, melanoma and glioblastoma, ≤0.3% had PD-L1 AMP. There was strong correlation between PD-L1 AMP and PD-L1 expression by IHC in NSCLC, with 89% AMP positive samples showing >50% IHC staining and 11% with positive but ≤50% staining. Major clinical responses to ICPI therapies for tumors with PD-L1 AMP will be presented.

**Conclusions:** PD-L1 AMP or other GA occur rarely across many cancer types. Many somatic PD-L1 GA are characterized VUS. PD-L1 AMP correlates with high membrane expression of PD-L1 measured by IHC and is linked to durable response to ICPI therapies. Further evaluation of PD-L1 AMP as a potential means to identify patients with improved outcomes is warranted.

**12091 Poster Session (Board #204), Mon, 1:15 PM-4:45 PM**

**PD-1R and PD-L1R immunotherapy efficacy: A comprehensive genomic profiling (GCP) assessment.**

First Author: Gennady Bratslavsky, SUNY Upstate Medical University, Syracuse, NY

**Background:** PD-1R, a member of the SWI/SNF family, is involved in chromatin remodeling. Recent evidence indicates that PD-1R blocking antibodies are associated with clinical benefit from immune checkpoint inhibitor treatments in clear cell renal cell carcinoma (ccRCC). **Methods:** PD-1R was evaluated (enhanced kinase activity, dimerization dependent) BRAF mt MM and to dMAPKi with BRAFi and MEKi improves survival in BRAF wt MM.

**Results:** We analyzed 3 MM datasets (PIM1 next generation sequencing (NGS) cohort, TCGA, GENIE) for clinicopathologic correlations and outcomes of nonV600 BRAF mt MM pts. Tumors from patients with BRAF WT, V600E/K MM were used to generate patient-derived xenografts (PDX); both were investigated with immunoblots, CRISPR screens. Conclusions: Dual MAPK inhibition (dMAPKi) as an effective therapeutic strategy for class II BRAF mutant (mt) metastatic melanoma (MM).

**12092 Poster Session (Board #205), Mon, 1:15 PM-4:45 PM**

**PBRM1 mutation and immunotherapy efficacy: A comprehensive genomic profiling (GCP) assessment.**

First Author: Gennady Bratslavsky, SUNY Upstate Medical University, Syracuse, NY

**Background:** PBRM1, a member of the SWI/SNF family, is involved in chromatin remodeling. Recent evidence indicates that PBRM1 blocking antibodies are associated with clinical benefit from immune checkpoint inhibitor treatments in clear cell renal cell carcinoma (ccRCC).

**Methods:** PBRM1 was evaluated (enhanced kinase activity, dimerization dependent) BRAF mt MM and to dMAPKi with BRAFi and MEKi improves survival in BRAF wt MM.

**Results:** PBRM1 GA were in 7% or 14% of samples. Most SV GA were in 7% or 14% of samples. Most SV GA were missense (88%), compared with truncating (10%) or splice site (2%) GA. Recurrent somatic variants of unknown significance (VUS) were observed, including frameshift and missense GA that may regulate PD-L1 stability. Of 10 common tumors, breast (213) and lung (210) carcinomas (CA) represented the most PD-L1 AMP cases. Select cancers with notable PD-L1 AMP frequencies were anaplastic thyroid CA (4%), head and neck squamous CA (HNSCC) (2.5%), cervical SCC (2.6%), and breast (1.4%), lung (0.7%) and bladder (0.6%) CA. Of common tumor types, such as colorectal, pancreatic, ovarian, or prostatic CA, melanoma and glioblastoma, ≤0.3% had PD-L1 AMP. There was strong correlation between PD-L1 AMP and PD-L1 expression by IHC in NSCLC, with 89% AMP positive samples showing >50% IHC staining and 11% with positive but ≤50% staining. Major clinical responses to ICPI therapies for tumors with PD-L1 AMP will be presented.

**Conclusions:** PD-L1 AMP or other GA occur rarely across many cancer types. Many somatic PD-L1 GA are characterized VUS. PD-L1 AMP correlates with high membrane expression of PD-L1 measured by IHC and is linked to durable response to ICPI therapies. Further evaluation of PD-L1 AMP as a potential means to identify patients with improved outcomes is warranted.

**12093 Poster Session (Board #206), Mon, 1:15 PM-4:45 PM**

**Dual MAPK inhibition (dMAPKi) as an effective therapeutic strategy for class II BRAF mutant (mt) metastatic melanoma (MM).**

First Author: Matthew Dankner, McGill University, Montréal, QC, Canada

**Background:** dMAPKi with BRAFi and MEKi improves survival in BRAF V600E/K mt MM, but the effects of these inhibitors on nonV600 BRAF mt MM is poorly understood. We sought to characterize nonV600/class II (enhanced kinase activity, dimerization dependent) BRAF mt MM and to ICPI treatment. We used GCP to evaluate the PD-L1 GA landscape in cancer. **Methods:** Specimens from 140,411 cancers representing >450 individual disease ontologies were sequenced using a hybrid capture-based, next-generation sequencing assay. PD-L1 protein expression was measured by immunohistochemistry (IHC) in a subset of cases using the Dako 22C3 anti-PD-L1 antibody.

**Results:** 1383 (0.9%) tumors had PD-L1 GA (1414 GA): 879 (62%) AMP, 471 (33%) short variants (SV) and 60 (0.4%) truncating rearrangements (RE). PD-L2 (PDCD1LG2) and JAK2 were co-amplified in 94% and 82% of PD-L1 AMP samples; other genes commonly altered with PD-L1 AMP included TP53 (77%), CDKN2A/B (28%/20%), MYC (21%), and TERT (13%). For samples with RE or SV, PIK3CA (19%; 21%) GA were common and TERT GA were in 7% or 14% of samples. Most SV GA were missense (88%), compared with truncating (10%) or splice site (2%) GA. Recurrent somatic variants of unknown significance (VUS) were observed, including frameshift and missense GA that may regulate PD-L1 stability. Of 10 common tumors, breast (213) and lung (210) carcinomas (CA) represented the most PD-L1 AMP cases. Select cancers with notable PD-L1 AMP frequencies were anaplastic thyroid CA (4%), head and neck squamous CA (HNSCC) (2.5%), cervical SCC (2.6%), and breast (1.4%), lung (0.7%) and bladder (0.6%) CA. Of common tumor types, such as colorectal, pancreatic, ovarian, or prostatic CA, melanoma and glioblastoma, ≤0.3% had PD-L1 AMP. There was strong correlation between PD-L1 AMP and PD-L1 expression by IHC in NSCLC, with 89% AMP positive samples showing >50% IHC staining and 11% with positive but ≤50% staining. Major clinical responses to ICPI therapies for tumors with PD-L1 AMP will be presented.

**Conclusions:** PD-L1 AMP or other GA occur rarely across many cancer types. Many somatic PD-L1 GA are characterized VUS. PD-L1 AMP correlates with high membrane expression of PD-L1 measured by IHC and is linked to durable response to ICPI therapies. Further evaluation of PD-L1 AMP as a potential means to identify patients with improved outcomes is warranted.

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Large-scale analyses of tumor mutation burdens (TMBs) across various advanced gastrointestinal (GI) malignancies in the nationwide cancer genome sequencing project (SCRUM-Japan GI SCREEN). Yoshiaki Nakamura, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Tumor mutation burdens (TMBs) in advanced gastrointestinal (GI) malignancies have not been well-characterized. We analyzed TMB in tissue samples from advanced GI malignancies using the Oncomine Cancer Research Panel (OCP), a targeted next-generation sequencing panel, as part of the Nationwide Cancer Genome Screening Project (SCRUM-Japan GI SCREEN). Methods: The performance of the OCP panel for TMB analysis was assessed using whole-exome sequencing (WES) data from 10,183 samples in the Cancer Genome Atlas (TCGA). Then, TMBs were calculated based on somatic non-synonymous mutations in the following 1,759 GI tumors: colorectal cancer (CRC, n = 751), gastric cancer (GC, n = 509), esophageal cancer (EC, n = 143), pancreatic cancer (PC, n = 136), biliary tract cancer (BTC, n = 92), small intestinal cancer (SIC, n = 30), gastrointestinal stromal tumor (GIST, n = 29), hepatocellular carcinoma (HCC, n = 27), neuroendocrine tumor/cancer (NET/NEC, n = 27), appendiceal cancer (AC, n = 12), and anal canal cancer (ACC, n = 3). High TMB was defined as more than 25 mutations per megabase (mtMb). CRC microsatellite instability (MSI) status was assessed using a PCR-based method. Results: TMBs estimated from the OCP-targeted region based on TCGA data were strongly correlated with those in 143).

Across cancers, alterations were independently associated with poor OS, with KRAS G12V, KRAS G13D, and KRAS alterations having the shortest survival. Most RAS-mutated tumors harbored co-altered genes. Therapy that included drugs matched to co-altered genes did not impact survival, suggesting that MAPK is an important resistance pathway even in the presence of other tractable genomic alterations. Clinical trial information: NCT02478931.

Conclusions: High FGFR1-mRNA is more common than FGFR1-AMP and was associated with worse OS. FGFR1-mRNA is a therapeutic target, and clinical trial information: NCT01935336.

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12098 Poster Session (Board #211), Mon, 1:15 PM-4:45 PM
Genetic variants within the glucocorticoids related genes to predict outcome in patients with metastatic colorectal cancer (mCRC). First Author: Alberto Puerto, MD, University of Washington, Seattle, WA. Second Author: Jared Vana, PhD, 2020 MD Anderson Cancer Center, Houston, TX.

Background: Glucocorticoids (GC) have important anti-inflammatory and pro-apoptotic activities. CRC cells produce immunoregulatory GC, a process regulated by nuclear receptor liver receptor homolog-1 (LRH-1). Additionally, LRH-1 plays a critical role in the control of cell cycle and tumorigenesis. Therefore, CRC cells have a strong stereogenic potential and tumor-derived GC may contribute to tumor immune evasion. Thus, we aim to evaluate whether variations in LRH1 and GC receptor (NR3C1) genes may predict outcome in mCRC patients treated with first-line FOLFIRI and bevacizumab.

Methods: Genomic DNA from whole blood samples was obtained from 378 mCRC patients who were treated with FOLFIRI/bev in the TRIBE (discovery cohort); N = 215, female/male 83/132, median age 60; median follow-up 48.9 months) and MAVERICC (validation cohort; N = 163, female/male 60/103; median age 62; median follow-up 23.3 months) trials, and subsequently genotyped through the OncoArray, a custom array manufactured by Illumina including approximately 530K SNP markers.

Results: In the discovery cohort, patients carrying NR3C1 rs10041520 A variant showed a longer OS compared to T/T genotype in univariate analysis (28.9 months vs 20.5 months; HR = 0.72; 95% CI = 0.51-0.93; P = 0.019). Patients carrying any C variant had a longer OS compared to T/T genotype in multivariate analysis (27.9 months vs 26.5 months; HR = 0.42; 95% CI = 0.21-0.84; P = 0.018). The same results were validated in the MAVERICC FOLFIRI/bev arm.

Conclusions: Variants within LRH1 and NR3C1 genes were associated with OS in mCRC patients treated with first-line FOLFIRI and bevacizumab.

12100 Poster Session (Board #212), Mon, 1:15 PM-4:45 PM
Phosphorylation of AKT kinase substrates to predict response to the AKT inhibitor MK2206 in the I-SPY 2 Trial in both HER2- and HER2+ patients. First Author: Julia Dell'Aringa, MD, City of Hope, Duarte, CA. Second Author: George Dermanis, MD, St. Jude Children’s Research Hospital, Memphis, TN.

Background: In the I-SPY 2 TRIAL, the allosteric AKT inhibitor MK2206 was available to all HR/HER2 subtypes and graduated in the HR-/HER2+ signature. Qualifying biomarker analysis was performed on 26 proteins/phosphoproteins in the HER-AKT-mTOR pathway to identify candidate proteins correlated with pCR in the HER2+ and HER2- populations treated with MK2206. We postulated that response to MK2206 could be predicted by the relative level of phosphorylation of AKT kinase substrates.

Methods: Of 151 patients in the MK2206 and control arms, 138 patients (MK2206: 87; controls: 51) had RPPA and pCR data. For 26 (phospho-) proteins involved in HER-AKT-mTOR signaling were assessed for association between biomarker and response in the MK2206 and control arms alone (likelihood ratio test), and relative performance between arms (biomarker x treatment interaction) using a logistic model. Analysis was also performed adjusting for HR/HER2 status. Markers were analyzed individually: p-values were descriptive and were not corrected for multiple comparisons.

Results: In the HER2+ cohort, phosphorylation of the AKT kinase substrates S448 (p = 0.0044), S473 (p = 0.0029), and S547 (p = 0.0036) were associated with response. For the HER2- cohort, phosphorylation of AKT T308 (p = 0.0083), Estrogen Receptor alpha (p = 0.012), AKT T552 (p = 0.013), GSK3 S9 (p = 0.016), and GSK3 S21 (p = 0.026) were associated with response. With MK2206 response, FOXO1 S253 (p = 0.031) and ERBB2 Y877 (p = 0.02) were both positively associated with response and had a significant interaction with treatment in this cohort.

Conclusions: There is too small a sample size to draw firm conclusions. In initial exploratory analyses, our results suggest that the measurement of AKT kinase substrate phosphoproteins could be predictive of MK2206 clinical activity in both HER2+ and HER2- tumors regardless of HR status. These results will need to be validated in independent study sets in order to judge the significance of these initial findings. Clinical trial information: NCT01042379.

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12102 Poster Session (Board #215), Mon, 1:15 PM-4:45 PM
Impact of tumor-infiltrating lymphocytes on response to neoadjuvant chemotherapy in triple-negative early breast cancer: Translational subproject of the WSG-ADAPT TN trial. First Author: Alexandra Liebtke, Charité - Universitätsmedizin Berlin, Berlin, Germany

Background: In triple-negative breast cancer (TNBC), pathological complete response (pCR, ypT0/is/ypNO) is associated with improved prognosis. The randomized prospective WSG-ADAPT TN phase II trial showed higher pCR with Nab-paclitaxel/Carboplatin (NPCI) compared to paclitaxel/gemcitabine (NPNG) as 12-week neoadjuvant therapy. Presence of tumor-infiltrating lymphocytes (TILs) is associated with increased pCR rates after neoadjuvant chemotherapy, but the role of TIL dynamics during specific chemotherapy regimens is still unknown. Methods: This pre-planned translational analysis focuses on semi-quantitative TIL measurements in ADAPT-TN among tumor samples at baseline (TIL-0) and after 3 weeks of chemotherapy (TIL-3). Associations of continuous TIL-0 and TIL-3 levels with pCR, with chemotherapy arm and with other clinical/pathological measurements were analyzed using logistic regression, rank correlations, t- and chi-square statistics. Results: 336 patients were enrolled. TIL-0 and TIL-3 were available among 311 (92.6%) and 223 (66.4%) patients, respectively. "Low cellularity" in 3-week biopsies (tumor necrosis, lack of invasive tumor cells) was recorded in 82 patients. TIL-0 and TIL-3 were strongly correlated (0.64, p < 0.001); average relative increase was about 30%. TIL-0 was significantly associated with baseline tumor grade, clinical tumor size, and nodal status. TIL-3 was significantly associated with nodal status and grade in both biopsies. In all patients, higher levels of both TIL-0 (p < 0.001) and TIL-3 (p = 0.003) were associated with pCR. Higher TIL-0 was also significantly associated with pCR in both arms separately. "Low cellularity" was also associated with pCR in all patients (OR = 3.9, 95%-CI: 2.3-6.8) and in both arms separately (NPNG: OR = 3.6, 95%-CI: 1.7 to 7.9; NPCI: OR = 4.2, 95%-CI: 1.9-9.3). Conclusions: In TNBC patients, higher levels of tumor-infiltrating lymphocytes were associated with pCR, both at baseline and after 3 weeks of neoadjuvant chemotherapy. "Low-cellularity" at week 3, which indicates extensive response to chemotherapy, was itself strongly associated with response to therapy.

12104 Poster Session (Board #217), Mon, 1:15 PM-4:45 PM
Single-cell profiling of NSCLC tumor treated with Durvalumab and in combination with Tremelimumab. First Author: Yashashwi Shrestha, MedImmune, Gaithersburg, MD

Background: Combination of anti-PD1/L1 and anti-CTLA4 is under investigation for treatment of multiple tumors. However, how this combination modifies the immune micro-environment of tumors is not well understood. Using single cell RNA sequencing (scRNAseq), we are systematically characterizing the ex vivo cellular and molecular effects of Durvalumab (D) and Tremelimumab (T) treatment on NSCLC tumors. Methods: Commercially available dissociated NSCLC tumor was treated with low dose interleukin-2 (IL-2) plus D, D+T or isotype control (IsoCtrl) at 20ug/ml each. For scRNAseq, T cells were isolated using cCD4 and cCD8 beads. Over 20,000 immune cells were profiled on D7 after treatment using 10X genomics. Exhausted T cells were defined based on the signature by Singer et al. (2016). Cell clustering and differential expression analyses were conducted using R package Seurat. Functional enrichment analyses, including KEGG and GO were performed by ClusterProfiler. Results: At D7 of D or D+T treatment, intracellular IFNG expression increased 60 and 80%, respectively. scRNAseq results were consistent with this functional data, showing 6% and 12% more IFNG expression in CD4+CD8+ T cells following D and D+T, respectively. Checkpoint inhibitor expression (PDCD1, CTLA4, TIGIT, LAG3, HAVCR2) increased 4-9% and 7-15% upon D or D+T treatment, respectively. D and D+T treatment increased fraction of total CD4+ cells from 21% to 27% and 28%, respectively; however, there was a reduction in the specific CD4A subtraction of Tregs (CD4+Foxp3+) in both treatments compared to IsoCtrl. D+T treatment shifted the molecular phenotype of exhausted T cells toward a more activated state by inducing a significant upregulation of PTPRCAP, ITGB1, and KLF2, genes important for T cell activation and/or reduced T reg function. Conclusions: Single-cell profiling of NSCLC tumor suggest that D+T treatment alters the molecular profile of exhausted T cells and Tregs to generate a more active phenotype, which may contribute to clinical benefit for patients treated with this combination.
12106 Poster Session (Board #219), Mon, 1:15 PM-4:45 PM
Circadian clock gene PER1 mutations in colorectal cancer (CRC). First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA

Background: PER1 encodes for one of the main negative regulator of the clock genes pathway, which modulates the circadian expression of key target genes at the cellular level. Downregulation of PER1 has been observed in CRC and lower expression levels have been associated with poor survival and increased incidence of liver metastases. Few data are available on PER1 gene mutations (PER1mut) in CRC. Therefore, we aimed to explore the clinical and molecular differences between PER1 mutated versus wild-type (WT) CRCs. Methods: 4079 CRCs tested with tumor profiling (Caris Life Sciences, Phoenix, AZ) were included in this analysis. NextGen sequencing (NGS) was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the NextSeq platform (Illumina, Inc., San Diego, CA) on 592 genes. Microsatellite instability high (MSI-H) status was estimated using Poly-Phen and SIFT. Results: Main characteristics in the global population were as follow: M/F 52:48.7%, median age 61 (16-90 yr), primary tumor right-sided 27.4% left-sided 43.5%/N0/S1 2.1%, mutational status all WT 38.7%/RASmut 53.4%/BRCAmut 7.9%, MSI-H 6.6% (n = 262). Overall, 185 unique PER1mut/variants were identified in 304 samples (7.45%); 45 were classified as pathologically/possibly pathological (PATHmut) according to predictive scores. PER1mut were significantly associated with right-sided tumor location (p < 0.001) and MSI-H (p < 0.001). Overall incidence of PER1mut and PATHmut in the MSI-H group were 24% and 3.4%, respectively. In the multivariate analyses PATHmut were independently associated with mutations in ARAF, BAP1, CHEK2, NFI, PIK3Ca and POLE. Conclusions: Our results provide the first exploratory data on PER1mut association with clinical and molecular features in CRC. A large proportion of patients with extensive testing. A deeper understanding of PER1mut pathogenicity and functional role is necessary to guide future analyses. Nevertheless, our results suggest a significant association with MSI-H, possibly reflecting an interplay between mismatch repair status and the clock genes pathway in CRC, consistent with previous data and warranting further investigation.

12107 Poster Session (Board #220), Mon, 1:15 PM-4:45 PM
Genetic variations in the β2M/HLA-E immunomodulatory complex to predict outcomes in metastatic colorectal cancer (mCRC) patients (pts) treated with first-line FOLFIRI/Bevacizumab. Data from the phase III FIRE-3 trial. First Author: Madhia Naseem, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA

Background: Cetuximab (cet) is an anti-EGFR mAb which enhances the antibody-dependent cellular cytotoxicity (ADCC) by Natural Killer (NK) cells in EGFR+ CRCs. Overexpression of MHC class I antigen E (HLAE), and its membrane stabilizer, β2-microglobulin (β2M) inhibit cet-induced ADCC. We hypothesize that single nucleotide polymorphisms (SNPs) in HLAE/β2M will influence cet-dependent NK cell lytic and clinical outcomes. Methods: Genome wide association studies were conducted on whole blood from 236 mCRC pts in the randomized phase III FIRE-3 trial treated with FOLFIRI/cet (n = 129) and FOLFIRI/bevacizumab (bev)(n = 107). The OncoArray database provided by Illumina containing 530K SNP markers from these pts was used to extract data on 4 functional SNPs from β2M and HLAE. Log-rank test and Cox proportional hazard regression models evaluated SNP associations with PFS/OS in uni- and multivariable analyses. Results: FOLFIRI/cet and FOLFIRI/bev cohort characteristics: median FU (27.2/26.7mo); DFS (11.8/11.5mo); OS (49.8/31.4mo); RAS WT/Δ4% (62% and 62%) and RAS mut (15%/16%). Multivariable analysis showed worse PFS in RAS WT pts treated with FOLFIRI/cet with HLAErs1059510 T/T alleles (12.2 vs 13.3 mo; HR = 2.59; 95%C1 = 1.05-6.39; p = 0.039) and HLAErs1264457 G/G alleles (12.3 vs 12.9 mo; HR = 2.36; 95%C1 = 1.14-4.88; p = 0.021). These variants were not observed in RAS mut pts. β2Mrs1910531 mut C allele carriers showed improved OS (67.4 vs 40.9 mo) independent of RAS status in FOLFIRI/cet arm in both univariate (HR = 0.27; 95%C1 = 0.12-0.59; p = 0.001) and multivariable analysis (HR = 0.19; 95%C1 = 0.07-0.48; p < 0.001). No significance was observed in FOLFIRI/bev overall or FOLFIRI/bev RAS WT pts. Conclusions: For the first time, we show that clinical outcomes in mCRC pts treated with FOLFIRI/cet are predicted by genetic variations in HLAE/β2M, which are not observed in FOLFIRI/bev. The predictive utility of HLAE is dependent on RAS status, whereas that of β2M is independent of RAS. The HLAE/β2M complex could be a promising therapeutic target for overcoming cet resistance. Validation in larger cohorts is required.

12108 Poster Session (Board #221), Mon, 1:15 PM-4:45 PM
Landscape of osimertinib resistant mutations between the two common subtypes of EGFR 19del or L858R in NSCLC. First Author: Yan Zhang, Geneplus-Beijing Institute, Changping District, Beijing, China

Background: Acquired EGFR mutations (C797, L792, G796) co-occurring with T790M were reported to lead the resistance to osimertinib. It was reported that for advanced NSCLC patients, exon 19 deletion (19del) might be associated with longer PFS compared to L858R mutation accepted only by WfG as level 1 and 74 variants identified only by OncoKB. Comparison of annotation services for the VA Precision Oncology Program. First Author: Evangelia (Eva) Katsoulakis, SUNY Downstate Medical Center, Bayside, NY

Background: Maligne NGS testing has become widespread, including through the VA healthcare system through the VA Precision Oncology Program (POP). Algorithms to interpret the pathogenicity of NGS-detected sequence variants and clinical actionability have been implemented as clinical services, but little is known about their relative performance in clinical practice. Methods: NGS testing results from patients who had NGS results from VA POP were included. NGS results were generated at Personal Genome Diagnostics and Personalized and annotated by a commercial annotation service (N-of-One) as well as through Watson for Genomics (WfG) and OncoKB. Comparison of annotation results consisted of two parts: determination of pathogenicity and treatment actionability recommendations. Cohen’s kappa statistic was calculated for agreement between annotation services. Results: Among 1228 NGS results, 1388 unique variants were observed in 117 genes (TP53 270, STK11 92, CDKN2A 81, ATM 67, PTEN 52). Cancer type was lung adenocarcinoma in 440 samples, colon adenocarcinoma in 346 samples, melanoma 57, H&N 41, NSCLC 40. For pathogenic and likely pathogenic variants, there was 87% agreement between WfG and N-of-One (kappa 0.729), 76% agreement between WfG and OncoKB (kappa 0.227) and 42% agreement between N-of-One and OncoKB (kappa -0.078). For level 1 drug actionability recommendations (not available from N-of-One) there was 91% agreement between WfG and OncoKB (kappa 0.19) with 54 variants identified only by WfG as level 1 and 74 variants identified only by OncoKB as level 1. Conclusions: There is substantial variability in assessment of pathogenicity of NGS variants in solid tumors by clinically available annotation services. In addition, there was only slight agreement in level 1 therapeutic actionability recommendations. Implementation of the oncology NGS annotation is needed.

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Identification of actionable genomic alterations utilizing cfDNA.

First Author: Nora Sylvia Sanchez, Sheik Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy/ University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cell-free DNA (cfDNA) next-generation sequencing has become a more accessible, non-invasive approach for genomic testing. We report alteration identification frequency and clinical actionability in patients with advanced/metastatic cancer. Methods: Enrollments criteria for prospectively consented patients: Active metastatic/local inoperable advanced cancer, completing clinic trial enrollment within next 2 lines of therapy, and either exhausted tissue block, archival tissue > 1 year, available tissue block but progressed on compelling interventional therapy. Patients had cfDNA testing on a CLIA-certified panel (Guardant360) for point mutations, indels, amplifications, fusions. Alterations were assessed and ranked for functional impact, therapeutic implications and patient's overall actionability profile was determined. Results: 295 patients with ≥ 6 months follow-up were evaluated. Major diseases represented (≥ 10 patients): hematopoietic (59), pancreatic (51), bile duct/cholangio(37), appendiceal(24), breast(20), sarcoma(18), lung(15), and colorectal(12). Majority of patients were male(167), Caucasian(222), median age 54.5 years. ECOG performance status (PS) upon enrollment (72), (185), (262), (32). 77.9% of patients (230/295) had ≥ 1 alteration detected; 56%(128/230) had an alteration in gene associated with FDA approved drug for specific biomarker/tumor type. Evaluation of variant functional significance in context of patient’s disease identified 30.5% (92/295) of alterations as high potential for clinical action. Of these, 124(41%) were matched to targeted therapy: clinical trial enrollment(4), off label drug use(1), standard of care (SOC)(2). Amongst unmatched patients, 37.5% (12/32) did not return to institution/lost to follow up, 31.4%(11) had poor PS after return of results, while the rest enrolled on another trial(2), continued existing therapy (2), or were lost to follow up (5). Conclusions: cfDNA testing represents a readily accessible method for genomic testing and allows for detection of genomic alterations in most patients with advanced disease. Utility may be higher in patients with interest in genetically selected therapy, adequate PS, and enhanced by earlier testing in treatment course.

Association of mucosal Fusobacterium with clinical stage and immune gene signature of rectal adenocarcinoma.

First Author: Michael Sangmin Lee, UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Alterations in gut microbial composition are associated with development and progression of colorectal cancer (CRC), and may contribute to interpatient biologic and clinical heterogeneity. Fusobacterium is enriched in CRC and is associated with a proinflammatory microenvironment. We hypothesized that Fusobacterium was associated with distinct clinicalopathologic characteristics and inflammatory gene signatures among patients with locally advanced rectal cancer. Methods: Patients with T3-4 or N+ rectal adenocarcinoma planned to receive neoadjuvant chemoradiation (n = 121) were enrolled prospectively to undergo pretreatment endoscopic biopsy. The V1-V2 region of the 165 bacterial ribosomal RNA gene was sequenced to identify tumor mucosal microbiota taxonomy. Tumor mRNA sequencing (RNASeq) was also completed and gene set enrichment analysis (GSEA) with curated immunologic signatures in MSigDB was performed. Multivariate analyses were conducted using PRIMER VII and SPSS v24 software. P-values were determined using Mann Whitney test, and Benjamini-Hochberg procedure was used and only results with false discovery rate < 0.25 are presented. Results: Of 43 total samples, 37 had adequate bacterial 165 RNA gene sequencing, and 31 also had adequate RNA quality for RNASeq analysis. Among the 37 patients, mean age at diagnosis was 54 (range 30-77) and pre-treatment clinical stage was II (30%) vs. III-IV (70%). Higher clinical stage (stage III-IV vs II) was associated with enrichment of Fusobacterium (16.2% vs 5.6%, p = 0.019) and Parvimonas (4.6% vs 1.4%, p = 0.033) genera. In the 9 subjects with alterations in key checkpoint molecules. Low expression of PD-L1-high patients, had relatively lower expression of TIM3-high patients, lacked expression of PD-L2-high patients (p < 0.05). The PD-L1-high category was especially enriched across a variety of tumor types, and employing combinations has enhanced predictive significance in context of patient’s disease identified 30.5% (92/295) of alterations as high potential for clinical action. Of these, 124(41%) were matched to targeted therapy: clinical trial enrollment(4), off label drug use(1), standard of care (SOC)(2). Amongst unmatched patients, 37.5% (12/32) did not return to institution/lost to follow up, 31.4%(11) had poor PS after return of results, while the rest enrolled on another trial(2), continued existing therapy (2), or were lost to follow up (5). Conclusions: cfDNA testing represents a readily accessible method for genomic testing and allows for detection of genomic alterations in most patients with advanced disease. Utility may be higher in patients with interest in genetically selected therapy, adequate PS, and enhanced by earlier testing in treatment course.

Pan-cancer mesenchymal assay to predict response to MEK inhibitors.

First Author: Nuala McCabe, Almac Diagnostics, CraigHAV, United Kingdom

Background: Unsupervised hierarchical clustering of gene expression data from 265 high grade serous ovarian cancer (HGSOC) patients identified 3 molecular subgroups. One subgroup showed substantial overlap with the MAPK-pathway and is associated with a mesenchymal phenotype, poor prognosis and resistance to platinum. The MAPK pathway is currently being targeted by novel therapeutics and hence an assay to detect activation of the pathway across cancers would be highly valuable as a clinical trial enrichment tool. Methods: Using TCGA data we show the existence of the mesenchymal subgroup across a range of solid tumours including stomach, bladder, colon, lung, melanoma and prostate cancer. Further to this, a common gene list was generated to include only transcripts with high variability and expression across diseases, and used as a starting list for the development of a 15 transcript assay which can be used to prospectively identify the mesenchymal subgroup from archived tissue. The 15 gene expression assay was tested in preclinical model systems to assess its utility at predicting response to MEK inhibitors. Results: The 15 gene expression mesenchymal assay was a poor prognostic marker in 13 different solid tumours: overall HR = 1.78 (95% CI 1.65-1.92) p = <0.0001. Additionally the assay was associated with a mesenchymal phenotype (migration, invasion) and activated MAPK (phospho-MAPK) signalling in preclinical cell line models. The assay also predicted phospho-MEK expression in clinical samples (p < 0.05). The assay score was reduced by MEK inhibition (p < 0.05) and elevated by KRAS, NRAS and MEK1(2) overexpression in vitro. The assay predicted response to the MEK inhibitors trametinib and selumetinib across cell line models from multiple diseases (p < 0.001) and to trametinib in mouse xenograft studies of lung cancer cell lines. Conclusions: A 15 gene expression assay has been developed from FFPE samples across multiple disease sites to detect a mesenchymal signature, an intermediate step for the development of a 15 transcript assay which can be used to prospectively identify MEK inhibitors in preclinical cell line and mouse model systems. Further work aims to validate the assay as a predictive biomarker in clinical samples from patients treated with MEK targeted therapies.

Co-expression patterns of immune checkpoint molecules in relation to PD-L1 expression.

First Author: Sumanta K. Pal, City of Hope, Duarte, CA

Background: Targeting immune checkpoints has led to clinical benefit across a variety of tumor types, and employing combinations has enhanced response rates even further. We hypothesize that profiling the tumor and associated microenvironment can help tailor rational combinations of immunotherapeutic strategies. Methods: Whole transcriptomic sequencing (RNA-Seq; ~200x10^6 reads per tumor) of 1,880 unselected clinical cases across a variety of tumor types were performed (NanoHealth; Culver City, CA). Cases reflected 38 distinct histologies including but not limited to breast (17.8%), colon (9.5%), lung (7.9%), pancreatic (6.5%), ovarian (5.4%), brain (4.9%) and prostate cancer (2.7%). Cases were categorized as PD-L1-low, PD-L1-normal and PD-L1-high by cutoffs defined in TCGA expression profiles. Expression and co-expression of 6 checkpoint markers (PD-L1, PD-L2, CTLA4, IDO1, LAG3 and TIM3) were analyzed for tissue-specific enrichment and within PD-L1-defined categories. Immune-cell infiltration was estimated using RNA deconvolution based on known immune cell marker genes (Bindea et al 2013). Results: Checkpoint expression did not cluster in a tissue-dependent manner. PD-L1 shows no significant co-expression pattern with any of the analyzed checkpoint markers aside from its ortholog PD-L2 (R = 0.77; P = 1.9x10^-285). Within the PD-L1-low category, IDO1 and TIM3 had relatively high expression and were highly correlated with each other (R = 0.81; P = 4.6x10^-11). The PD-L1-low category was especially deprived of memory T cells and eosinophils. Within the PD-L1-high category, overall expression of all checkpoint markers was higher. Amongst PD-L1 high patients, CTLA4 expression was highly variable (mean 2.5±1.1; log2[TPM+1]) and lacked correlation with PD-L1 (R = 0.09). In contrast, while LAG3 also had variable expression in the PD-L1-high setting, it was strongly correlated with CTLA4 (R = 0.79; P = 7.4x10^-13). The PD-L1-high category was especially enriched for Th1, NK CD56bright and CD8 T-cells. Conclusions: High and low PD-L1 expression in the tumor and adjacent microenvironment are associated with variations in key checkpoint molecules. Low expression of PD-L1 may be an ideal setting for use of IDO- or TIM3-directed therapies.
Genomic landscape of diverse rare tumors: Next-generation sequencing of paired DNA and RNA analysis. First Author: Ryosuke Okamura, Moores UCSD Cancer Center, La Jolla, CA

**Background:** Patients (pts) with rare tumors (defined as incidence of <15/100,000 per year) and ultra-rare tumors (prevalence <2,000 in the U.S.) may lack standard or investigational therapeutic options. We have recently shown that matched targeted therapy approach based on the molecular profiling may result in responses in these cancers. Herein, we interrogated paired DNA/RNA among rare tumors using next-generation sequencing (NGS). **Methods:** A total of 286 pts with a rare tumor diagnoses were available for this analysis from NantHealth database. Somatic-specific variants were identified using paired tumor/normal comprehensive NGS. Analysis was focused on the 200 most frequently mutated genes in this cohort. Deep whole transcripomic sequencing (RNA-Seq) (~200x106 reads per tumor) was used to determine expression of observed somatic variants. **Results:** Median age was 57.8 (range 0.60 – 87.7 y), 48.6% (139/286) were women. The most common diagnoses were bone and soft tissue sarcomas (39.5%, N = 113) followed by oral and throat cancers (9.4%, N = 27) and cholangiocarcinoma (7.3%, N = 21). Ultra-rare tumors such as carcinoma of the thymus (N = 10), adrenal (N = 5) and ampuulla of Vater (N = 1) were included. All 286 pts had at least one alteration (including characterized alterations and variant of unknown significance). 79.0% (226/286) had ≥1 characterized alteration, with median number of alteration = 1 (range: 0-42). Among pts with characterized alterations, 74.3% (168/226) had ≥1 potentially actionable target (median: 1, range: 0-12) (with FDA-approved [on- or off-label] or investigational drug). Paired DNA/RNA sequencing revealed 44.1% (126/286) of pts had ≥1 DNA alteration that was not seen at the RNA level. **Conclusions:** Most pts with rare and ultra-rare cancers had theoretically tractable alteration. Interestingly, not all the DNA alterations were seen in RNA level, indicating potential silencing at the RNA level.

Tumor Biology 627s

Detection of germline homologous recombination deficiency (HRD) in patients with metastatic esophagogastric (EG) cancer using clinical next generation sequencing (NGS). First Author: Yelena Yuriy Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** Although EG cancer is included in Lynch syndrome (LS) and hereditary diffuse gastric cancer (HDGC), the prevalence of HRD-associated germline mutations in patients with EG cancer remains to be elucidated. To determine the potential therapeutic implications, we assessed the prevalence of clinically actionable germline mutations detected by matched tumor-normal sequencing. **Methods:** The matched tumor-normal DNA were evaluated for somatic (up to 468 genes) and germline (76 genes) alterations under MSK IRB approved protocols. Prevalence of likely pathogenic and pathogenic germline alterations were reported in genes and correlated with clinical and somatic findings. **Results:** Of 400 consecutive pts with metastatic EG adenocarcinoma: 53% had esophagus/GEJ and 47% gastric cancer. 48 (12%) of patients had clinically actionable mutations conferring cancer susceptibility, including 38 moderate- to high- penetrance cancer syndromes. 30 of 400 pts (7.5%) had deleterious somatic (n = 17) or pathogenic germline (n = 19) mutations in the most commonly observed HRD genes (ATM, BRCA1, BRCA2). The prevalence of clinically actionable germline mutations among gastric versus esophagus/GEJ tumors was 15.5% and 8.9%, respectively (p = 0.043). Interestingly, one individual harbored both a BRCA1 and an ATM mutation. Germline DNA mismatch repair mutations, diagnostic of LS, were present in only two pts, both with gastric cancer. MSH2 mutations, with both tumors exhibiting a mismatch repair deficient signature. Other germline mutations of interest include: 6 CDH1, 1 TP53, 1 BRIP1, 1 STK11 pts as well as 1 biallelic MUTYH carrier diagnostic of MUTYH-associated polyposis. When available, correlutive tumor data, including somatic mutations and loss of heterozygosity in the gene(s) corresponding to the germline mutation will be presented. **Conclusions:** Clinical NGS in paired germline-tumor DNA samples increases detection of individuals with potentially clinically significant germline/somatic mutations. Analysis of therapeutic implications of these HRD mutations is ongoing and updated data will be presented.

Three-fold overestimation of tumor mutation burden using 248 gene panel versus whole exome. First Author: Andrew Nguyen, NanOmic, LLC, Santa Cruz, CA

**Background:** Next generation sequencing (NGS) Gene panel testing is used to imputed tumor mutational burden (ITMB) and has shown rough correlation with TMB derived from whole exome sequencing (WES). TMB is used to estimate immune checkpoint inhibitor (ICT) response based on potential neoantigen load. We hypothesized that actual TMB (aTMB), consisting of expressed genes, would differ substantially from iTMB. Of 400 consecutive pts with metastatic EG adenocarcinoma: 53% had esophagus/GEJ and 47% gastric cancer. 48 (12%) of patients had clinically actionable mutations conferring cancer susceptibility, including 38 moderate- to high- penetrance cancer syndromes. 30 of 400 pts (7.5%) had deleterious somatic (n = 17) or pathogenic germline (n = 19) mutations in the most commonly observed HRD genes (ATM, BRCA1, BRCA2). The prevalence of clinically actionable germline mutations among gastric versus esophagus/GEJ tumors was 15.5% and 8.9%, respectively (p = 0.043). Interestingly, one individual harbored both a BRCA1 and an ATM mutation. Germline DNA mismatch repair mutations, diagnostic of LS, were present in only two pts, both with gastric cancer. MSH2 mutations, with both tumors exhibiting a mismatch repair deficient signature. Other germline mutations of interest include: 6 CDH1, 1 TP53, 1 BRIP1, 1 STK11 pts as well as 1 biallelic MUTYH carrier diagnostic of MUTYH-associated polyposis. When available, correlutive tumor data, including somatic mutations and loss of heterozygosity in the gene(s) corresponding to the germline mutation will be presented. **Conclusions:** Clinical NGS in paired germline-tumor DNA samples increases detection of individuals with potentially clinically significant germline/somatic mutations. Analysis of therapeutic implications of these HRD mutations is ongoing and updated data will be presented.

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Seventeen percent of NGS 50 gene panel variants are not expressed in RNAseq. A total of 225,727 SNVs were detected in the 992 samples. 669 samples had at least 1 SNV in the 50 gene panel set for a total of 1661 SNVs, which were not expressed in the RNAseq (82.8%). Across 37 tumor types the range of expression was 52% (melanoma-1) to 6% (ototitane). All cases with high degree of TILs showed high expression of CD8 and PD-L1 in the tumor. High TILs is to be better prognostic factor, expressed variant status for SNVs of the following type: synonymous, silent, missense, nonsense. Expressed variants are based on whether at least 2 alternate reads in the RNA are present at that variant site. A 50 gene panel (AmpliSeq HotSpot V2) was used as the reference comparison: ABLI, EGFR, GNAS, KRAS, PTPN11, AKT1, ERBB2, GNAQ, MET, RIT, ALK, ERBB4, HNF1A, MLH1, RET, APC, EZH2, HRAS, MPL, SMAD4, FBXW7, IDH1, NOTCH1, SMARCBI, BRAF, FGFR1, JAK2, NPM1, SMO, CDH1, FGFR3, KRAS, Nras, SRC, CDKN2A, CDK4, IDH2, PDGFRB, STK11, CSF1R, FLT3, KDR, PIK3CA, TP53, CTNNB1, GNA11, KIT, Pten, VHL.

Results: In this retrospective analysis using a 50 gene commonly used hotspot panel as a hypothetical reference comparison, 17% of detected variants were not expressed in the RNAseq. The lack of RNA expression may contribute to less than expected clinical benefit with molecularly targeted therapies. Since the distribution is non-uniform, identification of these genes can yield improved testing algorithms and treatment strategies.

Survival outcome of breast cancer (BC) patients presenting with recurrent and de novo isolated contralateral lymph node metastases (CLNM). Methods: We identified metastatic BC patients treated at MD Anderson Cancer Center between 2000-2015. 235 patients had isolated recurrent CLNM (supraclavicular, infraclavicular and/or axillary) and 7617 patients had metastases other than CLNM. Overall survival (OS) and breast cancer-specific survival (BCSS) were calculated from date of diagnosis to the date of death with metastases other than CLNM. We divided the cases into two groups based on the value of SUVmax, low and high. The analysis revealed that large tumor size (p = 0.004), high nuclear grade (p = 0.019), high degree of TILs (p = 0.004) and positive expression of PD-L1 (p = 0.003) were significantly associated with high SUVmax in the primary tumor. There was no significant association between SUVmax and degree of TILs, and between SUVmax and positive expression of PD-L1 (r = 0.428, p < 0.001 and r = 0.413, p < 0.001, respectively). All cases with high degree of TILs showed high expression of CD8. Conclusions: The present study demonstrated that the finding of positive PD-L1 expression of FDG uptake in BC may be reflective of the grades of TILs and expression of PD-L1 in the tumor. High TILs is to be better prognostic factor, however, high expression of PD-L1 is to be a poor prognostic factor. In light of our results, FDG uptake may be predictive of immunological features in addition to aggressive features among patients with BC.

Results: Early mortality with immune checkpoint inhibitors (ICIs) in solid tumors: An inconvenient truth? First Author: Eric Winquist, Western University and London Health Sciences Centre, London, ON, Canada

Background: Overall survival (OS) benefit with ICIs has been demonstrated in several solid tumor types leading to their rapid adoption and use in practice. We noticed IO randomized controlled trials (RCTs) with early crossover of OS Kaplan-Meier (KM) curves favoring control therapy but with overall benefit favoring IO therapy. This suggests a subpopulation of patients at a higher risk of death on IO therapy compared to control therapy early in treatment. We performed a systematic review to examine the frequency and characteristics of IO RCTs showing this negative discordant crossover (NDC).

Methods: RCTs studying IOs and non-IOs in solid tumors with published OS KM curves were identified by electronic database search and FDA approvals 2015-17. Early OS divergence was identified by blinded reviewers. NDC of OS KM curves was defined as early divergence discordant with an overall beneficial survival trend.

Conclusions: Early NDC is a rare event but with overall survival benefit favoring IO therapy. RCT characteristics were compared using Fisher’s exact test. Results: 29 IO RCTs providing 33 comparisons and 24 non-IO RCTs providing 25 comparisons were identified. Nine IO RCTs (27%) and 1 non-IO RCT (4%) demonstrated NDC (p < 0.03). NCC involved in NSCLC (3/9), urothelial cancer (2/2), melanoma (2/9), SCLC (1/2) and CRC (1/2) RCTs. RCTs with NDC tended to less often study melanoma (22% v 4%) and squamous cancer (0% v 13%), and less often report OS benefit (22% v 71%). They tended to more often study urothelial cancer (22% v 0%) and 2nd-line treatment (56% v 38%), and more often have active treatment control arms (89% v 75%).

Conclusions: Early NDC of overall survival curves occurs commonly in IO RCTs. This suggests a subpopulation of patients at higher risk of early death with IO therapy. Causes of this mortality are unclear but could include toxicity of IO therapy, superior antitumor effects of control therapy, and/or tumor growth promoting effects of IO therapy. We are quantitating this risk. Such crossover complicates proportional hazards modeling. Further research to identify the causes of and patients at risk for early mortality with IO therapy should be a priority and patients should be informed of this potential risk.
12122 Poster Session (Board #235), Mon, 1:15 PM-4:45 PM
Acquired BRAF fusions as a mechanism of resistance to EGFR therapy. First Author: Morana Vojnic, Memorial Sloan Kettering Cancer Center, New York, NY

Background: While multiple genetic mechanisms have been identified in EGFR mutant lung cancers as mediators of acquired resistance (AR) to EGFR tyrosine kinase inhibitors (TKI), either first generation (EGFR T790M), or third generation (EGFR C797S), or both (gains of MET or ERBB2), many cases lack a known mechanism of AR. Methods: To identify novel mecha- nisms of AR, we performed targeted large panel sequencing (MSK- IMPACT assay; PMID: 28336552) on 374 consecutive patients with metastatic EGFR mutant lung cancer, including 200 tested prior to EGFR TKI, 136 tested after progression on EGFR TKI, and 38 patients with both types of samples. Genetic alterations hypothesized to confer AR were in- troduced into drug-sensitive EGFR-mutant lung cancer cell lines (H1975, HCC827, PC9) using CRISPR-Cas9 genome editing. We also generated a cell line from a biopsy of a patient with AR (MSK-LX138cl). A kinase-focused inhibitor library was used to screen for agents that would overcome AR.

Results: We identified 4 patients with a BRAF fusion (3 AGK/BRAF, 1 PJA2/ BRAF) in a sample obtained at AR to EGFR TKI (2 post-erlotinib; 2 post- erlotinib and post-osimertinib). A pre-TKI sample was available in one of these 4 patients and was negative for BRAF fusion. In the 200 patients only studied pre-EGFR TKI, no BRAF fusions were identified, further supporting the acquired nature of the BRAF fusion. Induction of AGK/BRAF formation in H1975 (L858R+T790M), PC9 (ex19del) and HCC827 (ex19del) cells by genotoxic stimulation increased phosphorylation of BRAF, MEK1/2, ERK1/2, STAT3, and conferred resistance to growth inhibition by osimertinib. A patient-derived cell line, MSK-LX138cl, with ex19del and the PJA2/BRAF fusion, was confirmed to be resistant to EGFR TKIs and then used to screen a library of 61 drugs targeting the MAPK pathway in the absence or presence of osimertinib. We identified the AGK/BRAF cells as a synergistic manner with osimertinib. Conclusions: Our findings identify acquired BRAF fusion as a recurrent mechanism of AR to EGFR TKIs including osimertinib and suggest combined MEK and EGFR inhibition as a possible therapeutic strategy.

12123 Poster Session (Board #236), Mon, 1:15 PM-4:45 PM
A comprehensive genomic analysis of squamous cell carcinomas of the lung, esophagus, and head and neck. First Author: Lara Ann Kujtan, University of Missouri at Kansas City, MO, USA

Background: Squamous cell carcinomas (SCC) of the lung, esophagus and head and neck (H&N) are indistinguishable by histology. Data from large-scale genomic studies have identified significant similarities in the muta- tional profiles of these tumors. Combined genomic analysis will lead to the discovery of unique molecular similarities and dissimilarities of these tu- mors. Methods: We analyzed whole exome, RNA, miRNA and methylation data of 1221 patients with lung (39.6%), esophagus (26.3%), and HPV- negative H&N SCC (34.1%) from the Cancer Genome Atlas (TCGA) and In- ternational Cancer Genome Consortium (ICGC). WTSI Mutational Signature Framework was used to develop mutational signatures (MS).

Results: Nine novel significantly mutated genes were identified in the combined analysis, including PPIH1, a key mediator in the inflammasome pathway. Mutations in the inflammasome pathway (PPIH1, MND1, CIITA, AIM2, IFIT, IFNG), which is key for tumor antigen processing and presentation to T cells, were identified in 136 SCC samples (11.1%). All mutations were mutually exclusive of one another. We also discovered a novel tumor suppressor gene mutation in Asian patients with esophageal SCC, NEFH (1%), which was mutually exclusive of the TP53 mutation. Seven novel gene amplifications and two deletions were detected in the combined population. Two novel MS with high stability (0.83 and 0.85) were recognized in H&N (7% and 13% of all mutations) with maximum cosine similarities of 0.37 and 0.34 respectively. All TCGA samples displayed COSMIC MS 13 (APOBEC), 14 (tobacco-related), while the esophageal ICGC sample showed COSMIC MS 13 (APOBEC) and 17 (unknown). Conclusions: Our analysis identified a novel tumor suppressor mutation in Asians with esophageal SCC. We report possible dysregulation of the tumor antigen-processing pathway in a small but significant proportion of patients. Two novel MS shared (30%) in SCC were identified, and the remaining MS were similar across all three tumor types in the TCGA. Esophageal ICGC tumors had different mutational profiles suggesting a unique mutational process in Asians.

12124 Poster Session (Board #237), Mon, 1:15 PM-4:45 PM
Molecular comparison of interval and screen-detected breast cancers. First Author: Dane Anthony Cheasley, Peter MacCallum Cancer Centre, North Melbourne, Australia

Background: Breast cancer diagnosed after a negative mammogram but prior to the next screening episode are termed an “interval breast cancer” (IBC) and account for ~20% of breast cancer diagnoses in women attending population-based screening programs. IBCs are a major issue limiting the effectiveness of mammographic screening particularly as IBCs are generally diagnosed at later stages and have a worse prognosis in compared to screen detected breast cancer (SDBC). To understand if IBC is biologically distinct from SDBC we assessed the frequency of germline and acquired somatic genomic aberrations in a prospective cohort is 1060 screen detected and interval breast cancers. Methods: Using the Lifepool cohort, an Australian prospective population-based cohort of over 54,000 women, 1001 cases of breast cancer (SDC) and 1212 breast cancer (SDC). To understand if IBC is biologically distinct from SDBC we assessed the frequency of germline and acquired somatic genomic aberrations in a prospective cohort is 1060 screen detected and interval breast cancers. To identify novel mecha- nisms of AR, we performed targeted large panel sequencing (MSK- IMPACT assay; PMID: 28336552) on 374 consecutive patients with metastatic EGFR mutant lung cancer, including 200 tested prior to EGFR TKI, 136 tested after progression on EGFR TKI, and 38 patients with both types of samples. Genetic alterations hypothesized to confer AR were in- troduced into drug-sensitive EGFR-mutant lung cancer cell lines (H1975, HCC827, PC9) using CRISPR-Cas9 genome editing. We also generated a cell line from a biopsy of a patient with AR (MSK-LX138cl). A kinase-focused inhibitor library was used to screen for agents that would overcome AR. Results: We identified 4 patients with a BRAF fusion (3 AGK/BRAF, 1 PJA2/ BRAF) in a sample obtained at AR to EGFR TKI (2 post-erlotinib; 2 post- erlotinib and post-osimertinib). A pre-TKI sample was available in one of these 4 patients and was negative for BRAF fusion. In the 200 patients only studied pre-EGFR TKI, no BRAF fusions were identified, further supporting the acquired nature of the BRAF fusion. Induction of AGK/BRAF formation in H1975 (L858R+T790M), PC9 (ex19del) and HCC827 (ex19del) cells by genotoxic stimulation increased phosphorylation of BRAF, MEK1/2, ERK1/2, STAT3, and conferred resistance to growth inhibition by osimertinib. A patient-derived cell line, MSK-LX138cl, with ex19del and the PJA2/BRAF fusion, was confirmed to be resistant to EGFR TKIs and then used to screen a library of 61 drugs targeting the MAPK pathway in the absence or presence of osimertinib. We identified the AGK/BRAF cells as a synergistic manner with osimertinib. Conclusions: Our findings identify acquired BRAF fusion as a recurrent mechanism of AR to EGFR TKIs including osimertinib and suggest combined MEK and EGFR inhibition as a possible therapeutic strategy.

12125 Poster Session (Board #238), Mon, 1:15 PM-4:45 PM
Are racial differences in obesity and insulin resistance related to aggressive breast cancer? First Author: Emily Gallagher, Division of Endocrinology, Diabetes and Bone Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Black women are more likely to die of breast cancer and develop more aggressive subtypes than white women. Black women are also more likely to be obese and have insulin resistance than white women. Insulin resistance has been associated with faster tumor growth but has not been studied as a potential mediator of racial disparities in women with breast cancer. We hypothesized that black women would present with more aggressive breast cancer and this would be associated with obesity and insulin resistance. Methods: We recruited 810 (83% white, 17% black) women with new primary breast cancer, measured fasting blood glucose and insulin, body mass index (BMI), triple negative breast cancer (TNBC) & Nottingham prognostic index (NPI). We classified aggressive breast cancer as NPI > 4.4. We calculated insulin resistance scores (HOMA) and classified insulin resistance as HOMA > 2.8. Patients self-identified race. Immuno- histochemistry (IHC) of insulin receptors (IR) was performed on a subset of tumor specimens (N = 181). Results: Of 810 women, average age was 58 years (sd = 12.2), 293 (37%) were stage 2+ at time of diagnosis; 18% had an NPI > 4.4. Black women presented with higher stage of cancer than white women (stage 2+: 48% vs 35%; p = 0.004), were more insulin resis- tant (18% vs 11%, p = 0.03), had higher BMI (31.1kg/m² vs 26.7 kg/m²; p < .0001), and NPI scores (4.0 vs 3.6; p < .05). Black women had more TNBC than white women (17% vs 6%, p = 0.0001). HOMA score was not associated with NPI score (r = 0.06; p = 0.12). IR expression was inter- mediate or highly expressed in 79% of cancers in black women & 51% in white women (p = 0.004) but was not significantly related to NPI > 4.4 (66% vs 54%; p = 0.2). Conclusions: In women with newly diagnosed breast cancer, black women are more likely to be obese, have higher HOMA & NPI scores than white women. While these data are consistent with the hy- pothesized relationship of hyperinsulinemia promoting more aggressive breast cancer, to date, insulin resistance does not appear to mediate the effect of race and poor prognostic breast cancer.

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A phase 1/2 dose-escalation and expansion study of a conditionally active anti-AXL humanized monoclonal antibody (BA3011) in patients with advanced solid tumors.

First Author: Jordi Rodon Ahnert, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The AXL receptor tyrosine kinase is often highly expressed in certain cancers. AXL appears to sustain resistance to anticancer therapies including chemotherapy, targeted therapy and immune checkpoint inhibitors. BA3011 is an anti-AXL humanized monoclonal antibody conjugated to monomethyl auristatin E using a cleavable linker (CAB-AXL-ADC) and specifically binds to AXL under conditions found within the tumor microenvironment. The pharmacokinetic (PK) and toxicity profile of BA3011 has been established in cynomolgus monkeys; anti-tumor activity has been shown in non-small-cell lung cancer (NSCLC), pancreatic, castration-resistant prostate cancer (CRPC) and other tumor models.

Methods: A multi-center, open-label, Phase 1/2 study will evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of BA3011 in patients with advanced solid tumors. The study consists of a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2). The primary objective of Phase 1 is to define the safety profile (including dose-limiting toxicity [DLT]), maximum tolerated dose, and recommended Phase 2 dose (RP2D). BA3011 will be administered every 3 weeks (q3w) via intravenous infusion, with a starting dose of 0.3 mg/kg, escalating to 2.4 mg/kg using a modified Fibonacci method, until DLT occurs. In Phase 2, patients will receive the RP2D. Treatment will continue q3w until disease progression or unacceptable toxicity; safety and efficacy will be evaluated in specific tumor types (NSCLC, CRPC, and pancreatic ductal adenocarcinoma). Approximately 120 patients will be enrolled (11-30 in Phase 1 and approximately 90 in Phase 2). Patients must have histologically or cytologically confirmed locally advanced, unresectable or metastatic solid tumors and have failed available standard-of-care therapy and for whom no curative therapy is available. Follow-up information will be collected approximately every 3 months after the last dose until disease progression for patients with stable disease or better at the end of treatment. Clinical trial information: NCT03425279.

Canadian profiling and targeted agent utilization trial (CAPTUR/PM.1): A phase II basket precision medicine trial.

First Author: Tanya Skamene, McGill University, Montreal, QC, Canada

Background: Genomic profiling of cancers is increasingly used to refine prognostication and aid in treatment decisions by allowing matching of targeted agents to specific genetic variants. Clinical reports to date suggest that 30-80% of advanced solid tumors harbor potentially actionable genomic variants but difficulties in obtaining matched targeted agents in clinical practice limits the application of precision medicine. CAPTUR is a pan-Canadian trial leveraging existing clinical genomic profiling platforms and the research capabilities of the Canadian Cancer Trials Group (CCTG) to evaluate targeted drug-genetic variant matches in patients with advanced cancers. CAPTUR was developed in collaboration, and plans to share data, with ASCO’s TAPUR and the Netherlands’ DRUP trials.

Methods: CAPTUR/PM.1 (NCT03297606) is a multi-centre, open-label, phase II basket trial, matching Canadian patients who have undergone genomic profiling with genetic variants to appropriate targeted agents. Drug matches are drawn from a list of 17 commercially available anticancer agents. Patients must have incurable metastatic solid tumours, multiple myeloma, or B cell non-Hodgkin lymphoma, must have no standard treatment options known to prolong life and must have an actionable genomic variant known to be a target of, or predict sensitivity to, the commercially available targeted anticancer drug. Patients who possess an actionable tumour genetic variant and meet non-drug specific study requirements are entered into the study. A drug-variant match is assigned based on protocol specified matching criteria or input of the Molecular Tumour Board. Determination of the best treatment is then made by physician and patient based on drug-specific eligibility requirements. Cohorts are defined by tumour type, genomic alteration and matched drug treatment. The primary endpoint is response rate, as determined by disease-appropriate objective criteria. Maximum sample size per cohort is 24 patients based on a Simon 2-stage admissible design. Maximum planned number of cohorts is 30 (maximum sample size for the trial of 720 patients). CAPTUR was activated November 2017 and is open to enrolment. Clinical trial information: NCT03297606.
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