2500 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase I study of pembrolizumab in people with HIV and cancer.

Thomas S. Uldrick, Priscila Hermont Goncalves, Mohammad Maher Abdul Hay, Alisa J Claeys, Brinda Emu, Marc S. Ernstoff, Lawrence Fong, Judith C Kaiser, Holbrook Edwin Kohrt, Andreanne Lacroix, Steve Young Lee, Lisa Lundgren, Kathryn Anne Lurain, Christopher Parsons, Sharavi Peeramsetti, Ramya Ramaswami, Elad Sharon, Chia-Ching Jackie Wang, Robert Yarchoan, Martin A. Cheever; HIV/AIDS Malignancy Branch, CCR, NCI, Bethesda, MD; New York University Medical Center, New York, NY; Fred Hutchinson Cancer Research Center, Seattle, WA; Yale University, New Haven, CT; Cleveland Clinic, Cleveland, OH; University of California San Francisco, San Francisco, CA; Center for Clinical Sciences Research Stanford, Stanford, CA; NYU Langone Medical Center, New York, NY; NCI/NIH, Bethesda, MD; Pardee Center for Infectious Disease, Hendersonville, NC; Axio Research, Seattle, WA; Division of Experimental Medicine, Imperial College London, Hammersmith Hospital, London, United Kingdom; National Cancer Institute, Bethesda, MD; Univ of California At San Francisco, San Francisco, CA

Background: People with HIV have been excluded from immuno-oncology (IO) studies. Anti- PD-1/PD-L1 therapies are approved for a growing number of cancers. We evaluated pembrolizumab (pembro) in people with HIV and cancer. **Methods:** CITN-12 is a multicenter phase 1 trial. Key eligibility: advanced cancer; ECOG $\leq$1; CD4 $\geq$100 cells/μL; $\geq$4 weeks antiretroviral therapy (ART), HIV viral load (VL) $<$ 200 copies/mL. Exclusion: uncontrolled HBV/HCV, autoimmune disease. Participants (pts) accrued into CD4 based cohorts (C): C1 100-199; C2 200-350; C3 $>$ 350 CD4 cells/μL. Pembro 200 mg IV administered Q3W for up to 35 doses. Adverse events (AE) evaluated by CTCAE. Immune related AE $\geq$ grade (Gr) 2 were events of clinical interest (irECI). Clinical benefit (tumor shrinkage or stable disease [SD] $\geq$24 weeks) was estimated. Data were locked for safety analysis and publication once C2 and C3 completed accrual and all pts completed $\geq$2 cycles. Accrual continued for 6 C1 pts and a new phase 1b Kaposi sarcoma (KS) cohort (C4). **Results:** 30 pts, characteristics: C1 (6), C2 and 3 (12 each), median (med) age 57 years (range 39-77), 28 men, 2 women, 60% White, 30% Black, 10% Hispanic. Med CD4 285 cells/μL (132 - 966). Cancers: KS (6), non-Hodgkin lymphoma (NHL) (5), non-AIDS defining (19) – most common: anal (6) and squamous cell skin (3). Prior radiation (19), med prior systemic therapies 2 (0-8). Safety observed over 183 cycles, med 5 (1-32). Treatment emergent AE $\geq$ possibly attributed to pembro mostly Gr 1-2, with 20% of pts having Gr 3. irECI: hypothyroidism (6), elevated AST/ALT (1), pneumonitis (3), rash (2), musculoskeletal (1).1 KS pt developed KSHV-associated multicentric Castleman disease (KSHV-MCD) and died of the AE. HIV was controlled and increasing CD4 counts were observed. Best response: complete (lung, 1), partial (NHL, 2), SD $\geq$24 weeks (KS, 2), SD $<$ 24 weeks (13), progressive disease (10), not evaluable (2). **Conclusions:** Pembro has acceptable safety in cancer pts with HIV on ART and $>$ 100 CD4 cells/μL, similar to patients without HIV. Anti-PD-1 may unmask KSHV-MCD and such KSHV-viremic patients should be excluded. Clinical benefit was noted in several tumor types. Anti-PD1 is appropriate for FDA-approved indications in this population. Patients with HIV meeting appropriate eligibility criteria should be included in IO studies. Clinical trial information: NCT02595866.

Phase II study of durvalumab (MEDI4736) in cancer patients HIV-1-infected.

María González-Cao, Teresa Moran, Judith Dalmau, Javier Garcia-Corbacho, Reyes Bernabé, Oscar Juan, Javier De Castro, Remei Blanco, Andreas Meyerhans, Julia Blanco, Niki Karachaliou, Christian Brander, Julia Garcia-Prado, Jorge Carrillo, Mariano Provencio, Miguel Angel Molina Vila, Bartomeu Massuti, Bonaventura Clotet, Javier Martinez-Picado, Rafael Rosell, Spanish Lung Cancer Group (SLCG); Instituto Oncológico Dr. Rosell, Barcelona, Spain; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain; AIDS Research Institute, IrsiCaixa, Badalona, Spain; Hospital Clinic i Provincial de Barcelona/IDIBAPS, Barcelona, Spain; Hospital Valme, Seville, Spain; Hospital Universitari i Politécnic La Fe, Valencia, Spain; Translational Oncology Unit at Medical Oncology Division, Hospital Universitario La Paz, IdipAZ, Madrid, Spain; Hospital Mutua Terrassa, Barcelona, Spain; Infection Biology Laboratory, University Pompeu Fabra, Barcelona, Spain; AIDS Research Institute, IrsiCaixa, Badalona, Spain, Barcelona, Spain; Translational Cancer Research Unit, Instituto Oncológico Dr Rosell, Dexeus University Hospital, Barcelona, Spain; Medical Oncology Service. Hospital Universitario Puerta de Hierro, Madrid, Spain, Madrid, Spain; Pangaea Oncology, Barcelona, Spain; Alicante University Hospital ISABIAL, Alicante, Spain; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain and Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain and Institute of Oncology Rosell (IOR), University Hospital Sagrat Cor, Badalona, Barcelona, Spain

Background: Durvalumab (MEDI4736), a programmed cell death-ligand 1 (PD-L1) blocking antibody, is currently approved for treatment of several cancer types. As HIV-1-infected (HIV+) patients have been excluded from cancer clinical trials, there are no data on the safety of durvalumab in this population. **Methods:** DURVAST (NCT03094286) is a multicenter, open-label, phase 2 clinical trial evaluating the safety and feasibility of durvalumab treatment at the recommended dose of 1500 mg Q4W in HIV+ cancer patients with solid tumors. Secondary endpoints include analyses of antitumoral activity in terms of objective response rate and duration of response (DOR). An associated translational sub-study includes the assessment of antiviral activity and the interaction of chronic viral infection with anti-cancer response and drug tolerance. **Results:** Twenty HIV+ individuals with advanced solid tumors were enrolled (Table). All participants maintained their standard-of-care antiretroviral therapy. Basal plasma viremia was undetectable and $CD4^+$ T-cell count was over 200/mm^3. There were no durvalumab-related serious adverse events. Only 8 patients (40%) presented drug-related adverse events (all grade 1-2) including diarrhea (15%), rash (15%), nausea (15%) and asthenia (10%). Best response includes: partial response in 5 (25%) (4 NSCLC and 1 anal cancer), stable disease in 4 (20%) (3 NSCLC and 1 melanoma) and progression disease in 11 (55%) patients. At data cut-off, 8 patients (40%) remained on therapy for a median of 10.5 months (range: 6-19 m). Median DOR has not been reached (range 1m to 19 m+). Plasma viremia remained suppressed during the study suggesting no viral reactivation upon durvalumab treatment. **Conclusions:** DURVAST study demonstrates durvalumab safety in HIV+ cancer patients and suggests an excellent tolerance profile. Understanding how chronic viral infection could contribute to a better tolerance towards immune checkpoint inhibitors will open a new way for the development of safer anti-cancer immunotherapy strategies. Clinical trial information: NCT03094286.

Total (n)	20
Age Median (Range)	54 (30-73)
Sex Male (%)	16 (80%)
NSCLC	14 (70%)
Melanoma	2 (10%)
Anal cancer	2 (10%)
Bladder cancer	1 (5%)
SCLC	1 (5%)
1^{st} line	8 (40%)
2^{nd} – 4^{th} line	12 (60%)

2502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A phase II study of pembrolizumab for HPV-associated papilloma patients with laryngeal, tracheal, and/or pulmonary involvement.

Sara I. Pai, Aaron D Friedman, Ramon Franco, Ashok Muniappan, Jong Chul Park, Nicholas Paul Campbell, Seth B. Krantz, Phillip C Song, Michiel Bove, Thomas L Carroll, William C Faquin, Anne M. O'Neill, Lori J. Wirth; Massachusetts General Hospital Cancer Center, Boston, MA; Northshore University HealthSystem, Northbrook, IL; Massachusetts Eye and Ear Infirmary, Boston, MA; Massachusetts General Hospital/Harvard Medical School, Boston, MA; Georgetown Univ Hosp, Boston, MA; Northshore Univ HealthSyst, Chicago, IL; Kellogg Cancer Center, NorthShore University Health System, Evanston, IL; Northwestern Feinberg School of Medicine, Chicago, IL; Brigham and Women's Hospital/Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard University, Boston, MA

Background: Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus (HPV) types 6 & 11. RRP proliferates in the respiratory tract impacting breathing, swallowing, and voice and carries a 1-4% risk of malignant transformation. There is no curative therapy for RRP. Given the tolerized host immune response against HPV, in part through upregulation of the PD1:PDL1 axis, the safety and efficacy of pembrolizumab (pembro) as a novel treatment for this benign tumor patient (pt) population was evaluated in a phase II clinical trial. **Methods:** RRP pts $>$ 12 years of age were treated with pembro 200mg every 3 weeks. Adjuvant surgical debridement of RRP was permitted for airway obstruction but not dysphonia. Primary endpoints were best overall response (ORR) (measured by endoscopic lesional burden) and safety. Greater than 5 pts with disease in response out of 21 (assuming $>$ 1 of first n = 11 with disease in response) provided 86% power to distinguish between a 15% and a 38% ORR (one-sided 8% binomial test). Serial biopsies (up to 8 biopsies/patient over the 24 months of treatment) to identify biomarkers of response and mechanisms of immune resistance (PD-L1 expression, mutations in HLA class I antigen presentation machinery, and tumor mutational burden) are underway. **Results:** Accrual is complete (n = 21 pts accrued between May 2016 and Jan 2019). Median age (range) was 45 (19-68), 57% (12/21) were male and 67% (14/21) were white. As of February 1, 2019, ORR is 43% (9/21) (.95 two-stage CI: 22%-66%) (4 of 11 with juvenile-onset RRP and 5 of 10 with adult-onset RRP disease responded). No complete responses have been observed. Fatigue was the most frequent treatment related adverse event (TRAEs); Grade 3 TRAEs included uveitis and hypophysitis, both were reversible upon pembro discontinuation. The frequency of surgical interventions was reduced in all pts undergoing surgery for airway palliation prior to study entry. **Conclusions:** Pembro reduces the need for routine surgical interventions based on the response rates being achieved. Further study of pembro +/- other agents is warranted to achieve and sustain complete responses in this population. Clinical trial information: NCT02632344.

2503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A phase II, randomized, double-blind, placebo-controlled trial evaluating efficacy and safety of namodenoson (CF102), an A_3 adenosine receptor agonist (A_3AR), as a second-line treatment in patients with Child-Pugh B (CPB) advanced hepatocellular carcinoma (HCC).

Salomon M. Stemmer, Nebojsa S. Manojlovic, Mihai Vasile Marinca, Petar Petrov, Nelly Cherciu, Doina Ganea, Tudor-Eliade Ciuleanu, Ioana Adriana Puscas, Muhammad Shaalan Beg, William T. Purcell, Adina-Emilia Croitoru, Rumyana Nedyalkova Ilieva, Sladjana Natošević, Amedeia Lavinir Nita, Dimitar Nikolaev Kalev, Zivit Harpaz, Motti Farbstein, Michael H. Silverman, Pnina Fishman, Josep M Llovet; Davidoff Cancer Center, Rabin Medical Center-Beilinson Hospital, Petah Tikva, Israel; Military Medical Academy, Belgrade, Serbia; Institutul Regional de Oncologie Iasi – Sectia Oncologie Medical, Iasi, Romania; Complex Oncology Center–Plovdiv, EOOD, Plovdiv, Bulgaria; Clinica Onco-Life, Craiova, Romania; Spitalul Judetean de Urgenta Sfantul Ioan cel Nou Suceava, Suceava, Romania; Institute of Oncology/University of Medicine and Pharmacy, Cluj-Napoca, Romania; S.C. Pelican Impex S.R.L. - Secţia Oncologie Medicală, Oradea, Romania; The University of Texas Southwestern Medical Center, Dallas, TX; University of Colorado Comprehensive Cancer Center, Aurora, CO; Fundeni Clinical Hospital, Bucharest, Romania; Multiprofile Hospital for Active Treatment Central Onco Hospital OOD Department of Medical Oncology, Plovdiv, Bulgaria; Zdravstveni Centar Kladovo Služba Onkologije, Kladovo, Serbia; County Hospital Pratova, Ploiesti, Romania; Sveta Marina University Hospital, Varna, Bulgaria; Can-Fite BioPharma, Petach Tiqwa, Israel; Biostrategics, Ltd.3, Boston, MA; Mount Sinai School of Medicine, New York University, New York, NY

Background: There is no established primary treatment for patients with advanced HCC and severe liver dysfunction (Child-Pugh B class; CPB), thus this representing a clear unmet need. Namodenoson, an A_3AR agonist, showed promising preliminary results in this population in an open label phase 1/2 clinical study (NCT00790218), with median overall survival (OS) of 8.1 months. We present the results of a double blind, randomized phase 2, placebo-controlled study (NCT02128958), assessing the efficacy and safety of namodenoson as a second-line therapy of patients with advanced HCC and CPB class. **Methods:** Patients were randomized 2:1 to BID namodenoson (25 mg; n = 50) or placebo (n = 28) in 15 centers globally. Primary endpoint was OS and secondary endpoints were safety, progression-free survival (PFS), objective response (OR) and disease control rate (DCR). Assessment of OS and PFS was done by log rank test at a one final analysis when 75 deaths had occurred. Response was assessed by RECIST (local investigator) and mRECIST (central review). **Results:** The study did not meet the primary end point, with median OS 4.1 months (mo) for namodenoson vs. 4.3 mo for placebo (HR: 0.82). Pre-planned subgroup analysis of Child-Pugh 7 patients (n=56; namodenoson=34, placebo=21) showed median survival 6.8mo vs 4.3 mo [HR: 0.77 (95% CI 0.49-1.40)]. Similarly, for this subgroup of patients PFS was 3.5 mo vs 1.9 (HR=0.87). In terms of objective response, 3/34 patients assessed achieved OR (9%) with namodenoson vs 0% for placebo. Namodenoson was generally well-tolerated, with no treated patients being withdrawn for toxicity and no cases of treatment-related deaths. The most common adverse event (>10%) were anemia, abdominal pain, ascites, nausea, asthenia, fatigue, peripheral edema, and increased AST. Treatment-related grade 3 toxicities accounted for anemia, fatigue and hyponatremia. **Conclusions:** Namodenoson has demonstrated favorable clinical safety profile in patients with advanced HCC and severe liver dysfunction. Although the primary end-point was not met, the subgroup analysis showed a positive signal of efficacy for OS in patients with Child-Pugh 7. Both safety and efficacy results warrant testing this drug in a phase III trial. Clinical trial information: NCT02128958.

2504 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Results from a first-in-man, open label, safety and tolerability trial of CAN04 (nidanilimab), a fully humanized monoclonal antibody against the novel antitumor target, IL1RAP, in patients with solid tumor malignancies.

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Background: Interleukin 1 receptor Accessory protein, IL1RAP, is expressed in several solid tumors, both on cancer cells and tumor-associated inflammatory cells. CAN04 is a first-in-class fully humanized monoclonal antibody targeting IL1RAP blocking IL-1 alpha and beta signaling and triggering antibody dependent cellular cytotoxicity. **Methods:** The primary objective was to assess safety and tolerability of weekly CAN04 in order to define the Recommended Phase 2 Dose (RP2D). Patients (pts) with relapsed or refractory non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), breast or colorectal cancer were included using a 3+3 dose escalation design. Key eligibility criteria were ECOG $\leq$1, normal organ function and no bleeding disorder/coagulopathy. Tumor responses were evaluated according to irRC every 8 weeks. PK and biomarkers were analyzed in serum. **Results:** 22 pts were enrolled across 5 cohorts (1-10 mg/kg). Demography: mean age 62 yrs (39-81); gender 14 M and 8 F; median number of prior lines of therapy 3 (range 1-11). AEs occurred mainly following the first dose and the most common AEs were: infusion related reaction (IRR) (41%), pyrexia (27%), fatigue (23%), chills (23%) and nausea (23%). AE grade 3 or 4: one IRR, one neutropenia/leukopenia and one hypokalemia, all of them grade 3. Serum CRP and IL-6 were reduced after two weeks of treatment. There were linear increases of AUC and Cmax (1-10 mg/kg) and CAN04 exposure at 10mg/kg was above levels associated with signs of efficacy in preclinical models. In pts receiving at least one dose of CAN04, 9/20 (45%) had SD by irRC (7/20 had SD by RECIST 1.1) at 8 weeks follow up. Two pts, one with NSCLC and one with PDAC, had SD for 6 and 4 months (latter still on therapy). **Conclusions:** CAN04 demonstrated a manageable safety profile and a RP2D of 10 mg/kg has been established. The dose expansion phase of the trial will evaluate CAN04 as monotherapy as well as in combination with relevant chemotherapy regimens in NSCLC and PDAC in separate arms. Clinical trial information: NCT03267316.

2505 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Immunobiology, preliminary safety, and efficacy of CPI-006, an anti-CD73 antibody with immune modulating activity, in a phase 1 trial in advanced cancers.

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Background: CPI-006 inhibits CD73, a nucelotidase that converts AMP to adenosine and functions as a lymphocyte adhesion molecule. CPI-006 is a humanized IgG1 FcγR binding-deficient antibody that binds to CD73+ T and B lymphocytes leading to activation of B cells and expression of CD69. This study investigates the immunobiology, safety, and efficacy of CPI-006 monotherapy and in combination with CPI-444, an adenosine A2A receptor (A2AR) antagonist (NCT03454451). **Methods:** Patients with relapsed solid tumors were treated in a 3 + 3 escalation study with 1, 3, 6 or 12 mg/kg CPI-006 (Q3w IV infusion) monotherapy or in combination with CPI-444 (100 mg, PO, BID). Flow cytometry was performed on blood samples for lymphocyte subset analysis and receptor occupancy. **Results:** 17 patients were enrolled; 11 monotherapy and 6 combination. CPI-006 was associated with Grade 1 infusion reactions occuring within 30 minutes of the first infusion and were eliminated by premedication with non-steroidals. No DLTs with monotherapy or combination therapy were seen. Receptor occupancy on peripheral lymphocytes was maintained for the full dosing interval at 12 mg/kg. Pharmacodynamic effects suggesting immune modulation were observed within 1 hr of infusion at all dose levels and included a decrease in peripheral blood $CD73^{pos}$ B cells (mean reduction 86%, $p < 0.05$), increased $CD73^{neg}$ CD4 T cells (mean increase 37%, $p < 0.01$), and decreased CD8 T cells (mean reduction 20%, $p < 0.01$) compared to baseline. Overall, CD4:CD8 ratios were increased. Tumor regression was observed in a prostate cancer patient after 5 cycles of monotherapy at 6 mg/kg; peripheral B cells partially returned by the second cycle and reached a new homeostatic level through subsequent cycles. No change in serum immunoglobulins were observed. **Conclusions:** CPI-006 induces a rapid lymphocyte redistribution, including a transient reduction of circulating $CD73^{pos}$ B cells suggesting redistribution to lymphoid tissues, and an increased CD4:CD8 ratio, consistent with increased T_H effector/memory cells in the blood. The treatment has been well-tolerated, and there is early evidence of anti-tumor activity of CPI-006 monotherapy. Clinical trial information: NCT03454451.

Determination of the recommended phase II dose of birinapant in combination with pembrolizumab: Results from the dose-escalation phase of BPT-201.

Russell J. Schilder, Mark Albertella, James Fredric Strauss, Malin Sydvander, Dung T. Le, Stefan Norin, Monica M. Mita, Emma Boström, Siqing Fu, Linda Basse, Richard Bethell; Thomas Jefferson University, Philadelphia, PA; Medivir AB, Huddinge, Sweden; Texas Oncology, Dallas, TX; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Birinapant is a bivalent SMAC mimetic targeting cIAP1. Synergistic effects of combining birinapant with immune checkpoint inhibitors have been demonstrated in preclinical models. Based on these observations, a clinical trial with birinapant and pembrolizumab was initiated (NCT02587962). **Methods:** Patients ≥18 years with advanced solid tumors without further suitable standard therapeutic options were eligible for inclusion. Birinapant (5.6-22 mg/m^2) was administered IV on day 1 and 8 in addition to pembrolizumab 200 mg on day 1 in a 21-day cycle until disease progression using standard 3+3 dose-escalation. The primary objective was to determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant in combination with pembrolizumab. Secondary and exploratory objectives included antitumor activity assessed by RECIST 1.1 and iRECIST, pharmacokinetics and assessment of biomarkers including serum cytokines, cIAP1, PD-L1 expression and tumor infiltrating lymphocytes. **Results:** Nineteen patients were enrolled at 4 dose levels of 5.6 (n = 3), 11 (n = 3), 17 (n = 6) and 22 (n = 7) mg/m^2. Most common tumors were pancreatic (n = 5), colorectal (n = 4), ovarian (n = 3) and sarcoma (n = 3). Median prior therapies were 4 (0-12). The most common AE related to any of the study drugs was rash occurring in 3 patients. Ten patients had 17 SAE's of which only one (stomatitis) was judged related to birinapant. Increased ALT/AST (G3/G2) leading to missed day 8 dose constituted a DLT at 22 mg/m^2. Grade 2 lipase increases were seen in 2 patients. No cases of Bell's palsy were detected. ORR by RECIST 1.1 was 5.6% (n = 1) in 18 evaluable patients. The responding patient had microsatellite stable colorectal carcinoma (MSS-CRC)) and remains on therapy 13+ months after first dose. By iRECIST, ORR was 11.1%. CBR (PR+SD) by RECIST was 22.2%. The exposure to birinapant generally increased with dose. The RP2D was determined to be 22 mg/m^2. **Conclusions:** Birinapant and pembrolizumab is a safe and tolerable combination that has shown encouraging signals of efficacy. A phase 2 study evaluating efficacy of this combination in MSS-CRC is ongoing. Clinical trial information: NCT02587962.

2507 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase Ib study of MIW815 (ADU-S100) in combination with spartalizumab (PDR001) in patients (pts) with advanced/metastatic solid tumors or lymphomas.

Funda Meric-Bernstam, Shahneen Kaur Sandhu, Omid Hamid, Anna Spreafico, Stefan Kasper, Reinhard Dummer, Toshio Shimizu, Neeltje Steeghs, Nancy Lewis, Craig C. Talluto, Sinead Dolan, Andrew Bean, Robert Brown, Damian Trujillo, Nitya Nair, Jason J. Luke; Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX; Peter MacCallum Cancer Centre, The University of Melbourne, Melbourne, Australia; The Angeles Clinic and Research Institute, Los Angeles, CA; Princess Margaret Hospital, Toronto, ON, Canada; Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany; University of Zürich, Zürich, Switzerland; National Cancer Center Hospital (NCCH), Tokyo, Japan; Netherlands Cancer Institute, Amsterdam, Netherlands; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Institutes for BioMedical Research, Cambridge, MA; Aduro Biotech Inc., Berkeley, CA; Aduro Biotech, Berkeley, CA; The University of Chicago Medicine, Chicago, IL

Background: MIW815 (ADU-S100) is a novel synthetic cyclic dinucleotide that activates the STimulator of INterferon Genes (STING) pathway impacting tumor cells, tumor microenvironment, vasculature, tumor-associated fibroblasts, and priming APC and CD8+ T cells. Spartalizumab is a humanized IgG4 mAb that blocks the binding of PD-1 to PD-L1/2. Preclinical data support synergistic antitumor effects when MIW815 (ADU-S100) is combined with checkpoint inhibitors. **Methods:** In this Phase Ib dose escalation study, pts with advanced/metastatic solid tumors or lymphoma received MIW815 (ADU-S100) (intratumoral injections [50–800 μg] either weekly [3 weeks on/1 week off] or Q4W) and spartalizumab (400 mg IV Q4W). Injected and non-injected tumor biopsies were obtained at baseline and on treatment. Primary objectives are to determine safety and identify a dose/schedule for future studies. Preliminary activity, pharmacokinetics (PK), and pharmacodynamics (PD) are also being explored. **Results:** As of Jan 11, 2019, 66 pts (median age: 61 y) with various solid tumors or lymphomas have been treated. Treatment was discontinued in 49 pts (74%) due to disease progression (n = 28), pt/physician decision (n = 18), AE (n = 2), or death (n = 1). No DLTs were reported during the first cycle at any dose level. Most common (≥5 pts) treatment-related AEs (TRAEs) were injection site pain (12%), pyrexia (11%), and diarrhea (9%). Grade 3/4 TRAEs (in ≥2 pts) were increased AST and ALT (3% each). Serious TRAEs were pyrexia (3%), increased amylase, increased lipase, diarrhea, fatigue, hyperthyroidism, partial seizures, dyspnea, and pneumonitis (all 2%). Partial responses in pts with PD-1–naive TNBC and PD-1–relapsed/refractory melanoma have been observed. MIW815 (ADU-S100) plasma exposure generally increased in a dose-dependent manner with a rapid terminal half-life. Response data, PK and PD analyses will be presented. **Conclusions:** Thus far, MIW815 (ADU-S100) + spartalizumab has demonstrated antitumor activity in PD-1–naive TNBC and PD-1–relapsed/refractory melanoma. The combination is well tolerated, with no DLTs reported to date. The MTD has not been reached and dose escalation is ongoing. Clinical trial information: NCT03172936.

First-in-human study of REGN3767 (R3767), a human LAG-3 monoclonal antibody (mAb), ± cemiplimab in patients (pts) with advanced malignancies.

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Background: We present initial safety, pharmacokinetics (PK), and efficacy from the dose escalation study of R3767, alone (mono) or in combination with cemiplimab (REGN2810), a PD-1 mAb (combo), in pts with advanced malignancies (NCT03005782). **Methods:** Pts who had progressed on prior therapy(ies) and/or for whom no therapy with clinical benefit was available were enrolled; most pts had received no prior anti-PD-1/PD-L1. Pts received R3767 1, 3, 10, or 20 mg/kg every 3 weeks (Q3W) ± cemiplimab 3 mg/kg or 350 mg Q3W IV for ≤51 weeks. Crossover from mono to combo was allowed at progression. R3767 PK were evaluated. Tumor measurements were performed Q6W for the first 24 weeks and subsequently Q9W. Data cut-off date was Aug 25, 2018. **Results:** *Mono*: 27 pts (median age: 66 yr; ECOG PS: 0 [n=4], 1 [n=23]) were treated. There were no dose-limiting toxicities (DLTs). The most common treatment-emergent adverse event (TEAE) was nausea (22.2%). Grade ≥3 immune-related adverse events (irAEs) of increased alanine and aspartate aminotransferases (each 3.7%) were reported. By investigator-assessment (per RECIST 1.1; INV), best response was stable disease in 11 pts. *Combo*: 42 pts (median age: 60 yr; ECOG PS: 0 [n=15], 1 [n=27]) were treated. One pt treated with R3767 3 mg/kg Q3W + cemiplimab 3 mg/kg Q3W experienced DLT of grade 4 elevated blood creatine phosphokinase, associated with grade 3 myasthenia syndrome and grade 1 elevated troponin. The most common TEAEs were fatigue (33.3%) and nausea (21.4%). Grade 3 irAE of hypothyroidism (2.4%) was also reported. By INV, 2 (both small cell lung cancer) combo pts and 2 (endometrial cancer and cutaneous squamous cell carcinoma) of 12 additional pts who crossed over from mono to combo had partial responses. *PK*: R3767 concentrations in serum increased in a dose-dependent manner and were unaffected by combo. **Conclusions:** The safety profile of R3767 ± cemiplimab was generally tolerable; PK was linear. Early efficacy signals were detected despite the difficult-to-treat pt population. Biomarker studies are ongoing. R3767 20 mg/kg or 1600 mg fixed dose equivalent Q3W as mono and combo were selected for further evaluation. Clinical trial information: NCT03005782.

2509 **Clinical Science Symposium, Tue, 8:00 AM-9:30 AM**

Phase I trial of Claudin 18.2-specific chimeric antigen receptor T cells for advanced gastric and pancreatic adenocarcinoma.

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Background: As a promising approach for some cancers, chimeric antigen receptor T cell therapy has limited success in solid tumors. Claudin18.2 (CLDN 18.2) is a stomach-specific isoform of Claudin-18, and highly expressed in gastric and pancreatic adenocarcinoma, the advanced form of both of which have urgent unmet medical needs. We previously developed and demonstrated ability of CLDN 18.2-specific CAR (CAR-CLDN18.2) T cells to eradicate CLDN 18.2-positive gastric cancer xenografts without obvious on-target off-tumor toxicity (Huang J. JNCI 2018). **Methods:** In this single-arm, open-label, first-in-human phase I pilot study (NCT03159819) to investigate the safety and explore the efficacy of the autologous CAR-CLDN18.2 T cells, patients with confirmed CLDN 18.2 positive advanced gastric or pancreatic adenocarcinoma aged 18 to 70 years received 1 or more cycles of CAR-CLDN18.2 T cell infusion(s) after lymphodepletion pretreatment (fludarabine and cyclophosphamide, with or without nab-paclitaxel) until disease progression or presence of intolerable toxicity. Adverse Event (AE) grade categorization is according to CTCAE 4.0, and tumor response was assessed per RECIST 1.1. **Results:** As of November 30th, 2018, 12 subjects with metastatic adenocarcinoma (7 gastric and 5 pancreatic) were treated with 1–5 cycles (total of 0.5 - 55 X 10^8) of CAR-positive T cells infusions. There were no serious adverse events, treatment-related death or severe neurotoxicity occurred in the study. No grade 4 AEs except for decreased lymphocytes, neutrophils and white blood cells. All cytokine release syndromes observed were grade 1 or 2. Among the 11 evaluable subjects, 1 achieved a complete response (gastric adenocarcinoma), 3 had partial responses (2 gastric adenocarcinomas and 1 pancreatic adenocarcinoma), 5 had stable disease and 2 had progression of disease. The total objective response rate was 33.3%, with median PFS of 130 days estimated using Kaplan-Meier method [95% CI (38, 230)]. **Conclusions:** This clinical study indicated that CAR-CLDN18.2 T cell therapy were safe and well tolerated and may have promising therapeutic efficacy in patients with advanced gastric and pancreatic adenocarcinoma. Clinical trial information: NCT03159819.

2510 **Clinical Science Symposium, Tue, 8:00 AM-9:30 AM**

Results of a phase I study of bispecific anti-CD19, anti-CD20 chimeric antigen receptor (CAR) modified T cells for relapsed, refractory, non-Hodgkin lymphoma.

Nirav Niranjan Shah, Fenlu Zhu, Dina Schneider, Carolyn Taylor, Winfried Krueger, Andrew Worden, Walter L. Longo, Mehdi Hamadani, Timothy Fenske, Bryon Johnson, Boro Dropulic, Rimas Orentas, Parameswaran Hari; Medical College of Wisconsin, Milwaukee, WI; Lentigen Technology Inc., A Miltenyi Biotec Company, Gaithersburg, MD; Univ of Wisconsin-Madison, Madison, WI; Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

Background: Anti-CD19 CAR-T cell therapy is a breakthrough treatment (tx) for patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL). Despite impressive outcomes, non-response and relapse with CD19 negative disease remain challenges. Through dual B-cell antigen targeting of CD20 and CD19, with a first-in-human bispecific lentiviral CAR-T cell (LV20.19CAR), we aim to improve response rates while limiting CD19 negative relapse. **Methods:** Pts were treated on a Phase 1 dose escalation + expansion trial (NCT03019055) to demonstrate safety of a 41BB/CD3z LV20.19CAR T cell for adults with R/R B-cell NHL. Safety was assessed by incidence of dose limiting toxicities (DLTs) within 28 days post-infusion. Starting dose was 2.5 x 10^5 cells/kg with a target dose of 2.5 x 10^6 cells/kg. All pts received fludarabine+cyclophosphamide for lymphodepletion. **Results:** 11 pts have completed tx to date. 9 pts in dose escalation and 2 pts in expansion phase. Median age was 54 years (46-67) and histology included DLBCL = 5 pts, MCL = 4 pts, and CLL = 2 pts. In dose escalation, 3 pts were treated at 2.5 x 10^5 cells/kg, 3 pts at 7.5 x 10^5 cells/kg, and 3 pts at 2.5 x 10^6 cells/kg with no DLTs. As a result, 2.5 x 10^6 cells/kg was selected for expansion. In terms of safety, 6 pts developed Grade 1-2 cytokine release syndrome (CRS) and 3 pts had Grade 1-2 neurotoxicity (NTX). No patient had grade 3-4 CRS or NTX and none required ICU level care. 4 pts required 1-2 doses of tocilizumab for CRS. The day 28 overall response rate (ORR) for all pts was 82% (6/11 = complete response (CR) and 3/11 = partial response). All CR pts remain in remission, the longest $>$ 1 year. All progressing pts underwent repeat biopsy, and all retained either CD19 or CD20 positivity. Additional pts are being enrolled in the expansion phase and updated data will be presented. **Conclusions:** Phase 1 results from the LV20.19 CAR T clinical trial demonstrate that infusion of 2.5 x 10^6 cells/kg is safe for further investigation with no DLTs among treated pts. Down-regulation of target antigens was not identified as a mechanism of resistance in progressing pts. With limited toxicity and encouraging ORR, dual targeted LV20.19CAR T cells merits further investigation. Clinical trial information: NCT03019055.

2511 **Clinical Science Symposium, Tue, 8:00 AM-9:30 AM**

Regional delivery of mesothelin-targeted CAR T cells for pleural cancers: Safety and preliminary efficacy in combination with anti-PD-1 agent.

Prasad S. Adusumilli, Marjorie Glass Zauderer, Valerie W. Rusch, Roisin O'Cearbhaill, Amy Zhu, Daniel Ngai, Erin McGee, Navin Chintala, John Messinger, Waseem Cheema, Elizabeth Halton, Claudia Diamonte, John Pineda, Alain Vincent, Shanu Modi, Stephen Barnett Solomon, David Randolph Jones, Renier J. Brentjens, Isabelle Riviere, Michel Sadelain; Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering, New York, NY

Background: We conducted a phase I dose escalation trial of first-in-human autologous chimeric antigen receptor (CAR) T-cell immunotherapy targeting mesothelin (MSLN), a cell-surface antigen that is highly expressed in pleural cancers- malignant pleural mesothelioma (MPM) and metastatic lung and breast cancers. **Methods:** A single dose of CD28-costimulated MSLN CAR T cells with the I-caspase-9 safety gene was administered intrapleurally in patients with MSLN-expressing pleural tumors. Following a 3+3 design, patients were treated in dose escalating cohorts (dose range 3E5 to 1E7 CAR T cells/kg) following IV cyclophosphamide lymphodepletion (first 3 patients did not receive cyclophosphamide). A subset of MPM patients received subsequent anti-PD-1 therapy, off-protocol, which we have shown to prolong CAR T-cell functional persistence in preclinical models. **Results:** Twenty patients (18 MPM, 1 lung cancer, 1 breast cancer) were treated (prior lines of therapy 1–8, 35% received $\geq$3 lines of therapy). No CAR T-cell–related toxicities higher than grade 1 were observed. Intense monitoring for on-target, off-tumor toxicity by clinical (chest or abdominal pain), radiological (CT/PET or echocardiogram for pericardial effusion, ascites), laboratory (troponin elevation), and EKG evaluation found no evidence of toxicity. Fourteen MPM patients received subsequent anti-PD1 therapy (1–21 cycles, pretreatment tumor PD-L1 $<$ 10% in all patients except one), with 1 patient developing grade 3 pneumonitis that responded to steroid treatment. CAR T cells were detected in the peripheral blood of 13 of 14 patients (1-39 weeks). At data cut-off date (Jan 31, 2019), among 14 MPM patients that received combination therapy (follow-up 13-77 weeks, median 31 weeks), best responses included 2 patients with complete metabolic response on PET (62 and 39 weeks ongoing); 5 partial responses and 4 stable disease by investigator assessment. **Conclusions:** Intrapleurally administered MSLN-targeted CAR T cells were safe. Encouraging antitumor activity of MSLN-targeted CAR T-cell therapy was observed when combined with anti-PD1 therapy and shows promise for future development of this approach. Clinical trial information: NCT02414269.

2512 **Poster Discussion Session; Displayed in Poster Session (Board #156), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM**

Ipilimumab versus placebo after complete resection of stage III melanoma: Long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial.

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Background: Since 2015, ipilimumab (Ipi) is an approved treatment for stage III melanoma based on a significantly (P=0.0013) prolonged recurrence-free survival (RFS) (Eggermont et al, Lancet Oncology, 2015). At a median follow-up of 5.3 years, RFS (HR=0.76) and distant metastasis-free survival (DMFS) (HR=0.76), assessed by an IRC, and overall survival (OS) (HR=0.72) were prolonged in the Ipi group as compared to the placebo (Pbo) group (Eggermont et al, NEJM, 2016), despite a 53.3% (Ipi) vs 4.6% (Pbo) treatment discontinuation rate due to adverse events. **Methods:** In this randomized double-blind trial, eligible patients (pts) included those ≥18 yrs of age who underwent complete resection of stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis). 951 pts were randomized (stratified by stage and region) 1:1 to Ipi 10 mg/kg (n=475) or placebo (Pbo, n=476) q3w for 4 doses, then every 3 mos for up to 3 yrs until completion, disease recurrence, or unacceptable toxicity. Here, we report the comparison between the Ipi and Pbo groups regarding the long-term efficacy outcomes using the local investigator assessments. **Results:** Overall, 20%/44%/36% of pts had AJCC-7 stage IIIA/IIIB/IIIC, 42% ulcerated primary, and 58% macroscopic lymph node involvement. Median follow-up was 6.9 yrs. The RFS, DMFS and OS benefit observed in the Ipi group was long-lasting (almost 10% difference at 7 years) and consistent across subgroups: no significant predictive factors could be detected. **Conclusions:** In this phase III trial, Ipi, administered at 10 mg/kg, as adjuvant therapy provided, at a 6.9 yr median follow-up, a sustained improvement in the RFS, DMFS, and OS long-term results in patients with high-risk stage III melanoma. Clinical trial information: NCT00636168.

	RFS		DMFS		OS	
	Ipi	Pbo	Ipi	Pbo	Ipi	Pbo
No. of events	273	323	247	292	173	223
5-year rate	43.9%	32.5%	49.9%	39.8%	65.2%	54.1%
7-year rate	39.2%	30.9%	44.5%	36.9%	60.0%	51.3%
Median (yrs)	2.7	1.5	5.0	2.4	NR	7.8
HR (95% CI)†	0.75 (0.63-0.88)		0.76 (0.64-0.90)		0.73 (0.60-0.89)	
Log-rank p-value†	0.0004		0.0018		0.0021	

HR: Hazard Ratio provided by the Cox model; CI: Confidence interval; NR: not reached; †stratified by stage provided at randomization.

2513 Poster Discussion Session; Displayed in Poster Session (Board #157), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

CX-072, a PD-L1 Probody therapeutic, as monotherapy in patients with advanced solid tumors: Preliminary results of PROCLAIM-CX-072.

Aung Naing, Fiona C. Thistlethwaite, Alexander I. Spira, Javier Garcia-Corbacho, Manreet Randhawa, Ferry Eskens, Bert O'Neil, Javier Lavernia, Nataliya Volodymyrivna Uboha, Omid Hamid, Anthony B. El-Khoueiry, Beverly A. Benson, William Garner, Vanessa Jessica Huels, Hendrik-Tobias Arkenau, Patricia LoRusso; MD Anderson Cancer Center, Houston, TX; The Christie NHS Foundation Trust and The University of Manchester, Manchester, United Kingdom; Virginia Cancer Specialists, Fairfax, VA; Hospital Clinic Barcelona, Barcelona, Spain; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Erasmus University Medical Center, Rotterdam, Netherlands; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Instituto Valenciano de Oncología, Valencia, Spain; University of Wisconsin, Carbone Cancer Center, Madison, WI; The Angeles Clinic and Research Institute, Los Angeles, CA; USC Norris Comprehensive Cancer Center, Los Angeles, CA; CytomX Therapeutics, Inc, South San Francisco, CA; Sarah Cannon Research Institute UK Limited, London, United Kingdom; Yale University School of Medicine, Yale Cancer Center, New Haven, CT

Background: Anti-programmed cell death ligand 1 (PD-L1) immunotherapies have improved survival in many cancers, but immune-related adverse events (irAEs) have been observed, especially in combination therapy. CX-072 is an investigational Probody therapeutic directed against PD-L1, designed to be preferentially activated in the tumor microenvironment and to reduce irAEs. **Methods:** This is an ongoing phase 1/2a study (PROCLAIM-CX-072; NCT03013491) evaluating CX-072 in patients (pts) with metastatic or unresectable solid tumors with no further standard curative treatment options and with no prior anti-PD1, PD-L1 or anti-CTLA4 treatment. Pts were unselected for PD-L1 expression. We report preliminary results from expansion cohorts in anal squamous cell carcinoma (SCCA), cutaneous squamous cell carcinoma (cSCC), small bowel adenocarcinoma (SBA), triple-negative breast cancer with skin lesions (TNBC), or undifferentiated pleomorphic sarcoma (UPS). Pts were treated with CX-072 monotherapy 10 mg/kg intravenously every 14 days. **Results:** As of 30 Nov 2018, 51 pts received CX-072 10 mg/kg monotherapy: SCCA (n = 9), cSCC (n = 5), SBA (n = 9), TNBC (n = 9), and UPS (n = 19). Median age was 63 y (range, 32-80), 67% were female, and pts had a median of 3 prior regimens (range, 1-12). Median treatment duration was 1.8 mo (range, 0.3-14.7). A grade 3/4 treatment-related adverse event (AE) was observed in 1 pt (2%; gr 3 generalized rash). No grade 3/4 irAEs were observed. Two pts discontinued treatment due to AEs: nausea (pt with SCCA) and sepsis (pt with SBA), neither treatment-related. Partial responses (confirmed and unconfirmed) were observed in cSCC (n = 1), TNBC (n = 2), and UPS (n = 1) (Table). **Conclusions:** CX-072 10 mg/kg monotherapy demonstrated anticancer activity in heavily pretreated pts with advanced solid tumors, including responses in cSCC, TNBC with skin lesions, and UPS, with a safety profile that compares favorably to historical controls. Clinical trial information: NCT03013491.

Best Available Response (efficacy evaluable* pts), n	SCCA (n = 3)	cSCC (n = 3)	SBA (n = 4)	TNBC (n = 2)	UPS (n = 16)
Confirmed or unconfirmed partial response	0	1	0	2	1
Stable disease	1	1	2	0	3
Progressive disease	2	1	2	0	12

*Required postbaseline assessment.

2514 Poster Discussion Session; Displayed in Poster Session (Board #158), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

A phase I study of ALX148, a CD47 blocker, in combination with established anticancer antibodies in patients with advanced malignancy.

Laura Quan Man Chow, Justin F. Gainor, Nehal J. Lakhani, Hyun Cheol Chung, Keun-Wook Lee, Jeeyun Lee, Patricia LoRusso, Yung-Jue Bang, F. Stephen Hodi, Philip Fanning, Yonggang Zhao, Feng Jin, Hong Wan, Jaume Pons, Sophia Randolph, Wells A. Messersmith; Division of Medical Oncology, University of Washington, Seattle, WA; Massachusetts General Hospital, Boston, MA; START-Midwest, Grand Rapids, MI; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Yale University School of Medicine, Yale Cancer Center, New Haven, CT; Seoul National University College of Medicine, Seoul, South Korea; Dana-Farber Cancer Institute, Boston, MA; ALX Oncology Inc., Burlingame, CA; University of Colorado Comprehensive Cancer Center, Aurora, CO

Background: CD47 is a myeloid checkpoint upregulated by tumor cells to evade the host's immune response. ALX148 (A) is a fusion protein comprised of a high affinity CD47 blocker linked to an inactive human immunoglobulin Fc region. ALX148 is well tolerated in combination with pembrolizumab (P) or trastuzumab (T) with no maximum tolerated dose (MTD) identified (ASCO 2018 #3068, SITC 2018 #P335). Safety and antitumor activity of ALX148 (10 mg/kg QW) in combination with T or P are reported in patients (pts) including those with anti-HER2 or checkpoint inhibitor (CPI) relapsed/refractory diseases. **Methods:** Patients with malignancy including non-small cell lung cancer (NSCLC: CPI resistant/refractory or PD-L1 tumor proportion score $<$50%) and head and neck squamous cell carcinoma (HNSCC: progressed on platinum therapy) received A+P. Patients with HER2 malignancy including gastric/gastroesophageal junction (GEJ) cancer (progressed on T + fluoropyrimidine-based therapy) received A+T. Safety, response, pharmacokinetic (PK), and pharmacodynamic (PD) markers were assessed. Preliminary data from fully enrolled cohorts are reported as of 20 Jan 2019 (safety)/28 Jan 2019 (efficacy). **Results:** Seventy-nine pts received A+P (All, n=50; NSCLC, n=23; HNSCC, n=20) or A+T (All, n=29; Gastric/GEJ, n=23) as of data cutoff. Forty-seven pts reported mostly low grade treatment related adverse events. The most common were fatigue (11%), AST increase (9%), ALT increase (8%), anemia (8%), and platelets decreased (6%). In select tumor histologies, anticancer activity was observed in initial response-evaluable pts [NSCLC (n=23) 1PR, 8SD; HNSCC (n=17) 3PR, 4SD; and Gastric/GEJ (n=21) 4PR, 6SD]. Preliminary results indicate favorable ALX148 PK and CD47 target occupancy profiles, and positive effects on tumor infiltrating immune cells. Results will be updated at presentation. **Conclusions:** ALX148 demonstrates excellent tolerability with favorable PK/PD characteristics to date. Objective responses were observed in patients with late line NSCLC, HNSCC, and Gastric/GEJ, including disease relapsed/refractory to prior CPI and HER2-targeted therapies. Clinical trial information: NCT03013218.

2515 Poster Discussion Session; Displayed in Poster Session (Board #159), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Distinct immunogenomic properties of melanomas with stable disease as best response to immune checkpoint blockade (ICB).

Natalie Vokes, Claire Margolis, David Liu, Bastian Schilling, Dirk Schadendorf, Eliezer Mendel Van Allen; Dana-Farber Cancer Institute, Boston, MA; Department of Dermatology, University Hospital Würzburg, Würzburg, Germany; Universitaetsklinikum Essen & German Cancer Consortium, Essen, Germany

Background: ICB has improved survival in melanoma. Patients with stable disease (SD) as best treatment response represent an intermediate response phenotype whose biology has been incompletely characterized. **Methods:** Whole exome and transcriptome sequencing from pre-treatment tumors in melanoma patients treated with ICB (anti-CTLA-4 and/or anti-PD-1) were assembled and uniformly analyzed (WES n = 293; WES+RNA-seq n = 159). RECIST (v1.1) was used to determine complete or partial response (CR/PR; n = 94), SD (n = 42), or progressive disease (PD; n = 157). Gene set enrichment analysis (GSEA) was performed on 50 "hallmark" gene sets to identify pathways differentially expressed in patients with SD. CIBERSORT was used to infer relative proportions of 22 immune cell types in each sample. Mutation antigenicity was determined by calculating patient-specific mutation affinity for MHC class I peptides. **Results:** GSEA identified enrichment of multiple immune-related gene sets in SD tumors, including TNF-α signaling and interferon-γ response (FDR $q < 0.1$, SD vs CR/PR and SD vs PD). SD tumors had higher HLA and antigen presentation pathway expression, and increased cytolytic T cell activity compared to CR/PR and PD. CIBERSORT analysis identified higher total immune infiltrate in SD patients compared to CR/PR and PD (Mann-Whitney U $p = 0.03$ and $p < 0.001$, respectively) but not in patients with CR/PR vs PD ($p = 0.124$). However, checkpoint expression, including PD-1, PD-L1, and LAG3, was also higher in SD patients. Mutation load did not differ between SD and CR/PR or PD patients (SD median 2.87 vs CR/PR median 7.98, Mann-Whitney U $p = 0.104$; PD median 3.42, $p = 0.210$). However, SD patients had more antigenic passenger mutations (SD vs CR/PR, $p = 0.001$; vs PD, $p < 0.001$); there was no difference in antigenicity of driver mutations. **Conclusions:** Pre-treatment melanomas from patients with SD contain more antigenic passenger mutations and demonstrate a global increase in immune signaling. This may describe a subset of patients with pre-existing dysfunctional immune response that is minimally responsive to ICB. Further characterization of the tumor-immune interaction in these patients may inform improved interventions.

2516 Poster Discussion Session; Displayed in Poster Session (Board #160), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Analysis of early mortality in randomized clinical trials evaluating anti-PD-1/PD-L1 antibodies: A systematic analysis by the United States Food and Drug Administration (FDA).

Flora Mulkey, Kunthel By, Marc Robert Theoret, Virginia Ellen Maher, Richard Pazdur, Rajeshwari Sridhara; U.S. Food and Drug Administration, Silver Spring, MD

Background: Many studies exhibit what seems to be dis-proportionately higher early mortality (EM) in anti-PD-1/PD-L1 containing arms (IO) when compared to active control arms (AC), resulting in early crossing of the Kaplan-Meier overall survival curves. We examine if EM with the use of IO is specific to certain demographic and disease characteristics. **Methods:** Data from 16 randomized AC trials submitted to FDA containing 6055 IO and 3604 AC patients in HNSCC, Melanoma, NSCLC, RCC, and Urothelial Carcinoma were evaluated for signs of EM. Study-specific and pooled piecewise hazard ratios (HRs) were used to quantify EM from 0 to 60 and $>$ 60 days. Additionally, HRs up to 60 days were used to assess the extent specific subgroups account for EM. **Results:** Piecewise HRs comparing OS between IO and AC changed direction, >1 to <1 in 11 trials; melanoma (5/6), NSCLC (3/7), HNSCC (1/1), RCC (1/1), and urothelial cancer (1/1). When pooled, NSCLC studies retained this EM pattern, although attenuated, with HR (95% CI) of 1.12 (0.91, 1.38) $\leq$60 days and 0.66 (0.61, 0.72) after 60 days. This was not observed in the pooled melanoma studies: 0.88 (0.63, 1.24) $\leq$ 60 days and 0.59 (0.53, 0.67) after 60 days. EM in both arms was associated with poor ECOG performance status (PS), increased LDH, and high tumor burden. Comparing EM patients in the IO and AC arms, a larger proportion were female in the melanoma trials (41% vs. 28%), a smaller proportion had squamous histology in the NSCLC trials (32% vs. 41%), and a larger proportion were PD-L1 negative (56% vs. 36% melanoma; 60% vs. 43% NSCLC). Analysis of the pooled melanoma studies suggests PD-L1 negative melanoma patients with high baseline tumor burden and PS played a role in EM with HR before 60 days of 1.49 (0.75, 2.97). However, these results were not reproducible in NSCLC. **Conclusions:** Potential risk factors for EM were assessed in individual and pooled trials. While several factors—negative PD-1/PD-L1 status and high ECOG, LDH and tumor burden—seem to play a role in EM, these high-risk subgroups do not fully explain the EM patterns observed in the IO treated patients.

2517 Poster Discussion Session; Displayed in Poster Session (Board #161), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Prognostic and predictive value of an immune-related adverse event among stage III melanoma patients included in the EORTC 1325/KEYNOTE-054 pembrolizumab versus placebo trial.

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Background: Several studies suggested that patients (pts) with an immune-related adverse event (irAE) during immunotherapy have better outcomes than those without. It remains uncertain whether these observations can be explained by guarantee-time bias or the role of irAE as an indicator of drug activity. Here, we investigated the association between irAEs and recurrence-free survival (RFS) in the double-blind EORTC 1325/KEYNOTE-054 trial that compared pembrolizumab and placebo in high-risk stage III melanoma pts. **Methods:** Eligible pts included adults with complete resection of cutaneous melanoma metastatic to lymph node(s), classified as stage IIIA (lymph node metastasis $>$ 1 mm), IIIB or IIIC (without in-transit metastasis) and with no active autoimmune disease that required systemic treatment in past 2 years. We used a Cox model adjusted for sex, age, and stage with a time-varying covariate taking a value zero before the irAE onset and a value one afterwards to estimate the association between the occurrence of irAEs and RFS. **Results:** Consistent with the main analysis in the ITT population (n = 1019, Eggermont et al, NEJM, 2018), RFS was longer in the pembrolizumab than in the placebo arm (HR = 0.56, 98.4% CI: 0.43-074) among pts who started the treatment (n = 1011). The incidence of irAE on study was 37.3% in the pembrolizumab (n = 509) and 9.0% in the placebo arm (n = 502) and, in each treatment group, it was similar in males and females. The occurrence of an irAE was significantly associated with a longer RFS in the pembrolizumab arm (HR = 0.61, 95% CI: 0.39-0.95, P = 0.03). This was true for both males and females. However, in the placebo arm, no association was observed (HR = 1.39, 95% CI: 0.83-2.32, P = 0.21). Compared to the placebo arm, the reduction in the hazard of recurrence or death in the pembrolizumab arm was greater (P = 0.028) after an onset of an irAE (HR = 0.37, 95% CI: 0.24-0.57) than without/before an irAE (HR = 0.61, 95% CI: 0.49-0.77). **Conclusions:** In the EORTC 1325/KEYNOTE-054 study conducted in high-risk stage III melanoma pts, the occurrence of an irAE was strongly associated with a longer RFS in those treated with pembrolizumab, but not with placebo. Clinical trial information: NCT02362594.

2518 Poster Discussion Session; Displayed in Poster Session (Board #162), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Safety and efficacy of cryopreserved autologous tumor infiltrating lymphocyte therapy (LN-144, lifileucel) in advanced metastatic melanoma patients who progressed on multiple prior therapies including anti-PD-1.

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Background: Treatment options are limited for patients with advanced melanoma who have progressed on checkpoint inhibitors and targeted therapies such as BRAF/MEK inhibitors (if BRAF-V600E mutated). Adoptive cell therapy utilizing tumor-infiltrating lymphocytes (TIL) has shown antitumor efficacy with durable long-term responses in heavily pretreated melanoma patients. Safety and efficacy of lifileucel (LN-144), a centrally manufactured autologous TIL therapy are presented. **Methods:** C-144-01 is a global Phase 2 open-label, multicenter study of the efficacy and safety of lifileucel in patients with unresectable metastatic melanoma. We report on Cohort 2 (N = 55) patients who received cryopreserved lifileucel. Tumors resected at local institutions were processed in central GMP facilities for TIL production in a 22-day process. Final TIL infusion product was cryopreserved and shipped to sites. Patients received one week of cyclophosphamide/fludarabine preconditioning lymphodepletion, a single lifileucel infusion, followed by up to 6 doses of IL-2. **Results:** In 55 patients with Stage IIIC/IV unresectable melanoma, 3.1 mean prior therapies (anti-PD1 100%; anti-CTLA-4 80%; BRAF/MEK inhibitor 24%), high baseline tumor burden (110 mm mean target lesion sum of diameters), ORR was 38% (2 CR, 18 PR, 1 uPR). Of 21 responders, 4 have progressed to date with median follow up of 7.4 months. Overall disease control was 76%. Improved responses in some patients were observed with longer follow up. Most (54) patients progressed on prior anti-PD1 and those with PD-L1 negative status (TPS $<$ 5%) were among responders. Mean cells infused was 28 x10^9. Median IL-2 doses administered was 6.0. Adverse events resolved to baseline, 2 weeks post TIL infusion, a potentially important benefit of one-time TIL therapy. **Conclusions:** Lifileucel treatment results in 38% ORR in heavily pretreated metastatic melanoma patients with high baseline disease burden who received prior anti-PD1 and BRAF/MEK inhibitor if BRAF mutated. Based on these data, a new Cohort 4 in C-144-01 has been initiated to support lifileucel registration. Clinical trial information: NCT02360579.

2520 Poster Discussion Session; Displayed in Poster Session (Board #164), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Impact of bridging chemotherapy on clinical outcome of CD19 CAR T therapy in adult ALL.

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Background: Autologous chimeric antigen receptor (CAR) T cell therapy has shown to be effective in CD19+ relapsed or refractory (R/R) B-ALL but requires a 2-4 week period of cell processing and manufacture. During this "bridging period," patients are vulnerable to disease progression and complications. We sought to characterize bridging strategies in our published study of CD19 CAR T cell therapy in adults with R/R ALL (Park et al., NEJM, 2018). **Methods:** We performed a retrospective review of adult patients with R/R ALL treated with 19-28z CAR T therapy at MSKCC. Bridging therapy was defined as any therapy given from trial enrollment to cell infusion and classified as either high intensity (remission-inducing or myelosuppressive regimens, eg hyper-CVAD or high-dose cytarabine based regimens) or low intensity (maintenance and/or less myelosuppressive regimens, eg POMP, Blinatumomab, TKI). **Results:** Of 53 patients who received CAR T cell infusion, 19 were bridged with a high intensity regimen and 34 with a low intensity regimen. There was no difference in number of prior therapies, pre-bridging chemotherapy disease burden, and prior transplant status between groups. High intensity therapy was associated with a higher rate of Gr3-4 infectious complications during the bridging period (78% vs 32%, $p < 0.002$ by Fisher's Exact) but not with response to bridging or CAR T cell therapy, relapse free survival, post-CAR Gr3-4 cytokine release syndrome (CRS) or neurotoxicity (NT). Patients in both groups who converted from morphologic to molecular disease during bridging (n=9) had a decreased rate of eventual severe CRS (0% vs 41%, p=0.01) or NT (0% vs 55%, $p < 0.01$) compared to patients with persistent morphologic disease. In all patients enrolled on trial (n=83), use of high compared to low intensity bridging was not associated with higher rates of successful CAR T cell infusion (63% vs 79%, $p > 0.05$) or a combined endpoint of CAR T cell infusion or alternative therapy including transplant (80% vs 86%, $p > 0.05$). **Conclusions:** High intensity bridging therapy is associated with a high risk of infectious complications without a clear benefit in outcome in R/R ALL receiving CD19 CAR T cells. Selection of bridging regimen therefore requires consideration of previous treatments and patient status to maximize the efficacy and safety. Clinical trial information: NCT01044069.

2521 Poster Discussion Session; Displayed in Poster Session (Board #165), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

First-in-human first-in-class phase I trial of murlentamab, an anti-Mullerian-hormone receptor II (AMHRII) monoclonal antibody acting through tumor-associated macrophage (TAM) engagement, as single agent and in combination with carboplatin (C) and paclitaxel (P) in AMHRII-expressing advanced/metastatic gynecological cancer patients (pts).

Alexandra Leary, Ahmad Awada, Jean-Pierre Delord, Anne Floquet, Isabelle Laure Ray-Coquard, Cyril Abdeddaim, Michel Fabbro, Elsa Kalbacher, Ignace Vergote, Susana N. Banerjee, François-Xavier Frenois, Grégory Noël, Olivier Lantz, Lydie Cassard, Agnès Coste, Marine Villard, Fanny Lemee, Isabelle Marie Tabah-Fisch, Christophe Le Tourneau; Gustave-Roussy Cancer Campus, Villejuif, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, France; Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium; Toulouse University Cancer Institute IUCT-Oncopole, Toulouse, France; Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, Bordeaux, France; GINECO Group and Centre Léon Bérard, Lyon, France; Centre Oscar Lambret, Lille, France; GINECO & Institut du Cancer de Montpellier, Montpellier, France; CHU Jean Minjoz, Besançon, France; University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; The Royal Marsden Hospital, London, United Kingdom; Institut Universitaire du Cancer Toulouse, CHU Toulouse, Toulouse, France; Institut Jules Bordet - Université Libre de Bruxelles, Brussels, Belgium; Institut Curie, Paris, France; Laboratory of Immunomonitoring in Oncology, Gustave Roussy, Villejuif, France; UMR152 UPS-IRD, Toulouse, France; Hospices Civils de Lyon, Pierre-Bénite, France; GamaMabs Pharma, Toulouse, France

Background: Membranous expression of AMHRII is found in ~70% of gynecological tumors. Murlentamab (M) binds with high affinity both AMHRII (at cell membrane) and CD16 (on macrophage, via its low fucose Fc). M reprograms TAMs, restoring their antitumoral functions (phagocytosis) resulting in cytotoxic T cell reactivation. **Methods:** Pts with advanced/metastatic AMHRII-expressing ovarian, cervical or endometrial cancer with measurable disease and performance status ≤ 1 received M as single agent (SA) in 8 dose escalating and 2 expansion cohorts. Combination with CP was studied in 2 escalating cohorts. Safety, recommended dose determination, antitumor activity, pharmacodynamics (PD) effects (circulating immune cells and tumor microenvironment (TME) from paired biopsies) were assessed. **Results:** 68 heavily pretreated (median 4 prior lines) pts received M for 0.5 to 11 months (mo) (59 pts M SA and 9 pts M + CP). No dose limiting toxicity was reported. Most common toxicity was G1-2 asthenia (29 %). Eight pts (12%) had G $\geq$ 3 reversible toxicities (asthenia, nausea/vomiting, anorexia, arthralgia). No antidrug antibody was detected. One partial response (PR) was achieved with M SA in a granulosa pt. In CP combination, 4/9 pts (44%) responded to treatment (1 Complete Response and 3 PRs). Overall, 22/67 (33%) pts were progression-free at 4 mos. Among 17 pts treated $\geq$ 6 mos, 6/9 (67%) granulosa pts with M SA and 4/5 (80%) endometrium and cervix with CP combination had a longer PFS than under previous regimen. PD blood assessment of 25 pts treated with M SA showed an increase in classical monocytes, and T cells and neutrophils activation. Changes in TME under M will be presented. **Conclusions:** Murlentamab was very well tolerated, demonstrated immune PD effects and showed hints of antitumor activity. These results together with its innovative immunological mode of action support development of M in AMHRII-expressing cancers, in combination with chemotherapy or other immune oncology drugs. Clinical trial information: NCT02978755.

2522 Poster Discussion Session; Displayed in Poster Session (Board #166), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603).

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Background: Immune suppressive cells such as regulatory T cells (Tregs) or tumor-associated macrophages (TAMs) may contribute to resistance to anti-PD-1/PD-L1 inhibitors (A-PD1). Regorafenib, a potent inhibitor of angiogenic and oncogenic kinases, reduced TAMs in tumor models. The combination of regorafenib plus A-PD1 exhibited superior tumor growth suppression compared to either treatment alone in murine models. **Methods:** In this study, we enrolled patients (pts) with previously treated, advanced GC or CRC. The pts received regorafenib plus nivolumab in a dose-finding phase to estimate the maximum tolerated dose (MTD). Additional pts were enrolled in a dose-expansion phase to further establish the safety and determine the preliminary efficacy. Regorafenib of 80 to 160 mg was administered once daily for 21 on 7 days off with intravenous nivolumab 3 mg/kg every 2 weeks. The primary endpoint was dose-limiting toxicity (DLT) during cycle one (4 weeks) to estimate the MTD and the recommended dose. **Results:** Fifty pts were enrolled (25 GC; 25 CRC) until October 2018. The median prior treatment line was 3 (range 2-8). During dose-escalation, 3 DLTs were observed with regorafenib 160 mg, including grade (G) 3 maculopapular rash, mucositis and proteinuria, while there was no DLT with 80 or 120 mg. In the dose expansion cohort with regorafenib 120 mg, the dose was reduced to 80 mg owing to frequent G3 skin toxicities. Grade $\geq$ 3 treatment related adverse events occurred in 17 pts; the common events ($>$ 5%) being rash (14%), palmar-plantar erythrodysesthesia (10%), and proteinuria (8%). Objective tumor response was observed in 19 pts (38%) including 11 MSS GC, 7 MSS CRC and 1 MSI-H CRC for response rates of 44% in GC and 29% in MSS CRC. Three of the 7 A-PD1 pretreated GC pts achieved a partial response. The pre- and post-treatment tumor samples showed a reduction of $FoxP3^{hi}CD45RA^{-}$Tregs fraction at the tumor response. **Conclusions:** The combination of regorafenib 80mg plus nivolumab had a manageable safety profiles and encouraging anti-tumor activity in MSS GC and CRC pts, which warrants further investigations in a larger cohort. Updated biomarker analysis will be presented. Clinical trial information: NCT03406871.

2523 Poster Discussion Session; Displayed in Poster Session (Board #167), Sat, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:45 PM

A phase I multicenter study to assess the safety, tolerability, and immunogenicity of mRNA-4157 alone in patients with resected solid tumors and in combination with pembrolizumab in patients with unresectable solid tumors.

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Background: T-cell targeting of mutation-derived epitopes (neoantigens) has been demonstrated to drive anti-tumor responses. Immunizing patients against such neoantigens in combination with a checkpoint inhibitor (CPI) may elicit greater anti-tumor responses than CPI alone. Mutations are rarely shared between patients, thus requiring a personalized approach to vaccine design. **Methods:** A phase I dose escalation study of mRNA-4157 as adjuvant monotherapy in patients with resected solid tumors (melanoma, bladder carcinoma, HPV negative HNSCC, NSCLC, SCLC, MSI-High, or TMB High cancers) and in combination with pembrolizumab in patients with advanced or metastatic cancer is being conducted to evaluate safety. mRNA-4157 is a lipid encapsulated personalized vaccine encoding multiple neoantigens selected using a proprietary algorithm designed to induce neoantigen specific T cells and associated anti-tumor responses. Patients may receive up to 9 cycles (Q3W) of mRNA-4157 by intramuscular injection (0.04 – 1 mg). In the combination arm, pembrolizumab (200 mg) is administered for two cycles prior to combination with mRNA-4157; patients may continue pembrolizumab after completion of 9 cycles of combination therapy. Primary end points include safety, tolerability, and recommended phase 2 dose. **Results:** 33 patients received mRNA-4157; 13 as monotherapy and 20 in combination with pembrolizumab. No DLTs were reported, and treatment related AEs have generally been of low grade and reversible, and no drug related SAEs or AEs $\geq$ grade 3 have been observed. Of the 13 patients on adjuvant monotherapy (3 melanoma, 8 NSCLC, 2 MSI-High), 12 patients remain disease free on study, median follow-up of 8 months. 20 patients have been treated in combination (1 TMB-high, 4 bladder, 2 HNSCC, 1 melanoma, 7 NSCLC, 2 SCLC, 3 MSI-high), 12 had progressed on prior CPI, 16 have been restaged and there are 1 CR (on pembrolizumab prior to vaccination), 2 PR, 5 SD for at least 5 combination cycles, 5 PD, 2 iuPD, and 1 patient is non-evaluable for response but remains on study. Neoantigen specific T cell responses have been detected by IFN-γ ELISpot from PBMCs. **Conclusions:** mRNA-4157 is safe and well tolerated at all dose levels tested. Clinical responses have been observed in combination with pembrolizumab and neoantigen-specific T cells have been induced, supporting the advancement of mRNA-4157 to phase 2. Clinical trial information: NCT03313778.

2524 **Poster Session (Board #168), Sat, 8:00 AM-11:00 AM**

Targeting MHC-linked wild type p53 with TCR mimic single chain diabody for cancer immunotherapy.

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Background: Increased tumor suppressor protein p53 expression is observed in a wide range of human cancers. As a result there is intense interest in targeting p53 for cancer therapy. Intracellular p53 is inaccessible to therapeutic antibodies that bind cell surface proteins. However, intracellular proteins including p53 are degraded into peptides that are presented on cell surface in association with HLA class I molecules. Thus p53 peptide-HLA (p53-HLA) complexes can be antibody targets. **Methods:** Using phage display we identified a novel anti-p53-HLA single chain variable fragment (scFv) clone-43 that recognizes a wild-type p53 10-mer epitope bound to HLA-A*2402. By coupling our clone-43 scFv with an anti-CD3 scFv, we generated a single chain diabody (scDb) designed to activate T-cells against p53-expressing target cells. **Results:** *In-vitro* co-culture of clone-43 scDb with donor human T-cells and p53 expressing SIG-M5 cancer cells results in SIG-M5 cell killing and concomitant T-cell interferon gamma (IFNγ) release. In contrast, similar co-culture with SIG-M5 p53-knock out (KO) cells showed no cell killing and minimal IFNγ release demonstrating specificity of clone-43 to p53 expressing cells. Additionally, *in-vivo* growth of p53 expressing SW480 cancer cell xenografts in NSG mice was completely terminated by clone-43 scDb injections. A major concern for wild-type p53 epitope targeting is potential on-target off-tumor effect on non-cancerous tissue. We observed significant *in-vitro* clone-43 scDb mediated killing of human HLA-A*24:02 peripheral blood mononuclear cells. To better evaluate effect of clone-43 scDb on non-neoplastic human cells, we engrafted HLA-A*24:02 human CD34+ hematopoietic stem cells into NSG mice to generate a humanized mouse model with circulating mature human CD45+ cells. Clone-43 scDb treatment resulted in selective depletion of circulating human cells while the same cells persisted in mice treated with unrelated control scDb. **Conclusions:** Our observation that immune targeting of wild-type p53 epitope results in significant off-tumor hematopoietic cell death is contrary to previously published reports and carries important implications for future anti-p53 antibody and vaccine design for cancer immunotherapy.

2525 **Poster Session (Board #169), Sat, 8:00 AM-11:00 AM**

First-in-human, dose-escalation, phase (ph) I trial to evaluate safety of anti-Axl antibody-drug conjugate (ADC) enapotamab vedotin (EnaV) in solid tumors.

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Background: Axl, a transmembrane receptor tyrosine kinase, is aberrantly overexpressed in various human cancers and associated with poor prognosis and treatment resistance. EnaV, a novel ADC of anti-Axl human IgG1 and monomethyl auristatin E, demonstrated potent anti-tumor activity in xenograft models. **Methods:** In a ph1 trial (NCT02988817), patients (pts) with relapsed/refractory cancer received single agent EnaV, 0.3–2.8 mg/kg once every 3 wks (1Q3W) or 0.45–1.4 mg/kg 3 times over 4 wks (3Q4W). Endpoints included dose-limiting toxicities (DLTs), adverse events (AEs) and pharmacokinetics (PK). DLTs were classed as hematological (e.g. Grade [G] 3/4 febrile neutropenia; G4 neutropenia or anemia) or non-hematological (e.g. severe skin toxicities; G3/4 neuropathy or infusion reactions; ≥G3 treatment-related AEs in first treatment cycle). Upon determining maximum tolerated dose (MTD) per arm and recommended ph2 dose (RP2D), ph2a (dose expansion) will enroll ≤297 pre-treated pts with advanced/metastatic cancer in 7 cohorts. **Results:** 47 pts with NSCLC (n=8), melanoma (n=9), ovarian (n=22), cervical (n=3) and endometrial (n=5) cancer enrolled in ph1 (1Q3W n=32; 3Q4W n=15). Most pts were female (87%), White (94%) and aged <65 y (66%). MTD was 2.2 mg/kg in 1Q3W arm and 1.0 mg/kg in 3Q4W arm; RP2D was 2.2 mg/kg 1Q3W. EnaV median elimination half-life: 0.9–2.2 d across doses/schedules. In 47 enrolled pts, there were 6 DLTs (Table). Most common AEs (any G; ≥40% pts) were fatigue (64%), nausea (57%), constipation (57%), diarrhea (47%), vomiting (45%) and decreased appetite (43%). 3 pts (1Q3W arm) had partial response (1 NSCLC [2.2 mg/kg dose]; 2 ovarian [1.5 and 2.4 mg/kg dose levels]). **Conclusions:** The RP2D of single agent EnaV in pre-treated pts with solid tumors was 2.2 mg/kg 1Q3W. EnaV had encouraging preliminary anti-tumor activity and will be evaluated in 7 ph2a expansion cohorts to further assess safety, tolerability, PK, anti-tumor activity and Axl expression. Funding: Genmab A/S. Clinical trial information: NCT02988817.

DLT	Dose, mg/kg (n)
1Q3W	
Constipation	2.0 (1); 2.2 (1)
Vomiting	2.2 (1)
γ-glutamyltransferase increase	2.4 (1)
3Q4W	
Febrile neutropenia	1.2 (1)
Diarrhea	1.2 (1)

2526 **Poster Session (Board #170), Sat, 8:00 AM-11:00 AM**

A phase Ia/Ib trial of the anti-PD-L1 human monoclonal antibody (mAb), CS1001, in patients (pts) with advanced solid tumors or lymphomas.

Lin Shen, Junning Cao, Jin Li, Hongming Pan, Nong Xu, Yan Zhang, Jingru Wang, Yin Wang, Hangjun Dai; Beijing Cancer Hospital, Beijing, China; Fudan University Shanghai Cancer Center, Shanghai, China; Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; The First Affiliated Hospital , Zhejiang University, Hangzhou, China; CStone Pharmaceuticals (Su Zhou) Co., Ltd., Suzhou, China

Background: CS1001 is the first full-length, fully human anti-PD-L1 mAb developed by the OMT transgenic rat platform, which mirrors natural IgG4 human antibody with expected PK profiles, and may potentially reduce the risk of immunogenicity and toxicity in pts. This first-in-human Phase Ia/Ib study of CS1001 was conducted to evaluate the safety, tolerability, PK profile, and anti-tumor activity of CS1001 in pts with advanced solid tumors or lymphomas. **Methods:** Pts with advanced solid tumors or lymphomas were enrolled in the dose escalation Phase Ia, receiving CS1001, Q3W, IV, at escalating doses from 3, to 10, 20, 40 mg/kg and 1200 mg. Dose escalation was aided by a 3+3 dose escalation scheme. DLT was evaluated within 3 weeks after the initial dose. Pts with various tumor types were enrolled in the dose expansion Phase Ib to assess anti-tumor activity and safety, including NSCLC, esophageal carcinoma, GC, HCC, cholangiocarcinoma, etc. Safety was assessed by monitoring AEs and the associated grades per NCI CTCAE v4.03, tumor assessed per RECIST v 1.1 (solid tumors) or Lugano 2014 (lymphomas). **Results:** As of 30 Nov 2018, 29 pts, median age of 53 (23-75) yrs, were enrolled in Phase Ia, 3 mg/kg (N = 3); 10 mg/kg (4); 20 mg/kg (3); 40 mg/kg (3) and 1200 mg flat dose (16). A total of 20 pts discontinued treatment due to disease progression (14), death (2), withdrawal by pts (2) and AEs (2; Grade [G] 4 hepatic function abnormal and G3 pulmonary tuberculosis, both were not related to treatment). 9 pts remain on treatment. Median treatment duration was 126 (21-408+) days. No DLTs were observed. 27 of 29 pts had TRAEs with the most frequent TRAEs including anaemia (14), proteinuria (13) and blood bilirubin increased (8). G3 TRAEs include anaemia (2) and platelet count decreased (1). SAEs were reported in 6 pts and they were TRAEs. Three G4 AEs were reported: anaemia (1), hypokalaemia (1) and hepatic function abnormal (1), they were not TRAEs as determined by the investigators. irAEs occurred in 7 pts (24%). Among the 29 evaluable pts, 7 pts had PR and 8 had SD, mDoR was not reached. In Phase Ib, 97 pts were enrolled, with 65 pts on treatment and 32 pts discontinued from treatment. The most frequent reason on the discontinuation was disease progression (21). Phase Ib enrollment is still ongoing. **Conclusions:** CS1001 is well tolerated without DLT across tested dose levels. Evidence of anti-tumor activities was observed. Currently, 1200 mg flat dose Q3W is being explored in various tumor types in Phase Ib, and safety and efficacy results will be displayed in the presentation. Clinical trial information: NCT03312842.

2527 **Poster Session (Board #171), Sat, 8:00 AM-11:00 AM**

A phase I study to assess safety, pharmacokinetics (PK), and pharmacodynamics (PD) of JNJ-64457107, a CD40 agonistic monoclonal antibody, in patients (pts) with advanced solid tumors.

Emiliano Calvo, Victor Moreno, Ruth Perets, Tamar Yablonski-Peretz, Nele Fourneau, Suzette Girgis, Yue Guo, Peter Hellemans, David Hokey, Natalia Pendas Franco, Qi Xia, Ravit Geva; START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; START Madrid - FJD, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Rambam Health Care Campus, Haifa, Israel; Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel; Johnson and Johnson Janssen Pharmaceutical Companies, Beerse, Belgium; Janssen Research & Development, LLC, USA, Philadelphia, PA; Janssen Research & Development, PA, USA, Spring House, PA; Janssen Research & Development, LLC, Beerse, Belgium; Janssen Research & Development, PA, USA, Philadelphia, PA; Janssen Research & Development, Madrid, Spain; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: JNJ-64457107 (JNJ-107) is an agonistic human monoclonal (IgG1) antibody targeting CD40, a novel target for anti-tumor immunotherapy with a central role in adaptive and innate immunity. **Methods:** JNJ-107 was administered intravenously Q2W in treatment cycles of 28 days. Dose escalation was pursued with (w) and without (wo) pre-infusion steroids for mitigation of infusion related reactions (IRRs). Dose-limiting toxicity (DLT), safety, PK, PD and antitumor activity were evaluated. **Results:** 95 pts of age 18-80 years (median 59) were enrolled in 7 cohorts (n = 50, 75μg/kg – 2000 μg/kg) w/steroids and 5 cohorts (n = 45, 75 μg/kg – 1200 μg/kg) wo/steroids and received 1-26 (median 3) cycles of JNJ-107. Two DLTs occurred: Grade (G) 3 headache lasting 5 days at 1200 μg/kg w/steroids and G3 ALT/AST + G2 bilirubin increase at 1200 μg/kg wo/steroids. Most frequent adverse events (≥20%) were pyrexia (41%), fatigue (39%), pruritus (39%), headache (26%), chills (26%), nausea (22%) and rash (21%). IRRs were reported in 51% of pts (G1-G2 50%, G3 1%). Most commonly reported IRRs (≥10%) were pruritus (31%), rash (15%), chills (13%) and flushing (12%). Cetirizine and Montelukast premedication during dose escalation wo/steroids significantly reduced IRRs. Preliminary PK of JNJ-107 suggest target mediated drug disposition with rapid decline in serum concentrations (half-life of ~13h at 600 μg/kg and ~ 24h at doses ≥1200 μg/kg). Dose proportional increase in C_{max} and AUC(last) was observed at doses ≥1200 μg/kg and more than dose proportional increase was seen at lower doses. PD of JNJ-107 demonstrated dose-independent reduction in peripheral blood B cells recovering in a dose-dependent manner. MCP-1, IP-10, MIP-1a, and MIP-1b cytokines showed high-level responses with cytokine/chemokine secretion kinetics consistent, but not confirmatory, for activation of antigen presenting cells. IFNg, TNF, and IL-8 showed moderate responses reflecting downstream T cell activation. Other tested cytokines were at low levels. A partial response lasting 9.2 months was observed in 1 pt with renal cell cancer. 13 (14%) and 10 (11%) pts showed stable disease lasting ≥3 months and ≥ 6 months, respectively. **Conclusions:** The CD40 agonist JNJ-107 has a manageable safety profile with favorable PK and PD properties. Future clinical development will require combination with either chemotherapy, or other immunotherapies such as antitumor vaccines or checkpoint inhibitors. Clinical trial information: NCT02829099.

2528 **Poster Session (Board #172), Sat, 8:00 AM-11:00 AM**

Ramucirumab (Ram) and durvalumab (Durva) treatment of metastatic non-small cell lung cancer (NSCLC), gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, and hepatocellular carcinoma (HCC) following progression on systemic treatment(s).

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Background: A Phase 1b study (NCT02572687) was conducted to examine the combined effects of Ram (anti VEGFR2) and Durva (anti PD-L1). **Methods:** Patients (pts) with previously-treated, advanced NSCLC (Cohort [CH] A), G/GEJ adenocarcinoma (CH B), HCC (CH C), ECOG PS 0-1, and no prior Ram or IO therapy, received Ram (10 mg/kg) + Durva (1125 mg) Q3W (CH A) or Ram (8 mg/kg) + Durva (750 mg) Q2W (CH B, C). Primary objective was to assess safety; efficacy was also examined. PD-L1 expression of tumor cells (TC) +/- immune cells (IC) in pretreatment tumor biopsies were assessed using SP263 immunohistochemistry. "High" PD-L1 is ≥25% TC for NSCLC and ≥25% TC or IC for G/GEJ, HCC. **Results:** CH A, B and C enrolled pts with ECOG PS 1 (%) of 43, 66, 68; and average of 2, 2, 1 prior regimens, respectively. The most common grade 3/4 treatment-emergent adverse events (AE) are hypertension (HTN) (14.3, 17.2, 17.9%), anemia (3.6, 24.1, 21.4%), and fatigue (10.7, 10.3, 10.7%). Grade 3/4 AEs of special interest (> 5% total pts) for Ram: HTN, bleeding events (3.6, 10.3, 10.7%), Venous thromboembolic events (0, 10.3, 7.1%); for Durva: increase in lipase (10.7, 3.4, 10.6%) and AST (3.6, 3.4, 17.9 %). Data from CH B,C suggest a trend toward increased efficacy in pts with high PD-L1 expressing tumors. **Conclusions:** Ram + Durva generated no unexpected toxicities and demonstrated antitumor activity. Results in pts with high PD-L1 HCC and G/GEJ cancer warrant further evaluation. Clinical trial information: NCT02572687.

PD-L1 subgroup	(A) NSCLC Total N = 28	(A) NSCLC High n = 5	(A) NSCLC Low n = 17	(B) G/GEJ Total N = 29	(B) G/GEJ High n = 14	(B) G/GEJ Low n = 12	(C) HCC Total N = 28	(C) HCC High n = 11	(C) HCC Low n = 15
ORR, n (%)	3 (11)	1 (20)	2 (12)	6 (21)	5 (36)	0	3 (11)	2 (18)	0
Disease control rate (ORR+SD rate), n (%)	16 (57)	3 (60)	9 (53)	16 (55)	10 (71)	4 (33)	17 (61)	8 (73)	7 (47)
Median duration of response, mo (95% CI)	- (16.6, -)			15.4 (3.25, -)			- (5.6, -)		
Median PFS, mo (95% CI)	2.7 (1.6, 5.8)	4.1 (1.4, -)	2.6 (1.3, 5.8)	2.6 (1.5, 7.1)	5.5 (1.8, 6.8)	1.5 (1.4, 2.6)	4.4 (1.6,5.7)	5.6 (1.5, -)	2.8 (0.7, 5.5)
Median OS, mo (95% CI)	11.0 (6.2, 15.2)	16.4 (11.0, -)	7.5 (3.7, 13.2)	12.4 (5.5, 16.9)	14.8 (7.2, -)	5.5 (3.3, 16.2)	10.7 (5.1, 18.4)	16.5 (5.1, 18.4)	5.7 (1.9, 14.4)

2529 **Poster Session (Board #173), Sat, 8:00 AM-11:00 AM**

Phase 1a/1b study of first-in-class B7-H4 antibody, FPA150, as monotherapy in patients with advanced solid tumors.

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Background: B7-H4, a transmembrane protein of the B7 family, is a negative regulator of T cell function, expressed at high levels on several cancers, including approximately 50% of breast, ovarian and endometrial cancers. FPA150 is a fully human antibody against B7-H4 that blocks inhibition of T cell activity and has enhanced antibody-dependent cell-mediated cytotoxicity. It is the first therapeutic molecule targeting B7-H4 to enter the clinic. We report preliminary results from an ongoing phase 1a/1b study of FPA150 in advanced solid tumors. **Methods:** Phase 1a included dose escalation in which B7-H4-unselected patients with advanced solid tumors were treated with FPA150 at doses between 0.01 to 20 mg/kg every three weeks (Q3W) in an accelerated titration followed by 3+3 design and a separate dose exploration cohort in which B7-H4+ (H-score≥100) patients were treated at doses of 3 or 10 mg/kg Q3W with mandatory pre- and on-treatment biopsies. **Results:** As of 12/31/2018, 24 patients with a median of 3 prior therapies were treated with FPA150, 6 of whom were in the B7-H4+ dose exploration cohort. Seven patients from dose escalation were also retrospectively identified as B7-H4+. Most patients received FPA150 at 3 mg/kg (n=8) or 10 mg/kg (n=6). Median number of doses was 3 (range 1-11). No dose-limiting toxicities or treatment-related serious adverse events were reported, and there were no treatment-related AEs (TRAEs) leading to discontinuation of FPA150. Most TRAEs were Grade 1-2, with diarrhea and fatigue most common (16.7%). Grade 3 TRAE hypertension occurred in 1 patient. FPA150 displayed approximately dose-proportional exposure at doses ≥0.3 mg/kg with half-life of 1-2 weeks. **Conclusions:** FPA150 monotherapy demonstrated a favorable safety profile and evaluation of anti-tumor activity is ongoing. 20 mg/kg Q3W was selected as the recommended dose. Phase 1b enrollment of FPA150 monotherapy in patients with B7-H4+ breast, ovarian and endometrial cancer began in February 2019. We will present updated safety, PK, and preliminary biomarker and efficacy data. Clinical trial information: NCT03514121.

2530 **Poster Session (Board #174), Sat, 8:00 AM-11:00 AM**

Tumor responses and early onset cytokine release syndrome in synovial sarcoma patients treated with a novel affinity-enhanced NY-ESO-1-targeting TCR-redirected T cell transfer.

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Background: Adoptive transfer of TCR-redirected T cells has been reported to exhibit efficacy in some of melanoma and sarcoma patients. However, there have not been well known about cytokine release syndrome (CRS) or its relations to tumor responses. This study evaluates clinical responses in association with the cell kinetics and CRSs after transfer of high-affinity NY-ESO-1 TCR-gene transduced T cells in NY-ESO-1-expressiong cancer patients (NCT02366546). **Methods:** We developed a novel-type affinity-enhanced NY-ESO-1-specific TCR and an originally-developed retrovirus vector that encodes siRNA to silence endogenous TCR creation. The NY-ESO-1/TCR sequence is mutated for high affinity with replacements of G50A and A51E in CDR2 region. This is a first-in-man clinical trial of the novel NY-ESO-1-specfic TCR-T cell transfer to evaluate the safety, in vivo cell kinetics and clinical responses. It was designed as a cell-dose escalation from 5×10^8 to 5×10^9 cells. NY-ESO-1-expressing refractory cancer patients were enrolled, with 3+3 cohort design. Cyclophosphamide (1,500mg/m^2) were administered prior to the TCR-T cell transfer as pre-conditioning. **Results:** 9 patients were treated with the NY-ESO-1/TCR-T cell transfer. The TCR-T cells expanded in peripheral blood with a dose-dependent manner, associated with rapid proliferation within 5 days after the cell transfer. 3 patients receiving 5×10^9 cells developed early-onset CRSs, with elevations of serum IL-6, IFN-γ. The CRSs developed on day1 or 2 after the cell transfer. They were well managed with tocilizumab treatment. 3 synovial sarcoma patients exhibited tumor shrinkages of partial responses, and they all had high-expression of NY-ESO-1 in the tumor samples, namely, 75% or more. Exploratory analysis revealed that multiple chemotactic cytokines including CCL2 and CCL7, and IL-3 increased in the serum from the patients with CRS. The proportions of effector-memory phenotype T cells in the infused cell-product were significantly associated with CRS development. **Conclusions:** The affinity-enhanced NY-ESO-1/TCR-T cell transfer exhibited early-onset CRS in association with in vivo cell proliferation and sequential tumor responses in the patients with high-NY-ESO-1-expressing synovial sarcoma. Clinical trial information: NCT02366546.

2532 **Poster Session (Board #176), Sat, 8:00 AM-11:00 AM**

Correlation of circulating EBV-targeted cytotoxic T lymphocyte precursors (EBV-CTLp) and clinical response following tabelecleucel (tab-cel) infusion in patients with EBV-driven disease.

Blake T. Aftab, Daniel Munson, Kevin Rasor, Philippe Foubert, Donald Edward Tsai, Wen-Kai Weng, Armin Ghobadi, Koen Van Besien, Yan Sun, Minoti Hiremath, Willis H. Navarro, Susan Prockop; Atara Biotherapeutics, Thousand Oaks, CA; Abramson Cancer Center, Philadelphia, PA; Stanford University Medical Center, Stanford, CA; Washington University in St. Louis, St. Louis, MO; Weill Cornell Medcl Coll, New York, NY; Atara Biotherapeutics, Inc., Thousand Oaks, CA; Atara Biotherapeutics, South San Francisco, CA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: EBV is implicated in a variety of diseases. Tab-cel is an investigational off-the-shelf, allogeneic T-cell immunotherapy utilizing endogenous T cell receptors targeting EBV antigens. We hypothesized the clinical activity of tab-cel is mediated by expansion and persistence of EBV-specific T cells. Therefore, we quantified circulating EBV- CTLp after tab-cel administration and examined the correlation between expansion and clinical response. **Methods:** Samples from 10 patients with EBV^+ post-transplant lymphoproliferative disease **(**PTLD) and other EBV-associated diseases enrolled in an multi-center expanded access protocol (EAP) study (NCT02822495) were analyzed. To evaluate CTLp frequencies, limited dilution analysis was performed on samples taken at baseline and day 34 post first tab-cel dose (end cycle 1). The day 34 persistence of circulating EBV-CTLp from best overall response to initial tab-cel product was tested using the two-tailed Mann-Whitney test. Changes in inflammatory cytokines were also measured. **Results:** Responders represented in this sampling (n=6; 2 PR and 4 CR) showed a median 5.8-fold increase in circulating CTLp between baseline and day 34 (range: 0.8 to 133-fold). Five of 6 responders showed an increase in EBV-CTLp at day 34 of $\geq$ 3.8-fold while 1 pt showed no change in CTLp (0.8-fold change). In contrast, the 4 non-responders (3 SD; 1 PD) showed a median 0.3-fold decrease in EBV-CTLp from baseline (range: 1.2 to 0.02-fold; ns). Cumulative analyses revealed a statistically significant correlation between the fold-change of circulating CTLp at day 34 and clinical response (p=0.038) which did not appear to correlate with the type of the EBV-associated disease. Inflammatory cytokines showed no meaningful change from baseline. The safety profile remains consistent with previously reported data. **Conclusions:** These data support the correlation of clinical activity of tab-cel with the expansion and persistence of EBV-specific T-cells at day 34 post-treatment, as well as the use of circulating CTLp as a biomarker for response in clinical studies. Clinical trial information: NCT02822495.

2533 **Poster Session (Board #177), Sat, 8:00 AM-11:00 AM**

Phase I study of OKT3 x hu3F8 bispecific antibody (GD2Bi) armed T cells (GD2BATs) in GD2-positive tumors.

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Background: With the proven success of anti-GD2 monoclonal antibodies in eradicating minimal residual disease in neuroblastoma (NB), exploiting antibody based anti-GD2 in T cell mediated strategies has potential to combat higher disease burden and improve patient outcome. We hypothesized that arming of ex vivo expanded and activated, autologous, blood derived T cells (ATC) with chemically heteroconjugated GD2Bi should redirect them to target NB. In vitro, ATC coated (armed) with 50 ng/10^6 cells of GD2Bi exhibited specific killing of NB and osteosarcoma (OS) cell lines. **Methods:** In this phase I study (NCT02173093), patients with GD2-positive tumors received 8, biweekly infusions of GD2BATs + daily low-dose IL-2 and biweekly granulocyte-macrophage colony stimulating factor (GM-CSF). The study followed the standard 3+3 design with dose levels of 40, 80, and 160 x 10^6 GD2BATs/kg/infusion. **Results:** Twelve patients (NB = 7, OS = 3, Desmoplastic Small Round Cell Tumor = 2) were enrolled from 11/2013 to 12/2017 and 9 completed therapy. Adequate ATCs could not be grown in one patient and two patients did not complete 8 infusions because of rapid disease progression. Infusions were given in outpatient settings. All patients developed a mild, dose-independent and manageable form of cytokine release syndrome with grades 2-3 fevers/chills, headaches and occasional hypotension for up to 48 hours after infusion. No patients developed significant pain. Maximum tolerated dose was not reached. Evidence of activity was seen in several patients including one patient with OS who had a PET response, one patient with NB who had complete bone marrow response (this patient had remained progression free for 2.5 years after completion of infusions), and another NB patient who had a minor response on MIBG scan. Four patients with NB are currently alive after additional therapies at 12, 14, 18, and 47 months post BAT infusions. **Conclusions:** Autologous T cells from heavily pretreated patients could be expanded ex vivo to large numbers, armed with GD2Bi, cryopreserved and thawed for safe IV administration up to total dose of 1.28x10^9/kg. Ongoing phase II arm of the trial will focus on evaluation of clinical activity of GD2BATs in patients with NB. Clinical trial information: NCT02173093.

2534 **Poster Session (Board #178), Sat, 8:00 AM-11:00 AM**

Efficacy and safety of CAR19/22 T-cell "cocktail" therapy in patients with refractory/ relapsed B-cell non-Hodgkin lymphoma.

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Background: Antigen escape relapse has emerged as a major challenge for long-term disease control post CD19-directed therapies, to which dual-targeting of CD19 and CD22 has been proposed as a potential solution. **Methods:** Between Mar 2016 and Jan 2018, we conducted a pilot study (ChiCTR-OPN-16008526) in 38 patients (pts), who had refractory/relapsed B-cell non-Hodgkin lymphoma (B-NHL), to evaluate the efficacy and safety of sequential infusion of anti-CD19 and anti-CD22, two single-specific, third-generation CAR19/22 T-cell "cocktail". The cutoff date for data collection was Apr 30, 2018. **Results:** At a minimum follow-up of 3 months (mos), 26 of the 36 evaluable pts achieved an overall response (ORR), including 18 with a complete response (CR) and 8 with a partial response (PR). The ORR at mo 3 was consistent in different subgroups, irrespective of pathologic subtypes, cell of origin, cytogenetic or genomic aberrations. At the data cutoff, 15 of the 18 pts who had a CR at mo 3 maintained their responses, 2 of 8 pts who had a PR within 3 mos continued to have a CR without additional therapies. Collectively, the best ORR was 83.3%, with a best CR rate of 55.5% and a best PR rate of 27.8%. With a median follow-up of 5.3 mos (range, 0.4 to 16.2), the median PFS was 5.8 mos, and the median OS was not reached (NR). Pts received therapy at first relapse had better PFS than those who received therapy at the time with primary refractory diseases or at multiple relapses. Notably, pts who achieved an overall response at mo 3 (R3m) had significantly extended PFS and OS when compared with pts who did not. Repeated biopsy and IHC was conducted in 3 of the 13 pts. However, loss of CD19 or CD22 was not detected. Of the 9 pts with *IgH/MYC* translocation, with a median follow-up of 10.1 mos, the median PFS and median OS were NR. At data cutoff, 7 pts who had achieved R3m maintained their responses, including all the 4 pts with double-hit lymphoma. However, of the 10 pts with del(17p) or *TP53* mutation, with a median follow-up of 5.3 mos (range, 2.7 to 14.5), the median PFS was 3.6 mos and the median OS was 9.9 mos. All pts experienced reversible CRS, with 21.1% were of high-grade. Neurotoxicity developed in 13.2% pts and were all low-grade. **Conclusions:** Our results indicated that sequential infusion of CAR19/22 T-cell is efficient and safe for pts with B-NHL. Dual antigen targeting is a promising approach to circumvent antigen loss relapse after CAR T-cell therapy. The impact of genetic subtypes and clinical parameters further underscores the critical importance of personalized immunotherapies. Clinical trial information: ChiCTR-OPN-16008526.

2535 **Poster Session (Board #179), Sat, 8:00 AM-11:00 AM**

The phase I clinical study of CART targeting BCMA with humanized alpaca-derived single-domain antibody as antigen recognition domain.

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Background: Several phase I clinical trials already shown Chimeric antigen receptor T cells (CART) targeting BCMA has the promised effects to treat the relapsed/refractory (RR) multiple myeloma (MM), RRMM. We developed CART cells (CART-BCMA) using one single-domain antibody as recognition domain. The anti-BCMA single-domain antibody was derived from the alpaca, and humanized with the affinity of 1.14nM. The CART-BCMA use the 4-1BB and CD3ζ intracellular regions as T cell activation domain. **Methods:** A phase I, single arm clinical study was conducted to assess safety and efficacy of CART-BCMA. The enrolled RRMM patients had received average 10 lines of prior treatment, no matter BCMA expression level on plasma cells. Patients were subjected to a lymphodepleting regimen with Cy (300-600 mg/m^2, d-5, -4) and Flu (30 mg/m^2, d-5 to d-3) before CART infusion at the dose of 2-10$\times$10^6 CAR$^+$ cells/kg. The efficacy was assessed based on the IMWG Criteria, and the toxicity was graded by CTCAE 4.02. **Results:** As of December 31, 2018, 16 patients were infused with autologous CART-BCMA cells, and had at least 1 month of follow-up. Many patients have M protein in serum, but haven't the high percent of plasma cells in bone marrow, which are difficult to be treated by CART cells because the tumor cells are aggregated, not diffused in bone marrow. 3 patiens were diagnosed with extramedullary diseases, were evaluated as PR at D28 (tumor SPD decreasing > 50%). 13 patients haven't extramedullary diseases, at D28, ORR is 84.6% (11/13); At 10 weeks, 7 patients were evaluated, ORR is 100% (sCR/CR 42.8%, VGPR 14.3% , PR 42.8%); 5 patients reached 16 weeks, 1 relapsed, 4 kept remission. The Pt3 and Pt6 shows the CRS grade 3 or 4, other patients shows the grade 0-2 CRS, the CRS is manageable. **Conclusions:** Our result demonstrates the promising efficacy compared with other reported results of CART targeting BCMA, and supports further development of this anti-RRMM cellular immunotherapy. Clinical trial information: NCT03661554.

2536 **Poster Session (Board #180), Sat, 8:00 AM-11:00 AM**

Ligand-inducible, prostate stem cell antigen (PSCA)-directed GoCAR-T cells in advanced solid tumors: Preliminary results with cyclophosphamide (Cy) ± fludarabine (Flu) lymphodepletion (LD).

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Background: Cell-surface protein PSCA is upregulated in many solid tumors and correlates with disease stage. BPX-601, an autologous T-cell product expressing a PSCA-CD3ζ CAR and a rimiducid (Rim)-inducible MyD88/CD40 co-activation switch to augment T-cell proliferation and persistence, is designed to have enhanced efficacy in solid tumors vs traditional CARs. This ongoing first-in-human study assesses safety, biologic, and clinical activity of BPX-601+Rim in PSCA+ cancers. Updated results, including those from patients (pts) who underwent LD with Flu/Cy, are presented. **Methods:** BP-012 is a 2-part, open-label trial. Part 1 is a 3+3 dose escalation of BPX-601 ($1.25–5.0x10^6$ cells/kg; Day [D] 0) given prior to a single, fixed Rim dose (0.4 mg/kg; D7) in pts with previously treated PSCA+ metastatic pancreatic, gastric, or prostate cancers with measurable disease. **Results:** As of Jan-22-2019, 15 pts have received BPX-601±Rim. Two pts at the highest cell dose received Flu/Cy for LD on D−5 to D−3 before BPX-601; LD after Flu/Cy was 96.6% and 84.3%. Thirteen pts received Cy alone on D−3; in these pts, LD ranged from 0–68.6%. Rapid cell expansion by D4 was observed in all pts with peak vector copy number 8.3-fold higher with Flu/Cy (n = 2) vs Cy LD (n = 13). Serum IP-10, IL-6 and TNFα increased > 2-fold from baseline in ≥1 pt in all Rim cohorts, with 3- to 20-fold Rim-dependent cell expansion in 6 pts. No CRS or DLTs were reported. After Rim, one Flu/Cy pt experienced a serious Grade 2 AE (encephalopathy) related to BPX-601+Rim that resolved with IV steroids; despite time-matched nonserious Grade 1 pyrexia, the pt had no other CRS symptoms. After BPX-601+Rim and ≥1 scan, best responses were 8 SD and 3 PD (1 non-evaluable). With a median follow-up of 9.8 wks, time to next treatment (tx) after BPX-601 ranged from 2.7–22.1 wks (n = 8) and ongoing tx-free intervals range from 9.1–30.1 wks (n = 4). **Conclusions:** BPX-601+Rim was well-tolerated with manageable safety and early evidence of enhanced CAR T-cell expansion and prolonged persistence after Flu/Cy vs Cy. Additional pts will undergo Flu/Cy LD prior to BPX-601 with single- and repeat-dose Rim. Clinical trial information: NCT02744287.

2537 **Poster Session (Board #181), Sat, 8:00 AM-11:00 AM**

Effect of minimal lymphodepletion prior to ACT with TBI-1301, NY-ESO-1 specific gene-engineered TCR-T cells, on clinical responses and CRS.

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Background: Adoptive transfer of T cell receptor (TCR) gene-engineered T cells can induce durable anti-cancer responses. Post-infusion cytokine release syndrome (CRS) has been associated with clinical utility. Pre-infusion lymphodepletion (LD) may influence CRS, graft persistence, and clinical responses. While the optimal LD regimen is not yet defined, most include both cyclophosphamide (CY) and fludarabine (FLU). TBI-1301 is a novel gene therapy produced by engineering autologous lymphocytes to express an NY-ESO-1-specific TCR using a retrovirus vector that encodes siRNA to silence endogenous TCR. Since less intensive LD may be sufficient with the use of this novel vector, we are conducting a study where patients are treated with TBI-1301 following LD with CY alone. **Methods:** Eligibility includes informed consent, HLA-A*02:01 or A*02:06 haplotype, and NY-ESO-1 expression by immunohistochemistry. Eligible patients undergo harvest of PBMC which are then processed locally to generate engineered TBI-1301 cells. The study design is to infuse $5x10^9$ cells (day 0) to patients following LD with CY (750 mg/m^2 on day -3 and -2). Endpoints include safety, efficacy, and biological correlates for persistence of NY-ESO-1-specific T cells post infusion. **Results:** Thus far, 9 patients have been treated, and 8 have received the target dose. To date, 8 patients are evaluable for response and toxicity, and no DLTs have been observed. Despite LD with CY alone, all 4 patients with synovial sarcoma and 1 with melanoma experienced clinical and laboratory evidence of grade 1-2 CRS with increased CRP, ferritin, and IL-6 levels. CRS resolved spontaneously in all but one patient who required tocilizumab due to grade 2 nausea/vomiting. Two subjects experienced grade 3 tumor-associated pain. Other treatment-associated grade 3 or 4 toxicities included neutropenia and hypophosphatemia. Best overall response by RECIST is as follows: 2 partial responses, 5 stable disease, and 1 progressive disease. Biomarker analysis demonstrates persistence of transferred TBI-1301 cells, $>$ 100 days in some patients. **Conclusions:** TBI-1301 appears to be safe and to possess anti-tumor activity. Despite LD with CY alone, grade 1-2 CRS is induced. Additional cohorts to this study will examine the role of repeat infusions to enhance anti-tumor activity. Clinical trial information: NCT02869217.

2538 **Poster Session (Board #182), Sat, 8:00 AM-11:00 AM**

Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma.

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Background: There is a high unmet medical need for effective treatments for patients with recurrent, metastatic, or persistent cervical cancer. Most patients are young and survival rates are poor. ORR for second line therapies is between 4 and 14% for chemotherapy and recently approved immunotherapy. Adoptive cell transfer using tumor infiltrating lymphocytes (TIL) have demonstrated durable responses in some patients with recurrent cervical cancer thus offering the potential for long-term disease control. **Methods:** Study C-145-04 is an ongoing, open-label, multicenter Phase 2 clinical trial evaluating the safety and efficacy of LN-145 TIL therapy in patients with advanced cervical cancer who have undergone at least one prior line of chemotherapy. Prior checkpoint inhibitor therapy is an exclusion criterion. The primary endpoint is ORR per RECIST 1.1; secondary endpoints include duration of response (DOR), disease control rate (DCR), and LN-145 safety. Tumors surgically harvested at local institutions are shipped to central GMP facilities for TIL generation in a 22-day manufacturing process. Final LN-145 TIL product is cryopreserved and shipped to sites. Patients receive one week of preconditioning lymphodepletion (cyclophosphamide, fludarabine), a single LN-145 infusion, followed by up to 6 doses of IL-2 (600,000 IU/kg). **Results:** As of 4 Feb 2019, 27 efficacy-c patients have received Gen 2 of LN-145, with a mean age of 47 years and 2.6 mean prior lines of therapy. Preliminary efficacy results: ORR was 44% (1 CR, 9 PR, 2 uPR), DCR was 89% at 3.5-month median study follow-up with 11/12 patients maintaining their response. Improved responses were observed in 4 patients with longer follow-up. Mean TIL cells infused was $28x10^9$. Median IL-2 doses administered was 6.0. The adverse event profile was generally consistent with the underlying advanced disease and the profile of the lymphodepletion and IL-2 regimens. **Conclusions:** LN-145 results in 44% ORR in previously treated cervical cancer patients with acceptable safety and efficacy profile. LN-145 offers patients a viable therapeutic option warranting further investigation. Clinical trial information: NCT03108495.

2539 **Poster Session (Board #183), Sat, 8:00 AM-11:00 AM**

Phase 1 trial of anti-CD19 chimeric antigen receptor T (CAR-T) cells with tumor necrosis alfa receptor superfamily 19 (TNFRSF19) transmembrane domain.

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Background: AntiCD19 CAR-T cells have shown encouraging anti-lymphoma activity. Decreasing the time from apheresis to CAR-T infusion can make this therapy available to pts with rapid progression. We present the interim results of a phase I clinical trial using on-site CAR-T manufacture. **Methods:** Adult pts with r/r CD19+ B cell lymphomas who failed $\geq$ 2 lines of therapy were enrolled. Autologous T cells were transduced with a lentiviral vector (Lentigen Technology, Inc,LTG1563) encoding an antiCD19 binding motif, CD8 linker and TNFRSF19 transmembrane region, and 4-IBB/CD3z domains. GMP-compliant manufacture was done using CliniMACS Prodigy, in a 12-day culture. Dose levels were 0.5, 1 and 2 x 10^6 CAR-T cells/kg. Lymphodepletion was done with cyclophosphamide (60mg/kg x 1) and fludarabine (25mg/m^2/d x 3). **Results:** 7 pts (4 women, 3 men) were enrolled. Median age was 60y [range 43-69]. Diagnoses were DLBCL (n = 3) PMBCL, follicular lymphoma (FL), transformed FL, and transformed lymphoplasmacytic lymphoma; with a median of 4 previous treatments. Six pts had symptomatic refractory disease. CAR-T cell product manufacture was successful in all pts. Mean transduction rate was 44% [range 29-57]. CAR-T cell doses were 0.5 x 10^6/kg (n = 3) and 1 x 10^6/kg (n = 4). Median apheresis to infusion time was 13 days [range 13–20], 5 products were infused fresh. CAR-T persistence based on vector sequence, peaked in peripheral blood MNCs between days 14-21. Five pts are evaluable for safety. CRS grade 1 - 2 (Lee) occurred in 4 pts; with 3 requiring treatment. Grade 4 CRES (CARTOX-10) occurred in 1 pt, with resolution after corticosteroids; considered a DLT as it lasted more than 72 hours. No treatment-related mortality has occurred. 4/5 evaluable pts have achieved complete response. One pt did not respond and died. After a median follow up 3 months, all responding pts are alive and 1 relapsed 6 mo after treatment. **Conclusions:** Second generation antiCD19 CAR-T cells with TNFRS19 transmembrane domain have clinical activity against refractory NHL. Short manufacture time achieved by local CAR-T cell manufacture with the CliniMACS Prodigy enables treatment of a very high risk NHL population. Clinical trial information: NCT03434769.

Comprehensive report of anti-CD19 chimeric antigen receptor T cells (CAR-T) associated non-relapse mortality (CART-NRM) from FAERS.

Kartik Anand, Ethan Burns, Dahlia Sano, Sai Ravi Pingali, Jason Westin, Loretta J. Nastoupil, Hun Ju Lee, Felipe Samaniego, Simrit Parmar, Michael Wang, Misha Hawkins, Sherry Adkins, Luis Fayad, Raphael Steiner, Ranjit Nair, Sairah Ahmed, Nathan Hale Fowler, Sattva Swarup Neelapu, Swaminathan Padmanabhan Iyer; Houston Methodist Cancer Center, Houston, TX; Houston Methodist Hospital, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas, MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center/University of Texas, Houston, TX

Background: CAR-T cells targeting CD19 positive B-cells have improved outcomes for relapsed/refractory non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia (B-ALL). CAR-T emergent toxicities for FDA approved therapies leading to non-progression related death have been reported in the pivotal studies. However, they are underreported and there remains a need to obtain a comprehensive report of NRM emergent with anti-CD19 CAR-T. **Methods:** We retrospectively searched FDA adverse events reporting system (FAERS) for all adverse events (AE) related to "Tisagenlecleucel(T)" and "Axicabtagene ciloleucel(AC)" reported from 2013-2018. FAERS contains AEs from clinical trials and standard of care patients. All cases with the outcome of death were analyzed. **Results:** Total numbers of anti-CD19 CAR-T pts reported were 636, out of which 288 cases received "T" and 348 received "AC". Out of total 129 total deaths, 95 died due to non-disease progression. Patient characteristics are summarized in Table. CART-NRM for entire cohort was 15%; 21% for "T" and 10% for "AC". Major toxicities reported include CRS, hematological, cardiovascular, neurological and infectious. Difference in mortality is likely related to different patient population, diagnoses and the CAR-T construct. **Conclusions:** CART-NRM remains considerably high at 15%. Our analysis highlights the major toxicities and informs the potential opportunities for interventions to reduce mortality. We will present updated data with comparative analysis of published clinical studies at the upcoming ASCO Meeting in Chicago.

Analysis of cases of anti-CD19 CAR-T NRM.

Total Deaths (n=95)	Tisangenlecleucel (n=61)	Axicabtagene ciloleucel (n=34)
Median age	21 years(3-78 years; n=57)	64 years(13-71 years; n=21)
Number of patients ≤18 years	26(median-age 7.5 years)	1(13 years)
Number of patients >18 years	31(median-age 48 years)	20(median-age 64 years)
Unknown age of patients	4	13
Sex	T	AC
Male	33	12
Female	25	17
Unknown	3	5
Indications	T	AC
ALL	31	2
NHL	13	23
Chronic lymphocytic leukemia	2	0
Unknown	15	9
Non Relapse Mortality*	T	AC
Cytokine release syndrome(CRS)	14(23%)	18(53%)
Hematological	28(46%)	9(26%)
Cardiovascular	29(47%)	14(41%)
Neurological	28(46%)	19(56%)
Renal	25(41%)	3(9%)
Gastrointestinal	17(28%)	9(26%)
Respiratory	20(32%)	8(23%)
Infectious	34(56%)	15(44%)
Hepatic	4(6%)	3(9%)
Median time to AEs	7 days	5 days

*Overlapping toxicities reported

2541 **Poster Session (Board #185), Sat, 8:00 AM-11:00 AM**

Clonal expansion of tumor infiltrating lymphocytes (TILs) in the peripheral blood of metastatic melanoma patients is significantly associated with response to CTLA4 blockade-based immunotherapy.

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Background: Patients with metastatic melanoma were treated on a clinical trial with tremelimumab and High Dose Interferon-Alfa (HDI) (Tarhini. J Clin Oncol. 2012). We previously reported that patients who achieved disease control and clinical response had significantly greater T-cell clonality ($p = 0.0008$) and T-cell fraction ($p = 0.044$) respectively in their pretreatment tumor biopsy samples (Tarhini. J Clin Oncol. 2017). In this study, we further characterize T-cell repertoire clonality and clonal expansion in the peripheral blood at different time points to evaluate the association between repertoire features and clinical response. **Methods:** Patients received tremelimumab 15 mg/kg I.V. every 12 weeks and HDI was given concurrently. Responses were assessed by RECIST as complete (CR) or partial (PR), stable disease (SD) or progression (PD). Peripheral blood mononuclear cells (PBMCs) from treated patients ($N = 33$) were obtained at baseline, day 29, and day 85 (following tremelimumab-HDI treatment); tumor samples at baseline were also obtained ($N = 18$). The T-cell receptor beta chain (TCRB) repertoire of PBMCs and tumor samples was immunosequenced using the immunoSEQ assay (Adaptive Biotechnologies), and repertoire clonality was assessed at baseline, day 29, and day 85. Differential abundance analysis was used to detect and quantify peripheral clonal expansion pre- versus post-treatment and identify the subset of peripheral clones also detected in the tumor repertoire. The Morisita Index of repertoire similarity was also calculated to compare global repertoire changes between pre- and post-treatment PBMC samples. **Results:** T-cell repertoire turnover, as measured by the Morisita Index, showed a trend towards responders (CR/PR) having greater turnover (lower Morisita Index) post-treatment than non-responders (SD/PD). Similarly, the total number of clones expanding in the peripheral repertoire varied over time within an individual ($p = 0.034$) but was not significantly affected by response to therapy ($p = 0.275$) or by on-treatment time point ($p = 0.768$). When the analysis was restricted to peripherally expanded clones that were also found in the tumor repertoire, responders had significantly more TILs expanded in the periphery at day 29 than non-responders ($p = 0.036$). **Conclusions:** Our analysis of the peripheral T-cell repertoire following treatment showed that detection of TILs in early peripheral clonal expansion correlates with response to therapy.

2542 **Poster Session (Board #186), Sat, 8:00 AM-11:00 AM**

Bespoke circulating tumor DNA (ctDNA) analysis as a predictive biomarker in solid tumor patients (pts) treated with single-agent pembrolizumab (P).

Marco Adelmo James Iafolla, Cindy Yang, Scott Dashner, Wei Xu, Aaron Richard Hansen, Philippe L. Bedard, Stephanie Lheureux, Anna Spreafico, Albiruni Ryan Abdul Razak, Hsin-Ta Wu, Svetlana Shchegrova, Zhihui (Amy) Liu, Pamela S Ohashi, Dax Torti, Maggie C Louie, Himanshu Sethi, Alexey Aleshin, Lillian L. Siu, Scott Victor Bratman, Trevor John Pugh; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Natera, San Carlos, CA; University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; Natera Inc., San Carlos, CA; Ontario Institute for Cancer Research, Toronto, ON, Canada; Natera, San Rafael, CA; Natera, Inc, San Carlos, CA; Stanford University Hospital, Palo Alto, CA; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Limited data exist in the clonal dynamics of serial ctDNA as a predictive biomarker in advanced solid tumor pts receiving immune checkpoint blockade. **Methods:** Pts with mixed solid tumors received single agent P (anti-PD-1) 200 mg IV Q3wks in the investigator-initiated phase II INSPIRE trial (NCT02644369). ctDNA was assayed at baseline (B) and start of cycle 3 (C3) using a pt-specific amplicon-based NGS assay (Signatera™). Samples were considered ctDNA positive if ≥2 of 16 pt-specific targets met the qualifying confidence score threshold. **Results:** Results of 70 pts are presented. Demographics: male 46%; median age=60 yrs (range 21–82); head and neck (20%), triple negative breast (14%) and ovarian (14%) cancers comprised the major malignancies. Median no. of P cycles=4 (range 2–35); follow up was 14m (range 2–29); RECIST responses: CR 2.9% (n=2), PR 17% (n=12), CBR (CR+PR+SD≥6 cycles) 31% (n=22), RECIST/clinical PD (n=43/10; 65%/15%). Median PFS=3.3m and median OS=17.8m. 68/70 pts had ctDNA detected at baseline (median=16/16 variants) demonstrating 97% sensitivity. Table shows correlation of ΔctDNA ($ctDNA_B$ compared to $ctDNA_{C3}$) with clinical efficacy parameters, whereas $ctDNA_B$ values did not reach statistical significance. **Conclusions:** A strong correlation exists between ΔctDNA with OS, PFS, CBR and ORR with P, suggesting it is a potential predictive biomarker in pts with mixed solid tumors. Clinical trial information: NCT02644369.

Endpoint	ORR N = 68*		CBR N = 68*		Endpoint	PFS N = 69*		OS N = 69*	
Subgroup	CR/PR N = 13	SD/PD N = 55	CR/PR/ SD≥6 cycles N = 20	SD<6 cycles/PD N = 48	Subgroup	↓ from baseline N = 31	↑ from baseline N = 38	↓ from baseline N = 31	↑ from baseline N = 38
ΔctDNA (% change)	Median = -91.5% Range = -100% to 18.1%	Median = 31.5% Range = -98.7% to 2,458.1%	Median = -75% Range = -100% to 96.1%	Median = 49% Range = -94.6% to 2,458.1%	Results based on ΔctDNA	Median = 5.6m 6m = 48.4%	Median = 2.9m 6m = 10.5%	Median = 24.0m 6m = 90.3% 12m = 79.9%	Median = 9.5m 6m = 73.7% 12m = 46.7%
P-value	P < 0.001		P < 0.001		Adjusted HR (95% CI)^	0.49 (0.28–0.84) P = 0.01		0.38 (0.18–0.80) P = 0.01	

^Adjustment on cohorts; *2 pts were excluded from ORR/CBR analyses as baseline ctDNA = 0; 1 of these 2 pts (with PR) excluded from PFS/OS analyses as C3 ctDNA = 0.

2543 Poster Session (Board #187), Sat, 8:00 AM-11:00 AM

Evolution of the myeloid-derived suppressor cells in advanced breast cancer and comparative analysis with a healthy population cohort.

Natalia Palazón-Carrión, Carlos Jiménez-Cortegana, Esther Holgado, Josefina Cruz Jurado, Jose Luis Alonso Romero, María Luisa Sánchez Leon, Victor Sanchez Margalet, Esteban Nogales, Fernando Moreno Anton, Vanesa Quiroga Garcia, Raquel Andres, Marta Santisteban, Javier Cortes, Luz Milva Rodríguez-Rodríguez, Asuncion Soto Gutierrez, Mana Gion Cortes, A. Nieto Garcia, Massimo Chiesa, Susana Bezares, Luis De la Cruz-Merino; Virgen Macarena University Hospital, Seville, Spain; Hospital Universitario Ramón y Cajal, GEICAM Spanish Breast Cancer Group, Madrid, Spain; Hospital Universitario de Canarias, GEICAM Spanish Breast Cancer Group, Santa Cruz de Tenerife, Spain; Hospital Clinico Universitario Virgen de la Arrixaca, GEICAM Spanish Breast Cancer Group, Murcia, Spain; Hospital Universitario Virgen Macarena, Seville, Spain; Biochemistry Department, Hospital Universitario Virgen Macarena, Seville, Spain; Hospital Universitario Virgen Macarena, Marbella, Spain; Hospital Clínico Universitario San Carlos, Madrid, GEICAM, Spanish Breast Cancer Group, Madrid, Spain; Badalona-Applied Research Group in Oncology: B-ARGO Group, Catalan Institute of Oncology, Spain-GEICAM, Spanish Breast Cancer Group, Barcelona, Spain; Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain, GEICAM Spanish Breast Cancer Group, Zaragoza, Spain; Clínica Universidad de Navarra, Pamplona, GEICAM, Spanish Breast Cancer Group, Pamplona, Spain; IOB Institute of Oncology, Quironsalud Group, Madrid & Barcelona, Vall d´Hebron Institute of Oncology (VHIO), Barcelona, GEICAM, Spanish Breast Cancer Group, Madrid & Barcelona, Spain; Hospital Universitario de Canarias, Santa Cruz de Tenerife, GEICAM, Spanish Breast Cancer Group, Tenerife, Spain; Hospital Universitario Virgen de la Arrixaca, GEICAM, Spanish Breast Cancer Group, Murcia, Spain; Hospital Ramon y Cajal. GEICAM, Spanish Breast Cancer Group, Madrid, Spain; Universidad de Sevilla, Seville, Spain; GEICAM Spanish Breast Cancer Group, Madrid, Spain; Hospital Universitario Virgen Macarena, GEICAM Spanish Breast Cancer Group, Seville, Spain

Background: High levels of myeloid-derived suppressor cells (MDSCs) seem a negative prognostic factor in advanced breast cancer (ABC) patients (pts). Preclinical studies suggest an immunomodulatory effect of some classical anti-tumor agents through alteration of MDSCs homeostasis. We analyzed the association of MDSCs and clinical evolution of ABC pts, taking into account the systemic treatment (tx) modulation of MDSCs levels in pts from two studies ("A": GEICAM/2015-04 PANGEA-BREAST, NCT03025880 "Efficacy and Safety of Pembrolizumab and Gemcitabine in HER2-negative ABC", and "B": PI-0502-2014 "Peripheral blood analyses of immune response induced by 1st line tx of ABC according to clinical guidelines"). **Methods:** MDSCs (CD33+ CD11b+) levels were determined by flow-cytometry in peripheral blood samples at three time points (basal, at cycles 3 and 6) from: 39 HER2-negative heavily pretreated pts from study "A", 43 non-pretreated pts (all subtypes) from study "B" and 20 women from a healthy cohort (HC), with no cancer diagnosis. MDSCs levels from the different cohorts were compared and correlated with pts with Clinical Benefit (CB: partial/complete response + disease stabilization) vs pts with Progressive Disease (PD). **Results:** Tx response was assessed in 33 pts (85%) from study "A" and 39 pts (91%) from study "B". CB was observed in 11 pts (28%) from study "A" and in 34 (79%) from study "B" while PD was observed in 22 pts (56%) from study "A" and in 5 (12%) from study "B". Basal MDSCs levels were significantly higher in ABC pts (studies "A"+"B") than in HC (15.95 vs 0.81 cells/μl, $p = 0.009$). At cycle 6, MDSCs were considerably lower in pts with CB vs DP (2.90 vs 13.75 cells/μl, $p < 0.001$). This decrease was more pronounced in study "B" than in study "A" pts ($p < 0.001$ vs $p = 0.074$, respectively), probably due to differences in number of events, tumor subtypes and tx between both studies. **Conclusions:** Our results suggest that ABC pts show alterations in MDSCs and that their decrease along tx may have a positive predictive value, highlighting the importance that immune-competent status may play in the evolution of ABC. MDSCs may represent a target for therapeutic purposes in ABC.

2544 **Poster Session (Board #188), Sat, 8:00 AM-11:00 AM**

Development of a baseline prognostic cytokine signature that correlates with nivolumab (NIVO) clearance (CL): Translational pharmacokinetic/pharmacodynamic (PK/PD) analysis in patients with renal cell carcinoma (RCC).

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Background: CL of checkpoint inhibitors has been identified as a predictive covariate of overall survival (OS) in several tumors. Determination of CL requires post-treatment samples, which negates its utility as a baseline prognostic biomarker. This study aims to identify a baseline composite cytokine signature that correlates with NIVO CL in patients with RCC using translational PK/PD analysis. **Methods:** Peripheral serum PK (NIVO CL) and serum biomarkers to assess PD (Myriad Rules-Based Medicine customized inflammatory cytokine panel) were analyzed from 985 patients with RCC enrolled in 3 clinical trials. CheckMate (CM) 009 (NCT01358721) and CM 025 (NCT01668784) of NIVO (n = 481) were used for model development (training dataset). CM 010 (NCT01354431) of NIVO and a cohort treated with everolimus in CM 025 were included in model application (test dataset; n = 504). PK/PD analyses were conducted using a machine learning algorithm with performance assessed by receiver operating characteristic (ROC) curve and accuracy by confusion matrix. **Results:** The model selected the top-10 baseline inflammatory cytokines to form a composite cytokine signature, which predicted NIVO CL (high vs low) that was significantly associated with OS ($p < 0.001$) across all 3 studies (training and test datasets). The same cytokine features were associated with OS of everolimus ($p < 0.01$), suggesting the potential prognostic nature of the composite signature. The PK/PD analysis provided a robust description of the association between selected cytokines and CL (ROC = 0.71). Identified cytokines (eg, serum C-reactive protein known to reflect immune cell modulation) have been shown individually to be associated with RCC prognosis. A multivariable approach resulting in tumor-specific composite signatures may provide more accurate prognostic value. **Conclusions:** The baseline composite cytokine signature could serve as a clinically useful biomarker for patients with RCC, pending further evaluation, as it may provide improved prognostic accuracy for long-term clinical outcome compared to individual cytokines.

2545 **Poster Session (Board #189), Sat, 8:00 AM-11:00 AM**

$CD4^+$ T-cell immunity predicts long-lasting antitumor immunity after PD-1 blockade therapy.

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Background: Patients treated with programmed cell death 1 (PD-1)-blockade therapy fall into 3 distinct subgroups: non-responders presenting early disease progression, long survivors who achieve durable disease control, and the remaining short-term responders. We reported that the prediction formula comprised of the percentages of CD62L-downregulated ($CD62L^{low}$) and $CD25^+FOXP3^+CD4^+$T cells in the peripheral blood predicted non-responders of non-small cell lung cancer patients (n = 50) scheduled to receive anti-PD-1-antibody (nivolumab) therapy in the 2017 ASCO meeting. In this study, we included 171 patients with NSCLC who were scheduled for nivolumab treatment after obtaining written informed consent. Peripheral blood mononuclear cells (PBMC) were examined before and after Nivolumab therapy up to 2 years to investigate the differences between long survivors and short-term responders. **Methods:** The patients received Nivolumab at a dose of 3 mg per kilogram of body weight every 2 weeks. Tumor response was assessed with the use of the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, at week 8 and every 8 weeks thereafter. PBMCs were analyzed with a 18-color microfluorometer, LSR Fortessa and a masscytometer, CyTOF. **Results:** The responder-type patient group whose prediction formula values were greater than 192 showed significantly longer PFS ($P< 0.0001$) and OS ($P< 0.0001$). The long survivors who consisted of tail plateau of PFS exhibited significantly more $CD62L^{low}CD4^+$T cells than the short-term responders as pre-existing immunity. The remaining responders kept significantly higher percentages of $CD62L^{low}CD4^+$T cells ($P= 0.0088$) and prediction formula values ($P= 0.017$) than the patients with acquired resistance. **Conclusions:** The pre-existing $CD4^+$T cell balance between primed effector and regulatory T cells correlated with anti-PD-1 therapy response. Further, $CD62L^{low}$cell-dominant $CD4^+$T cell immunity was required to maintain durable antitumor reactivity induced by anti-PD-1 antibody therapy. These results have important clinical implication, as they support anti-PD-1 therapy provision to all potentially responding patients and pave the way for new treatment strategies for patients with distinct $CD4^+$T cell immune statuses. Clinical trial information: UMIN000020719.

2546 **Poster Session (Board #190), Sat, 8:00 AM-11:00 AM**

Molecular circulating tumor DNA response to identify long-term survival in patients receiving immunotherapy with initial radiologic stable disease.

Matthew David Hellmann, Qu Zhang, Shaad Essa Abdullah, Jamie E. Chaft, Neil Howard Segal, Chen Gao, Phillip A. Dennis, Brandon W. Higgs; Thoracic Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; AstraZeneca, Gaithersburg, MD; MedImmune, Gaithersburg, MD

Background: Early on-treatment changes in ctDNA may identify responders to immunotherapy and complement radiologic assessment of benefit. Here we investigate how early changes in ctDNA associate with long-term survival following treatment with immunotherapy, and if differential patterns in molecular ctDNA response (MCR) among patients with radiologic stable disease (SD) at first on-treatment scan could identify patients deriving benefit from treatment. **Methods:** Paired pre- and on-treatment (week 6-8) plasma samples from 3 cohorts of patients treated with durvalumab (D) +/- tremelimumab (D+T) were evaluated (NCT01693562, NCT02087423, NCT02261220). CtDNA was profiled with the 73-gene Guardant 360 assay. Nonsynonymous variants were summarized per patient to calculate variant allelic frequency changes (dVAF) and on-treatment variant allele frequency (pVAF). A combination of dVAF and pVAF was used to define MCR. **Results:** The reduction of ctDNA (dVAF$<$0) and undetectable on-treatment ctDNA (pVAF=0) were each associated with improved OS and PFS. An optimal threshold for MCR was determined from one cohort, then applied to the other cohorts. MCR associated with significantly improved PFS and OS across all three cohorts (Table). MCR was then applied to a pooled subgroup of patients with initial radiologic SD from all three cohorts (n=78). Patients with radiologic SD and MCR were significantly more likely than those without MCR to achieve radiologic CR or PR (pooled Odds ratio 12.7, p$<$0.001), had improved PFS (stratified pooled HR 0.36, p$<$0.001), and improved OS (stratified pooled HR 0.38, p=0.005). **Conclusions:** MCR is an early on-treatment tool that may identify patients with improved long-term survival and patients with radiologic SD who derive clinical benefit from immunotherapy. MCR may be a supportive endpoint in prospective clinical trials. MCR and survival benefit.

Study	NCT01693562 D (n=72)	NCT02087423 D (n=71)	NCT02261220 D+T (n=36)
MCR, n (%)	34 (47)	28 (39)	16 (44)
PFS HR (95% CI)	0.28 (0.16,0.50)**	0.40 (0.22,0.73)*	0.12 (0.05,0.32)**
OS HR (95% CI)	0.25 (0.13,0.49)**	0.34 (0.14,0.83)*	0.15 (0.05,0.44)**

*$<$0.05, *$<$0.01, **$<$0.001

2547 **Poster Session (Board #191), Sat, 8:00 AM-11:00 AM**

ctDNA analysis for personalization of consolidation immunotherapy in localized non-small cell lung cancer.

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Background: Detection of molecular residual disease via circulating tumor DNA (ctDNA) analysis after chemoradiation (CRT) in localized non-small cell lung cancer (NSCLC) predicts risk of relapse. We explored the hypotheses that (1) patients with undetectable ctDNA after CRT may not require consolidation immunotherapy (CI) and (2) ctDNA analysis could monitor the effectiveness of CI in patients with residual ctDNA after CRT. **Methods:** We applied CAPP-Seq ctDNA analysis to 88 plasma and matched leukocyte samples collected pre-CRT, post-CRT but pre-CI, and mid-CI in 22 patients with Stage IIB-IIIB NSCLC treated with CRT followed by CI. Identification of patient-specific tumor variants was performed using tumor tissue or pretreatment plasma, and ctDNA was quantified using a tumor mutation-informed bioinformatic strategy. Freedom from progression (FFP) defined radiographically by RECIST 1.1 criteria was compared in patients with ctDNA detected or not detected at pre-CI and mid-CI landmarks. **Results:** Median follow up from the start of CRT was 11 months. ctDNA detection was associated with inferior rates of FFP when compared to patients with ctDNA not detected both pre-CI (12-month 33% vs. 76%, P = 0.015, HR 7.51, 95% CI 1.47-38.24) and mid-CI (12-month 0% vs. 86%, P < 0.0001, HR 123.3, 95% CI 16.21-937.8). In patients with undetectable ctDNA after CRT, FFP was similar to a historical cohort of patients with undetectable ctDNA after CRT alone (12-month 88% vs. 87%, P = 0.56, HR 0.55, 95% CI 0.07-4.18), suggesting that such patients may not benefit from CI. All patients with detectable ctDNA pre-CI in whom ctDNA increased mid-CI developed progressive disease. Finally, in 2 patients with ctDNA detected after CRT, CI led to elimination of ctDNA at the mid-CI timepoint. One of these patients developed an isolated local recurrence 22 months after CRT and the other patient is currently disease free at 11 months, suggesting clinical benefit from CI. **Conclusions:** Our results suggest that ctDNA analysis may allow personalization and response monitoring of CI following CRT for NSCLC. Validation in more patients followed by prospective testing in clinical trials will be required to establish clinical utility of such an approach.

2548 **Poster Session (Board #192), Sat, 8:00 AM-11:00 AM**

Phase 1 study of LY3022855, a colony-stimulating factor-1 receptor (CSF-1R) inhibitor, in patients with metastatic breast cancer (MBC) or metastatic castration-resistant prostate cancer (MCRPC).

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Background: Tumor-associated macrophages (TAM) correlate with increased invasiveness, growth, and immunosuppression. Activation of CSF-1R results in proliferation, differentiation, and migration of monocytes/macrophages. CSF-1R inhibition with LY3022855 (LY), a human immunoglobulin G subclass 1 (IgG1) monoclonal antibody (mAB), may have favorable anti-tumor effects. We evaluated the safety and clinical response of LY monotherapy. **Methods:** Patients (pts) with advanced refractory MBC and MCRPC received LY intravenously in 6-week cycles in cohorts: A) 1.25 mg/kg every 2 weeks [Q2W]; B) 1.0 mg/kg on Weeks 1, 2, 4, and 5; C) 100 mg once weekly; D)100 mg Q2W. MCRPC pts were enrolled in cohorts A and B; MBC pts were enrolled in all cohorts. Anti-tumor activity was assessed using RECIST v1.1 by radiological imaging every 6 weeks. **Results:** Thirty-four pts (22 MBC; 12 MCRPC) received $\geq$1 dose of LY. Median age was 57.0 years (range: 32.0–81.0) for MBC pts and 72.5 years (range: 58.0–84.0) for MCRPC pts. Baseline Eastern Cooperative Oncology Group performance status was 0 (n = 13, 38.2%), 1 (n = 18, 52.9%), or 2 (n = 3, 8.8%). MBC pts were hormone receptor (HR) positive (n = 20), HR negative (n = 1), or unknown (n = 1); 3 MBC pts received concurrent hormone therapy. Common treatment-related adverse events of any grade were fatigue (38.2%), decreased appetite (26.5%), nausea (26.5%), increased lipase (23.5%), and increased creatine phosphokinase (20.6%). No complete or partial response was observed. Stable disease (SD) was observed in 5/22 MBC pts (duration 82–302 days) and 3/7 evaluable MCPRC pts (duration 50–124 days). Two MBC pts (9%; Cohort A) had durable SD $>$ 9 months and 1 pt had palpable reduction in a nontarget neck mass. Circulating CSF1 and IL-34 increased at Day 8 suggestive of target engagement. Pharmacokinetics of LY were consistent with other IgG1 mAbs. **Conclusions:** LY3022855 was well tolerated and showed evidence of target engagement. Clinically meaningful SD $>$ 9 months was observed in 2 MBC pts. Tumor biomarker analyses are underway. Clinical trial information: NCT02265536.

2549 **Poster Session (Board #193), Sat, 8:00 AM-11:00 AM**

Safety and immunobiological activity of guadecitabine sequenced with ipilimumab in metastatic melanoma patients: The phase Ib NIBIT-M4 study.

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Background: DNA hypomethylating agents show broad immuno-modulatory activity in neoplastic cells, and may improve the effectiveness of cancer immunotherapies. The phase 1b NIBIT-M4 trial investigated a previously unexplored therapeutic strategy using the next-generation DNA hypomethylating agent guadecitabine sequenced with ipilimumab for the treatment of advanced melanoma. **Methods:** Patients with unresectable Stage III/IV melanoma received escalating doses of guadecitabine 30, 45 or 60 mg/m^2 subcutaneously on Days 1–5 every three weeks, and ipilimumab 3 mg/kg intravenously on Day 1 every three weeks, starting one week after guadecitabine, for four cycles. Primary endpoints were the safety, tolerability and maximum tolerated dose of treatment; secondary endpoints included immune-related disease control and objective response. Genome-wide methylation, RNA sequencing, and immunohistochemistry analyses were performed on tumor samples collected at baseline, W4 and W12. (NCT02608437). **Results:** 19 patients were treated and evaluable for safety and efficacy. The most common treatment-related adverse events of any grade were myelotoxicity (n = 17; 89%) and immune-related adverse events (n = 12; 63%). Grade 3 or 4 myelotoxicity occurred in 15 (79%) patients. There were no dose limiting toxicities. Rates of immune-related disease control and objective response were 8/19 (42%) and 5/19 (26%), respectively. Exploratory analyses of tumour samples (n = 8) showed that median CpG site methylation at Week 4 (74.5%) and Week 12 (75.5%) was significantly lower ($p < 0.05$) than at baseline (80.3%), with a median of 2454 (Week 4) and 4131 (Week 12) differentially expressed genes identified compared to baseline; among the 136 pathways significantly modulated by treatment, the most frequently activated were immune-related. Tumour immune contexture analysis (n = 11) demonstrated up-regulation of Human Leukocyte Antigen (HLA) class I molecules on melanoma cells, and an increase in CD8$^+$, PD-1$^+$ T cells and in CD20$^+$ B cells in post-treatment tumour core specimens. **Conclusions:** Sequential guadecitabine and ipilimumab is safe and tolerable in patients with metastatic melanoma, and has promising immunological and anti-tumour activity. Clinical trial information: NCT02608437.

2550 **Poster Session (Board #194), Sat, 8:00 AM-11:00 AM**

An open label, multicenter phase II study combining imprime PGG (PGG) with pembrolizumab (*P*) in previously treated metastatic triple-negative breast cancer (mTNBC).

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Background: Checkpoint inhibitor (CPI) monotherapy shows limited clinical response in previously treated mTNBC patients (pts) (Table). Agents are needed that extend this benefit to more mTNBC pts. PGG is a novel, IV administered PAMP that, in pts with 20ug/ml anti-beta glucan antibody (ABA+), activates innate immune cells. Preclinically, PGG reprograms myeloid cells to repolarize the immunosuppressive tumor microenvironment & enhance antigen presentation, driving T cell activation- the mechanistic basis to explore PGG + *P* in mTNBC patients. **Methods:** 44 mTNBC pts (1 line of chemotherapy [Tx] for metastatic disease, ABA) received PGG (4 mpk IV weekly) + *P* (200 mg IV q3w) until PD or intolerable toxicity. 1° endpoints were ORR by RECIST v1.1 & safety. 2° endpoints included OS & DCR. CT scans (q6 wks) were reviewed locally. Tumor biopsies (pre & 6 wks on Tx) & blood samples were assessed for PGG-mediated immune activation. **Results:** Table shows *IMPRIME 1* clinical response data (Keynote086, PCD4989g shown for context). Confirmed response was also evident in pts with liver or visceral metastases, high LDH. 10 *IMPRIME 1* pts were originally ER/PR+, received hormonal Tx and progressed to TNBC. Of these, 5 are confirmed PR, 4 SD (3 still on Tx), 1 PD. No unexpected safety signals were observed. **Conclusions:** These are the first clinical data to suggest that PGG provides added clinical benefit for pts with previously treated mTNBC and support further development of PGG + *P* for mTNBC. Clinical trial information: NCT02981303.

	IMPRIME 1 % (N= 44)	Keynote 086[a] % (N=170)	PCD4989g[b] % (N=94)
ORR	13.6 (6)	5.3	6.4
SD	40.9 (18)	18	13
PD	40.9 (18)	60.6	64
DCR - CR+PR+SD ≥ 24wks	22.7 (10)	7.6	10
Median OS in months	13.7	9.0	7.3
% OS 6/ 12 months	83.0/ 65.5	69.7/ 39.8	60/ 37

[a]Adams 2018, [b]Emens 2019 In peripheral blood, Tx increased activated (HLA-DR/CD86+) monocyte & dendritic cell subsets as well as CD8 T cells (Ki67/HLA-DR/PD1+), particularly in responsive pts. All tumor biopsy pairs showed heavy infiltration by activated myeloid (PDL1+) and CD8 T cells (Ki67/granzyme B+) after Tx. These data support the mechanistic basis for PGG-based combination with *P*. NCT02981303 sponsored by Biothera in collaboration with Merck & Co., Inc.

2551 **Poster Session (Board #195), Sat, 8:00 AM-11:00 AM**

Community and academic partnerships: Moving a new generation of clinical trials in NCI Community Oncology Research Program (NCORP) into community oncology practices.

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Background: NCORP is a model program that bridges academic and community oncology practices and research. Over the past decade, community cancer investigators have adopted new technology, encountered new treatment sequalae, and faced rising cost of care with its financial toxicity imposed upon individuals seeking care. Opportunities are abundant for community investigators to assess feasibility and uptake of research advances into community practice settings, yet these opportunities are met with the challenges of dynamic changes in types of organizations delivering cancer care and diversity of populations within their catchment areas. Little information is shared about how and to what extent the health environment influences this partnership and the implementation of a broad cancer research portfolio. **Methods:** This abstract reports on the continued interest and participation of community oncologists in research which is demonstrated by 987 practices with over 4000 investigators in NCORP. Since 2014, over 30,000 individuals enrolled in symptom management, screening, surveillance, quality of life, and treatment trials. An additional 4500 patients and clinicians have enrolled in care delivery studies. **Results:** NCORP has been central in evaluating the most effective strategies for investigators to effectively communicate to patients the science of genomically-driven trials. It has also provided ways of bringing the pediatric and AYA patients access to the most up-to-date treatment strategies and new therapies in their community. This creates the least disruption on family structure/dynamics, diminished traveling requirements/costs, and reduced the financial burden. NCORP promotes involvement of treating oncologists in research activities. This also improves care for patients not enrolled in clinical trials. Therefore, NCORP serves as a laboratory to determine the most effective strategies for co-management of cancer patients and survivors. **Conclusions:** Several questions however remain to be addressed using this clinical trial model. These include: how to continue to reduce disparities in cancer care and clinical trial participation; and, what are the best strategies for fostering implementation of cancer care models in community practice.

2552 **Poster Session (Board #196), Sat, 8:00 AM-11:00 AM**

Re-evaluating eligibility criteria: Analysis of factors leading to nonparticipation and outcomes of patients (pt) with advanced cancer who signed consent but were not treated in early-phase immunotherapy (IO) trials.

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Background: Eligibility criteria protect the safety of trial pt and delineate the study population. Excessively restrictive criteria, however, can negatively impact accrual and prevent access to beneficial investigational treatments. Recently, ASCO issued a statement on the need to broaden eligibility criteria and make trials more representative. We aim to characterize the factors leading to non-participation and the outcomes of pt who signed consent for phase I IO trials but ultimately did not receive any therapy on that trial. **Methods:** We identified 696 consecutive pt w/ advanced cancer who consented to participate on IO phase I trials from 10/2015-12/2017, and collected pt characteristics as well as clinical outcomes, and compared participants (P) to non-participants (NP). **Results:** Among the 696 pt who initially consented to participate on IO phase I trials, 178 (25.6%) were never treated. Median age was 60 in both groups, and there were no differences regarding median number of metastatic sites (n = 2 vs 2) or sex distribution (F 53% vs 54%); NP had received less lines of therapy (median = 3 vs 4, p = 0.016). Reasons for non-participation were: 48 (26%) alternate therapy (for 18, geography was the main reason), 29 (16%) clinical progression/ decline in PS, 14 (8%) did not have enough biopsy tissue, 13 (7%) new lab abnormality, 11 (6%) new brain mets, 63 (35%) had other reasons (death, concurrent medications, financial factors). Median time from signature of consent to final exclusion of trial was 19 days (0-82). 54 of NP eventually enrolled in other trial, including 29 in immunotherapy trial. Median overall survival (OS) was significantly lower for NP vs P (median 6.9 vs 18.0, HR 0.5; $p < .0001$). **Conclusions:** One quarter of patients who signed consent for early-phase immunotherapy trials were unable to start on study. NP had significantly decreased OS. Detailed examination of these reasons can lead to recognition of modifiable factors and streamline the pretrial period, to guarantee this vulnerable population has maximal access to start therapy on study.

2553 **Poster Session (Board #197), Sat, 8:00 AM-11:00 AM**

Phase II study of spartalizumab (PDR001) and LAG525 in advanced solid tumors and hematologic malignancies.

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Background: Spartalizumab and LAG525 are monoclonal antibodies targeting PD-1 and LAG-3, respectively. Dual blockade of PD-1 and LAG-3 has shown synergistic antitumor activity in preclinical models. Here we describe preliminary efficacy of spartalizumab + LAG525 across seven tumor types. **Methods:** Phase II, open-label, parallel-cohort study was conducted in pts with solid or hematologic malignances relapsed and/or refractory to standard-of-care therapies. Prior immunotherapy was prohibited. LAG525 (400 mg) and spartalizumab (300 mg) were dosed intravenously every 3 weeks. Primary endpoint was clinical benefit rate at 24 weeks (CBR24), assessed using a Bayesian hierarchical model-based futility analysis. Posterior probability that clinical benefit exceeds historical control (Pr) was estimated to determine futility at interim against prespecified thresholds. **Results:** As of January 7 2019, 76 pts received spartalizumab + LAG525; 72 pts were eligible for analysis (Table). The Pr cut-off for all arms was > 0.70. Hence, neuroendocrine tumors (NET), small cell lung cancer (SCLC) and diffuse large B-cell lymphoma (DLBCL) cohorts all met the expansion criteria with Pr of 0.971, 0.975 and 0.804 respectively. CBR24 were as follows; NET: 0.86, SCLC: 0.27, DLBCL: 0.43. Prostate, sarcoma and ovarian cohorts did not meet the expansion criterion ($Pr > 0.70$) but were not declared futile; enrollment was paused pending results of next analysis. Gastroesophageal (GE) cancer cohort was stopped for futility due to Pr (0.071) below the futility threshold. **Conclusions:** Spartalizumab and LAG525 showed promising activity in NET, SCLC and DLBCL that met expansion criteria. The GE cohort was declared futile. Remaining cohorts are paused pending further analysis. Clinical trial information: NCT03365791.

Cohort	Pts treated ≥24 weeks (n)	Pts with clinical benefit (n)	Observed CBR24	Posterior probability	Enrollment recommendation
SCLC	15	4	0.27	0.975	Expansion criteria met
GE cancer	12	2	0.17	0.071	Stopped for futility
Prostate	11	5	0.46	0.432	Expansion threshold not met
Sarcoma	10	4	0.40	0.629	Expansion threshold not met
Ovarian	10	2	0.20	0.420	Expansion threshold not met
NET	7	6	0.86	0.971	Expansion criteria met
DLBCL	7	3	0.43	0.804	Expansion criteria met

2554 **Poster Session (Board #198), Sat, 8:00 AM-11:00 AM**

Preliminary safety, efficacy, and pharmacokinetics (PK) results of KN046 (bispecific anti-PD-L1/CTLA4) from a first-in-human study in subjects with advanced solid tumors.

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Background: KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD1 and CTLA-4 interaction with CD80/CD86. KN046 has a wild type IgG1 Fc portion that preserves intact effector functions, such as depletion of T_{regs} in tumor microenvironments. This first-in-human study evaluated the safety, tolerability, PK and preliminary efficacy of KN046 in subjects with advanced solid tumors. **Methods:** This traditional "3+3" dose-escalation design study enrolled patients (pts) with advanced unresectable or metastatic solid tumors refractory or intolerant to standard therapies. Previous treatment from PD1 or PD-L1 immune checkpoint inhibitors was allowed. KN046 was administered intravenously Q2W. Dose limit toxicity (DLT) evaluation period is 28 days. The planned dose levels (DL) were 0.3, 1, 3, 5 and 10 mg/kg. Efficacy evaluation was performed by RECIST 1.1 every 8 weeks. **Results:** As of Dec 13, 2018, 10 pts had been enrolled (0.3 mg/kg, n = 1; 1 mg/kg, n = 3; 3 mg/kg, n = 3; and 5 mg/kg, n = 3). Median duration of treatment was 8 (range: 2-24) weeks. 1 DLT was observed at 5 mg/kg dose (a grade 3 immune-related hepatitis without elevation in total bilirubin; reversible in two weeks). The most common (≥30%) treatment-emergent AEs (TEAE) were Fatigue, Diarrhea, Nausea, Vomiting. Six immune-related TEAEs (Abdominal pain lower, Arthralgia, Hepatic function abnormal, Hyperthyroidism, Nausea and Transaminitis) were observed in 3 pts. One pt with NSCLC from 3 mg/kg cohort had confirmed completed response. Two pts (TNBC and nivolumab refractory RCC) from 1 mg/kg cohort had shown long-term stable disease (> 12 weeks). Faster clearance of KN046 was observed at lower dose might be due to target-mediated clearance. T1/2 is approximately 7~9 days at doses of 3 mg/kg and above when saturation occurs. **Conclusions:** Single agent KN046 has an acceptable safety profile and is in line with previously reported safety data from other immune checkpoint inhibitors. Preliminary efficacy results are promising. PK data from initial 4 cohorts support Q2W schedule. The study is currently ongoing at dose level of 5 mg/kg Q2W. Clinical trial information: NCT03529526.

2555 **Poster Session (Board #199), Sat, 8:00 AM-11:00 AM**

Assessment of the Fanconi anemia repair pathway as a predictor of clinical activity of pembrolizumab (PEM).

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Background: Given the activity of immune checkpoint inhibitors (ICI) in mismatch repair deficient tumors, we evaluated if homologous recombination repair deficiency associates with solid tumor response to ICI. **Methods:** We conducted a phase 2 trial (NCT03274661) of PEM in metastatic solid tumor patients progressing on standard of care and for whom PEM had no FDA approved indication. We evaluated a triple stain (FANCD2foci/DAPI/Ki67) immunofluorescence functional assay of the Fanconi Anemia pathway (FATSI) in treated patients' archived tumors as a correlative biomarker. Patients with microsatellite unstable tumors were not eligible. The primary objective was objective response rate (iORR, CR+PR) by Immune Response Criteria, with the hypothesis that patients with FATSI negative tumors will have better clinical outcome. Secondary objectives were progression free survival (PFS), 6 months PFS and survival. PEM was given every 3 weeks and computed tomography scans were performed every 6 weeks. We utilized a two-stage phase II trial design to detect an iORR $\geq$ 20% in the whole population tested vs. the null hypothesis that the true iORR $\leq$5%. If $\geq$ 2 of the first 20 evaluable patients had an objective response the trial proceeded to full accrual of 39 evaluable patients. Outcomes were evaluated according to FATSI staining. **Results:** 42 patients (40 evaluable) (35F,7M; median age 62[36-83]) enrolled. Median # of prior regimens was 2[1-7]. Primary Dx included ovarian/fallopian (13), endometrial (10), colorectal (3), cervix (2), pancreatic(2), vaginal (2) and 1 each of various others. No unexpected toxicities occurred. Response evaluation showed 2 CR, 5 PR, 11 SD, 22 PD and 2 NE (iORR 18%). FATSI tumor analyses results are available in 34 patients; 25 FATSI positive, 9 negative. 2 PR, 8 SD, 14 PD, 1 NE occurred among the FATSI (+) (iORR 8%) and 2 CR, 2 PR, 2 SD, 3 PD among the FATSI (-) patients (iORR 44%). mPFS and 6m-PFS were 54 days and 12% (3/25) in FATSI (+), versus 248 days and 56% (5/9) in FATSI (-) patients; p = 0.017. **Conclusions:** PEM has meaningful antitumor activity in non MSI-high malignancies with no current FDA approved indications. Evaluation of FATSI as a biomarker supports a biomarker selected population approach. Clinical trial information: NCT03274661.

2556 **Poster Session (Board #200), Sat, 8:00 AM-11:00 AM**

Preliminary results with tislelizumab, an investigational anti-PD-1 antibody, in Chinese patients with nasopharyngeal cancer (NPC).

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Background: Epidemiology of NPC is characterized by a unique geographic distribution, with China having one of the highest incidence rates of NPC worldwide. Tislelizumab is an investigational monoclonal antibody with high affinity and specificity for PD-1. Tislelizumab was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Previous reports from this phase 1/2 study (CTR20160872) have shown that single-agent tislelizumab was generally well tolerated and demonstrated preliminary antitumor activity in Chinese patients (pts) with advanced solid tumors. In the dose-verification part of this study, the recommended dose was established as 200 mg IV Q3W. Here we present preliminary results from the NPC cohort of this study. **Methods:** Chinese pts with advanced or metastatic, histologically or cytologically confirmed WHO type II-III NPC were enrolled in the indication-expansion phase of this study. Enrolled pts received tislelizumab 200 mg IV Q3W until unacceptable toxicity, consent withdrawal, or no evidence of continued clinical benefit. Antitumor activity (per RECIST v1.1) and safety/tolerability (per NCI-CTCAE v4.03) were assessed. **Results:** As of 11 May 2018, 20 NPC pts (median age 49 yr [range 35–61]) were enrolled. Most pts were male (85%) and non-smokers (65%). All pts received prior radiotherapy; 19 pts (95%) received ≥1 line of systemic treatment and the median number of prior lines of systemic treatment was 2 (range 0–10). At the cut-off date, 15 pts remain on treatment and the median study follow-up was 5.5 mo (range 0.46–9.0). Of 15 response-evaluable pts, 3 achieved a confirmed partial response (PR) and 9 achieved stable disease; 1 patient had an unconfirmed PR. Seven patients experienced ≥1 treatment-related AE (TRAE); hypothyroidism (n = 3) was the only TRAE that occurred in ≥2 pts. No grade ≥3 TRAEs or serious AEs were reported. Furthermore, no AEs led to either treatment interruption or discontinuation. **Conclusions:** Tislelizumab was generally well tolerated and demonstrated antitumor activity in previously treated pts with advanced NPC. Clinical trial information: CTR20160872.

2557 **Poster Session (Board #201), Sat, 8:00 AM-11:00 AM**

Association between MDM2/MDM4 amplification and PD-1/PD-L1 inhibitors-related hyperprogressive disease: A pan-cancer analysis.

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Background: Immune checkpoint inhibitors have demonstrated a clear survival benefit in various tumor types. However, accelerated disease progression, documented as hyperprogressive disease (HPD), was reported in a subset of patients treated with PD-1/PD-L1 inhibitors. Until now, the mechanisms underlying HPD have not been elucidated. Previous studies have demonstrated that MDM2/MDM4 amplification were associated with HPD. In the present study, we evaluated the relationship between MDM2/MDM4 amplification and HPD. **Methods:** We reviewed extensive clinical trials of PD-1/PD-L1 inhibitors in advanced solid tumor patients updated to January 2019, and estimated the incidence of HPD, which was defined as time-to-treatment failure (TTF) $<$ 2 months, and $>$ 50% increase in tumor burden compared with pre-immunotherapy imaging in this study. The proportions of MDM2/MDM4 amplification across different cancer types were obtained from The Cancer Genome Atlas (TCGA) and our own database respectively. Then we plotted the incidence of HPD and the corresponding proportion of MDM2/MDM4 amplification across various cancer types in TCGA. **Results:** Overall, 19 published clinical trials of 1318 patients treated with PD-1/PD-L1 inhibitors were included for analysis, covering 12 types of solid cancers. The incidences of HPD among these studies were ranging from 1.58% in renal clear cell carcinoma to 24.3% in sarcoma. Correspondingly, the proportions of MDM2/MDM4 amplification for these cancer types in TCGA were 0.74% in renal clear cell carcinoma to 20.38% in sarcoma. In our database, in total, 60 patients with MDM2/MDM4 amplification were identified in 2931 patients with the highest proportion of MDM2/MDM4 amplification in sarcoma (22 of 152, 14.5%). A significant correlation was detected between the incidence of HPD and the corresponding proportion of MDM2/MDM4 amplification in TCGA across various cancer types ($P < 0.001$, $R^2 = 0.67$). **Conclusions:** Our results suggest that MDM2/MDM4 amplification may be associated with rapid disease progression in patients receiving PD-1/PD-L1 inhibitors among various tumor types. The exact mechanisms underlying HPD are needed to be further evaluated.

2558 **Poster Session (Board #202), Sat, 8:00 AM-11:00 AM**

Antitumor activity and safety of MK-1308 (anti-CTLA-4) plus pembrolizumab (pembro) in patients (pts) with non-small cell lung cancer (NSCLC): Updated interim results from a phase I study.

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Background: An ongoing multicenter, open-label, phase 1 study of the anti–CTLA-4 antibody MK-1308 in combination with pembro in advanced solid tumors (NCT03179436) revealed a manageable safety profile and promising efficacy in pts with first-line (1L) advanced NSCLC. Data from a larger sample size and longer follow-up are presented. **Methods:** In dose escalation (DE), pts with advanced solid tumors received MK-1308 by IV administration at 25, 75, or 200 mg Q3W $\times$1 cycle then in combination with pembro 200 mg Q3W $\times$4 cycles followed by pembro monotherapy (up to 35 cycles). In dose confirmation (DC), pts with 1L advanced NSCLC received MK-1308 at 25 or 75 mg—Q3W or Q6W—plus pembro 200 mg Q3W (up to 35 cycles). Safety (all treated pts), efficacy (subset of 1L NSCLC pts), pharmacokinetics (PK, all treated pts), and PD-L1 tumor expression (subset of 1L NSCLC pts) were analyzed. **Results:** 213 pts were treated (DE, n=39; DC, n=174). All pts were included in the safety analyses (median follow-up, 8 months); 113 pts from DC were included in the efficacy analyses (median follow-up, 8 months). PK showed a dose-dependent increase in MK-1308 exposure. Neither target dose-limiting toxicity ($\geq$10%) nor maximum tolerated dose were reached for MK-1308 plus pembro; however, toxicity increased with increasing MK-1308 dose and shorter dosing intervals. Treatment-related adverse events grade $\geq$3 occurred at the lowest rates at 25 mg Q3W in DE (0%) and 25 mg Q6W in DC (25%) and at the highest rates at 200 mg Q3W in DE (75%) and 75 mg Q3W in DC (50%). Efficacy was observed at all MK-1308 dose levels and intervals: confirmed ORR per RECIST 1.1 by central review in 1L advanced NSCLC was 39% at 25 mg Q3W, 33% at 25 mg Q6W, 22% at 75 mg Q6W, and 25% at 75 mg Q3W; 6-month PFS and OS rates are 67% and 89% for the 25 mg Q6W arm. There was a 25% ORR in PD-L1–negative 1L advanced NSCLC pts. **Conclusions:** MK-1308 plus pembro was generally well tolerated with no unexpected toxicity and conferred encouraging antitumor activity in 1L advanced NSCLC pts. Efficacy, safety, and PK data suggest that 25 mg given Q6W is the recommended phase 2 dose for MK-1308 in combination with pembro. Clinical trial information: NCT03179436.

2559 **Poster Session (Board #203), Sat, 8:00 AM-11:00 AM**

Family history of cancer as surrogate predictor for immunotherapy with anti-PD-1/PD-L1 immune checkpoint inhibitors: The FAMI-L1 study.

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Background: In the preliminary analysis of the FAMI-L1 study, we found a significant association between family history of cancer (FHC) and better clinical outcomes with anti-PD1/PD-L1 inhibitors. **Methods:** We retrospectively evaluated advanced cancer patients treated with single agents PD1/PD-L1 inhibitors. Patients were categorized as follow: FHC-high (in case of at least one cancer diagnoses in both straight and collateral family line), FHC-low (in case of a cancer diagnoses in only one family line) and FHC-negative. FHC was collected till the second degree of relatedness. **Results:** Between September 2013 and May 2018, 772 consecutive patients were evaluated. Median age was 68 years; male/female ratio was 521/251. Primary tumors were: NSCLC (58.3%), melanoma (22.1%), renal cell carcinoma (16.6%) and others (3%). 114 patients (14.9%) had ECOG-PS $\geq$ 2. 341 patients (44.3) were FHC-positive: 268 of them (34.75) were FHC-low while 74 (9.6%) were FHC-high. FHC-high patients had a significantly higher incidence of irAEs compared to FHC-negative (55.4% vs 35.6%; p = 0.0012) and to FHC-low (41.4%; p = 0.0323). No significant differences were found in terms of ORR among subgroups (data not shown). At median follow-up of 15.8 months, median PFS was 9.1 months (95%CI: 8.1-10.4; 452 events) and median OS was 19.7 months (95%CI: 15.7-24.4; 436 censored). No significant differences were found regarding PFS (data not shown). Median OS of FHC-high patients was 31.6 months (95%CI: 26.2-31.6; 50 censored patients), which was significantly longer than 18.2 months (95%CI: 14.7-21.3; 229 censored patients) of FHC-negative patients (HR = 0.60 [95%CI: 0.39–0.92), p = 0.0213). No significant differences in terms of OS were found between FHC-high/low patients (data not shown). After adjusting for primary tumor, sex, treatment-line, number of metastatic sites and ECOG-PS, FHC-high was confirmed an independent predictor of longer OS compared to FHC-negative (HR: 0.57 [95%CI: 0.37-0.88], p = 0.0098). **Conclusions:** FHC-high seems to be an independent predictor for longer OS in cancer patients treated with anti-PD-1/PD-L1. DNA damage and response (DDR) genes alterations may underlie that results.

2560 **Poster Session (Board #204), Sat, 8:00 AM-11:00 AM**

IOLite: Multipart, phase 1b, dose-finding study of the PD-1 inhibitor dostarlimab in combination with the PARP inhibitor niraparib ± bevacizumab (bev), or with platinum-based chemotherapy ± bev for advanced cancer.

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Background: Novel combinations of drugs may overcome resistance in patients (pts) with solid tumors who had progressed on standard therapy. **Methods:** IOLite (NCT03307785) is a multicenter, open label, multipart study to determine dosing and evaluate safety and efficacy of dostarlimab in combination with approved therapies in pts with advanced solid tumors. Pts were enrolled in each part based on tumor histology, prior treatment (tx) history, and physician preference. Primary endpoint is dose-limiting toxicities (DLTs) deemed as tx-related per investigator, and safety and tolerability of the combination. Tumor responses were assessed per RECIST v1.1. **Results:** Parts A-D (see Table) are fully enrolled. One complete response was reported in part B (endometrial); confirmed partial responses in part A (ovarian, small cell lung [SCLC], gastrointestinal stromal [GIST]); part B (breast [2], bladder, SCLC); part C (prostate, fallopian tube), and part D (endometrial, non-SCLC). Stable disease was reported in part A (colorectal, prostate [2], breast, GIST, gastric); part B (SCLC, squamous cell, head and neck, prostate); part C (pancreatic, ovarian, GIST, breast [2], liver, endometrial); part D (ovarian, head & neck, cholangiocarcinoma). At data cutoff, 24 pts remain on treatment. PK's of dostarlimab and niraparib (nir) were not altered by any of the combination agents tested. **Conclusions:** Dostarlimab is well tolerated in combination with nir ± bev, or carbo-pac ± bev. Preliminary efficacy data show responses in various histologies. No new safety signals were identified. Clinical trial information: NCT03307785.

Part	Dose	N	DLT	Grade
A	Dostarlimab + nir 200 mg	16	Mucosal inflammation (n = 1)	3
			Hypertension (n = 1)	3
	Dostarlimab + nir 300 mg	6	None	
B	Dostarlimab + carbo-pac	14	Aspartate aminotransferase increased (reversible) (n = 1)	3
C	Dostarlimab + nir 200 mg + bev	6	Carotid artery intimal tear (n = 1)	3
	Dostarlimab + nir 300 mg + bev	7	Neutropenia (n = 1)	4
D	Dostarlimab + carbo-pac + bev	6	None	

Dosing: Dostarlimab: 500 mg IV Q3W×4, then 1000 mg Q6W;
Niraparib: 200 or 300 mg QD;
Carboplatin: area under curve 5 or 6 Q3W;
Paclitaxel: 175 mg/m^{2}Q3W; Bev: 15 mg/kg Q3W

2561 **Poster Session (Board #205), Sat, 8:00 AM-11:00 AM**

Fatal adverse events associated with pembrolizumab in cancer patients: A meta-analysis.

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Background: Pembrolizumab, an immune checkpoint inhibitor (ICI) against programmed cell death-1(PD-1) protein has emerged as an effective treatment for many cancers. Although better tolerated than chemotherapy, it has unique immune related adverse event and little is known about its risk of fatal adverse events (FAE). Therefore, we conducted a meta-analysis of clinical trials to determine the incidence and risk of fatal adverse events with pembrolizumab. **Methods:** A systematic search for phase I-III clinical trials of pembrolizumab was conducted using databases from PUBMED, and abstracts presented at the American Society of Clinical Oncology (ASCO) conferences until October 2018. Eligible studies included prospective clinical trials of pembrolizumab with available data on FAE. Data on FAE was extracted from each study and pooled for calculations. Incidence, relative risk (RR) and 95% confidence intervals (CI) were calculated by employing fixed or random-effects models. **Results:** A total of 11 clinical trials of pembrolizumab, with 3713 patients were included for analysis. The overall incidence of FAE with pembrolizumab was 1.2% (95% CI: 0.5-2.8%).The incidence of FAE significantly varied among different tumor types (P=0.02), ranging from 0.2% in melanoma to 3.1% in breast cancer.The incidence of FAE was significantly higher (P<0.001) with chemotherapy plus pembrolizumab (7.0%, 95%CI: 4.9-10%) as compared to pembrolizumab alone (0.7%, 95% CI: 0.4-1.2, p=<0.001). There was no significant difference in the risk of FAEs when pembrolizumab was compared with chemotherapy with RR=1.24 (95% CI: 0.8-1.89, P=0.31). **Conclusions:** Pembrolizumab is similar to chemotherapy in the risk of fatal adverse events in cancer patients. Combination of pembrolizumab with chemotherapy increased the risk of FAE in comparison with pembrolizumab alone. Further studies are needed to identify risk factors.

Incidence and relative risk of FAE with pembrolizumab by tumor type and with combination chemotherapy.

	Number of studies	Incidence% (95% CI)	RR (95% CI)	P value
Type of treatment.				
Pembrolizumab alone	8	0.7 (0.4-1.2)	0.69 (0.3-1.5)	0.3
Pembrolizumab & Chemo	3	7 (4.9-10)	1.58 (0.9-2.5)	0.07
Tumor type.				
NSCLC	6	2 (08-5.2)	1.27 (0.8-1.9)	0.9
Urothelial	2	0.8 (0.2-3.9)	0.94 (0.2-3.7)	0.9
Melanoma	2	0.2 (0-1.3)	1.5 (0.1-36.8)	0.8
Breast	1	3.1 (0.4-19.1)	N/A*	N/A*
Overall	11	1.2 (0.5-2.8)	1.24 (0.8-1.9)	0.3

*No control arm available

Open-label, multicenter, phase I study to assess safety and tolerability of adavosertib plus durvalumab in patients with advanced solid tumors.

Manish R. Patel, Gerald Steven Falchook, Judy Sing-Zan Wang, Esteban Rodrigo Imedio, Sanjeev Kumar, Pejvack Motlagh, Kowser Miah, Ganesh M. Mugundu, Suzanne Fields Jones, David R. Spigel, Erika Paige Hamilton; Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL; Sarah Cannon Research Institute at HealthONE, Denver, CO; AstraZeneca, Cambridge, United Kingdom; Quantitative Clinical Pharmacology, ECD, IMED Biotech Unit, AstraZeneca, Boston, MA; Sarah Cannon Research Institute, Nashville, TN; Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN

Background: Adavosertib (AZD1775; A) is a highly selective inhibitor of WEE1. This Phase I study (NCT02617277) investigated a range of doses and schedules for oral A plus IV durvalumab (DV), a human monoclonal antibody targeting PD-L1, to determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) in patients (pts) with advanced solid tumors. **Methods:** Four 28-day schedules (Sch) were evaluated with pts receiving DV 1500 mg on day (d) 1 of each schedule (Table). Patients continued treatment if they showed clinical benefit in the absence of any discontinuation criteria. Pts received A monotherapy for PK analysis prior to the start of combination therapy in Sch B, C (d –7 to –5) and D (d –9 to –5). MTD was determined using a 3+3 dose-escalation cohort design. Predefined dose-limiting toxicities (DLTs) were evaluated during the first cycle of study treatment. **Results:** 54 pts received A (most common primary tumor sites: colon, 19%; lung, 13%; breast, 11%). The most common grade ≥3 AEs were fatigue (15%), diarrhea (11%) and nausea (9%). DLTs were nausea (n = 2) and diarrhea (n = 1). 7 pts (13%) had A-related SAEs, including reversible and confounded drug-induced liver injury (Sch B 125 mg and Sch C; 1 each). Disease control rate (DCR) for the total cohort was 36%. Preliminary PK at 150 mg BID suggests adequate coverage for cell kill activity and no drug–drug interaction. **Conclusions:** The MTD/RP2D was A 150 mg BID (3 d on, 4 d off; treatment d 15–17, 22–24) with DV 1500 mg (d 1 Q4W); safety profile was considered acceptable. Preliminary evidence of antitumor activity was observed. Clinical trial information: NCT02617277.

Sch	A dose (days on/off)	A treatment days	N	DLTs, n (%)	Grade ≥3 AEs, n (%)	A discontinuations due to AE, n (%)	A dose reductions due to AE, n (%)	DCR, n (%)
A	125 mg BID (5/9)	1–5, 15–19	6	2 (33)	4 (67)	1 (17)	1 (17)	1 (17)
B	125 mg BID (3/4)	15–17, 22–24	7*	0	3 (43)	0	0	3 (50)*
	150 mg BID (3/4)	15–17, 22–24	12	0	7 (58)	0	1 (8)	5 (42)
	175 mg BID (3/4)	15–17, 22–24	7	0	5 (71)	1 (14)	2 (29)	4 (57)
C	125 mg BID (3/4)	8–10, 15–17, 22–24	7†	1 (17)†	6 (86)	1 (14)	0	1 (14)
D	200 mg QD (5/2)	15–19, 22–26	6	0	3 (50)	0	0	2 (33)
	250 mg QD (5/2)	15–19, 22–26	6	0	4 (67)	1 (17)	1 (17)	3 (50)
	300 mg QD (5/2)	15–19, 22–26	3	0	2 (67)	0	1 (33)	0

*Only 6 pts received DV; †DLT evaluable in 6 pts only

2563 **Poster Session (Board #207), Sat, 8:00 AM-11:00 AM**

Early incidence of immune-related adverse events (irAEs) predicts efficacy in patients (pts) with solid tumors treated with immune-checkpoint inhibitors (ICIs).

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Background: Treatment with ICIs can manifest immune-related adverse events (irAEs), which have correlated with clinical outcomes in certain tumors. However, timing of these events and how early irAEs correlate with outcomes is unclear. We assessed whether early occurring irAEs could predict survival in pts treated with durvalumab (D), an anti-PDL1 and combined with tremelimumab (D+T), an anti-CTLA4 in two clinical studies. **Methods:** Two phase 2 non-randomized clinical trials evaluating D (D4190C00001 (1108), N=756; available data per internal data re-use policy) or D+T (D4190C00010 (C10), N=327; expansion and ICI naïve cohorts) in multiple solid tumor types were analyzed. Prevalence of pts experiencing irAEs, regardless of grade was 30% and 59% in studies 1108 and C10, respectively, with most frequent including dermatitis/rash (25%), thyroid (15%), diarrhea/ colitis (14%), and pancreatic enzyme elevation (5%). Overall survival (OS) was correlated with irAE timing prior to 6, 8, 12, 16, 20 and 24 weeks following D or D+T treatment. Kaplan Meier and log-rank analyses were used. **Results:** In both studies, pts who experienced at least one irAE by study completion had improved median OS (mOS, 1108: 23.1 mos [18.2, 26.9]; C10: 16.3 mos [12.5, 31.4]) relative to those who experienced none (1108: 6.3 mos [5.4, 7.3]; C10 4.6 mos [3.3, 6.1]). Median time (weeks) to first and second irAE occurred earlier in C10 compared to 1108, 3.9 vs. 5.6 and 6.9 vs. 10.1, respectively. When associating timing of irAEs with survival, there was a significant differential in mOS at each time interval evaluated between pts with at least one irAE and those with none, with differentiation at 6 weeks and maximal survival benefit at 24 weeks following treatment with D or D+T (Table). **Conclusions:** Early occurrence of irAEs may be predictive of survival benefit in pts treated with D or D+T. OS by 1+ or no irAE(s) occurring up to 6 or 24 weeks post treatment.

		No irAE		1+ irAE	
Study	**Time Interval (weeks)**	**N**	**mOS mos (95% CI)**	**N**	**mOS mos (95% CI)**
1108	<6	631	8.6 (7,9.8)	125	15.2 (9.5,20.2)
	<24	550	6.7 (5.9,8.3)	206	20.2 (15.4,24.3)
C10	<6	197	7.3 (5.6,9.8)	130	13.1 (10.8,22.9)
	<24	139	5 (3.6,6.5)	188	15 (11.4,31.4)

2564 **Poster Session (Board #208), Sat, 8:00 AM-11:00 AM**

Severe immune-related adverse events in anti-PD-1-treated patients are clustered into distinct subtypes by peripheral blood T-cell profiles.

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Background: Although anti-programmed death-1 (PD-1) treatment has shown remarkable anti-tumor efficacy, immune-related adverse events (irAEs) develop with heterogeneous clinical manifestations. Immunological understanding of irAEs is currently limited. In the present study, we analyzed peripheral blood T cells obtained from cancer patients who received anti-PD-1 treatment to determine the immunological characteristics of severe irAEs. **Methods:** This study included 31 patients with refractory thymic epithelial tumor (TET) who were enrolled in a phase II trial of pembrolizumab (NCT02607631) and 60 patients with metastatic non-small cell lung cancer (NSCLC) who received pembrolizumab or nivolumab. T-cell profiling was performed by multi-color flow cytometry using peripheral blood obtained immediately before treatment and 7 days after the first dose of anti-PD-1 antibodies. **Results:** Severe irAEs ($\geq$ grade 3) occurred in 7 TET patients (22.6%) and 6 NSCLC patients (10.0%). Patients with severe irAEs exhibited a significantly lower fold increase in the frequency of effector regulatory T (eTreg) cells after anti-PD-1 treatment, higher ratio of T helper-17 (Th17) and T helper-1 cells at baseline, and higher percentage of Ki-67^{+}cells among PD-$1^{+}CD8^{+}$T cells post-treatment. In clustering analysis, patients with severe irAEs were grouped into four distinct subtypes: Th17-related, TNF-related,Treg-related, and CD8-related. **Conclusions:** Severe irAEs after anti-PD-1 treatment were clustered into four immunological subtypes, indicating that development of severe irAEs is not attributed to a single mechanism. Further investigations in larger cohorts are needed to validate our current findings.

2565 **Poster Session (Board #209), Sat, 8:00 AM-11:00 AM**

Association between past medical history (PMH) of autoimmune events and adverse events of special interest (AESI).

Jamie Renee Brewer, Virginia Ellen Maher, Chana Weinstock, Sundeep Agrawal, Michael Holman Brave, Yang-Min Ning, Harpreet Singh, Daniel L. Suzman, James Xu, Amna Ibrahim, Julia A. Beaver, Richard Pazdur; U.S. Food and Drug Administration, Silver Spring, MD; U. S. Food and Drug Administration, Silver Spring, MD; US Food and Drug Administration, Silver Spring, MD; Food and Drug Administration, Silver Spring, MD

Background: PD-1/L1 inhibitor therapy has become the standard of care for many advanced solid tumors. A notable limitation of PD-1/L1 inhibitor therapy is the concern for AESI that are likely to be immune related. It is unclear whether a history of autoimmune events is a predisposing risk making these adverse events more likely. We aimed to evaluate the association between autoimmune-associated PMH and AESI on PD-1/L1 inhibitors. **Methods:** We pooled data across seven pivotal trials for PD-1/L1 inhibitors in urothelial cancer (UC) identifying patients with AESI submitted from 2016 - 2017. AESI were determined using a pooled preferred term list for each trial. Information collected from trials included PMH, AESI events and toxicity grade. **Results:** In total, 1747 immunotherapy treated patients were identified, with 1068 (61%) having an AESI and 277 (26%) having an autoimmune-related PMH. The most common autoimmune-associated events in the PMH were thyroid disorders (64%), asthma (23%), atopic dermatitis/eczema (6%), irritable bowel syndrome (5%), and psoriasis (4%). AESI occurred in 68% of patients with an autoimmune-related PMH and 60% of patients without an autoimmune-related PMH. The most common AESI in patients with an autoimmune-related PMH were diarrhea (35%), rash (27%), renal disorder (27%), and pruritis (23%). The most common AESI in the general trial population were diarrhea (28%), pruritis (26%), rash (25%), increased creatinine (14%), and elevated AST and ALT (10% and 9%). The majority of events were Grade 1-2 (87% in patients with an autoimmune-related PMH and 84% in the general trial population). **Conclusions:** Pooled clinical trial data shows a slight numeric increase in AESIs in patients with autoimmune-associated PMH. Limitations include potential lack of consistency of PMH documentation and adverse event reporting. There did not appear to be a pattern of association between PMH and type of AESI event. Grades of AESI events in the population with autoimmune-associated PMH were similar to the general trial population. This suggests that PD-1/L1 inhibitors may be safely administered to patients with UC and a PMH of some autoimmune-associated events. Further exploration is needed.

2566 **Poster Session (Board #210), Sat, 8:00 AM-11:00 AM**

Characteristics of patients receiving immune checkpoint inhibitors (ICI) in ASCO's CancerLinQ.

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Background: ICI's have demonstrated significant clinical benefit since the first FDA approval in 2011 of ipilimumab for metastatic melanoma. Five additional ICI therapies have since been approved across several indications. The objectives of this study were to describe the clinical and demographic features of patients receiving ICI treatment along with utilization patterns in real-world settings. **Methods:** We conducted a retrospective, observational cohort study using statistically de-identified data from January 2011 to November 2018 in CancerLinQ, ASCO's real-world oncology database, which now contains EHR data from 49 diverse oncology practices in the U.S. Adult patients diagnosed with any cancer type who received $\geq$1 dose of an ICI (see Table) and had $\geq$2 clinical visits were eligible for inclusion. Patients were excluded if they received an ICI prior to its first FDA approval date to avoid inclusion of clinical trial patients. Descriptive statistics were used to examine treatment patterns and clinical characteristics of patients receiving ICIs. **Results:** This analysis included 12,712 patients who received an ICI. Median patient age was 67.4 years [IQR 59.3, 75.3]; 58% were male. White race made up the highest percent (83%) of ICI patients, followed by Black race (9%) and Other (8%). The most common primary cancers at the start of treatment were lung cancer (36%), melanoma (8%), urothelial cancer (2%) and renal cell carcinoma (2%). Of the 8,444 patients with known disease stage, 5,446 (64%) had Stage IV cancer. Breakdown of ICI treatment patterns can be found in the accompanying table. Uptake of ICIs was the most rapid for nivolumab, which had the highest use (49%), followed by pembrolizumab for rapid adoption and use (30%). **Conclusions:** This analysis gives insights into patient characteristics and real-world treatment patterns for ICIs. ICIs were used most widely in males, lung cancer patients and patients with advanced disease. These baseline characteristics inform our analyses of ICI use in patients with autoimmune disease, also reported herein.

ICI Medication	N (%)
Atezolizumab	644 (5)
Avelumab	22 (0)
Combination ICI	619 (5)
Durvalumab	116 (1)
Ipilimumab	1303 (10)
Nivolumab	6219 (49)
Pembrolizumab	3789 (30)

2567 **Poster Session (Board #211), Sat, 8:00 AM-11:00 AM**

Understanding contribution and independence of multiple biomarkers for predicting response to atezolizumab.

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Background: No biomarker satisfactorily predict response to anti-PD-L1 therapies. Biomarker studies suffer from small sample size, presence of disease subtypes, and lack of simultaneous measurement of multiple biomarkers. The IMvigor210 dataset (Mariathasan et al., Nature 2018) provides baseline measurements for multiple biomarkers of response to atezolizumab (n range: 105-298) coupled with genomewide RNAseq profiles. We examined predictive performance of individual biomarkers and combined information from multiple biomarkers to measure changes in predictive performance. **Methods:** We built classification models (PR/CR vs. PD/SD) using genes and gene sets that provide information on pathways (mSigDB), immune components (xCell, Cibersort), and predictors of response (IMPRES, Immunophenoscore, and TIDE). Prognostic features were removed based on survival association in TCGA. All experiments were done with repeated five-fold double cross validation. Predictions from the gene sets model were used as a single biomarker. PD-L1 expression by IHC in tumor core and immune cells, tumor mutation burden(TMB), neo-antigen burden (NB), location of metastatic disease, immune phenotype and genomic subtypes were then systematically merged with the gene set based model. **Results:** NB was the best predictor of response (AUC 0.77), while a model combining NB, TMB, ECOG and expression signatures was marginally better (AUC 0.81) with a chance of over fitting. Chi-square tests for independence suggested that examined biomarkers do not provide independent information explaining lack of increase in AUC. Signatures for TP53 mutations, M1 macrophages, CD8+ T effector cell and DNA repair, among others, were present frequently in classification using gene expression information (AUC 0.71), suggesting their independent contributions to response. Adding gene expression information to NB didn't improve AUC for response but provided better survival stratification. **Conclusions:** Integration of examined biomarkers with machine learning did not improve response prediction significantly. We are now examining sizes of subgroups defined by combination of low NB/TMB with these biomarkers.

2568 **Poster Session (Board #212), Sat, 8:00 AM-11:00 AM**

Cardiovascular complications of immune checkpoint inhibitor therapy.

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Background: Cardiac toxicity has largely been underestimated toxicity of checkpoint inhibitors. There have been several cases of myocarditis and fatal heart failure reported in patients treated with checkpoint inhibitors. We did a retrospective analysis of data of adverse effects of drugs that has been made available to public by the FDA. **Methods:** The FDA has made the data on adverse effects of various treatments available to general public through the FDA Adverse Events Reports System (FAERS) public dashboard. We investigated the cardiac toxicities of various immune check point inhibitor therapies available at FDERS for the years 2017-2018. **Results:** The reviewed the reported side effects of pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab and ipilimumab from FDA data. A total of 36,848 toxicities from immunotherapies were reported. Out of that, 2316(6.2 %) were cardio toxicities and 816 were fatal. The most common cardiac complications were as follows: myocarditis (15%), atrial fibrillation (13%), pericardial disease including pericardial effusion (13%), cardiac failure (17%) and coronary artery disease (19%). Approximately 50%, 43%, 40% 22% and 15 % of cases with myocarditis, ischemic heart disease, cardiac failure, atrial fibrillation and pericardia disease were fatal. **Conclusions:** Out of the reported cases of adverse reaction to check point inhibitor, 6.2% were cardio toxicities. 35% of cardio toxicities were fatal. Half of the cases who developed myocarditis died. There was no statistical difference in rate of cardiotoxicities caused by PD1, PDL1 or CTLA 4 inhibitors.

2569 **Poster Session (Board #213), Sat, 8:00 AM-11:00 AM**

Organ dysfunction (dys) and clinical outcomes in patients (pts) treated with immune checkpoint inhibitors (ICIs).

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Background: ICIs (anti-PD-L1/PD-1/CTLA-4) are approved in multiple cancers. The impact of organ dys on the pharmacokinetics of ICIs is known, but associated clinical outcomes are not well characterized. We compared real-world (rw) clinical outcomes in ICI-treated pts by liver and renal function. **Methods:** This retrospective study used longitudinal, patient-level data from community practices in the Flatiron Health electronic-health record (EHR)-derived database. We included pts diagnosed with advanced cancers (NSCLC, renal cell, melanoma, gastric/esophageal, or head and neck) on or after 1/1/2011, treated with an ICI with follow-up through 12/31/2018 and with baseline liver or renal function results in the EHR $\leq$30 days prior to ICI start. Organ function was stratified as normal, mild, moderate, or severe dys based on NCI CTCAE. We computed unadjusted median estimates for rw time to treatment discontinuation (rwTTD) for any reason and overall survival (OS) across baseline groups using the Kaplan-Meier method. **Results:** Of 15,979 pts, we identified 12,978/12,840 pts with evaluable renal/liver function, respectively; median follow-up was 5.1 mos and median age was 69.0 yrs (IQR: 61.0, 76.0) for both. Most pts had NSCLC (69.4/69.0%), were men (60.1/60.0%), white (73.5/73.6%), and diagnosed at stage IV (58.7%/58.6%). Most ICI was given in 1st-line (42.3/42.1%) (outcomes in Table). **Conclusions:** Pts with categorically worse baseline liver function had progressively worse on-treatment outcomes, including shorter OS, which differed from trends in renal dys. Whether baseline dys is prognostic or predictive of ICI outcomes should be further investigated in addition to reasons for discontinuation. Clinical outcomes (unadjusted median times, mos [95% CI]) by organ function.

	Normal	Mild	Moderate	Severe
RENAL, n (%)	10,996 (84.7)	1,593 (12.3)	324 (2.5)	65 (0.5)
OS	10.0 (9.6, 10.4)	11.4 (10.6, 12.4)	10.0 (7.9, 11.8)	8.2 (7.4, 14.8)
rwTTD	3.4 (3.2, 3.4)	3.7 (3.3, 4.1)	3.4 (3.1, 4.2)	3.4 (2.1, 7.3)
LIVER, n (%)	11,116 (86.6)	1,495 (11.6)	159 (1.2)	70 (0.5)
OS	10.8 (10.4, 11.2)	6.8 (5.8, 7.6)	3.3 (2.0, 5.8)	2.2 (1.3, 4.3)
rwTTD	3.6 (3.4, 3.7)	2.3 (2.3, 2.8)	1.8 (0.9, 2.3)	0.9 (0.5, 1.4)

2570 **Poster Session (Board #214), Sat, 8:00 AM-11:00 AM**

A phase II clinical trial of ipilimumab/nivolumab combination immunotherapy in patients with rare upper gastrointestinal, neuroendocrine, and gynecological malignancies.

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Background: Patients (pts) with rare cancers represent an unmet medical need and have an inferior overall survival compared to patients with more common malignancies. Due to their low frequency, no therapies, including immunotherapies, have systematically been investigated in this population. Ipilimumab (ipi)/Nivolumab (nivo) combination treatment has demonstrated significant clinical activity in pts with advanced melanoma and renal cell carcinoma and response rates with this regimen are higher compared to single agent anti-PD-1 therapy. This phase II study assessed the efficacy and safety of ipi/nivo in rare cancer pts. **Methods:** 60 pts with advanced rare upper gastrointestinal (GI), neuroendocrine (NE) and gynaecological (GY) malignancies were enrolled in 3 cohorts. Patients received nivo 3mg/kg and ipi 1mg/kg every 3 weeks for four doses, followed by nivo 3mg/kg every 2 weeks. Treatment continued for up to 96 weeks, or until disease progression or the development of unacceptable toxicity. Response (RECIST 1.1) was assessed every 12 weeks. The primary endpoint was clinical benefit rate (CBR), CR, PR and SD. Exploratory endpoints include correlation of efficacy with relevant biomarkers including PDL1 status and tumour mutation burden. **Results:** 42 pts have so far undergone restaging, 11 pts clinically progressed prior to their first restaging scan. 50 pts have received prior therapy (1-5 lines). Objective responses have been observed in a range of different malignancies. Clinical trial information: NCT02923934. Grade 3/4 immune related adverse events were detected in 31% of pts. The results of correlative biomarker studies will be presented at the meeting. **Conclusions:** Ipi/Nivo combination treatment has efficacy in a wide range of advanced rare malignancies. Immune related toxicity is in keeping with previously reported clinical trials using the same dosing regimen.

# pts	53	GI (16)	NE (20)	GY (17)
ORR	32%	31% 3 pts Cholangioca 2 pts Gallbladder ca	25% 3 pts Atypical bronchial carcinoid 1 pt Pancreatic NET 1 pt Adrenocortical ca	41% 1 pt Ovarian clear cell ca 1 pt Ovarian germ cell tumor 1 pt Uterine clear cell ca 1 pt Uterine carcinosarcoma 1 pt Uterine leiomyosarcoma 1 pt Vaginal SCC 1 pt low grade serous ovarian ca
SD	36%	19%	55%	29%
CBR	68%	50%	80%	70%
PD	32%	50%	20%	30%

2571 **Poster Session (Board #215), Sat, 8:00 AM-11:00 AM**

Outcomes after early initiation of nonsteroidal immunosuppressive therapy in patients with immune checkpoint inhibitor-induced colitis.

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Background: Current treatment guidelines for immune-mediated colitis (IMC) recommend 4 to 6 weeks of steroids as first-line therapy, followed by nonsteroidal immunosuppressive therapy (NSIST) (infliximab or vedolizumab) in patients who do not respond to steroids. We assessed the effect of early NSIST introduction and number of NSIST infusions on clinical outcomes. **Methods:** We performed a retrospective review of patients with IMC who received NSIST between January and December 2018. Logistic regression analyses were used to assess associations between clinical features and outcomes of IMC (Table). **Results:** Of the 1,459 patients who received immune checkpoint inhibitor, 179 developed IMC of any grade; 84 of them received NSIST. Of the 84 patients who received NSIST, 79% were males with mean age of 60. Compared with patients who received NSIST >10 days after IMC onset, patients who received early NSIST (≤ 10 days) required fewer hospitalizations ($P=0.03$), experienced steroid taper failure less frequently ($P=0.03$), had fewer steroid tapering attempts ($P<0.01$), had a shorter course of steroid treatment ($P=0.09$), and had a shorter duration of symptoms ($P<0.01$). Risk factors of IMC recurrence after weaning off steroids included: 1) needing multiple hospitalizations ($P<0.01$), 2) experiencing steroid taper failure after NSIST ($P=0.02$), 3) receiving infliximab rather than vedolizumab ($P=0.02$), 4) receiving fewer than three infusions of NSIST ($P=0.02$), 5) having higher fecal calprotectin levels after NSIST ($P=0.01$), and 6) receiving a longer course of steroids ($P=0.02$), hospitalization ($P<0.01$) and IMC symptoms ($P<0.01$). Unsuccessful weaning from steroids after NSIST was associated with high IMC grades ($P<0.01$); multiple hospitalizations ($P<0.01$); steroid-resistant IMC ($P<0.01$); long interval from IMC to NSIST initiation ($P=0.01$); and long duration of steroids ($P<0.01$), IMC symptoms ($P<0.01$), and hospitalization ($P<0.01$). **Conclusions:** NSIST should be introduced early in the disease course of IMC instead of waiting until failure of steroid therapy or steroid taper. Patients who received three or more infusions of NSIST had more favorable clinical outcomes.

2572 **Poster Session (Board #216), Sat, 8:00 AM-11:00 AM**

Immunomodulation by HDAC inhibition: Results from a phase Ib study with vorinostat and pembrolizumab in metastatic urothelial, renal, and prostate carcinoma patients.

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Background: Immunosuppressive factors such as regulatory T cells (Tregs) and myeloid-derived suppressive cells (MDSCs) limit the efficacy of immunotherapies. Histone deacetylase (HDAC) inhibitors have been shown to have immunomodulatory effects. We have previously reported that HDAC inhibitors have synergistic antitumor effects in combination with PD-1 inhibition in tumor models by inhibiting the function of Tregs and MDSCs. Thus, we conducted a Phase Ib clinical study with the HDAC inhibitor vorinostat and the PD-1 inhibitor pembrolizumab in patients (pts) with metastatic urothelial, renal and prostate carcinoma. **Methods:** The primary objective was to evaluate the safety and tolerability of this combination strategy. The phase I portion consisted of two dose levels of vorinostat (100 and 200 mg, PO daily 2 weeks ON and one week OFF) and a fixed, standard dose of pembrolizumab (200 mg IV every 21 days). Patients were assigned to three cohorts: Cohort A (previously treated, anti-PD1/PD-L1 naïve urothelial and renal cancer pts = 15), Cohort B (previously treated, anti-PD1/PD-L1 resistant urothelial and renal cancer pts = 14), and Cohort C (prostate cancer pts = 14). **Results:** Dose levels 1 (4 enrolled, 3 evaluable) and 2 (4 enrolled, 3 evaluable) were completed without DLTs and 200 mg was the Phase II recommended dose for vorinostat. The most common resolved grade 3/4 toxicities were acute kidney injury (n = 1), anemia (n = 1), diarrhea (n = 1), and hypothyroidism (n = 1) in the dose expansion cohorts. We have enrolled 43 pts (37 evaluable) in the dose expansion cohorts. For Cohort A, B, and C the median PFS were 2.8 months, 5.2 months, and 3.5 months. Two PR were observed including the dose escalation phase. Two PCA pts have achieved undetectable PSA. We have performed several correlative studies including flow cytometry and gene expression analysis on peripheral blood mononuclear cells, PDL-1 staining and PSMA PET scans in a subset of pts. **Conclusions:** The results from this phase Ib suggest that the combination of vorinostat and pembrolizumab is relatively well tolerated and may be active in a subset of immune checkpoint resistant UC/RCC pts and immune checkpoint naïve PCA pts. Clinical trial information: NCT02619253.

2573 **Poster Session (Board #217), Sat, 8:00 AM-11:00 AM**

Efficacy and a novel clinicopathologic-genomic nomogram of atezolizumab in advanced non-small cell lung cancer (POPLAR and OAK): A combined analysis of two multicenter, randomized, phase II/III trials.

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Background: Atezolizumab, a programmed death ligand 1 (PD-L1) inhibitor, prolonged overall survival (OS) compared with docetaxel among patients with previously treated advanced non–small-cell lung cancer (NSCLC) in two independent multicentre, randomized trials (POPLAR and OAK). We conducted a combined analysis of the two trials to evaluate its efficacy and genomic biomarkers, and to further developed a novel predictive clinicopathologic-genomic nomogram of immunotherapy in NSCLC. **Methods:** Patients (N = 1,137) with stage IIIB/IV NSCLC and disease progression after previously platinum-based chemotherapy were randomly assigned (1:1) to receive atezolizumab (1200 mg/kg every 3 weeks) or docetaxel (75 mg/m^2 every 3 weeks). The primary endpoint was OS. We applied a two-stage meta-analysis of pooled individual patient data in the intention-to-treat population. In OAK trial, patients treated with atezolizumab were randomly assigned (1:1) to the training group or the validation group to develop a predictive clinicopathologic-genomic nomogram of immunotherapy. POPLAR and OAK were registered with ClinicalTrials.gov, numbers NCT02008227 and NCT01903993. **Results:** In the pooled analysis, the median overall survival was 13.49 months (95% confidence interval [CI], 11.95 to 15.22) with atezolizumab versus 9.66 months (95% CI, 8.73 to 10.70) with docetaxel. The risk of death was 28% lower with atezolizumab than with docetaxel (hazard ratio [HR], 0.72; 95% CI, 0.62 to 0.83; $P <$ 0.001). The race, sex, tumor histology, eastern cooperative oncology group performance status, PD-L1 expression, and especially pretreatment mutation (TP53, DNMT3A and KEAP1) were significantly associated with OS, and were used for the development of the predictive nomogram. The clinical use of the nomogram showed a closer association with 3-year OS than the blood-based tumor mutational burden (bTMB) or PD-L1 expression alone (nomogram, AUC = 0.818; bTMB, AUC = 0.701; PD-L1, AUC = 0.526) among NSCLC patients who had received atezolizumab. The superior predictability of the nomogram was further confirmed in the validation and entire OAK cohorts. **Conclusions:** Among patients with advanced, previously treated NSCLC, OS was significantly better with atezolizumab than with docetaxel. Furthermore, we constructed a novel and powerful clinicopathologic-genomic nomogram for personalized immunotherapy options.

2574 **Poster Session (Board #218), Sat, 8:00 AM-11:00 AM**

Neoadjuvant presurgical PD-1 inhibition in oral cavity squamous cell carcinoma.

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Background: Oral cavity squamous cell carcinoma (OCSCC) is a highly prevalent surgically-treated subset of head and neck cancer with frequent recurrence and poor survival. Immunotherapy has demonstrated efficacy in recurrent/metastatic head and neck cancer, but has not been validated in the neoadjuvant presurgical setting. **Methods:** A Simon two stage design was used in this single-arm, Phase II clinical trial with a preplanned analysis after completion of stage one. The first stage included 9 patients with stage II-IVA OCSCC who received 3-4 biweekly doses of 3mg/kg Nivolumab (anti-programmed death 1 [PD-1]) followed by definitive surgical resection for cure. The primary endpoint was overall response rate to treatment. Secondary endpoints were safety and feasibility. **Results:** Presurgical Nivolumab therapy resulted in an overall response rate of 44% (95% CI: 14-79%) with four patients having >30% reduction in tumor size consistent with partial response. An additional patient had stable disease while the remaining four patients progressed through treatment. Neoadjuvant Nivolumab was not associated with delays in definitive surgical treatment. There were no grade 3-4 adverse events and no treatment interruptions. At median follow up of 10 months (2-16), there were 4 recurrences in 3 patients and one death. Objective response by RECIST 1.1 criteria on interval imaging predicated eventual pathologic response in 100% of patients. **Conclusions:** Neoadjuvant presurgical PD-1 blockade is associated with encouraging response rate and demonstrates feasibility and safety for OCSCC. Clinical trial information: NCT03021993.

2575 **Poster Session (Board #219), Sat, 8:00 AM-11:00 AM**

Feasibility and toxicity of neoadjuvant nivolumab with or without ipilimumab prior to extensive (salvage) surgery in patients with advanced head and neck cancer (the IMCISION trial, NCT03003637).

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Background: surgery w/wo adjuvant radiotherapy (RT) for (recurrent) advanced head and neck squamous cell carcinoma (HNSCC) results in 30-50% 5-year OS, indicating the need for novel treatment options. In recurrent metastatic HNSCC nivolumab nearly tripled the 2-year OS. Aiming at improving clinical outcome in advanced HNSCC in a curative setting, we tested the feasibility of nivolumab ± ipilimumab neoadjuvant to (salvage) surgery w/wo RT. **Methods:** investigator-initiated phase-IB/II trial to assess feasibility of neoadjuvant nivolumab monotherapy (240 mg in week 1&3: arm-A) or in combination with ipilimumab (1 mg/kg in week 1: arm-B) before surgery (≤ week 5) w/wo RT for advanced HNSCC. **Results:** 12 patients were included (3+3 design, both arms) in phase-IB of this study; 7/12 (58%) patients had pre-existent moderate-to-severe comorbidities (ACE-27). All patients were HPV negative. All patients received surgery as planned (25-33 days after start of immunotherapy) with no unexpected wound healing problems. In both groups, 4 patients (67%) experienced immune-related toxicity: grade 1-2 (n = 4) and grade 3-4 (n = 1; colitis) in arm-A; grade 1-2 (n = 5) and grade 3-4 (n = 2; colitis and elevated liver enzymes) in arm B. Immune-related toxicity was managed with prednisone (n = 2) and infliximab (n = 1). There was 1/6 (12.5%) pathological response in arm-A (1 near complete response, nCR) and 3/6 (50%) in arm-B (1x partial response and 2x nCR). No patients with nCR had a recurrence at follow-up (median 10 months). Preliminary data (mutational load will be added) show increased H7-B3 gene expression in non-responders before treatment, and increased endothelial cell and NK cell gene expression in responders post-treatment. Overall, in these 12 patients, neoadjuvant ipilimumab + nivolumab resulted in a significant increase in immune-related gene expression when compared to nivolumab only, irrespective of treatment response. **Conclusions:** neoadjuvant ipilimumab + nivolumab can safely be administered prior to major surgery for advanced HNSCC. Efficacy is promising and will be further evaluated in the phase-II trial continuation. Clinical trial information: NCT03003637.

2576 **Poster Session (Board #220), Sat, 8:00 AM-11:00 AM**

Effect of exonic microsatellite instability of B2M on the predictability of MSI/dMMR for immunotherapy.

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Background: Microsatellite instability/mismatch repair deficiency (MSI/dMMR) has been approved as a biomarker for immune checkpoint inhibitor therapy (ICI) . However, the deficiency of mismatch repair system also caused wide-spreading insertion/deletion (indel) mutations in the exonic microsatellite sites of critical immunotherapy related genes such as β-2-macroglobulin (B2M) whose product is critical to antigen presentation. Cases of aquired resistance to ICI treatment caused by the inactivation of B2M have been reported. Therefore, we investigated the mutational profile of B2M across the MSI/dMMR high prevalent cancers such as colorectal cancer (CRC), gastric cancer (GC) and endometrial cancer (EC). **Methods:** FFPE tumor samples from 37 CRC, 46 GC and 25 EC patients with matched normal tissues were collected for next-generation sequencing (NGS)-based 450 genes panel assay. Genomic alterations including single base substitution, short and long insertions/deletions, copy number variations, and gene rearrangement and tumor mutational burden were assessed. Immunohistochemistry (IHC) with antibody against B2M were performed on available samples to estimate the expression and localization of these proteins. **Results:** Exonic microsatellite sites of B2M gene have been found instable in 51% (19/37) of CRC, 22% (10/46) of GC and 8% (2/25) of EC. MSI caused small indels at B2M coding region leads to reading frame shift and the production of nonfunctional truncated proteins. Biallelic frameshift mutations, causing non-functional proteins, were found in 47% (9/19) of CRC and 30% (3/10) of GC patients carrying Indels in B2M gene. IHC assays showed the impaired expression of B2M proteins due to frameshift mutations. In addition, NGS test confirmed concurrent mutation in B2M for a MSI-H CRC patient with primary resistance to forth-line anti-PD1 treatment. **Conclusions:** The extensive mutations in the coding region of genes caused by the dMMR render the cancer cell sensitive to ICI. However, the concomitant variants in exonic microsatellite sites of B2M gene may compromise the predictability of MSI/dMMR as an ICI biomarker. Biallelic mutation of B2M may cause primary resistance to ICI while the mono-allelic mutation of B2M may gain acquired resistance. Therefore, B2M status could be considered when using MSI/dMMR as a biomarker for ICI.

2577 **Poster Session (Board #221), Sat, 8:00 AM-11:00 AM**

Immune-mediated colitis after resumption of immune checkpoint inhibitor therapy.

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Background: Immune checkpoint inhibitor (ICI) therapy is often suspended because of immune-mediated diarrhea and colitis (IMDC). We examined the recurrence rate and risk factors for IMDC after ICI resumption. **Methods:** This retrospective multicenter study examined patients who resumed ICI therapy after improvement of IMDC between 1/2010 and 11/2018. Univariate and multivariate logistic regression analyses assessed the association of clinical covariates and IMDC recurrence. **Results:** Of the 167 patients in our analysis, 32 resumed an anti-CTLA-4 agent and 135 an anti-PD-1/L1 agent. The median duration from IMDC to restart of ICI treatment was 49 days (IQR, 23-136). IMDC recurred in 57 (34%) patients overall (44% of those resuming an anti–CTLA-4 and 32% resuming an anti–PD-1/L1 agent); 47 of these patients (82%) required immunosuppressive therapy for recurrent IMDC (Table). The median duration from ICI resumption to IMDC recurrence was 53 days (IQR 22-138). On multivariate logistic regression, patients who received anti-PD-1/L1 therapy at initial IMDC had a higher risk of IMDC recurrence (odds ratio [OR], 3.45, 95%CI, 1.59-7.69; $P<0.01$). Risk of IMDC recurrence was higher for patients who required immunosuppression for initial IMDC (OR, 3.22; 95%CI, 1.08-9.62; $P=0.02$) or had longer duration of IMDC symptoms in the initial episode (OR, 1.01; 95%CI, 1.00-1.03; $P=0.03$). Risk of IMDC recurrence was lower for those who resumed anti–PD-1/L1 therapy than for those who resumed anti–CTLA-4 therapy (OR, 0.30; 95%CI, 0.11-0.81; $P=0.02$). **Conclusions:** One-third of patients who resumed ICI treatment after IMDC experienced recurrent IMDC. IMDC recurrence was less frequent after resumption of anti–PD-1/L1 than after anti–CTLA-4. Characteristics of recurrent IMDC based on resumed ICI therapy.

Characteristic	Anti–CTLA-4 N = 32 (%)	Anti–PD-1/L1 N = 135 (%)	P
Recurrence of symptoms	14 (44)	43 (32)	0.30
Time from ICI resumption to IMDC recurrence, days (IQR)	26 (2-43)	79 (27-141)	0.02
Treatment of recurrence			0.31
Symptomatic only	3 (9)	8 (6)	
Steroid	8 (25)	31 (23)	
Infliximab/vedolizumab add-on	3 (9)	4 (3)	
Grade of recurrent diarrhea[a]			0.50
1	2 (6)	9 (7)	
2	11 (34)	29 (22)	
3-4	1 (3)	5 (4)	
Grade of recurrent colitis[a]			0.39
1	7 (22)	23 (17)	
2-3	6 (19)	20 (15)	

2578 **Poster Session (Board #222), Sat, 8:00 AM-11:00 AM**

Tumor mutational burden (TMB) and response rates to immune checkpoint inhibitors (ICIs) targeting PD-1, CTLA-4, and combination.

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Background: ICIs targeting PD-1/L1 and/or CTLA-4 have activity against many different cancers. We and others have previously shown that a higher TMB, a surrogate for an increased number of expressed tumor neoantigens, is an important biomarker for response to anti-PD-1/L1 monotherapy. Whether the relationship between the TMB and response to ICIs extends beyond anti-PD-1/L1 is unknown. **Methods:** We identified 30 major solid tumor types for which TMB has been described using a genomic profiling assay performed by Foundation Medicine. We conducted searches of MEDLINE (from Jan 1, 2010 to Jan 20, 2019), as well as abstracts presented at ASCO, ESMO, AACR Annual Meetings 2010-2018 to identify the objective response rate (ORR) for anti-PD-1/L1, anti-CTLA-4 and combination anti-PD-1/L1 plus anti-CTLA-4, in each of these cancer types. We pooled the response data from the largest published studies that evaluated the ORR. We excluded studies that; enrolled < 10 evaluable patients, investigated ICI therapies in combination with other agents, and studies that selected patients based on immune-related biomarkers. Across tumor types, median TMB was compared to ORR utilizing the coefficient of determination (r^2) derived from simple linear regressions. **Results:** TMB is strongly associated with response to anti-PD-1/L1 monotherapy ($n = 8798$, $r^2 = 0.4704$, $p < 0.001$), and combination anti-PD-1/L1 plus anti-CTLA-4 ($n = 2280$, $r^2 = 0.4082$, $p = 0.004$). Available ORR data were more limited with CTLA-4 monotherapy and the relationship between ORR and TMB did not meet statistical significance ($n = 1377$, $r^2 = 0.2606$, $p = 0.1086$). The additional ORR benefit of adding a CTLA-4 inhibitor to anti-PD-1/PDL1 therapy increased with increasing TMB. In tumor types with a lower TMB (< 10 mutations/MB), combined ICI therapy led to an average improvement of 5.5% in ORR over PD-1/L1 monotherapy, versus 21.8 % ORR improvement in high TMB tumors (≥ 10 mutations/MB). **Conclusions:** A strong relationship exists between TMB and clinical activity of both PD-1/L1 monotherapy and combination ICIs with PD-1/L1 plus CTLA-4. The clinical benefit of adding anti-CTLA-4 to anti-PD-1/L1 is greatest in high TMB tumors and limited in low TMB tumors.

2579 **Poster Session (Board #223), Sat, 8:00 AM-11:00 AM**

MEDIPLEX: A phase 1 study of durvalumab (D) combined with pexidartinib (P) in patients (pts) with advanced pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC).

Philippe Alexandre Cassier, Gwenaelle Garin, Lauriane Eberst, Jean-Pierre Delord, Sylvie Chabaud, Catherine Terret, Laure Montane, Anne-Sophie Bidaux, Séverine Laurent, Lise Jaubert, Celine Ferlay, Mathilde Bernardin, Séverine Tabone-Eglinger, Laurence Gilles-Afchain, Christine Menetrier-Caux, Christophe Caux, Isabelle Treilleux, David Pérol, Carlos Alberto Gomez-Roca; Centre Léon-Bérard, Lyon, France; Medical Oncology Department, Centre Léon Bérard, Université Claude Bernard Lyon 1, Lyon, France; Institut Universitaire du Cancer de Toulouse, Toulouse, France; Statistician - GINECO - Centre Léon-Bérard, Lyon, France; Centre Leon Berard, Lyon, France; Centre Léon Bérard, Lyon, France; Institut Claudius Regaud, Toulouse, France

Background: Targeting tumor associated macrophages is an emerging strategy to increase the responsiveness of PDAC and CRC to anti-PD(L)1. Pexidartinib (P) is an orally active, small-molecule kinase inhibitor that targets the colony-stimulating factor-1 receptor (CSF1R) on macrophages. **Methods:** Adult pts with advanced/ metastatic PDAC or CRC were treated with a fixed dose of D (1500mg q4w, IV) and ascending doses of P (400, 600, 800 and 1000mg/d, orally). Dose escalation was conducted according to a Likelihood Continual Reassessment Method with a 28-day window to evaluate dose-limiting toxicity (DLT), a stopping rule advised dose escalation termination in case of a high probability ($>$ 90%) for the next 6 pts to be assigned to the same dose. Following the determination of RP2D, 14 pts with PDAC and 14 pts with CRC who consented to serial tumor biopsies were enrolled in expansion cohorts to assess preliminary anti-tumor activity and biomarkers. **Results:** 19 pts (12M, 7F, median age, 56 y [range, 43-76y]) were enrolled in 4 dose escalation cohorts (P 400, 600 and 800mg/d: 3 pts each and P 1000mg/d: 10 pts). Pharmacokinetic analysis showed dose-dependent increase in the exposure of P from 400 to 1000 mg. Two DLTs (AST/ALT elevations including one with bilirubin increase) were seen at dose level P 1000mg/d. The most frequent ($>$ 2pts) related (to either D, P or both) AEs were: fatigue, maculopapular rash/pruritus/dry skin, hair color changes, anorexia, edema (periorbital, limbs or face), AST/ALT increases, bilirubin increases, nausea, vomiting and diarrhea. The most frequent ($\geq$2pts) Grade $\geq$ 3 AEs related to P were: AST/ALT increase, ALP increase, neutrophil or white blood cell count decrease, and fatigue. Clinical benefit rate at 2 months was 21% (4 SD /19pts), 2 pts with MSI-H CRC had SD for more than 6 months including 1 pt still receiving single agent D after $>$ 18 months. The RP2D for the combination was P 800mg/d + D 1500mg q4w. Enrolment in the expansion cohorts was completed in January 2019. **Conclusions:** Toxicity was consistent with the expected profiles of the individual drugs and no unexpected events were seen with the combination. Updated data will be presented at the meeting. Clinical trial information: NCT02777710.

2580 **Poster Session (Board #224), Sat, 8:00 AM-11:00 AM**

Patient survival with immune checkpoint inhibitors and targeted agents in phase 1 trials: A propensity score weighted analysis.

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Background: There have been important changes in early drug development units with an unprecedented increase of immune-oncology (IO) trials. Currently at the Vall d'Hebron Institute Oncology (VHIO) close to 50% of our Phase 1 trials (Ph1t) portfolio includes IO drugs, while from 2011 to 2015 more than 80% of our trials assessed targeted agents (TA). We wanted to investigate whether this swift had a positive impact on patient (pts) outcome. **Methods:** We performed a retrospective analysis of the pts treated with IO and TA at VHIO Ph1t Unit from Jun'11 to May'18. Only patients treated with IO in $\geq 2^{nd}$ line were included (and without an approved IO therapy as per standard-of-care) and those with TA classified as tiers II-III-IV by the ESMO scale for clinical actionability of molecular targets ESCAT (which also represents unapproved indications). The aim of this study was to compare overall survival (OS) for the two cohorts. Given the non-randomized nature of the study a propensity score weighting (PSW) was used to control for selection bias in treatment effect estimation. **Results:** Out of 545 eligible pts, 281 (51.5%) received TA and 264 (48.5%) IO, with unadjusted median OS (mOS) of 7.7 months (m) and 9.2m, respectively. In univariate analysis, OS was associated with tumor type, number of previous treatment lines, regimen (monotherapy vs combination), and clinical-laboratory prognostic factors (Vioscore: albumin < 3.5 g/dl; LDH $>$ upper limit of normal; neutrophil/[leukocytes minus neutrophils] ratio (dNLR) > 3; more than 2 sites of metastasis; and presence of liver metastasis) ($p < 0.05$). After adjusting for these factors in a PSW model, the IO group showed statistically significant longer OS with HR = 0.75 (CI95% 0.65 – 0.86, $p < 0.0001$). The In a stratified analysis by tumor type we found no significant heterogeneity in the relative benefit of IO over TA. **Conclusions:** In real world data from our Ph1t population, treatment with IO was associated with longer OS than treatment with TA, even after adjusting for known prognostic factors and treatment selection biases. These results suggest that the likelihood of patient benefit with IO therapies in Ph1t is increasing.

2581 **Poster Session (Board #225), Sat, 8:00 AM-11:00 AM**

Using machine learning algorithms to predict response and toxicity to immune checkpoint inhibitors (ICIs) in melanoma patients.

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Background: There is growing interest in optimizing patient selection for treatment with immune checkpoint inhibitors (ICIs). We postulate that phenotypic features present in metastatic melanoma tissue reflect the biology of tumor cells, immune cells, and stromal tissue, and hence can provide predictive information about tumor behavior. Here, we test the hypothesis that machine learning algorithms can be trained to predict the likelihood of response and/or toxicity to ICIs. **Methods:** We examined 124 stage III/IV melanoma patients who received anti-CTLA-4 (n = 81), anti-PD-1 (n = 25), or combination (n = 18) therapy as first line. The tissue analyzed was resected before treatment with ICIs. In total, 340 H&E slides were digitized and annotated for three regions of interest: tumor, lymphocytes, and stroma. The slides were then partitioned into training (n = 285), validation (n = 26), and test (n = 29) sets. Slides were tiled (299x299 pixels) at 20X magnification. We trained a deep convolutional neural network (DCNN) to automatically segment the images into each of the three regions and then deconstruct images into their component features to detect non-obvious patterns with objectivity and reproducibility. We then trained the DCNN for two classifications: 1) complete/partial response versus progression of disease (POD), and 2) severe versus no immune-related adverse events (irAEs). Predictive accuracy was estimated by area under the curve (AUC) of receiver operating characteristics (ROC). **Results:** The DCNN identified tumor within LN with AUC 0.987 and within ST with AUC 0.943. Prediction of POD based on ST-only always performed better than prediction based on LN-only (AUC 0.84 compared to 0.61, respectively). The DCNN had an average AUC 0.69 when analyzing only tumor regions from both LN and ST data sets and AUC 0.68 when analyzing tumor and lymphocyte regions. Severe irAEs were predicted with limited accuracy (AUC 0.53). **Conclusions:** Our results support the potential application of machine learning on pre-treatment histologic slides to predict response to ICIs. It also revealed their limited value in predicting toxicity. We are currently investigating whether the predictive capability of the algorithm can be further improved by incorporating additional immunologic biomarkers.

2582 **Poster Session (Board #226), Sat, 8:00 AM-11:00 AM**

High prevalence of IBD-associated genetic variants in patients (pts) with immune checkpoint inhibitor (ICI) enteritis/colitis.

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Background: Colitis is a frequent toxicity of ICI therapy but there is paucity of data on risk factors. Specific serological markers and genetic polymorphisms have been associated with inflammatory bowel disease (IBD) (ulcerative colitis, Crohn's disease). However, the prevalence of these markers in pts with ICI colitis is unknown. We performed a pilot study to determine the prevalence of IBD-associated genetic and serologic biomarkers in pts with ICI colitis. **Methods:** Cancer pts with histologically confirmed ICI enteritis/colitis and no history of IBD underwent commercial IBD panel testing. The panel included 4 genetic markers (*ATG16L1, NXK2–3, ECM1*, *STAT3*), 8 serological markers (anti-A4-Fla2, anti-A4-FlaX, anti-CBir1, anti-OmpC, ASCAIgA, ASCA-IgG, pANCA, ANCA), and 5 inflammatory markers (vascular endothelial growth factor [VEGF], intracellular adhesion molecule 1[ICAM-1], vascular cell adhesion molecule 1 [VCAM-1], C-reactive protein, serum amyloid A [SAA]). Clinical testing on serum samples was performed by Prometheus Laboratories (San Diego, CA). **Results:** Of 15 cancer pts with biopsy confirmed ICI colitis, 10 (67%) were homozygous for 1 or more of 4 genetic markers. The remaining 5 pts were all heterozygous for two or more of the genetic markers. One or more serologic markers associated with IBD were elevated in 7/15 (47%) pts. Serum reactivity was noted for ASCA-IgA (1/15, 7%), ASCA-IgG (1/15, 7%), anti-OmpC (3/15, 20%), anti-CBR IgG (2/15, 13%), anti-A4-FlaX (1/15, 7%), and ANCA (2/15, 13%). One or more inflammatory markers were elevated in 13/15 (88%) pts. Elevations in VEGF, VCAM-1, ICAM-1, and SAA were noted in 2 (13%), 8 (53%), 8 (53%), and 11 (73%) pts, respectively. Only 6 (40%) pts had elevations in CRP levels despite the presence of active inflammation on biopsy. The IBD panel was reported as being consistent with Crohn's disease in 2 pts, ulcerative colitis in 1 pt and inconclusive for type but consistent with IBD in 1 pt. **Conclusions:** In this pilot study, all patients with ICI colitis, were either homozygous or heterozygous for two or more high risk IBD alleles. If validated, such testing may prospectively identify pts at risk for developing ICI colitis.

2584 **Poster Session (Board #228), Sat, 8:00 AM-11:00 AM**

Overcoming genetically based resistance mechanisms to PD-1 blockade.

Davis Yuri Torrejon, Gabriel Abril-Rodriguez, Jennifer Tsoi, Ameya Champhekar, Anusha Kalbasi, Katie Marie Campbell, Giulia Parisi, Cristina Puig-Saus, Gardenia Cheung-Lau, Tom Wohlwender, Beata Berent-Maoz, Catherine Grasso, Begoña Comin-Anduix, Siwen Hu-Lieskovan, Antoni Ribas; University of California Los Angeles Jonsson Comprehensive Cancer Center, Los Angeles, CA; University of California, Los Angeles, Los Angeles, CA; UCLA JCCC, Los Angeles, CA; JCCC UCLA, Los Angeles, CA; Department of Radiation Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA; Department of Medicine, Division of Hematology-Oncology, University of California, and the Jonsson Comprehensive Cancer Center, Los Angeles, CA; University of California Los Angeles, Los Angeles, CA; Department of Surgery, Division of Surgical-Oncology, and the Jonsson Comprehensive Cancer Center, Los Angeles, CA; University of California, Los Angeles and the Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Mechanism-based strategies to overcome resistance to anti-PD1 therapy are urgently needed. Using CRISPR/Cas9 genome editing tools, we developed acquired resistant models through JAK1/2 and B2M loss of function (LoF) mutations in human melanoma cell lines and in the murine MC38 colon carcinoma, known for high mutational load and good response to anti-PD-1. We hypothesized that the downstream activation of the IFN-receptor pathway or the activation of natural killer (NK) cells would overcome this resistance. **Methods:** We studied signaling changes in four human cell lines (parental and LoFs) exposed to IFN-gamma using RNAseq. In addition, we analyzed the *in-vivo* antitumor activity in MC38 variants with anti-PD1 and characterized the tumor microenvironment using mass cytometry (CyTOF). Finally, we tested strategies to overcome resistance mechanisms with SD-101 (TLR-9 agonist) and bempegaldesleukin (NKTR-214, CD-122 biased agonist) with the extent of CD8 and NK1.1 depletion. **Results:** RNAseq differential gene expression analysis showed that the IFN-gamma induced increased expression of antigen presenting machinery, IFN-gamma signaling and chemokines (CXCL9/10) was lost in JAK1/2-LoF human melanoma cell lines. The significant antitumor activity of anti-PD-1 against MC38 parental cell line was lost in JAK1/2 and B2M LoF sublines, and CyTOF analysis revealed that anti-PD-1 therapy was unable to increase tumor CD8+ T-effectors in these LoF tumors. The intratumoral administration of SD-101 (50 μg/injection q4dx3wks) was able to overcome local resistance even in non-injected sites in JAK1/2 and IFNAR-type-I LoF tumors, and systemic administration of bempegaldesleukin (0.8 mg/kg, q9dx2, i.v.) was able to overcome resistance in B2M LoF with significantly increased survival (Table). Depletion studies showed complete abrogation of anti-tumor response with anti-NK1.1 in JAK1 LoF and B2M LoF, and partial abrogation with anti-NK1.1 or anti-CD8 in JAK2 LoF tumors. **Conclusions:** Even in the extreme setting of genetic resistance to PD-1 blockade by JAK1/2 LoF, resistance can be overcome by SD-101, a TLR9 agonist, while resistance of B2M LoF can be overcome by bempegaldesleukin (NKTR-214), a CD-122 biased agonist. Our findings support the testing of these rational mechanistic strategies in patients with a-PD1 resistance.

	JAK1				JAK2				B2M			
	Iso	aPD1	SD101	aPD1+SD101	Iso	aPD1	SD101	aPD1+SD101	Iso	aPD1	NKTR-214	a-PD1+NKTR-214
n	5	5	5	5	5	5	5	5	5	5	5	5
Median survival (days)	27	27	64	94	21	21	32	36	19	21	90	100
p (Log-rank test)		ns	***	***		ns	***	***		ns	***	***

***p < 0.0005

2585 **Poster Session (Board #229), Sat, 8:00 AM-11:00 AM**

Measuring the long-term "tail of curve" survival benefits in oncology trials: A comparison of the ASCO Value Framework and the ESMO Magnitude of Clinical Benefit Scale.

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Background: Recently, anti-cancer agents have generated excitement due to their capacity to preserve long-term survival in some patients, represented by a "tail of the survival curve". However, as traditional measures of clinical benefit may not accurately capture long-term survival, amendments to various valuation frameworks have been proposed to capture this benefit. The purpose of this study was to determine how frequently immune checkpoint inhibitor vs. non-immune checkpoint inhibitor anti-cancer agents, displayed trends of long-term survival, as defined by the American Society of Clinical Oncology Value Framework (ASCO-VF) and European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS), as well as to analyze the degree of agreement between ASCO and ESMO frameworks. **Methods:** Anti-cancer agents from phase II or III randomized controlled trials (RCTs) cited for clinical efficacy evidence in drug approval by the Food and Drug Administration (FDA) between January 2011 and March 2018 were identified. Data required for ASCO-VF and ESMO-MCBS were extracted. Difference in how often long-term survival bonuses were awarded were calculated in all RCTs, as well as immune checkpoint inhibitor and non-immune checkpoint inhibitor RCTs individually. Cohen's Kappa statistic was calculated to evaluate agreement between ASCO-VF and ESMO-MCBS. **Results:** 100 RCTs were analyzed. RCTs were awarded ASCO-VF version 2 (v2) "tail of the curve" bonuses more often than ESMO-MCBS version 1.1 (v1.1) "immunotherapy-triggered" long-term plateau adjustments (45% vs. 2.6%). Comparing to non-immune checkpoint inhibitor RCTs, immune checkpoint inhibitor RCTs were not more likely to receive ASCO-VF v2 bonuses/ESMO-MCBS v1.1 adjustments ($p = 0.32$/ $p = 0.40$). Long-term survival agreement between the two frameworks was poor (kappa: 0.01; $p = 0.50$). **Conclusions:** The ASCO-VF v2 and ESMO-MCBS v1.1 may require additional refinement in order to accurately capture the benefit of long-term survival or immune checkpoint inhibitor and non-immune checkpoint inhibitor agents may not preserve substantially different long-term survival populations.

2586 **Poster Session (Board #230), Sat, 8:00 AM-11:00 AM**

Genetic determinants of adverse events in cancer patients receiving immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICI) can cause profound immune-related adverse events (irAEs). The host genetic background is likely to play a role in irAEs susceptibility as the phenotype of toxicity varies among patients (pts) and many pts do not develop toxicity despite continued inhibition. **Methods:** Genotyping was performed for 89 melanoma pts who received ICI using the Infinium Multi-Ethnic Global-8 v1.0 Bead Chip. The genotype data was extracted using PLINK (v1.90b3.34) and processed for quality control including on call rate (>99%), genotyping rate (>95%), minor allele frequency (no less than 5%), and Hardy-Weinberg Equilibrium ($p<1x10-6$). The pairwise genetic distance was calculated using identity-by-state (IBS matrix) implemented in the genome option of PLINK, and the population-structure-based clustering was carried out using IBS matrix, pairwise population concordance test ($p<1x10-3$) and phenotype distribution for all pts, resulting in 7 structure groups. In the analytical stage, 602,463 variants in autosomal chromosomes were included for the association test. The test was performed using additive genetic model with exact logistic regression, adjusted for age, sex, and population cluster. **Results:** 44 pts had arthritis, colitis, hypohysitis, thyroiditis, or multiple irAEs (cases), and 45 did not have irAEs after a minimum of one year of treatment (controls); median age was 64 (23-92) years; 71% were male. A total of 30 variants/single nucleotide polymorphisms (SNPs) had p-value smaller than 10^-5 level were identified. The top variants/SNPs are listed in table. **Conclusions:** Genetic variants associated with irAEs were identified. Additional larger studies are needed to validate these findings, and to establish their potential functional relevance.

Top variants/SNPs from the association testing with irAEs.

CHR	SNP	BP	P	Gene
3	rs11711517	65,112,627	2.39E-06	
5	rs11743438	170,218,232	5.56E-06	GABRP
5	rs11743735	170,213,256	8.34E-06	GABRP
20	JHU_20.57183980	58,608,925	8.85E-06	DSC2
15	JHU_15.93602126	93,058,898	8.89E-06	
15	JHU_15.93604000	93,060,772	8.89E-06	
18	rs470753	65,315,670	1.65E-05	
15	rs4778080	93,060,296	1.92E-05	
12	rs2117997	29,143,428	2.44E-05	ANKRD42

2587 **Poster Session (Board #231), Sat, 8:00 AM-11:00 AM**

Real-world outcomes of underrepresented patient populations treated with immune checkpoint inhibitors (ICIs): African American descent, poor ECOG performance status, and chronic viral infections.

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Background: ICIs have now become standard of care treatment for multiple malignancies. However, patients (pts) who are African American decent (AA), have a poor ECOG performance status (PS) or chronic viral infections [human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV)] were underrepresented in early clinical trials with ICIs and outcome data in these pt populations is not well reported. **Methods:** We performed a retrospective analysis of pts treated with ICIs (anti-PD(L)-1, anti-CTLA-4, or combination ICIs) across five MedStar Health hospitals from January 2011 to April 2018. Investigator-assessed best responses were noted. CTCAE v4.03 was used to capture immune-related adverse events (irAEs). **Results:** We identified 765 pts treated with 829 unique ICIs therapies across different malignancies. A total of 203 AA pts, 178 pts with a pre-treatment ECOG PS $\geq$2, 21pts with HIV, and 50 pts with HBV/HCV were noted. Any grade and grade $\geq$ 3 irAEs in the HIV cohort were 24% and 10% with an ORR of 29%. Any grade and grade $\geq$ 3 irAEs in HBV/HCV were 50% and 26% with an ORR of 21%. No viral reactivation or changes in pts anti-viral medications were noted during ICIs treatment. The ORR in AA pts was 35%. Any grade and grade $\geq$ 3 irAEs in the AA cohort were 27% and 8%, respectively. The ORR in pts with ECOG PS $\geq$2 was 14%. Any grade and grade $\geq$ 3 irAEs in this cohort were 20% and 4%. Similar trends were seen in the subset of patients with NSCLC treated with anti-PD(L)1 monotherapy (Table). Outcomes of NSCLC pts treated with anti-PD(L)-1 monotherapy. **Conclusions:** ICI therapy was not associated with any new safety signal in the above underrepresented populations. Prospective studies are needed to validate this data.

Cohorts (N)	ORR (N)	Any grade irAEs (N)	Grade ≥3 irAEs (N)
Entire cohort (232)	21% (44/214*)	31% (66)	10% (22)
African American (102)	19% (18/94*)	22% (22)	5% (5)
Caucasian (112)	21% (22/104*)	37% (41)	13% (14)
ECOG PS 0-1(163)	23% (34/148*)	34% (55)	10% (17)
ECOG PS ≥2 (75)	16% (10/64*)	21% (16)	7% (5)

*Response evaluable patients.

2588 **Poster Session (Board #232), Sat, 8:00 AM-11:00 AM**

Intra and perinodular CT delta radiomic features associated with early response to predict overall survival (OS) in immunotherapy-treated non-small cell lung cancer (NSCLC): A multisite multi-agent study.

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Background: None of the current biomarkers for predicting response to checkpoint inhibitors (ICIT) for advanced NSCLC are associated with long-term benefits, such as improved OS. In this multi-agent (nivolumab, pembrolizumab, or atezolizumab) multi-site study (Cleveland Clinic, Univ. of Pennsylvania), we demonstrate that changes in computer-extracted textural patterns, from within and 30mm outside the nodules, between baseline and post-treatment CT following ICIT correlate with RECIST-derived responses, and are prognostic of OS. **Methods:** CT scans from 139 NSCLC patients both pre-, and post 2-3 cycles of ICIT were acquired from 2 sites. Patients with objective response/stable disease per RECIST v1.1 were defined as 'responders', and those with progressive disease were 'non-responders'. The cohort was divided into a discovery (D1 = 50) and two validation sets (D2 = 62, D3 = 27). 454 intranodular texture (IT) features, and 7426 perinodular features (PT) were extracted from the temporalscans, Relative differences were computed to yield a set of 'delta-radiomic' descriptors. In D1, 8 features that evolved the most between baseline and post-treatment CT, and performed the best in identifying responders, were determined. These were then used with a Linear Discriminant Analysis classifier to identify the responders from the non-responders. We then computed a radiomic risk score (RRS) system and tested its prognostic ability in assessing differences in OS. **Results:** A combination of 5 IT, 3 PT delta radiomic features yielded an AUC of 0.88 $\pm$ 0.08 in D1 and a corresponding AUC = 0.85 and 0.81 in D2 and D3, respectively. Multivariate survival metrics are shown in Table. **Conclusions:** Delta-radiomic features, both from inside and outside the nodules, could be used to identify patients likely to derive clinical benefit from ICIT (eg: OS) beyond anatomic response.

	HR, p-val		
Variable	**D1**	**D2**	**D3**
Gender (M vs F)	0.95 (0.48 - 1.87), .87	0.84 (0.28 – 2.53), .76	0.89 (0.31 – 2.6), .83
Smoking (Y vs N)	1.14 (0.49 - 2.68), .75	2.32 (0.6 – 8.9), .22	2.29 (0.67 – 7.8), .3
RRS	3.07 (1.74 - 5.42), .0001	2.75 (1.48 – 3.2), .004	2.05 (1.28 – 3.25), .003

2589 **Poster Session (Board #233), Sat, 8:00 AM-11:00 AM**

Tumor mutation burden analysis in a 5,660 cancer patient cohort reveals cancer type-specific mechanisms for high mutation burden.

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Background: Tumor mutation burden (TMB), calculated by whole-exome sequencing (WES) or large NGS panels, has an important association with immunotherapy responses. Elucidating the underlying biological mechanisms of high TMB might help develop more precise and effective means for TMB and immunotherapy response prediction. Meanwhile, the landscape of TMB across different cancer types and its association with other molecular features have not been well investigated in large cohorts in China. **Methods:** Cancer patients whose fresh tissue (n = 1556), formalin-fixed, paraffin-embed (FFPE) specimen (n = 1794), and pleural fluid (n = 84) were profiled using 295- or 520-gene NGS panel. The association of the TMB status with a series of molecular features and biological pathways was interrogated using bootstrapping. **Results:** TMB, measured by 295- or 520-cancer-related gene panels, were correlated with WES TMB based on in silico simulation in the TCGA cohort. We compared the TMB landscape across 11 cancer type groups and found the highest average TMB in lung squamous cell carcinoma, whereas the lowest TMB was established in sarcoma. High microsatellite instability, DNA damage response deficiency, and homologous recombination repair deficiency indicated significantly higher TMB. The independent predictive power for TMB of twenty-six biological pathways was tested in 10 cancer groups. FoxO signaling pathway most commonly correlated with low-TMB; significant association was identified in four cancer groups. In contrast, no pathway was significantly correlated with high-TMB in more than two cancer groups. Overall, we discovered that the underlying pathways which may be the main drivers of TMB status varied greatly and sometimes had an opposite association with TMB across different cancer types. Moreover, we developed a 14- and 22-gene signature for TMB prediction for LUAD and LUSC, respectively, with only 10 genes shared by both signatures, indicating a histology-specific mechanism for driving high-TMB in lung cancer. **Conclusions:** The findings extended the knowledge of the underlying biological mechanisms for high TMB and might be helpful for developing more precise and accessible TMB assessment panels and algorithms in more cancer types.

2590 **Poster Session (Board #234), Sat, 8:00 AM-11:00 AM**

Association of the imbalance between early and late differentiated intra-tumor CD4 T cells with mutational burden in non-small cell lung cancer.

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Background: CD4 T helper cells are key orchestrators of immunity in states of persistent antigen exposure. In chronic viral infection, loss of immune control is associated with CD4 differentiation skewing ($CD4^{ds}$) resulting from decline of early progenitors and gain in abundance of exhausted and terminally differentiated subsets. Here, we set out to identify whether a similar process occurs within the tumour microenvironment, contributing to immune dysfunction. **Methods:** Multiregional samples of tumour and non-tumour lung tissue from patients with untreated, surgically resected non-small cell lung cancer (NSCLC) within the first 100 recruited to the prospective lung TRACERx study were analysed by high dimensional flow cytometry of tumour infiltrating lymphocytes (TILs) and paired bulk tumour exome and RNA sequencing. We additionally reanalysed publically available single T cell and bulk tumour RNA sequencing from patients with NSCLC. **Results:** Unsupervised clustering and dimension reduction revealed a heterogenous landscape of CD4 TILs, with evidence of $CD4^{ds}$ in association with tumour mutational burden. Loss of $PD1^{-}CCR7^{+}$ T central memory enriched early differentiated cells was accompanied by gain in abundance of $PD1^{+}$ populations with exhausted ($CD57^{-}ICOS^{hi}CTLA4^{hi}$) and terminally differentiated effector ($CD57^{+}Eomes^{+}$) phenotypes. Further characterisation of these populations by single cell RNA sequencing revealed differential expression of key genes involved in transcriptional regulation, co-inhibition and co-stimulatory pathways. A validated gene signature of $CD4^{ds}$ was associated with worse outcomes in TRACERx and TCGA cohorts. **Conclusions:** Our findings reveal remodelling of the CD4 differentiation landscape in association with tumour genomic characteristics, underscoring how mutational burden in the context of chronic stimulation may lead to loss of immune fitness and elucidating key regulatory pathways in potentially clinically relevant CD4 subsets.

2591 **Poster Session (Board #235), Sat, 8:00 AM-11:00 AM**

Evidence for selective silencing of MHC-binding neoepitopes to avoid immune surveillance.

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Background: Overall response rates to immune checkpoint inhibition (ICI) are < 50% even in TMB-high patients (e.g. Checkmate-227), suggesting other mechanisms of immune escape exist beyond expressing checkpoints. At least 18% of somatic-specific exonic DNA variants are not expressed into mRNA (Rabizadeh, 2018), yet the selection criteria for which variants to silence remains unclear. We sought to determine if immunogenicity of variants factors into their suppression. **Methods:** Somatic-specific single nucleotide variants (SNVs) were identified from paired tumor/normal whole-exome sequencing (WES), and annotated as expressed if observed in > = 2 RNAseq reads. MHC1 binding affinity for 9-mer neoepitope peptides resulting from said SNVs were predicted using NetMHC within presented HLA-types. Cases with > 200 non-synonymous exonic mutations were designated as TMB-high in accordance with Rizvi et al, 2015. Tumor immune activity was inferred by RNAseq expression of 6 checkpoint/TME markers, as well as by estimating immune infiltration using RNAseq deconvolution of immune genesets (Bindea et al 2013). Significant associations between TMB, neoantigen-load, expressed neoepitope binding affinities, and immune activity were analyzed. **Results:** Within a clinical database of 1,363 cases with T/N/R sequencing, a total of 147,015 potential neoepitopes were identified. A small but significant enrichment was observed for silencing neoepitopes that are predicted to bind MHC1 (OR = 1.22, p = 2.4e-78 one-sided Fishers test). The silencing rate was similar between the 17% of patients with high TMB vs others, but was increased in 35% of all patients with high inferred immune infiltration (N = 490, OR = 1.30, p = 1.8e-31). A further silencing enrichment was observed in 19% of all patients displaying high immune activity but low PDL1 expression (N = 263, OR = 1.44, p = 4.0e-45). **Conclusions:** We observe significant preferential silencing of MHC binding neoepitopes. Specifically, when tumor infiltrating immune cells are activated, silencing neoepitopes may be an alternative to checkpoint expression for avoiding an immune cascade. Patients with TILs and silenced neoepitopes may benefit from epigenetic priming therapy prior to ICI therapy.

2592 **Poster Session (Board #236), Sat, 8:00 AM-11:00 AM**

Can serum IL-6 levels predict sarcopenia and poor outcome in relapsed/refractory gynecologic cancer patients?

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Background: Cancer cachexia occurs in more than half of cancer patients and can be the primary cause of death for at least 20% of all patients. Cancer cachexia also lowers quality of life in cancer survivors due to a severe loss of skeletal muscle mass. Although a multitude of cytokines have been implicated in facilitating a cachectic state, the correlation of serum IL-6 and cancer-induced muscle wasting in gynecologic cancer patients has not been elucidated. **Methods:** The correlation between serum level of IL-6 and skeletal muscle volume in the patients with gynecologic cancers that received multiple lines of therapy was retrospectively evaluated. We used the psoas muscle index [PMI (cm2/m2)], the psoas major muscle area at the fifth lumber level divided by the height squared, measured using digital axial CT images, for the value of skeletal muscle volume. The level of IL-6 cut-off for elevation was defined as more than 12.0 pg/mL. The comparison of the survival distributions from the day of IL-6 measuaments was made using a log-rank test. **Results:** A total of 74 cases were assessed for the serum IL-6 and PMI: 32 cases with Mullerian cancers, 24 cases with endometrial cancers, 13 cases with cervical cancers, and 5 patients with others. The group with elevated IL-6 were associated with the lower PMI (t-test, $p = 0.0154$). The patients with IL-6 elevation had significantly worse survival compared with those with normal IL-6 (1y-OS; 31% vs. 80%, $p < 0.0001$). In 28 patients with more than two-point measurements of IL-6, the patients with the decrease to the level of IL-6 cut-off had favorable survival compared with those without the decrease (6m-OS; 100% vs. 52%, $p = 0.0069$). **Conclusions:** Serum level of IL-6 could be a sentinel biomarker for cancer-induced sarcopenia in the patients with gynecologic cancers. Additionally, IL-6 could be a biomarker to determine further continuation of aggressive chemotherapy for the patients that had received multiple lines of chemotherapy.

2593 **Poster Session (Board #237), Sat, 8:00 AM-11:00 AM**

Association of an inflammatory gene signature with CD8 expression by immunohistochemistry (IHC) in multiple tumor types.

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Background: A multiparameter tumor inflammation assay based on gene expression profiling (TIA-GEP) can extend the utility of IHC to interrogate the tumor microenvironment (TME). Using CD8 expression assessed by IHC (CD8-IHC) as a surrogate for inflammation, statistical modelling was used to develop a specific gene signature on the TIA-GEP panel to predict CD8-IHC. The correlation between TIA-GEP and CD8-IHC and the prevalence of inflammation were explored across multiple tumor types. **Methods:** Levels of inflammation were measured by CD8-IHC and TIA-GEP on 1778 procured samples across 12 tumor types. Quality control metrics involved sample input quality, technical errors, and inter-run variability. Generalized linear models were used to identify an inflammation score that predicts the CD8-IHC score in melanoma and SCCHN tissue. The predictive accuracy of this signature was also examined in 10 additional tumor types. **Results:** Assessment of TME inflammation by CD8-IHC was consistent with that observed by TIA-GEP in multiple tumor types. The range of inflammation varied across different tumor types, with relatively lower inflammation range and scores in SCLC, ovarian, and prostate cancers, and higher values in NSCLC, melanoma, SCCHN, and gastric cancers. R^2 x 100 values reflecting percent variation in CD8-IHC associated with TIA-GEP ranged from 62.4% to 79.2% ($P < 0.0001$) for all tumor types except prostate cancer (32.5%). Low correlation in prostate cancer may be a result of low prevalence of inflammation by CD8-IHC. Estimated linear regression slopes between CD8-IHC and TIA-GEP ranged from 0.74 in SCLC to 1.27 in gastric cancer. **Conclusions:** The results suggest that the inflammation signature is a robust potential diagnostic tool predicting inflammation in the TME. The inflammation signature not only correlates with CD8-IHC for multiple tumor types, but also leverages the alternative benefits associated with TIA-GEP, which include information related to tumor inflammation-associated biomarkers and flexibility in exploring the value of other genomic signatures.

2594 **Poster Session (Board #238), Sat, 8:00 AM-11:00 AM**

CD8+ T cells in tumor parenchyma and stroma by image analysis (IA) and gene expression profiling (GEP): Potential biomarkers for immuno-oncology (I-O) therapy.

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Background: Distribution patterns of CD8+ T cells within the tumor microenvironment (TME) can be assessed by IA, which may reflect underlying tumor biology and serve as a potential biomarker to assess the utility of I-O therapy. These patterns are variable and may be classified as immune desert (minimal infiltrate), excluded (T cells confined to tumor stroma or to the invasive margin), or inflamed (T cells diffusely infiltrating tumor parenchyma and stroma). We hypothesized that association of a GEP signature with abundance of parenchymal and stromal T-cell infiltrates may identify biomarkers of response or resistance to I-O therapy. To test this, we applied an AI-powered IA platform to quantify CD8+ T cells by geographical location and used GEP to define both CD8 abundance and associated geographic localization to tumor parenchyma and stroma. **Methods:** We performed an analysis using a tumor inflammatory GEP assay and CD8 immunohistochemistry on procured specimens (335 melanoma, 391 SCCHN). Digitized slides were used to train a convolutional neural network to quantify the number of CD8+ T cells in stroma, tumor parenchyma, parenchyma-stromal interface, and invasive margin. Generalized constrained regression models were used to predict GEP signatures specifically for stromal and parenchymal CD8+ T cells. **Results:** Parenchymal and stromal GEP scores were highly concordant with CD8+ infiltrate geography (adj-r^2: 0.67, 0.65, respectively; $P \leq 0.01$). Little overlap existed between gene sets associated with parenchymal and stromal CD8 T-cell geographies. *CSF1R* and *NECTIN2* gene expression was observed to correlate inversely with parenchymal localization and directly with stromal CD8+ T-cell abundance. **Conclusions:** GEP signatures can be identified that are concordant with various CD8+ T-cell localization patterns in melanoma and SCCHN, demonstrating that GEP-IA can be developed to identify the immune status of interest in the TME. The specific genes identified have potential to elucidate mechanisms of resistance and/or inform I-O targets that can be further evaluated in relation to clinical significance in future studies.

2595 **Poster Session (Board #239), Sat, 8:00 AM-11:00 AM**

Evaluation of tumor microenvironment and biomarkers of immune checkpoint inhibitor (ICI) response in metastatic renal cell carcinoma (mRCC).

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Background: ICIs are now standard of care for mRCC; however, there are few biomarkers to predict ICI response. Recent data from atezolizumab/bevacizumab trials in mRCC suggest tumors with high T_{eff}^{high}/PD-L1+ are more likely to respond to ICI. Here, we use two gene panels as well as other inflammation markers in the tumor microenvironment to correlate with ICI responses. **Methods:** This multicenter study evaluated 86 patients (pts) with mRCC treated with ICIs. FFPE tumor samples were evaluated by RNA sequencing for T_{eff} status. Two gene panels were analyzed: a T_{eff} Gene Panel (CD8, CD27, IFNG, GZMA, GZMB, PRF1, EOMES, CXCL9, CXCL10, CXCL11, CD274, CTLA4, FOXP3, TIGIT, IDO1, PSMB9, TAP1) and a 5-Gene panel (FOXP3, CCR4, KLRK1, ITK, and TIGIT) based on the gene expression pattern of tumors in our cohort. Objective response rates (ORRs, defined as CRs and PRs) were correlated with PD-L1 status (positivity was defined as $\geq$1% TPS based on Dako 22C3 IHC assay), and TMB (0-10, 10-20, $\geq$20 mut/Mb), and tumor inflammation (high CD8 expression compared to a large reference population). Best responses to ICI was determined by an expert radiologist using RECIST 1.1 criteria. Inflamed tumor status, T_{eff} gene panel, 5-gene panel, PD-L1 status, and TMB were associated with ORR and tested using a chi-squared test with Yates's continuity correction. **Results:** ORR was 50% (4/8) for PD-L1 positive pts and 14% (9/65) for PD-L1 negative pts (p = 0.042). The majority of tumors (95%, 82/86) had TMB $<$ 10 mut/mb. 43 pts (50%) were classified as T_{eff}^{high} and 43 pts were classified as T_{eff}^{low}. ORR was 23% (10/43) in the T_{eff}^{high} cohort and 12% (5/43) in the T_{eff}^{low} cohort (p = 0.256). ORR was 31% (14/45) in the 5-Gene high cohort and 2% (1/41) in the 5-Gene low cohort (p = 0.001). **Conclusions:** TMB and tumor inflammation based on CD8 did not reliably predict for objective responses in this study of mRCC pts treated with ICIs. Gene expression signatures provide a more comprehensive evaluation of the tumor microenvironment and may lead to better predictive biomarkers for ICI response than individual biomarkers such as PD-L1, TMB, or CD8 expression.

2596 **Poster Session (Board #240), Sat, 8:00 AM-11:00 AM**

Dynamic changes of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lactate dehydrogenase (LDH) during treatment with immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC).

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Background: ICIs have revolutionized the therapeutic landscape of NSCLC. However, with the exception of PD-L1 expression, predictive biomarkers are lacking. The aim of this study was to evaluate the dynamic changes of some markers of inflammation over time and the outcome of NSCLC patients (pts) treated with nivolumab (N) or pembrolizumab (P). **Methods:** All consecutive NSCLC pts treated with N or P between Aug. 2015-Dec. 2018 were analyzed. Laboratory results were collected at baseline, 6 weeks (6-wk), and 12 weeks (12-wk) and correlated with the outcome. NLR and PLR were defined as absolute neutrophil and platelet count divided by lymphocyte count, respectively. NLR $\geq$5, PLR $\geq$200, and LDH levels $\geq$ upper normal limit were considered high. Overall survival (OS) was defined as time from ICI start to death and Progression Free Survival (PFS) as time from treatment start to progression disease or death for any cause. OS and PFS curves were estimated using the Kaplan–Meier method and compared with the log-rank test. **Results:** We included 71 consecutive NSCLC pts treated with either N (75%) or P (25%). Baseline characteristics: median age 69 years (range 46-80), sex male 76%, squamous histology in 39%. PD-L1 expression (39/71): $<$ 1% in 20%, 1-49% in 45%, and $\geq$50% in 35%. NLR $\geq$5 was associated with lower PFS and OS, with an increased predictive value over time (p =0.01 and p =0.009 at baseline; p =0.007 and $p <$0.001 at 6-wk; $p <$0.001 and $p <$0.001 at 12-wk, respectively). PLR $\geq$200 at baseline and 12-wk was significantly associated with shorter OS (p =0.05 and p =0.004, respectively), but no in terms of PFS at all the three time points. Finally, LDH $\geq$UNL at baseline was associated with shorter PFS and OS (p =0.02 and p =0.03), as well as a reduction of LDH levels at 12-wk compared with baseline values (p =0.006 and p =0.004). **Conclusions:** Baseline evaluation of NLR, PLR and LDH levels is significantly associated with outcome in NSCLC treated with single agent ICIs. Moreover, dynamic changes of LDH levels at 12 weeks significantly predicted outcome. These easy to determine parameters may have a place in the selection process of pts candidate for immunotherapy.

2598 **Poster Session (Board #242), Sat, 8:00 AM-11:00 AM**

Application of artificial intelligence to predict a new class of novel synthetic lethal targets.

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Background: Synthetic lethal targets are proteins that are contextually vulnerable. Inhibitors of PARP1, for example, selectively produce a lethal phenotype in the context of cancer cells which have lost BRCA1 or BRCA2 function. As a high mutation rate is a hallmark of many cancers, targeting synthetic lethal interactions to selectively inhibit cancer cells with altered genetic backgrounds may increase the specificity and efficacy of therapeutics. Recently, clinical trials have targeted synthetic lethal pairs such as EGFR and BRAF, TP53 and BCL2, and PTEN and CHD1. Previous attempts to identify synthetic lethal targets have relied on empirical results from published studies of biological pathways perturbed in cancer cells. Developing strategies to rapidly identify synthetic lethals by combining multiple experimental and computational approaches would result in a new class of potential cancer drug targets beyond the existing efforts that rely on single experimental or computational methods alone. **Methods:** Here we present Expansive AI, an artificial intelligence augmented knowledge network that enables rapid hypothesis generation for accelerated discovery research. Using a purpose-built, hypergraph database of massive, integrated genomic and biomedical data, we can query all synthetic lethals and their component genes, as well as a wealth of data related to these genes. The database of biological data includes 11,000+ cancer genomes from TCGA, prior knowledge resources such as gene ontology and pathway resources, and experimental data including chemical and protein interaction and patent data. The hypergraph's architecture allows for linking and nesting data, enabling efficient extraction of biologically-relevant features. **Results:** Using these features, a neural network classified 540 new candidate pairs that have previously not been reported. The candidate pairs were filtered to include only known oncogenes and least-studied genes. This produced a list of gene pairs which may represent the most novel class of synthetic lethal target candidates identified to date. **Conclusions:** We highlight the results of this AI-based approach and discuss validation efforts of the predicted interactions in specific cancer contexts.

2599 **Poster Session (Board #243), Sat, 8:00 AM-11:00 AM**

A dose-finding study of the SMAC mimetic Debio 1143 when given in combination with avelumab to patients with advanced solid malignancies.

Rosalyn A. Juergens, Quincy S. Chu, Daniel John Renouf, Scott Andrew Laurie, Daniela Purcea, Elaine McWhirter, Diane Arndt, Karen A. Gelmon, John Hilton, Bruno Gavillet, Peter Michael Ellis, Michael B. Sawyer, Christian K. Kollmannsberger, Natalie Andrews Wright, Elisabeth Rouits, Frank Brichory, Gregoire Vuagniaux, Sergio A. Szyldergemajn, Glenwood Goss; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; Cross Cancer Institute/University of Alberta, Edmonton, AB, Canada; BC Cancer, Vancouver, BC, Canada; Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada; Debiopharm International S.A., Lausanne, Switzerland; Cross Cancer Institute, Edmonton, AB, Canada; BC Cancer Agency, Vancouver, BC, Canada; Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; Debiopharm International SA, Lausanne, Switzerland; Juravinski Cancer Centre, Hamilton, ON, Canada; BC Cancer–Vancouver Cancer Centre, Vancouver, BC, Canada; The Ottawa Hospital Research Institute, Ottawa, ON, Canada

Background: Second mitochondria-derived activator of caspase (SMAC) mimetics regulate apoptosis and modulate NFκB signaling which drives the expression of genes involved in immune and inflammatory responses. In patient (pt) tumors, Debio 1143 increased PD-1/PD-L1 expression and tumor infiltrating lymphocytes. In pre-clinical models, it synergizes *in vitro* and *in vivo* with PD1/PD-L1 checkpoint inhibitors (CPIs). **Methods:** In a phase I study, using a mCRM model, avelumab (10 mg/kg i.v. on D1&15 q4w) was combined with escalating doses of Debio 1143 (100 mg/d to 250 mg/d orally, D1-10 & D15-24 q4w) to define the RP2D. Consenting adult pts with advanced solid tumors, normal organ function, and PS-ECOG = 0-1 were eligible provided none received prior CPI. Dose-limiting toxicities (DLTs), efficacy, safety, PK, PD and biomarkers were assessed. **Results:** As of DEC'18, 16 pts were treated; M/F: 8/8; ECOG = 0 in 6 (38%); median age = 58 (28-79); 5 pts had NSCLC, 2 MPM, 2 ovarian and 7 had other tumors (n = 1 each). Common AEs were: nausea (69%); fatigue (62%); vomiting (50%); cough, dyspnea, myalgia (44% each); diarrhea, anorexia (38% each); pruritus and constipation (31% each). These were generally grade 1-2, occasionally grade 3. One pt had a DLT at 250 mg/d dose: a grade 3 AST/ALT increase. No treatment-related AEs grade 4 or higher occurred. No dose-relationships for laboratory abnormalities were observed, except for ALT/AST increases, which at 200 mg/d were all grade 1 and asymptomatic. Maximal tolerated dose was not reached and there were no dose reductions. In 15 evaluable pts, 1 PR (NSCLC) and 5 SD (RECIST v1.1) were observed. Tumor shrinkage $>$ 15% was seen in 2 other NSCLC pts. PK showed high interpatient variability and dose-proportional increase. TNFα and IFNγ peaked in plasma following Debio 1143 dose on D1 after 8 hrs, and on D17/22, in a dose-proportional manner. Four pts developed anti-avelumab antibodies. **Conclusions:** Debio 1143 at 200 mg/d can be safely combined with avelumab. Toxicity was predictable and mild. Clinical activity was observed in NSCLC pts. PK was linear; no drug interaction was suspected. PD and biomarker analysis is ongoing. Expansion at this RP2D is ongoing in NSCLC. Clinical trial information: NCT03270176.

2600 **Poster Session (Board #244), Sat, 8:00 AM-11:00 AM**

First-in-human (FIH) trial evaluating immune activation and safety of PIN- 2 administered intravenously to patients with advanced solid tumors.

Colin Bier, Michael Millward, Dusan Kotasek, Kenneth J Gorelick, Joshua Brian Goldberg; PIN Pharma, Inc., New York, NY; School of Medicine and Pharmacology, Nedlands, WA, Australia; Adelaide Cancer Centre and University of Adelaide, Kurralta Park, Australia

Background: Innate immunity is an integral component necessary to initiate systemic anti-tumor immunity in patients with progressive malignancy. PIN-2 is a novel immunomodulating agent derivatized from a transactivator (Tat) protein that stimulates innate immunity *in vivo* by promoting differentiation of peripheral blood monocytes into activated APC's linking the innate and adaptive immune systems resulting in endogenous T-cell priming against a multitude of tumor associated antigens unique to the individual. **Methods:** A FIH clinical trial was conducted in patients (pts) with extensively pretreated solid tumors to evaluate the pharmacodynamics (PD) and safety of PIN-2. 8 pts (2 men), mean age 62.7 ($\pm$7.9) years, and a median of 4.5 prior treatment lines, were enrolled in 2 Australian centers. 2 pts received 1 cycle of treatment and 6 received 2 cycles. Pts were given 300 μg of PIN-2 IV 3 times/wk for 2 wks followed by a 1 wk rest period. A 2nd cycle of treatment was offered based on pt and investigator preference. Plasma was collected at 6 and 24H post-infusion 1 to evaluate immune activation. Th1 cytokines (TNF-α, IFN-γ, IL-12, CSF-2) were analyzed to assess PD activity. **Results:** A significant increase in TNF-α was seen 6H following PIN-2 infusion ($p = 0.0142$), demonstrating rapid onset of immune activation. There were no clear changes in the other parameters evaluated. PIN-2 was rapidly cleared from plasma, with mean $T_{1/2}$ = 24.0 (8.07) min, T_{max} = 1.06 (0.665) min, C_{max}= 77,500 (61,600) pg/mL, and $AUC_{0\text{-}inf}$ = 690,000 (493,000) pg $\bullet$ min/mL. 3 pts discontinued treatment, 2 for adverse events (1 gr 2 infusion reaction, 1 unrelated SAE of abdominal pain) and 1 for disease progression on day 12. Treatment related AEs were grade 1 and 2, and readily managed. There was a single unrelated gr 3 event (anemia) and no AEs $>$ gr3. 2 pts developed anti-drug antibodies; however, these did not result in changes in the immuno-PD profile. **Conclusions:** PIN-2 was generally well tolerated with an acceptable safety profile. PIN-2 caused an early increase in TNF-α, consistent with PD activity predicted by preclinical data. Further study alone and in combination with other agents in pts with advanced solid tumors is warranted. Clinical trial information: ACTRN12617001597381.

2601 **Poster Session (Board #245), Sat, 8:00 AM-11:00 AM**

Preliminary results from CLASSICAL-Lung, a phase 1b/2 study of pepinemab (VX15/2503) in combination with avelumab in advanced NSCLC.

Michael Rahman Shafique, Terrence Lee Fisher, Elizabeth E. Evans, John E. Leonard, Desa Rae Electa Pastore, Crystal L. Mallow, Ernest Smith, Maurice Zauderer, Andreas Schröder, Kevin M. Chin, J. Thaddeus Beck, Megan Ann Baumgart, Ramaswamy Govindan, Rachel E. Sanborn, Jonathan Wade Goldman; Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; Vaccinex, Inc., Rochester, NY; Merck KGaA, Darmstadt, Germany; EMD Serono, Inc., Billerica, MA; Highlands Oncology Group, Fayetteville, AR; University of Rochester, Rochester, NY; Washington University School of Medicine, St. Louis, MO; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; UCLA Medical Center, Los Angeles, CA

Background: Rational combination therapies are needed to overcome resistance mechanisms in NSCLC. Pepinemab is an IgG4 humanized monoclonal antibody targeting semaphorin 4D (SEMA4D, CD100). *In vivo* preclinical models demonstrated antibody blockade of SEMA4D promoted immune infiltration and reduced function and recruitment of immunosuppressive myeloid cells within the tumor. Importantly, preclinical combinations of anti-SEMA4D with various immunotherapies enhanced T cell activity and tumor regression. The CLASSICAL-Lung clinical trial tests the combination of pepinemab with avelumab to couple immune activation via checkpoint inhibition with beneficial modifications of the immune microenvironment via pepinemab. **Methods:** This ongoing phase 1b/2, open label, single arm, first-in-human combination study is designed to evaluate the safety, tolerability and efficacy of pepinemab in combination with avelumab in 62 patients (pts) with advanced (stage IIIB/IV) NSCLC (NCT03268057). The trial is split into dose escalation (n = 12) and dose expansion (n = 50) phases and includes 2 cohorts; 1) pts who are immunotherapy naïve, and 2) pts whose tumors progressed during or following immunotherapy (IO failure). Pts in the dose escalation cohorts received ascending doses of pepinemab i.v. (5, 10, 20 mg/kg, Q2W) in combination with avelumab i.v. (10mg/kg, Q2W). **Results:** Dose escalation is complete and the RP2D was selected as 10mg/kg pepinemab, Q2W. No pts experienced a TRAE leading to study discontinuation or death. The most frequent related AEs were grades 1 or 2 fatigue, pyrexia, or chills; no grade 3 AEs occurred in more than one subject. One DLT, a grade 3 pulmonary embolism occurred in the 10mg/kg pepinemab cohort, and resolved without reoccurrence. The disease control rate for pts treated $>$ 2 months is 90% (19/21), and, at this early stage, a PR with a 49% reduction in target lesion was observed in at least 1 of 8 pts in the IO failure cohort. Updated data from the dose expansion phase will be presented. **Conclusions:** Preliminary data suggest the combination is well tolerated and shows initial signals of antitumor activity. Dose escalation is complete and the expansion phase is ongoing. Clinical trial information: NCT03268057.

2602 **Poster Session (Board #246), Sat, 8:00 AM-11:00 AM**

Safety profile of INT230-6, a novel intratumoral (IT) formulation, during injections into a variety of refractory deep and superficial tumors with evidence of tumor regression and immune activation.

Anthony B. El-Khoueiry, Jacob Stephen Thomas, Diana L. Hanna, Lillian L. Siu, Nilofer Saba Azad, Giles Francis Whalen, Lewis H. Bender, Ian B. Walters, Anthony J. Olszanski; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of Massachusetts Memorial Medical Center, Worcester, MA; Intensity Therapeutics Inc, Westport, CT; Intensity Therapeutics, Westport, CT; Fox Chase Cancer Center, Philadelphia, PA

Background: INT230-6 is comprised of cisplatin (CIS), vinblastine (VIN) and an amphiphilic penetration enhancer which facilitates dispersion throughout tumors and diffusion into cancer cells. In preclinical experiments, INT230-6 led to necrosis and recruitment of immune cells with high rates of complete responses of injected and bystander tumors. This abstract highlights the safety and early pharmacodynamic activity of this approach. **Methods:** Patients with solid tumors that progressed on all standard treatments were enrolled. Dose escalation occurred by increasing number of tumors injected, loading per tumor, and total dose. INT230-6 was injected once every 2 weeks in multiple lesions for 5 sessions. Patients were monitored for safety and tolerability weekly. Pharmacokinetic(Pk) samples and peripheral blood were collected for flow cytometry and circulating cytokines. Pre and on study biopsies are ongoing. **Results:** 28 patients (14 unique cancer types) receiving a median of 3 prior treatments were enrolled. Doses from 0.3 ml up to-80 ml of INT230-6 were given into single lesions with some patients receiving a total of 120 mL (= 9.7mg VIN exceeding the IV VIN dose) without significant systemic absorption or typical cytotoxic adverse events. Pk analysis suggests that systemic exposure of VIN or CIS is ~10% of injected. No DLT's or drug-related SAE's reported. The most frequent adverse event was grade 1 or 2 pain at injected site. Superficial tumors showed signs of response including flattening, areas of necrosis and ulceration. Tumor reduction, apparent in in both injected and bystander tumors, may indicate an abscopal effect. An increase $>$ 30% in CD8 T-cells was seen in the blood of 3/9 evaluable patients. **Conclusions:** INT230-6 was safe and well tolerated in $>$ 100 injections (28 patients) with encouraging activity and pharmacodynamic effects in advanced refractory tumors. Additional analysis of immune cells from on study biopsies will be presented. A new cohort will evaluate combination with an anti-PD1 antibody to understand if local tumor destruction can increase systemic antigen load, increase immune cell recognition and initiate a systemic immune response. Clinical trial information: NCT 03058289.

2603 **Poster Session (Board #247), Sat, 8:00 AM-11:00 AM**

THOR-707: Using synthetic biology to reprogram the therapeutic activity of interleukin-2 (IL-2).

Marcos E Milla, Jerod Ptacin, Carolina E. Caffaro, Hans R. Aerni, Lina Ma, Lilia Koriazova, Ingrid B. Joseph, Laura K. Shawver; Synthorx Inc. Research & Development, La Jolla, CA

Background: Recombinant interleukin-2 (rIL-2; aldesleukin) is an approved immunotherapy in melanoma and renal cell carcinoma based on complete durable remissions. The anti-neoplastic properties of IL-2 are mediated by interactions with the beta-gamma chain (IL-2Rβγ) on naïve CD8+ T cells, which lead to their expansion and differentiation into T effector and T memory cells directed against the tumor. However, the widespread use of IL-2 in oncology is limited by interaction with the high affinity IL-2 receptor alpha chain (IL-2Rα) on regulatory CD4+ T cells (Tregs), which leads to immunosuppression, and on innate lymphoid cells in the vascular endothelium, which leads to eosinophilic recruitment and activation, and the sometimes fatal complication of vascular leak syndrome (VLS). A rIL-2 biased toward IL-2βγ affinity with no IL-2Rαinteraction could fill unmet needs in oncology. **Methods:** Using a synthetic biology platform, we have engineered THOR-707, a rIL-2 that contains a novel amino acid encoded in the IL-2 gene via a new DNA base pair (X-Y). The novel amino acid serves as a hook for site specific pegylation that extends half-life, blocks IL-2Rα engagement and binds to the IL-2Rβγ. **Results:** In non-human primates, THOR-707 can be dosed to maximize the level of cytotoxic CD8+ T lymphocytes without elevation of VLS-inducing eosinophils. In murine tumor models, THOR-707 induced the expansion of peripheral and intratumoral CD8+ T cells without expansion of suppressive Tregs. Single-agent dose-dependent anti-tumor efficacy was observed in two syngeneic mouse models. In combination with a PD-1 inhibitor, survival of tumor-bearing mice was longer than either agent as monotherapy. Efficacy in tumor models was durable, suggesting activation of CD8+ memory T cell populations. **Conclusions:** THOR-707 is a reprogrammed, site-directed, singly-pegylated rIL-2 that changes the pharmacologic profile of IL-2, potentially providing a favorable risk-benefit profile. First-in-human studies are expected to begin this year evaluating THOR-707 as monotherapy and in combination with a PD-1 inhibitor. Based on preclinical evidence to-date, THOR-707 may potentially address existing and emerging unmet needs across multiple solid tumors.

2604 **Poster Session (Board #248), Sat, 8:00 AM-11:00 AM**

AB928, a novel dual adenosine receptor antagonist, combined with chemotherapy or AB122 (anti-PD-1) in patients (pts) with advanced tumors: Preliminary results from ongoing phase I studies.

John D. Powderly, Paul L. de Souza, Rodolfo Gutierrez, Lisa Horvath, Lisa Seitz, Devika Ashok, Adam Park, Matthew J. Walters, Joyson Joseph Karakunnel, Wade Berry, Aimee Rieger, Amanda Garofalo, Dominic W. Lai, Arvind Chaudhry; Carolina BioOncology Institute, Huntersville, NC; Western Sydney University, Campbelltown, NSW, Australia; The Angeles Clinic and Research Institute, Los Angeles, CA; Chris O'Brien Lifehouse, Camperdown, NSW, Australia; Arcus Biosciences, Inc., Hayward, CA; Summit Cancer Center, Spokane, WA

Background: AB928, a selective, small-molecule $A_{2a}R/A_{2b}R$ antagonist, potently blocks the immunosuppressive effects of high adenosine concentrations in the tumor microenvironment. Preclinically, combining adenosine receptor inhibition with either chemotherapy or anti-PD-1 resulted in greater tumor control, suggesting AB928 may have additive activity when paired with either of these agents in cancer pts. **Methods:** Three dose-escalation (3+3 design) studies are assessing the safety, pharmacokinetics (PK), pharmacodynamics, and clinical activity of increasing doses of AB928 (75, 150, 200 mg orally once daily) in combination with: standard pegylated liposomal doxorubicin in triple-negative breast cancer (TNBC) and ovarian cancer (OC); standard mFOLFOX6 in gastroesophageal cancer (GEC) and colorectal cancer (CRC); and AB122 (240 mg every 2 weeks) in various advanced tumors. Following identification of the recommended phase 2 dose of AB928 in combination with chemotherapy or AB122 in dose escalation, the following tumor cohorts may be expanded (15-40 pts/cohort) to further test the combinations: TNBC and OC, GEC and CRC, and renal cell carcinoma. **Results:** As of 01Feb2019, 9 pts were treated across the 3 studies, and time on treatment ranged from 1-182 days (table). Overall, AB928 combination therapy was well tolerated. Two pts underwent post-baseline disease assessment; both had stable disease. Preliminary data indicate that AB928 PK and adenosine receptor coverage in cancer pts are similar to what was previously assessed in healthy volunteers. AB122 PK and PD-1 coverage are equally unaffected by AB928 co-administration. Updated data, including biomarker data, will be presented at the meeting. **Conclusions:** Early results showed a favorable safety profile of AB928 combination therapy. All 3 studies are actively recruiting pts. Clinical trial information: NCT03719326; NCT03720678; NCT03629756.

	Study in TNBC & OC (NCT03719326)	Study in GEC & CRC (NCT03720678)	Study in various tumors (NCT03629756)
Pts treated	1	2	6
Days on treatment	49	1-7	7-182
Safety, n			
Related ≥G3 AE	0	0	0
SAE	0	1	2
Related SAE	0	0	0
Dose-limiting toxicity	0	0	0
Best response, n			
Stable disease	Not yet assessed	Not yet assessed	2

2605 **Poster Session (Board #249), Sat, 8:00 AM-11:00 AM**

2D and 3D thermally bioprinted human MCF-7 breast cancer cells: A promising model for drug discovery.

Aleli Campbell, Alexander Philipovskiy, Rosalinda Heydarian, Armando Varela-Ramirez, Denisse A. Gutierrez, Luis H. Solis, Michael E. Furth, Thomas Boland; University of Texas at El Paso, El Paso, TX; Westchester Med Ctr, Staten Island, NY; Texas Tech University Health Sciences Center, El Paso, TX; UTEP, El Paso, TX

Background: Breast cancer (BC) is the second leading cause of cancer death following lung cancer. Bioprinting, the use of computer aided process to print biological living and non-living material to create patterns in 2D or 3D structures, is a novel technique that has been proposed to be used to develop tissue engineered solutions for a wide array of clinical applications, e.g., skin grafting. We investigate here if bioprinted breast cancer cells show some of the hallmarks of cancer tissues, and thus may represent good *in vitro* models for drug discovery. **Methods:** For this study, MCF-7 BC cells were cultured, stained, counted and turned into a bioink solution by suspending in phosphate buffered saline solution. The cells were bioprinted over a 96-well plate and pre-incubated for 18 hours in DMEM and RPMI media with 10% Fetal Bovine Serum and Charcoal Stripped Serum, respectively. After 18 hours of incubation the media was supplemented with Tamoxifen at 5μM, 10μM, 50μM, 90μM and 110μM concentrations. Cytotoxicity was measured 24 hours post-treatment using a differential nuclear staining assay and an INCell 2000 bioimager system. **Results:** Bioprinted cells exposed to high concentrations of Tamoxifen (90 μM and 110μM) exhibited a viability of 8.2% and 10.8%, respectively. Whereas viability of manually seeded cells at those concentrations was 0.11% and 0.05%. Viability of negative and positive controls was at 7.6% and 97.0% for the bioprinted samples and for the normally seeded cells was 4.9% and 98.8% respectively. **Conclusions:** In our study, we have established a novel 2D/3D breast tumor model applying bioprinting technology for drug discovery. The higher cell viability of MCF-7's at high concentrations of Tamoxifen could be attributed to the hormesis effect and activation of chaperone proteins, e.g., HSP70 and HSP90, possibly caused by bioprinting. We hypothesize that bioprinted MCF-7 cells also show increased levels of chaperone proteins, which may in a way mimic their *in vivo* behavior. In this novel *in vitro* 2D/3D model, the bioprinted cells show a more biological relevant behavior than normally cultured cells. Insights into the cell behavior after bioprinting may elucidate how to build improved in vitro models for BC research.

2606 **Poster Session (Board #250), Sat, 8:00 AM-11:00 AM**

Balixafortide (a CXCR4 antagonist) + eribulin in HER2-negative metastatic breast cancer (MBC): Survival outcomes of the phase I trial.

Peter A. Kaufman, Sonia Pernas Simon, Miguel Martin, Marta Gil-Martin, Patricia Gomez Pardo, Sara Lopez-Tarruella, Luis Manso, Eva Ciruelos, Jose Alejandro Perez-Fidalgo, Cristina Hernando, Foluso Olabisi Ademuyiwa, Katherine N. Weilbaecher, Ingrid A. Mayer, Timothy J. Pluard, Maria Martinez Garcia, Linda T. Vahdat, Debra Barker, Barbara Romagnoli, Javier Cortes; Breast Oncology, Division of Hematology/Oncology, Burlington, VT; Institut Català D'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; Hospital General Universitario Gregorio Marañón, Instituto Investigación Sanitaria Gregorio Marañón, Madrid, Spain; Institut Català d'Oncologia-ICO L'Hospitalet, Barcelona, Spain; Breast Cancer Center, Vall d'Hebron University Hospital, Barcelona, Spain; Instituto de Investigación Sanitaria Gregorio Marañón, Spain, Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII, GEICAM Spanish Breast Cancer Group, Madrid, Spain; Medical Oncology Department. Hospital 12 de Octubre, Madrid, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; Hospital Clínico Universitario de Valencia, Valencia, Spain; Washington University School of Medicine in St. Louis, St. Louis, MO; Vanderbilt-Ingram Cancer Center, Nashville, TN; St Luke's Cancer Institute, Kansas City, MO; Hospital Del Mar, Barcelona, SC, Spain; Weill Cornell Medicine, New York, NY; Polyphor, Allschwil, Switzerland; Polyphor, Ltd, Allschwil, Switzerland; IOB Institute of Oncology, Quironsalud Group, Madrid and Barcelona, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Balixafortide (B) is a potent antagonist of the chemokine receptor CXCR4. Preclinical evidence suggests that disrupting CXCR4 dependent pathways prevents development of breast cancer metastases, enhances the cytotoxic effect of chemotherapy and immunotherapy, and counteracts tumor cell evasion of the immune system. Encouraging safety and efficacy data were published recently from the ongoing Phase 1 trial investigating B + eribulin (E) in patients with HER2 negative MBC (Pernas S. et al. Lancet Oncol. 2018; 19: 812−24). The objective response rate, median progression free survival and median overall survival (OS) for the expanded cohort (EC) and the overall efficacy population (OEP) were 37.5% and 29.6%, 6.2 months and 4.5 months, and 18 months and 16.8 months, respectively. Here we report the 18 and 24 months landmark OS data from this trial. **Methods:** This trial enrolled 56 patients with HER2-negative, CXCR4-positive MBC, previously treated with 1−3 chemotherapy regimens for MBC. A 3+3 dose escalation design was used, followed by an EC. All cohorts received E on days 2 and 9, and B on days 1−3 and 8−10 of 21 day cycles. The association between various baseline biomarkers and treatment outcomes including OS is currently being investigated in a multivariate analysis (MVA). **Results:** Landmark survival data for the trial are shown in the table. Clinical trial information: NCT01837095. **Conclusions:** Landmark 18 months and 24 months OS data are consistent with the positive trend of all efficacy read-outs observed in this study and safety information is consistent with what was previously reported. Although inter-trial comparisons should be interpreted with caution, these survival rates, especially for the EC, are higher than those reported for eribulin monotherapy in similar MBC populations. These promising results suggest that B + E could potentially provide a new treatment option in heavily pre-treated patients with HER2 negative MBC and this is currently being investigated in a pivotal, randomized trial.

Landmark (months)	OS for EC (95% CI)	OS for OEP (95% CI)
18	50% (29.1–67.8)	42.4% (28.9–55.2)
24	33.3% (15.9–51.9)	25% (14.3–37.3)

The results from the MVA will be presented at the meeting.

2607 **Poster Session (Board #251), Sat, 8:00 AM-11:00 AM**

Immune profiling of tumor-infiltrating T cells using mass cytometry.

David Roumanes, Evan Newell, Michael Fehlings; Immunoscape, Cambridge, MA; Immunoscape, Singapore, Singapore

Background: Immunotherapy recent successes have opened new avenues for the treatment of cancer and the presence of tumor-specific CD8+ T cells in tumor-bearing individuals offer a promising therapeutic target. However, the detection and profiling of such T cells are challenging due to the need to detect rare antigen-specific T cell subpopulations in patient samples that are limited in size thus making it difficult to exploit these parameters for predictive signatures of clinical response. Moreover, the identification and analysis of neoantigen-specific $CD8^+$ T-cells in tumor-bearing individuals is challenging due to the small pool of such cells. **Methods:** In order to identify therapy-relevant tumor antigens and to facilitate a concurrent in-depth characterization of cells directed towards these targets, immunoSCAPE leverages the high-dimensional immune profiling capabilities of cytometry by time of flight (CyTOF) combined with a unique technology allowing the identification rare antigen-specific T-cell subsets. **Results:** We applied this technology to patient tumor-infiltrating lymphocytes from human cancer samples and tumor-derived neoantigens recognized by T-cells were identified and characterized. Interestingly, the majority of patient-derived tumor infiltrates consisted of tumor-unrelated T-cells characterized by a diverse phenotype. Strikingly, the expression of CD39 was absent from these bystander cells, suggesting that CD39 could be a useful biomarker for the identification of putative tumor-reactive T cells. **Conclusions:** Simultaneous immune profiling revealed that tumor-unrelated, bystander $CD8^+$ T-cells are phenotypically different in human tumor infiltrates and identified CD39 as a putative marker of neoantigen-specific T-cells. By providing insights into the nature, frequency and phenotype of antigen-specific T-cells, immunoSCAPE's unique target discovery and high-dimensional immune profiling platform is a valuable tool for the development of novel diagnostic and therapeutic strategies in immunotherapy.

2608 **Poster Session (Board #252), Sat, 8:00 AM-11:00 AM**

Phase I study of KN035, the first subcutaneously administered, novel fusion anti-PD-L1 antibody in patients with advanced solid tumors in China.

Jian-Ming Xu, Shukui Qin, Yun Zhang, Yaoyue Zhang, Ru Jia, Rongrui Liu, Gairong Zhang, Chuanhua Zhao, Ni Lu, Huilong Liu, Wenlian Xu, Meng Fu, Walt Cao, Haolan Lu, David Liu, Ruiping Dong, Xiaoxiao Wang, Pilin Wang, Ting Xu, John Gong; 307 Hospital of PLA, Beijing, China; PLA Cancer Center of Bayi Hospital Affiliated to Nanjing University of Chinese Medicine, Nanjing, China; 3D Medicines Co., Ltd, Sichuan, China; 3D Medicines Co. Ltd, Sichuan, China; Alphamab Co., Ltd., Suzhou, China; 3D Medicines Co., Ltd., Beijing, China

Background: KN035 is a novel fusion protein of humanized anti-PD-L1 single domain antibody and human IgG1 Fc fragment, formulated for subcutaneous (SC) injection. **Methods:** The escalation phase followed a modified 3+3 design with a 28-day DLT evaluation period and 8 dose levels were planned at 0.1, 0.3, 1.0, 2.5, 5 and 10 mg/kg SC weekly. One patient each was enrolled at 0.1 and 0.3 mg/kg dose levels. Additional dose levels followed traditional 3+3 design. Response was assessed per RECIST 1.1 every 12 weeks. **Results:** As of 11/2/2018, 17 patients were enrolled in the escalation phase (urothelial carcinoma (n=2), hepatic cell carcinoma (n=2), intrahepatic cholangiocarcinoma (n=2), thymic carcinoma (n=2), colorectal cancer£¨n=2£©£¬renal cell carcinoma (RCC, n=3), Squamous-cell lung carcinoma (n=1) and ovarian cancer (n=1)). The majority of subjects had advanced disease stage, stage IV (15/17) and stage III (2/17). A total of 7 subjects received radiotherapy, 16 subjects received surgery, and 13 subjects received systematic anti-cancer therapies from previous treatment. None had received prior checkpoint inhibitor treatment. Planned maximum dose of 10 mg/kg was reached (n=3) without DLT occurred. There was only one Grade 3 drug related Treatment Emergent Adverse Event (TEAE) occurred at 0.3 mg/kg dose level, which was immune related dermatitis and resolved later. All other drug related TEAEs were either Grade 1 or 2, with the most common events as elevated ALT (5/17) and elevated AST (4/17). Among all enrolled subjects, three subjects had confirmed PR, including one RCC subject at 2.5 mg/kg and one Intrahepatic cholangiocarcinoma subject at 5 mg/kg, and one cholangiocarcinoma subject at 10 mg/kg. **Conclusions:** KN035 exhibits a favorable safety profile and promising preliminary anti-tumor activity in patients with advanced malignancies. Clinical trial information: NCT03101488.

2609 **Poster Session (Board #253), Sat, 8:00 AM-11:00 AM**

Phase I safety and pharmacokinetic study of KN035, the first subcutaneously administered, novel fusion anti-PD-L1 antibody in Japanese patients with advanced solid tumors.

Toshio Shimizu, Takako Eguchi Nakajima, Ni Lu, Shilin Xue, Wenlian Xu, Meng Fu, Walt Cao, Haolan Lu, David Liu, RuiPing Dong, Xiaoxiao Wang, Pilin Wang, Danming Zhu, Ting Xu, John Gong; National Cancer Center Hospital (NCCH), Tokyo, Japan; Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan; 3D Medicines Co., Ltd, Sichuan, China; 3D Medicines Co. Ltd, Sichuan, China; 3D Medicines Co., Ltd., Beijing, China; Alphamab Co., Ltd., Suzhou, China; Suzhou Alphamab Co. Ltd, Suzhou, China

Background: KN035 is a novel fusion protein of humanized anti-PD-L1 single domain antibody and human IgG1 Fc, formulated for subcutaneous (SC) injection. A phase I safety and pharmacokinetic (PK) study was conducted in Japanese patients. **Methods:** Patients with advanced solid tumors were treated with KN035 SC once every-7-days (QW) or once every-14-days (Q2W) schedules with the dose limiting toxicities (DLT) evaluation period of 28 days. For the QW schedule, the starting dose was 1 mg/kg (n=3) with escalations to 2.5 (n=4), and 5 (n=3) mg/kg. For the Q2W schedule, 6 patients were planned at the dose levels of 2.5 and 5 mg/kg. **Results:** No DLT was observed up to the highest dose level of 5 mg/kg QW. No maximum tolerated dose (MTD) was reached. Among evaluable treated subjects (n=14), there were two confirmed partial responses. Preliminary PK analysis suggested that after SC administration, KN035 was slowly absorbed (Tmax ~ 4 d) and the mean residual time (MRT) was 21 days. Apparent clearance (CL/F) and volume of distribution (Vz/F) were on average 0.58 L/day and 11 L, respectively. Plasma levels generally decreased mono-exponentially with an average terminal elimination half time around 13 days after reaching the peak concentration post SC administration. Exposures of KN035 increased approximately proportionally with dose. Trough concentrations were maintained above 15 μg/mL post administration of 5 mg/kg Q2W. No apparent exposure-body weight relationship was observed. **Conclusions:** KN035 exhibits a favorable safety profile in patients with advanced malignancies and preliminary results demonstrate encouraging anti-tumor activity. Based on PK data from the Q2W schedule, a fixed dose with less frequent dosing schedule of every 3 or 4 weeks is presently being evaluated. Clinical trial information: NCT03248843.

2610 **Poster Session (Board #254), Sat, 8:00 AM-11:00 AM**

Immunological impact of canerpaturev (C-REV, formerly HF10), an oncolytic viral immunotherapy, with or without ipilimumab (Ipi) for advanced solid tumor patients (pts).

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Background: C-REV, an oncolytic, spontaneous mutant of Herpes Simplex Virus type 1 (HSV-1), is a cancer immunotherapy agent that combine direct tumor cell killing with immune modulation. A phase I study for solid tumors with cutaneous and/or superficial lesions treated with C-REV monotherapy and a phase II study for unresectable or metastatic melanoma treated with C-REV and Ipi combination therapy were conducted. Immune status of cancer pts before and after administration of C-REV with/without Ipi has been unclear. **Methods:** A phase I study (n = 6) included solid tumor pts with cutaneous and/or superficial lesions treated with C-REV monotherapy (1×10^6 and 1×10^7 $TCID_{50}$/mL/dose; 4 injections q2-4wk). In phase II study (n = 28), C-REV (1×10^7 $TCID_{50}$/mL/dose; 4 injections q1wk; then up to 15 injections q3wk) was injected into each tumor for advanced melanoma pts. Four Ipi infusions (3 mg/kg) were administered at q3wk. Immune-monitoring was conducted before and after treatment in tumor microenvironment usingpaired biopsy samples by multiplex immunohistochemistry (mIHC) and in peripheral blood by flow cytometry (FCM). **Results:** In the phase I study, significant infiltrations of $CD8^+$and $CD4^+$ T cells were observed at tumor local site statistically in three pts (60%) among five pts. In the phase II study, FCM of peripheral blood (n = 10) showed that the responders (irSD, n = 7, 70%) tend to express the higher levels of ICOS on $CD4^+$ T cells as a pharmacodynamic biomarker of ipi monotherapy reported previously (Ng Tang D, et al. Cancer Immunol Res. 2013) and lower levels of PD-L1 on monocyte after two months of treatment. Moreover, mIHC analysis of paired tumor biopsy samples (n = 11) revealed that five pts (45%) among 11 pts were confirmed persistent infection of C-REV at the injected site by qPCR. Disease control rate of pts with the virus DNA detected on Days 85/169 was higher than that without it (100% [n = 5, irPR; 1, irSD; 4] vs. 33% [n = 6, irSD; 2, irPD; 4]). Furthermore, median OS of pts with or without the DNA detected was 342 or 251 days respectively. **Conclusions:** Our results suggest C-REV injection in the tumor local site have potential to enhance systemic immune response of Ipi. Clinical trial information: NCT03153085.

2611 **Poster Session (Board #255), Sat, 8:00 AM-11:00 AM**

A phase 1/2a study of GEN-009, a neoantigen vaccine based on autologous peptide immune responses.

Roger B. Cohen, Melissa Lynne Johnson, Przemyslaw Twardowski, Mark N. Stein, Ulka N. Vaishampayan, Jason R. Dobson, James Foti, Parul Agnihotri, Louisa Dowal, Wendy Broom, Lisa McNeil, Thomas A. Davis, Jessica Flechtner; University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; Sarah Cannon Research Institute, Nashville, TN; John Wayne Cancer Institute, Providence Saint John's Health Center, Santa Monica, CA; Columbia University Medical Center, New York, NY; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Genocea, Cambridge, MA

Background: Tumor-specific neoantigens provide individualized targets for immunotherapy. *In silico* selection methods are sub-optimal at predicting immunogenic targets, missing up to 70% of true neoantigens. ATLAS is a powerful tool that screens all candidate neoantigens for pre-existing patient-specific CD4 or CD8 responses in an HLA agnostic assessment. ATLAS also identifies inhibitory peptides that may suppress tumor immunity and accelerate tumor progression. The GEN-009 vaccine contains stimulatory but no inhibitory peptide antigens. **Methods:** GEN-009-101 is a first-in-human phase 1/2a study testing platform feasibility, safety, immunogenicity and clinical activity in selected solid tumors. After next-generation tumor sequencing and cytokine-based ATLAS assessment using autologous T cells and APCs, up to 20 stimulatory synthetic long peptides are used in each personalized vaccine. GEN-009 is administered with poly-ICLC on weeks 0, 3, 6, 12 and 24. Part A, a safety and immunogenicity pilot, has completed target enrollment of patients without evidence of disease to receive GEN-009; Part B has 5 tumor-specific cohorts of up to 15 pts naïve to PD-1 blockade who will receive GEN-009 with a SOC immunotherapy; Part C: up to 15 pts refractory to PD-1 inhibitors will receive GEN-009 monotherapy. **Results:** GEN-009 has been successfully generated for patients. Repeated dosing has been well tolerated with mild local discomfort and no DLT. ATLAS screening results below show notable interpatient variability; one subject had only CD4 neoantigens, one had only CD8, another had a strong CD8 bias, and one patient had prominent inhibitory peptides. **Conclusions:** GEN-009 is a neoantigen vaccine that personalizes tumor specific targets and the individual patient's capacity to respond. Immunogenicity data will assess CD4 and CD8 T cell responses to each vaccine neoantigen. Clinical trial information: NCT03633110.

Pt	Tumor type	Somatic mutations/ Mb	Stimulatory neoantigens	Inhibitory antigens	CD4	CD8
1	NSCLC	1.25	6	0	*	
2	Bladder	3.15	16	4		*
3	Melanoma	28.69	199	41	*	*
4	Bladder	3.53	18	1		*
5	NSCLC	3.56	16	9		*

2612 **Poster Session (Board #256), Sat, 8:00 AM-11:00 AM**

A donor-dependent in vivo model for single agent and drug combination cytokine release syndrome safety evaluation.

James G. Keck, Mingshan Cheng, Michael Brehm, Dale Greiner, Lenny J. Shultz, Jens Rueter, Chunting Ye; The Jackson Laboratory, Sacramento, CA; University of Massachusetts Medical School, Worcester, MA; The Jackson Laboratory, Bar Harbor, ME

Background: Although antibodies and CART cells therapies have been successfully used for cancer therapy, they can have lethal adverse effects such as cytokine release syndrome (CRS). The animal models and in vitro human PBMC assays presently in use can't reliably predict the CRS in patients. A predictive marker for identifying patients at risk for developing CRS upfront would improve the safety of immune-oncology drug development. **Methods:** We have developed a rapid, sensitive and reproducible in vivo humanized mouse model for quantitating CRS. The NSG mouse and its derivatives are engrafted with human PBMCs. On day 6 we induced cytokines release with pembrolizumab, avelumab, atezolizumab, ipilimumab, anti-CD28, ATG and OKT3 in single dose; as well as combination treatments involving pembrolizumab, lenalidomide, ATG and anti-CD28. Furthermore, we compared our method versus the in vitro PBMC assay. The cytokine levels were also compared to the dose response. **Results:** There are about 10-15% CD45+ human cells on day 5 of engraftment; and among of them, there were approximately 70% CD3 T cells and 25% CD56 NK cells. All tested cytokines, human IFN-γ, IL-2, IL-4, IL-6, IL-10 and TNF were upregulated after 2 and 6 hours of OKT3, ATG, anti-CD28, pembrolizumab, avelumab and atezolizumab drug treatment. Mouse's rectal temperatures dropped from 37-38 °C to about 36 °C at 6 hours' time point in the treated groups. There is various cytokines release levels, low to high response in different donors with anti-CD28 treatment. All donors showed high response to OKT3. The cytokine release levels were consistent with a dose response or variable PBMC engraftment. The cytokine levels were also higher in some drug combination studies such as pembrolizumab combined with lenalidomide or ATG; anti-CD28 combined with ATG. Our in vivo method was able to determine CRS missed in the in vitro testing method. **Conclusions:** We have developed a rapid, sensitive and reproducible novel in vivo PBMC humanized mouse model that is able to differentiate human PBMC donors based on individual safety response to single agent and combination therapeutics of immune checkpoint inhibitors and possibly CAR-T therapy. This assay could be employed in future drug development.

2613 **Poster Session (Board #257), Sat, 8:00 AM-11:00 AM**

Interim analysis of a phase II study of nivolumab combined with ipilimumab in patients with pediatric solid tumors in adulthood (GETHI021).

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Background: Solid pediatric tumors that appear in adulthood are a heterogeneous group characterized by a low incidence, lack of standard therapeutic options and reduced survival. We have designed the first phase II clinical trial of nivolumab and ipilimumab in this setting, Here, we present the results of the first cohort with 30 evaluable patients. **Methods:** This is a multicenter, open-label, single arm Phase II study conducted in 15 centers of the Spanish Group for Rare Cancer (GETHI). We aimed to evaluate efficacy and safety of the combination of nivolumab and ipilimumab in adult patients (18 years) with locally advanced or metastatic childhood malignancies that have progressed or are not candidates to standard therapy. Treatment consisted on nivolumab 3 mg/kg IV q2w + ipilimumab 1 mg/kg IV q6w for 6 months or until progression/unacceptable toxicity, for a maximum of 24 months. Primary endpoint was overall response rate (ORR) according to RECIST v1.1 criteria. We used a Simon optimal two-stage design, with a first stage including first 30 evaluable patients. **Results:** 20 patients were male and median age was 43 (range 20-75). Most frequent histologies were medulloblastoma (4) neuroblastoma (4) and Ewing family tumors (3). 90% had received prior systemic therapy with 37% presenting progressive disease as best response. Median previous treatment lines were 3 (range 1-9). 27 patients were PS0-1, and 3 PS2. 6 patients have been treated for $\geq$6 months . Only one discontinued for adverse events. With a median follow up of 4,3 months (range 0,4-11,3), 1 patient has achieved a deep partial response (PR) (3,6%), 10 stable disease (SD) (35,7%) and 17 progressive disease (PD) (60,7%). 2 patients died before radiologic evaluation. Clinical benefit rate (CR+PR+SD) was 39,3%. Median progression free survival (PFS) was 1,8 months (95% CI 1,3-2,3), with a 3-months-PFS of 32,7% and 6-months-PFS of 20%. Median overall survival (OS) was 6,8 months (95% CI 3,3-10,2). 12 (40%) patients presented adverse events (AE) of any grade and 6 (20%) experienced a grade AE deemed as possibly related to treatment. **Conclusions:** The combination of nivolumab and ipilimumab showed significant clinical benefit in this population with little therapeutic options. One case of metastatic esthesioneuroblastoma, achieved a dramatic tumor response and represents the first patient with this extremely rare histology treated with immunotherapy. Clinical trial information: EudraCT 2016-003946-99.

2614 **Poster Session (Board #258), Sat, 8:00 AM-11:00 AM**

Gut microbiota and clinical outcomes treated with nivolumab in Chinese non-small cell lung cancer.

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Background: Gut microbiome affecting responses to immune checkpoint inhibitors (ICIs) against non-small cell lung cancer (NSCLC) has been investigated in western population. However, considering genetic variation, this phenomenon remains in vague in east-Asian NSCLC population. The study is designed to explore the relationships between gut microbiome and clinical outcomes treated with anti-PD-1 blockade in Chinese patients. **Methods:** 37 NSCLC patients received the treatment of Nivolumab were enrolled in the study from the clinical trials CheckMate870 (NCT03195491). Fecal samples were collected at the starting point, every time point performing clinical evaluation and that with disease progression. 16s sequencing was applied to assess the gut microbiota characteristics. Peripheral immune profiles were determined by multi-color flow cytometry in parallel. **Results:** When subgrouping patients into responders (R) and non-responders (NR) groups according to the clinical response assessed by RECIST1.1, patients in R group harbored higher diversity of gut microbiome at the starting point with consistent composition along the treatment. Analyzing progression-free survival (PFS) according to RECIST 1.1, patients with higher microbiome diversity had significantly prolonged PFS when compared to those with low diversity. Compositional difference was observed between two groups as well with the enrichment of Alistipes putredinis, Bifidobacterium logum, Prevotella corpri in R group whereas Ruminococcus_unclassified in NR group. Analysis of systemic immune responses using multi-color flow cytometry revealed that patients with a high abundance of microbiome diversity in the gut had more frequencies of memory CD8+ T cell subset in the periphery in response to anti-PD-1 therapy. **Conclusions:** Our results report the strong correlation between the gut microbiome diversity and the responses to anti–PD-1 immunotherapy in Chinese NSCLC patients regardless of genetic variation between Western and Chinese population. Patients with a favorable gut microbiome (such as high diversity) have enhanced immune responses mediated by effector T cell function in the periphery. These findings thus provide important implications for the prediction and the evaluation of anti-PD-1 immunotherapy against NSCLC.

2615 **Poster Session (Board #259), Sat, 8:00 AM-11:00 AM**

Response to immune checkpoint inhibition and survival in *BRCA*-associated recurrent ovarian cancer.

Ying L Liu, Julia Lindsay Boland, Karen Anne Cadoo, Claire Frances Friedman, Jason A. Konner, Roisin Eilish O'Cearbhaill, Carol Aghajanian, Dmitriy Zamarin; Memorial Sloan-Kettering Cancer Center - Fellowship (GME Office), New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Alterations in the DNA mismatch repair pathway increase susceptibility to immune checkpoint inhibition (ICI). Tumors with *BRCA*-related DNA repair defects may have increased antigenicity, which could drive response to ICI. Responses to ICI in ovarian cancer (OC) have been modest. We seek to evaluate the association of *BRCA* mutations with response to ICI and survival in recurrent OC. **Methods:** A single-center, retrospective review identified 103 women with recurrent OC and known *BRCA* mutation status (90 germline and 33 somatic testing) who received ICI between 1/2013-7/2018 (98 on study). Clinical characteristics and duration of ICI (Long $>$ = 24 vs. Short $<$ 24 weeks) were compared by *BRCA* status. Kaplan Meier survival analysis was used to calculate progression-free (PFS) and overall survival (OS) from start of ICI, and CoxPH models/logrank test were used to assess survival differences by *BRCA* status. **Results:** Deleterious germline (g) or somatic (s) *BRCA* 1/2 mutations were present in 29 (28%) women (12 g*BRCA1*, 9 g*BRCA2,* 3 s*BRCA1*, 5 s*BRCA2,* 1 g*BRCA1*/s*BRCA1*, 3 g*BRCA2*/s*BRCA2*, and 1 g*BRCA2*/s*BRCA1*). Patients (pts) with *BRCA* mutations had more lines of treatment prior to ICI (median 5 vs. 4, p = 0.03) and a longer time from diagnosis to ICI (median 54 vs. 38.5 months (mo), p = 0.01), but there were no significant differences in other variables including histology (86% high grade serous), stage at diagnosis (96% Stage III/IV), and platinum status (83% resistant), p $>$ 0.05. Four pts (15%) with *BRCA* mutations had long duration of ICI as compared with 20 pts (27%) in those without mutations, p = 0.20. Median PFS was 2.2 mo (95% CI 1.7-2.7) in those with *BRCA* mutations and 3.4 mo (95% CI 2.1-4.0) in those without mutations, HR 1.22 (95% CI 0.78-1.91, p = 0.38). At a median follow-up of 23.3 mo, median OS was 21.3 mo (95% CI 13.7-31.8) in those with *BRCA* mutations and 19.8 mo (95% CI 13.8-25.3) in those without. This was not significantly different, HR 1.00 (95% CI 0.54-1.87, p = 0.99), after adjustment for prior lines and time from diagnosis to ICI. **Conclusions:** In our study of heavily pretreated OC pts receiving ICI, *BRCA* 1/2 mutations were not associated with improved response or survival. These findings should be validated in larger studies.

2616 **Poster Session (Board #260), Sat, 8:00 AM-11:00 AM**

Interleukin-6 is potential target to de-couple checkpoint inhibitor-induced colitis from antitumor immunity.

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Background: A deep understanding of the immunobiology of checkpoint inhibitor (CPI) induced immune related toxicities, such as immune related enterocolitis (irEC), and how these compare to the immune signatures in tumors could lead to the development of strategies that de-couple autoimmunity from anti-tumor immunity. **Methods:** Total RNA from patient-matched irEC and normal colon FFPE tissue from patients [n = 12] receiving CPIs were profiled with the 770 gene NanoString nCounter PanCancer Immune Profiling Panel (NanoPCIP). The mean fold change in gene expression from normal vs. irEC inflamed colonic tissue and baseline vs. on-treatment tumor samples from patients responding or non-responding to ipilimumab based therapy were analyzed. C57BL/6 mice with B16.BL6 melanoma tumors were treated with systemic anti-IL-6 + anti-CTLA-4 vs. anti-CTLA4 alone vs. placebo and tumor size was measured. **Results:** In patients with irEC, the highest significantly upregulated differentially expressed gene (DEG) in inflamed colon tissue encoded for IL-6 (Fold change +24.1). None of the significant and highest upregulated DEGs in the colitis, including IL-6, were significantly upregulated in responding tumors. Interestingly, IL-6 was also the highest upregulated DEG in non-responding tumors numerically. When comparing mean fold changes across these analyses, the gene with the largest difference in upregulatation between colitis and responding tumors was IL-6; the other highest upregulated genes in colitis encoded for neutrophil and monocyte chemotactic molecules. In our mouse models, the addition of IL-6 blockade to anti-CTLA-4 therapy significantly improved tumor shrinkage compared to anti-CTLA-4 alone. **Conclusions:** Our data demonstrates that IL-6-mediated inflammation may be more prevalent in irEC and tumors not responding to CPIs than in tumors responding, and blocking IL-6 enhances CPI anti-melanoma activity. Targeting IL-6 may ameliorate irEC without hindering anti-tumor immunity.

2617 **Poster Session (Board #261), Sat, 8:00 AM-11:00 AM**

Frameshift mutations (Fsindel) complement tumor mutation burden (TMB) in predicting survival after immune checkpoint inhibitors (ICI) in a pancancer analysis.

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Background: ICI benefit certain patients (pts) with various malignancies and discovering biomarkers for response is an active research field. Recently, higher TMB (top 20% in each histology) based on nonsynonymous single nucleotide variants from MSK-IMPACT was shown to correlate with superior survival in a pancancer cohort. Fsindels may generate more immunogenic neoantigens and robust T cell infiltrates, thus predicting better responses to ICI. We previously demonstrated the clinical implication of fsindel in lung cancer pts on ICI. However, its value in other solid cancers has not been evaluated. **Methods:** Comprehensive genomic profiling (CGP) of the tumors was performed by FoundationOne to derive fsindel and TMB as previously described. Pts with advanced solid cancers who received ICI and had CGP available were included. We categorized pts into two groups; 0 fsindel (FS-) and more than 1 fsindel (FS+). Also, they were categorized into TMB high (top 20%) and TMB low (bottom 80%) within their own histology. Progression free survival (PFS) and overall survival (OS) were compared. **Results:** One hundred thirty-one pts excluding lung cancer were included. There were 11 histology groups: 14 soft tissue sarcomas, 19 GU, 23 GI, 23 skin, 10 HEENT, 10 RCC, 9 GYO, 6 pancreas, 5 mucosal melanoma, 4 breast, and 8 others. 74 pts received pembrolizumab, 25 nivolumab, 29 ipilimumab/nivolumab, and 3 atezolizumab. All pts had metastatic disease, mean age was 61 years and 55 (42%) were women. Among the 131 pts, 74 were FS- and 57 FS+. The presence of fsindel (FS+) was significantly correlated with overall response ($p = 0.032$) and clinical benefit rates ($p = 0.025$). TMB-high did not show any significant difference in PFS ($p = 0.1$) or OS ($p = 0.28$) when compared to the TMB low. However, in a combined model of TMB and fsindel, TMB high and FS+ patients had significantly better PFS compared to patients who had either TMB high or FS+ or neither (TMB low and FS-) ($p = 0.021$). **Conclusions:** Combined model of TMB high and fsindel (+) correlated with superior PFS in advanced solid cancer pts on ICI, in concordance with previous report for lung cancer. Validation in a larger cohort is underway.

2618 **Poster Session (Board #262), Sat, 8:00 AM-11:00 AM**

Pan-tumor prognostic value of multiple immune protein expressions.

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Background: Using multiple immune-checkpoint proteins (ICP) screening in clinical routine could improve the evaluation of patients' prognosis and ultimately tailor their treatment choice. We have evaluated this hypothesis in the context of early drug clinical trials. **Methods:** Patients included in MOSCATO-02 trial had refractory cancers and were candidate for phase 1 study. They were proposed to have a biopsy on an accessible tumor site for the analysis of four proteins by immunohistochemistry (IHC) and RNAseq: PD-L1, CD3, CD8 and FOXP3. Quantification of IHC staining was separated between intratumoral, intersitial and stromal by semi-quantitative method. Their relations to prognosis have been evaluated by survival Random Forest and compared to classical prognosis clinical variables, such as age and RMH score (calculated by the number of metastatic sites, lactate dehydrogenase (LDH) and serum albumin). **Results:** From April 2016 to September 2017, 228 patients included in MOSCATO-02 had a successful biopsy procedure with available IHC expression analysis. The main tumor subtypes were gastro-intestinal, urological, head and neck, breast and lung. RNAseq analyzes were performed for two thirds of the patients (N=170). Median overall survival was 8.1 months (CI95% 7.79 – 10, 65). We found that, in a cohort of phase I patients, RMH score was the most important variable used to estimate prognosis. Prognosis value of immune proteins were considerably inferior compared to clinical criteria. Among those proteins, the percentage of PD-L1 low score (1+) and average staining intensity of CD3 were the most valuables for prognosis evaluation. Variables with very few importance to prognosis estimation were CD8 and FOXP3 IHC scores, biopsy site and cancer types, subsequent treatments by immunotherapies or targeted therapies. **Conclusions:** In this cohort of patients with refractory cancers, the RMH score is confirmed as highly prognosis. Immune proteins could be used as a support to guide patient's selection but does not constitute effective prognosis criteria.

2619 **Poster Session (Board #263), Sat, 8:00 AM-11:00 AM**

Phase I trial of the combination of the heat shock protein-90 inhibitor onalespib (AT13387) and the cyclin-dependent kinase inhibitor AT7519M in patients with advanced solid tumors.

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Background: The 90kDa heat shock protein (HSP90) participates in the folding, stabilization, activation, and proteolytic turnover of aberrant proteins that contribute to the growth and survival of cancer cells. HSP90 inhibition leads to degradation of these aberrant proteins through the ubiquitin-proteosome pathway, allowing for simultaneous targeting of multiple pathways. Inhibition of HSP90 alone stimulates a compensatory upregulation of HSP70. The transcriptional induction of HSP70 has been linked to the activity of CDK9. Combined inhibition of onalespib-mediated HSP90 inhibition and AT7519-mediated CDK9 inhibition has demonstrated synergistic anti-tumor activity in preclinical models at NOAEL doses, justifying a Phase 1 study. **Methods:** We conducted an open-label phase 1 study following a 3+3 trial design. Patients received a 1-week lead-in of onalespib alone (C0), followed by onalespib/AT7519M on days 1,4,8, and 11 of a 21-day cycle. Pharmacokinetic samples were obtained on C0D1 after onalespib alone, and on C1D1 and D11 with the combination. HSP70 protein levels were analyzed in PBMC and plasma samples collected at baseline, after onalespib alone, and after the combination, in order to demonstrate AT7519-mediated suppression of HSP70 expression. Patients enrolled to the expansion phase underwent optional paired tumor biopsies for assessment of proof-of-mechanism demonstration of modulation of client proteins. **Results:** Twenty-eight patients have been treated, 10 of whom were enrolled to the expansion cohort with optional tumor biopsies. The MTD is DL2: onalespib 80 mg/m^2 IV + AT7519M 21 mg/m^2 IV on days 1,4,8, and 11 of a 21-day cycle. At DL3, DLTs included Grade 3 troponin elevation and mucositis. Drug-related adverse events occurring in $\geq$ 30% of patients include diarrhea, fatigue, mucositis, nausea, and vomiting, consistent with known toxicities of these agents. Two patients with colorectal and endometrial cancer, respectively, remained on study for 10 cycles with SD as the best response. Modulation of HSP70 were demonstrated in patient plasma samples. **Conclusions:** The combination of onalespib and AT7519 is tolerable, although the doses of both agents were below the monotherapy MTDs. Prolonged disease stabilizations were observed. Pharmacokinetic and pharmacodynamic analyses are ongoing, including assessment of HSP70 expression in plasma and tumor. Clinical trial information: NCT02503709.

2620 **Poster Session (Board #264), Sat, 8:00 AM-11:00 AM**

Non-small cell lung cancer (NSCLC) next generation sequencing (NGS) using the Oncomine Comprehensive Assay (OCA) v3: Integrating expanded genomic sequencing into the Canadian publicly funded health care model.

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Background: Standard of care (SOC) molecular diagnostics for stage IV NSCLC patients in Ontario, Canada includes publicly reimbursed *EGFR*/*ALK,* and selected *BRAF* and *ROS-1* testing. Other genomic alterations are not tested routinely; however, enhanced molecular testing may broaden treatment options for patients. This study evaluated costs, identified actionable targets, and determined clinical trial eligibility as a result of using the OCAv3 NGS in stage IV NSCLC patients. **Methods:** In a prospective study of stage IV NSCLC out-patients at Princess Margaret Cancer Centre (Toronto) without *EGFR/ALK/KRAS/BRAF* alteration (unless failure of prior targeted therapy), diagnostic samples were tested by OCAv3 (ThermoFisher; 161 genes: hotspots, fusions, and copy number variations). Primary endpoints were incremental actionable targets and clinical trial opportunities as a result of broader OCAv3 testing. Secondary endpoints include feasibility and cost from the Canadian public healthcare perspective, and treatment outcomes. **Results:** Of 65 enrolled patients (Feb 2018-Jan 2019; 40 (62%) completed/14 (21%) screen fail/ 11 (17%) pending), median age of completed cohort was 65, 60% (N = 24) female, never/light smokers 68% (N = 27), Asian 38% (N = 15), previously treated 33% (N = 13). Actionable targets beyond SOC were identified in 33% (N = 13): *ERBB2* (N = 8), *BRAFV600* (N = 3), *NRG* fusion (N = 1), *MET* exon 14 (N = 1). New clinical trial options were identified in 70%. Failure of NGS was secondary to insufficient tissue [91% (N = 10) of screen failures; usually due to tissue exhaustion from prior SOC molecular testing]. Incremental costs per case beyond *EGFR/ALK* are estimated at $540 CAD. If *ROS-1* and *BRAF* testing were publicly reimbursed at current rates, the incremental profiling cost with OCAv3 would be $90 CAD per case. **Conclusions:** Although a key barrier to implementation is lack of funding for NGS in the Canadian publicly funded system, the OCAv3 consolidates genomic testing, identifies additional actionable targets, and substantially increases clinical trial eligibility for patients at a small incremental cost. Clinical trial information: NCT03558165.

2621 **Poster Session (Board #265), Sat, 8:00 AM-11:00 AM**

Overestimation of tumor mutational burden (TMB) using algorithms compared to germline subtraction.

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Background: TMB is an emerging predictor of survival with immunotherapy. TMB is determined by taking the difference between somatic and germline datasets when tumor-normal pairs are available. In the case of commonly utilized tumor-only sequencing, additional steps are needed to estimate the somatic alterations. Computational tools have been developed that determine germline contribution based on sample copy state, purity estimates and occurrence of the variant in population databases. Given the potential bias of population datasets, we hypothesized that tumor-only filtering approaches may overestimate the actual TMB. **Methods:** We assessed the TMB from 50 tumors in 10 diseases including all missense, indels, and frameshift variants with an allelic fraction (AF) $\geq$5% and Coverage $\geq$100X within the tumor. Tumor-only TMB was evaluated against the gold standard of matched germline subtracted TMB at three levels. Level 1 removed all the tumor-only variants with AF in the non-TCGA ExAC database $\geq$1%. Level 2 removed all variants observed in population databases simulating a naive approach of removing germline variation. Level 3 used an internal tumor-only pipeline for calculating TMB. **Results:** There were significantly higher estimates of TMB with Level 1, Level 2 and Level 3 tumor-only filtering approaches than that determined by germline subtraction, resulting in significant bias. Whereas there was no correlation between TMB estimates and tumor-germline TMB for Level 1 filtering, there were improvements in correlations for Level 2 and Level 3. **Conclusions:** The tumor-only approaches that filter variants in population databases overestimate TMB compared to that determined by germline subtraction. Despite improved correlations with more stringent filtering approaches, these falsely elevated estimates may result in the inappropriate categorization of tumor specimens and negatively impact clinical trial results and patient outcomes.

	Level 1	Level 2	Level 3
Difference above germline subtraction (mean, SD)	42.2 (±13.4)	4.67 (±2.25)	1.62 (±1.69)
P value of paired t test	p = 8.12e-28	p = 6.74e-15	p = 0.0003
95% limits of agreement (Bland-Altman)	16 to 68	0.26 to 9.07	-1.7 to 4.9
Correlation coefficient	*r* = 0.09	*r* = 0.62	*r* = 0.69
Pearson correlation p value	p = 0.52	p = 1.23e-06	p = 2.71e-08

2622 **Poster Session (Board #266), Sat, 8:00 AM-11:00 AM**

Breast cancer with insertion or deletion exhibits the immunogenic phenotype.

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Background: Although immunotherapy has been proven to be effective in a wide range of malignant tumors, breast cancer remains to be one of poorly immunogenic tumors and only a small subset of patients with breast cancer achieved benefits from immunotherapy. Therefore, identification of better predictive biomarkers to guide patient selection is highly desirable. It has been reported that insertion or deletion (indels) could create a novel open reading frame and generate more neoantigen which may mediate response to immunotherpay. However, the pattern of indels mutations in breast cancer is still unclear. **Methods:** Whole-exome sequencing data, RNA-Seq data and clinical data of 1096 breast tumors from The Cancer Genome Altas (TCGA) database were used to analyze the pattern of indels in breast cancer. Next generation sequencing (NGS) data of 81 metastatic breast tumors from clinical dataset were also used to validate the indels mutation pattern in different molecular subtype. **Results:** 81.7% (895/1096) of breast tumors in TCGA dataset harbored at least one indels mutation. Hormonal receptor (HR) negative tumors were associated with higher burden of indels mutations than HR positive tumors in both TCGA dataset ($P = 0.05$) and NGS-clinical dataset ($P = 0.003$). Indels were significantly correlated with higher TMB and neoantigen level in TCGA cohort ($P < 0.0001$). In addition, tumors with at least eight indels mutations (cut off as 80% percentile) exhibited even higher TMB ($P < 0.0001$) and neoantigen ($P < 0.0001$) level. Among 45 immune related genes, the mRNA expression of 22 genes were significantly higher in tumors with indels mutations, such as LAG3, IL18, IL6, CTLA4 and PDCD1. Indels group also showed a high levels of genome instability in terms of HRD-LOH ($P = 0.004$), NtAI ($P = 0.000$), wGII ($P = 0.001$) and LST ($P = 0.014$). **Conclusions:** Breast tumors with indels mutations exhibited the immunogenic phenotype. Further studies are warranted to investigate the potential value of indels as a predictive biomarker for immunotherapy in breast cancer.

2623 **Poster Session (Board #267), Sat, 8:00 AM-11:00 AM**

Baseline tumor-immune signatures associated with response to bempegaldesleukin (NKTR-214) and nivolumab.

Michael E. Hurwitz, Daniel C. Cho, Arjun Vasant Balar, Brendan D. Curti, Arlene O. Siefker-Radtke, Mario Sznol, Harriet M. Kluger, Chantale Bernatchez, Christie Fanton, Ernesto Iacucci, Yi Liu, Tuan Nguyen, Willem Overwijk, Jonathan Zalevsky, Mary Ann Tagliaferri, Ute Hoch, Adi Diab; Yale School of Medicine, New Haven, CT; Perlmutter Cancer Center New York University Langone Health, New York, NY; Perlmutter Cancer Center at NYU Langone Health, New York, NY; Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR; The University of Texas MD Anderson Cancer Center, Houston, TX; Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT; Nektar Therapeutics, San Francisco, CA

Background: PIVOT-02 is an ongoing phase 1/2 study of bempegaldesleukin (NKTR-214), a CD122-preferential IL-2 pathway agonist, plus nivolumab in patients with advanced solid tumors. Bempegaldesleukin (NKTR-214) increases proliferative tumor infiltrating lymphocytes (TIL) and cell surface PD-1 on immune cells and PD-L1 on tumor cells, demonstrating potential synergy with anti-PD-1 therapy. Pre-treatment tumor biopsies from metastatic 1L melanoma (MEL) and urothelial carcinoma (UC) patients were analyzed to correlate baseline immune phenotype to response. **Methods:** Pre-treatment TIL (CD8+ T cells/mm^2 and %CD3+ by IHC; 29 MEL; 22 UC) were measured and divided into high and low groups based on median values. PD-L1 (% PD-L1 on tumor cells by IHC [28-8 PharmDx]; 33 MEL; 23 UC) was scored negative ($<$1%) or positive ($\geq$1%). Interferon gamma gene score (IFNG; 11 MEL) was scored as high or low based on median p value of $<$0.1 for 15 genes (EdgeSeq). High and low groups were correlated with responses per RECIST 1.1. **Results:** Baseline demographics and prognostic factors were balanced in the biomarker subgroups. Response rates for response evaluable MEL and UC were 53% (SITC 2018) and 48% (ASCO-GU 2019), respectively. In MEL, median values of CD3-TIL and CD8-TIL were 19% and 203 cells/mm^2, respectively. Response rate correlations were 67% and 20% with IFNG high and low, 79% and 29% with CD3-TIL high and low, 79% and 33% with CD8-TIL high and low, and 68% and 43% with PD-L1 positive and negative. Most importantly, responses were observed in patients with the least favorable tumor microenvironment, characterized as both PD-L1 negative and TIL low, with responses of 17% (1/6 CD8-TIL), and 25% (2/8 CD3-TIL), respectively. Similar correlative trends were observed in UC, with 50% (4/8 CD8-TIL) and 38% (3/8 CD3-TIL) responses in patients with least favorable microenvironment. **Conclusions:** The biomarker program included in PIVOT-02 identified baseline immune signatures correlated with response for MEL and UC. The response rates observed in both the favorable and unfavorable tumor microenvironments indicate the potential of this combination and support its broad development. Clinical trial information: NCT02983045.

2624 **Poster Session (Board #268), Sat, 8:00 AM-11:00 AM**

TMB standardization by alignment to reference standards: Phase II of the Friends of Cancer Research TMB Harmonization Project.

Diana M. Merino, Lisa McShane, Matt Butler, Vincent Anthony Funari, Matthew David Hellmann, Ruchi Chaudhary, Shu-Jen Chen, Wangjuh Sting Chen, Jeffrey M. Conroy, David Fabrizio, Laura E MacConaill, Aparna Pallavajjala, Arnaud Papin, Mark Sausen, Victor J Weigman, Mingchao Xie, Ahmet Zehir, Chen Zhao, Paul M. Williams, Friends of Cancer Research TMB Harmonization Team; Friends of Cancer Research, Washington, DC; Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; SeraCare, Gaithersburg, MD; NeoGenomics Laboratories, Aliso Viejo, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Thermo Fisher Scientific, San Francisco, CA; ACT Genomics, Taipei, Taiwan; Caris Life Sciences, Phoenix, AZ; OmniSeq, Inc., Buffalo, NY; Foundation Medicine, Inc., Boston, MA; Center for Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, MA; Johns Hopkins University, Baltimore, MD; QIAGEN, Waltham, MA; Personal Genome Diagnostics, Inc., Baltimore, MD; Q Squared Solutions, EA Genomics, Morrisville, NC; AstraZeneca, Waltham, MA; Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; Illumina, Inc., San Diego, CA; Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Tumor mutational burden (TMB) is a predictive biomarker of response to immune checkpoint inhibitors across multiple cancers. In Phase 1 of the Friends of Cancer Research Harmonization Project, we demonstrated a robust correlation between TMB estimated using targeted next-generation sequencing (NGS) gene panels and whole exome sequencing (WES) applied to MC3-TCGA data. These findings demonstrated variability in TMB estimates across different panels. Phase 2 evaluates sustainable TMB reference standard materials for TMB alignment to assess this variability. The goal of this effort is to establish best practices for estimating TMB in order to improve consistency across panels, for the sake of optimizing clinical application and facilitating integration of datasets generated from multiple assays. **Methods:** Fifteen laboratories with targeted panels at different stages of development participated. We identified a set of reference standards consisting of 10 well-characterized human-derived lung and breast tumor-normal matched cell lines. WES was performed using a uniform bioinformatics pipeline agreed upon by all team members (WES-TMB). Each laboratory used their own sequencing and bioinformatics pipelines (tumor-only and tumor-normal) to estimate TMB according to genes represented in their respective panels (panel-TMB). The association between WES-TMB and each panel-TMB was investigated using regression analyses. Bias (relative to WES-TMB) and variability in TMB estimates across panels were rigorously assessed. All analyses were blinded. **Results:** The set of reference standards spanned a clinically meaningful TMB range (4.3 to 31.4 mut/Mb). Preliminary data from 12 laboratories shows a good correlation between panel-TMB and WES-TMB in this empirical analysis. Across panels, regression R^2 values range 0.77-0.96 with slopes ranging 0.60-1.26. Calibration analyses that seek to minimize variability of TMB estimates across panels using the established set of reference standards are ongoing, as well as investigating cancer type dependence on the relationship between panel-TMB vs. WES-TMB, which will be available at the time of presentation. **Conclusions:** Preliminary findings demonstrate feasibility of using sustainable reference control cell lines to standardize and align estimation of TMB across different targeted NGS assays. Future studies aim to validate reference standard material as a reliable alignment tool by using formalin-fixed paraffin-embedded human tumor samples.

2625 **Poster Session (Board #269), Sat, 8:00 AM-11:00 AM**

Tissue immune response in epithelial ovarian carcinoma.

Jon Henriksen, Frede Donskov, Marianne Waldstrøm, Mette Hjortkjær, Christina Braad Petersen, Caroline Brenner Thomsen, Anders Kristian Moeller Jakobsen, Karina Dahl Steffensen; Department of Oncology, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark; Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; Department of Pathology, Vejle Hospital, Vejle, Denmark; Department of Oncology, Vejle Hospital, Vejle, Denmark

Background: Epithelial ovarian cancer (EOC) is a highly malignant disease with a fatal outcome for most patients. During recent years immunological mechanisms have proven important in relation to the treatment and prognosis of cancer, but within EOC the knowledge is still sparse. Understanding the importance of immune markers to the prognosis of ovarian cancer is essential for the future treatment of EOC. The aim of the present study was to investigate the prognostic impact of intratumoral PDL-1 expression, T cells, neutrophil granulocytes (NG) and Natural Killer (NK) cells in a population based cohort. **Methods:** All patients diagnosed with ovarian cancer in Denmark in 2005 were included in the study. Immunohistochemical staining was performed on tumor tissue from 412 patients. Antibodies for PD-L1, T cells (CD8), NG (CD66b), and NK cells (CD57) were used. Cell densities were analyzed using a digital image analysis method. The primary endpoint was overall survival (OS). **Results:** In high grade serous carcinoma (HGSC) the median OS in patients with a high level of tumor infiltrating T cells was 37 vs 25 months in patients with a low level($p = 0.0008$). Multivariate analysis showed a hazard ratio (HR) of 0.72 ($p = 0.020$). The median OS in patients with a high level of tumor infiltrating NK cells was 45 vs 29 months in patients with a low level ($p = 0.0310$). Multivariate analysis showed a HR of 0.67 ($p = 0.041$). PD-L1 and NG had no statistically significant impact on OS. Only T cells showed prognostic significance across histological subtypes with a HR of 0.72 ($p = 0.007$) in favor of a high density of T cells. **Conclusions:** The present population based study demonstrated prognostic importance of tumor infiltrating T cells and NK cells in HGSC. Neither PD-L1 nor NG held prognostic significance.

2626 **Poster Session (Board #270), Sat, 8:00 AM-11:00 AM**

Tumor mutational burden (TMB) profile of *K-RAS/TP-53* co-mutation in metastatic non-small cell lung cancer (m-NSCLC).

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Background: Early data suggests that co-occurring genetic events define biological heterogeneity in K-RAS mutant NSCLC, with *K-RAS/ TP-53* (KP) co-mutated subset having potential therapeutic vulnerabilities to immune checkpoint blockade (ICB). To explore the immunological basis for these findings, we evaluated the immune biomarker profile (TMB/PD-L1) in KP mutant m-NSCLC using a large next-generation sequencing (NGS) dataset. **Methods:** Caris life sciences NGS dataset consisting of 1317 m-NSCLC tissue samples from 2016-18 was queried. PD-L1^{pos} was defined as $\geq$ 1% staining using 22c3 Dako assay. TMB was measured by counting all somatic non-synonymous missense mutations using targeted NGS (592 genes). TMB-high (H) was defined as $\geq$ 10 mutations/Megabase (mut/Mb). *P*-values were calculated using Chi-square and Mann-Whitney test. **Results:** *K-RAS* mutations were identified in 28.7% (378/1317). Within this *K-RAS* mutant group, KP subset constituted 49.4% (187/378), remaining were *K-RAS* mutated/ *TP-53* wild type (K-Pwt). 72.2 % (135/187) of KP had PD-L1^{pos} with 51.9% (97/187) having PD-L1 $\geq$ 50%. KP had higher median TMB vs. K-Pwt (14.5 vs. 9.0 mut/Mb, $p<0.001$) and higher % of TMB-H vs. K-Pwt (79.9 vs. 45.1%, $p<0.001$; Table). Even in the PD-L1^{neg} group, KP had higher % of TMB-H vs. K-Pwt (86.5 vs. 41.5%, $p<0.001$). *K-RAS or TP-53* exon-subtypes had no difference in median TMB or % of TMB-H. Across metastatic sites, brain tissue had the highest % of KP subset (38.3%, 68/187) followed by bone (28.9%, 54/187). Within KP subset, brain tissue had higher median TMB vs. bone (16 vs. 11 mut/Mb, $p<0.01$) as well as greater % of TMB-H vs. bone (86.5 vs. 68.5%, $p=0.01$). **Conclusions:** This is the largest dataset to date highlighting the unique immune profile of KP mutant m-NSCLC. Our results show that KP subset has a significantly higher TMB than K-Pwt, especially in the PD-L1^{neg} subgroup. Metastatic site-specific variations in TMB were also observed for the KP subset. These findings could have therapeutic implications in guiding patient selection for ICB and merit prospective investigation.

Variable	KP vs. K-Pwt	*p*
TMB high (%)	79.9 vs. 45.1	<0.001
Median TMB (mut/Mb)	14.5 vs. 9.0	<0.001

2627 **Poster Session (Board #271), Sat, 8:00 AM-11:00 AM**

Impact of prior chemotherapy or radiation therapy on tumor mutation burden in NSCLC.

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Background: Higher non-synonymous tumor mutation burden (TMB) in non-small cell lung cancer (NSCLC) is associated with a higher likelihood of response to checkpoint inhibitors. Tissue samples subject to TMB analysis may be obtained after exposure to cytotoxic chemotherapy or radiation therapy – both of which introduce somatic mutations in DNA and can influence the number of identified mutations. The role of TMB as a potential predictive marker for immunotherapy is evolving, and the impact of prior therapy on TMB could influence interpretation. **Methods:** Eligible cases were from patients with confirmed NSCLC, available clinical annotation and tumor molecular profiling including TMB analysis at a CLIA-certified genomics laboratory (Caris Life Sciences, Phoenix, AZ) using the Illumina NextSeq platform. TMB was calculated using only missense mutations that had not been previously reported as germline alterations. Treatment history was obtained for each patient under an IRB approved protocol to determine whether patients had had received chemotherapy or radiation therapy in the year prior to collection of the tissue subject to TMB analysis. Data analysis was performed using the chi-square test of deviance to evaluate whether TMB was statistically significantly different between groups, correcting for smoking status. **Results:** Out of 1,118 patients identified, 459 cases met all eligibility criteria and were evaluated. 76 patients (17%) received either chemotherapy or radiation prior to tissue collection. Samples acquired prior to any therapy had a median TMB of 10 mut/Mb vs. 11 mut/Mb in samples acquired after any therapy. After adjusting for smoking, there was no significant difference in TMB between these cohorts ($p = 0.41$). Secondary pair wise analysis showed no statistically significant difference in TMB from chemotherapy-naïve and chemotherapy-treated samples ($p = 0.28$). The same was true for radiation ($p = 0.75$). Collection of clinical data is ongoing and further analysis, including additional cases will be presented. **Conclusions:** Though cytotoxic chemotherapy and radiation therapy can introduce somatic mutations, prior exposure to either was not associated with a significant difference in TMB.

2628 **Poster Session (Board #272), Sat, 8:00 AM-11:00 AM**

The consensus Immunoscore adapted to biopsies in patients with locally advanced rectal cancer: Potential clinical significance for a "Watch and Wait" strategy.

Carine El Sissy, Amos Kirilovsky, Marc Van Den Eynde, Alfredo Romero, Florence Marliot, Christine Lagorce, Frédéric Bibeau, Ilma Soledad Iseas, Enrique Luis Roca, Carlos Alberto Vaccaro, David Tougeron, Carlos Torres Carvalho, Nuno Figueiredo, Rodrigo O Perez, Angelita Habr Gama, Viorel Scripcariu, Jean-Pierre Gerard, Jerome Galon, Guy Zeitoun, Franck Pages; Hopital Européen Georges Pompidou, Paris, France; Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; Hospital Britanico de Buenos Aires, Buenos Aires, Argentina; INSERM, Paris, France; HEGP, Paris, France; CHU Caen, Caen, France; Clinical Oncology Unit, Hospital Bonorino Udaondo, Buenos Aires, Argentina; Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; Poitiers University Hospital, Poitiers, France; Champalimaud Clinical Centre, Lisbon, Portugal; Champalimaud Fundation, Lisboa, Portugal; Insituto Angelita and Joaquim Gama, São Paulo, Brazil; Angelita and Joaquim Gama Institute, São Paulo, Brazil; Hosp SF Spiridon Univ of Medicine and Pharmacy, Iasi, Romania; Centre Antoine Lacassagne, Nice, France; Laboratory of Integrative Cancer Immunology, INSERM, Paris, France; INSERM, Laboratory of Integrative Cancer Immunology, Equipe Labellisée Ligue Contre le Cancer, Paris, France

Background: We investigated whether an adaptation to rectal biopsies of the recently validated consensus Immunoscore, could predict the response to neoadjuvant treatment and delineate clinical responders that could benefit from a "Watch and Wait" (W&W) strategy with acceptable outcomes. **Methods:** Initial biopsies from 273 patients with locally advanced rectal cancer (LARC) treated by neoadjuvant chemoradiotherapy (nCRT) followed by Total Mesorectal Excision (TME), were immunostained for CD3+ and cytotoxic CD8+ T cells and quantified by digital pathology to determine the Immunoscore within pre-treatment Biopsy (IS_B). Expression level of 44 immune related genes post-neoadjuvant treatment was investigated by Nanostring technology (n = 64 patients). Results were correlated with response to neoadjuvant treatment, disease free survival (DFS) and time to recurrence (TTR). Prognostic performance of IS_B was finally assessed in 73 LARC treated by W&W strategy. **Results:** IS_B Low, Intermediate and High were respectively observed in 23.3, 50.4 and 26.3 % of the cohort. IS_B was positively and significantly correlated with the response to nCRT, as evaluated by Dworak classification (P = .0034), ypTNM (P = .0003), down-staging (P = .0014), and neoadjuvant rectal (NAR) score, ($P < .0001$). IS_B status was also positively associated with the degree of local immune activation post-neoadjuvant treatment. IS_B High patients were at low risk of relapse, with 5-year DFS rates of 81.1 % (CI, 71.3-92.1 %) as compared to 57.8 % (CI, 45.9-72.9 %) in IS_B low patients. In multivariate analysis, IS_B was the only significant parameter at presentation associated with DFS (High vs Low: P = .001). Among W&W patients, significant difference was observed for TTR according to IS_B status (High vs Low: P = .025). **Conclusions:** IS_B could provide a reliable estimate of the response to nCRT and risk of recurrence in LARC patients' treated by TME or W&W strategy.

2629 **Poster Session (Board #273), Sat, 8:00 AM-11:00 AM**

A multiplex immunofluorescence assay to assess immune checkpoint inhibitor-targeted CD8 activation and tumor colocalization in FFPE tissues.

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Background: Immune checkpoint inhibitors promote antitumor immune responses by enhancing T-cell activity. Measuring the pharmacodynamic effects of these drugs is challenging, as it requires assessing both immune cell and cancer cell populations. To evaluate T cell activation in tumor tissue from patient biopsies, we developed a robust multiplexed immunofluorescence assay. **Methods:** Our assay uses novel oligo-conjugated antibodies (Ultivue) for simultaneous quantitation of TCR activation (phospho-CD3zeta), immune checkpoint signaling via PD-1 (p-SHP1/p-SHP2), and the net stimulation/inhibition resulting from the integration of these two pathways in CD8 cells (p-ZAP70), while also providing the proximity of CD8 cells to tumor tissues, identified by β-catenin. The method was clinically validated using custom tissue microarrays (TMA) containing tumor biopsies of 3 different histologies (CRC, NSCLC, and breast). **Results:** From a total of 192 tumor core biopsies, 20/64 NSCLC, 9/64 CRC, and 3/65 breast TMA cores were found to have a significant number of CD8+ tumor infiltrating lymphocytes (TILs) at baseline ($>$ 50 cells in the examined section). In 18 of the 20 NSCLC cores, $\geq$50% of CD8 cells both inside and outside of the tumor were activated (CD3z-pY142+). In 6/9 CRC cores, $\geq$50% of CD8+ cells inside tumor tissues were activated, and in 4/9 CRC cores, $\geq$50% of CD8+ cells in stroma were activated. In 2/3 breast tumor cores, 90% of CD8+ cells inside tumor tissues were activated; in the remaining core, 90% of CD8+ cells in stroma were activated. Interestingly, all 192 cores had minimal to no expression of activated Zap70 (pY493) in CD8+ cells. **Conclusions:** Depending on tumor histology, baseline biopsy samples may contain variable numbers of activated CD8+ TILs (CD3z-pY142+), which may reside inside or outside of tumor regions and express very low levels of Zap70-pY493. Anti-PD-1 therapy is predicted to enhance T-cell cytotoxic activity, as demonstrated by an increased number of TILs and elevated Zap70-pY493 expression. This assay is being used for pharmacodynamic evaluations in ongoing immunotherapy clinical trials. Funded by NCI Contract No HHSN261200800001E.

2630 **Poster Session (Board #274), Sat, 8:00 AM-11:00 AM**

Tumor mutational burden (TMB) and PD-L1 expression as predictors of response to immunotherapy (IO) in NSCLC.

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Background: PD-L1 expression and TMB, as a proxy for neoantigen burden, have been correlated with response to IO in advanced NSCLC (aNSCLC) clinical trials, but their combined utility is unclear. We assessed TMB and PD-L1 as predictors of response in aNSCLC patients (pts) after IO monotherapy in a real-world setting. **Methods:** Pts had a diagnosis of aNSCLC, comprehensive genomic profiling of 186-315 genes/1.1 megabase (Mb), PD-L1 testing of pre-IO specimens, and were treated in the Flatiron Health network (1/2011 - 6/2018). Clinical characteristics and real-world tumor response (rwTR) were obtained via technology-enabled abstraction of clinician notes and radiology/pathology reports, and linked to genomic data in the Flatiron Health-Foundation Medicine Clinico-Genomic Database. A general additive model examined the predictive value of TMB (as continuous measure) and PD-L1 level on rwTR. A reduced PD-L1-only model was compared to the full model using Akaike Information Criterion (AIC). rwTR predictions at representative TMB and PD-L1 levels were calculated. **Results:** Of 426 pts, PD-L1 expression was high (≥50%) in 140, low (1-49%) in 123, and negative (<1%) in 163. Median TMB was 9.6 mut/Mb (IQR 4.4 - 14.8) overall, 11.3 in responders and 8.7 in non-responders. TMB did not correlate with PD-L1 level (Kruskal-Wallis p=0.29). The TMB + PD-L1 model had superior prediction of rwTR than the PD-L1 model, as assessed by lower AIC score. In the combined model, higher TMB and PD-L1 levels were each associated with higher rwTR likelihood (Table). Predicted rwTR probability, % (95% CI), by TMB and PD-L1 in line 1. **Conclusions:** TMB and PD-L1 expression are independent markers that, when combined, have increased predictive power for response to IO. High TMB + low/neg PD-L1 behaved similarly to low TMB + high PD-L1, and high TMB + high PD-L1 predicted the highest rwTR. Investigation of these biomarkers as complementary predictors of progression and overall survival is ongoing.

PD-L1 level	Negative	Low	High
TMB (mut/Mb)			
1	21 (11 - 38)	13 (4 - 39)	43 (29 - 59)
5	25 (15 - 39)	22 (10 - 42)	47 (35 - 60)
10	30 (19 - 44)	39 (24 - 56)	52 (41 - 62)
15	36 (23 - 51)	53 (36 - 70)	56 (44 - 67)
20	41 (25 - 59)	58 (38 - 77)	60 (46 - 73)
30	51 (28 - 73)	51 (21 - 81)	69 (46 - 85)

2631 **Poster Session (Board #275), Sat, 8:00 AM-11:00 AM**

Quantitative MHC II protein expression levels in tumor epithelium to predict response to the PD1 inhibitor pembrolizumab in the I-SPY 2 Trial.

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Background: Response to immune checkpoint inhibitors has been associated with immune activation and mutational load within a tumor. Previous results in other tumors have implicated MHC II protein tumor cell expression as a response predictor to immune checkpoint inhibitors. In the I-SPY 2 TRIAL, the anti-PD1 therapeutic antibody pembrolizumab (P) was available to HER2-negative subtypes and graduated in both the HR+/HER2- and TNBC signatures. Pre-specified biomarker analysis was performed to test tumor MHC II expression as a predictor of response to P in the I-SPY 2 TRIAL based on its central role in tumor antigen presentation. **Methods:** 156 patients (P: 67, controls: 89) had RPPA and pCR data. RPPA-based quantitative data for pan-MHC II protein isotypes HLA-DR/DP/DQ/DX and HLA-DR protein isotype was obtained from LCM-enriched tumor epithelium, and protein levels were assessed for association with pCR in the P and control arms separately using the Wilcoxon Rank Sum test ($p < 0.05$). Analysis was also performed in the HR+ and HR- subgroups. Markers were analyzed individually; p-values are descriptive and were not corrected for multiple comparisons. **Results:** Across all P- treated patients, the HLA class II molecules –DR and -DR/DP/DQ/DX had a positive association with response to P ($p = 0.014$ and $p = 0.001$). Expression of HLA-DR/DP/DQ/DX also had a positive association with response to P in HR+ tumors. Neither of these associations were seen in the control arm samples. **Conclusions:** The observation of elevation of MHC II protein expression in HER2- responding patients treated with P suggests that activation of antigen peptide exchange facilitated by these molecules in T and B cells may enhance response to P treatment.

2632 **Poster Session (Board #276), Sat, 8:00 AM-11:00 AM**

Evaluation of TMB estimates for the prediction of response to immune checkpoint blockage.

Jan Budczies, Michael Allgäuer, Kevin Litchfield, Eugen Rempel, Petros Christopoulos, Daniel Kazdal, Volker Endris, Michael Thomas, Stefan Fröhling, Solange Peters, Charles Swanton, Peter Schirmacher, Albrecht Stenzinger; Institute of Pathology, University of Heidelberg, Heidelberg, Germany; Institute of Pathology, Heidelberg, Germany; The Francis Crick Institute, London, United Kingdom; University Hospital Heidelberg, Heidelberg, Germany; Institute of Pathology, University Hospital and National Center for Tumor Diseases, Heidelberg, Germany; Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany; National Center for Tumor Diseases (NCT), Heidelberg, Germany; Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland; Translation Cancer Therapeutics Laboratory, The Francis Crick Institute, London, United Kingdom; Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Background: Tumor mutational burden (TMB) is an emerging biomarker in immuno-oncology (IO). Panel sequencing (PS) is a promising approach for its implementation in clinical practice. **Methods:** We analyzed TMB as predictor of IO response in a multi-cancer cohort published by Miao et. al. The performance of three large panels (Illumina TSO500, Qiagen TMB [QIAseq] and Oncomine TMB [OTMB]) and two small panels (Illumina TST170 and Oncomine Comprehensive Assay [OCAv3]) was compared to WES by in silico simulations. Separation of responders (PR/CR) from non-responders (PD) was analyzed in the multi-cancer cohort (n = 193), in the lung cancer (n = 36) and in the melanoma (n = 125) subcohort. We also simulated PS in the TCGA pan-cancer cohort. **Results:** In lung cancer, TMB was strongly predictive for IO response (area under ROC curve [AUC] 0.78-0.94). WES performed (borderline)-significantly better than PS for all five panels (OCAv3: p = 0.011, TST170: p = 0.01, QIAseq: p = 0.048, OTMB: p = 0.063, TSO500: p = 0.11). For the cut-point of 199 mutations, misclassification rates compared to WES (16.7%) were borderline-significantly higher for the small panels OCAv3 (33.3%, p = 0.087) and TST170 (36.1%, p = 0.054), but not for the large panels. In melanoma, TMB was moderately predictive (AUC 0.58-0.63) and WES performed (borderline)-significantly better than the OCAv3, TST170, QIAseq and TSO500 panels. In the multi-cancer cohort, WES did not perform better than PS. TBM estimates from PS include an inherent fuzziness originating from restriction to a limited part of the coding sequence. Based on a random mutation model, we derived a mathematical formula for the coefficient of variation (CV) of TMB: The CV decreases inversely proportional with both the square root of the TMB level and with the square root of the panel size. We showed that the mathematical law is valid for real-word mutation data. **Conclusions:** Small panels (size $<$ 1 Mpb) performed imprecise in diagnostic TMB estimation. Even using the largest commercially available panels it can be challenging to capture the full predictive information of TMB. The detrimental effect of small panel size can be addressed by using larger panels, but halving the CV of TMB necessitates quadruplication of the panel size.

2633 **Poster Session (Board #277), Sat, 8:00 AM-11:00 AM**

Association of genetic variations within the T-cell costimulatory LIGHT gene with outcome in stage II and III colon cancer.

Martin D. Berger, Shu Cao, Inti Zlobec, Yuji Miyamoto, Mitsukuni Suenaga, Diana L. Hanna, Shivani Soni, Alberto Puccini, Ryuma Tokunaga, Madiha Naseem, Francesca Battaglin, Wu Zhang, Alessandro Lugli, Heinz-Josef Lenz; Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA; Department of Preventive Medicine, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA; University of Bern, Bern, Switzerland; Kumamoto University, Kumamoto, CA, Japan; Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; USC Keck School of Medicine, Los Angeles, CA; University of Southern California, Los Angeles, CA

Background: T-cell activation plays a key role in maintaining an effective host immunity and antitumor control. Targeting costimulatory immune checkpoint proteins can lead to increased antitumor immunity. We hypothesize, that variations in genes encoding for T-cell activation molecules may predict outcome in stage II and III colon cancer patients. **Methods:** The impact of 4 functional single nucleotide polymorphisms (SNPs) within the LIGHT, ICOS, CD80 and GITR genes on time to recurrence and overall survival was evaluated in 209 patients with stage II and III colon cancer. Genomic DNA was extracted from formalin-fixed paraffin embedded tissue and the SNPs were analyzed by PCR-based direct sequencing. **Results:** Baseline characteristics were as follows: median age = 70y (19-91); female/male ratio = 41.6% / 58.4%; 111 patients had stage II, and 98 stage III colon cancer. The LIGHT rs3760746 SNP showed significant association with recurrence rate in the overall population. Patients harboring any G allele had a lower 3-years recurrence rate compared to those with a A/A genotype (16% vs 30%) in both univariate (HR 0.53, 95% Confidence intervall (CI) 0.29-0.96, p = 0.033) and multivariate analyses (HR 0.52, 95% CI 0.29-0.95, p = 0.034). This trend was most evident among patients with stage III colon cancer. Here again, G allele carriers had both a lower 3-years recurrence and a longer 5-years overall survival rate compared to those having a A/A genotype (21% vs 40% and 77% vs 43%) in both univariate (HR 0.42, 95% CI 0.19-0.90, p = 0.021 and HR 0.51, 95% CI 0.25-1.03, p = 0.046) and multivariate analyses (HR 0.43, 95% CI 0.20-0.93, p = 0.033 and HR 0.30, 95% CI 0.14-0.65, p = 0.002). **Conclusions:** Our results provide the first evidence that polymorphisms within the T-cell costimulatory LIGHT gene might serve as prognostic markers in patients with stage II and III colon cancer. Targeting LIGHT might be a promising approach to further optimize treatment options and to improve outcome of colon cancer patients in the adjuvant setting.

2634 **Poster Session (Board #278), Sat, 8:00 AM-11:00 AM**

Comparison between whole exome sequencing (WES) and single nucleotide polymorphism (SNP)-based tumor mutation burden analysis.

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Background: Immune checkpoint inhibitors (ICI) block proteins which enable cancer cells to evade the immune system. Recent studies have shown that the higher the tumor mutation burden (TMB) the greater the likelihood of response to ICI therapy. Analysis of TMB has focused on WES of paired tumor and normal samples. This study tests the feasibility of measuring TMB from a SNP-based resequencing assay (myChoice HRD Plus). **Methods:** WES and myChoice HRD Plus were performed on matched tumor and normal DNA from 44 breast and 12 colon tumors. myChoice HRD Plus combines homologous recombination deficiency analysis with resequencing of 108 genes and microsatellite instability analysis. WES-based TMB was calculated by identifying all variants in paired samples, and subtracting germline variants. Two SNP-based TMB (SbTMB) methods were utilized to calculate TMB. The first used germline subtraction similar to the WES-based method. The second utilized an algorithm which removed background germline variants. Median sequence length to calculate TMB was 9.7 Mb for WES, 4.6 Mb for SbTMB (germline subtraction), and 1.9 Mb for SbTMB (algorithm). **Results:** Correlation coefficients for WES vs. SbTMB (germline subtraction) and SbTMB (algorithm) were 0.895 and 0.908, respectively. The two SbTMB methods had a correlation coefficient of 0.834. SbTMB measures of TMB were generally higher than WES-based TMB with a mean increase in score of 1.6 variants/Mb for SbTMB (germline subtraction; $p = 4.6x10^{-6}$) and 1.5 variants/MB for SbTMB (algorithm; $p = 1.2x10^{-5}$). No significant difference in magnitude of TMB score between the SbTMB measures was observed (0.04 variants/Mb; $p = 0.88$). **Conclusions:** SNP-based methods for calculating TMB produced highly concordant scores compared to WES-based methods. SbTMB assays produced elevated TMB scores, consistent with selective pressure against mutations in coding regions of genes, necessitating a higher score threshold for when using a SbTMB assay. This SbTMB analysis expands the utility of myChoice HRD Plus, and provides a method for calculation of TMB without sequencing a germline comparator.

2635 **Poster Session (Board #279), Sat, 8:00 AM-11:00 AM**

Electrostatic human leukocyte antigen-neoantigen interactions and durable benefit in non-small cell lung cancer patients treated with immunotherapy.

Amy Lauren Cummings, Jaklin Gukasyan, Henry Lu, Benji Bachrach, John Madrigal, James M. Carroll, Wisdom O Akingbemi, Zorawar Singh Noor, Aaron Elliott Lisberg, Edward B. Garon; David Geffen School of Medicine at UCLA, Los Angeles, CA; UCLA, Los Angeles, CA; University of Virginia School of Medicine, Charlottesville, VA; University of California Berkeley, Berkeley, CA; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; UCLA Medical Center, Los Angeles, CA; Univ of California Irvine, Orange, CA; David Geffen School of Medicine, University of California/ TRIO-US Network, Los Angeles, CA

Background: Human leukocyte antigen (HLA) binding relies on energy from the interaction of B-pocket residues with anchor amino acids (AA). Among HLA class I supertypes, only HLA-B has distinct electrostatic B-pocket specificities, and of 7 HLA-B supertypes, B08, B27, and B44 feature binding pockets with preferences for charged AAs (Lund Immunogen). Whether electrostatic interactions in HLA-neoepitope binding would identify superior neoantigens and associate with survival in NSCLC patients treated with immunotherapy was unknown. **Methods:** Forty patients with advanced NSCLC treated with single agent pembrolizumab on a clinical trial with at least 5 years follow-up underwent paired tumor-normal whole-exome sequencing (WES) with Illumina HiSeq 2000/3000. HLA typing used normal (germline) WES from peripheral blood mononuclear cells analyzed with BWA-ALN and Athlates software (Liu Nuc Acids Res); supertype was determined by 2008 criteria (Sidney BMC Immunol). Tumor nonsynonymous coding mutations were identified with GATK v3.8, annotated with Ensembl-VEP, and passed through pVAC-Seq using a NetMHC 4.0 algorithm to identify potential neoepitopes 9 AAs in length (Hundal Genome Med). Neoepitopes were characterized based on mutant AA charge (D/E negative, H/K/R positive) and position. High affinity neoepitopes (HAN) were defined as those an with IC50 $<$ 50 nM with wildtype IC50 $>$ 50 nM (Ghorani Annals Oncol) and a mutation to a known B-pocket supermotif (K in position 3 or 5 for B08, R in position 2 for B27, E in position 2 for B44) (Lund Immunogen). Progression-free survival (PFS) was compared with logrank tests and proportional hazards (JMPv14, Cary, NC). **Results:** Of the 40 patients, 29 (72.5%) had at least one B08, B27, or B44 allele. One or more supertype-matched HAN were found in 10 of the 29 (34.5%), including 6/7 with PFS $>$ 2 years, 3 of whom continue on therapy beyond 5 years. Median PFS in those with HAN was 26.7 months (m) vs 4.3 m in those without (HR 0.34, 95% CI 0.11-0.88, p = 0.024). **Conclusions:** Electrostatic charge may serve as a mechanism for enhanced binding affinity in HLA-B supertypes with a preference for charged AA in their B-pockets. Identification of favorable HLA-matched neoepitopes may identify distinct prognostic groups and potentially durable responders to immunotherapy in NSCLC.

2636 **Poster Session (Board #280), Sat, 8:00 AM-11:00 AM**

Effect of subcutaneous multipeptide active antigen-specific immunotherapy at lymph nodes and tumor sites on clinical outcomes in progressive tumors.

Juan Pablo Marquez-Manriquez, Pedro Alejandro Lucero-Diaz, Jose Antonio Matute-Briseno, Alejandro Camacho-Hernandez, Dolores Gallardo-Rincon; CICS USA, Seattle, WA; Centro de Investigacion de Cancer en Sonora Campus Ciudad Obregon, Sonora, Ciudad Obregon, Mexico; Sonora Cancer Research Center (CICS USA), Lynnwood, WA; Centro de Investigacion de Cancer en Sonora Campus Ciudad Obregon, Sonora, Ciudad Obregon, SO, Mexico; Department of Medical Oncology, Ovarian Cancer Program, Instituto Nacional de Cancerología, Mexico City, DF, Mexico

Background: The tumor and lymph nodes (LN) microenvironment clinically speaking are mainly unexplored and there are limited clinical studies of immunotherapeutic approaches manipulating those in progressive cancer patients. The tumor and LN microenvironment offers an opportunity to treat locally with multi-peptide immunotherapy in challenging clinical situations where we can have still a potential safe and effective therapeutic approach using the concept treat locally treat systemically. **Methods:** N = 11 patients were enrolled after the local IRB ethic committee approved the pilot clinical study number CICS/SS/0035. Previous identified targets such as FAP, b-2-microglobulin, Fascin, RCAS1/EBAG9, Bcl-2, survivin, Sox2, Ape-1, Valosin containing-protein (VCP) and EGFR were analyzed by IHC, Th1 and CD8 long-peptides were predicted, immune assays using PBMCs including tumor microenvironment were performed to detect Granzyme B by ELISPOT, naturally processed epitopes by T-cell expansion and cytokines. Patients were treated subcutaneously (S.C.) eight times in the axillary and inguinal LN area one week apart. Afterwards we treated S.C. as well but now in the areas with tumor activity according with the CT or PET every week 10 times. Initial DTH and at the end of the treatment was performed. Pathological, clinical and immunological correlations were made using multivariate analysis. **Results:** Despite progressive disease 100% of the patients responded to the treatment. 80% had CR and 20% pseudo-progression and then CR. 100% of the patients increased the levels of Granzyme B against Bcl-2 ($p = 0.001$), VCP ($p = 0.0001$), Ape-1 ($p = 0.005$) and RCAS1 ($P = 0.0001$) and this correlated with the scans post-treatment. The patients showed more CD8 infiltration in the DTH test at the tumor site ($p = 0.002$) than in the non-tumor site ($p = 0.01$). The number of metastatic lesions in lungs ($p = 0.004$) and hepatic tissue ($p = 0.001$) disappeared and correlated with increased levels of IL-12 production *in vivo*. **Conclusions:** Treating immunologically the LN and the microenvironment of the areas with tumor activity is a feasible and safe approach to limit systemic toxicity and improve the clinical outcomes in patients with progressive cancer including bone sarcoma, epithelial ovarian cancer, PDAC, pediatric sarcomas and TNBC.

2637 **Poster Session (Board #281), Sat, 8:00 AM-11:00 AM**

Survival by stage and tumor measurability in metastatic melanoma patients treated with autologous dendritic cell tumor cell vaccines.

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Background: Survival of cancer patients is greatly affected by stage and tumor burden. The purpose of this study was to determine survival for melanoma patients who were treated with patient specific vaccines in the context of prospective clinical trials, by cohorts defined by stage and tumor measurability. **Methods:** Metastatic melanoma patients were treated with autologous dendritic cells loaded with antigens from irradiated cells from short-term autologous tumor cell lines (DCV). All patients had a metastatic melanoma lesion surgically resected, from which a tumor cell line was established. Irradiated tumor cells (ITC) were incubated with autologous dendritic cells (DC) to produce the DCV, which were injected s.c. in 500 micrograms GM-CSF weekly x 3 weeks, then monthly for 5 months. Data was pooled for DCV-treated patients enrolled in either of two phase II trials: one single-arm (NCT00948480), one randomized (NCT00436930). Patients were assigned to one of three cohorts based on their most advanced stage of disease prior to treatment, and whether they had measurable disease at the time of treatment. Survival was determined per Kaplan and Meier. **Results:** The final therapeutic products consisted of autologous DC with non-phagocytosed ITC making up 0% to 20% of cells in the final product. There were 45 men and 27 women. Median age was 52 years (range 17 to 83). Tumor sources were 37-lymph node, 20-viscera, and 15-soft tissue. No patients were lost to follow up; all surviving patients were followed 5 years. Toxicity was minimal. Median overall survival (OS) for all 72 patients was 49.4 mos; 5-year OS 46%. There was no correlation between survival and the number of DC or ITC in the first three injections. Patients with recurrent stage 3 disease that had not recurred (n=18) had a 72% 5-year OS; patients with non-measurable stage 4 (n=30) had a 53% 5-year OS. Patients with measurable stage 4 (n=18) had received an average of four prior therapies. They had a median OS of 18.5 months, and 2-year OS of 46%. **Conclusions:** This patient-specific DCV was associated with encouraging survival in all three clinical subsets. Because of its mechanism of action and absence of toxicity, it should be evaluated further. Clinical trial information: NCT00948480, NCT00436930.

2639 **Poster Session (Board #283), Sat, 8:00 AM-11:00 AM**

Preliminary results of a phase I clinical trial using an autologous dendritic cell cancer vaccine targeting HER2 in patients with metastatic cancer or operated high-risk bladder cancer (NCT01730118).

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Background: We developed a HER2 targeting autologous dendritic cell (DC) vaccine transduced with an adenovirus expressing the extracellular and transmembrane domains of HER2 (AdHER2). In mice, the homologous vaccine cured virtually all mice with established or metastatic tumors. Protection was dependent on antibodies against HER2 that inhibited phosphorylation, but was ADCC independent. We translated these findings into a clinical trial. **Methods:** This is an open-label, phase I study in patients with 1) metastatic cancer that progressed after ≥ 1 standard therapies, or 2) history of high risk bladder cancer with definitive treatment, whose tumor is HER2 immunohistochemistry (IHC) score ≥ 1+ or FISH HER2/CEP17 ratio ≥ 1.8. Part 1 of the study enrolled patients naïve to HER2-directed therapies and Part 2 enrolled patients who progressed with ≥ 1 anti-HER2 therapy. **Results:** In Part 1, the lowest dose level (5E+6 viable DCs, N=7, 2 inevaluable) showed no benefit. At the second and third dose level (10E+6 and 20E+6; N=7 and N=4; 0 and 1 inevaluable in each), 1 CR (ovarian), 1 PR (stomach), and 3 SD (1 ovarian carcinosarcoma and 2 colon) were observed. Two bladder cancer patients who received vaccine as an adjuvant did not recur for +24 and +36 month each. In Part 2 (N=6, 2 inevaluable), 1 male breast cancer patient showed SD. Response assessed by Modified Immune Related Response Criteria is summarized in the Table. Injection-site reactions occurred in all patients and were self-limited. Echo, EKG and troponin follow up to 2 years showed no cardiac toxicity. Dose-expansion cohort (40E+6) is enrolling. **Conclusions:** We have translated a cancer vaccine from mice to a clinical trial. Preliminary results of a phase I trial of an autologous AdHER2 DC vaccine show potential clinical benefit in select patients with HER2 expressing tumors with no cardiac toxicity. Clinical trial information: NCT01730118.

Part I						Part II		
10E+6			20E+6			20E+6		
Primary/HER2 IHC	Response	Duration (wk)	Primary/HER2 IHC	Response	Duration (wk)	Primary/HER2 IHC	Response	Duration (wk)
Colon/3	PD	-	Colon/1	PD	-	Breast/2	SD	24
Stomach/3	PR(-50%)*	16	Ovary/3	CR*	89**	Breast/3	PD	-
Colon/2	SD	16	Ovary/1	SD(-20%)	48	Breast/3	PD	-
Colon/1	SD	16				Breast/3	PD	-
Ovary/2	PD	-						
Colon/3	PD	-						
Ovary/2	PD	-						

* Peptide array showed antibody response > x3 against HER2 peptides in select responders. ** Recurred with HER2 IHC 0 in a metastatic lesion suggesting immune escape.

2640 **Poster Session (Board #284), Sat, 8:00 AM-11:00 AM**

Phase I trial of a modified vaccinia ankara (MVA) priming vaccine followed by a fowlpox virus (FPV) boosting vaccine modified to express brachyury and costimulatory molecules in advanced solid tumors.

Julie Marie Collins, Renee Nicole Donahue, Yo-Ting Tsai, Claudia Palena, Jennifer L. Marte, Ravi Amrit Madan, Fatima Karzai, Christopher Ryan Heery, Julius Strauss, Margaret Elena Gatti-Mays, Lisa M. Cordes, Jeffrey Schlom, James L. Gulley, Marijo Bilusic; National Cancer Institute, Bethesda, MD; Laboratory of Tumor Immunology and Biology, National Cancer Institute at the National Institutes of Health, Bethesda, MD; Laboratory of Tumor Immunology and Biology, National Cancer Institute, Bethesda, MD; National Cancer Institute at the National Institutes of Health, Bethesda, MD; Bavarian Nordic, Inc., Morrisville, NC; Georgetown Univ Hosp, Bethesda, MD; National Institutes of Health, Bethesda, MD; The National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Brachyury, a transcription factor, plays an integral role in epithelial-to-mesenchymal transition, metastasis, poor prognosis, and resistance to chemotherapy. It is expressed in many tumor types, and rare in normal tissue, making it an ideal immunologic target. BN-Brachyury comprises heterologous vaccination with recombinant MVA priming followed by FPV boosting, each encoding transgenes for brachyury and three costimulatory molecules (B7-1, ICAM1, and LFA-3). Heterologous prime boost approach is intended to optimize immunogenicity, as previously observed. **Methods:** Pts with metastatic solid tumors were treated with 2 monthly doses of MVA-brachyury SC at the previously tested dose, 2.2×10^9 infectious units (IU), followed by FPV-brachyury SC, 1×10^9 IU, for 6 monthly doses and then every 3 months for up to 2 years. The primary objective was to determine safety and tolerability and establish the RP2D. Immune assays were conducted to evaluate immunogenicity. **Results:** In 10 pts (3 chordoma, 6 GI, 1 papillary thyroid), no dose-limiting toxicities or serious treatment-related adverse events (TRAEs) were observed. The only Grade 3 TRAE was sedation associated with fever, which resolved spontaneously and did not recur with subsequent cycles. All other TRAEs were Grade 1 or 2; the most common was injection-site reaction in all patients. Five pts have had stable disease for $>$ 24 wks (per RECIST v1.1) and remain on treatment. One pt with chordoma, for which BN-Brachyury was granted orphan drug designation, has had a 13.2% reduction in tumor size. As previously demonstrated, brachyury-specific T cell responses were observed, as were responses against cascade antigens (non-encoded antigens) CEA and MUC-1. **Conclusions:** Heterologous MVA- and FPV-brachyury is well tolerated and induced immune responses to brachyury and cascade antigens, suggesting induction of immunologically relevant tumor cell destruction. These data have informed combining BN-Brachyury with checkpoint inhibition (NCT03493945) and radiation (NCT03595228) to evaluate potential for synergetic activity in selected populations. Clinical trial information: NCT03349983.

2641 **Poster Session (Board #285), Sat, 8:00 AM-11:00 AM**

A phase I study (EO11-MEL) of a TriMix-based mRNA immunotherapy (ECI-006) in resected melanoma patients: Analysis of safety and immunogenicity.

ANA Maria Arance Fernandez, Jean-Francois Baurain, Christof Vulsteke, Annemie Rutten, Ainara Soria, Javier Carrasco, Bart Neyns, Brenda De Keersmaecker, Tim Van Assche, Bertil Lindmark; Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Barcelona, Spain; Department of Medical Oncology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Bruxelles, Belgium; Integrated Cancer Center Ghent, Department of Oncology and Hematology, AZ Maria Middelares, Ghent, Belgium; Department of Oncology - GZA Sint-Augustinus, Antwerpen, Belgium; Hospital Universitario Ramón y Cajal, Madrid, Spain; Grand Hôpital de Charleroi (GHdC), Charleroi, Belgium; Universitair Ziekenhuis Brussel, Brussels, Belgium; eTheRNA immunotherapies NV, Niel, Belgium

Background: ECI-006 is a combination of TriMix (mRNAs encoding for dendritic cell [DC] activating molecules [CD40L, CD70 and caTLR4]), and mRNAs encoding for melanoma-specific tumor-associated antigens (TAAs): tyrosinase, gp100, MAGE-A3, MAGE-C2, and PRAME. DCs transfected *ex vivo* with TriMix and TAAs mRNAs showed significant clinical activity in combination with ipilimumab in metastatic melanoma without increasing toxicity. This study aims to assess the safety and immunogenicity of ECI-006 vaccine administered intranodally (i.n.) in an adjuvant setting for patients with resected melanoma. **Methods:** Twenty patients who underwent resection of stage IIc/III/IV cutaneous melanoma received 5 administrations of ECI-006 (either 600 μg or 1800 μg [n = 10, each]) injected i.n. on Day 1 and after 2, 4, 6 and 14 weeks. Treatment-emergent adverse events (TEAEs) were graded using CTCAE version 4.0.3. Blood samples for immune monitoring (ELISPOT and intracellular cytokine staining [ICS]) were collected pre-dose and at weeks 4, 7, 14 and 15. **Results:** Nineteen patients completed the treatment. One patient in the low dose group discontinued the study after 4 doses due to disease relapse. Administration of ECI-006 was well tolerated. No serious adverse events or TEAEs Grade 3 or higher were reported. Of all TEAEs, myalgia and fatigue were the most reported in 3 (15%) and 5 (25%) patients, respectively. ELISPOT and ICS were performed on T cells pre-stimulated *in vitro* for 10-12 days, using a previously in-house validated protocol. Vaccine-induced immune responses according to predefined criteria were detected in 4/10 and 3/9 patients treated with the low and high dose, respectively. Samples from these patients are currently being subjected to T-cell receptor repertoire analysis. **Conclusions:** Among patients undergoing resection of stage IIc/III/IV melanoma, i.n. administration of ECI-006 at 600 or 1800 μg was generally well tolerated. ECI-006 demonstrated to be immunogenic in a proportion of patients. These results warrant further development of ECI-006 in combination with anti-PD-1 therapy in melanoma patients. Clinical trial information: NCT03394937.

2642 **Poster Session (Board #286), Sat, 8:00 AM-11:00 AM**

Final results of a phase I study evaluating INVAC-1, a novel DNA vaccine expressing an inactive form of human telomerase reverse transcriptase (hTERT) in patients with advanced solid tumors.

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Background: INVAC-1 is an optimized DNA plasmid encoding an inactive form of human Telomerase Reverse Transcriptase (hTERT), a universal tumor antigen expressed in most of human tumors with little or no expression in somatic cells. We report here the final results of a First-In-Human Phase I study evaluating INVAC-1 as a single agent in patients (pts) with advanced solid tumors, ended in June 2018. **Methods:** A two center Phase I trial evaluated INVAC-1 given monthly for a minimum of 3 cycles and up to 9 cycles by intradermal injection followed by electroporation (n = 20) or using a needle-free injection system (n = 6). Primary objectives included safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose and recommended phase 2 dose. Secondary objectives included immune response (assessed by IFN-γ Elispot) and anti-tumor activity. Immuno-monitoring included detection of autoantibodies, lymphocyte phenotyping and inflammatory cytokine levels in blood. Anti-tumor activity was evaluated through RECIST 1.1 adapted to immune response, and plasma circulating tumor DNA (ctDNA). **Results:** 26 pts with refractory/progressive tumors were enrolled and treated with 3 escalating doses of 100, 400 and 800 μg. 15 pts experienced stable disease according to RECIST. For 11 of them, the treatment was extended, up to 9 months. INVAC-1 was well tolerated with no dose-limiting toxicities. No significant biological signs of autoimmunity were observed. No significant modification in inflammatory plasma cytokines levels was observed after INVAC-1 administration. INVAC-1 triggered *de novo* or enhanced pre-existing CD4/CD8 specific anti-hTERT response in 63% of pts. This specific anti-hTERT immune response was enhanced *ex vivo* by adding the immune checkpoint inhibitor nivolumab. ctDNA was evaluated in 17 pts. We observed a ctDNA decrease in 6 cases, a stable level in 5 cases and an increase in 6 cases. **Conclusions:** Results indicate that INVAC-1 was well tolerated and immunogenic at the doses and schedule tested. Disease stabilization was obtained for the majority of pts (58%) according to RECIST criteria or ctDNA levels. Clinical trial information: NCT02301754.

2643 **Poster Session (Board #287), Sat, 8:00 AM-11:00 AM**

Immunogenicity and tolerability of personalized mRNA vaccine mRNA-4650 encoding defined neoantigens expressed by the autologous cancer.

Gal Cafri, Jared J. Gartner, Kristen Hopson, Robert S. Meehan, Tal Z. Zaks, Paul Robbins, Steven A. Rosenberg; National Cancer Institute Surgery Branch, Bethesda, MD; National Cancer Institute at the National Institutes of Health, Bethesda, MD; Moderna, Cambridge, MA; Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD; Sanofi US, Cambridge, MA; National Cancer Institute Center for Cancer Research, Bethesda, MD

Background: Therapeutic vaccination against cancer has proven very challenging with little clinical benefit. Vaccines against non-viral tumors have mainly targeted differentiation antigens, cancer testis antigens, and over-expressed antigens. However, negative selection in the thymus against these normal non-mutated antigens severely limits the ability to generate high avidity anti-cancer T-cells. The importance of neoantigens to each patient's unique cancer as targets for immunotherapy has been extensively studied, by our group and others. It is now clear that neoantigen-specific T-cells are present in most cancers and these neoantigens derived from somatic mutations offer a specific and highly immunogenic target for personalized vaccination. We developed a process to identify immunogenic T-cell epitopes derived from tumor-specific mutations using tumor-infiltrating lymphocytes. **Methods:** We combined, for the first time, validated defined neoantigens, predicted neoepitopes and mutations in driver genes into a single mRNA concatemer (mRNA-4650) to vaccinate patients with metastatic common epithelial cancers. We are conducting a phase I/II trial in patients with metastatic melanoma, gastrointestinal, or genitourinary cancers with at least one lesion that is resectable. Patients must have an ECOG status of ≤ 1 with adequate organ and bone marrow function. Patients are vaccinated intramuscularly at two-week intervals for four cycles, and dosing may be repeated for a second course of vaccination. Key primary endpoints are safety, tolerability and the development of T-cell reactivity as well as objective response rate. **Results:** mRNA-4650 is safe at all dose levels studied to date with no reported DLTs or drug related SAEs. Neoantigen specific CD8 and CD4 T cells responses against neoepitopes included in the vaccine have been observed and no tumor regressions were seen. **Conclusions:** Our data show that such a personalized mRNA vaccination is feasible and can elicit neoantigen specific T cell responses. Combination of vaccines with checkpoint inhibitors or adoptive T cell therapy can open the possibility to develop effective immunotherapies for patients with the common epithelial cancers. Clinical trial information: NCT03480152.

TPS2644 **Poster Session (Board #288a), Sat, 8:00 AM-11:00 AM**

A first-in-human study of KY1044, a fully human anti-ICOS IgG1 antibody as monotherapy and in combination with atezolizumab in patients with selected advanced malignancies.

Sonia Quaratino, Richard Sainson, Anil Thotakura, Simon J Henderson, Kerstin Pryke, Anthea Newton, Nuala Brennan, Elisabeth Oelmann; Kymab Ltd, Cambridge, United Kingdom

Background: The Inducible T-cell costimulator (ICOS/CD278) is related to the CD28 superfamily and is induced upon T cell activation. There is a hierarchical order of ICOS expression level, in which highly immunosuppressive TReg ($CD4^{+}Foxp3^{+}$) present in the tumor microenvironment (TME) are at the top level of expression and CD8 T_{Eff} cells are at the bottom level. In addition, ICOS expression on T_{Regs} is higher in the TME than in the blood or spleen. **Methods:** KY1044, a fully human anti-ICOS IgG1 kappa monoclonal antibody, selectively binds to ICOS with high affinity (which is maintained at intratumoral acidic pH) and has a dual mechanism of action: it promotes the preferential depletion of intratumoral $ICOS^{High}$ T_{Regs} resulting in an increase in the T_{Eff}:T_{Reg} ratio in the TME; and it stimulates $ICOS^{Low}$ T_{Eff} cells. Preclinical data demonstrate that KY1044 monotherapy or in combination with anti-PD-L1 is associated with immune cell activation and anti-tumor response. In order to validate the dual mechanism of action *in vivo*, studies in mice and cynomolgus monkeys were conducted. Firstly, KY1044 injected i.v. at doses up to 100 mg/kg weekly were well tolerated in non-human primates. In addition, pharmacodynamic studies in mice and cynomolgus monkey confirm preferential depletion of $ICOS^{High}$ cells. KY1044-CT01 is an open-labelled first in human Phase I/II study assessing the safety, tolerability, PK, PD and anti-tumor activity of KY1044 administered every 3 weeks (Q3W) as an i.v. single agent infusion and in combination with atezolizumab (1200 mg, Q3W IV) in adult patients with advanced/metastatic malignancies. The primary endpoint of the Phase I dose escalations, designed as sequential but overlapping arms of KY1044 monotherapy and combination with atezolizumab, is safety and tolerability. Secondary endpoints are the characterization of pharmacokinetic, pharmacodynamic and efficacy profiles in all patients. In the Phase II part, the primary endpoint is overall response rate (ORR), and the measure of clinical efficacy will be confirmed as per RECIST 1.1. and immune-related (ir)RECIST. An intensive biomarker plan is integral to the study design to underpin the phenotypic and molecular changes in both peripheral blood and tumor. Clinical trial information: NCT03829501.

TPS2645 **Poster Session (Board #288b), Sat, 8:00 AM-11:00 AM**

Phase 1 with expansion cohorts in a study of NEO-201 in adults with chemo-resistant solid tumors.

Maria Pia Morelli, Justin M. David, Nicole D. Houston, Stan Lipkowitz, Jung-min Lee, Alexandra Dos Santos Zimmer, Farah Z. Zia, Irene Ekwede, Erin Nichols, Mira Pavelova, Rebecca Trupp, Stephen M. Hewitt, Massimo Fantini, Philip M. Arlen, Kwong Y. Tsang, Christina M. Annunziata; NCI, Bethesda, MD; National Institutes of Health, Bethesda, MD; Women's Malignancies Branch, National Cancer Institute, Bethesda, MD; National Cancer Institute, Bethesda, MD; National Cancer Institute Women's Malignancies Branch, Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; Natl Cancer Inst, Bethesda, MD; Frederick National Laboratory for Cancer Research, Frederick, MD; NIH/NCI, Gaithersburg, MD; Laboratory of Pathology, CCR, NCI, NIH, Bethesda, MD; Precision Biologics, Inc., Rockville, MD; Precision Biologics, Rockville, MD

Background: NEO-201 is a novel humanized IgG1 monoclonal antibody (mAb) generated against the Hollinshead allogenic colorectal cancer vaccine platform. Briefly, tumor-associated antigens (TAA) derived from tumor membrane fractions pooled from colorectal cancer surgical specimens were screened for delayed-type hypersensitivity and evaluated in clinical trials. The original vaccine was used to generate monoclonal antibodies, one of which is NEO-201. In preclinical data generated in our laboratory, we have demonstrated that NEO-201 exert anti-tumor activity by natural killer (NK)-mediated antibody-dependent cytotoxicity (ADCC) against several tumor type including colorectal and pancreatic cancer models (Fantini, et al. 2018). We have identified NEO-201 antigen as a glycosylated form of CEACAM-5 and -6, which is expressed by tumor tissue but is not present in the surrounding healthy tissue (David, et al. 2018). This could result in a specific anti-tumor activity without significant normal tissue toxicity. Nevertheless, toxicity was further assessed in non-human primates and transient neutropenia was the only adverse event observed. Based on this data we designed a first in human phase I trial to evaluate the safety, maximum-tolerated dose (MTD), pharmacokinetics (PK) and pharmacodynamics (PD) of the humanized monoclonal antibody NEO-201. **Methods:** This is a first-in-human phase 1 study with expansion cohort to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of NEO-201 in adults with advanced solid tumors that have high likelihood pof expression NEO201 antigen and have progressed to standard of treatments and have a PS0-2 ECOG. Study design is a classic Fibonacci (3+3) dose escalation, with a cohort expansion at the MTD. NEO-201 is administered intravenously every two weeks, and four different dose levels will be explored (DL1 = 1mg/kg, DL2 = 2mg/kg, DL3 = 4mg/kg and DL4 = 6mg/kg). No intra-patient dose escalation is allowed. Patients will be evaluated for safety every two weeks, with weekly laboratory testing, according to CTCAEv4.0. and with a DLT window of 28 days (cycle 1). Response will be assessed every 8 weeks (2 cycles of treatment) according to RECISTv1.1. Additionally, biological samples will be collected to understand NEO-201 pharmacokinetic, the effect on the immune process and their correlation with treatment toxicity and response. As of February 2019 we have completed enrollment in the first DL and are evaluating for DLT. Clinical trial information: NCT03476681.

TPS2646 **Poster Session (Board #289a), Sat, 8:00 AM-11:00 AM**

A phase I/Ib multicenter study to evaluate the humanized anti-CD73 antibody, CPI-006, as a single agent, in combination with CPI-444, and in combination with pembrolizumab in adult patients with advanced cancers.

Mehrdad Mobasher, Richard A. Miller, Long Kwei, Deborah Strahs, Vaijayanti Das, Gabriel Luciano, John D. Powderly, Jaime R. Merchan, Minal A. Barve, Patricia LoRusso, Abhishek Tripathi, Jason J. Luke; Corvus Pharmaceuticals Inc, Burlingame, CA; Carolina BioOncology Institute, Huntersville, NC; University of Miami, Miami, FL; Mary Crowley Cancer Research Center, Dallas, TX; Yale University School of Medicine, Yale Cancer Center, New Haven, CT; University of Oklahoma, Stephenson Cancer Center, Oklahoma City, OK; University of Chicago Comprehensive Cancer Center, Chicago, IL

Background: CD73 expression is elevated in tumors and contributes to increasing levels of immunosuppressive adenosine in the tumor microenvironment. CD73 knockout mice exhibit reduced tumor growth and resistance to experimental metastasis. Inhibition of CD73 activity with an anti-CD73 antibody blocks adenosine production, shown to inhibit tumor growth in syngeneic models. CPI-006 is a humanized IgG1 FcγR binding-deficient anti-CD73 antibody now being investigated in this Phase 1/1b multicenter, open label trial as single agent (SA) or combination with CPI-444, an oral, small molecule, selective A2aR antagonist or in combination with pembrolizumab, an anti-PD1 indicated for the treatment of patients across a number of malignancies (NCT03454451). **Methods:** Up to 462 subjects will be enrolled at approximately 35 sites in the US, Canada and Australia. Eligible patients must have: non-small cell lung, renal cell carcinoma, urothelial bladder, cervical, colorectal, ovarian, pancreatic, prostate, head and neck, triple-negative breast, endometrial, select sarcomas and non-Hodgkin lymphoma malignancies relapsed, refractory or intolerant to 1 to 5 standard therapies; aged $\geq$ 18 yo; adequate organ function and measurable disease. The objectives of the study are 1) evaluate the safety and tolerability of SA CPI-006, in combination with CPI-444 and in combination with pembrolizumab, 2) evaluate the pharmacokinetics of each regimen and 3) identify potential biomarker signals predictive of response. Study design in table. Study Design. Clinical trial information: NCT03454451.

Dose escalation.								
3+ 3 Design: 1, 3, 6, 12, 18, 24 mg/kg								
CPI-006 SA			CPI-006 + CPI-444			CPI-006 + pembrolizumab		
Dose Expansion Stage 1 (N=11 per cohort)								
CPI-006 SA			CPI-006 + CPI-444			CPI-006 + pembrolizumab		
NSCLC	RCC	Others	NSCLC	RCC	Others	NSCLC	RCC	Others
If 1 or more responses observed in a disease cohort, proceed to Stage 2								
Dose Expansion Stage 2 (N=17 per cohort)								

TPS2647 **Poster Session (Board #289b), Sat, 8:00 AM-11:00 AM**

A phase I clinical trial using armored GPC3 CAR T cells for children with relapsed/ refractory liver tumors.

David Henry Michael Steffin, Sai A Batra, Purva Rathi, Linjie Guo, Wenpeng Li, Amy N Courtney, Leonid S Metelitsa, Andras Heczey; Baylor College of Medicine, Houston, TX

Background: CAR T therapies have been successful against hematologic malignancies, but have benefited only a handful of patients with solid cancers. Glypican 3 (GPC3) is an attractive immunotherapeutic target due to its preferential expression on multiple pediatric and adult solid cancers and lack of expression on non-malignant tissues. GPC3-CAR T cells were tested preclinically and inclusion of the 4-1BB costimulatory endodomain with IL-15 and IL-21 co-expression enabled CAR T cells to expand and persist the most *in vitro* and *in vivo* and led to robust antitumor activity *in vivo*. We are now testing GPC3-CAR T cells with IL15 and IL-21 for the first time in children with relapsed/refractory liver tumors. **Methods:** In this Phase 1 trial (GAP, NCT02932956), we are evaluating patients in 3 cohorts: 1) GPC3-CAR alone; 2) GPC3-CAR and IL-15; 3) GPC3-CAR with IL-15 and IL-21. We will 1) define the safety and establish the Recommended Phase 2 Dose (RP2D) of GPC3-CAR T cells co-expressing IL-15 and IL-21; 2) determine persistence and anti-tumor activity of GPC3-CAR T cells; 3) examine changes in gene and protein expression in the tumor microenvironment associated with potential immune escape mechanisms. Inclusion criteria are the following: age $\leq$18; histology proven, GPC3-positive tumor; life expectancy$>$12 weeks; Child-Pugh-Turcotte score$<$7; serum AST$<$5 times ULN; total bilirubin$<$3 times ULN for age; INR $\leq$1.7; absolute neutrophil count$>$500/μl; platelet count$>$20,000/μl; Hgb$\geq$9.0 g/dl. Toxicity will be monitored using the Common Terminology Criteria of Adverse Events v4. The RP2D will be determined by the standard 3+3 dose escalation method using 5 dose levels. Persistence will be quantified using RT-PCR and flow cytometry. Antitumor activity will be defined by 3D imaging using RECIST 1.1 criteria and the immune-related response criteria. Immune-escape will be examined using single cell RNA sequencing and imaging of paraffin-embedded tissues using codetection by indexing to evaluate candidate proteins. Data will be analyzed via descriptive statistics. Cohort 1 of this study is now open for enrollment. Clinical trial information: NCT02932956.

TPS2648 **Poster Session (Board #290a), Sat, 8:00 AM-11:00 AM**

A phase II study of autologous tumor infiltrating lymphocytes (TIL, LN-144/LN-145) in patients with solid tumors.

Jason Alan Chesney, Jose Lutzky, Sajeve Samuel Thomas, Jorge J. Nieva, Eva Munoz Couselo, Juan Martin-Liberal, Juan Francisco Rodriguez-Moreno, Alex Cacovean, Huiling Li, Maria Fardis, Scott N. Gettinger; James Graham Brown Cancer Center, University of Louisville, Louisville, KY; Mount Sinai Medical Center, Miami Beach, FL; University of Florida Health Cancer Center, Windermere, FL; University of Southern California, Los Angeles, CA; Hospital Universitario Vall d'Hebron–PPDS, Barcelona, Spain; ICO Hospitalet, Hospital Duran i Reynals, Barcelona, Spain; Hospital Universitario HM Sanchinarro–CIOCC, Madrid, Spain; Iovance Biotherapeutics, Inc., San Carlos, CA; Yale Cancer Center, New Haven, CT

Background: Adoptive cell therapy (ACT) with tumor infiltrating lymphocytes (TIL) has demonstrated durable complete responses in immunogenic tumors with high mutational burden in metastatic melanoma patients who had not received prior immune checkpoint inhibitors (ICI); CR rate 24%. Pembrolizumab is an approved agent for the treatment of metastatic melanoma and head & neck cancers, among others. Further, ICI have been reported to potentially enhance the efficacy of TIL therapy. One aim of this study is to improve the efficacy response for early line patients by combining TIL with anti-PD-1 in ICI-naïve patients with metastatic melanoma (Cohort 1) and head & neck cancers (Cohorts 2). In Cohort 3, TIL therapy alone is offered to NSCLC patients who have received prior systemic therapy, including ICI. **Methods:** IOV-COM-202 is a prospective, Phase 2 multicenter, open-label study in which 36 patients (12 per cohort) are to be enrolled in one of three cohorts; Cohorts 1 and 2: TIL therapy in combination with pembrolizumab, or Cohort 3: TIL therapy alone. Patients will have tumors resected at local centers and shipped to a central GMP facility to undergo a 22-day manufacturing process that yields cryopreserved infusion product (LN-144/LN-145) that is shipped back to treating center. All patients receive TIL therapy consisting of 1 week of preconditioning cyclophosphamide/fludarabine, followed by a single infusion of LN-144/LN-145 (Day 0) and up to 6 doses of IL-2 (600,000 IU/kg). Patients in Cohorts 1 and 2 also receive pembrolizumab on Day -1 and then Q3W for up to 2 years or until disease progression or acceptable toxicity. Co-primary endpoints for each cohort are objective response rate (ORR) per RECIST 1.1, and safety (grade $\geq$ 3 TEAE). Eligibility criteria: Cohorts 1 (melanoma) and 2 (head & neck): patients must not have received prior ICI (eg, anti-PD-1, anti-CTLA-4) and may have received up to 3 lines of prior systemic therapy, Cohort 3 (NSCLC): patients must have received 1-3 prior lines of systemic therapy including ICI. After tumor resection for TIL manufacturing, patients must have additional measurable disease for assessment per RECIST 1.1. Adequate bone marrow/organ function and ECOG PS of 0 or 1 is required. Clinical trial information: NCT03645928.

TPS2649 **Poster Session (Board #290b), Sat, 8:00 AM-11:00 AM**

Intravenous administration of ALKS 4230 as monotherapy and in combination with pembrolizumab in a phase I study of patients with advanced solid tumors.

Ulka N. Vaishampayan, Mayer N. Fishman, Daniel C. Cho, Christopher J. Hoimes, Vamsidhar Velcheti, David F. McDermott, William J. Slichenmyer, Emily Putiri, Heather Losey, Sean Rossi, Marc S. Ernstoff; Wayne State University, Detroit, MI; Moffitt Cancer Center, Tampa, FL; New York University Langone Hospitals, New York, NY; Case Western Reserve University, Cleveland, OH; Beth Israel Deaconess Medical Center, Boston, MA; Alkermes, Inc, Waltham, MA; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: ALKS 4230 is a fusion protein of circularly permuted IL-2 and IL-2 Receptor (IL-2R) α designed to selectively bind the intermediate-affinity (ia) IL-2R, comprised of IL-2Rβ and γ_c, for activation of $CD8^+$ T cells and NK cells, which drive antitumor immune responses. In contrast, unmodified IL-2 activates high-affinity (ha) IL-2R, driving the expansion of immunosuppressive $CD4^+$ regulatory T cells (T_{regs}) at concentrations below those that activate iaIL-2R expressing cells. Binding of IL-2 to haIL-2R on endothelial cells may contribute to capillary leak syndrome seen with high-dose IL-2. Thus, selective activation of the iaIL-2R by ALKS 4230 has the potential to enhance tumor killing and improve tolerability. ALKS 4230 has previously been shown to improve antitumor activity relative to IL-2 in murine models. In this clinical study, ALKS 4230 will be assessed as monotherapy and in combination with anti-PD-1 therapy. **Methods:** ALKS 4230 is being studied in adults with advanced solid tumors in a phase I first-in-human trial designed primarily to assess the safety of ALKS 4230 alone and with pembrolizumab. The study will also determine a monotherapy recommended phase 2 dose (RP2D) and characterize pharmacokinetics, pharmacodynamics (PD), immunogenicity, and evidence of anti-tumor activity. It will be conducted in 3 parts: monotherapy dose escalation (Part A), monotherapy dose expansion at the RP2D (Part B), and combination therapy with pembrolizumab (Part C). ALKS 4230 is administered as a 30 minute IV infusion once daily for five days in each 14 or 21 day cycle. Part A is inpatient. Eligibility requires ECOG PS 0-1 and adequate bone marrow, liver and kidney function. Part B will enroll 21 patients each in renal cell carcinoma and melanoma cohorts. Part C will enroll up to 79 patients total into 3 cohorts based on tumor type and prior anti-PD-1 therapy; a 4th cohort will enroll patients from Part A or B who received at least 4 cycles of ALKS 4230 or experienced disease progression on monotherapy. The primary PD endpoint is change from baseline in $CD8^+$ T, NK, and T_{reg} cell counts. Inflammatory cytokine levels will also be measured. Parts A and C are currently enrolling. Clinical trial information: NCT02799095.

TPS2650 **Poster Session (Board #291a), Sat, 8:00 AM-11:00 AM**

Adoptive transfer of tumor-infiltrating lymphocytes in patients with sarcomas, ovarian, and pancreatic cancers.

Rodabe Navroze Amaria, Chantale Bernatchez, Marie-Andree Forget, Cara L. Haymaker, Anthony Paul Conley, J. Andrew Livingston, Gauri Rajani Varadhachary, Milind M. Javle, Anirban Maitra, Ching-Wei David Tzeng, Emily Hinchcliff, Virginia Bayer, Yvonne Gasior, Tyler Hilton, Joseph Celestino, Kelly M Rangel, Ying Yuan, Karen H. Lu, Patrick Hwu, Amir A. Jazaeri; The University of Texas - MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX

Background: Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has a long history of efficacy in metastatic melanoma, and is being increasingly considered across other solid tumors. Preclinical data generated at MD Anderson Cancer Center has demonstrated the ability to grow TIL from a variety of tumor types including various types of sarcomas, ovarian and pancreas cancers. We are testing the efficacy of TIL across multiple tumor types using two different manufacturing protocols. **Methods:** We are conducting two ongoing investigator initiated basket TIL therapy trials. The first (NCT03449108) includes cohorts with poorly differentiated soft tissue and bone sarcomas, osteosarcoma, and platinum resistant ovarian cancer. The TIL product used in this trial is an investigational cell product (LN-145, Iovance Biotherapeutics, Inc.). The second trial (NCT03610490) includes cohorts of osteosarcoma, platinum resistant ovarian cancer, and pancreatic cancer (who have progressed on, or received maximal benefit from, front-line therapy). For this trial, TIL are manufactured at MD Anderson Cancer Center using a protocol that includes the use of urelumab (an agonistic anti-CD137 antibody) combined with T cell receptor activation during TIL expansion. In both trials eligible subjects undergo tumor harvest using a surgical excisional biopsy of the tumor for TIL manufacturing, receive a modified cyclophosphamide and fludarabaine lymphodepletion regimen and up to six doses of IL-2 (600,000 IU/kg) following TIL infusion. No intervening therapy is allowed between tumor harvest and initiation of lymphodepletion. The primary endpoint for each cohort is ORR as assessed by investigators using RECIST 1.1 criteria. The Simon's two stage design is used to monitor the efficacy of each cohort independently. In the first stage, 10 patients will be treated per cohort. If there is no confirmed response in these 10 evaluable patients, the cohort will be terminated. If the cohort moves forward to Stage II, an additional 8 patients will be treated leading to a total of 18 patients. Three or more responders out of 18 treated patients for the cohort will be considered clinically relevant to justify further investigation. Enrollment is ongoing in all cohorts in both trials. An accrual update will be provided at the annual meeting. Clinical trial information: NCT03449108, NCT03610490.

TPS2651 **Poster Session (Board #291b), Sat, 8:00 AM-11:00 AM**

The "INSIGHT" Trial: Two new strata of an explorative, open-labeled phase I study evaluating the feasibility and safety of subcutaneous IMP321 injections (LAG-3Ig fusion protein, eftilagimod alpha) combined with either standard-of-care drug therapy or PD-L1 inhibition (avelumab) in advanced-stage solid tumor entities.

Daniel Wilhelm Mueller, Thorsten Oliver Goetze, Akin Atmaca, Mohammad-Reza Rafiyan, Eckhart Weidmann, Christian H. Brandts, Urs Pabst-Giger, Markus Duex, Thomas Werner Kraus, Simon Stahn, Regina Eickhoff, Salah-Eddin Al-Batran; University Cancer Center Frankfurt, Institut für Klinisch-Onkologische Forschung and IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest, Frankfurt, Germany; Department of Hematology and Oncology, Institute of Clinical Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany; Krankenhaus Nordwest, Frankfurt, Germany; Universitätsklinikum Frankfurt, Frankfurt, Germany; Universitätsklinikum Muenster, Muenster, Germany; Krankenhaus Nordwest GmbH, Allgemein-, Viszeral- und Minimal Invasive Chirurgie, Frankfurt Am Main, Germany; IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest, Frankfurt, Germany

Background: The two new strata of the INSIGHT trial evaluate feasibility and safety of s.c. injections of IMP321 (eftilagimod alpha) in combination with either SOC first/second-line drug therapy (Stratum C) or in combination with an PD-L1 inhibitor (avelumab; Stratum D) in 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 combinations of active immunotherapy using IMP321 with SOC drug therapies or immunotherapies targeting the PD-1/PD-L1 axis in various solid tumor entities. IMP321 is a MHC class II agonist that activates antigen-presenting cells (primary target cells) and then CD8 T cells (secondary target cells). Activation of the dendritic cell network and subsequent T cell recruitment at the tumor site with IMP321 may lead to enhanced anti-tumor CD8 T cell responses. Thus, especially combinations with PD-1/PD-L1 inhibitors might display interesting effects by activating immune cells and disabling immune inhibitory mechanisms at the same time. **Methods:** This is a prospective investigator initiated phase I trial consisting of four strata. New stratum C: Patients with solid tumors treated with SOC chemo- or targeted therapy in first or second line receive concomitant s.c. IMP321 injections. This combination is aimed to enhance the immune response against tumor cells compared to chemo-/targeted SOC therapy alone. New stratum D: Patients will receive avelumab i.v. q2w along with s.c. IMP321 injections. This combination is aimed to enhance efficacy by combining IMP321's activating effects on immune cells with the release of immune inhibitory effects caused by interruption of the PD-1/PD-L1 axis. It is planned to enroll 20 patients in Stratum C and 12 patients in stratum D. Main efficacy endpoint is the overall response rate (RECIST 1.1). Overall recruitment has started; currently (Feb 2019) 14 patients have been enrolled. EudraCT: 2016-002309-20. Clinical trial information: NCT03252938.

TPS2652 **Poster Session (Board #292a), Sat, 8:00 AM-11:00 AM**

A first-in-human phase I study of FS118, an anti-LAG-3/PD-L1 bispecific antibody in patients with solid tumors that have progressed on prior PD-1/PD-L1 therapy.

Timothy A Yap, Kyriakos P. Papadopoulos, Patricia LoRusso, Deborah J.L. Wong, Siwen Hu-Lieskovan, Josefin-Beate Holz, FS118-17101 Study Team; The University of Texas MD Anderson Cancer Center, Houston, TX; South Texas Accelerated Research Therapeutics, San Antonio, TX; Yale University School of Medicine, Yale Cancer Center, New Haven, CT; Department of Medicine, University of California Los Angeles, Los Angeles, CA; University of California, Los Angeles, Los Angeles, CA; F-Star Biotechnology Ltd., Cambridge, United Kingdom

Background:PD-1/PD-L1 checkpoint inhibitors demonstrated remarkable anti-tumor activity, but only a minority of patients achieve full clinical benefit with deep and durable responses. Translational studies suggest resistance to cancer immunotherapy can be mediated by additional immune checkpoints e.g. lymphocyte-activation gene 3 (LAG-3). The combination of LAG-3 and PD-1 mAbs synergistically improved anti-tumor response in murine models and early clinical trials. In a small cohort, TIL LAG-3 expression enriched for responsiveness in PD-1/PD-L1 relapsed/refractory patients. FS118 is a novel bispecific antibody incorporating a LAG-3 binding Fc-region into a PD-L1-specific IgG1 antibody to potentially deliver superior anti-tumor efficacy while limiting immunotherapy-related adverse effects by dual targeting. **Methods:** The FiH study (NCT03440437) is being conducted in adult patients with solid tumors who failed prior PD-1/PD-L1 treatment. Primary objectives of the study are to determine safety, PK and the maximum tolerated/recommended Phase 2 dose of FS118. Secondary objectives include preliminary evidence of efficacy, immunogenicity, PD profile and exposure/response correlation. 50 subjects from four study sites in the USA are planned to enrol in dose escalation initiated with accelerated titration (5 single subject cohorts) followed by 3+3 design and expansion cohorts. FS118 is administered weekly IV in 21-day treatment cycles until progression, unacceptable toxicity, withdrawal, or death. Patients are followed for safety, overall survival and initiation of subsequent therapy. DLT clearance, dose escalation and cohort expansion (to further characterise safety, PK/PD or clinical efficacy) are supervised by a safety review committee (SRC). Translational studies assess PD-L1/LAG-3 receptor occupancy, soluble PD-L1/LAG-3 levels and the correlation of FS118 exposure with selected PD markers of target engagement and response. Translational endpoints include TIL analysis, transcriptomic profiles and target expression analyses on tumor tissues. Cohorts 1 through 6 have been completed, enrollment in cohort 7 began December 2018. Clinical trial information: NCT03440437.

TPS2653 **Poster Session (Board #292b), Sat, 8:00 AM-11:00 AM**

A first-in-human, multicenter, open label, phase I study in patients with advanced and/or refractory solid malignancies to evaluate the safety of intravenously administered ATOR-1015.

Jeffrey Yachnin, Gustav J Ullenhag, Ana Carneiro, Dorte Nielsen, Kristoffer Staal Rohrberg, Anne Månsson Kvarnhammar, Anna Dahlman, Erika Bågeman, Camilla Wennersten, Charlotte Astrid Russell; Karolinska Institutet, Stockholm, Sweden; Akademiska Sjukhus, Uppsala, Sweden; Lund University Hospital and Lund University, Lund, Sweden; Department of Oncology, Herlev and Gentofte Hospital, Herlev, Denmark; University Hospital of Copenhagen Rigshospitalet, Copenhagen, Denmark; Alligator Bioscience, Lund, Sweden

Background: ATOR-1015 is a human bispecific IgG1 antibody targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and the tumor necrosis factor receptor superfamily member 4, OX40 (also known as CD134). Both *in vitro* and *in vivo*, ATOR-1015 induces activation of cytotoxic T cells and depletion of regulatory T cells (1). In syngeneic tumor models, using human OX40 transgenic mice cross-reacting with both targets, ATOR-1015 is demonstrated to localize to the tumor. Further, the effects of ATOR-1015 are shown to occur in the tumor area and not in the spleen (1). Treatment with ATOR-1015 also reduces tumor growth and improves survival in several tumor models in mice, including bladder, colon and pancreatic cancer (1). The non-clinical safety profile and the pharmacokinetics were established in cynomolgus monkeys and the data were used for the dosing schedule. **Methods:** This is a multicenter, open-label, dose escalation study enrolling patients with advanced and/or refractory solid malignancies (NCT03782467). The primary objective of the study is to determine the maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) and to establish the safety profile of ATOR-1015. ATOR-1015 is administered intravenously biweekly as a single agent until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. The study will start with single patient cohorts until grade 2 toxicities are observed, thereafter the study follows a modified 3+3 design. At the MTD/RP2D, or a lower dose, up to 20 patients are planned for additional safety and efficacy evaluation. Study enrollment was initiated in January 2019. A total of up to 53 patients are estimated to be enrolled in the study. (1) Månsson Kvarnhammar *et al. Journal for ImmunoTherapy of Cancer* 2018; 6(Suppl 1):115. Abstract P683. Clinical trial information: NCT03782467.

TPS2654 **Poster Session (Board #293a), Sat, 8:00 AM-11:00 AM**

A phase Ia/b study of TIM-3/PD-L1 bispecific antibody in patients with advanced solid tumors.

Matthew David Hellmann, Toshio Shimizu, Toshihiko Doi, F. Stephen Hodi, Sylvie Rottey, Philippe Georges Aftimos, Zhuqing Tina Liu, Nieves Velez de Mendizabal, Anna M. Szpurka, Yongzhe Piao, Burkhard Vangerow, Leena Gandhi, Ching Ching Leow; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; National Cancer Center Hospital (NCCH), Tokyo, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Dana-Farber Cancer Institute, Boston, MA; Ghent University Hospital, Heymans Institute of Pharmacology, Ghent, Belgium; Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; Eli Lilly and Company, Indianapolis, IN; Eli Lilly Japan K.K., Kobe, Japan; Eli Lilly and Company, Bad Homburg, Germany; NYU Perlmutter Cancer Center, New York, NY; Eli Lilly and Company, New York, NY

Background: Programmed cell death 1 immune checkpoint inhibitors (anti-PD-1, anti-PD-L1) have demonstrated clinical benefit in a subset of patients with manageable safety across a variety of tumor types. T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM-3) can be co-expressed with PD-1 on exhausted T-cells and may be upregulated in tumors refractory to anti-PD-1 therapy (Koyama et al. 2016). Pre-clinical studies demonstrated that blockade of both PD-1 and TIM-3 improved survival of tumor-bearing mice compared to blocking anti-PD-1 only (Koyama et al. 2016). LY3415244 is a TIM-3/PD-L1 bispecific antibody that has the ability to target and inhibit both TIM-3 and PD-L1 and the potential to overcome primary and acquired anti-PD-(L)1 resistance by a novel mechanism to bridge TIM-3- and PD-L1-expressing cells. **Methods:** Study JZDA is a multicenter, nonrandomized, open-label, Phase 1a/1b study of LY3415244 in patients with advanced solid tumors. In Phase 1a, subjects with any tumor type who are either PD-(L)1 inhibitor-naïve or exposed are eligible. In Phase 1b, expansion cohorts are planned in subjects with PD-(L)1-experienced NSCLC, urothelial carcinoma, and melanoma. Patients with malignant mesothelioma are not required to have received prior anti-PD-(L)1 therapy. The primary objective is to assess safety and tolerability of LY3415244 and identify the recommended Phase 2 dose (RP2D) in Phase 1a (dose escalation). Safety and tolerability of the RP2D will be assessed in Phase 1b (dose expansion). The secondary objectives are to assess the pharmacokinetics of LY3415244 in Phase 1a/1b and assess early antitumor activity of LY3415244 in Phase 1b cohorts. Pre- and on-treatment biopsies will be obtained to explore potential biomarkers of response. During Phase 1a, dose escalation cohorts will proceed via a modified toxicity probability interval-2 (mTPI-2) design with a 1-cycle (28-day) dose-limiting toxicity (DLT) observation period. LY3415244 will be dosed intravenously every 2 weeks. Data from Phase 1a will determine the RP2D, which will be used for all cohorts in Phase 1b. The study is currently open to enrollment. Clinical trial information: NCT03752177.

TPS2655 **Poster Session (Board #293b), Sat, 8:00 AM-11:00 AM**

A phase III trial-in-progress comparing tislelizumab plus chemotherapy with placebo plus chemotherapy as first-line therapy in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

Rui-hua Xu, Hendrik-Tobias Arkenau, Yung-Jue Bang, Crystal S. Denlinger, Ken Kato, Josep Tabernero, Jin Wang, Jiang Li, Henry Castro, Markus Hermann Moehler; Sun Yat-sen University Cancer Center, Guangzhou, China; Sarah Cannon Research Institute UK, London, United Kingdom; Seoul National University College of Medicine, Seoul, South Korea; Fox Chase Cancer Center, Philadelphia, PA; Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; BeiGene (Beijing) Co., Ltd., Beijing, China; BeiGene USA, Inc., San Mateo, CA; Johannes Gutenberg-University of Mainz, Mainz, Germany

Background: In patients (pts) with locally advanced or metastatic G/GEJ cancer, fluoropyrimidine- and platinum (plt)-based combination chemotherapy is first-line standard of care. Despite improvement in chemotherapy regimens, outcomes are poor and survival remains low. Tislelizumab, an investigational anti-PD-1 antibody, was engineered to minimize binding of FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Previous reports suggested tislelizumab, as a single agent and in combination with chemotherapy, was generally well tolerated and had antitumor activity in pts with advanced solid tumors, including G/GEJ cancer. **Methods:** This global, double-blind, randomized, phase 3 study (NCT03777657) is designed to compare plt/fluoropyrimidine + tislelizumab versus plt/fluoropyrimidine + placebo as first-line therapy for pts with locally advanced or metastatic G/GEJ cancer. Approximately 720 pts from 160 centers will be randomized 1:1 to receive tislelizumab (200 mg IV Q3W) or placebo (IV Q3W) in combination with chemotherapy. Oxaliplatin (130 mg/m^2 IV Q3W) plus capecitabine (1000 mg/m^2 orally twice daily for 2 weeks) or cisplatin (80 mg/m^2 IV Q3W) plus 5-fluorouracil (800 mg/m^2/day IV on Days 1–5 Q3W) will be used as backbone chemotherapy on an individual basis. Chemotherapy will be administered for up to 6 cycles; capecitabine maintenance therapy is optional for pts who received capecitabine and oxaliplatin. PD-L1 expression will be assessed using the VENTANA PD-L1 (SP263) assay. Progression-free survival and overall survival are primary endpoints in the intent-to-treat and PD-L1-positive analysis sets of the study. Secondary endpoints include overall response rate, duration of response, quality-of-life outcomes, and the safety/tolerability profile of combination therapy. Exploratory endpoints include disease control rate, time to response, and an analysis of potential predictive biomarkers including, but not limited to, PD-L1 expression. Clinical trial information: NCT03777657.

TPS2656 **Poster Session (Board #294a), Sat, 8:00 AM-11:00 AM**

A randomized, placebo-controlled, phase III trial-in-progress to evaluate the efficacy and safety of tislelizumab plus chemotherapy as first-line treatment for unresectable, locally advanced recurrent/metastatic esophageal squamous cell carcinoma (ESCC).

Jian-Ming Xu, Ken Kato, Richard Hubner, Eric Raymond, Yihuan Xu, Sumei Liu, Ibrahim Qazi, Harry H. Yoon; The Fifth Medical Center, People's Liberation Army General Hospital, Beijing, China; National Cancer Center Hospital, Tokyo, Japan; Christie NHS Foundation Trust, Manchester, United Kingdom; Centre Hospitalier Paris Saint-Joseph, Paris, France; BeiGene USA, Inc., San Mateo, CA; BeiGene (Beijing) Co., Ltd., Beijing, China; Mayo Clinic, Rochester, MN

Background: ESCC remains the predominant histological subtype of, and accounts for most deaths from, esophageal cancer. PD-1 inhibition has demonstrated antitumor activity and was generally well tolerated in patients (pts) with advanced unresectable or metastatic ESCC. Tislelizumab, an investigational anti-PD-1 antibody, was engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Results from early phase clinical studies suggest single-agent tislelizumab was generally well tolerated and had antitumor activity in pts with solid tumors, including ESCC. **Methods:** This phase 3, randomized, placebo-controlled, double-blind study (NCT03783442) is designed to evaluate the efficacy and safety of tislelizumab plus chemotherapy as first-line treatment of unresectable, locally advanced recurrent or metastatic ESCC. Adult pts with histologically confirmed ESCC that had metastatic disease either at first diagnosis or with a ≥6 month treatment-free interval will be eligible. Additional eligibility criteria include measurable/evaluable disease, ECOG performance score ≤1, and no prior anti-PD-(L)-1, PD-L2, or other first-line therapy or palliative radiation treatment ≤4 weeks before treatment. Approximately 480 pts will be randomized 1:1 to receive investigator-chosen chemotherapy (ICC) plus tislelizumab 200 mg IV Q3W or ICC plus placebo. Chemotherapy options include: platinum (cisplatin 60–80 mg/m^2 or oxaliplatin 130 mg/m^2 IV Q3W) plus 5-FU 750–800 mg/m^2 IV daily for 5 days Q3W; or platinum plus capecitabine 1000 mg/m^2 orally BID for 14 days Q3W; or platinum + paclitaxel 175 mg/m^2 IV Q3W. Progression-free survival and overall survival are coprimary endpoints; secondary endpoints include objective response rate, duration of response, and health-related quality-of-life. Safety will be assessed by monitoring adverse events, physical examinations, vital signs, and electrocardiograms. This study is actively enrolling. Clinical trial information: NCT03783442.

TPS2657 **Poster Session (Board #294b), Sat, 8:00 AM-11:00 AM**

A phase I study evaluating COM701 in patients with advanced solid tumors.

Drew W. Rasco, Daniel A. Vaena, Ryan J. Sullivan, Jason J. Luke, Adam ElNaggar, John Hunter, Adeboye H. Adewoye, Judy Olweny, Amita Patnaik, Erika Paige Hamilton; South Texas Accelerated Research Therapeutics (START), San Antonio, TX; West Cancer Center, Memphis, TN; Massachusetts General Hospital, Boston, MA; University of Chicago Comprehensive Cancer Center, Chicago, IL; Compugen USA Inc., South San Francisco, CA; South Texas Accelerated Research Therapeutics, San Antonio, TX; Tennessee Oncology, PLLC and Sarah Cannon Research Institute, Nashville, TN

Background: There is a high unmet medical need for the treatment (tx) of patients (pt) who are refractory to or relapse following tx with checkpoint inhibitors. Newer checkpoint therapies with novel mechanisms of action that can activate T cells and demonstrate antitumor activity in this pre-tx pt population are urgently needed. COM701 is a novel first-in-class humanized IgG4 monoclonal antibody that binds with high affinity to PVRIG (poliovirus receptor related immunoglobulin domain containing) blocking its interaction with its ligand, PVRL2. Both PVRIG and PVRL2 are part of the DNAM axis as are TIGIT and PD1. Inhibition of PVRIG leads to enhanced activation of T and NK cells, and PVRIG results in tumor growth inhibition in mouse tumor models. We hypothesize that COM701 will demonstrate antitumor activity in pts who are checkpoint inhibitor pre-tx. **Methods:** NCT03667716 is an ongoing open-label first-in-human phase 1 study in pts with advanced solid tumors. The initial part of this study (Arm A) will evaluate escalating doses of COM701 monotherapy IV Q3 weekly with single pt cohorts for the initial 4 and then 3+3 design. Key Inclusion Criteria: Age $\geq$18 yrs, histologically confirmed locally advanced/metastatic solid malignancy and has exhausted available standard therapy, ECOG 0-1, prior anti-PD-1, anti-PD-L1, anti-CTLA-4, OX-40, CD137 permissible. Key Exclusion Criteria: Active autoimmune disease requiring systemic therapy in the last 2 years, symptomatic interstitial or inflammatory lung disease, untx or symptomatic central nervous system metastases. Primary objectives are safety and tolerability of COM701 as measured by the incidence of adverse events (AEs) and dose-limiting toxicities (21-day DLT window), pharmacokinetics of COM701, and to identify the maximum tolerated dose and/or the recommended dose for expansion. Secondary objectives are to characterize the immunogenicity and preliminary antitumor activity of COM701. Statistical Considerations: AEs graded as per CTCAE v4.03, responses as per RECIST v1.1. The analyses of all study objectives will be descriptive and hypothesis generating. No DLTs have been observed in the single pt cohorts. Assessment of pts enrolled into cohort 5 is ongoing at the time of this submission. Clinical trial information: NCT03667716.

TPS2658 **Poster Session (Board #295a), Sat, 8:00 AM-11:00 AM**

SWOG 1609 (DART): A phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors.

Sandip Pravin Patel, Megan Othus, Young Kwang Chae, Frank Giles, Jourdain Hayward, Christine McLeod, Helen X. Chen, Elad Sharon, Edward Mayerson, Christopher W. Ryan, Melissa Plets, Charles David Blanke, Razelle Kurzrock; University of California, San Diego, Moores Cancer Center, San Diego, CA; Fred Hutchinson Cancer Research Center, Seattle, WA; Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Developmental Therapeutics Consortium, Chicago, IL; SWOG Data Operations Center, Seattle, WA; CTEP National Cancer Institute, Rockville, MD; National Cancer Institute, Bethesda, MD; SWOG Statistical Center, Seattle, WA; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; Oregon Health and Science University, Portland, OR; University of California San Diego, Moores Cancer Center, La Jolla, CA

Background: Immune checkpoint blockade, in particular anti-CTLA-4 and anti-PD-1-directed approaches, have improved outcomes in various tumor types. However, little is known about the efficacy of these agents in advanced rare solid tumors. We sought to investigate the activity of ipilimumab and nivolumab in previously unstudied rare solid tumors, with planned biomarker evaluation pending including whole exome sequencing, RNAseq, and multiplex immune profiling via the NCI CIMACs. **Methods:** We performed a prospective, open-label, multicenter phase II clinical trial of ipilimumab (1mg/kg iv q6weeks) plus nivolumab (240mg iv q2weeks) across 37 cohorts of rare tumors. Eligible patients had incurable rare cancer, defined histologically with an incidence of less than 6 in 100,000 per year, and did not have an approved or standard therapy available that had been shown to prolong overall survival. Patients were required to be 18 years of age or older, have a Zubrod performance status of 0-2, with absolute neutrophil count $\geq$ 1,000/mcL, platelets $\geq$ 75,000/mcL, hemoglobin $\geq$ 8 g/dL, creatinine clearance $\geq$ 50 mL/min, total bilirubin $\leq$ 2.0 x institutional upper limit of normal (IULN), AST and ALT $\leq$ 3.0 x IULN, TSH or free T4 serum $\leq$ IULN, and normal adrenocorticotropic hormone (ACTH) $\leq$ IULN. The primary endpoint was overall response rate (ORR) by RECIST v1.1 (complete (CR) and partial responses (PR)); secondary endpoints included progression-free (PFS) and, overall survival (OS), stable disease (SD) $\geq$ 6 months, and toxicity. The primary objective of this Phase II trial was to evaluate the overall response rate (ORR, confirmed complete and partial responses [CR and PR]) by RECIST v1.1. Our objective was to distinguish between a true ORR 15% (null hypothesis) versus 30% (alternative hypothesis). A Simon's two-stage design was used, which required an analysis on the first 6 eligible patients who received therapy. If 1 or more of the 6 patients had a response (confirmed CR or PR), an additional 10 patients were to be accrued. The study was activated on 1/13/17 with the first patient treated on 3/1/17. The trial is currently open at 862 sites across the NCTN (with 352 sites having enrolled patients) and 554 patients enrolled to date. Clinical trial information: NCT02834013.

TPS2659 **Poster Session (Board #295b), Sat, 8:00 AM-11:00 AM**

Pembrolizumab in MMR-proficient metastatic colorectal cancer pharmacologically primed to trigger dynamic hypermutation status: The ARETHUSA trial.

Salvatore Siena, Andrea Sartore-Bianchi, Nicola Personeni, Filippo Pietrantonio, Giovanni Germano, Alessio Amatu, Emanuela Bonoldi, Emanuele Valtorta, Ludovic Barault, Federica Di Nicolantonio, Giulia Siravegna, Giovanni Crisafulli, Lorenza Rimassa, Filippo G. De Braud, Armando Santoro, Luca Lazzari, Paolo Luraghi, Nabil Amirouchene-Angelozzi, Alberto Bardelli, Silvia Marsoni; Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; Humanitas Research Hospital, Rozzano, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Candiolo Cancer Institute-FPO, IRCCS, Candiolo, Italy; Department of Oncology, University of Torino, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy; Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, IRCCS, Rozzano, Italy; Humanitas Research Hospital, Rozzano (MI), Italy; IFOM - the FIRC Institute of Molecular Oncology, Milan, Italy

Background: Metastatic colorectal cancer (CRC) harbouring genetic defects in the mismatch-repair pathway (MMRd) presents with a high tumor mutational burden (TMB), and is highly sensitive to anti–programmed cell death protein 1 (PD-1) immune checkpoint inhibitors. We recently showed in preclinical models that the pharmacological treatment with temozolomide (TMZ) can induce the inactivation of MMR genes, and consequently the increase of TMB and immunogenic neoantigens, thus suggesting that TMZ could be used to prime MMR proficient (MMRp) tumors for response to checkpoint inhibitors. Accordingly, mCRC patients recruited in previous clinical trials where TMZ was administered, acquired alterations of MMR genes upon treatment and showed remarkable increase in TMB at disease progression (PD). We thus designed the ARETHUSA clinical trial to test whether a priming course with TMZ in patients can sensitize mCRC to the anti-PD1 inhibitor pembrolizumab. **Methods:** Arethusa (NCT03519412) is a 2-cohorts, phase II trial consisting of three different phases. In the *SCREENING*, 348 mCRC *RAS*-mutated patients will be tested for MMR status. MMRd patients will proceed directly to *TRIAL* for immediate pembrolizumab treatment (expected 14). MMR-proficient (MMRp) patients will be further tested for expression of O^6-methylguanine-DNA methyltransferase (MGMT) by immunohistochemistry and by promoter methylation analysis. IHC-negative, promoter methylation-positive MMRp patients (expected 67) will enter in the *PRIMING* phase and will be treated with TMZ until PD. TMB will then be assessed on tumor biopsies at resistance. Those patients that will have $>$ 20 mutations/megabase will proceed to *TRIAL* (expected 20) and will be treated with pembrolizumab. Overall response rate (primary outcome), Progression Free, and Overall Survival, and treatment related toxicities (secondary outcomes) in MMRp pembrolizumab-treated patients will be estimated., while the MMRd cohort will be used for comparison. Tissue biopsies, longitudinal blood and stool collection will be used for discovery of predictive molecular biomarkers and assessment of tumor evolution. Clinical trial information: NCT03519412.

TPS2660 **Poster Session (Board #296a), Sat, 8:00 AM-11:00 AM**

JAVELIN BRCA/ATM: A phase 2 trial of avelumab (anti–PD-L1) plus talazoparib (PARP inhibitor) in patients with advanced solid tumors with a BRCA1/2 or ATM defect.

David Michael Hyman, Amelia B. Zelnak, Todd Michael Bauer, Susanna Varkey Ulahannan, James M. Ford, Rossano Cesari, Margaret Hoyle, Colombe Chappey, Ross Stewart, Umberto Conte, Timothy A Yap; Memorial Sloan Kettering Cancer Center, New York, NY; Northside Hospital Inc, Atlanta, GA; Sarah Cannon Cancer Research Institute/Tennessee Oncology, PLLC, Nashville, TN; Stephenson Cancer Center, Oklahoma City, OK; Stanford Cancer Center, Stanford, CA; Pfizer, Milan, Italy; Pfizer, San Francisco, CA; Pfizer, San Diego, CA; Pfizer, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Defects in DNA damage response genes, including *BRCA1/2* and *ATM*, confer sensitivity to PARP inhibitors. Talazoparib is a potent, oral PARP inhibitor with a dual mechanism of action (PARP enzyme inhibition and PARP trapping). Avelumab is a human anti–PD-L1 IgG1 monoclonal antibody with a wild-type Fc region that has shown clinical activity in multiple tumor types. Preclinical and early clinical data suggest that combining a PARP inhibitor with an immune checkpoint inhibitor may provide improved activity. **Methods:** JAVELIN BRCA/ATM (NCT03565991) is an ongoing, open-label, multicenter, phase 2 trial assessing the combination of avelumab and talazoparib. Enrollment of ≈200 patients with a histologically confirmed locally advanced or metastatic solid tumor that has progressed on $>$ 1 line of standard-of-care treatment for locally advanced or metastatic disease and has a germline or somatic defect in *BRCA1* or *2* (cohort 1) or *ATM* (cohort 2) genes is planned. Patients with concomitant defects in $>$ 1 gene (*BRCA1*, *BRCA2*, or *ATM*) will be enrolled in cohort 1. Exclusion criteria include prior treatment with an immune checkpoint or PARP inhibitor, prior treatment with any other anticancer or radiation therapy within 2 weeks prior to enrollment, a known history of an immune-mediated or autoimmune condition, and known symptomatic brain metastases requiring steroids. The primary endpoint is confirmed objective response by blinded independent central review according to RECIST v1.1 and according to the Prostate Cancer Working Group 3 (PCWG3) for patients with metastatic castration-resistant prostate cancer (mCRPC). Secondary endpoints include safety; investigator-assessed confirmed objective response, time to tumor response, duration of response, and progression-free survival (per RECIST v1.1 and per PCWG3 for patients with mCRPC); overall survival; pharmacokinetic parameters; and potential predictive biomarkers. The study is currently enrolling patients at centers in the United States and Europe. Clinical trial information: NCT03565991.

TPS2661 **Poster Session (Board #296b), Sat, 8:00 AM-11:00 AM**

A phase I, first-in-human, open label, dose-escalation and cohort expansion study of MGD019, a bispecific DART protein binding PD-1 and CTLA-4 in patients with unresectable or metastatic neoplasms.

Jason J. Luke, Manish Sharma, Rachel E. Sanborn, Gregory Michael Cote, Johanna C. Bendell, Glen J. Weiss, Alexey Berezhnoy, Sharad Sharma, Paul A. Moore, Ezio Bonvini, Kerri Cali, Jan E. Baughman, Jon M. Wigginton, Brad Sumrow; University of Chicago Comprehensive Cancer Center, Chicago, IL; START Midwest, Grand Rapids, MI; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; Massachusetts General Hospital, Boston, MA; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Beth Israel Deaconess Medical Center, Boston, MA; MacroGenics, Inc., Rockville, MD

Background: Immune checkpoint molecules, including CTLA-4 and PD-1, attenuate the duration and strength of adaptive immune responses to limit immune-mediated tissue damage. Tumors may inhibit cellular immune activation by expressing ligands that bind checkpoint molecules and inhibit T-cell function in the tumor microenvironment. Blockade of these inhibitory pathways is the primary mechanism of action of several novel cancer immunotherapy agents. Combined blockade of PD-1 and CTLA-4 with two checkpoint inhibitors, ipilimumab and nivolumab, increases antitumor activity beyond either single agent alone in patients with metastatic melanoma or other malignancies. MGD019, a novel bispecific molecule that co-engages and coordinately inhibits both PD-1 and CTLA-4 signaling, was developed to potentially improve antitumor activity and/or safety relative to the monoclonal antibody combination. MGD019 is an Fc-bearing tetravalent DART molecule (bivalent for each antigen) that can independently block either checkpoint molecule, with preferential co-blockade in cells co-expressing both molecules demonstrated in vitro. It is hypothesized that MGD019 might be clinically active in either checkpoint naïve or checkpoint experienced patients after prior PD-1/PD-L1 inhibitors. **Methods:** This Phase 1 study will characterize safety, dose limiting toxicities, and maximum tolerated dose (MTD)/maximum administered dose (MAD) of MGD019. Dose Escalation will enroll patients with advanced solid tumors of any histology in sequential escalating doses in cohorts of 3 to 9 patients in a 3+3+3 design. Once the MTD/MAD is reached, a Cohort Expansion phase will characterize safety and initial antitumor activity per RECIST v1.1 and irRECIST in patients with specific tumor types anticipated to be sensitive to dual checkpoint blockade. Additional endpoints include pharmacokinetics; immunogenicity; impact of MGD019 on various measures of immune-regulatory effects in peripheral blood and biopsy specimens; and relationship between antitumor activity and gene profiles, tumor mutational burden, and PD-1, PD-L1, and CTLA-4 expression on tumor cells and immune cell infiltrates within biopsy specimens. Patients will be followed for survival approximately every 3 months for 2 years. Clinical trial information: NCT03761017.

TPS2662 **Poster Session (Board #297a), Sat, 8:00 AM-11:00 AM**

The IRX-2 regimen combined with nivolumab in recurrent/metastatic solid tumors: A phase 1b study to evaluate the safety, determine recommended phase 2 dose (RP2D), and investigate the biologic and clinical activity.

Rohit K. Jain, Jingsong Zhang, Zeynep Eroglu, Ben C. Creelan, Andrew Scott Brohl, Michael Rahman Shafique, Jhanelle Elaine Gray, Jameel Muzaffar, Julia Ida, Mensura Lacevic, Youngchul Kim, Christine H. Chung, Solmaz Sahebjam; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; H. Lee. Moffitt Cancer Center & Research Institute, Tampa, FL; Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Moffitt Cancer Center, Tampa, FL; H. Lee Moffitt Cancer Center & Research Center, Tampa, FL; Moffit Cancer Center, Tampa, FL; Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL

Background: IRX-2 is a biologic immunotherapeutic containing a mixture of cytokines including IL-2, IL-1β IL-6, IL-8, TNFα, GM-CSF, and IFN-γ. It is derived from stimulating human PBMCs with phytohemagglutinin. Preclinical studies have shown that IRX-2 enhances dendritic cell maturation, T cell activation, and NK cell stimulation. In a Phase 2 trial of head and neck squamous cell carcinoma (HNSCC) patients, IRX-2 increased immune activation in the tumor microenvironment and was correlated with greater progression free survival and overall survival. Moreover, it has been shown that the degree of lymphocyte infiltration is an important prognostic factor for treatment with anti-programmed cell death protein 1 (PD-1) monoclonal antibodies. These data provide a compelling rationale for incorporating IRX-2 regimen into anti-PD-1 treatment strategies to increase the level of lymphocyte infiltration in the TME and improve immune response. **Methods:** This is a phase Ib trial exploring safety and tolerability of IRX-2 regimen in combination with nivolumab. Patients with recurrent or metastatic renal cell carcinoma, urothelial carcinoma, non-small cell lung cancer, HNSCC and melanoma are eligible. Patients who have received prior anti-PD-1/PD-L1 antibodies are eligible. IRX-2 regimen consists of cyclophosphamide 300mg/m2 (Day 1) and subcutaneous IRX-2 injections in 2 or 4 lymph node-bearing regions (based on dose level) for 10 days every 3 months. Two dose levels of IRX-2 regimen will be studied. Nivolumab is administered at 240 mg Q2W. Once the RP2D is determined, an additional 88 pts will be enrolled in an expansion phase, for a planned total enrollment of approximately 100 pts. Dose expansion phase will include cohorts of the 5 different diseases. Each cohort will include two groups: 1) anti-PD-1/PD-L1 antibody naïve tumors, and 2) progressed during or after anti-PD-1/PD-L1 antibodies. The primary study objective is to determine safety and tolerability of combination therapy. Secondary objectives are to evaluate the objective response rate, progression-free survival, and overall survival. Study Progress: Study is actively accruing. Clinical trial information: NCT03758781.

TPS2663 **Poster Session (Board #297b), Sat, 8:00 AM-11:00 AM**

A phase Ib/IIa study of rucaparib (PARP inhibitor) combined with nivolumab in metastatic castrate-resistant prostate cancer and advanced/recurrent endometrial cancer.

Raanan Alter, Gini F. Fleming, Walter Michael Stadler, Akash Patnaik; University of Chicago, Chicago, IL; The University of Chicago Medicine, Chicago, IL; Beth Israel Deaconess Medical Center/Dana-Farber Cancer Institute, Boston, MA

Background: Immune checkpoint blockade (ICB) antibodies have made a major impact in a wide range of cancers. However, only subsets of patients across all malignancies benefit from ICB. In particular, metastatic castrate-resistant prostate cancer (mCRPC) and advanced endometrial cancers (EC) have shown very limited responses to ICB. The central hypothesis of this trial is that the combination of PARP inhibitor (rucaparib) with PD-1 inhibitor (nivolumab) will enhance ICB efficacy in mCRPC and mEC patients. Given that PTEN loss has also been associated with poor response to ICB, a secondary hypothesis of this study is that the combination therapy will have differing efficacy based on the PTEN mutation status of the tumor. **Methods:** This is an investigator-initiated Phase 1b/IIa clinical trial of rucaparib and nivolumab singly and in combination, in mCRPC and mEC patients. Patients are randomized to one of three arms – rucaparib, nivolumab, or both drugs in combination for 4 weeks. Metastatic biopsy samples are collected at baseline and after 4 weeks on treatment, after which all arms will switch to combination therapy. The primary objective is to assess feasibility of the combination, and to elucidate changes in immune infiltrates by Nanostring RNA sequencing, multiplex immunofluorescence, 3D mapping, IHC, and flow cytometry. Secondary objectives are to assess clinical response, and correlate changes in TME with PTEN status. We have currently enrolled 4 patients to the study, and collected pre- and 4 week on-treatment biopsies. This study presents an opportunity for in-depth TME analysis that will enable the delineation of the effects of PARP inhibition singly and in combination with PD-1 blockade, on immune subsets within the TME. The correlative analyses will also lead to the discovery of novel biomarkers of response/resistance, and suggest additional immunooncology combinations for specific molecular subsets of prostate and endometrial cancers. Clinical trial information: NCT03572478.

TPS2664 **Poster Session (Board #298a), Sat, 8:00 AM-11:00 AM**

Feasibility study of microbial ecosystem therapeutics (MET-4) to evaluate effects of fecal microbiome in patients on immunotherapy (MET4-IO).

Tira Jing Ying Tan, Marcus O. Butler, Aaron Richard Hansen, David Hogg, Adrian G. Sacher, Philippe L. Bedard, Kendra Ross, Helen Chow, Aida Al-Kindy, Sarah Boross-Harmer, Wei Xu, Bryan Coburn, Lillian L. Siu, Anna Spreafico; Princess Margaret Cancer Centre, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada; Toronto General Hospital, University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada

Background: Differences in microbiome diversity and composition in immune checkpoint inhibitor (ICI)-responders vs non-responders have been demonstrated. Transplantation of responder feces in mouse models recapitulated the ICI-responsive phenotype. MET-4 is an oral alternative to fecal transplant consisting a well-defined mixture of intestinal bacteria isolated from healthy donor stool sample. We hypothesize that co-administration of MET-4 with ICI is safe and results in alterations of the gut microbiota. **Methods:** Three cohorts (n = 65) of subjects with any advanced solid tumor type treated with monotherapy anti- PD1/PD-L1 antibody outside of a therapeutic clinical trial will be enrolled. Group A: safety cohort of 5 subjects already on ICI will receive MET-4 in addition to standard of care (SOC) ICI. If < 2 subjects report adverse events of CTCAE grade ≥ 3 within 4 weeks at least possibly related to MET-4, this dose will be declared safe and groups B/C may start enrolling. Group B (n = 40): subjects with advanced solid tumors starting on ICI, randomized 3:1 to MET-4 plus SOC vs. SOC. Group C (n = 20): subjects with advanced solid tumors already on ICI with first unconfirmed disease progression randomized 1:1 to MET-4 plus ICI continuation vs. continuing ICI. Serial stool samples will be collected for taxonomic composition, diversity, metagenomics content and MET-4 species abundance. We anticipate the following analyses: 16S rRNA sequencing, shotgun metagenomics sequencing, qPCR, Nanostring nucleic acid detection and metabolomics profiling. Serial blood sampling for flow cytometry/CyTOF. Immune microenvironment of tumor specimen will be examined using immunohistochemistry. Other major inclusion criteria: willingness to provide correlative samples, RECIST v1.1 measurable disease and ECOG 0-2. Subjects unable to swallow oral medications are excluded. For the primary objective of cumulative relative abundance and changes of ICI-responsiveness associated species between baseline and day 12 MET-4, assuming a change of 0.5 standard deviation (SD) of microbial alpha diversity, our study will have $\geq 84\%$ power to identify a significant difference given a significance level at 0.05 in group B. Assuming a change of 0.9 SD of microbial alpha diversity, we will have $\geq 83\%$ power to identify a significant difference in group C. Response rates and progression free survival will be assessed per RECIST v1.1 and compared with historical data. Clinical trial information: NCT03686202.

TPS2665 **Poster Session (Board #298b), Sat, 8:00 AM-11:00 AM**

Phase 1/1b multicenter trial of TPST-1120, a peroxisome proliferator-activated receptor alpha (PPARα) antagonist as a single agent (SA) or in combination in patients with advanced solid tumors.

Ginna Laport, John D. Powderly, Saurin Chokshi, Jason J. Luke, Johanna C. Bendell, Amanda Enstrom, Chan C Whiting, Thomas Walter Dubensky; Tempest Therapeutics, San Francisco, CA; Carolina BioOncology Institute, Huntersville, NC; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; University of Chicago Comprehensive Cancer Center, Chicago, IL

Background: Tumor cells initially favor glucose metabolism via aerobic glycolysis. As tumors rapidly proliferate and metastasize, glucose stores are depleted and facilitated by a hypoxic tumor microenvironment (TME) and metabolic reprogramming shifts intracellular metabolism(IcM) towards fatty acid oxidation (FAO). Fatty acids support metabolism of suppressive immune cells in the TME in addition to tumor growth. PPARα is a ligand-activated nuclear transcription factor which regulates lipid metabolism and FAO. TPST-1120 is a first in class, oral selective PPARα antagonist that blocks transcription of PPARα target genes leading to an intracellular metabolism shift from FAO to glycolysis. Reduction of fatty acids in the TME leads to direct killing of tumor cells dependent on FAO, skews macrophages from immune suppressive M2 phenotype to an effector M1 phenotype and facilitates the cytotoxicity of immune effector cells. TPST-1120 also restores thrombospondin-1, a known natural inhibitor of angiogenesis, to homeostatic levels within the TME. TPST-1120 has an IC_{50} of 0.04 nM with $>$ 35 fold selectivity over other PPAR isoforms. Preclinical studies in multiple tumor models show efficacy of TPST-1120 as a SA and in combination(combo) with an anti-PD1 monoclonal antibody (mAb) and chemotherapy. **Methods:** We have initiated a phase 1/1b multicenter, open label Dose Escalation (DEs) and Dose Expansion (DEx) trial to evaluate TPST-1120 as a SA and in combo with nivolumab, an anti-PD1 mAb; docetaxel, a chemotherapeutic agent and cetuximab, an anti-EGFR mAb. Objectives: 1) evaluate safety and tolerability of continuous dosing of TPST-1120 2) identify a recommended phase 2 dose (RP2D) and 3) evaluate efficacy. Eligibility: 1) patients with select advanced solid tumors who have failed 1 and up to 5 prior therapies. This phase 1/1b adaptive design has 4 DEs arms, 1 SA arm and 3 combination arms in which TPST-1120 is combined with nivolumab, docetaxel or cetuximab. The RP2D of TPST-1120 to proceed to DEx will be determined by safety and biomarkers during DEs. The DEx arms have 8 histology-specific cohorts, 4 SA arms and 4 combo arms and will follow a 2-stage expansion design. Biomarker analyses include gene expression profiling of PPARα-associated genes, tumor markers of immune modulation and serum lipid profiling. The total sample size is up to 338 pts. This trial is accruing at U.S sites. Clinical trial information: NCT03829436.

TPS2666 **Poster Session (Board #299a), Sat, 8:00 AM-11:00 AM**

An open label, multicenter, phase 1b/2 study of rebastinib (DCC-2036) in combination with carboplatin to assess safety, tolerability, and pharmacokinetics in patients with advanced or metastatic solid tumors.

Anthony W. Tolcher, Pamela N. Munster, Lee S. Rosen, Curran Murphy, Christian Argueta, Keisuke Kuida, Rodrigo Ruiz-Soto, Filip Janku; NextOncology, San Antonio, TX; University of California San Francisco, San Francisco, CA; UCLA Division of Hematology-Oncology, Los Angeles, CA; Deciphera Pharmaceuticals, LLC, Waltham, MA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Rebastinib is a potent, orally administered, kinase switch control inhibitor selectively targeting the tunica interna endothelial cell kinase (TIE2). TIE2 is primarily expressed in endothelial cells and has critical roles in angiogenesis. In addition, TIE2 is highly expressed in a subset of macrophages, TIE2-expressing macrophages (TEMs), which are known to have proangiogenic, pro-metastatic, and immunosuppressive properties. Accumulating evidence suggests that chemotherapies, such as carboplatin, increase the recruitment and activity of pro-tumoral TEMs, leading to chemotherapy resistance. Taken together, investigation of rebastinib in combination with a chemotherapy such as carboplatin, one of the most commonly used agents across different tumor types, is warranted in advanced solid tumors. **Methods:** This study is an open-label, Phase 1b/2, multicenter study in patients with advanced or metastatic solid tumors. The study has two parts: the first part is the 3+3 dose escalation phase designed to evaluate the safety, tolerability and pharmacokinetics of 50 mg and 100 mg rebastinib twice daily in combination with carboplatin of AUC 5 or 6 administered once every three weeks to determine the recommended phase 2 dose (RP2D). Patients who have exhausted all therapies and for whom carboplatin is considered appropriate treatment will be enrolled. The second part is the dose expansion phase with three cohorts: previously treated breast cancer, recurrent, platinum-sensitive ovarian cancer, and malignant mesothelioma to evaluate the safety, tolerability, and efficacy of the RP2D. A Simon's two-stage design will be used in the second part and initially up to 18 patients will be enrolled into each cohort. If more than 4 responses are observed, then the cohort will be expanded up to 33 patients. This trial is expected to enroll up to 117 patients in total, with approximately 18 patients in the first part and up to 99 patients in the second part. The study is currently open only in the US. Clinical trial information: NCT03717415.

TPS2667 **Poster Session (Board #299b), Sat, 8:00 AM-11:00 AM**

A multicenter, phase II study of soluble LAG-3 (Eftilagimod alpha) in combination with pembrolizumab (TACTI-002) in patients with advanced non-small cell lung cancer (NSCLC) or head and neck squamous cell carcinoma (HNSCC).

Julio Antonio Peguero, Pawan Bajaj, Enric Carcereny, Timothy Dudley Clay, Bernard Doger, Enriqueta Felip, Matthew Krebs, Martin Forster, Santiago Ponce Aix, Patricia Roxburgh, Frederic Triebel; Oncology Consultants PA, Department of Research, Houston, TX; Griffith University, Brisbane, Australia; Badalona-Hospital Germans Trias i Pujol, Badalona, Spain; St. John of God Hospital, Perth, Australia; START Madrid Fundacion Jimenez Diaz, Madrid, Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; The Christie NHS Foundation Trust and The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; The Christie NHS Foundation Trust, London, United Kingdom; Hospital 12 de Octubre, Madrid, Spain; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Immutep SAS, Orsay Cedex, France

Background: Eftilagimod alpha (efti, IMP321) is a recombinant LAG-3Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. Pembrolizumab binds to the PD-1 receptor, blocking both immune-suppressing ligands, PD-L1 and PD-L2, from interacting with PD-1 to help restore effector T-cell responses. The rationale to combine efti and pembrolizumab comes from their complementary mechanisms of action. Efti activates APCs and lead to an increase in activated T cells which effect potentially reduces the number of non-responders to pembrolizumab. Combining an APC activator like efti to pembrolizumab is therefore fundamentally different from many other trials combining two checkpoint inhibitors like an anti-LAG-3 mAb with an anti-PD-1 mAb. In a previous phase I study (NCT 02676869) in metastatic melanoma the combination was found to be safe and well tolerable with encouraging signs of clinical activity. **Methods:** In the course of this multicenter, open label, Phase II study, patients will be recruited for each of three indications: A: 1st line, PD-X (PD-1 or PD-L1) naïve non-small cell lung cancer (NSCLC); B: 2nd line, PD-X refractory NSCLC; C: 2nd line PD-X naive head and neck squamous cell carcinoma (HNSCC). The study is designed according to Simon's optimal two-stage design, with objective response rate acc to iRECIST as primary endpoint. Secondary endpoints include progression free survival and overall survival. In case there are more responses achieved than a predefined threshold (each part counted separately) in pts recruited in the initial stage (n = 58), additional pts (51) will be recruited in stage 2. Efti will be administered for a maximum of 18 cycles (1 cycle = 3 weeks) as 30 mg subcutaneous injection every 2 weeks for the first 8 and every 3 weeks for the 10 following cycles. Pembrolizumab (200 mg intravenous infusion every 3 weeks) is administered in parallel for up to 35 cycles. Patients are followed up for progression and survival. Clinical trial information: 03625323.

TPS2668 **Poster Session (Board #300a), Sat, 8:00 AM-11:00 AM**

A multicenter, open label, first-in-human study of an oncolytic viral vector expressing an agonistic anti-CD40 antibody (NG-350A) in patients with epithelial tumors (FORTITUDE).

Aung Naing, Ecaterina Elena Ileana Dumbrava, Ravi Murthy, Funda Meric-Bernstam, Andrew Fox, David Krige, Jo Carter, Brian Champion, Paul Cockle, Barbara Koetz, Hilary McElwaine-Johnn; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; PsiOxus Therapeutics Ltd, Abingdon, United Kingdom; PsiOxus, Abingdon, United Kingdom; PsiOxus Therapeutics Ltd., Abingdon, United Kingdom; PsiOxus Therapeutics Ltd., Oxford, United Kingdom

Background: NG-350A is a transgene modified variant of the oncolytic platform virus enadenotucirev (EnAd) which expresses a fully human agonist anti-cluster of differentiation 40 (anti-CD40) antibody. The principal advantage of encoding anti-CD40 within an oncolytic virus is the ability to potentially achieve very high levels within the tumor coupled with direct cytotoxicity due to viral lysis and stimulation of the immune-system. NG-350A infects and selectively replicates in tumor cells. The anti-CD40 antibodies are expected to activate the patient's own dendritic cells, macrophages and B-cells to drive CD4+ and CD8+ T-cell immuno-inflammatory responses and immune mediated tumor cell killing. EnAd is a tumor-selective chimeric Ad11/Ad3 group B oncolytic adenovirus developed using directed evolution. Phase I clinical studies have identified a well-tolerated systemic dose and regimen for EnAd monotherapy. EnAd shows a high level of selective replication and cell killing for a broad range of carcinoma cell lines (of epithelial origin) with little replication in normal and non-carcinoma cells.
Methods: This first in human study will evaluate the safety, tolerability and preliminary efficacy of NG-350A together with virus kinetics, immunogenicity and other pharmacodynamic effects to elucidate the mechanism of action of NG-350A in patients with advanced or metastatic epithelial tumours. In the dose escalation phase up to 33 patients evaluable for dose-limiting toxicity will receive NG-350A by IV infusion on Day 1, 3 and 5 at 6 US sites. The first IV cohort in the dose-escalation phase will utilize the conventional '3+3' design; thereafter dose recommendations will be based on a continual reassessment method. Following determination of the recommended phase 2 dose up to 20 patients will be treated in a dose-expansion cohort. In a parallel cohort, up to 12 patients will receive a single dose of NG-350A by intratumoural (IT) injection on Day 1 for direct delivery of high viral titres to tumor. Up to six patients are planned to undergo surgical resection of a tumor lesion to optimize translational research. Clinical conduct of the study was initiated in February 2019.

TPS2669 **Poster Session (Board #300b), Sat, 8:00 AM-11:00 AM**

Phase 1 trial of TLR9 agonist lefitolimod in combination with CTLA-4 checkpoint inhibitor ipilimumab in advanced tumors.

Matthew Reilley, Apostolia Maria Tsimberidou, Sarina Anne Piha-Paul, Timothy A Yap, Siqing Fu, Aung Naing, Jordi Rodon, Ly Minh Nguyen, Casey Ager, Martin Meng, Priyamvada Jayaprakash, Manuel Schmidt, Matthias Baumann, Funda Meric-Bernstam, Michael A. Curran, David S. Hong; University of Virginia, Charlottesville, VA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; University of Texas M. D. Anderson Cancer Center, Houston, TX; Mologen AG, Berlin, Germany

Background: Drugs targeting pathogen associated molecular patterns are an attractive strategy to stimulate the immune system. Toll-like receptors (TLR) have generated significant interest as an effective means of stimulating the immune system that result in the killing of tumor cells. TLR-9 agonists can function to promote an early immune response and are an appealing partner for combination with checkpoint blockade to improve immune activation. Lefitolimod (MGN1703) is a covalently closed dumbbell-shaped DNA molecule that functions as a TLR-9 agonist. We developed a clinical trial combining lefitolimod with ipilimumab (anti-CTLA4) in patients with advanced malignancies. In the dose-escalation phase 19 patients were enrolled and no DLTs were encountered. Safety data and maximum planned dose level of lefitolimod at 120mg weekly and ipilimumab 3mg/kg every 3 weeks was previously presented. Adverse events related to the combination included fatigue, appetite loss, rash, and anemia. **Methods:** This trial (NCT02668770) was designed to evaluate the safety profile and maximum tolerated dose of lefitolimod with ipilimumab. A 3+3 trial design was used to establish safety of the combination at each dose level and guide the decision to escalate dose. Lefitolimod is administered via subcutaneous (SC) injection weekly while ipilimumab is given at 3mg/kg intravenous on day 8 of each 3 week cycle. Lefitolimod starting dose was 15mg SC weekly with 3 dose level escalations up to 120mg SC weekly. Patients receive treatment for 4 cycles (total 12 weeks) with the combination, and those with stable disease or response were eligible to remain on lefitolimod therapy for up to 1 year. Eligible patients have a metastatic or unresectable solid tumor refractory to standard therapies, ECOG $\leq$ 2, and normal organ and bone marrow function. Patients are allowed to have received prior checkpoint blockade agents. Enrollment in expansion cohorts in ongoing. To better understand relevant immunologic changes associated with treatment, paired pre- and post-treatment biopsies of target lesions and peripheral blood collection during treatment is required for target expansion cohort patient populations. In addition to evaluating target patient populations at the combination dose established during escalation, an expansion cohort for patients with cutaneous metastases involves combination treatment with intratumoral delivery of lefitolimod. Clinical trial information: NCT02668770.

TPS2670 **Poster Session (Board #301a), Sat, 8:00 AM-11:00 AM**

A phase I/II study of live biotherapeutic MRx0518 in combination with pembrolizumab in patients who have progressed on prior anti-PD-1 therapy.

Shubham Pant, Imke Mulder, Amishi Yogesh Shah, Pavlos Msaouel, Mehmet Altan, John Weinberg, Alex Stevenson, Funda Meric-Bernstam, Timothy A Yap, Vivek Subbiah, Jordi Rodon Ahnert; University of Texas MD Anderson Cancer Center, Houston, TX; 4D Pharma Reseach Ltd, Aberdeen, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic/ Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; 4 D Pharma Plc, Leeds, United Kingdom; 4D Pharma Plc, Leeds, United Kingdom

Background: The gut microbiome has emerged as a new therapeutic target to augment the efficacy of immune checkpoint blockade. MRx0518 is a novel, gut microbiome-derived, oral live biotherapeutic, designed to induce a broad immunostimulatory response to re-engage PD-1 inhibitor activity. Pre-clinical studies showed that MRx0518 reduced tumour growth in models of kidney, lung and breast cancer. MRx0518 increased CD4 and CD8 T cell and NK cell infiltration into the tumour and decreased Tregs. Upregulation of tumour TLR5 was observed and linked to the bacterial flagellin moiety, which was shown to strongly induce NFκB, cytokine responses and IFNγ+ CD4 and CD8 T cells. The study, one of the first oncology trials conducted with live biotherapeutics, is a single center, open label, safety and preliminary efficacy study of MRx0518 in combination with pembrolizumab in patients with solid tumors who have progressed on PD-1 inhibitors. **Methods:** Trial consists of 2 parts. In Part A, 12 patients receive pembrolizumab 200 mg every 3 weeks plus 1 capsule (bid) of MRx0518 with a DLT period of 1 cycle (21 days). In Part B, up to 30 patients per cohort (NSCLC, Urothelial, Renal and Melanoma) will receive pembrolizumab 200 mg every 3 weeks plus 1 capsule (bid) of MRx0518 for up to 35 cycles or until disease progression per RECIST 1.1. The primary end points are safety and tolerability of MRx0518 in combination with pembrolizumab (Parts A and B) and clinical benefit of MRx0518 in combination with pembrolizumab (Part B). Secondary end points are objective response rate, duration of response, disease control rate, and progression-free survival. Exploratory end points include bio-markers of treatment effect, effect on microbiota and overall survival. Recruitment is ongoing. Clinical trial information: NCT03637803.

TPS2671 **Poster Session (Board #301b), Sat, 8:00 AM-11:00 AM**

An open label, multicenter, phase I/II study of RP1 as a single agent and in combination with PD1 blockade in patients with solid tumors.

Mark R. Middleton, Joseph J. Sacco, Jaime R. Merchan, Brendan D. Curti, Ari M. Vanderwalde, Anna Claire Olsson-Brown, Francesca Aroldi, Nicos Fotiadis, Scott Baum, Robert S. Coffin, Howard Kaufman, Kevin J. Harrington; Churchill Hospital, Oxford, United Kingdom; Clatterbridge Cancer Centre, Merseyside, United Kingdom; University of Miami, Miami, FL; Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR; Division of Hematology/Oncology, The University of Tennessee Health Science Center, West Cancer Center, Germantown, TN; University of Liverpool, Liverpool, United Kingdom; Department of Medical Oncology, Fondazione Poliambulanza, Brescia, Italy; The Royal Marsden NHS Foundation Trust, London, United Kingdom; West Clinic/UTHSC, Memphis, TN; Replimune, Inc., Woford, MA; Replimune, Inc., Woburn, MA; The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, United Kingdom

Background: RP1 is an attenuated oncolytic HSV-1 that expresses a fusogenic glycoprotein from gibbon ape leukemia virus (GALV-GP R-) and GM-CSF. RP1 induces potent GALV-GP R- enhanced immunogenic cell death and host anti-tumor immunity in murine tumor models and increases PD-L1 expression. This clinical trial (NCT03767348) was designed to test the hypotheses that RP1 is safe when given alone and together with nivolumab (phase 1) and has efficacy together with nivolumab in four tumor types (phase 2). **Methods:** The primary goals of this clinical trial in a total of ~150 patients are to define the safety profile of RP1 alone and together with nivolumab, determine the recommended phase 2 dose (phase 1), and then in four phase 2 cohorts, to determine objective response rate in patients with melanoma, non-melanoma skin cancer, urothelial carcinoma and MSI-H solid tumors. Secondary objectives include duration of response, CR rate, PFS, viral shedding, and immune biomarker analysis. Patients with advanced cancer who failed prior therapy were eligible for the phase I component. In Phase 2 patients with histologic diagnoses of the four tumor types (N=30 for each) and who meet safety criteria for nivolumab treatment are eligible. Prior treatment with checkpoint blockade is not allowed except for the melanoma cohort. In the phase 1 portion patients are treated by intratumoral injection every two weeks for 5 total doses followed by 12 patients dosed 8 times at the RP2D in combination with nivolumab. Phase 1 patients were divided into two groups based on presence of clinically accessible lesions amenable to direct injection or those with visceral/deep lesions requiring image guidance for injection. In the phase 2 portion patients will receive the RP2D for eight injections and nivolumab will be given starting with the second RP1 injection. For the phase 1 portion, a modified 3+3 dose escalation design is used to assess safety and in the phase 2 portion, statistical analysis will be performed using a two-stage three-outcome optimum design with objective responses determined by RECIST criteria. As of February 11, 2019, 27 patients have been enrolled. Clinical trial information: NCT03767348.