2500 **Oral Abstract Session**

Clinical activity of systemic VSV-IFNβ-NIS oncolytic virotherapy in patients with relapsed refractory T-cell lymphoma.

Joselle Cook, Kah Whye Peng, Susan Michelle Geyer, Brenda F. Ginos, Amylou C. Dueck, Nandakumar Packiriswamy, Lianwen Zhang, Beth Brunton, Baskar Balakrishnan, Thomas E. Witzig, Stephen M Broski, Mrinal Patnaik, Francis Buadi, Angela Dispenzieri, Morie A. Gertz, Leif P. Bergsagel, S. Vincent Rajkumar, Shaji Kumar, Stephen J. Russell, Martha Lacy; Mayo Clinic, Rochester, MN; The Ohio State University, Columbus, OH; Mayo Clinic, Scottsdale, AZ; Division of Hematology, Mayo Clinic, Rochester, MN; Vyriad and Mayo Clinic, Rochester, MN

Background: Oncolytic virotherapy is a novel immunomodulatory therapeutic approach for relapsed refractory hematologic malignancies. The Indiana strain of Vesicular Stomatitis Virus was engineered to encode interferon beta (IFNβ) and sodium iodine symporter (NIS) to produce VSV-IFNβ-NIS. Virally encoded IFNβ serves as an index of viral proliferation and enhances host anti-tumor immunity. NIS was inserted to noninvasively assess viral biodistribution using SPECT/PET imaging. We present the results of the phase 1 clinical trial NCT03017820 of systemic administration of VSV-IFNβ-NIS among patients (pts) with relapsed refractory Multiple Myeloma (MM), T cell Lymphoma (TCL) and Acute myeloid Leukemia (AML). **Methods:** VSV-IFNβ-NIS was administered at $5x10^9$ $TCID_{50}$ (50% tissue culture infectious dose) dose level 1 to dose level 4, $1.7x10^{11}$ $TCID_{50}$. The primary objective was to determine the maximum tolerated dose of VSV-IFNβ-NIS as a single agent. Secondary objectives were determination of safety profile and preliminary efficacy of VSV-IFNβ-NIS. Correlative objectives included monitoring viremia and virus shedding. Adverse events (AEs) are reported based on CTCAE V4; cytokine release syndrome (CRS) grading was based on Lee (Blood 2014) criteria. **Results:** 15 pts received VSV-IFNβ-NIS: MM (7), TCL(7) and AML(1); 3 pts were treated at each dose level (DL) 1 through 3 (respectively 0.05, 0.17, and 0.5 x 10^{11} $TCID_{50}$), & 6 pts were treated at dose level 4 ($1.7x10^{11}$ $TCID_{50}$). There were no dose limiting toxicities. The most frequent grades 3 & 4 AEs were hematologic: lymphopenia (46.6 & 26.6%), neutropenia (13.3% & 6.7%). CRS grades 1 (6.7%) and 2 (46.6%) were the non-hematologic AEs of note; mostly at DL 4. Only 1 pt required transient pressor support. Responses were seen in pts with T cell lymphoma. At DL2, there was a partial response (PR) lasting 3 months in a pt, post 12 prior lines of therapy. At DL4 there was a 6 month PR in a pt with PTCL and another pt with cutaneous relapse of PTCL who enjoys an ongoing CR, more than 1 year post VSV infusion; both pts received 5 prior lines of therapy. Viremia was detected in all pts at the end of infusion only up to 72 hrs post infusion; no infectious virus was recovered in buccal swabs or urine. Neutralizing anti-VSV antibodies were present by day 29. IFN levels were detectable within 30 mins of infusion, peaking between 4 & 48 hrs. TCL pts mounted higher hIFNβ levels within 48 hrs; the pt with CR mounted peak hIFNβ response of 18213.3pg/ml at 48 hrs post infusion, 15-fold higher than any other pt. **Conclusions:** VSV-IFNβ-NIS can be safely administered by IV infusion among heavily pretreated pts with hematologic malignancies. VSV-IFNβ-NIS as a single agent appears to be most effective at DL4 among patients with TCL, with an ongoing CR in a patient at DL4 more than 1 year post administration. Future trials of combination strategies with immune-modulatory drugs are currently being planned. Clinical trial information: NCT03017820. Research Sponsor: Mayo Myeloma SPORE.

2501 **Oral Abstract Session**

Phase II evaluation of the triple combination of PDS0101, M9241, and bintrafusp alfa in patients with HPV 16 positive malignancies.

Julius Strauss, Charalampos S. Floudas, Houssein Abdul Sater, Michell Manu, Elizabeth Lamping, Deneise C Francis, Lisa M. Cordes, Jenn Marte, Renee Nicole Donahue, Caroline Jochems, Jason Redman, Ravi Amrit Madan, Marijo Bilusic, Fatima Karzai, Scott Norberg, Christian S. Hinrichs, Lauren V Wood, Frank K Bedu-Addo, Jeffrey Schlom, James L. Gulley; Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD; Genitourinary Malignancies Branch, NCI, NIH, Bethesda, MD; NIH, Bethesda, MD; Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; Laboratory of Tumor Immunology and Biology, National Cancer Institute, Bethesda, MD; National Cancer Institute-National Institute of Health, Bethesda, MD; National Cancer Institute at the National Institutes of Health, Bethesda, MD; PDS Biotechnology, Princeton, NJ; Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: There are more than 630,000 cases of HPV associated malignancies including cervical, oropharyngeal and anal cancer worldwide annually. HPV 16 is responsible for the majority of these cases. About 15-20% of HPV associated malignancies respond to PD-(L)1 inhibitors, but for the overwhelming majority of patients who progress on these immunotherapies there is no effective standard of care therapy. Preclinical studies have shown that the triple combination of PDS0101 (Versamune-HPV), a liposomal multipeptide therapeutic vaccine targeting HPV 16 E6/E7, M9241, a tumor-targeting immunocytokine composed of IL-12 heterodimers fused to a monoclonal antibody targeting free DNA in necrotic tumor regions, and bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, resulted in maximum HPV-specific T cell responses, T cell tumor infiltration and tumor reduction as compared to any one or two of these agents alone. **Methods:** Fourteen pts with HPV 16+ relapsed or refractory advanced cancer were enrolled to the triple combination of PDS0101, M9241 and bintrafusp alfa (NCT04287868). Pts received bintrafusp alfa at 1200 mg flat dose i.v. every 2 weeks, M9241 at 16.8 mcg/kg s.c. every 4 weeks and PDS0101 given as two separate 0.5 ml s.c. injections every 4 weeks. Dose reductions of M9241 to 8 mcg/kg were allowed as well as skipped doses of any agent for ongoing toxicities. **Results:** Fourteen pts with advanced HPV 16+ cancers (5 cervical, 2 vaginal/vulvar, 4 anal, 3 oropharyngeal) were treated. 4/14 (28.6%) pts had a grade 3 treatment related toxicity including grade 3 hematuria in 2 pts with cervical ca and prior pelvic radiation and grade 3 AST/ALT elevation in 2 pts, one with anal ca and one with vaginal ca. For one patient with grade 3 AST/ALT elevation dose reduction of M9241 from 16.8 to 8 mcg/kg allowed for continued treatment with AST/ALT remaining at grade 1 or less. One additional patient had transient asymptomatic grade 4 neutropenia. No other treatment related grade 3 or greater toxicities were noted. 10/14 (71%) pts have had objective responses: 1 CR (anal ca) and 9 PRs (3 cervical, 2 vulvar/vaginal, 2 anal, 2 oropharyngeal) with 9/10 of these responses ongoing after a median 5 month of follow up. Of the 14 pts, 6 pts have checkpoint nave disease and 8 pts have checkpoint refractory disease. 5/6 (83%) pts with checkpoint nave disease and 5/8 (63%) pts with checkpoint refractory disease have had objective responses. Analyses of immune responses and other immune correlates are ongoing. **Conclusions:** Triple combination of PDS0101, M9241 and bintrafusp alfa appears to have a manageable safety profile along with early evidence of notable clinical activity for pts with both checkpoint nave as well as checkpoint refractory HPV 16+ advanced malignancies. Clinical trial information: NCT04287868. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

2502 **Oral Abstract Session**

First report of the safety/tolerability and preliminary antitumor activity of HB-201 and HB-202, an arenavirus-based cancer immunotherapy, in patients with HPV16+ cancers.

Alan Loh Ho, Marshall R. Posner, Jiaxin Niu, Siqing Fu, Rom S. Leidner, Alexander T. Pearson, Ki Y. Chung, Debra L. Richardson, Ding Wang, Agustin Pimentel, Jorge J. Nieva, Ari Rosenberg, Bharat Burman, Corinne Iacobucci, Xiaoping Qing, Andy Hwang, Kia Katchar, Katia Schlienger, Igor Matushansky, David G. Pfister; Memorial Sloan Kettering Cancer Center, New York, NY; Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY; Banner MD Anderson Cancer Center, Gilbert, AZ; The University of Texas MD Anderson Cancer Center, Houston, TX; Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR; Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; Institute for Translational Oncology Research, Prisma Health-Upstate Cancer Institute, Greenville, SC; Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Oklahoma City, OK; Henry Ford Hospital, Detroit, MI; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; University of Southern California, Los Angeles, CA; University of Chicago, Chicago, IL; Hookipa Pharma Inc., New York, NY

Background: Human papillomavirus 16 (HPV16) is linked to several cancer types. Treatment options are limited for patients with HPV16 positive (HPV16+) recurrent or metastatic cancers. Generation and maintenance of HPV16+ malignant state require stable expression of HPV16-specific E7 and E6 oncoproteins, also a source of immunogenic neoantigens. HB-201 and HB-202 are replicating live-attenuated vectors based on lymphocytic choriomeningitis virus and Pichinde virus, respectively, which express the same non-oncogenic HPV16 E7E6 fusion protein to induce tumor-specific T-cell responses. This is a first-in-human phase 1/2 study of HB-201 monotherapy and HB-201 & HB-202 alternating 2-vector therapy. Dose escalation is ongoing with a 3+3 design. **Methods:** Phase 1 is assessing different regimens and dose levels of HB-201 monotherapy and HB-201 & HB-202 alternating 2-vector therapy given intravenously (IV) with or without an initial intratumoral administration. The patient population includes HPV16+ head and neck squamous cell carcinoma (HNSCC) and other HPV16+ cancers. Safety, tolerability, and preliminary antitumor activity by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or immune RECIST are assessed. **Results:** As of Jan 2021, 25 patients with a median of 3 prior anticancer treatments have been enrolled. All had HPV16+ confirmed genotype; the most common primary site was oropharynx (72%). No dose-limiting toxicities were reported. Treatment-emergent adverse events (TEAEs) occurred in 21 patients (84%), were generally mild or moderate, with events related to study drug reported in 14 patients (56%). TEAEs reported in $>$10% of patients regardless of causality included fatigue, pyrexia, nausea, decreased appetite, anemia, arthralgia, chills, constipation, diarrhea, hypertension, influenza-like illness, pneumonia, and vomiting. Serious TEAEs developed in 6 patients (24%), including 1 with grade 5 hemorrhagic shock deemed unrelated to study drug. Grade 3 fatigue was the only serious or grade $\geq$3 TEAE assessed as related to study drug. TEAEs caused no treatment discontinuation. There were 18 patients evaluable for efficacy. For the 16 patients on HB-201 monotherapy, assessment of target lesions showed 2 partial responses (including 1 patient with an unconfirmed immune CR) and 6 patients had stable disease (SD). For the 2 patients on HB-201 & HB-202 alternating therapy, both had SD. So far, the longest duration of response was 4.8 months (144 days) and the maximum decrease in tumor diameter was 60%, both seen in HNSCC patients receiving HB-201 IV. **Conclusions:** HB-201 monotherapy and HB-201 & HB-202 2-vector alternating therapy were generally well-tolerated and showed preliminary antitumor activity as monotherapy in heavily pretreated patients with HPV16+ HNSCC and other solid tumors. Clinical trial information: NCT04180215. Research Sponsor: Hookipa Biotech Gmbh.

2503 **Oral Abstract Session**

Phase 1 study of SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with advanced solid tumors.

Dan Liu, Jifang Gong, Tianshu Liu, KunYan Li, Xianli Yin, Yunpeng Liu, Yongsheng Wang, Linna Wang, Wenliang Wang, Yanyan Zhang, Lin Shen; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Early Drug Development Center, Peking University Cancer Hospital & Institute, Beijing, China; Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology/Early Drug Development Center, Peking University Cancer Hospital & Institute, Beijing, China; Internal Medicine-Oncology, Zhongshan Hospital Fudan University, Shanghai, China; GCP Center, Hunan Cancer Hospital, Changsha, China; Hunan Cancer Hospital, Hunan, China; Medical Oncology, The First Hospital of China Medical University, Shenyang, China; Ward of GCP Center, West China Hospital of Sichuan University, Chengdu, China; Clinical Research & Development, Jiangsu Hengrui Medicine Co., Ltd, Shanghai, China

Background: Dual inhibition of PD-1/PD-L1 and TGF-β pathways is a promising therapeutic strategy for multiple tumor types. SHR-1701 is a novel bifunctional anti-PD-L1/TGF-βRII agent. This dose escalation and expansion phase 1 study aimed to evaluated the safety and preliminary anti-tumor acitivity of SHR-1701 in refractory solid tumors. **Methods:** The dose escalation period was initiated by accelerated titration (1 mg/kg Q3W) and then switched to 3+3 scheme (3, 10, 20, and 30 mg/kg Q3W and 30 mg/kg Q2W). The dose expanded at doses of 10, 20, and 30 mg/kg Q3W and 30 mg/kg Q2W. The primary objectives were to determine the safety profile, MTD, and RP2D of SHR-1701. **Results:** 17 pts (1 mg/kg Q3W [n = 1]; 3, 10, 20 and 30 mg/kg Q3W [n = 3 each]; 30 mg/kg Q2W [n = 4]) were enrolled in dose escalation part. No DLT was observed and MTD was not reached. Another 32 pts (10 mg/kg Q3W [n = 8]; 20 and 30 mg/kg Q3W [n = 9 each]; 30 mg/kg Q2W [n = 6]) were enrolled in dose expansion part. Of 49 enrolled pts, 33 pts (67.3%) had received $\geq$2 lines of prior systemic therapy. As of data cutoff on Oct 30, 2020, the median duration of SHR-1701 exposure was 6.0 weeks (range, 2.0-78.6). The most common reported TRAEs were increased ALT/AST, anemia, hypothyroidism, and increased bilirubin/conjugated bilirubin, with incidence $>$ 15%. The incidence of irAEs reported by the investigator was 46.9% and 4 pts received systemic corticosteroids. Hypothyroidism and rash were the most common irAEs with incidence $>$ 10%. The incidence of Grade $\geq$3 TRAEs was 18.4%. The incidence of Grade $\geq$3 irAEs was 10.2%. 1 pt suffered early death for liver failure more likely caused by tumor progression. PK analysis showed a linear dose-exposure relationship with SHR-1701 dosing from 1 to 30 mg/kg. The peripheral PD-L1 target occupancy rate exceeded 90%, and nearly complete TGF-β1 trapping was detected in all dose groups. Of 49 enrolled pts, 45 pts completed at least once efficacy evaluation. The ORR was 17.8% (95% CI, 8.0%-32.1%), with 8 pts achieving PR (2 lung adenocarcinoma, 1 HCC, 1 ESCC, 1 dMMR-CRC, 1 renal cancer, 1 epiglottis cancer, and 1 pancreatic acinar cell carcinoma). The DCR was 40.0% (18/45; 95% CI, 25.7%-55.7%). Majority of responses (7/8) were still ongoing, and the median DoR had not been reached yet. Based on data of saftety, PK, PD, and efficacy, we recommended 30 mg/kg Q3W as the RP2D. **Conclusions:** SHR-1701 showed acceptable safety profile and encouraging antitumor activity in refractory solid tumors, establishing the foundation for further exploration. Clinical trial information: NCT03710265. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

2504 **Oral Abstract Session**

COM701 with or without nivolumab: Results of an ongoing phase 1 study of safety, tolerability and preliminary antitumor activity in patients with advanced solid malignancies (NCT03667716).

Daniel A. Vaena, Gini F. Fleming, Bartosz Chmielowski, Manish Sharma, Erika P. Hamilton, Ryan J. Sullivan, Dale Randall Shepard, Kyriakos P. Papadopoulos, Amita Patnaik, Adam ElNaggar, Adeboye H. Adewoye, Robina Smith, Emerson A. Lim, Ecaterina Elena Dumbrava, Drew W. Rasco; West Cancer Center and Research Institute., Memphis, TN; University of Chicago Medicine, Chicago, IL; UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; START-Midwest, Grand Rapids, MI; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; Massachusetts General Hospital, Boston, MA; Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH; START-San Antonio, San Antonio, TX; START, San Antonio, TX; West Cancer Center, Memphis, TN; Compugen USA Inc., South San Francisco, CA; Columbia University-Herbert Irving Comprehensive Cancer Center, New York, NY; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: COM701 is a novel first in class humanized IgG4 monoclonal antibody that binds with high affinity to poliovirus receptor related immunoglobulin domain containing (PVRIG), blocking its interaction with its ligand, PVRL2. Blocking of PVRIG leads to enhanced activation of T/NK cells and in mouse models inhibits tumor growth. We report new and updated results on safety/tolerability/pharmacokinetics and antitumor activity from this ongoing study including final results in dose escalation combination cohort, monotherapy expansion cohort (MEC). **Methods:** We enrolled a total of 51 DLT-evaluable pts: Arm A (COM701 mono dose escalation), 16 pts in 8 cohorts (0.01 – 20 mg/kg IV Q3/4 wks); Arm B (COM701 0.3 – 20 mg/kg + nivolumab (NIVO) 360 mg/480 mg IV Q3/Q4 wks), 15 pts in 5 cohorts; 20 pts in MEC (NSCLC, OVCA, breast, endometrial and CRC) at the recommended dose for expansion(RDFE), 20 mg/kg IV Q4 wks. Key inclusion criteria: Age ≥18 yrs, histologically confirmed metastatic solid malignancy, has exhausted available standard tx, ECOG 0-1, prior ICI permissible (except prior tx with a PVRIG inhibitor). Key exclusion criteria: active autoimmune disease requiring systemic tx, hx inflammatory lung disease. Primary objectives – safety/tolerability of COM701 ± NIVO (AEs, CTCAE v4.03), PK, RDFE. Key secondary/exploratory objectives - antitumor activity of COM701 ± NIVO (RECIST v1.1), evaluation of PVRL2 expression in tumor biopsy, blood cytokines and immunophenotyping. **Results:** No DLTs were reported in Arms A or B. COM701 PK profile similar in Arm A, 20 mg/kg IV Q4 wks (cohort 8) and Arm B cohort 5 (COM701 20 mg/kg + NIVO 480 mg; all IV Q4 wks). Frequency of TEAEs in safety population (N=54 pts): pts on COM701 mono (N=38)- No AE (4), Grade≤2 (21), G3 (11), G4 (1), G5 (1, PD), pts on combo (N=16) - Grade≤2 (8), G3 (7), G5 (1, PD). Serious TEAE: pts on COM701 mono 11/38, pts on combo 6/16. Most frequent AEs in Arm A: Grade ≤2 fatigue 12/38 pts (31%), nausea 9/38 (23%); Arm B: fatigue 7/16 pts (44%) and AST increased 4/16 pts (25%). Antitumor activity - in Arm A (cohort 8), a pt with platinum resistant primary peritoneal cancer had confirmed PR ongoing 14 months. In Arm B (COM701 10 mg/kg + NIVO 480 mg, all IV Q4 wks), a pt with anal SCCA; confirmed CR, ongoing 18 months, last tx with prior PD on NIVO. In addition, a pt with renal cell CA had confirmed SD [ongoing 13 months, COM701 0.3 mg/kg + NIVO 360mg; IV Q3 wks],] In MEC, 30% (6/20 pts) had best response of SD [1-endometrial, 3 NSCLC, 2 OVCA], 2 pts [NSCLC, OVCA] ongoing at 6/4 months. Overall 16pts had prior tx-refractory disease, 9(56%) had best response of ≥SD. Of 18 pts with prior tx with ICI, 13 (72%) had best response of ≥SD. Datacut 14Dec2020. **Conclusions:** COM701 ± NIVO well tolerated with no new safety signals. Encouraging signal of antitumor activity including in pts with prior tx with ICI or prior tx-refractory disease. Clinical trial information: NCT03667716. Research Sponsor: Compugen Ltd.

2505 **Oral Abstract Session**

Preliminary clinical and biologic results of GB1275, a first-in-class oral CD11b modulator, alone and with pembrolizumab, in advanced solid tumors (KEYNOTE A36).

Haeseong Park, Johanna C. Bendell, Wells A. Messersmith, Drew W. Rasco, Johann S. De Bono, John H. Strickler, Lei Zhou, Laura L Carter, Jean-Marie Bruey, Jack Li, Kartik Raghupathi, Jakob Dupont, Marya F. Chaney, Wungki Park; Washington University School of Medicine in St. Louis, St. Louis, MO; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; University of Colorado School of Medicine, Aurora, CO; START-San Antonio, San Antonio, TX; The ICR and Royal Marsden, London, United Kingdom; Duke University School of Medicine, Durham, NC; Gossamer Bio, Inc., San Diego, CA; Merck & Co., Inc., Kenilworth, NJ; Memorial Sloan Kettering Cancer Center, New York, NY

Background: GB1275 is a first-in-class, oral CD11b modulator that reduced myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs), repolarized M2 immunosuppressive TAMs to an M1 phenotype, resulting in increased tumor infiltration of activated CD8+ T cells and antitumor efficacy in preclinical models. Here, we report preliminary results from an ongoing, first-in-human dose-escalation study in specific advanced tumors using GB1275 alone or with pembrolizumab. (NCT04060342). **Methods:** Phase 1 comprises dose escalation and expansion. During dose escalation, cohorts of 3 to 6 subjects were sequentially assigned to ascending dose levels of GB1275 from 100 mg to 1200 mg BID in one of two dosing regimens: Regimen A [GB1275 monotherapy orally (PO) twice a day (BID)] and Regimen B [GB1275 PO BID plus pembrolizumab 200 mg IV every 3 weeks (q3wks)]. Dose escalation was based on safety including dose-limiting toxicities (DLTs). Following dose escalation, up to 40 subjects with specific tumor types are to be treated in expansion with the selected GB1275 dose plus pembrolizumab to assess safety, pharmacokinetics, and preliminary clinical and biomarker activity. **Results:** As of January 8, 2021**,** 45 subjects were treated [44 in dose escalation: 23, Regimen A; 21, Regimen B. 1 in expansion, Regimen B], with median (range) GB1275 exposure of 42.0 days (4-263). No DLTs were reported. GB1275-related adverse events occurred in 24/45 (53.3%) subjects; photosensitivity reaction (20.0%), dysesthesia (13.3%) and pruritus (13.3%) were most frequent (≥10%). Stable disease was reported in 6/19 (31.6%) response-evaluable subjects in Regimen A and 9/16 (56.3%) in Regimen B. In Regimen B (800 mg), one partial response was reported in a subject with MSS-CRC treated for 263 days, and one prolonged stable disease (227 days) was reported in a gastric cancer (GC) subject previously treated with pembrolizumab plus bavituximab for less than 3 months due to progression; both subjects are continuing study treatment. A dose-dependent increase in GB1275 systemic exposure was observed up to 800 mg BID. Down-regulation of peripheral MDSCs was seen with both regimens. Regimen-dependent gene clusters in whole blood were noted. An increase in tumor infiltrating lymphocyte (TIL) counts was noted in both Regimens A and B. **Conclusions:** Dose escalation of GB1275, up to 1200 mg in Regimens A and B, demonstrated tolerability as monotherapy and combined with pembrolizumab in subjects with advanced cancers. Encouraging antitumor activity in Regimen B (800 mg) was observed in subjects with MSS-CRC and GC. Biological activity reflected by MDSC modulations in blood and TIL Increases in tumor biopsies with GB1275 alone and with pembrolizumab supports the mechanism of GB1275. GB1275 800 mg BID plus pembrolizumab 200 mg IV q3wks was selected for evaluation in the expansion phase. Clinical trial information: NCT04060342. Research Sponsor: Gossamer Bio, Inc.

2506 **Oral Abstract Session**

Preliminary results of a phase II study of alrizomadlin (APG-115), a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients (pts) with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic (I-O) drugs.

Anthony W. Tolcher, James Andrew Reeves, Meredith McKean, Bartosz Chmielowski, Joseph Thaddeus Beck, Montaser F. Shaheen, Neeta Somaiah, Melissa Wilson, Alexander I. Spira, Joseph J. Drabick, Yuefen Tang, Robert Winkler, Mingyu Li, Mohammad Ahmad, Ming Lu, Zhiyan Liang, Dajun Yang, Yifan Zhai; Texas Oncology-San Antonio Babcock, San Antonio, TX; Florida Cancer Specialists South/ Sarah Cannon Research Institute, Fort Myers, FL; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA; Highlands Oncology Group, Springdale, AR; University of Arizona Cancer Center, Tucson, AZ; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; Department of Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, PA; Ascentage Pharma Group Inc., Rockville, MD; State Key Laboratory of Oncology in South China Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Alrizomadlin (APG-115) restores *TP53* function, activating p53-mediated apoptosis in tumor cells with wild-type *TP53* and/or MDM2 amplification. Alrizomadlin also functions as a host immunomodulator and hence may restore antitumor activity in pts with cancers failing PD-1/PD-L1 blockade. **Methods:** This US multicenter trial assessed alrizomadlin combined with pembrolizumab in pts with unresectable/metastatic melanoma or advanced solid tumors that had failed I-O drugs; or pts with malignant peripheral nerve sheath tumor (MPNST), liposarcoma, or ATM mutant solid tumors that had failed any standard therapy. Eligible pts had ECOG performance status of 0-2 and no CNS metastases. The phase II study cohorts included pts with melanoma, NSCLC, solid tumor with ATM mutation, well-differentiated/dedifferentiated liposarcoma, urothelial carcinoma, and MPNST. Alrizomadlin was administered orally at 150 mg once every other day for 2 consecutive weeks with 1 week off and pembrolizumab at 200 mg via IV infusion for 30 minutes on Day 1 of a 21-day cycle. **Results:** As of December 25, 2020, 84 pts had been treated in 6 cohorts: melanoma (n = 26), NSCLC (n = 23), ATM mutation (n = 9), liposarcoma (n = 14), urothelial (n = 9), and MPNST (n = 3). In the PD-1/PD-L1 inhibitor-failed melanoma cohort, there was 1 confirmed partial response (PR) out of 5 pts with uveal melanoma, 2 PR (1 confirmed and 1 unconfirmed) of 5 pts with mucosal melanoma, and 1 confirmed PR of 11 pts with cutaneous melanoma. ORR in the melanoma cohort was 17.4% (4/23 evaluable pts), and the disease control rate was 60.9% (14/23). In the MPNST cohort, 1 of 3 pts had an unconfirmed ongoing PR. In I-O drug-failed NSCLC (n = 14 evaluable) and urothelial (n = 5 evaluable) cohorts, each reported 1 confirmed PR. Common treatment (alrizomadlin or pembrolizumab)-related adverse events (TRAEs) ($\geq$ 10%) were nausea (63.1%), thrombocytopenia (36.9%), vomiting (33.3%), fatigue (31.0%), decreased appetite (27.4%), diarrhea (21.4%), neutropenia (15.4%), and anemia (11.9%). Grade $\geq$ 3 TRAEs ($\geq$ 5%) included thrombocytopenia (20.2%), neutropenia (14.2%), and anemia (8.3%). Eleven pts discontinued treatment due to AEs: 5 were treatment related, including 2 grade 4 thrombocytopenia, and 1 each of grade 2 vomiting, grade 2 fatigue, and grade 2 posterior reversible encephalopathy syndrome (PRES). Three treatment-related SAEs were PRES, pyrexia, and asthenia. **Conclusions:** Alrizomadlin combined with pembrolizumab is well tolerated and may restore antitumor effects in pts with cancer resistant to or intolerant of I-O drugs, as suggested by preliminary antitumor activities in multiple tumor types. Internal study identifiers: APG-115-US-002; Keynote MK-3475-B66. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp Ltd (Hong Kong).

2507 **Oral Abstract Session**

Safety and efficacy of a novel anti-CD20/CD19 bi-specific CAR T-cell therapy (C-CAR039) in relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL).

Aibin Liang, Lili Zhou, Ping Li, Wenjuan Yu, Min Yang, Yangyang Xu, Shiguang Ye, Judy Zhu, Jiaqi Huang, Yan Zhang, Lanfang Li, Jing Zhao, Jing Li, Chengxiao Zheng, Kevin Zhu, Liping Lan, Huilai Zhang, Daobin Zhou, Yihong Yao, Jie Jin; Tongji Hospital of Tongji University, Shanghai, China; The First Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; Cellular Biomedicine Group Inc, Shanghai, China; Cellular Biomedicine Group Inc, Rockville, MD; Peking Union Medical College Hospital, Beijing, China; Tianjin Medical University Cancer Insitute & Hospital, Tianjin, China; University of Maryland School of Medicine, Baltimore, MD; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

Background: C-CAR039 has been developed as a novel 2nd generation 4-1BB bi-specific CAR-T targeting both CD19 and CD20 antigens with an optimized bi-specific antigen binding domain. C-CAR039 can eradicate CD19/CD20 single or double positive tumor cells *in vitro* and *invivo*. The tissue cross reactivity and whole genome membrane proteome array studies further confirmed the specificity of C-CAR039. **Methods:** GMP manufacturing of C-CAR039 was carried out in a serum free and fully closed semi-automatic system. Dose escalation and expansion studies were conducted to evaluate the safety and efficacy of C-CAR039 in r/r B-NHL patients. C-CAR039 was administered as a single intravenous dose after a 3-day cyclophosphamide plus fludarabine conditioning regimen. **Results:** As of 1/31/2021, 28 patients were infused and 25 (DLBCL, n = 22; PMBCL, n = 1; tFL, n = 1; FL, n = 1) were evaluable for safety and efficacy at dose ranges of 1.0×10^6 to 5.0×10^6 CAR-T cells/kg. The median age was 54 (range, 28-71) years, median number of prior lines of therapy was 3 (range, 1–5), 76% (19/25) of patients were in Ann Arbor Stage III/IV, and 80% (20/25) were refractory to their last treatment. 5 patients (20%) received bridging therapy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT 2019 criteria. Of the 25 patients, 24 (96%) experienced CRS, 23 (92%) were grade 1 or 2, 1 patient was grade 3. Median time to onset of CRS was 3 days (range, 0-10), with median duration of 4 days (range, 1-25). 2 patients had a grade 1 ICANS. Grade≥3 neutropenia, anemia, thrombocytopenia and infection were reported in 88%, 40%, 16% and 0% of patients, respectively. The best overall response rate was 92%, complete response (CR) rate was 84% and median time to response was 1.0 month (range, 0.9-1.2). With a median follow-up of 5.3 months, 76% remained in CR. Kaplan Meyer estimation of PFS at 6 months was 87.3% (95% CI, 71.2 to 100.0). Median duration of response has not been reached. Furthermore, C-CAR039 showed an encouraging cellular kinetic profile. In 25 evaluable patients, the median T_{max} was 11 day, the median C_{max} was 139,497 copies/mg gDNA, and the median $AUC_{0\sim28DAY}$ of 1,673,844 day*copies/μg gDNA. **Conclusions:** C-CAR039 demonstrated a favorable safety profile and promising efficacy in this early clinical trial in patients with r/r B-NHL that might allow it to differentiate from existing therapies. The early clinical efficacy signal is encouraging and compares favorably to anti-CD19 CAR-T and peer therapies. These findings will be evaluated in more patients with longer follow-up to confirm safety, efficacy and duration of response. Clinical trial information: NCT04317885, NCT04655677, NCT04696432, NCT04693676. Research Sponsor: Cellular Biomedicine Group Inc.

2508 **Oral Abstract Session**

Safety and efficacy of a novel anti-CD20 chimeric antigen receptor (CAR)-T cell therapy in relapsed/refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL) patients after failing CD19 CAR-T therapy.

Aibin Liang, Shiguang Ye, Ping Li, Jiaqi Huang, Shigui Zhu, Xin Yao, Lili Zhou, Yangyang Xu, Judy Zhu, Chengxiao Zheng, Shiyi Chen, Liping Lan, Xiaoteng Lv, Yutian Wei, Michael Humphries, Yihong Yao; Tongji Hospital of Tongji University, Shanghai, China; Cellular Biomedicine Group Inc, Rockville, MD; Cellular Biomedicine Group Inc, Shanghai, China; Cellular Biomedicine Group Inc, Shanghai, CA, China

Background: Relapse due to loss of the CD19 targeted epitope presents a therapeutic challenge of CD19 CAR-T therapy. These patients universally have a poor outcome and the unmet medical need is high. CD20 is a proven therapeutic target for B-NHL, supported by approved and widely used monoclonal antibody therapy. C-CAR066 is a novel 2nd generation chimeric antigen receptor T (CAR-T) therapy targeting CD20 antigen. Preclinical studies suggest that C-CAR066 has superior anti-tumor activity compared to CAR-Ts derived from scFVs of Leu16, Rituximab and Obinutuzumab and anti-CD19 BBZ CAR with FMC63. **Methods:** A phase I clinical trial (NCT04036019) was conducted to evaluate the safety and efficacy of C-CAR066 in subjects with r/r B-NHL who were previously treated with anti-CD19 CAR-T therapy. Patients ($\geq$ 18 years) with r/r DLBCL, r/r FL or r/r MCL, ECOG $<$ 2 were eligible. GMP manufacture of C-CAR066 was in a serum free and fully closed semi-automatic system. A 3-day cyclophosphamide plus fludarabine regimen was followed by a single infusion of C-CAR066. Bridging therapy was allowed. **Results:** As of Jan 31, 2021, 7 patients (6 DLBCL, 1 tFL) were enrolled and infused with C-CAR066 at dose ranges of 2.0 x 10^6 to 4.8x10^6 CAR-T cells/kg. The manufacturing success rate was 100%. The median age was 51 (range, 41-62) years, and 42.9% (3/7) patients were male. The median number of prior lines of therapy was 5 (range, 2-6). One patient (14.3%) underwent autologous stem cell transplant (ASCT) and one patient received bridging therapy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT 2019 criteria. All 7 patients experienced CRS and most (85.7%) were grade 1 or 2. One patient had grade 4 CRS and recovered after treatment with tocilizumab and corticosteroids. Median time to onset of CRS was 5 days (range, 1-9), with median duration of 4 days (range, 2-17). There were no episodes of ICANS. Grade $\geq$3 neutropenia, anemia, thrombocytopenia, and infections were reported in 57.1%, 42.9%, 28.6%, and 14.3% of patients, respectively. At a median follow-up of 7.8 months, the best overall response rate was 100%, with 71.4% (5/7) achieving complete response (CR). Median time to response was 1.0 month (range, 0.9-2.7). Median time to CR was 2.7 months (range, 0.9-2.8). By the cutoff date, 3 patients (2 PR, 1 CR) had disease progression. Median duration of response was not reached. **Conclusions:** C-CAR066 has shown a favorable safety profile and promising efficacy in patients with r/r B-NHL following failure of CD19 CAR-T therapy. These results show that C-CAR066 has a different mechanism of action compared to anti-CD-19 CAR-T therapy and could provide a solution to address the unmet medical need in B-NHL patients that have failed anti-CD19 CAR-T therapy. Clinical trial information: NCT04036019. Research Sponsor: Cellular Biomedicine Group Inc.

2509 **Poster Discussion Session**

Phase Ib study of the anti-TGF-β monoclonal antibody (mAb) NIS793 combined with spartalizumab (PDR001), a PD-1 inhibitor, in patients (pts) with advanced solid tumors.

Todd Michael Bauer, Chia-Chi Lin, Richard Greil, Maria-Elisabeth Goebeler, Marie Luise Huetter-Kroenke, Ignacio Garrido-Laguna, Armando Santoro, Antonella Perotti, Anna Spreafico, Thomas Yau, Markus Joerger, Viviana Cremasco, Mirek Dostalek, Marc Pelletier, Louise Barys, Darlene Lu, Vicky Katsanou, Claire Fabre, Toshihiko Doi; Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute-SCRI-CCCIT and Cancer Cluster Salzburg, Salzburg, Austria; Department of Hematology/Oncology, University of Wuerzburg, Wuerzburg, Germany; Department of Internal Medicine III, University of Ulm, Ulm, Germany; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Humanitas Clinical and Research Center–IRCCS, Rozzano, Milan and Humanitas University, Department of Biomedical Sciences, Pieve Emanuele Hospital, Milan, Italy; San Raffaele Hospital, Milan, Italy; Princess Margaret Cancer Centre, Toronto, ON, Canada; Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong; Kantonsspital St. Gallen, St. Gallen, Switzerland; Novartis Institutes for BioMedical Research, Cambridge, MA; Novartis Institutes for BioMedical Research, Basel, Switzerland; National Cancer Center Hospital East, Kashiwa, Japan

Background: TGF-β plays a key role in regulating the tumor microenvironment. Emerging evidence suggests TGF-β is a key activator of cancer-associated fibroblasts, leading to fibrotic network development and immune exclusion. Preclinical data in murine models showed that TGF-β blockade alleviates intratumoral fibrosis, augmenting the efficacy of PD-1 immunotherapy. NIS793 is a human IgG2 mAb that binds to TGF-β. This study investigates NIS793 + spartalizumab in pts with advanced solid tumors. **Methods:** Pts initially received NIS793 (0.3–1 mg/kg Q3W) monotherapy; following evaluation of two dose levels, dose escalation continued with NIS793 + spartalizumab (NIS793 0.3–30 mg/kg Q3W + spartalizumab 300 mg Q3W; or NIS793 20–30 mg/kg Q2W + spartalizumab 400 mg Q4W) in pts with/without prior anti-PD-(L)1 therapy. In dose expansion, pts with non-small cell lung cancer (NSCLC) resistant to prior anti-PD-(L)1 or pts with microsatellite stable colorectal cancer (MSS-CRC) were treated at the recommended dose for expansion (RDE). Paired tumor biopsies were required from all pts. The primary objectives were to characterize safety and tolerability of the combination and determine the RDE. **Results:** By December 1, 2020, 60 pts were treated in the dose-escalation phase, mainly with NIS793 + spartalizumab (n = 49), and 60 pts were treated in dose expansion (MSS-CRC: n = 40; NSCLC: n = 20). Two pts were still receiving treatment. No dose-limiting toxicities were observed, and the RDE was established as 30 mg/kg (2100 mg) NIS793 + 300 mg spartalizumab Q3W. Overall 50% pts experienced $\geq$1 treatment-related AE (TRAE). The most common were rash (n = 15/120), pruritus (n = 10/120), fatigue (n = 9/120), and nausea (n = 8/120). Grade 3/4 TRAEs occurred in 11% pts, with rash (3%) being the most common. Treatment-related serious AEs were reported in 8 pts; 6 were grade 3/4 in severity. No deaths occurred due to AEs; 3 (2.5%) pts discontinued due to AEs. PK for NIS793 was linearly dose proportional with no obvious correlation between exposure and response. Two pts achieved a partial response (PR; one confirmed in clear cell renal cell carcinoma and one unconfirmed in NSCLC) during dose escalation of the combination. Two confirmed PRs were achieved in the MSS-CRC dose-expansion group. Biomarker data showed evidence of target engagement through increased TGF-β/NIS793 complexes and depleted active TGF-β in peripheral blood. Gene expression and protein analyses in tumor biopsies displayed decreased TGF-β target genes, decreased TGF-β signatures and increased immune signatures suggesting modulation of the TGF-β pathway and preliminary evidence of biological activity. **Conclusions:** Data showing target engagement and TGF-β pathway inhibition supported the proof of mechanism of NIS793. The RDE of the combination was established and well tolerated in pts with advanced solid tumors. Clinical trial information: NCT02947165. Research Sponsor: Novartis.

2510 **Poster Discussion Session**

Safety, pharmacokinetic and pharmacodynamic results from dose escalation of SAR439459, a TGFβ inhibitor, as monotherapy or in combination with cemiplimab in a phase 1/1b study.

Stephen K. Williamson, F. Stephen Hodi, Melissa Lynne Johnson, Minal A. Barve, Dejan Juric, Joaquina Celebre Baranda, Reva Elaine Schneider, Todd Michael Bauer, Tun Tun Lin, Rui Wang, Amele Amrate, Helene Guillemin-Paveau, Ryan J. Sullivan; University of Kansas Medical Center, Westwood, KS; Dana-Farber Cancer Institute, Boston, MA; Sarah Cannon Research Institute, Nashville, TN; Mary Crowley Cancer Research Center, Dallas, TX; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; University of Kansas Cancer Center, Fairway, KS; Mary Crowley Cancer Rsrch Ctr, Somerville, MA; Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; Sanofi, Cambridge, MA; Sanofi, Paris, France; Sanofi, Chilly-Mazarin, France; Massachusetts General Hospital, Boston, MA

Background: SAR439459 is a human anti-TGFβ monoclonal antibody that neutralizes all isoforms of TGFβ. In preclinical models, combining SAR439459 with an anti-PD-1 showed improved anti-tumor activity compared to single agent. Here we report preliminary results of SAR439459 ± cemiplimab in a first in human study. **Methods:** This is an open-label study (dose escalation and expansion) of SAR439459 ± cemiplimab administered intravenously in adult patients with advanced solid tumors to determine safety and tolerability, the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) of SAR439459 ± cemiplimab, pharmacokinetics (PK); pharmacodynamic (PD) and preliminary clinical benefit. In Part 1A, SAR439459 (0.05-15 mg/kg) was administered as monotherapy Q2W in an adaptive Bayesian design with overdose control. In Part 1B, SAR439459 doses cleared from monotherapy were administered in combination with fixed dose of cemiplimab (3 mg/kg Q2W or 350 mg Q3W) in a 3+3 design. **Results:** As of 31 January 2020, 28 (1A) and 24 (1B) patients with ECOG performance status of 0-1 with a median age of 60.5 and 63 years respectively were enrolled. In Part 1A, 25 patients (89.3%) had at least one treatment emergent adverse event (TEAE) and 15 (53.5%) experienced grade (G)$\geq$ 3 events. In Part 1B, 22 patients (91.7%) had at least one TEAE and 14 (58.3%) experienced G $\geq$ 3 events. Dose-limiting toxicities (DLTs) were evaluable in 24 and 21 patients respectively. In 1A, 2 DLTs were reported in 2 of 8 evaluable patients in dose level (DL) 4: G5 brain stem hemorrhage in a patient on concomitant low molecular weight heparin treatment and G3 myocardial infarction in a patient with diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and hypertension. In 1B, 1 of 6 evaluable patients in DL5 had DLTs (G3 ALT and AST increase). MTD was not reached in either part. Ten patients had best overall response of stable disease: 6 in 1A and 4 in 1B. The PK of SAR439459 was dose proportional over the dose range tested with no evidence of cemiplimab effect on SAR439459 PK, when given in combination. Treatment with SAR439459 ± cemiplimab led to rapid reduction in total plasma TGFβ level in all dose levels tested and induced CD8 & NK cells expansion and Th1 cytokines production, suggesting peripheral T cell activation. Preliminary results from paired tumor biopsies collected from patients treated with SAR439459 ± cemiplimab in expansion showed trend of TGFβ signaling pathway inhibition and conversion from excluded to inflamed tumor-immune phenotype. **Conclusions:** SAR439459 ± cemiplimab showed an acceptable tolerability profile overall. MTD was not reached. Peripheral and tumor target engagement and modulation of key immune cells was observed in treated patients. Dose expansion cohorts are currently enrolling selected solid tumor patients. Funding: Sanofi. Clinical trial information: NCT03192345. Research Sponsor: Sanofi.

2511 **Poster Discussion Session**

Preliminary safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical efficacy of ulilediimab (TJ004309), a differentiated CD73 antibody, in combination with atezolizumab in patients with advanced cancer.

Francisco Robert, Ecaterina Elena Dumbrava, Yan Xing, Elizabeth Mills, James L. Freddo, Charles P. Theuer, Bonne J. Adams, James Lawrence, Alicia A Trigeiro, Claire Xu, Yuan Meng, Linda Lee, Yonggang Zhao, Jerry Wang, Huaqiong Joan Shen, Michael S. Gordon; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; The University of Texas MD Anderson Cancer Center, Houston, TX; City of Hope Comprehensive Cancer Center, Duarte, CA; University of Alabama at Birmingham, Birmingham, AL; Tracon Pharmaceuticals, San Diego, CA; TRACON Pharmaceuticals, Inc., San Diego, CA; Tracon Pharmaceuticals Inc, San Diego, CA; Tracon Pharmaceuticals Inc., San Diego, CA; I-Mab Biopharma, Rockville, MD; I-MAB BioPharma, Shanghai, China; I-MAB BioPharma, Rockville, MD; I-Mab Biopharma, Shanghai, China; HonorHealth Research and Innovation Institute, Scottsdale, AZ

Background: CD73 is implicated in tumor resistance to checkpoint immunotherapy (CPI) and plays a critical role in adenosine-mediated immune suppression. Ulilediimab, a differentiated CD73 antibody, inhibits the adenosine pathway in a non-competitive and unique intra-dimer binding mode. Ulilediimab suppresses tumor growth when combined with a PD-(L)1 inhibitor in multiple pre-clinical models. **Methods:** This 3+3 dose-escalation phase 1 study (NCT03835949) evaluated safety, tolerability, PK, PD and preliminary efficacy in cancer patients. Ulilediimab was administered intravenously at doses of 5, 10 or 15 mg/kg weekly (QW) or 15 or 20 mg/kg every 3 weeks (Q3W) alone in the first cycle and in combination with atezolizumab (1,200 mg Q3W) starting on week 4. Soluble CD73 in serum and CD73 receptor occupancy (RO) in circulating $CD19^+$ B cells were measured. Expression of PD-L1, CD73 and A2A receptor was analyzed in baseline tumor specimens (n = 14). Tumor responses were assessed by RECIST/iRECIST. **Results:** As of 17 January 2021, 20 patients with advanced solid tumors were enrolled (M:F 8:12; mean age = 64; median prior regimens = 3 (range 1-9)). Ulilediimab was well-tolerated with no dose limiting toxicity. The most common treatment-related adverse events were first dose infusion related reactions (65%, n = 13) most commonly comprising chills/rigors, nausea, and vomiting (Grade 1 or 2) that resolved in subsequent infusions. PK appears linear at doses ≥ 10 mg/kg and modelling indicated a mean derived effective half-life of ~19 days. Soluble CD73 was undetectable and complete RO was achieved in all patients after the first dose at ≥ 10 mg/kg. Anti-drug antibody was detected in 3/20 patients (15%). Among 13 efficacy-evaluable patients dosed at ≥ 10 mg/kg, complete response (CR = 1) and partial response (PR = 2) were observed in 3 patients (ORR = 23%) together with 3 stable disease (SD) patients (DCR = 46%). One PD-(L)1 inhibitor nave patient with clear cell ovarian cancer achieved CR at 10 mg/kg QW and remains on study after 12 months. Two patients with NSCLC dosed at 15 mg/kg QW and 20 mg/kg Q3W, respectively, achieved PR. One patient failed nivolumab and the other received no prior PD-(L)1 inhibitor treatment. CD73 was expressed on 78% (mean) of malignant cells from archival tumor specimens in responders compared to 23% in non-responders. **Conclusions:** Ulilediimab is safe and well tolerated up to 20 mg/kg Q3W and 15 mg/kg QW. Full saturation of circulating and cell-bound CD73 was achieved at doses ≥ 10 mg/kg. Ulilediimab exhibited evidence of clinical activity in both PD-(L)1 treatment nave and refractory cancer patients with high archival tumor expression of CD73. The results of this phase 1 study encourage further clinical investigation to evaluate the efficacy of ulilediimab in the treatment of solid tumors. Clinical trial information: NCT03835949. Research Sponsor: TRACON Pharmaceuticals Inc.

2512 **Poster Discussion Session**

BDB001, an intravenously administered toll-like receptor 7 and 8 (TLR7/8) agonist, in combination with pembrolizumab in advanced solid tumors: Phase 1 safety and efficacy results.

Manish R. Patel, Anthony W. Tolcher, Drew W. Rasco, Melissa Lynne Johnson, Angela Tatiana Alistar, Lixin Li, Alexander H. Chung, Robert H.I. Andtbacka; Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL; Texas Oncology-San Antonio Babcock, San Antonio, TX; START, San Antonio, TX; Sarah Cannon Research Institute, Nashville, TN; Atlantic Health System, Morristown, NJ; Seven and Eight Biopharmaceuticals Inc., Edison, NJ

Background: BDB001 is an intravenously administered TLR 7/8 dual agonist immune modulator capable of reprogramming dendritic cells to produce antitumor activities. BDB001 monotherapy has demonstrated favorable tolerability and robust systemic immune activation leading to durable clinical responses in a phase I dose escalation trial. Here, we report on the safety and efficacy of BDB001 in combination with pembrolizumab in a phase I dose escalation trial in advanced solid tumors (NCT03486301). **Methods:** BDB001-101 is a phase 1, open label, dose escalation/expansion trial of BDB001 (IV, Q1W) in combination with pembrolizumab (IV, Q3W) in patients with advanced solid tumors. The primary endpoint was safety and tolerability. Secondary endpoints included efficacy, pharmacokinetics and pharmacodynamic profiling of immune activation. **Results:** Twenty-three subjects with 13 different tumor types were enrolled across 4 dose levels. Sixty one percent were female, median age was 63 years (range, 33-86), median number of prior therapies was 3 (range, 1-8), and 48% of tumors had progressed on prior anti-PD-(L)1 therapy. Overall, BDB001 in combination with pembrolizumab was well tolerated and dose-limiting toxicities were not observed. The most common treatment related adverse events (TRAEs) were fever (39.1%), fatigue (39.1%), chills/rigor (34.8%), pruritus/rash (21.7%), and nausea (13.0%). Most of these TRAEs were grade 1 or 2 and transient. Only 3 (13.0%) subjects experienced grade 3 TRAEs of fatigue, rash, stomatitis, and alkaline phosphatase elevation. There were no grade 4 or 5 TRAEs. Pharmacodynamic evaluation of plasma cytokine levels showed robust increases in interferon gamma and interferon inducible protein-10 (IP-10) at BDB001 Dose Level 3 and 4. Preliminary efficacy evaluation of the 14 subjects treated at Dose Level 3 and 4 showed durable and deep clinical responses in 4 (29%) subjects with anti-PD-(L)1 mAb refractory melanoma, hepatocellular carcinoma, cholangiocarcinoma, and platinum-resistant ovarian carcinoma. The responses were observed by the initial efficacy assessment at 9-weeks, with some seen as early as 4-weeks. In addition, 4 (29%) subjects had stable disease for a disease control rate of 57%. To date, median time on treatment is 14.4 weeks (range, 6.0 – 42.1+) with 3 subjects still active on treatment. **Conclusions:** Intravenously administered BDB001 in combination with pembrolizumab is well tolerated. Rapid and deep clinical responses were observed, supported by robust systemic immune activation. BDB001 in combination with pembrolizumab is a promising novel therapeutic option for patients with advanced solid tumors and is being evaluated in an ongoing dose expansion trial. Clinical trial information: NCT03486301. Research Sponsor: Seven and Eight Biopharmaceuticals Inc.

2513 **Poster Discussion Session**

ARTISTRY-1: Nemvaleukin alfa monotherapy and in combination with pembrolizumab in patients (pts) with advanced solid tumors.

Valentina Boni, Ira Seth Winer, Lucy Gilbert, Ulka N. Vaishampayan, Seth David Rosen, Jameel Muzaffar, Anna Spreafico, David F. McDermott, Quincy S. Chu, Olivier Dumas, Aman Chauhan, Arvind Chaudhry, Piotr Tomczak, MD, Debora S. Bruno, Yangchun Du, Ilda Bidollari, Jessicca Martin Rege, Marc S. Ernstoff, James F. Strauss, Vamsidhar Velcheti; START Madrid CIOCC Madrid, Madrid, Spain; Karmanos Cancer Institute, Detroit, MI; McGill University Health Centre, Royal Victoria Hospital, Montréal, QC, Canada; University of Michigan Cancer Center, Detroit, MI; Hem Onc Assoc of the Treasure Coast, Port St Lucie, FL; Moffitt Cancer Center, Tampa, FL; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; Centre Hospitalier Universitaire De Quebec, Quebec, QC, Canada; University of Kentucky, Division of Medical Oncology, Lexington, KY; Med Onc Assoc. P. S., Spokane, WA; Clinical Hospital No. 1 of the Poznan University of Medical Sciences, Poznań, Poland; The MetroHealth System, Cleveland, OH; Alkermes, Inc., Waltham, MA; Cleveland Clinic, Cleveland, OH; Mary Crowley Cancer Research Center, Dallas, TX; NYU Langone-Laura and Isaac Perlmutter Cancer Center, New York, NY

Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds the intermediate-affinity interleukin-2 (IL-2) receptor complex to preferentially activate $CD8^+$ T cells and natural killer cells with minimal expansion of regulatory T cells, designed to leverage antitumor effects of the IL-2 pathwaywhile mitigating potential toxicity that would limit use. **Methods:** ARTISTRY-1 (NCT02799095) is a phase 1/2 study. Parts A (dose escalation 0.1-10 μg/kg) and B (6 μg/kg [recommended phase 2 dose]) are monotherapy; pts receive intravenous nemvaleukin for 5 days every 14 or 21 days. In Part C, pts receive nemvaleukin (3 or 6 μg/kg) every 21 days in combination with pembrolizumab (200 mg on day 1). We present safety and antitumor activity (RECIST v1.1, iRECIST) data as of 12/02/2020. **Results:** In Part A, 39 pts received nemvaleukin. No dose-limiting toxicities were observed; maximum tolerated dose was not reached. Part B enrolled immune checkpoint inhibitor–pretreated pts into melanoma or renal cell carcinoma (RCC) cohorts. 18 pts with melanoma enrolled; 10 were evaluable, 2 (both with metastatic mucosal melanoma) achieved a partial response (PR; 1 unconfirmed). 24 pts with RCC enrolled; 1 of 16 evaluable pts achieved a PR (awaiting confirmation). 12 pts in each cohort continue on study. In Parts A and B, treatment-related adverse events in ≥40% included chills (74.4% and 52.4%, respectively) and pyrexia (74.4% and 47.6%, respectively). In Part C (83 evaluable pts), 12 objective responses (OR) were observed; an additional 5 pts had stable disease (SD) >6 months (1 pt with breast cancer, 2 with ovarian cancer, and 2 with non-small-cell lung cancer). Nemvaleukin did not demonstrate any additive toxicity to that already established with pembrolizumab alone. OR data are summarized in the table. **Conclusions:** Nemvaleukin was generally well tolerated and demonstrated antitumor activity as monotherapy and in combination with pembrolizumab. Pharmacodynamic studies to identify biomarkers are ongoing. Future research of monotherapy and combination therapy with nemvaleukin is warranted. Clinical trial information: NCT02799095. Research Sponsor: Alkermes, Inc.

Study Part	Monotherapy		Combination Therapy[a]							
Tumor Type	Melanoma (n=10)	Renal Cell Carcinoma (n=16)	Ovarian Cancer (n=15)	Cervical Cancer (n=5)	Breast Cancer[b] (n=4)	Pancreatic Cancer (n=2)	Esophageal Cancer (n=5)	Melanoma (n=1)	Bladder Cancer (n=4)	Hodgkin's Lymphoma (n=1)
Pts with OR (n)	2	1	3	1	2	1	2	1	1	1
Pts on therapy ≥6 months (n)[c]	1	0	5	0	2	0	2	0	0	0
Best response for each pt[d]	PR, uPR	PR (awaiting confirmation)	CR, PR, uPR	PR	iPR, uPR	PR	PR, PR	CR	PR	PR (awaiting confirmation)
Weeks on study for each pt with OR[c]	15, 57+	16+	34, 43+, 99+	17+	88, 16	17	35+, 40+	16+	8+	15+

[a]CPI pretreated or nave pts.
[b]TNBC, ER+Her2-.
[c]Investigator assessed.
[d]Additional pts experienced SD >6 months.
CR, complete response; iPR, immune partial response; PR, partial response; uPR, unconfirmed PR.

2514 **Poster Discussion Session**

Preliminary results of a phase 1b study of fruquintinib plus sintilimab in advanced colorectal cancer.

Ye Guo, Weijie Zhang, Jieer Ying, Yanqiao Zhang, Yueyin Pan, Wensheng Qiu, Weiguo Su, Panfeng Tan, Hongyan Yin, Yan Wang, Yang Luo, Hui Zhou, Jin Li; Shanghai East Hospital, Shanghai, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Abdominal Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Beijing, China; Affiliated Tumor Hospital of Harbin Medical University, Harbin, China; Anhui Provincial Hospital, Hefei, China; The First Affiliated Hospital of Qingdao University, Qingdao, China; Hutchison MediPharma Limited, Shanghai, China; Innovent Biologics, Inc., Beijing, China; Innovent Biologics, Inc., Shanghai, China

Background: To explore the safety and synergistic anti-tumor effect of fruquintinib (a VEGFR inhibitor) in combination with sintilimab (an anti-PD-1 Ab) in patients (pts) with advanced colorectal cancer (CRC) and other solid tumors. **Methods:** This is an ongoing phase Ib/II, multicenter, two-stage study. Pts with variety cancer types, including CRC, were enrolled and is continuously enrolling in the study. For this interim analysis, all pts were analyzed for safety whereas only CRC pts were analyzed for efficacy. MMR status were analyzed for all enrolled CRC pts. Stage 1 was classical 3+3 dose escalation with pts assigned to one of the following 4 cohorts, fruquintinib taken orally at 3mg (Cohort A, 3 weeks on/ 1 week off), 4mg (Cohort B, 3 weeks on/ 1 week off), 5mg-intermittent (Cohort C, 2 weeks on/ 1 week off) or 3mg-continuous (Cohort E, once daily), while sintilimab was given at 200mg intravenously with Q4W in Cohort A and Cohort B whereas Q3W in Cohort C and Cohort E. DLT was observed for 28 days. Stage 2 was dose expansion with pts receiving 5mg-intermittent or 3mg-continuous fruquintinib plus sintilimab (200mg, Q3W). The primary endpoints were safety and tolerability and secondary endpoint was objective response rate (ORR). **Results:** As of Jan 5, 2021, 44 CRC pts which failed to at least 2 previous lines of therapy containing fluoropyrimidine, oxaliplatin or irinotecan were enrolled. They received either 5mg-intermittent or 3mg-continous dosage (n = 22, each), the ORR was 22.7% (10/44, 95% CI: 11.5-37.8%) with 27.3% (6/22, 95% CI: 10.7-50.2%) in 5mg-intermittent group and 18.2% (4/22, 95% CI: 5.2-40.3%) in 3mg-continuous group. With a median follow-up time of 8.3 (range: 0-9.6) months, the K-M estimated median PFS was 6.8 (95% CI:5.6-NA) months and 4.3 (95% CI:3.5-NA) months for 5mg-intermittent group and 3mg-continuous group, respectively. Overall, 60 pts were enrolled for safety analysis, including 23 in stage1 and 37 (only CRC) in stage 2. In stage 1, all pts experienced TEAEs, 52.2% of which were $\geq$ grade 3. The most frequently reported TEAEs were TSH increasing (73.9%), fecal occult blood positive (56.5%), and Palmar-plantar erythrodysaesthesia syndrome (PPES) (56.5%). SAEs occurred in 8 (34.8%) pts and no treatment-related death was reported. One patient in Cohort B reported manageable DLT. In stage 2, all pts experienced TEAEs, 18 (48.6%) pts experienced $\geq$ grade 3 TEAEs with 6 (31.6%) in 5mg-intermittent group and 12 (66.7%) in 3mg-continuous group. The most common TEAEs were proteinuria (45.9%) and TSH increasing (37.8%). TEAEs leading to either fruquintinib or sintilimab discontinuation occurred in 3 (5%) pts each. **Conclusions:** Fruquintinib plus sintilimab showed promising efficacy and favorable safety profile in advanced CRC. Clinical trial information: NCT03903705. Research Sponsor: Hutchison MediPharma Limited, Pharmaceutical/Biotech Company.

2515 **Poster Discussion Session**

Safety and efficacy of AK112, an anti-PD-1/VEGF-A bispecific antibody, in patients with advanced solid tumors in a phase I dose escalation study.

Jermaine Coward, Anna Rachelle Austria Mislang, Sophia Frentzas, Charlotte Rose Lemech, Adnan Nagrial, Xiaoping Jin, Baiyong Li, Zhongmin Maxwell Wang, Kon Yew Kwek, Yu Xia; ICON Cancer Care, South Brisbane, QLD, Australia; Adelaide Cancer Centre, Kurralta Park, SA, Australia; Monash Health, Melbourne, VIC, Australia; Scientia Clinical Research, Randwick, Australia; Blacktown Hospital Cancer and Haematology Centre, Blacktown, NSW, Australia; Akeso Biopharma, Inc., Zhongshan, China

Background: AK112 is a tetrameric bispecific antibody targeting PD-1 and VEGF-A. Published data suggests that the combination of anti-VEGF-A with immune checkpoint inhibitor (ICI) therapy produces complementary and synergistic antitumor effects. Given the strong correlation between VEGF-A and PD-1 expression in the tumor microenvironment, it is postulated that the simultaneous blockade of these 2 targets by AK112 as a single agent might achieve higher target binding specificity and produce enhanced antitumor activity, with an improved safety profile, compared to the co-administration of anti-PD-(L)1 and anti-VEGF therapies. Here, we present preliminary safety and efficacy data from a dose escalation study of AK112. **Methods:** A multicenter, phase I, open-label dose escalation and expansion study in advanced solid tumors that are resistant/refractory to standard therapies, began in December 2019 to determine the safety and efficacy of AK112 (0.3 mg/kg to 30 mg/kg) administered IV every 2 weeks (Q2W) using an accelerated titration followed by 3+3+3 dose escalation design. Selected dose escalation cohorts were expanded to a maximum of 18 subjects with selected solid tumor types for further evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and antitumor activity. Pts with prior exposure to ICI were eligible. PD studies examined serum VEGF levels and PD-1 receptor occupancy (RO) on circulating T-cells as an indication of target engagement. **Results:** As of 13 Jan 2021, 29 pts, median age 60 years [30-76], have received AK112 at doses of 0.3 mg/kg (n = 1), 1.0 mg/kg (n = 3), 3.0 mg/kg (n = 3), 10.0 mg/kg (n = 13), 20.0 mg/kg (n = 8), and 30.0 mg/kg (n = 1) Q2W. Treatment-related adverse events (TRAEs) occurred in 55.2% of pts. G3 TRAEs occurred in 10.3% [3/29] and treatment-related SAEs occurred in 3.4% [1/29] of pts. There was no G4 TRAE. No DLT occurred. TRAEs leading to treatment discontinuation occurred in 6.9% of pts [2/29]. Most frequent TRAEs were arthralgia (17%), diarrhea (14%), rash (10%), and fatigue (10.3%). Of the 17 evaluable pts treated at doses $\geq$ 3 mg/kg Q2W, the ORR was 23.5% (4/17) and disease control rate (DCR) was 64.7% (11/17). Among the 4 responders, a responder (endometrial ca) had not received prior ICI or bevacizumab, 2 responders (ovarian ca, mesothelioma) had received prior ICI therapy; and a responder (microsatellite stable colorectal ca) was previously treated with bevacizumab. **Conclusions:** AK112, up to 20 mg/kg Q2W (inclusive), can be given safely to pts and demonstrated encouraging anti-tumor activity with an ORR of 23.5% when dosed $\geq$ 3 mg/kg Q2W in a pt population with various solid tumors resistant/relapsed to standard therapies. Enrolment is currently ongoing at 30.0 mg/kg Q2W and in dose escalation cohorts selected for expansion. Updated data, including PK, serum VEGF, and RO will be presented. Clinical trial information: NCT04047290. Research Sponsor: Akeso Biopharma, Inc.

2516 **Poster Discussion Session**

A first-in-human study of AO-176, a highly differentiated anti-CD47 antibody, in patients with advanced solid tumors.

Howard A. Burris III, Alexander I. Spira, Matthew H. Taylor, Oladapo O. Yeku, Joyce F. Liu, Pamela N. Munster, Erika P. Hamilton, Jacob Stephen Thomas, Frances Gatlin, Richard T. Penson, Thomas Adam Abrams, Mallika Sachdev Dhawan, Jacqueline M. Walling, John W. Frye, Kevin Romanko, Victoria Sung, Carrie Brachmann, Anthony B. El-Khoueiry; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; Providence Cancer Institute, Portland, OR; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; University of California San Francisco, San Francisco, CA; Division of Oncology, USC Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA; Virginia Cancer Specialist, Fairax, VA; Harvard Medical School, Massachusetts General Hospital, Boston, MA; Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; Arch Oncology, Brisbane, CA; University of Southern California, Los Angeles, CA

Background: AO-176 is a humanized IgG2 antibody that specifically targets CD47. Expressed by multiple tumor types, CD47 binds to signal regulatory protein a (SIRPa) on phagocytes, including macrophages and dendritic cells. The CD47-SIRPa complex results in a don't eat me signal that allows the tumor to escape removal by the innate immune system, disabling the generation of an adaptive immune response. The differentiated mechanisms of action of AO-176 include promotion of phagocytosis, direct tumor cell killing through programmed cell death type III and induction of damage associated molecular patterns/immunogenic cell death, preferentially binding to tumor cells vs. normal cells, and enhanced binding at an acidic pH as found in tumor microenvironments. AO-176 has negligible binding to RBCs. **Methods:** In a phase 1/2 first-in-human study (NCT03834948) of AO-176, pts with advanced solid tumors associated with high CD47 expression and an ECOG PS of 0-1 were enrolled into escalating dose cohorts of AO-176 given IV every 7 days. Objectives included evaluation of safety, dose-limiting toxicity (DLT) and recommended phase 2 dose (RP2D), antitumor activity, pharmacokinetic (PK) parameters and exploratory biomarkers. **Results:** As of 4 Jan 2021, 27 pts were enrolled (median age 64 years; 67% female; 67% ECOG PS 1; median [range] of 4 [1-7] prior therapies for metastatic disease). Dose levels of 1, 3, 10, 20 and 20 (using step-up dosing) mg/kg were evaluated in >250 infusions. Most common (>10%) treatment-related adverse events (TRAEs) of any grade were thrombocytopenia and infusion-related reaction (IRR) (33% each), anemia (22%) with no evidence of hemolysis, nausea (19%), and fatigue (15%). The only G3+ TRAE occurring in >10% of pts was asymptomatic, brief thrombocytopenia (22%). No platelet transfusions were given. DLTs included IRRs in 2 pts dosed at 20 mg/kg, and asymptomatic thrombocytopenia and a cerebrovascular accident in 1 pt each in the 20 mg/kg step-up cohort. The RP2D was 10 mg/kg. Implementation of additional premedication and a 6-hr infusion duration in cycle 1 eliminated subsequent IRRs. Dexamethasone tapering and shortening of the infusion duration to 2 hrs was successful in all pts after cycle 1. Interim PK analysis of AO-176 demonstrated consistent exposure with linear PK. The $T_{1/2}$ was ~5 days. One pt with endometrial carcinoma who had not responded to any of 4 prior systemic regimens had a confirmed PR and remains on study for >1 year. 7 pts had SD as a best response, with 2 pts (endometrial carcinoma, gastric cancer) on study for >6 mos. **Conclusions:** AO-176 is a well-tolerated, differentiated anti-CD47 therapeutic. Durable anti-tumor activity was observed. Evaluations of AO-176 in combination with paclitaxel in pts with select solid tumors (NCT03834948) and as a single-agent in pts with multiple myeloma (NCT04445701) are ongoing. Clinical trial information: NCT03834948. Research Sponsor: Arch Oncology.

2517 **Poster Discussion Session**

First-in-human phase 1 dose escalation study of HX009, a novel recombinant humanized anti-PD-1 and CD47 bispecific antibody, in patients with advanced malignancies.

Aflah Roohullah, Vinod Ganju, Faming Zhang, Lei Zhang, Ting Yu, Kate Wilkinson, Adam Cooper, Paul de Souza; South Western Sydney LHD, Liverpool, Australia; Peninsula and Southeast Oncology, Frankston, VIC, Australia; HanX Biopharmaceuticals, Inc., Hangzhou, China; HanX Biopharmaceutical Inc., Hangzhou, VA, China; Sydney Southwest Private Hospital & St George Private Hospital, Liverpool, NSW, Australia; St George Private Hospital, Kogarah, NSW, Australia; University of Western Sydney School of Medicine, Sydney, Australia

Background: HX009 is a novel humanized antibody fusion protein which binds to CD47 and PD-1 concurrently. HX009 significantly inhibited tumor growth in mouse xenograft models. In Cynomolgus monkeys, the highest non-severely toxic dose in repeat dose testing was 15mg/kg. HX009-I-01 (ClinicalTrials.gov： NCT04097769) is a first-in-human study evaluating the safety and efficacy of HX009 in subjects with advanced malignancies. Here we report the preliminary results from this study. **Methods:** The study is being conducted in Australia at 3 sites. The study design follows a 3+3 dose-escalation scheme, enrolling cohorts of at least 3 subjects (except the first dose level) sequentially until MTD or the maximum dose is reached. HX009 is administered as single agent every 2 weeks via intravenous infusion. The 7 dose levels planned are: 0.1mg/kg (1 subject), 0.3mg/kg, 1mg/kg, 2mg/kg, 3mg/kg, 5mg/kg, 7.5mg/kg. All AEs are graded using NCI CTCAE v5.0. Efficacy assessments are per RECIST 1.1. Blood samples are obtained for pharmacokinetics (PK) and for immunogenicity assessments by the development of Antidrug Antibodies. **Results:** As of the January 22 2021 cutoff date, 21 patients (12M/9F) with a median age of 69.0 years (range 38-86) have received dose levels of 0.1-7.5 mg/kg. Patients with the following tumor types have been enrolled: colorectal cancer (7), squamous cell carcinoma (3), endometrial cancer (2), breast cancer (3), malignant epithelioid mesothelioma (1), gallbladder cancer (1), pancreatic cancer (1), glioblastoma(1), ovarian cancer (1), gastroesophageal junction adenocarcinoma (1). Patients had received a median of 3 (range 1-9) prior anti-cancer regimens. Treatment-related AEs have been reported in 10 (47.6%) patients to date. Most AEs are grade 1 or 2. The most frequent treatment-related AEs include nausea (n = 2, G1), rash (n = 2, G1), vomiting (n = 2, G1), and decreased appetite (n = 2, G1). Only 1 treatment-related SAE of pneumonitis. One treatment-related anemia (G2), and no thrombocytopenia. No DLT was observed in all 7 dose levels. Among 18 patients who have had at least one post-baseline tumor assessments, partial responses (PR) have been achieved in 3 patients with the following tumor types (dose level): gallbladder adenocarcinoma (1mg/kg), triple negative breast cancer (5mg/kg), metastatic squamous cell carcinoma of head and neck (5mg/kg). In addition, there are 6 patients with best overall response of stable disease. As of the data cutoff date, 6 patients are still receiving treatment. Updated clinical and PK results will be presented at the meeting. **Conclusions:** HX009, on an every 2 weeks dosing schedule, up to 7.5 mg/kg, is well-tolerated, without any DLT to date. Antitumor activity was seen at 1 mg/kg and 5 mg/kg cohorts with objective responses in multiple tumor types; Further investigation in phase Ib/II studies is warranted. Clinical trial information: NCT04097769. Research Sponsor: HanX Biopharmaceutical Inc, Hangzhou, China.

2518 **Poster Discussion Session**

Phase I INSIGHT platform trial: Advanced safety and efficacy data from stratum D evaluating feasibility and safety of eftilagimod alpha (soluble LAG-3 protein) combined with avelumab in advanced solid tumors.

Thorsten Oliver Goetze, Daniel Wilhelm Mueller, Mohammad-Reza Rafiyan, Dragan Kiselicki, Timursah Habibzade, Marina Schaaf, Regina Eickhoff, Elke Jäger, Salah-Eddin Al-Batran; Krankenhaus Nordwest, University Cancer Center Frankfurt and Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany; Krankenhaus Nordwest, Frankfurt, Frankfurt Am Main, Germany; Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany; Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt, Germany

Background: Stratum D of the INSIGHT platform trial evaluates s.c. eftilagimod alpha (efti, IMP321) combined with avelumab in advanced solid tumors. Efti is an MHC class II agonist which activates antigen-presenting cells followed by CD8 T-cell activation. Combination with PD-1/PD-L1 blockade aims at enhanced efficacy. **Methods:** This IIT platform trial consists of 5 strata: intratumoral (A) or intraperitoneal efti (B); s.c. efti with SOC (C) or with PD-L1 inhibition (D). Strat E is currently under development and starts soon with a new efti combination. This abstract focuses on preliminary data of Strat D. Patients (pts) received 800mg avelumab i.v. q2w along with s.c. efti: 6mg in cohort 1 (coh 1, 6 pts), 30mg in cohort 2 (coh 2, 6 pts). Primary endpoint: safety. **Results:** Recruitment has been completed with 12 pts (coh 1: gastric, gallbladder, colon cancer, pleural mesothelioma; coh 2: gastric, gastroesophageal, anal, rectum, cervix uteri). No dose limiting toxicities (DLTs) occurred. 10 serious adverse events (SAEs) were reported, none of them considered causally related (4 in 3 pts of coh 1 [1 acute renal insufficiency grade 5 in 1 pt, 2 preileus grade 3 in 1 pt, hearing impaired grade 4 in 1 pt] and 6 in 4 pts of coh 2 [1 anal hemorrhage and 1 gallbladder obstruction in 1 pt, 1 eye pain and 1 surgery to replace the feeding tube in 1 pt, each grade 3, 1 skin infection grade 2, 1 diffuse myocardial fibrosis grade 5]. 1 AE of special interest (AESI) possibly related with avelumab (sarcoidosis grade 1) occurred in coh 1. 2 pts completed max treatment duration with 24 cycles. In coh 1, 47 adverse events (AEs; grade 1-2, 29; grade 3, 14; grade 4, 3; grade 5, 1) occurred in 5 pts. Most common grade 1-2 AEs were nausea, pain in 33%, 33% of the pts. Most common grade 3 AEs were ileus, vomiting in 33%, 33% of the pts. 2 AEs grade 4 (hearing impaired, sepsis) and 1 AE grade 5 (acute renal insufficiency) were reported. All AEs grade 3-5 were considered causally unrelated. In coh 2, 51 adverse events (AEs; grade 1-2, 29; grade 3, 19; grade 4, 2; grade 5, 1) occurred in 5 pts. The most common grade 1-2 AE was hypothyroidism in 33% of the pts. 1 AE grade 5 (diffuse myocardial fibrosis) was reported. Only 1 AE grade 3-5 was considered causally related (urinary tract infection grade 3 related with avelumab). 5 pts showed partial response as best response (2 coh 1: colon, pleural mesothelioma; 3 coh 2: gastric, anal, cervical), 1 stable disease with clinical progression (coh 2) (all but one of these pts still alive), 5 disease progressions acc. to RECIST 1.1 (3 coh 1, 2 coh 2), 1 clinical progression (coh 1). Signals of activity were also observed in pre-treated *MSS/PD-L1$_{low}$* pts. **Conclusions:** Combined treatment with avelumab 800mg and efti 6mg (coh 1) or 30 mg efti (coh 2) seems feasible and safe. No unexpected AEs occurred. Signals of efficacy with CPI combination were seen (DCR 50%). Clinical trial information: NCT03252938. Research Sponsor: IMMUTEP.

2519 **Poster Discussion Session**

Pan cancer analysis of the intra-tumoral microbiome's correlation with racial disparities.

Wei Tse Li, Matthew Uzelac, Jaideep Chakladar, Lindsay M. Wong, Aditi Gnanasekar, Abby C. Lee, Daniel John, Jay Patrick Lopez, Weg M. Ongkeko; University of California San Diego, San Diego, CA; UC San Diego Health System, La Jolla, CA; UC San Diego, La Jolla, CA; UCSD, Cupertino, CA; New York Presbyterian Hospital Cornell, New York, NY

Background: Microbiome composition can influence cancer development and is moderated by diet, hygiene, sanitation, and other environmental variables. For example, a Mediterranean diet could increase breast *Lactobacillus* abundance, while the gut microbiome changes dramatically with fructose intake. Recent studies have revealed correlations between microbial abundance and racial disparities in cancer. Given these reports, it is critical to examine whether environmental influences on the microbiome contribute to racial disparities in cancer incidence and prognosis. **Methods:** We examined the intra-tumoral microbiome in the lungs, breasts, bladder, colon, rectum, cervix, head and neck, prostate, and pancreas (n = 4,169). Raw tumor RNA sequencing data were downloaded from The Cancer Genome Atlas (TCGA) and aligned to bacterial genomes. Microbial abundance was correlated to race, ethnicity, and prognostic variables (Kruskal-Wallis test or Cox regression, $p < 0.05$). **Results:** We identified several microbes correlated with racial disparities for breast and bladder cancer, two microbes for lung squamous cell carcinoma, and one microbe for colon cancer. For breast cancer, African Americans have the highest mortality rate, followed by white Americans and Asian Americans. We found that four microbes, all under the order Burkholderiales, were positively correlated with poor prognosis and were most abundant in African Americans and least abundant in Asian Americans. Therefore, increased abundance of these microbes may contribute to the observed mortality differences between races. For bladder cancer, Asian Americans have the lowest incidence and mortality rates. Seven microbes, including two *Geobacillus*, two *Pseudomonas*, and two Burkholderiales, positively correlate with good prognosis and are upregulated in Asian Americans. High *Pseudomonasfluorescens* abundance is positively correlated with decreased risk of death (HR: 0.57, 95% CI: 0.38-0.85). High abundance of the Burkholderiales *R. pickettii* (HR: 0.62, 95% CI: 0.42-0.92) and *V. paradoxus* (HR: 0.59, 95% CI: 0.36-0.98) also exhibit the same trend. *Geobacillus* and *Pseudomonas* are both present in food, while Burkholderiales can cause nosocomial infections and are altered by diet. **Conclusions:** Our study is the most comprehensive to date investigating racial differences in the intra-tumoral microbiome. Our data serve as a starting point for exploring whether environmental influence of microbial abundance contributes to racial disparities in cancer. Research Sponsor: None.

2520 **Poster Discussion Session**

Safety and efficacy of neoadjuvant pembrolizumab in mismatch repair deficient localized/ locally advanced solid tumors.

Kaysia Ludford, Kanwal Pratap Singh Raghav, Mariela A. Blum Murphy, Nicole D. Fleming, Douglas A. Nelson, Michael Sangmin Lee, Brandon George Smaglo, Y. Nancy You, Matthew Murray Tillman, Carlos Kamiya-Matsuoka, Selvi Thirumurthi, Craig Messick, Benny Johnson, Eduardo Vilar Sanchez, Arvind Dasari, Jane V Thomas, Wai Chin Foo, Wei Qiao, Scott Kopetz, Michael J. Overman; The University of Texas MD Anderson, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, The Woodlands, TX; Department of Colon and Rectal Surgery, University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; Department of Gastroenterology, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Surgical Oncology; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Departments of Gastrointestinal Medical Oncology and Clinical Cancer Prevention, University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pembrolizumab (Pembro), anti-PD1 therapy, is FDA approved for refractory microsatellite instability high (MSI-H)/deficient mismatch repair (dMMR) advanced/metastatic solid tumors. The robust activity of anti-PD1 therapy in these tumors argues for a neoadjuvant organ-sparing approach. However, the role of anti-PD1 monotherapy in the neoadjuvant setting is unknown. **Methods:** This is a phase 2 open-label, single center trial (NCT04082572) of MSI-H/dMMR non-metastatic solid tumors with localized unresectable or high risk resectable (defined as $\geq$ 20% recurrence) with measurable disease per RECISTv1.1 and ECOG PS 0/1. Treatment is Pembro 200mg every 3 wks for 8 cycles (6 months) followed by surgical resection with option to continue therapy for 18 cycles (12 months) followed by observation. First restaging is at 6 wks and includes baseline and 3-week 70-gene ctDNA assessment. To continue on study, patients are required to have PR/CR, SD with tumor shrinkage or SD with decline in ctDNA [highest variant allele frequency (VAF) baseline mutation]. The co-primary endpoints are safety and pathological complete response (pCR). Key secondary endpoints are response rate and organ-sparing at one year for patients who declined surgery. **Results:** Between 12/2019 and 2/2021, 32 pts were enrolled and treated. Enrolment goal of 35 anticipated to be met by 4/2021. Baseline characteristics included 13 females, median age of 63 yrs (range 26 - 91), Lynch syndrome in 12 pts, BRAF V600E mutation in 11 pts. Tumor type included 24 CRC and 8 non-CRC (1 endometrial, 1 gastric, 1 meningeal, 2 duodenal, 1 ampullary, 2 pancreatic). At baseline disease was resectable in 23 (72%). Among 30 evaluable pts, best overall response rate was 77%: 30% CR (n = 9), 47% PR (n = 14), 20% SD (n = 6), 3% PD (n = 1). Only one pt progressed after initial SD of -18%. Median follow-up is 6.1 months (range 0.1 - 14). Among the 6 (20%) pts who underwent surgery, pCR was seen in 3 (50%). A non-operative approach (pembro for 12 months) has been chosen in 15 pts and 1-year organ-sparing was seen in 2/2 evaluable pts. Treatment-related grade 3/4 immune adverse events (TRAE) were seen in 3 (9%) pts: grade 3 immune hepatitis (2) and grade 3 type 1 diabetes (1). Baseline ctDNA was positive in 17 (53%) pts with a median of 4 mutations per pt (1 - 35) and median highest VAF of 0.9% (range 0.3% to 38.2%). Among 26 pts with successful tumor tissue testing, median tumor mutations were 10.5, range 1 to 21 (Oncomine 134 gene panel). ctDNA decline at 3 weeks was seen in 14/17 (82%) patients. Luminal disease was present in 24 pts with endoscopic response of: CR in 13 (54%), major response 1, pending follow-up evaluation 6, not evaluated 3, and no response in 1. **Conclusions:** Neoadjuvant pembrolizumab is safe with encouraging clinical activity and this data suggests that a non-operative management for dMMR/MSI-H localized solid tumors should receive further investigation. Clinical trial information: NCT04082572. Research Sponsor: Merck and Co.

2521 **Poster Session**

Early safety and efficacy from a phase I open-label clinical trial of CD137(4-1BB) agonistic antibody LVGN6051 as monotherapy and in combination with pembrolizumab.

Siqing Fu, Wael A. Harb, Sapna Pradyuman Patel, Charles Lu, Daniel M. Halperin, Yi Hsin Hsu, Naiyi Shi, Yuko Yamamura, Tony Tang, Lynn Jiang, Fusheng Su, Julia Wanda Cohen, Emmett V. Schmidt, Jieyi Wang; The University of Texas MD Anderson Cancer Center, Houston, TX; Horizon Oncology Center, Lafayette, IN; Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; Lyvgen Biopharma, Suzhou, China; Lyvgen Biopharm, Suzhou, China; Lyvgen Biopharma, New Jersey, NJ; Merck & Co., Inc., Kenilworth, NJ; Lyvgen Biopharma, Belmont, CA

Background: LVGN6051, a monoclonal antibody against CD137 (also known as 4-1BB or TNFRSF9) with an engineered Fc capable of selectively binding to the Fcγ receptor IIB, acts as a conditional CD137 agonist, resulting in immune activation optimally in tumor microenvironment (Qi, Nat. Commun. 2019). In preclinical models, LVGN6051 demonstrated robust anti-tumor efficacy and safety as a single agent and in combination with anti-PD-1 antibodies. Therefore, we have initiated this first--in-human study of LVGN6051 alone or in combination with pembrolizumab for the treatment of advanced or metastatic malignancy. **Methods:** This study includes accelerated dose escalation monotherapy up to 2 mg/kg of LVGN6051, and traditional 3 + 3 design for higher doses of LVGN6051 alone or in combination with pembrolizumab. Then, this study will enroll patients with specific types of malignancies following Simon's two-stage design. Both agents are administered once every 3 weeks. Primary objectives of this study were to define the safety profile and to establish the recommended phase 2 dose (RP2D) of LVGN6051 alone or in combination with pembrolizumab. Pharmacokinetics, immunogenicity, pharmacodynamics and clinical efficacy will be also evaluated. **Results:** At the cut-off date on January 18, 2021, 16 subjects have been enrolled into the monotherapy cohorts (n=12, no DLT observed up to 7 mg/kg), and the combination cohort (n=4, ongoing at LVGN6051 2 mg/kg and pembrolizumab 200 mg, one DLT observed). No treatment-related adverse event (TRAE) was observed in monotherapy. Treatment-emergent adverse events (TEAE) in combination included increased ALT/AST, thrombocytopenia, and fatigue. In the combination cohort, one patient with predominant hepatic metastases and history of intermittent grade 2 hepatic impairment experienced grade 3 increased ALT/AST (DLT) on cycle 1 day 15 that were resolved to her baseline without corticosteroids on cycle 1 day 18. TRAE included increased ALT/AST, thrombocytopenia, neutropenia, nausea and fatigue. Seven of 10 evaluable patients in the monotherapy cohorts demonstrated stable disease with the longest treatment being 8+ months. Tumor reductions by $>$10% were observed in melanoma and neuroendocrine tumor on monotherapy. One patient with metastatic head and neck squamous cell carcinoma who had progressed on an anti-PD-L1 based therapy showed an immune partial response (iPR) for 6+ months to the combination therapy. **Conclusions:** Preliminary evidence showed that LVGN6051 was well tolerated and tumor shrinkages were observed. While we continue assessing its safety profile, antitumor activity was observed in the LVGN6051 and pembrolizumab cohort. The favorable safety profile and preliminary antitumor activity warrant further evaluation in patients with advanced malignancies. Clinical trial information: NCT04130542. Research Sponsor: Lyvgen Biopharma Holdings Limited.

2522 **Poster Session**

Activity results of the GATTO study, a phase Ib study combining the anti-TA-MUC1 antibody gatipotuzumab with the anti-EGFR tomuzotuximab or panitumumab in patients with refractory solid tumors.

Elena Garralda, Gianluca Del Conte, Marina Macchini, Ignacio Matos, Konrad Friedrich Klinghammer, Omar Saavedra Santa Gadea, Walter M. Fiedler, Christina C Rolling, Maxim Kebenko, Francesco Raspagliesi, Domenica Larusso, Isabelle ahrens-Fath, Beate Habel, Hans Baumeister, Alfredo Zurlo, Sebastian Ochsenreither; Early Drug Development Unit (UITM), Vall d'Hebron University Hospital and Institute of Oncology (VHIO) and Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Department of Medical Oncology, San Raffaele Scientific Institute, Milan, Italy; Early Drug Development Unit (UITM), Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Charité Comprehensive Cancer Center, Berlin, Germany; University Medical Center Hamburg-Eppendorf, Hubertus-Wald University Cancer Center, Hamburg, Germany; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Glycotope GmbH, Berlin, Germany

Background: The phase I GATTO study explored the feasibility, tolerability and preliminary activity of combining Gatipotuzumab (GAT), a novel humanized monoclonal antibody binding to the tumor-associated epitope of mucin-1 (TA-MUC1), and an anti-EGFR antibody. Preclinical evidence suggests a complex interaction between TA-MUC1 and EGFR on the cell surface of epithelial tumors and synergistic antibody dependent cell cytotoxicity activity with the double targeting. **Methods:** Initially 20 patients with refractory metastatic disease were treated with GAT administered at 1400 mg Q2W in combination with the glyco-optimized anti-EGFR antibody Tomuzotuximab (TOM) at 1200 mg Q2W. Due to the risk of infusion related reactions, three cycles of TOM were given before start of combined treatment with GAT. After this regimen was proven safe and no DLT was observed, 30 additional patients including colorectal cancer (CRC) already treated with anti-EGFR antibodies, non-small cell lung cancer (NSCLC), head and neck and breast cancers received TOM and GAT administered at the same doses, with GAT treatment starting already one week after the first dose of the anti-EGFR antibody. As allowed in the study expansion, Panitumumab (PAN) was used in place of TOM in 9 CRC patients at investigator's choice. **Results:** By the time of the final analysis in January 2021, 52 patients were enrolled, and 50 received at least one dose of both GAT and anti-EGFR antibodies. Safety was overall good and results are reported in a separate abstract. Because of the difference in treatment schedule, activity results of the two parts of the study are summarized separately. There were 2 and 4 RECIST partial responses in the first and second part of the study, all in CRC patients. In the expansion phase, the median Progression Free Survival (PFS) of CRC patients who received TOM (10) and PAN (9) was 1.9 and 5.5 months, respectively. There were 2 responses in each subgroup and the duration of response was 3.8 and 7.2 months in patients receiving TOM and PAN, respectively. The PFS for NSCLC was 5.3 months and 2 heavily pretreated patients achieved a prolonged control of disease of 10.6 and 9.4 months. The trial was accompanied by a comprehensive translational research program for identification of biomarkers, including soluble TA-MUC1 in serum. In the extension phase patients with baseline values above median appeared to have improved PFS and overall survival; this was not the case for patients of the first part of the study who received GAT only after 3 doses of TOM. **Conclusions:** Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible. Interesting anti-tumor activity was observed in heavily pretreated CRC and NSCLC patients. Levels of soluble TA-MUC1 may have predictive value and potentially be a companion biomarker for further development of the combination Clinical trial information: NCT03360734. Research Sponsor: Glycotope GmbH.

2523 **Poster Session**

Phase I study of LBL-007, a novel anti-human lymphocyte activation gene 3 (LAG-3) antibody in patients with advanced solid tumors.

Yuankai Shi, Suxia Luo, Huan Zhou, Shengyu Zhou, Shan An, Zishu Wang, Sheng Yang, Ning Li, Xiaoli Li, Xinyi Yang; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China; Henan Cancer Hospital, the Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; The First Affiliated Hospital of Bengbu Medical College, Bengbu, China; Henan Cancer Hospital, Zhengzhou, China

Background: LAG-3 is an immune checkpoint receptor expressed on activated T cells to negatively regulate these cells, resulted in tumor immune escape. LBL-007, a novel anti-LAG-3 antibody, was developed by screening of a human antibody phage display library and demonstrated specific binding to human LAG-3, stimulation of IL-2 release and blockage of LAG-3 binding to its ligands including MHC II. It has shown that LBL-007 significantly inhibited tumor growth in a mouse MC38 tumor model in hLAG-3 knock-in mice with more pronounced tumor inhibition when combined with an anti-PD-1 antibody. **Methods:** A phase I, multicenter, open-label and first-in-human study was conducted to evaluate the safety, tolerability, and PK in patients with advanced solid tumors. The dose escalation phase was designed with 6 dose cohorts of LBL-007 at 0.05, 0.25, 1, 3, 6 and 10 mg/kg (iv every 2 weeks), using a modified 3+3 design. Key inclusion criteria included: age$\geq$18 years, histologically/cytologically confirmed advanced solid tumors, failed $\geq$2 lines of prior standard therapies, ECOG of 0-1, and adequate hematologic, renal, hepatic, and cardiac function. Patients who received anticancer or immunotherapy 4 weeks from first dose of LBL-007 were excluded. The primary endpoints were tolerability and safety. Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Any potential efficacy was assessed by objective response rate (ORR) evaluated by CT/MRI per RECIST 1.1. **Results:** From March 12th, 2020 to Feb 9th, 2021, 17 patients were evaluated in this study. There were no dose limiting toxicities (DLTs) at any dose cohorts, and patients were tolerated very well. Overall, there were 129 adverse events (AEs), and 8 events were serious adverse event (SAE), of which 5 were defined as suspected unexpected serious adverse reaction (SUSAR), but most unlikely treatment related AEs (TRAEs). All AEs regardless of attribution included anemia, hypocalcemia, and flu related respiratory infection, etc. The most common AEs were anemia (14, 10.9%), hypocalcemia (6, 4.7%) and thrombocytopenia (4, 3.1%). Totally, there were 8 patients without disease progression, defined as SD at the first evaluation and sustained for 3.5-9 months. The target lesions in 2 of these 8 patients were reduced by 18.9% and 23.2% (both in esophagus cancer). The progression-free survival of these 2 patients was 4.4 and 9.0 months, respectively. Patients are also being enrolled into the indication exploratory phase (3 and 6 mg/kg), testing the combination therapy with an anti-PD-1 antibody in patients with melanoma and other solid tumors. **Conclusions:** The dose escalation part of the study revealed tolerability of LBL-007 with an impressive safety profile, and potentially some encouraging signs of anti-tumor activities. Clinical trial: Chinaclinicaltrials.org.cn (1900025904). Clinical trial information: CTR20210196. Research Sponsor: Leads Biolabs.

2524 **Poster Session**

Safety and tolerability results of the GATTO study, a phase Ib study combining the anti-TA-MUC1 antibody gatipotuzumab with the anti-EGFR tomuzotuximab or panitumumab in patients with refractory solid tumors.

Sebastian Ochsenreither, Alfredo Zurlo, Elena Garralda, Ignacio Matos, Konrad Friedrich Klinghammer, Gianluca Del Conte, Marina Macchini, Christina C Rolling, Maxim Kebenko, Omar Saavedra Santa Gadea, Francesco Raspagliesi, Domenica Larusso, Isabelle ahrens-Fath, Beate Habel, Hans Baumeister, Walter M. Fiedler; Charité Comprehensive Cancer Center, Berlin, Germany; Glycotope GmbH, Berlin, Germany; Early Drug Development Unit (UITM), Vall d'Hebron University Hospital and Institute of Oncology (VHIO) and Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Early Drug Development Unit (UITM), Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Department of Medical Oncology, San Raffaele Scientific Institute, Milan, Italy; University Medical Center Hamburg-Eppendorf, Hubertus-Wald University Cancer Center, Hamburg, Germany; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The phase I GATTO study explored the feasibility, tolerability and preliminary activity of combining gatipotuzumab (GAT), a novel humanized monoclonal antibody binding to the tumor-associated epitope of mucin-1 (TA-MUC1) and an anti-EGFR antibody. Preclinical evidence suggests a complex interaction between TA-MUC1 and EGFR on the cell surface of epithelial tumors driving carcinogenesis processes and synergistic antibody dependent cell cytotoxicity activity with the dual targeting. **Methods:** Initially the study enrolled in a primary phase (PP) 20 patients with EGFR positive metastatic solid tumors, for whom no standard treatment was available. The first 6 patients were enrolled into a safety run-in phase and the number of dose-limiting toxicities (DLTs) was evaluated, in order to de-escalate the doses if needed. Patients received GAT administered at 1400 mg Q2W in combination with the glyco-optimized anti-EGFR antibody tomuzotuximab (TOM) at 1200 mg Q2W. Due to the risk of infusion related reactions (IRR), the first dose of TOM was reduced to 720 mg split over 2 consecutive days and three cycles of TOM monotherapy were given before start of treatment with GAT. As this regimen was proven safe, no DLT was observed and the initial dose remained unchanged, the study was amended to enroll in an expansion phase (EP) 30 additional patients with refractory colorectal cancer (CRC), non-small cell lung cancer (NSCLC), head and neck and breast cancers. TOM and GAT were given at the same doses and GAT treatment started already one week after the first dose of the anti-EGFR antibody. Additionally investigator had the choice to use a commercial anti-EGFR antibody in place of TOM. **Results:** By the time of the final analysis in January 2021, 52 refractory patients were enrolled and 50 received at least one dose of both GAT and anti-EGFR antibodies. Panitumumab (PAN) was used in 9 CRC patients. Because of the difference in treatment schedule, results are summarized separately for the 20 and 30 patients in PP and EP. Overall, the combined treatment was well tolerated and no DLT was observed in the whole study, nor related SAE or death. There were no treatment emergent adverse events (TEAEs) leading to dose interruptions or reductions in the PP and 2/30 (6.7%) patients in EP stopped both TOM and GAT. 16 IRRs were reported in 8/20 (40%) PP patients, and 40 IRRs in 10 (33.3%) EP patients. Only one event of chills was severe and only 6 events were related to GAT in the EP, all others to TOM. Other frequent TEAEs were those commonly observed with anti-EGFR treatment such as skin toxicity in 17 (85%) PP and 26 (86.7%) EP patients and hypomagnesemia in 10 (50%) PP and 7 (23.3%) EP patients. **Conclusions:** Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible. Future studies should test this combination together with chemotherapy Clinical trial information: NCT03360734. Research Sponsor: Glycotope GmbH.

2525 **Poster Session**

Changes in T lymphocyte subsets in different tumors before and after radiotherapy: A meta-analysis.

Xiaoxia Zhu, Qin Wang, Shangbiao Li, Simiao Qiao, Zhihao Zheng, Xiaotong Duan; Radiation Oncology Department, Zhujiang Hospital, Southern Medical University, Guangzhou, China

Background: Radiation therapy (RT) induces an immune response, but the relationship of this response with tumor type is not fully understood. **Methods:** We searched English-language electronic databases including PubMed, EMBASE, and the Cochrane Library to collect studies about the changes in CD3+ T lymphocytes, CD4+ T lymphocytes, and CD8+ T lymphocytes before and after radiotherapy in tumor patients from January 2015 to December 2019. The quality of the included literature was evaluated using the NOS scale provided by the Cochrane Collaboration, and statistical software RevMan 5.4 was used to analyze the included literature. $p < 0.05$ was considered to indicate statistical significance. **Results:** A total of 17 studies in 15 articles involving 1735 tumor patients were included. All data were collected within 1 month before or after radiotherapy. Meta-analysis showed that numbers of $CD3^+$ T lymphocytes were significantly reduced after radiotherapy compared with before treatment (standard mean difference [SMD]: -0.76; 95% CI [-1.46, -0.06]; p = 0.03), as were those of $CD4^+$ T lymphocytes (SMD: -0.50; 95% CI: [-0.88, -0.12]; p = 0.01), but there was no statistically significant difference for CD8+ T lymphocytes (SMD: 0.19; 95% CI: [-0.23, 0.62]; p = 0.38). Subgroup analysis showed significant decreases in CD3+ T lymphocytes in liver cancer,esophageal cancer, head and neck cancer, pancreatic cancer and breast cancer after radiotherapy**.** Numbers of CD4+T lymphocytes increased after radiotherapy in breast cancer,and a decrease was observed in liver cancer, esophageal cancer, colorectal cancer, and head and neck cancer. CD8+ T lymphocyte numbers also increased compared with before radiotherapy in esophageal cancer, lung cancer, and colorectal cancer. But a decrease in liver cancer and head and neck cancer. **Conclusions:** Numbers of CD3+ and CD4+ T lymphocytes decreased after radiotherapy, whereas CD8+ T lymphocytes showed no significant change. Within 1 month of radiotherapy, the tumor microenvironment showed an immunosuppressive state. The degree of immune response induced by radiotherapy differed between tumor types. Research Sponsor: National Natural Science Foundation of China [No. 81972853, No.81572279], Clinical Research Startup Program (LC2019ZD009).

2526 **Poster Session**

A phase 1, open-label, dose escalation study of the safety and tolerability of T3011 in advanced cutaneous or subcutaneous malignancies.

Andrew Mark Haydon, Ganessan Kichenadasse, John M. Kirkwood, Howard E. Kaufman, Elizabeth Iannotti Buchbinder, Vinod Ganju, Minal A. Barve, Haifang Jiang, Huinan Xu, Xusha Zhou, Huan J. Zhu, Dongyao Ni, Jiaxin Niu; Alfred Health, Melbourne, VIC, Australia; Southern Oncology Clinical Research Unit, Bedford Park, SA, Australia; Melanoma Program, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Peninsula and Southeast Oncology, Frankston, VIC, Australia; Mary Crowley Cancer Research Center, Dallas, TX; ImmVira Co. Ltd., Shenzhen, China; ImmVira Co. Ltd., Shenzhen, CA, China; Banner MD Anderson Cancer Center, Gilbert, AZ

Background: T3011 is a genetically modified, next-generation oncolytic HSV-1 with 2 exogenous genes encoding the active heterodimer human interleukin 12 (IL-12) and the Fab fragment of an anti-human PD-1 antibody. Locally produced IL-12 induces the synthesis of interferon-gamma (IFN-γ) production, enhancing cytolytic activity of natural killer cells and cytotoxic T lymphocytes. The anti PD-1 antibody blocks checkpoint inhibition of T effector cells. Extensive preclinical studies demonstrate that T3011 (and murine equivalent T3855) has potent antitumor activities. **Methods:** This phase 1 multicenter, open-label, dose escalation study evaluates the safety of intratumoral (IT) T3011 given once every other week (Q2W) in patients (pts) with advanced cutaneous or subcutaneous malignancies. The primary objective is to determine the Recommended Phase 2 Dose of T3011 based on the overall safety, pharmacokinetic and pharmacodynamic profile. Eligible pts are $\geq$ 18 years, have cutaneous or subcutaneous advanced cancer that has progressed on standard treatment and at least 1 measurable tumor lesion ($\geq$ 10 mm) suitable for T3011 IT injection. Part 1 of the study uses a 3+3 design to evaluate the safety and tolerability of T3011 monotherapy in 4 escalating doses (1×10^6, 1×10^7, 5×10^7, and 1×10^8 PFU/mL). Up to 4 mL of T3011 may be injected based on tumor size. Total enrollment will be determined by toxicities observed. **Results:** As of Feb. 14, 8 pts have received IT T3011 (Q2W): 3 in Cohort 1 (1×10^6), 3 in Cohort 2 (1×10^7), and 2 in Cohort 3 (5.0×10^7 PFU/ml). Maximum doses per pt was 11. Enrollment continues in Cohort 3. T3011 was well tolerated with no $\geq$ Grade 3 treatment-related adverse events (AEs), no DLTs or treatment-related SAEs reported to date. Common AEs were pain at injection site, leukopenia, anemia, hypocalcemia, nausea, fever, headache, dermatitis, and diaphoresis. Viral shedding was analyzed in blood, urine and saliva at various times during the study. No Viral DNA was detected in blood or urine samples (first 3 pts analyzed) to date. Biopsy samples taken from injected tumors from 2 melanoma pts (Cohort 1) revealed significant reduction of viable tumor cells after 4 injections (Week 9) compared with baseline. In particular, one post-treatment biopsy contained 45% tumor necrosis area with dramatic increases of CD8 + and NKT cells. CD3+ and CD4+ cells as well as PD-1 expression were increased in post-treatment biopsies of both pts. **Conclusions:** T3011 IT injection was well tolerated at the first 2 dose levels. Post treatment biopsies from 2 pts (Cohort 1) demonstrated significantly reduced tumor cell viability as well as increased lymphocyte infiltration indicating on-target anti-tumor activities of T3011. To date, 5 out of 6 evaluable pts had SD as best response and 6 enrolled pts remain on study. Dose escalation is continuing. Clinical trial information: NCT04370587. Research Sponsor: None.

2527 **Poster Session**

Safety and PK/PD of ALLO-647, an anti-CD52 antibody, with fludarabine (Flu)/ cyclophosphamide (Cy) for lymphodepletion in the setting of allogeneic CAR-T cell therapy.

Michael Timothy Tees, Sattva Swarup Neelapu, Parameswaran Hari, Sham Mailankody, David Bernard Miklos, Frederick Lundry Locke, Rajneesh Nath, Sacha Leandra Prashad, Xiangdong Zhou, Eren Demirhan, Srinand Ponnathapura Nandakumar, Dennis Fisher, Gregory Opiteck, Ena Wang; Moffitt Cancer Ctr and Rsrch Inst, Tampa, FL; The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX; Medical College of Wisconsin, Milwaukee, WI; Memorial Sloan Kettering Cancer Center, New York, NY; Stanford University School of Medicine, Stanford, CA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Univ of Mass Memor Medcl Ctr, Southboro, MA; Allogene Therapeutics, San Francisco, CA; Allogene Therapeutics, South San Francisco, CA; P Less Than, San Francisco, CA

Background: Allogeneic chimeric antigen receptor (CAR) T cell therapy holds promise in addressing logistical/manufacturing challenges of autologous CAR T cell therapy. ALLO-501 (anti-CD19; uses Cellectis technologies) and ALLO-715 (anti-BCMA) are allogeneic CAR T cell products whose a) disrupted TCRα constant gene may reduce GvHD risk, and b) edited CD52 gene may permit use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells. **Methods:** The ongoing ALPHA (ALLO-501) and UNIVERSAL (ALLO-715) trials include patients (pts) with relapsed/refractory large B-cell or follicular lymphoma and multiple myeloma, respectively. The lymphodepletion regimen included ALLO-647 (39 mg [low dose, LD; n = 33], 60 mg [n = 12], or 90 mg [high dose, HD; n = 27]) with Flu 30 mg/m^2/d x 3d +/- Cy 300 mg/m^2/d x 3d (Flu+Cy, n = 66; Cy, n = 6) (ALLO-647/Flu +/- Cy) before CAR T infusion. A mixed-effects population pharmacokinetic (PK) model was fit to ALLO-647 concentration *vs.* time data. Pharmacodynamic (PD) effects on host T cells, IL15, and CAR T cell expansion were also studied. **Results:** As of the data cut, 72 pts were treated. Common Grade $\geq$3 AEs were neutropenia (71%), thrombocytopenia (42%), anemia (39%), and lymphopenia (28%). Neutrophil, hemoglobin, and platelet counts did not differ by ALLO-647 dose, suggesting these dim-CD52$^+$ cells were unaffected. Gr $\geq$3 infections were seen in 21% pts; 33 had infusion-related reactions (IRR; Gr 1: 13%; Gr 2: 32%; Gr 3: 1.4%). IRR incidence and severity were higher with HD ALLO-647. The optimal PK model included a saturable (concentration-dependent) elimination pathway; clearance varied as a function of baseline lymphocyte count (LC). Serum ALLO-647 levels increased with dose; median modelled Cmax was 4,224 and 14,139 ng/mL for LD and HD, respectively. With ALLO-647/Flu +/- Cy, all but 2 pts reached a LC nadir $< 0.05 \times 10^9$ cells/L, typically by D-3. Duration of lymphodepletion was typically longer with HD ALLO-647. Median duration of T-cell suppression ($<$ 10 cells/μl) was ~ 8.5 and 13.6 days from CAR T infusion, respectively, for LD and HD ALLO-647. With HD, T cell counts were $<$ 10 through D+28 in 17 pts and $>$ 10 in 2. In 68 evaluable pts, compared to LD, HD ALLO-647 was associated with higher D0 serum IL15 levels, which have been linked to improved clinical response (eg, Kochenderfer *JCO* 2017). Higher CAR T expansion was also observed post D+14 with HD ALLO-647 compared to LD, creating an opportunity for clinical response. **Conclusions:** ALLO-647/Flu +/- Cy had a tolerable safety profile and produced a deep and durable window of lymphocyte depletion. ALLO-647 exhibited target-mediated drug disposition; clearance increased with higher baseline LC. HD was associated with higher IL15 levels and better CAR T expansion, suggesting dose responses. Enrollment in both studies is ongoing; updated safety and PK/PD data will be presented. Clinical trial information: NCT04093596. Research Sponsor: Allogene Therapeutics.

2528 **Poster Session**

Novel CoupledCAR technology for treating colorectal cancer.

Lei Xiao, Song Li, Chengfei Pu, Zhiyuan Cao, Xinyi Yang, Ning Li, Youli Luo, Haiyan Zhao, Hang Yang, Xi Huang, Xiaogang Shen, Xiuwen Wang, Yongping Song, Junjie Mao, Pengfei Pang, Qun Hu, Zhao Wu, Victor Lu; Innovative Cellular Therapeutics Co., Ltd, Shanghai, China; Shandong University, Jinan, China; Innovative Cellular Therapeutics, Shanghai, China; Zhengzhou University, Zhengzhou, China; Sun Yat-sen University, Guangzhou, China; Inner Mongolia Medical University, Neimenggu, China; InnInner Mongolia Medical University, Neimenggu, China

Background: Chimeric antigen receptor (CAR) T cell therapy has made significant progress in the treatment of blood cancers such as leukemia, lymphoma, and myeloma. However, the therapy faces many challenges in treating solid tumors. These challenges include physical barriers, tumor microenvironment immunosuppression, tumor heterogeneity, target specificity, and limited expansion *in vivo*. **Methods:** We designed a CAR lentivirus vector that consisted of a humanized CD19-specific single-chain variable fragment (scFv), a 4-1BB costimulatory domain, and a CD3ζ signaling domain.The lentivirus was produced by transfecting HEK-293T cells with CAR lentiviral vectors and viral packaging plasmids. Patient's CD3 T cells was cultured in X-VIVO medium containing 125U/mL 1interleukin-2 (IL-2), and transduced with CAR lentivirus at certain MOI 24h after stimulated by anti-CD3/CD28 magnetic beads. Transduction efficiency was evaluated at 7 to 9 days after CAR lentivirus transduction, and quality controls for fungi, bacteria, mycoplasma, chlamydia, and endotoxin were performed. After infusion, serial peripheral blood samples were collected, and the expansion and the cytokine release of CART cells were detected by FACS and QPCR,respectively. The evaluation of response level for patients were performed at month 1,month 3,and month 6 by PET/CT. **Results:** We engineered CoupledCAR T cells with lentiviral vectors encoding an anti-GCC (guanylate cyclase 2C) CAR molecule. To verify the safety and efficacy of CoupledCAR-T cells for treating solid tumors, we conducted several clinical trials for different solid tumors, including seven patients with colorectal cancer. These seven patients failed multiple rounds of chemotherapy and radiotherapy. In the clinical trial, the metastatic colorectal cancer patients were infused with autologous anti-GCC CoupledCAR-T cells range from 4.9×10^5/kg to 2.9×10^6/kg. We observed that CoupledCAR-T cells expanded significantly in the patients and infiltrated tumor tissue sites, demonstrating enhanced anti-tumor activities. PET/CT showed significant tumor shrinkage and SUV max declined, and the ongoing responses were monitored. Patient 3 achieved complete response and the best overall response rate (ORR, include complete remission, complete metabolic response, and partial response.) was 57.1% (4/7), complete remission (CR) rate was 14.3% (1/7). **Conclusions:** In conclusion, the clinical data demonstrated that CoupledCAR-T cells effectively expanded, infiltrated tumor tissue sites, and kill tumor cells in patients with colorectal cancer. We used immunotherapy to achieve complete remission in patients with advanced colorectal cancer for the first time. We are recruiting more colorectal cancer patients to further test the safety and efficacy of anti-GCC CoupledCAR T cells. Since our CoupledCAR technology is a platform technology, we are expanding it to treat other solid tumors using different target tumor markers. Research Sponsor: N/A.

2529 **Poster Session**

First-in-human data of ALLO-501A, an allogeneic chimeric antigen receptor (CAR) T-cell therapy and ALLO-647 in relapsed/refractory large B-cell lymphoma (R/R LBCL): ALPHA2 study.

Frederick Lundry Locke, Shahbaz Malik, Michael Timothy Tees, Sattva Swarup Neelapu, Leslie Popplewell, Jeremy S. Abramson, Jennifer T. McDevitt, Chu Ri Shin, Eren Demirhan, Cyril Konto, Lazaros J. Lekakis; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; SCRI Austin, Austin, TX; Moffitt Cancer Ctr and Rsrch Inst, Tampa, FL; The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX; City of Hope, Duarte, CA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; MedImmune, Gaithersburg, MD; Allogene Therapeutics, San Francisco, CA; Allogene Therapeutics, South San Francisco, CA; Rinat-Pfizer, South San Francisco, CA; University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Background: Allogeneic CAR T cell therapy addresses logistical/manufacturing challenges inherent in autologous (auto) CAR T therapy. ALLO-501A, which uses Cellectis technologies, is an allogeneic anti-CD19 CAR T cell product whose a) disrupted TCRα gene may reduce GvHD risk, and b) edited CD52 gene may permit use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells. **Methods:** The ongoing ALPHA2 study is a single-arm, open-label, 2 phase study of ALLO-501A in non-HLA matched patients (pts) with R/R LBCL and $\geq$2 prior lines of therapy. Prior auto CD19 CAR T therapy is allowed if tumors remain $CD19^+$. Following lymphodepletion (LD) with ALLO-647 (60 mg or 90 mg), fludarabine 30 mg/m^2/d x 3d (Flu), and cyclophosphamide 300 mg/m^2/d x 3d (Cy), escalating doses of ALLO-501A (40 [DL1] or 120 [DL2] x 10^6 viable CAR T cells) were administered. Retreatment was allowed for PD or SD with suboptimal CAR T expansion. Pts who had $\geq$SD at D28 could receive a second dose in a consolidation cohort. Phase 1 assessed safety/tolerability and cell kinetics of escalating doses of ALLO-501A following LD. **Results:** By 1/15/21, 11/11 enrolled pts received ALLO-647 (60 mg: n=6; 90 mg: n=5). Mean duration from enrollment to start of therapy was 6 days. After LD, 1 and 9 pt(s) were treated with ALLO-501A at DL1 and DL2, respectively; 1 pt developed CNS lymphoma and was not treated. Of 10 pts treated, 1 pt received retreatment and 4 pts were enrolled in the consolidation cohort. Pts had a median age of 60 years; 8 were $\geq$ stage III at diagnosis, 5 had IPI scores $\geq$3, and 3 had baseline LDH $>$ 2x ULN. Median number of prior therapies was 3 (range 2 – 7); 3 pts had received auto CD19 CAR T cell therapy. 4/8 evaluable pts had rapidly PD at study entry. Median FU was 1.7 months. No dose modifications were required and no pt experienced DLTs. The most common AEs were anemia, leukopenia, neutropenia and thrombocytopenia (73%); and lymphopenia (64%). No GvHD or ICANS were reported. CRS was seen in 2 (18%) pts, both Grade $<$ 3. Infusion-related reactions, all grade $<$3, were observed in 4 (36%) pts. D28 response data are available for 8 pts: 1 died of PD before D28; 4 additional pts had PD, including 2 who progressed 2 and 3 mos. after auto CAR T; 1 had SD; and 2 (both DL2) had CR. Of those in CR, 1 had peak ALLO-501A expansion at D14, persistence until D42, and ongoing CR at 4 mo; 1, with a 4-mo response to prior auto CAR T, had peak expansion at D28 and remains in ongoing CR at D56 after ALLO-501A with pending persistence. **Conclusions:** This dose escalation cohort contained heavily pretreated, actively progressing pts, some of whom had failed auto CAR T. Preliminary data suggest an acceptable safety profile following ALLO-501A and ALLO-647 and early signs of efficacy in LBCL. Enrollment into the consolidation cohort is ongoing; updated clinical/biomarker data of resistance and clinical activity will be presented. Clinical trial information: NCT04416984. Research Sponsor: Allogene Therapeutics.

2530 **Poster Session**

CAR-T cells to deliver engineered peptide antigens and reprogram antigen specific T cell responses against solid tumors.

Daniel Lee, Andy J Minn, Lexus R Johnson; University of Pennsylvania, Philadelphia, PA

Background: Neoantigen depleted malignancies such as colorectal cancer demonstrate primary resistance to immune checkpoint blockade, and solid tumors in general have shown resistance to chimeric antigen receptor (CAR) T cell therapy. However, CAR-T cells have been shown to be capable of delivering various therapeutic molecules in a targeted fashion to the tumor microenvironment, in some cases through extracellular vesicles (EVs). In vivo studies have shown that the presentation of foreign viral peptides by solid tumors can reprogram bystander virus-specific cytotoxic T cells (CTLs) against tumor cells. In this study, we demonstrate that CAR-T cells can deliver engineered peptide antigens to solid tumors, leading to presentation on tumor cells and anti-tumor response. **Methods:** Second generation CAR-T cells (41BB endodomain) targeting human CD19 (19BBz) or human mesothelin (M5BBz) were generated via retroviral and lentiviral transduction respectively. CAR-T cells were engineered to co-express peptides such as SIINFEKL of ovalbumin and NLVPMVATV of CMV pp65 among others. Peptides were isolated from EVs via ultracentrifugation. For in vivo studies, C57BL/6 or NSG mice were injected on the flank with relevant tumors and treated with peptide-CAR-T cells. In vitro studies utilized flow cytometry and xCELLigence killing assays. **Results:** Murine 19BBz CAR-T cells expressing the SIINFEKL peptide of ovalbumin (ova-19BBz) were found to transfer SIINFEKL peptide to tumor cells via EVs *in vitro* and *in vivo*, leading to peptide presentation on MHC-I of tumor cells. This resulted in significantly delayed tumor growth in tumor bearing mice transfused with OT-I T cells to mimic an existing antigen specific T cell pool. We expanded on these findings by isolating EVs from human M5BBz CAR-T cells expressing CMV viral peptides. Peptide-CAR-T EVs were co-cultured with human ovarian cancer cells to assess presentation to Jurkat T cells. Finally, we utilized primary human T cells from CMV+ healthy donors to assess the clinical feasibility of our peptide delivery approach. **Conclusions:** CAR-T cells can be engineered to deliver peptides to tumor cells for presentation and subsequent targeting by antigen specific CTLs. This represents a novel strategy for the treatment of non-immunogenic tumors. Research Sponsor: Mark Foundation for Cancer Research, Other Foundation, U.S. National Institutes of Health.

2531 **Poster Session**

A single-arm phase Ib study of autologous cytokine-induced killer (CIK) cell immunotherapy in combination with sintilimab plus chemotherapy in patients with advanced non-small cell lung cancer (NSCLC)-CCICC-002.

Xiubao Ren, Li Zhou; Department of Biological Therapy, Tianjin Cancer Institute & Hospital, Tianjin, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

Background: Immune checkpoint inhibitors plus chemotherapy had showed benefits for advanced non–-small-cell lung cancer (NSCLC) patients without targetable mutations. Autologous cytokine-induced killer (CIK) cells can restore the antitumor immunity to improve patient outcome. Combining CIK cells with anti-PD-1 mAb plus chemotherapy may strengthen the results in patients with advanced NSCLC. **Methods:** This is a single-center, open-label, phase 1b trial of combination CIK cells with sintilimab (anti-PD-1 mAb) plus chemotherapy in stage IIIB-IV NSCLC patients. Systemic therapy nave patients received platinum-based doublet chemotherapy, sintilimab, and CIK cells every 3 weeks for 4 cycles，then sintilimab, and CIK cells for maintenance therapy until disease progression or unacceptable toxicity. **Results:** From May 2019 to Jan 2021, 34 patients (19 squamous，15 non-squamous NCSLC)aged 46-73 years (median age 64 years) were enrolled. Among 32 evaluable patients, the ORR was 81.3% (73.7% in squamous and 92.3% in non-squamous NSCLC)and DCR was 100%. Among the 25 PR assessed by RECIST, CMR was demonstrated in 5 (23.1%) by PET-CT. Among 3 patients with brain metastases, 2 patients achieve intracranial CR, and 1 was PR. With a median follow-up of 7.5 months, the median DOR was not reached (range 0.5m-NA), and the median PFS and OS were not mature. Grade 3 or more TRAEs included pneumonia (n = 3); thrombocytopenia, leukopenia (n = 2 each); anemia, dysphagia, cardiomyopathy, rash (n = 1 each). Biomarkers and subgroups which correlated with efficacy and AEs are being analyzed included TMB, PDL1 expression, distribution of TILs, cytokines and so on. **Conclusions:** CIK cells therapy in combination with sintilimab plus chemotherapy were well tolerated and showed encouraging efficacy. Further studies are warranted to confirm these preliminary results. Research Sponsor: Tianjin Medical University Cancer Institute and Hospital. Clinical trial information: NCT03987867. Research Sponsor: National Key Technologies R&D Program of China grant Awards No. 2015BAI12B12 and 2018YFC1313400.

	All pts (n=32)	Squamous NCSLC (n=19)	Non-Squamous- NCSLC (n=13)
MCR, n (%)	5 (15.6%)	2 (10.5%)	3 (23.1%)
PR, n (%)	21 (65.6%)	12 (63.2%)	9 (69.2%)
SD, n (%)	6 (18.8%)	5 (26.3%)	1 (7.7%)
ORR：% (95%CI)	81.3% (67%-95.5%)	73.7% (51.9%-95.5%)	92.3% (75.5%-109.1%)
PFS at 6 month	84.4% (70.4%-98.6%)	81.2% (61.8%-100.6%)	90% (71.4%-108.6%)

2532 **Poster Session**

A phase I-IIa study of genetically modified Tie-2 expressing monocytes in patients with glioblastoma multiforme (TEM-GBM Study).

Gaetano Finocchiaro, Bernhard Gentner, Francesca Farina, Alessia Capotondo, Marica Eoli, Elena Anghileri, Matteo Giovanni Carabba, Valeria Cuccarini, Francesco DI Meco, Federico Legnani, Bianca Pollo, Maria Grazia Bruzzone, Marco Saini, Paolo Ferroli, Roberto Pallini, Alessandro Olivi, Stefania Mazzoleni, Carlo Russo, Luigi Naldini, Fabio Ciceri; Neuro-Oncology Unit-IRCCS San Raffaele Scientific Institute, Milan, Italy; San Raffaele Telethon Institute for Gene Therapy-IRCCS San Raffaele Scientific Institute, Milan, Italy; Hematology and Bone Marrow Transplantation Unit-IRCCS San Raffaele Scientific Institute, Milan, Italy; Neuro-Oncology Unit-Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Neuroradiology Unit-Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Neurosurgery Unit-Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Neuropathology Unit-Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Neurosurgery Unit-Policlinico Gemelli Hospital, Rome, Italy; Genenta Science, Milan, Italy; San Raffaele Telethon Institute for Gene Therapy, San Raffaele Vita-Salute University, Milan, Italy

Background: Genetically modified cell-based therapies are relevant in immuno-oncology due to their potential for tumor specificity & potential durability. We developed a cell-based treatment, Temferon, relying on ex-vivo transduction of autologous HSPCs to express therapeutic payloads within the tumor microenvironment. Temferon targets IFNa to Tie-2 expressing macrophages (TEMs). **Methods:** TEM-GBM is an open-label, Phase I/IIa dose-escalation study evaluating safety & efficacy of Temferon in up to 21 newly diagnosed patients with glioblastoma & unmethylated MGMT promoter. Autologous HSPCs are transduced ex-vivo with a lentiviral vector encoding for IFNa. The transgene expression is confined to TEMs due to the Tie2 promoter & the post-transcriptional regulation by miRNA-126. **Results:** As of January 17 2021, 15 patients have been enrolled; 9 received Temferon (D+0) with follow-up of 61 – 559 days. There was rapid engraftment & hematological recovery after the conditioning regimen. Median neutrophil & platelet engraftment occurred at D+13 & D+12, respectively. Temferon-derived differentiated cells, as determined by the presence of vector genomes in the DNA of peripheral blood & bone marrow cells, were found within 14 days post treatment & persisted subsequently, albeit at lower levels (up to 18 months). We also detected very low concentrations of IFNa in the plasma (median 5pg/ml at D+30; baseline $<$ LLOQ) & in the cerebrospinal fluid, suggesting tight regulation of transgene expression. Three deaths occurred: two at D+343 & +402 after Temferon administration due to disease progression, & one at D+60 due to complications following the conditioning regimen. Seven patients had progressive disease (PD; range D+27-239) as expected for this tumor type. SAEs include infections, venous thromboembolism, brain abscess, hemiparesis, GGT elevation & poor performance status compatible with autologous stem cell transplantation, concomitant medications & PD. Four patients underwent second surgery. These recurrent tumors had gene-marked cells present & increased expression of IFN-responsive gene signatures compared to diagnosis, indicative of local IFNa release by TEMs. In one patient a stable lesion (as defined by MRI) had a higher proportion of T cells & TEMs within the myeloid infiltrate & an increased IFN-response signature than in a progressing lesion. The T-cell immune repertoire changed with evidence for expansion of tumor-associated clones. Tumor microenvironment characterization by scRNA & TCR sequencing is ongoing. **Conclusions:** Our interim results show that Temferon is well tolerated by patients, with no dose limiting toxicities identified to date. The results provide initial evidence of Temferon potential to modulate the TME of GBM patients, as predicted by preclinical studies. Clinical trial information: NCT03866109. Research Sponsor: Genenta Science.

2533 **Poster Session**

In-depth immune and molecular profiling of melanoma patients receiving adoptive T-cell therapy reveals biomarkers of efficacy in ATATIL study.

Angela Orcurto, Johanna Chiffelle, Eleonora Ghisoni, David Barras, Isaac Crespo, Blanca Navarro Rodrigo, María Ochoa de Olza, Martina Imbimbo, Sylvie Rusakiewicz, Stephanie Tissot, Philippe O Gannon, Urania Dafni, Stefan Zimmermann, Lana E. Kandalaft, Olivier Michielin, Michal Bassani-Sternberg, Denarda Dangaj, Lionel Trueb, Alexander Harari, George Coukos; Department of Oncology, Ludwig Institute for Cancer Research Lausanne, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; Faculty of Nursing, National and Kapodistrian University of Athens, Athens, Greece

Background: Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TIL) has demonstrated a curative potential for patients with metastatic melanoma (MM). Nevertheless, activity remains unsatisfactory in many patients, requiring development of biomarkers that predict therapeutic efficacy. We report results of a single-center phase I study to assess feasibility, safety and efficacy of TIL-ACT in MM patients (NCT03475134). **Methods:** Patients with MM refractory to at least one prior line of therapy received TIL therapy with lymphodepleting chemotherapy before T-cell infusion, followed by high-dose interleukin-2. RDG- and FDG-PET imaging was performed before and after TIL infusion. Multispectral immuno-fluorescence (mIF) imaging and bulk-RNA sequencing (Seq) were performed on tumor samples pre-ACT and post-ACT (day+30 and upon progression). Single-cell RNA-Seq and TCR-Seq were performed on pre-ACT tumor and ACT product, as well as on tumor-reactive and neoantigen-specific TILs and on longitudinal blood samples. **Results:** As of 02/02/2021, thirteen patients (enrolled between March 2018 and December 2020) have successfully completed TIL-ACT therapy, with a median follow-up of 9.5 months (IQR 3.0 -24.6). Median age was 53 years (range 20-69) and all were previously treated with PD-1 based blockade. Median number of TILs infused was 55.0 $x10^9$ cells (range 12.8-84.7). The best overall response rate by RECIST 1.1 and disease control rate in evaluable patients was 41.7% (5/12) and 50% (6/12) respectively at 3 months. Two patients have an ongoing near-complete response at 3 years. Up to data cut-off, 10 patients have progressed by RECIST v1.1, with median PFS of 4.8 months (95% CI 1.5 - 9.6), while median OS is not reached. mIF revealed biomarkers of response, which may allow proper identification of patients in subsequent studies. In addition, deep sequencing of bulk and neoepitope-specific TIL clonotypes highlighted transcriptomic signatures revealing cell programs regulating *in vitro* expansion, *in vivo* blood persistence as well as tumor infiltration post-ACT. RGD-PET data will also be presented. **Conclusions:** We demonstrate reproducibility of TIL-ACT in our center, consistently with previous reports. Comprehensive translational studies reveal immune correlates of clinical responses that contribute to the understanding of mechanisms of TIL potency and will guide the development of next-generation cell products. Clinical trial information: NCT03475134. Research Sponsor: Ludwig Institute for Cancer Research, Canton de Vaud, and BMS.

2534 **Poster Session**

PSMA targeted armored chimeric antigen receptor (CAR) T-cells in patients with advanced mCRPC: A phase I experience.

Matthew H. Carabasi, Meredith McKean, Mark N. Stein, Michael Thomas Schweizer, Jason J. Luke, Vivek Narayan, Russell Kent Pachynski, Rahul Atul Parikh, Jingsong Zhang, Thomas J. Fountaine, Jamie Rosen, Pam Hufner, Whitney Gladney, Karen Chagin; Thomas Jefferson University, Philadelphia, PA; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; Columbia University Medical Center, New York, NY; University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; University of Pittsburgh, Pittsburgh, PA; University of Pennsylvania, Philadelphia, PA; Washington University, St. Louis, MO; Kansas University Medical Center, Kansas City, KS; Moffitt Cancer Center, Tampa, FL; Tmunity Therapeutics, Inc, Philadelphia, PA

Background: CART-PSMA-TGFβRDN cells are autologous T cells engineered via lentiviral transduction to express a dominant negative form of TGFβRII (TGFβRDN) and a chimeric antigen receptor (CAR) with specificity to prostate specific membrane antigen (PSMA). The TGFβRDN renders CAR T cells resistant to TGFβ-mediated immunosuppression. CART-PSMA-02 is a multi-center, open-label, Phase 1 study evaluating the safety and feasibility of dosing patients with metastatic castration resistant prostate cancer (mCRPC) with CART-PSMA-TGFβRDN (NCT04227275). **Methods:** This is a 3+3 dose escalation study to determine the recommended phase 2 dose and schedule of CART-PSMA-TGFβRDN cells following lymphodepleting chemotherapy with cyclophosphamide and fludarabine. Single and fractionated doses are being evaluated. A cohort expansion will enroll patients to further explore the safety of the selected dose and schedule. **Results:** As of January 2021, 6 patients (pts) have been treated. Two pts were treated in the first dose level (1-3 x10^7 transduced T cells (TDN)). Four pts were treated in the second dose level (1-3 x 10^8 TDN with fractionated dosing). AEs occurring in $\geq$50 % of pts included cytokine release syndrome (CRS), anemia, thrombocytopenia, increased creatinine, nausea, fatigue, pyrexia and dehydration. No DLTs occurred in the 1st dose level. Four pts in the 2nd dose level developed CRS (3 Gr 1 and 1 Gr 2). One pt developed rapid G2 CRS that progressed to Gr 5 encephalopathy and Gr 5 multi-organ failure. Ferritin levels peaked at 56,974 ng/ml (baseline 2,903 ng/mL) despite aggressive immunosuppressive therapy including tocilizumab, dexamtheasone and anakinra. The post infusion cytokine profile indicated elevations in IL-1RA, TNF-alpha, VEGF, IL-10, MIP-1b, IFN-gamma, GM-CSF and notably lower levels of IL6 compared to published reports of CD19 CART-mediated CRS. Autopsy findings were consistent with HLH/MAS, confirming overactivity of the monocyte/macrophage compartment. Based on these observations, a modified immune toxicity management strategy that includes prophylactic anakinra (an IL1R antagonist) was instituted. Preliminary evidence of clinical activity of CART-PSMA-TGFβRDN was noted in the 2nd dose level. Two of 3 pts with 1 month follow-up demonstrated PSA decreases from baseline (1 with $>$95% decrease, 1 with $>$50% decrease). Both pts had stable disease per RECIST v1.1. A third pt with only 1 week follow-up had a 40% PSA decrease. Additional data analyses from all infused patients are ongoing and data from pts managed with modified immune toxicity management will be presented. **Conclusions:** Initial data indicates a unique immune toxicity profile and the potential for anti-tumor activity in mCRPC pts treated with CART-PSMA-TGFβRDN. Modified immune toxicity management could lead to identification of a manageable safety profile and therapeutically active dose. Clinical trial information: NCT04227275. Research Sponsor: Tmunity Therapeutics, Inc.

2535 **Poster Session**

A single-arm phase Ib study of multiple target cytotoxic T-lymphocyte (MCTL) in combination with toripalimab as second-line therapy in advanced non-small cell lung cancer (NSCLC).

Xiubao Ren, Weihong Zhang; Department of Biological Therapy, Tianjin Cancer Institute & Hospital, Tianjin, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Anti-PD-1/ PD-L1 (programmed cell-death 1) mAb treatment has been approved in the US and in Europe as second-line treatment for advanced NSCLC because of the good tolerance and efficacy in comparison with docetaxel. Unfortunately, The objective response rate is only around 20%. Multiple Target Cytotoxic T-lymphocyte (MCTL) cells can restore the antitumor immunity to improve patient outcome. Combining MCTL cells with anti-PD-1 mAb may strengthen the results as second-line treatment in patients with advanced NSCLC. (NCT04193098). **Methods:** This is a single-center, open-label, phase 1b trial of combination MCTL cells with toripalimab (anti-PD-1 mAb)as second-line treatment for advanced NSCLC. Systemic therapy patients received toripalimab every 3 weeks for 12 cycles and received MCTL cells every 3 weeks for 9 cycles, then toripalimab and MCTL cells for maintenance therapy until disease progression or unacceptable toxicity. **Results:** From June 2019 to October 2020, 14 pts aged 43-70 years (median age 59 years) were enrolled. The squamous/non-squamous ratio was 50%/ 50%. 8 (57.1%) were men, 13(92.8%) were ECOG PS=0-1, 5 (35.7%) had pleural effusion, and 3 (21.4%) had bone metastases. Among 13 evaluable pts, the ORR and DCR were 38.4% and 71.4%, At the time of data cutoff, the median DOR was not reached (range 8.25m-NA), the median PFS was 399 days (range 192d-NA), and the median OS were not mature. Adverse events (AEs) occurred in 5 (38.4%), No grade≥3 AEs events occurred. Immune-related AEs were thyroid hypofunction (3, 23%) and weak (2, 15.4%). Biomarkers which correlated with efficacy and AEs are being analyzed. **Conclusions:** Multiple Target Cytotoxic T-lymphocyte (MCTL) in combination with toripalimab as second-line treatment for advanced NSCLC because of the well tolerated and encouraging efficacy. Further studies are warranted to confirm these results. Research Sponsor: Tianjin Medical University Cancer Institute and Hospital. Clinical trial information: NCT04193098. Research Sponsor: National Natural Science Foundation of China grants Awards No. U20A20375.

2536 **Poster Session**

Initial results of a first-in-human, dose escalation study of a cell-based vaccine in HLA A*02+ patients (pts) with recurrent, locally advanced or metastatic HPV16+ solid tumors: SQZ-PBMC-HPV-101.

Antonio Jimeno, Joaquina Celebre Baranda, Monica M. Mita, Michael S. Gordon, Matthew H. Taylor, Wade Thomas Iams, Filip Janku, Ursula A. Matulonis, Howard Bernstein, Scott Loughhead, Martin Kornacker, Ricardo F. Zwirtes, Oliver Rosen, Cathy Eng; University of Colorado Comprehensive Cancer Center, Aurora, CO; University of Kansas Cancer Center, Fairway, KS; Cedars-Sinai Medical Center, Los Angeles, CA; Pinnacle Oncology Hematology, Arizona Center for Cancer Care, HonorHealth Research Institute Clinical Trials Program, Virginia G. Piper Cancer Center, Scottsdale, AZ; Providence Cancer Institute, Portland, OR; Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Chicago, IL; The University of Texas MD Anderson Cancer Center, Houston, TX; Dana-Farber Cancer Institute, Boston, MA; SQZ Biotechnologies, Watertown, MA; Roche, Basel, Switzerland

Background: Ineffective MHC-I presentation of tumor antigens to CD8+ T cells limits T cell activation and the efficacy of cancer vaccines. The Cell Squeeze technology drives peripheral blood mononuclear cells (PBMCs) through a microfluidic chip leading to temporary cell membrane disruption and delivery of HPV16 E6 and E7 antigens cytosolically. These antigen presenting cells (APC) were matured with CpG7909 and were not genetically modified. Preclinically, this approach showed improvement in MHC-I presentation for human and murine cells. In murine tumor studies, m-SQZ-PBMC-HPV elicited robust CD8+ T cell responses and improved anti-tumor effects when compared to other vaccine modalities. **Methods:** SQZ-PBMC-HPV-101 included pts with incurable HPV16+ cancers progressing after unlimited prior therapy, ECOG 0-1, adequate organ function and a biopsiable lesion. After leukapheresis at the study site, manufacturing of the cryopreserved product took $<$ 24 hours with a vein-to-vein time of approx. 1 week. Out-patient SQZ-PBMC-HPV was given IV q 3 weeks without a conditioning regimen. Double antigen priming (DP) was introduced with Cohort 3 and occurred on Cycle 1 Days 1 and 2. Maximum treatment duration for each patient was determined by the cell batch size. Response was assessed via RECIST 1.1 and iRECIST. Investigational biomarkers were measured pre- and post-treatment. **Results:** 12 pts [anal (7), head and neck (3), and cervical (2)] were dosed in 3 cohorts (3 pts in 0.5 x10e6/kg, 5 pts in 2.5 x10e6/kg, and 4 pts in 2.5x 10e6/kg [DP]). Median lines of prior Tx were 4 (range 1 - 7) and all but one pt were pretreated with checkpoint inhibitors (CPI); 10 pts had liver or lung metastases. All batches of SQZ-PBMC-HPV demonstrated CD8 activation in vitro after thawing, and batch size did not limit therapy duration at dose levels tested to date. Median number of doses were 3 (3 - 10), 3 (2 - 4), and 3 (3 – 4) in the 3 cohorts, respectively. One pt (10 doses) remained on study for 42 weeks. Tx was well-tolerated and there were no DLTs, Grade (G) $>$3 related SAEs or related G $>$3 AEs. One pt in cohort 1 experienced both a G2 infusion-related reaction and cytokine release syndrome. One pt in cohort 2 was not evaluable for DLT. Four out of 10 evaluable pts had stable disease per RECIST 1.1 as the best response. Preliminary tumor analyses pre- and post-therapy indicated increased immune activity in some patients after SQZ infusion. **Conclusions:** SQZ-PBMC-HPV-101 demonstrated clinical feasibility of the Cell Squeeze technology and favorable tolerability of engineered APCs. The study allows for the characterization of the immunogenicity of engineered APCs in humans. Preliminary results warrant the testing in combination with CPI. Efficacy, safety, and correlative biomarker data will be presented, from pre- and post-therapy biopsies and blood samples. Clinical trial information: NCT04084951. Research Sponsor: SQZ Biotechnologies.

2537 **Poster Session**

Anakinra (AKR) prophylaxis (ppx) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) receiving orvacabtagene autoleucel (orva-cel).

Luciano J. Costa, Sham Mailankody, Paul Shaughnessy, Parameswaran Hari, Jonathan L. Kaufman, Sarah Marie Larson, David Dingli, Kelvin Lee, Kristin Conte, Todd DeVries, Julia Piasecki, Meng Li, Ronald L. Dubowy, Myo Htut; University of Alabama at Birmingham, Birmingham, AL; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon-Methodist Healthcare System, San Antonio, TX; Medical College of Wisconsin, Milwaukee, WI; Winship Cancer Institute of Emory University, Atlanta, GA; Univ of California Los Angeles, Los Angeles, CA; Mayo Clinic, Rochester, MN; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Bristol Myers Squibb, Summit, NJ; Bristol Myers Squibb, Seattle, WA; Bristol Myers Squibb, Princeton, NJ; Judy and Bernard Briskin Center for Myeloma, City of Hope, Arcadia, CA

Background: Orva-cel is a B-cell maturation antigen–targeted chimeric antigen receptor (CAR) T cell therapy being evaluated in the phase 1/2 EVOLVE study (NCT03430011) in pts with RRMM who had at least 3 prior lines of therapy (Tx). We previously reported safety and efficacy in the phase 1 study and established the recommended dose (RD) of orva-cel as 600×10^6 CAR^+ T cells (Mailankody et al, ASCO 2020). Cytokine release syndrome (CRS), a dominant toxicity of CAR T cell therapy, is mediated in part by IL-1. We explore the role of ppx with AKR, an IL-1 signaling inhibitor, on reducing the incidence of grade (G) ≥2 CRS after orva-cel treatment at the RD. **Methods:** Fourteen pts were enrolled sequentially for AKR ppx and treated with orva-cel at the RD. The non-AKR ppx control group comprised the remainder of the phase 1 pts receiving orva-cel at the RD (n = 19). The median follow-up (range) was 3.0 mo (1.8–6.2) for the AKR ppx group and 8.8 mo (5.3–12.2) for the non-AKR ppx group. AKR was administered as 100 mg SC the night before orva-cel infusion, 3 h before the infusion (Day 1), and q24 h on Days 2–5. Dosing was increased to q12 h if CRS developed. CRS was graded by Lee (2014) criteria. Tocilizumab (T) and steroids (S) were used per protocol-specified treatment management guidelines. **Results:** Disease characteristics and outcomes are shown in the table. In AKR ppx and non-AKR ppx groups, median number of prior regimens was 6 and 5, and bridging Tx was used in 57% and 68% of pts, respectively. The total frequency of CRS was similar in the 2 groups, but with less G 2 in the AKR ppx pts; relative risk (95% CI) = 0.54 (0.21, 1.38). No G ≥3 CRS was seen in either group. The incidence of neurological events (NE), G ≥3 infection, and macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH) was similar. T and S use was numerically lower with AKR ppx. Orva-cel expansion kinetics were similar in the 2 groups. All pts had a 2-month efficacy assessment, with ORR in 100% of AKR ppx and 95% of non–AKR ppx pts. **Conclusions:** In this nonrandomized evaluation of AKR ppx with orva-cel treatment, the incidence of G ≥2 CRS was lower in pts receiving AKR ppx. The use of AKR ppx produced no adverse effect on the incidence of NE, infection, or MAS/HLH, nor on orva-cel expansion or disease response. These results warrant further study of AKR ppx in CAR T cell therapy. Clinical trial information: NCT03430011. Research Sponsor: Bristol-Myers Squibb Company.

Disease characteristics and safety outcomes in the phase 1 EVOLVE study.

	AKR ppx, n = 14	Non–AKR ppx, n = 19
International staging system, stage I / II / III, %	43 / 36 / 21	47 / 37 / 16
Measurable serum and/or urine M-protein, n (%)	13 (93)	14 (74)
LDH >ULN, n (%)	3 (21)	0 (0)
CRS, G 1 / G 2 / G ≥3, %	64 / 29 / 0	37 / 53 / 0
CRS time to onset / duration, median (range), days	2 (1–11) / 3 (2–8)	2 (1–2) / 3 (1–7)
NE, G 1 / G 2 / G ≥3, %	7 / 7 / 7	5 / 5 / 0
Infection, G 1 / G 2 / G ≥3, %	0 / 0 / 14	16 / 11 / 11
MAS/HLH, G 1 / G 2 / G ≥3, %	0 / 7 / 0	5 / 0 / 5
Any T / multiple T / any S / T + S, %	79 / 29 / 43 / 43	90 / 37 / 63 / 63

2538 **Poster Session**

Preliminary analysis of a phase 1/2 study of NEXI-001 donor-derived multi-antigen-specific CD8$^+$ T-cells for the treatment of relapsed acute myeloid leukemia (AML) after allogeneic hematopoietic cell transplantation (HCT).

Monzr Al Malki, Sumithira Vasu, Dipenkumar Modi, Miguel-Angel Perales, Donna Bui, Vineetha Edavana, Sojung Kim, Lauren Suarez, Mathias Oelke, Dan BednÃ¡rik, Robert D. Knight, Juan Carlos Varela; City of Hope Medical Center, Duarte, CA; The Ohio State University, Columbus, OH; Karmanos Cancer Institute/Wayne State University, Detroit, MI; Memorial Sloan Kettering Cancer Center, New York, NY; City of Hope, Duarte, CA; NexImmune, Gaithersgurg, MD; NexImmune, Gaithersburg, MD; Neximmune, Inc., Gaithersburg, MD; Advent Health Blood and Marrow Transplant Program, Orlando, FL

Background: Allogeneic HCT is a potentially curative therapy for many patients with AML that relies on a graft-versus-leukemia (GvL) effect. Patients who relapse after allogeneic HCT have a poor prognosis and few treatment options. Donor lymphocyte infusion (DLI) can achieve a GvL effect in some patients, however, efficacy is frequently associated with the development graft-versus-host disease (GVHD). There is a substantial need for treatment approaches that enhance the benefit of GVL while decoupling toxicities associated with GVHD. **Methods:** We report ongoing results from a first-in-human study (NCT04284228) of a non-genetically engineered, donor-derived adoptive cellular therapy product, NEXI-001, which contains multiple populations of CD8$^+$ T cells that recognize different HLA 02.01-restricted peptides from the WT1, PRAME, and Cyclin A1 antigens. NEXI-001 contains T cell memory subtypes that combine anti-tumor potency with long-term persistence. **Results:** At the time of this analysis, 7 patients with relapsed AML after allogeneic HCT were enrolled. Five Patients were treated with single infusions of NEXI-001 at three different dose levels: 50, 100 and 200 million. Currently, the median follow-up is 5 months. Significantly, GVHD, cytokine release syndrome, neurotoxicity, or NEXI-001-related adverse events were not observed. NEXI-001 treatment resulted in reductions in red blood cell and platelet transfusions and increased donor chimerism. Decreases in myeloblasts in bone marrow and peripheral blood and reduction in the size of an extramedullary myeloid sarcoma were suggestive of an anti-leukemia effect (Table). Correlative studies indicate that NEXI-001 CD8$^+$ cells undergo a rapid proliferation after infusion and are also associated with a robust hostlymphocyte recovery that occurs as quickly Day 3 after infusion. NEXI-001 infused CD8$^+$T cells are detectable by multimer staining in peripheral blood of patients and proliferate over time. TCR sequencing analyses determined that infused NEXI-001 cells contain T cell clones that were undetectable in the peripheral blood of patients at baseline but were detected in blood and bone marrow and persist over time. **Conclusions:** NEXI-001 has the potential to enhance GvL effect without the associated toxicities of GVHD, cytokine release syndrome, and neurotoxicity. Due to these encouraging results, the trial will proceed with an evaluation of repeated NEXI-001 dosing Clinical trial information: NCT04284228. Research Sponsor: NexImmune Inc.

Pt	NEXI-001 Dose	SAE	Initial Clinical Response
1	50m	No	Stable BM blasts Decreased need for transfusions Increased ANC Improved donor chimerism
2	100m	No	Stable BM blasts 18% reduction in size of myeloid sarcoma
3	100m	No	No response
4	100m	No	Stable BM blasts Decrease in PB blasts Decreased need for transfusions Increased ANC
5	200m	No	Stable BM blasts

2539 **Poster Session**

Progression prediction model for solid tumors with clinical and immunological parameters.

Aleksei Viktorovich Novik, Dmitrii Viktorovich Girdyuk, Tatyana Leonidovna Nekhaeva, Natalia Viktorovna Emelyanova, Anna Semenova, Gulfiya Midhatovna Teletaeva, Dilorom Khamidovna Latipova, Svetlana Protsenko, Irina Alexandrovna Baldueva; N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russian Federation; N.N. Petrov National Medical Researc Center of Oncology, Saint-Petersburg, Russian Federation; N.N.Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russian Federation

Background: The immune system has well-known relation to tumor progression. Numerous immune-related parameters exist, but only a minor part could be used as biomarkers, especially dynamic ones. We trained a progression prediction model based on clinical features and peripheral immune system assessments. **Methods:** Patients with immunogenic (melanoma, 295, kidney cancer, 81), non-immunogenic (soft tissue sarcoma, 47, colorectal cancer, 26) and multiple primary tumors (29) with immunologic assessments before treatment (23.5%), on therapy (58.3), and in follow-up after the treatment (18.2%) were randomly divided in 7:3 ratio to the training and test groups. Counts of lymphocytes, T-, B, NK cells, cytotoxic lymphocytes, T-helpers were used as immunologic parameters. Age, sex, disease, stage, therapy, mutational status, last response on treatment, disease and therapy duration, previous treatments were used as clinical ones. The model was trained to predict disease progression in the next three months using Catboost gradient boosting. We used ROC AUC to test model performance and Yoden's index for optimal cutoff calculation. We also studied the influence of model prediction on overall survival (OS) and time to progression (TTP) on the test dataset using the Kaplan-Meyer method and Cox regression. **Results:** We used 1682 assessments of immune parameters (immune status, IS) done in 354 patients (average 5 per patient) to train the model and 616 IS in 124 patients for validation. All IS of one patient were in the same group. The ROC AUC value of the model was 0.801. The model prediction of progression increased the probability of progressive disease from 37.5 to 62% and decreased the response rate from 37,5% to 8.4% ($p = 0.016$). The model prediction did not add information over known prognostic factors for OS in the multifactorial model but was an independent prognostic factor for TTP (HR 2.204, $p = 0.011$). False-positive results separate the group of patients with poor prognosis (OS 16 months, TTP 6 months) among patients with clinical benefit from patients with favorable prognosis (OS 61 months, TTP 18 months, $p < 0.001$), who had a truly negative model prediction. The possibility of prognosis improvement with therapy change was an essential factor for OS and TTP prediction ($p < 0.001$). The model was useful in predicting higher OS in patients with disease progression ($p = 0.033$) and shorter response duration in patients with clinical benefit ($p = 0.03$). **Conclusions:** Our progression prediction model provides clinically useful information and can be used for decision making in several clinical situations. Its utility should be tested in a prospective trial.
Research Sponsor: None.

Concordance of blood and tissue TMB from NGS testing in real-world settings and their ability to predict response to immunotherapy.

Emma Sturgill, Amanda Misch, Carissa Jones, Daniel Luckett, Xiaotong Fu, Suzanne Fields Jones, Howard A. Burris III, David R. Spigel, Andrew Jacob McKenzie; Sarah Cannon Research Institute, Nashville, TN; Genospace, Boston, MA; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN

Background: Tumor mutational burden (TMB) detected by tissue-based Next Generation Sequencing (NGS) is a biomarker for immunotherapy (IO) response. Plasma-based NGS vendors have developed methods for quantifying TMB from circulating tumor DNA; however, the concordance of blood-TMB (bTMB) and tissue-TMB (tTMB) in real-world settings has not been examined. In this study, we analyzed paired bTMB-tTMB values from cancer patients in community oncology clinics who underwent both plasma- and tissue-based NGS testing to determine whether bTMB predicts response to IO equal to tTMB. **Methods:** We analyzed 112 patient-matched bTMB-tTMB pairs from 102 unique patients in community oncology settings who received both plasma- and tissue-based NGS profiling at any point in care. NGS results were reported by Foundation Medicine (n = 28 plasma, n = 66 tissue), Guardant Health (n = 78 plasma), and Caris Life Sciences (n = 42 tissue). NGS results were linked with electronic medical records in Genospace, Sarah Cannon's precision medicine platform. Pearson's correlation (r) and Lin's concordance (ρ) coefficients were used for statistical analysis. **Results:** bTMB exceeded the patient-matched tTMB by an average 2.4-fold; therefore, while the two values showed a positive linear correlation (r^2= 0.62, p = 0.01e-27) their concordance was only moderate (ρ = 0.58, n = 112). Gastrointestinal cancers exhibited the lowest correlation (r^2= 0.01, p = 0.5) and concordance (ρ = 0.03, n = 35). The discordance between bTMB and tTMB was not an outcome of the specimens being collected on different dates, as the bTMB/tTMB ratio did not correlate with the time between plasma and tissue specimen collection (r^2= 0.003, p = 0.84, n = 112). While a majority of bTMB-tTMB pairs had agreement in high *vs.* low status (High $\geq$ 10 mut/Mb; Low $<$ 10 mut/Mb), a considerable portion were bTMB-High/tTMB-Low (see table). Strikingly, the bTMB-High/tTMB-Low patients who received IO had an average time to treatment failure (TTF) that surpassed that of the bTMB-High/tTMB-High cohort (see table). Considering bTMB alone, patients with a high status outperformed those with a low status on IO (bTMB-High: TTF = 200 days, n = 21; bTMB-Low: TTF = 125 days, n = 12). **Conclusions:** In real-world settings where tissue- and plasma-based NGS panels are ordered as standard of care, bTMB values are consistently higher than tTMB values. This discrepancy leads to plasma-based tests resulting a TMB-High designation more frequently than tissue-based NGS tests. Patients who are TMB-High by plasma perform relatively well on IO, indicating that bTMB may be a particularly effective biomarker of IO sensitivity. Research Sponsor: None.

	tTMB-High	tTMB-Low
bTMB-High	n = 19 (17%) TTF = 183 days (n = 13)	n = 34 (30%) TTF = 227 days (n = 8)
bTMB-Low	n = 5 (5%) TTF = N/A	n = 54 (48%) TTF = 125 days (n = 12)

2541 **Poster Session**

Genomic immunotherapy (IO) biomarkers detected on comprehensive genomic profiling (CGP) of tissue and circulating tumor DNA (ctDNA).

Takayuki Yoshino, Hanna Tukachinsky, Jessica Kim Lee, Ethan Sokol, Dean C. Pavlick, Aparna Aiyer, David Fabrizio, Jeffrey Michael Venstrom, Saori Mishima, Yoshiaki Nakamura, Geoffrey R. Oxnard; National Cancer Center Hospital East, Kashiwa, Japan; Foundation Medicine, Inc, Cambridge, MA; Foundation Medicine, Inc., Cambridge, MA; Cancer Genomics Research, Foundation Medicine, Cambridge, MA; Foundation Medicine, Cambridge, MA; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: The dramatic impact of IO on treatment outcomes has heightened interest in predictive biomarkers, including genomic markers such as tumor mutational burden (TMB) and microsatellite instability (MSI). The recent FDA approval of pembrolizumab for previously treated advanced solid tumors with elevated TMB (≥10 mut/Mb on FoundationOne CDx, F1CDx) now requires a better understanding of the prevalence of this and other IO biomarkers detected on CGP, including differences between TMB detected in tissue and mutational burden detected in blood (bTMB). **Methods:** Tissue and plasma biopsies were profiled with two CGP panels of 324 genes with 0.8 Mb genome coverage (F1CDx and FoundationOne LiquidCDx). Mutational burden was calculated by counting somatic variants (single nucleotide and indels, including synonymous variants, excluding germline and driver mutations) with variant allele frequency (VAF) ≥5% in tissue (TMB) or ≥0.5% in ctDNA (bTMB). MSI score was assessed using 95 repetitive loci and principal component analysis (tissue) or >1,800 repetitive loci (plasma). ctDNA levels were estimated using composite tumor fraction (cTF), a metric based on aneuploidy and VAF. **Results:** Pan-cancer, TMB ≥10 was detected in 19% of tissue cases (29,238/156,294) and was common in melanoma (53%), small cell (41%), NSCLC (40%), bladder (39%), and endometrial (24%). bTMB ≥10 was detected in 13% of liquid biopsies (806/6,295); prevalence by cancer type was correlated with prevalence of elevated TMB (r = 0.81). Samples with bTMB ≥10 had an elevated cTF (median 13%, IQR 5 - 31%) as compared to samples with bTMB <10 (median 1.8%, IQR 0.6 - 7%, $p < 0.001$). Among 353 cases with both tissue and liquid CGP results (median 11 months apart), the relative prevalence of TMB ≥10 (12%) and bTMB ≥10 (13%) were similar, with concordant detection in 303 cases (86%). MSI-high (MSI-H) was seen in 2.2% of tissue CGP (3,461/156,294), most often in endometrial (19%), stomach (6.0%), and colorectal (5.3%) cancers, while MSI-H was detected in 0.68% of ctDNA specimens (43/6,295), which were also those with elevated cTF (median 11%, IQR 7 - 23%). Of 3,504 cases with MSI-H signature on tissue or liquid CGP, 1,619 (46%) had a pathogenic mutation detected in *MLH1/MSH2/MSH6/PMS2* (15% predicted germline). *CD274* amplification was detected in 1,207 cases (0.77%) of tissue CGP and 11 cases (0.17%) in ctDNA. **Conclusions:** Elevated bTMB is overall less prevalent than elevated tissue TMB, though these biomarkers are detected in similar cancer types. Detection of bTMB ≥10 and MSI-H in liquid biopsy was associated with elevated ctDNA levels, suggesting a limit of detection, and potentially indicating a more aggressive biology in samples positive for these biomarkers. Further investigation is needed to understand the utility of bTMB for identifying high TMB tumors that may benefit from IO. Research Sponsor: Foundation Medicine.

Impact of circulating tumor DNA (ctDNA) detection on survival outcomes of patients (pts) treated with immune-checkpoint inhibitors (ICIs) in early clinical trials.

Vladimir Galvao, Ignacio Matos, Ana Moreno, Guzman Alonso, Irene Brana, Maria Villar, Omar Saavedra Santa Gadea, Honey Kumar Oberoi, Javier Ros, Roger Berche, Natassia Ann Wornham, Carlota Arenillas, Cristina Saura, Ana Oaknin, Enriqueta Felip, Eva Muñoz-Couselo, Elena Elez, Josep Tabernero, Rodrigo Toledo, Elena Garralda; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Hospital Univ Vall d'Hebron, Barcelona, Spain; Vall dHebron Institute Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology and Vall d'Hebron University Hospital, Barcelona, Spain; Vall d'Hebron University Hospital, Vall d'Hebrón Institute of Oncology, Barcelona, Spain; Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Vall dHebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), UVic-UCC, Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, TX; Hospital Universitario Vall d'Hebron, Barcelona, Spain

Background: Detection of ctDNA is a promising tool for managing pts in oncology. Most methods require whole-genome sequencing of tumor samples followed by the design of personalized panels for tracking purposes. In this work, we evaluated the prognostic and predictive value of total ctDNA quantification, using shallow whole-genome sequencing (shWGS) exclusively from plasma samples, in a prospective cohort of pts treated with ICIs in early clinical trials. **Methods:** IchorCNA pipeline was used to quantify ctDNA of shWGS from plasma ctDNA samples of pts treated with ICIs in phase 1 trials, collected at baseline and prior to cycle 2 (prec2). We investigated the association and correlation of ctDNA levels with surrogate markers for tumor burden (LDH levels, summatory of target lesions (TL), liver metastasis) using Spearman and Kruskal-Wallis tests. Kaplan-Meier estimates of overall survival (OS) of pts with baseline detectable ctDNA levels versus undetectable ctDNA were calculated. A multivariate Cox proportional hazards model, including continuous classical prognostic factors (LDH, albumin, hemoglobin, derived Neutrophil-to-Lymphocyte ratio (dNLR), platelets, number of metastases sites, ECOG PS) and ctDNA was performed. An estimate of progression free survival (PFS) of pts with ctDNA increase levels in preC2 versus a non-increase group was evaluated. **Results:** Since January 2018, 113 pts with no standard-treatment options were included. Median (m) follow up was 14.8 months (mo). Baseline ctDNA levels correlated significantly with baseline TL ($R = 0.4$, $p < 0.001$) and LDH levels ($R = 0.61$, $p < 0.001$). Pts with liver metastasis had higher levels of ctDNA (11,68 ng/ml) versus pts with no liver disease (2,31 ng/ml) ($p < 0,001$). In the survival analysis pts with detectable baseline ctDNA (74 pts) had significantly shorter OS compared with pts with undetectable ctDNA (39 pts); median 9.6 m (8.4 – 16.4) and NA m (13.6-NA), respectively (HR = 2.25 [1.18-4.29] $p < 0.01$). In the multivariate analysis, only ctDNA and albumin levels maintained the impact in OS (HR = 1.03, $p < 0.05$ and HR = 0.22, $p < 0.05$, respectively). Pts with early increases in ctDNA had a shorter PFS compared with those with a stabilization or decrease, median 1.9 m (1.6 – 4.0) and 3.0 m (2.6 – 3.8), respectively (HR = 2.19 [1.31-3.67], $p < 0.01$). **Conclusions:** Quantification of baseline ctDNA using shWGS is a strong independent prognostic factor. Early dynamic changes of ctDNA could be a useful tool to predict PFS outcomes. Research Sponsor: Swiss Bridge Award and BBVA Foundation.

2543 **Poster Session**

Analysis of immune checkpoint blockade biomarkers in elderly patients using large-scale cancer genomics data.

Rossin Erbe, Zheyu Wang, Sharon Wu, Joanne Xiu, Neeha Zaidi, Marc E. Lippman, Claudine Isaacs, Reva K Basho, Heinz-Josef Lenz, Igor A. Astsaturov, John Marshall, Stephen Baylin, Elizabeth M. Jaffee, Evanthia T. Roussos Torres, Ashani Weeraratna, Hariharan Easwaran, Elana J. Fertig; Johns Hopkins School of Medicine, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Caris Life Sciences, Phoenix, AZ; Johns Hopkins Hospital, Baltimore, MD; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; Cedars-Sinai Medical Center, Houston, TX; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Fox Chase Cancer Center, Philadelphia, PA; Georgetown University, Washington, DC; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; University of Southern California, Keck School of Medicine, Department of Oncology, Los Angeles, CA; Johns Hopkins School of Public Health, Baltimore, MD; The Johns Hopkins University, Baltimore, MD

Background: Immune checkpoint blockade (ICB) immunotherapy in some cases elicits striking patient responses, but its efficacy appears to be dependent on several incompletely understood factors. Most studies of ICB therapies in elderly patients have concluded that they received no reduced benefit or even increased benefit compared to the younger patients analyzed, despite the systemic age-related immune changes that might be expected to produce a less effective immune response, such as loss of the capacity to generate new naive T cells. To understand and apply these results, it is necessary to investigate the relationship of age and the immune tumor microenvironment. **Methods:** We apply bioinformatics methods to genomic, transcriptomic, and clinical data from 9,523 patients across 31 cancer types from TCGA, 15,557 patients with breast, colon, or head and neck cancers from Caris Life Sciences, and 37,961 patients across 8 cancer types collected by GENIE. From these data we apply multivariate linear models across and within individual tumor types to estimate age-related associations to tumor mutational burden (TMB), T cell receptor diversity (miTCR), differential gene expression (edgeR), pathway enrichment (mSigDB and fgsea), and immune cell type infiltration (Quantiseq and MIXTURE). **Results:** Our analysis of large-scale molecular and clinical databases associates patient age with changes in several major biomarkers of ICB response. Notably, a robust correlation between increased tumor mutational burden and age was found across three different large cohorts (TCGA, Caris Life Sciences, and GENIE) in most ICB-approved cancer types. In the TCGA data, TMB increased with age pan-cancer ($p < 1x10^{-16}$) and in 7 of 9 ICB-approved cancer types. These associations were validated in the larger cohort of patient samples in GENIE, which demonstrated correlations between increased TMB levels and patient age in all eight ICB-approved cancer types assayed (Table), as well as in the Caris colorectal ($q < 0.001$) and breast ($q < 0.001$) cancer cohorts. Significant associations of age to other biomarkers of ICB response (checkpoint gene expression, immune infiltration, and immune related pathway signaling) will be presented. **Conclusions:** These results provide context for the efficacy of ICB in elderly patients, highlight potential biomarkers for the treatment of elderly patients with immunotherapies, and strongly suggest the value of large-scale prospective study of elderly cancer patients treated with ICB. Research Sponsor: U.S. National Institutes of Health.

Cancer Type	Estimated change in logTMB per year of age	Adjusted p-value	n
Breast	0.00550	9.17×10^{-28}	9485
Melanoma	0.0152	4.16×10^{-26}	3120
Esophagogastric	0.0120	8.23×10^{-20}	2133
Renal Cell Carcinoma	0.00942	5.91×10^{-15}	1329
Head and Neck	0.0125	5.90×10^{-12}	1255
Bladder	0.0107	3.14×10^{-10}	1762
Non-Small Cell Lung	0.00260	6.13×10^{-4}	10620
Colorectal	0.00230	1.34×10^{-3}	8257

SER-ONCOVID: Seroconversion in solid-tumor cancer patients after COVID-19 diagnosis.

Anna Pous, Eudald Felip, Olatz Etxaniz, Ainhoa Hernandez Gonzalez, Sofia España, Margarita Romeo, David James Pinato, Anna Esteve, Ricard Mesia; ICO Badalona, Barcelona, Spain; Medical Oncology Department, Germans Trias i Pujol Hospital, Catalan Institute of Oncology (ICO), Badalona, Spain; Medical Oncology. Institut Català d'Oncologia (ICO) Hospital Germans Trias i Pujol, Badalona, Spain; Institut Catala d'Oncologia Badalona. Applied Research Group in Oncology (B- ARGO Group), Institut Investigació Germans Trias i Pujol (IGTP), Badalona Barcelona, Spain; Medical Oncology Department, Institut Català d'Oncologia (ICO) Badalona, B-ARGO, Badalona, Spain; Institut Català d'Oncologia Badalona, Hospital Germans Trias i Pujol, Badalona, Spain; Department of Surgery and Cancer, Imperial College, London, United Kingdom; Cancer Statistics Department, Catalan Institute of Oncology-Hospital Germans Trias i Pujol, Badalona, Spain; Catalan Institute of Oncology, IDIBELL, Barcelona, Spain

Background: Cancer patients (pts) represent a high-risk population for severe COVID-19. Cancer-associated immunosuppression may hinder in the development of anti-SARS-CoV-2 antibodies. **Methods:** Data regarding baseline characteristics, COVID-19 and anti-SARS-Cov2 IgG were collected from cancer pts (solid tumors) who tested positive for COVID-19 (PCR+) between March and April 2020 at Catalan Institute of Oncology. We prospectively assessed anti-SARS-Cov2 IgG seroprevalence at 3 and 9 months post infection and explored clinico-pathologic factors associated with IgG positivity. We explored the impact of potential factors influencing antibody production at >9 months. **Results:** Of 49 pts registered between 10th March-26th April 2020, 21 died <3 months after the infection and 5 pts refused to participate, leaving 23 eligible pts for IgG testing. With respect to those not tested, IgG tested cohort was younger (median age: 64.0 vs 72.9 years, p = 0.001) and presented oncologic remission in 68.2% of cases (vs 34.6%, p = 0.043) at COVID-19 diagnosis. Median time from PCR+ to first and second IgG determination was 3.2 months (Interquartile range [IQR]: 2.9-4.1) and 9.5 months (IQR: 8.8-9.8), respectively. Out of 23 pts, 15 had both determinations and 8 had only one (3 in the first time point, 5 in the second one). We identified 16/18 pts IgG+ (88.9%) at 3 months and 17/20 pts IgG+ (85%) at 9 months. One IgG+ pt became IgG- at the second determination, one was IgG- at both timepoints, and one had an inconclusive result at the first but negative at the second timepoint. Key characteristics of patients by IgG result 9 months after COVID-19 diagnosis are shown in the table. **Conclusions:** We describe a high seroprevalence of anti-SARS-CoV-2 IgG at 3 and 9 months after COVID-19 diagnosis in solid tumour patients, irrespective of anti-cancer therapy exposure. Pts who were IgG+ at 9 months were older, and more likely to have required oxygen during prior COVID-19 in comparison to IgG- pts suggesting that infection severity may promote durable immunity. Frequency of early stage cancers was higher among IgG+ pts, suggesting less cancer-related immunosupression. Older (>70 years) and advanced cancer pts were under-represented in this series, warranting confirmation of these preliminary results in a larger cohort. Research Sponsor: None.

Characteristics of patients by IgG result determined at 9 months after COVID-19 diagnosis.

Characteristics assessed at COVID infection	IgG- (n=3)	IgG+ (n=17)
Median Age (years)	49.0 [49.0; 50.0]	66.0 [62.0; 70.0]
Neoplasms Breast	1 (33%)	6 (35%)
Urogenital	1 (33%)	4 (24%)
Digestive	0 (0%)	3 (17%)
Others	1 (33%)	4 (24%)
Early stage/Metastatic cancer	1(33%)/2(67%)	13(77%)/4(24%)
Active Cancer Treatment*	3 (100%)	14 (82%)
O2 support during COVID-19	0 (0%)	12 (61%)
COVID treatment (Tocilizumab/Remdesivir)	0 (0%)	4 (24%)

*Chemotherapy, immunotherapy, hormonal therapy, targeted therapy.

2545 **Poster Session**

Using the tumor microenvironment to identify predictors of immunotoxicity to checkpoint inhibitors.

William Alexander, Kristopher Attwood, Kayla Catalfamo, Grace K. Dy, Saby George, Marc S. Ernstoff, Yara Abdou; University at Buffalo, Buffalo, NY; Biostatistics, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Cleveland Clinic, Cleveland, OH

Background: While Immune checkpoint inhibitors (ICI) have revolutionized the field of oncology, the benefits have come at the cost of serious side effects known as immune-related adverse events (irAEs). Approaches that can predict patients' susceptibility to irAEs are key to their early detection and management. In the present study, we investigate the association between irAEs reported during ICI therapy across multiple cancer types and markers of tumor immune response. Our primary objective is to explore potential biomarkers for assessing patients' risk of irAEs. **Methods:** 472 patients were evaluated who had tumor immune profiling performed paraffin embedded formalin fixed archival tumor biopsy samples using Omniseq Immune Report Card (IRC) and subsequently underwent ICI therapy. The IRC consisted of enumeration of tumor infiltrating lymphocytes (TILs) by immunohistochemistry (IHC) and TIL-associated genes by RNA-Seq, PD-L1 expression by IHC, and tumor mutational burden (TMB) by DNA-Seq. irAE type and grade were determined based on retrospective chart review. Fisher's exact test was used to determined statistically significant associations between immune markers and irAE development. **Results:** Patients with lung (55%), ovarian (9%), and melanoma (5%) cancers constituted the majority of the cases. The median age of patients was 61, with 56% being female and 44% male. Most patients underwent treatment with (94%). irAEs developed in 36% of patients, with 2% of patients developing high-grade irAEs (Grade 3 or 4). Skin (11%), thyroid (10%), and GI (9%), were the most commonly affected organ systems. Increased TILs were associated with increased risk for any irAE ($p = 0.04$). A stronger association was noted in patients who underwent anti-PD-1/L1 monotherapy ($p = 0.01$) and/or in cases of lung cancer ($p = 0.01$). Interestingly, subanalyses by gender showed a statistically significant correlation between increased TILs and risk for any irAE in males ($p = 0.006$) but not in females ($p = 0.63$). High PD-L1 (defined as $> 70\%$ by IHC) was also significantly associated with increased risk for any irAE ($p = 0.03$). Subanalyses by gender and age again showed a similar association in females ($p = 0.0002$) and/or patients < 65 years ($p = 0.04$). high TMB and any irAE in female patients ($p = 0.01$) and in breast cancer cases ($p = 0.03$). On multivariate analysis, TILs by IHC appeared to be the strongest predictor of irAEs ($p = 0.03$). **Conclusions:** The tumor immune microenvironment (TME) has been shown to influence response to ICI, yet its association with irAEs has not been well studied. Our analysis sheds light on potential TME predictors for irAE in patients receiving ICI therapy. Further studies are needed to deepen our understanding of immune toxicity and to develop tools for identifying patients who are at risk. Research Sponsor: U.S. National Institutes of Health.

2546 **Poster Session**

A 4-chemokine signature to predict intermediate immunogenicity in homologous recombination repair deficient tumors.

Joan Miguel Romero, Yifan Wang, Alain Pacis, Robert Edward Denroche, Gun Ho Jang, Barbara Grunwald, Steven Gallinger, George Zogopoulos; Research Institute of the McGill University Health Centre, Montreal, QC, Canada; Rosalind and Morris Goodman Cancer Research Centre of McGill University, Montreal, QC, Canada; Ontario Institute for Cancer Research, Toronto, ON, Canada; McGill University Health Center, Montréal, QC, Canada

Background: Treatment responses to immune checkpoint blockade (ICB) associate with T cell tumor inflammation. Tumors with mismatch repair deficiency display an inflammatory tumor phenotype and respond to ICB. Similarly, tumors with homologous recombination repair deficiency (HR-d) may be primed for ICB treatment. We have previously shown that a panel of 4 chemokines identifies a subclass of pancreatic cancer with markers of T cell-inflammation. Here, we evaluated this 4-chemokine signature in cancer types with HR-d molecular subclasses. **Methods:** We combined paired transcriptomes and genomic data of breast (n = 699), ovarian (n = 174) and prostate (n = 457) cancers from the Cancer Genome Atlas and tumor-enriched pancreas cancers (n = 121) to evaluate the 4-chemokine signature in HR-d vs. HR-proficient tumors across these 4 cancers. Metrics of antitumor immunity were also compared. **Results:** Across tumor types, elevated expression of the 4-chemokine signature (chemokine-hi) associated with transcriptional hallmarks of a T cell-mediated antitumor response, including antigen presenting cell stimulation, antigen presentation, and T cell activity. In tumors with a predominant COSMIC signature 3, which associates with HR-d, the 4-chemokine signature predicted intermediate levels of T cell-inflammation. **Conclusions:** These data suggest that 1) the 4-chemokine signature may be a clinically relevant biomarker in identifying subclasses of tumours responsive to immunotherapies, and that 2) HR-d tumors harbor intermediate immunogenicity. Correlation of treatment responses to immunotherapies with the 4-chemokine signature is needed validate its predictive value as a biomarker for treatment stratification with immunotherapies. Research Sponsor: Quebec Cancer Consortium.

	Lo+Med score	Hi score	HR-d (Signature 3*) score	Lo+Med vs Hi p-value	Lo+Med vs HR-d p-value
Pancreas		n = 84	n = 29	n = 8**	
APC costimulation	-0.095	0.46	0.20	< 0.01	0.23
Batf3DC score	0.087	0.59	0.36	< 0.01	0.21
MHC I presentation	-0.26	0.42	0.0086	< 0.001	0.50
Cytolytic activity score	-0.28	1.36	0.0078	< 0.001	0.172
T effector score	-0.30	1.34	0.60	< 0.001	< 0.05
Breast		n = 495	n = 164	n = 40	
APC costimulation	-0.28	0.95	0.24	< 0.001	< 0.01
Batf3DC score	-0.37	1.00	0.094	< 0.001	0.15
MHC I presentation	-0.32	1.06	0.28	< 0.001	< 0.05
Cytolytic activity score	-0.60	1.93	0.46	< 0.001	< 0.001
T effector score	-0.58	1.94	0.77	< 0.001	< 0.001
Ovarian		n = 93	n = 32	n = 49	
APC costimulation	-0.29	0.58	0.48	< 0.001	< 0.001
Batf3DC score	-0.33	0.84	0.16	< 0.001	< 0.001
MHC I presentation	-0.30	0.99	0.49	< 0.001	< 0.001
Cytolytic activity score	-0.57	1.72	0.68	< 0.001	< 0.001
T effector score	-0.68	1.31	0.68	< 0.001	< 0.001
Prostate		n = 327	n = 110	n = 20***	
APC costimulation	-0.32	0.71	0.31	< 0.001	< 0.001
Batf3DC score	-0.25	0.93	0.26	< 0.001	< 0.01
MHC I presentation	-0.211	0.73	0.12	< 0.001	< 0.01
Cytolytic activity score	-0.39	1.10	0.35	< 0.001	< 0.01
T effector score	-0.044	1.10	0.17	< 0.001	< 0.01

2547 **Poster Session**

First-in-human dose escalation of ALPN-202, a conditional CD28 costimulator and dual checkpoint inhibitor, in advanced malignancies.

Justin C Moser, Mark Voskoboynik, Nehal J. Lakhani, Michael Millward, Diwakar Davar, Wael A. Harb, Jing Yang, Gary Means, Kristi Manjarrez, Almudena Tercero, Hany Zayed, Jan Hillson, Christine Dela Cruz, Graciela Noemi Perez, Stanford L. Peng; HonorHealth Research and Innovation Institute, Scottsdale, AZ; Nucleus Network, Melbourne, Australia; START Midwest, Grand Rapids, MI; Linear Clinical Research & University of Western Australia, Nedlands, Australia; University of Pittsburgh Medical Center, Pittsburgh, PA; Horizon Oncology Center, Lafayette, IN; Alpine Immune Sciences, Inc., Seattle, WA; PRA Health Sciences, Singapore, Singapore; PRA Health Sciences, San Diego, CA

Background: Strong preclinical rationale has emerged for combining checkpoint inhibition (CPI) with T cell costimulatory agonists, particularly CD28, a critical T cell costimulatory molecule recently recognized as a key target of checkpoint inhibition. ALPN-202 is a variant CD80 vIgD-Fc fusion that mediates PD-L1-dependent CD28 costimulation and inhibits the PD-L1 and CTLA-4 checkpoints. It has demonstrated superiority to CPI-only therapies intumor models, while demonstrating favorable safety in preclinical toxicology studies. **Methods:** This is a cohort-based, open-label dose escalation and expansion study of ALPN-202 in adults with advanced solid tumors or lymphoma (NCT04186637). Subjects with cancers refractory to standard therapies (including approved CPIs), or cancers without available standard or curative therapy are eligible. After two planned single-subject cohorts, a standard 3+3 dose escalation has been implemented with two dose schedules in parallel, Q1W and Q3W. Objectives include evaluation of safety and tolerability, PK, PD and preliminary anticancer activity of ALPN-202. Disease assessments are evaluated by RECIST v1.1 for solid tumors or by Lugano Classification for lymphoma. **Results:** As of January 2021, 20 subjects with advanced malignancies have received ALPN-202. Dose-dependent PK and target saturation have been preliminarily observed. So far, ALPN-202 has been well tolerated at dose levels ranging from 0.001 to 1 mg/kg weekly, with no DLTs. Low-grade skin toxicities (grade 1-2 rash) have been observed in 4 subjects (20%). Among 11 evaluable subjects, an unconfirmed partial response has been observed in one subject with colorectal carcinoma, while stable disease has been observed in 5 subjects with colorectal carcinoma, mesothelioma (2), cholangiocarcinoma, and renal cell carcinoma – for a preliminary clinical benefit (PR+SD) rate of 100% (4/4) at dose levels of 0.3 mg/kg and higher, or 54% (5/11) overall (table). The meeting presentation will update this data, which is expected to include the conclusion of Q1W dose escalation, as well as immune correlates. **Conclusions:** First-in-human dose escalation with ALPN-202 has been well tolerated at doses capable of engaging CD28 costimulation *in vivo* in association with dual PD-L1/CTLA-4 checkpoint inhibition, with early signs of anti-tumor activity. These findings suggest that CD28 agonism can be safely achieved in humans, and further suggest that dose expansion with ALPN-202 is warranted to assess the relevance of controlled CD28 costimulation as a novel approach to cancer immunotherapy. Clinical trial information: NCT04186637. Research Sponsor: Alpine Immune Sciences.

Regimen	Weekly					Every 3 Weeks			
Dose	0.001 mg/kg	0.01 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg	0.3 mg/kg	1 mg/kg	All Dose Regimens	Doses ≥ 0.3 mg/kg
N Enrolled	1	2	4	6	3	3	1	20	13
N Evaluable	1	2	4	1	0	3	0	11	4
PD	-	2 (100%)	3 (75%)	-	-	-	-	5 (45%)	-
SD	-	-	1 (25%)	1 (100%)	-	3 (100%)	-	5 (45%)	4 (100%)
PR	1 (100%)	-	-		-	-	-	1 (9%)	-

Phase 1A clinical trial of the first-in-class fascin inhibitor NP-G2-044 evaluating safety and anti-tumor activity in patients with advanced and metastatic solid tumors.

Vincent Chung, Komal L. Jhaveri, Daniel D. Von Hoff, Xin-Yun Huang, Edward Graeme Garmey, Jillian Zhang, Frank Yung-Chin Tsai; City of Hope, Duarte, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Translational Genomics Research Institute (TGen) and HonorHealth, Phoenix, AZ; Weill Cornell Medical College, New York, NY; CMO Consulting, Inc., Concord, MA; Novita Pharmaceuticals, Inc., New York, NY; HonorHealth Research Institute, Scottsdale, AZ

Background: Fascin inhibitors block tumor metastasis and increase antigen uptake in intra-tumoral dendritic cells. Filopodia, finger-like protrusions on cell surfaces, are necessary for migration of metastatic tumor cells and intra-tumoral dendritic cells. Fascin is the primary actin cross-linker in filopodia and elevated levels correlate with increased risk of metastasis, disease progression and mortality. NP-G2-044 is a novel small molecule that inhibits function of fascin. Pre-clinical data demonstrate drug-associated reductions in tumor growth and metastasis, enhanced immune response and survival in treated animals, and drug-drug synergism when combined with anti-PD-1 antibodies. **Methods:** This multicenter phase 1A clinical trial was designed to evaluate safety and tolerability of NP-G2-044 and to identify the drug's recommended phase 2 dose (RP2D) using a 3+3 dose escalation design. NP-G2-044 was administered to patients (pts.) with treatment-refractory solid tumor malignancies as a single oral daily dose for 6-week cycles that included 4 weeks on (daily dosing) and 2 weeks off (rest). **Results:** A total of 23 pts. were enrolled in 7 dose cohorts ranging from 200-2100 mg. QD. Overall, NP-G2-044 appeared well-absorbed and distributed with Tmax of ~4 hrs and T1/2 of 20-24 hrs. Across all cohorts, no DLTs, drug-related SAEs or patient deaths were observed. Based on PK and safety findings, 1600 mg. daily was selected as the provisional RP2D. While no formal RECIST-based objective responses were observed, consistent with the drug's non-cytotoxic mechanism of action, preliminary signals of anti-tumor and anti-metastatic activity were observed. These include dose proportional increases in duration of treatment, progression-free-survival, and metastasis-free interval, in particular for 4/4 late-stage ovarian cancer patients (table). Comparison of time on treatment (TOT) for ovarian cancer patients. **Conclusions:** In this first-in-human clinical trial, the novel fascin inhibitor, NP-G2-044, appeared safe and well tolerated. Signals of single-drug anti-tumor and anti-metastatic activity were observed. A phase 2A clinical trial with a particular focus on Ovarian Cancer will seek to elucidate signals of RP2D activity in both monotherapy and the combination of NP-G2-044 with anti-PD-(L)1 immune checkpoint inhibitors. Clinical trial information: NCT03199586. Research Sponsor: Novita.

Patient	Cancer Type	Last Prior Therapy	Time on Last Prior Therapy	Time on NP-G2-044	TOT Improvement	Metastatic Sites Prior to NP-G2-044	New METS on NP-G2-044
023	Ovary	CSF1R Inhibitor	~60 days	170 days	~183%	Liver, Colon, Pancreas, Bladder	No
027	Ovary	Doxorubicin	~105 days	170 days	~62%	Lung, Lymph Node, Peritoneum	No
028	Fallopian Tube	Anti-LIF1	~90 days	158 days	~76%	Lung, Lymph Node	No
031	Ovary	Liposomal Doxorubicin	~90 days	251 days	~179%	Peritoneum, Liver, Abdominal wall, Ilium	No

2549 **Poster Session**

Preliminary results from a phase 1/2 study of BDC-1001, a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), in patients (pts) with advanced HER2-expressing solid tumors.

Manish Sharma, Richard D. Carvajal, Glenn J. Hanna, Bob T. Li, Kathleen N. Moore, Mark D. Pegram, Drew W. Rasco, Alexander I. Spira, Michael Alonso, Liang Fang, Amreen Husain, Edith A. Perez, Ecaterina Elena Dumbrava; START-Midwest, Grand Rapids, MI; Columbia University Irving Medical Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Stephenson Cancer Center, Oklahoma City, OK; Stanford Women's Cancer Center, Stanford, CA; START, San Antonio, TX; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; Bolt Biotherapeutics, Redwood City, CA; F. Hoffmann-La Roche, Ltd., Basel, Switzerland; Mayo Clinic, Jacksonville, FL; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BDC-1001 is a novel ISAC consisting of an investigational trastuzumab biosimilar chemically conjugated to a TLR 7/8 agonist with a non-cleavable linker. BDC-1001 was designed to activate the innate immune system, eliciting antibody-mediated effector functions (eg, antibody-dependent cellular phagocytosis) and a durable adaptive immune response. In preclinical tumor models resistant to anti-HER2 treatments, BDC-1001 demonstrated potent and durable immune-mediated antitumor efficacy. **Methods:** A 4-part, phase 1/2 dose-escalation/expansion study was initiated to evaluate BDC-1001 ± PD1 inhibitor pembrolizumab in pts with HER2-expressing solid tumors who had progressive disease on standard of care (NCT04278144). Preliminary results of the monotherapy dose escalation (Part 1) are reported. Pts with advanced metastatic HER2-expressing (IHC2/3+) or amplified solid tumors received BDC-1001 IV q3w in a 3+3 design w/ 12 pts/cohort backfill allowed. Primary objectives were to evaluate safety, tolerability, dose-limiting toxicities (DLTs) and determine a phase 2 dose; secondary objectives were to assess pharmacokinetics (PK), pharmacodynamics and preliminary anti-tumor activity. **Results:** As of Jan 29, 2021, 20 pts w/ a median age of 65 (46-85) have enrolled in 4 dose levels (0.15mg/kg to 5 mg/kg). Cancer types include breast, biliary, cervical, colorectal (CRC), lung, gastroesophageal, salivary, urinary tract and endometrial. Pts had received a median of 4 (1-7) prior therapies; 65% received >1 prior anti-HER2 therapy. All pts completed the 21-day DLT period; no DLTs or drug-related serious adverse events (AEs) have been observed. AEs deemed related to BDC-1001 have been mild to moderate including infusion-related reactions. The MTD has not been reached (treatment duration 5-17+wk); enrollment is ongoing. PK evaluations showed Cmax levels consistent with predicted modeling based on non-human primates (NHP). One pt with microsatellite stable (MSS) HER2+ CRC with lung metastases had a confirmed partial response after 4 cycles and remains on study; 2 additional pts with metastatic MSS HER2+ CRC had stable disease (SD) and a pt with heavily pretreated MSS endometrial cancer with lung metastases had confirmed SD and remains on treatment 17+ wk; 3 of these pts had received 2 prior anti-HER2 therapies. **Conclusions:** In this first-in-human study, BDC-1001 appears to be well-tolerated up to the dose tested to date (5 mg/kg), with Cmax levels achieved as predicted by NHP modeling. Evidence of clinical activity have been observed, including in pts previously treated with anti-HER2 therapy. Dose escalation is ongoing and will be followed by combination dosing with CPI and the phase 2 component in selected tumors. Clinical trial information: NCT04278144. Research Sponsor: Bolt Biotherapeutics.

2550 **Poster Session**

Preliminary results of a first-in-human phase I dtudy of IMM01, SIRPα Fc protein in patients with relapsed or refractory lymphoma.

Mingyuan Sun, Junyuan Qi, Weiwei Zheng, Lin Song, Bo Jiang, Zhenzhen Wang, Cheng Huang, Wenzhi Tian, Lugui Qiu; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Hematological Disorders, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College., Tianjin, China; ImmuneOnco Biopharmaceuticals (Shanghai) Co.,Ltd, Shanghai, China; ImmuneOnco Biopharmaceuticals (Shanghai) Co.,Ltd., Shanghai, China

Background: IMM01 is a recombinant human signal regulatory protein α (SIRPα) IgG 1 fusion protein that exerts dual-mechanism antitumor activity via engagement of activating tumor cell phagocytosis and stimulating T-cell anti-tumor responses by binding CD47 on tumor cell membrane. IMM01 displays promising preclinical characteristics regarding its receptor occupancy/tumor exposure/efficacy relationship. Unlike anti-CD47 monoclonal antibodies, IMM01 shows unique property of weak human erythrocyte conjugation so as avoiding severe hemolysis. **Methods:** Monotherapy of IMM01 was conducted in 14 enrolled subjects with relapsed or refractory lymphoma who had failed standard therapies. Dose escalation was performed in routine design of accelerated single-patient followed by standard 3+3 to establish the preliminary data of safety as well as determination of a recommended expansion dosage. Each cycle contains 4 dosing weekly followed by a week rest. The tumor responses were evaluated based on Lugano Classification 2014. IMM01 pharmacokinetics (PK) and pharmacodynamics (PD) analyses were performed. **Results:** As of February 08, 2021, a total of 14 patients (median age 49 y; median prior therapy 3) were enrolled in 6 escalated dose cohorts (0.003 mg/kg, 0.01 mg/kg, 0.05 mg/kg, 0.15 mg/kg, 0.5 mg/kg and 1.0 mg/kg). The common tumor types were follicular lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma. No DLTs were observed up to 1.0 mg/kg. One SAE (grade 2 increased amylase and grade 3 increased lipase) was reported, which induced by disease progression on pancreas. The most common treatment related adverse events were thrombocytopenia (54%), neutrophil count decreased (36%), Pyrexia (36%) and Anaemia (27%). There were grade 1 or 2 except for one patient experienced a grade 3 platelet count decreased (lower baseline at 70×10^9/L). Transient platelet count decrease after 2 hours and return to baseline at 24 to 48 hours post first infusion. In 12 evaluated patients, one patient with FL had a CR and maintained a 26-week response at the dose of 0.01 mg/kg. One patient with HL who had failed PD-1 inhibitor was confirmed PR at 27 weeks and continues the therapy, and one patient with MZL maintained SD for 12 weeks at the dose of 0.15 mg/kg. One patient with HL failed PD-1 inhibitor and one patient with FL maintained a shrunk SD for 12 weeks at the dose of 0.5 mg/kg. One patient with AITL was evaluated as a shrunk SD after 5 doses treatment at the dose of 1.0 mg/kg. Terminal half-life of IMM01 range from 53.8 hours to 73.3 hours. The AUC and C_{max} of IMM01 show nonlinear increases in the dose range of 0.05 mg/kg to 0.5 mg/kg. **Conclusions:** Preliminary data from the present phase 1 study of IMM01, a SIRPα IgG 1 fusion protein, demonstrate that IMM01 has an excellent preliminary safety, tolerability and promising anti-tumor activity up to doses of 1.0 mg/kg. Clinical trial information: ChiCTR1900024904. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Co.,Ltd.

2551 **Poster Session**

Results of a phase 1 study of SRF388, a first-in-human, first-in-class, high-affinity anti-IL-27 antibody in advanced solid tumors.

Amita Patnaik, Daniel Morgensztern, Charlene Mantia, Nizar M. Tannir, Lauren C Harshman, Jonathan Hill, Kerry White, Jou-Ku Chung, Beth Bowers, Gaia Sciaranghella, Benjamin Lee, Toni K. Choueiri, Lon S. Smith, Aung Naing; START, San Antonio, TX; Washington University School of Medicine, St. Louis, MO; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Surface Oncology, Cambridge, MA

Background: IL-27 is an immunosuppressive cytokine, consisting of two subunits p28 and EBI3, that upregulates immune checkpoint receptors (eg, PD-L1, TIGIT) and downregulates proinflammatory cytokines such as IFNγ, TNFα, and IL-17. SRF388 is a first-in-class, fully human IgG1 antibody to IL-27 that blocks the interaction between IL-27 and its receptor, thereby promoting immune activation in the tumor microenvironment. The IL-27 pathway is activated in hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC), and high circulating levels of EBI3 are associated with inferior outcomes in both. Circulating EBI3 levels may serve as a predictive biomarker of SRF388 activity. **Methods:** Patients with advanced solid tumors refractory to standard therapy were enrolled in a phase 1 dose-escalation study (accelerated single patient followed by standard 3+3) to establish the preliminary safety of SRF388 as a monotherapy and to identify a dose suitable for expansion (NCT04374877). SRF388 was administered intravenously every 4 weeks. Tumor response was assessed by RECIST v1.1. SRF388 pharmacokinetic (PK) and pharmacodynamic (PD) [phospho-STAT (pSTAT) inhibition] analyses were performed. **Results:** As of January 26, 2021, 12 patients have received SRF388 at doses ranging from 0.003 to 10 mg/kg with 2 patients undergoing intra-patient dose escalation. Median age was 68 years, 67% were female, and ECOG PS was 0/1 (42%/58%). Median number of prior therapies was 2 (range 1–9), and 75% were anti-PD-(L)1 experienced (n = 9). The only treatment-related adverse events observed across dose levels were low-grade fatigue (n = 1, 8%), nausea (n = 1, 8%) and excess salivation (n = 1, 8%). No dose-limiting toxicities (DLTs) or $\geq$ Grade 3 related toxicity have occurred. Mean time on study is 12.5 weeks (range 4–40). One patient with RCC who received prior anti-PD-1 has prolonged stable disease for $>$ 9 months. SRF388 PK are linear with estimated $T_{1/2}$ ranging from 6–19 days. There is evidence of accumulation and no anti-drug antibody development to date. Maximal inhibition of the IL-27 signaling pathway as measured by $>$ 90% pSTAT inhibition in whole blood was achieved starting at 0.3 mg/kg. Given combined evidence of near-complete pathway inhibition and preclinical human equivalent dose modeling projecting biologically active doses, additional slots were opened for RCC and HCC starting at 1 mg/kg. **Conclusions:** Preliminary results of IL-27 pathway blockade with a first-in-class therapeutic demonstrates that SRF388 is well tolerated at doses that achieve maximal inhibition of downstream pSTAT signaling through the dosing period. Expansions are planned in HCC and RCC. Updated data including the recommended phase 2 dose, clinical outcomes, PK/PD and correlative analyses will be presented. Clinical trial information: NCT04374877. Research Sponsor: Surface Oncology.

2552 **Poster Session**

Selection of the recommended phase 2 dose (RP2D) for subcutaneous nemvaleukin alfa: ARTISTRY-2.

Omid Hamid, Stephen V. Liu, Ralph V. Boccia, Justin A Call, Trisha Michel Wise-Draper, Angela Tatiana Alistar, John D. Powderly, Bradley Curtis Carthon, Ulka N. Vaishampayan, Anthony J. Olszanski, John M. Wrangle, Anthony Frank Shields, Sarina Anne Anne Piha-Paul, Monali Desai, MD, Yangchun Du, Lei Sun, PhD, Yan Wang, Heather Losey, Craig Hopkinson, Marc S. Ernstoff; The Angeles Clinic and Research Institute, Los Angeles, CA; Georgetown University, Department of Hematology and Oncology, School of Medicine, Washington, DC; Center for Cancer and Blood Disorders, Bethesda, MD; Utah Cancer Spclsts, Salt Lake City, UT; University of Cincinnati Cancer Center, Cincinnati, OH; Atlantic Health System, Morristown, NJ; Carolina BioOncology Institute, Huntersville, NC; Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; University of Michigan Cancer Center, Detroit, MI; Fox Chase Cancer Center, Philadelphia, PA; Johns Hopkins Univ School of Medcn, Baltimore, MD; Karmanos Cancer Institute, Wayne State University, Detroit, MI; The University of Texas MD Anderson Cancer Center, Houston, TX; Alkermes, Inc., Waltham, MA; Alkermes Inc, Waltham, MA; Alkermes, Inc, Waltham, MA; Cleveland Clinic, Cleveland, OH

Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine that selectively binds the intermediate-affinity interleukin-2 receptor to preferentially activate $CD8^+$ T and natural killer (NK) cells with minimal expansion of regulatory T cells (T_{regs}),designed for use as a cancer immunotherapy. ARTISTRY-2 (NCT03861793) is an ongoing phase 1/2 study evaluating the safety, efficacy, and pharmacokinetic and pharmacodynamic (PD) responses of subcutaneous (SC) nemvaleukin in combination with pembrolizumab in patients (pts) with advanced solid tumors. **Methods:** In phase 1, cohort-specific doses of SC nemvaleukin are administered on an every-7-day (q7d) or every-21-day (q21d) schedule during a 6-week monotherapy lead-in period, followed by combination with pembrolizumab 200 mg q21d. We present safety, PD effects, and preliminary clinical activity outcomes as of 12/02/2020. **Results:** 57 pts received nemvaleukin doses ranging from 0.3 mg to 6 mg q7d or 1 mg to 10 mg q21d. The most frequent tumor types ($>$ 5 pts) were colorectal, pancreatic, ovarian, and lung; median number of prior therapies was 4. Treatment-related adverse events (TRAEs) in $>$ 30% pts overall were pyrexia (43.9%), chills (38.6%), injection site erythema (33.3%), injection site reaction (33.3%), and fatigue (31.6%). 3 mg q7d (n = 7) had no drug-related dose reductions, discontinuations, or deaths during the monotherapy or combination periods. 6 mg was declared the maximum tolerated dose (MTD) for q7d dosing as 2 of 8 pts experienced dose-limiting toxicities (DLTs). For 6 mg q21d (n = 7), no drug-related dose reductions, discontinuations, or deaths have occurred during the monotherapy period; combination period data are not mature. 10 mg was declared the MTD for q21d dosing as 1 of 9 pts experienced DLTs and 3 had TRAEs leading to dose reductions. Systemic exposure to nemvaleukin increased with increasing dose. Increases in NK cells and $CD8^+$ T cells of approximately 16-fold and 3-fold, respectively, at 3 mg q7d, and approximately 8-fold and 3-fold, respectively, at 6 mg q21d were observed, with minimal change in T_{regs}. 46 pts had at least 1 on-treatment scan as of the data cutoff date, and 30 (65%) had stable disease (SD) on the first scan. Of the 30 pts with $\geq$2 scans, 13 (43%) had 2+ consecutive scans of SD. 16 of 57 pts remain on therapy. Antitumor activity data for more recent cohorts are still maturing. Based on the totality of the safety, PD effects, and antitumor activity data, 3 mg q7d was selected as the RP2D for SC nemvaleukin. **Conclusions:** SC nemvaleukin 3 mg q7d was generally well tolerated as monotherapy and in combination with pembrolizumab, and demonstrated robust PD effects on NK cells and $CD8^+$ T cells with minimal expansion of T_{regs}. These PD effects are similar to or greater than those observed with intravenous nemvaleukin. Thus, 3 mg q7d was selected as RP2D; phase 2 expansion cohorts for combination with pembrolizumab are enrolling. Clinical trial information: NCT03861793. Research Sponsor: Alkermes, Inc.

2553 **Poster Session**

Initial results from a phase 1b study of ORIC-101, a glucocorticoid receptor antagonist, in combination with nab-paclitaxel in patients with advanced solid tumors.

Raghad Muhsin Abdul-Karim, Anthony W. Tolcher, Shivaani Kummar, Manish R. Patel, Alexander I. Spira, Shekeab Jauhari, Maureen Duff, Rongda Xu, Ann Johnson, Anneleen Daemen, Pratik S. Multani, Edna Chow Maneval, Pamela N. Munster; NEXT Oncology, San Antonio, TX; Knight Cancer Institute, Oregon Health and Science University, Portland, OR; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; Florida Cancer Specialists /Sarah Cannon Research Institute, Lake Mary, FL; ORIC Pharmaceuticals, South San Francisco, CA; University of California San Francisco, San Francisco, CA

Background: ORIC-101 is a potent and selective, orally bioavailable, small molecule antagonist of the glucocorticoid receptor (GR). Preclinical studies have demonstrated that activation of GR signaling leads to decreased responsiveness to chemotherapeutics (eg, taxanes) and antiandrogens across multiple tumor types. Mechanistically, ORIC-101 inhibits GR transcriptional activity and blocks the prosurvival signals mediated by the activated nuclear hormone receptor. **Methods:** A 3+3 dose escalation design was used to assess safety, pharmacokinetics (PK), pharmacodynamics (PD), and select the Recommended Phase 2 Dose (RP2D) of ORIC-101 in combination with nab-paclitaxel (nab-pac; NCT03928314). ORIC-101 doses ranging from 80 to 240 mg once daily, given either intermittently or in a continuous dosing regimen, were evaluated in combination with weekly nab-pac at 75 or 100 mg/m^2. Plasma PK and PD biomarkers were assessed on day 1 and after repeat dosing. PD modulation in blood-derived peripheral blood mononuclear cells (PBMCs) was assessed by RT-qPCR for GR target genes. Antitumor activity was assessed by RECIST v1.1. **Results:** 21 patients with 10 different solid tumors, with and without a prior taxane, were treated in 5 cohorts. ORIC-101 exposure increased with dose, with no evidence for drug-drug interaction with nab-pac. In the initial cohort at 240 mg ORIC-101 and 100 mg/m^2 nab-pac, 2 patients experienced dose limiting toxicities (DLTs) of Grade 3 fatigue and Grade 4 neutropenia/thrombocytopenia, respectively. No further DLTs were observed in subsequent cohorts and the RP2D was established as 160 mg ORIC-101 dosed once daily continuously for 21 days with nab-pac 75 mg/m^2 given on days 1, 8, and 15 of each 28-day cycle, without requirement for prophylactic granulocyte colony-stimulating factor (G-CSF). The most common ($>$ 15%), all grade treatment-related adverse events (AEs) were nausea (38%), diarrhea (33%), fatigue (29%), leukopenia (29%), neutropenia (29%), anemia (24%), and 19% of patients had increased liver function tests and alopecia. Biomarker data demonstrated ORIC-101-induced reduction in GR target gene expression in PBMCs, indicating PD modulation at all dose levels of ORIC-101. Preliminary antitumor activity was observed in 3 taxane-refractory patients with breast, endometrial, and pancreatic cancers. **Conclusions:** The combination of ORIC-101 and nab-paclitaxel demonstrated an acceptable tolerability profile and does not require prophylactic G-CSF. PK and PD showed no evidence of drug-drug-interaction and demonstrated GR target inhibition. Preliminary antitumor activity was observed in patients with solid tumors that previously progressed on a taxane-containing regimen. Dose expansion is ongoing at the RP2D in dedicated pancreatic, ovarian, triple negative breast cancers, and tissue-agnostic cohorts. Clinical trial information: NCT03928314. Research Sponsor: ORIC Pharmaceuticals.

2555 **Poster Session**

Results of a phase 1 dose-escalation study of AMV564, a novel T-cell engager, alone and in combination with pembrolizumab in patients with relapsed/refractory solid tumors.

Niharika B. Mettu, Alexander Starodub, Sarina Anne Anne Piha-Paul, Raghad Muhsin Abdul-Karim, Gabriel Tinoco, Michael Rahman Shafique, Victoria Smith, Christina Baccei, Patrick Youngwhan Chun; Duke University Medical Center, Durham, NC; The Christ Hospital, Cincinnati, OH; The University of Texas MD Anderson Cancer Center, Houston, TX; NEXT Oncology, San Antonio, TX; The Ohio State University, Columbus, OH; Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; Amphivena Therapeutics, South San Francisco, CA

Background: Myeloid-derived suppressor cells (MDSC) contribute to an immunosuppressive tumor environment and are a barrier to immune therapy. CD33 signaling in immature myeloid cells promotes expansion of MDSC and production of immunosuppressive factors. AMV564 is a potent T cell engager that selectively depletes MDSC while promoting T cell activation and proliferation, via preferential binding to areas of high CD33 density. **Methods:** In this 3+3 dose escalation study, patients with relapsed/refractory solid tumors for whom no recognized standard therapy exists received AMV564 once daily via subcutaneous (SC) injection on Days 1-5 and 8-12 of a 21-day cycle, either alone or in combination with pembrolizumab (200 mg IV q3w). Study endpoints included incidence and severity of adverse events (AEs), pharmacokinetics (PK), and preliminary anti-tumor activity (using RECISTv1.1 criteria). **Results:** As of January 29, 2021, 20 patients were dosed in 3 monotherapy dose cohorts (15, 50, and 75 mcg/day), and 10 patients were dosed in 3 combination therapy cohorts (5, 15, and 50 mcg/day). Enrolled patients were: median age 64 years, 47% female, had received median 3.5 prior lines of therapy; 7 patients (35%) had received prior checkpoint inhibitor therapy (6 monotherapy patients, 1 combination therapy patient). No dose-limiting toxicity was observed and a maximum-tolerated dose was not reached in either the monotherapy or combination therapy cohorts. The most common treatment-related AEs (occurring in $>$ 10% of patients, in order of decreasing frequency) in the monotherapy cohort were pyrexia, injection site reactions, fatigue, anemia, hypotension, pruritis, chills, and nausea. There were 2 cases of grade 2 cytokine release syndrome (CRS) at 75 mcg/day, both of which resolved after anti-IL6 therapy and study treatment was resumed. The most common treatment-related AEs in the combination cohorts ($>$ 10% frequency) were injection site reaction, pyrexia, fatigue, pruritis, and anemia. No cases of CRS were noted in the combination cohorts. In preliminary PK analysis, estimated median plasma half-life for AMV564 after SC injection was $>$ 48 hours, with dose-related increases in peak plasma concentration. Clinical responses were seen with monotherapy and combination therapy, including a complete response (CR) in a monotherapy-treated patient with ovarian cancer refractory to all standard therapies and anti-PD-1 therapy. **Conclusions:** AMV564 was well tolerated across multiple dose levels as monotherapy and in combination with pembrolizumab. Subcutaneous injection resulted in clinically relevant plasma exposures. Single-agent and combination therapy anti-tumor activity was observed. Further exploration of AMV564 clinical efficacy in expansion cohorts is ongoing. Clinical trial information: NCT04128423. Research Sponsor: Amphivena Therapeutics.

2556 **Poster Session**

A phase 1b, open-label, dose-escalation study to evaluate camidanlumab tesirine (Cami) as monotherapy in patients (pts) with advanced solid tumors.

Igor Puzanov, Patricia LoRusso, Kyriakos P. Papadopoulos, Christopher T. Chen, Yvan LeBruchec, Xiaomin He, Thierry Cousin, Karin Havenith, Joseph Boni, Johanna C. Bendell; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Yale Cancer Center, New Haven, CT; START-San Antonio, San Antonio, TX; Stanford Cancer Center, Stanford, CA; ADC Therapeutics SA, Epalinges, Switzerland; ADC Therapeutics America, Inc., Murray Hill, NJ; ADC Therapeutics (UK) Ltd., London, United Kingdom; Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN

Background: Depletion of tumor-infiltrating CD25+ regulatory T cells (T_{regs}), which inhibit tumor-specific immune responses, could contribute to tumor eradication. Cami (ADCT-301), an anti-CD25, pyrrolobenzodiazepine-based antibody-drug conjugate, targets CD25+ T_{regs}. A mouse surrogate has shown potent antitumor activity in solid tumor models. Here we report preliminary data from the monotherapy arm of a phase 1b trial of Cami in pts with selected advanced solid tumors. **Methods:** The monotherapy dose-escalation part of this open-label study enrolled pts (aged ≥18 years) with selected advanced solid tumors and no suitable existing therapy. The primary objective was to characterize safety and tolerability, and to identify the recommended phase 2 dose of Cami monotherapy. Secondary and exploratory objectives included evaluation of preliminary antitumor activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity. Pts received Cami every 3 weeks (1 cycle) with dose escalation per a 3+3 design. Disease control rate (DCR) was assessed (complete and partial responses [CR, PR] and stable disease). **Results:** At data cut-off (Dec 17, 2020), 44 pts were enrolled, with primary tumor types (stage IVA/B: 27 pts; 61.4%) of colorectal (15 pts; 34.1%), pancreatic (14 pts; 31.8%), head and neck, ovarian/fallopian tube, and renal cell carcinoma (all 3 pts; 6.8%), non-small cell lung cancer (2 pts; 4.5%), gastric, esophageal/GEJ, melanoma, and triple-negative breast cancer (each 1 pt; 2.3%). Median (range) age was 60.5 (33–82) years; median (range) number of prior systemic therapies was 4 (1–9). Pts received a median (range) of 2 (1–6) Cami cycles at doses of 20–150 μg/kg. Median (range) treatment duration was 22 (1–178) days. No dose-limiting toxicities were reported. The maximum tolerated dose (MTD) was not reached. All-grade treatment-emergent adverse events (TEAEs) in ≥20% pts were nausea (18 pts; 40.9%), decreased appetite and fatigue (each 16 pts; 36.4%), constipation (13 pts; 29.5%), abdominal pain (11 pts; 25%), and rash (10 pts; 22.7%). The only Grade ≥3 TEAE in ≥10% pts was anemia (5 pts; 11.4%). Grade 3 autoimmune AEs (colitis, immune-mediated AE, systemic inflammatory response syndrome) and neurologic AEs (dysphagia and asthenia, but not GBS) were reported in 3 (6.8%) and 2 (4.5%) pts, respectively. 1 (2.3%) Cami-related TEAE led to treatment withdrawal; no Cami-related TEAEs were fatal. DCR was 25% (95% CI: 11.1, 34.7); 11/44 pts attained stable disease. No pts had CR or PR. **Conclusions:** Dose escalation of Cami monotherapy is complete. The safety profile is encouraging and MTD was not reached. PK/PD data will be presented. 150 μg/kg is the highest dose investigated for single-agent Cami and the highest to be investigated combined with pembrolizumab in selected advanced solid tumors in the current protocol. Funding: ADC Therapeutics SA NCT03621982. Clinical trial information: NCT03621982. Research Sponsor: ADC Therapeutics SA.

2557 **Poster Session**

ItRECIST adapted efficacy assessment in solid tumors treated with intratumoral immunotherapy.

Honey Kumar Oberoi, Xavier Serres-Créixams, Guzman Alonso, Ignacio Matos, Alberto Hernando-Calvo, Eva Muñoz-Couselo, Marc Diez, Iosune Baraibar, Maria Vieito, Omar Saavedra Santa Gadea, Vladimir Galvao, Gemma Mur-Bonet, Guillem Cunill-Macià, Mafalda Oliveira, Enriqueta Felip, Teresa Macarulla, Elena Elez, Josep Tabernero, Irene Brana, Elena Garralda; Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Radiology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall dHebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Hospital Universitari Vall d'Hebron, Barcelona, Spain; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), UVic-UCC, Barcelona, Spain; Vall d'Hebron University Hospital, Vall d'Hebrón Institute of Oncology, Barcelona, Spain

Background: The development of human intratumoral therapy (HIT-IT) has surged as a promising strategy to overcome resistance to checkpoint inhibitors (CPI), promoting a stronger tumor-specific immune response while reducing systemic exposure. A broad variety of agents (i.e: oncolytic viruses, toll-like receptors agonists) administered both in superficial- and deep-seated lesions are being currently tested in clinical trials (CT). Due to the local intervention on tumors, radiological assessment by standard RECIST is challenging and new methods of response that capture and integrate the local and systemic response to HIT-IT are needed. We aimed to evaluate the feasibility and clinical utility of itRECIST (Goldmacher et al., 2020) in patients (pts) treated with HIT-IT in early phase CT. **Methods:** Retrospective analysis of a cohort of pts with different solid tumor types enrolled in CT including HIT-IT in our institution between August'18 and January'21. Clinical characteristics were collected. Efficacy in target-injected (T-I) and target-non-injected (T-NI) lesions was assessed by objective response rate (ORR) and disease control rate (DCR), as per itRECIST. Overall disease ORR and DCR were assessed per RECIST 1.1/iRECIST. Treatment-related adverse events (TRAEs) were assessed with CTCAE v.5.0. ORR was calculated with Clopper-Pearson method. Survival analysis was made using Kaplan-Meier method. **Results:** A total of 37 pts were included. Median age was 66 years, 19 pts (51%) were male, all pts had ECOG 0-1. 24 pts (65%) were CPI-nave. Median previous lines of therapy was 2 (range [r]: 0-11). All pts (100%) received minimum 1 dose of HIT-IT. 6 pts (16%) were treated with monotherapy and 31 pts (84%) in combination with CPI. Median HIT-IT and CPI doses administered were 4 (r: 1-9) and 2 (r: 1-13), respectively. Injected lesions: cutaneous (16.2%), subcutaneous (21.6%), lymph node (32.4%), liver (29.7%). Median size of T-I lesions was 40 mm (r: 19-260). At data cutoff, 32 pts were evaluable. Median follow-up was 14.4 weeks (r: 1.0-81.1). Per RECIST 1.1, overall ORR was 6% (95% CI, 5-7) and DCR was 38% (95% CI, 21-56). Per itRECIST, ORR was 19% (95% CI, 7-36) and DCR was 63% (95% CI, 44-79) in T-I lesions (n = 32), and 10% (95% CI, 22-27) and 48% (95% CI, 29-67) in T-NI lesions (n = 29). Mean decrease in responding T-I and T-NI lesions was -47% (r: -21 to -100) and -41% (r: -26 to -59), respectively. No non-target (NT) lesion was injected. Median progression-free survival was 7.4 weeks (95% CI, 6.6 – 8.2). Median overall survival was 10.0 months (95% CI, 2.3 – 17.7). Incidence of TRAE was 58% (grade 1-2 IT-related pyrexia 43%; grade 3-4, 5%). No treatment-related deaths were recorded. **Conclusions:** ItRECIST is feasible to implement and adds precision to the radiological assessment of local and distant anti-tumor activity of HIT-IT. No safety issues were detected in our cohort. Research Sponsor: BBVA Foundation.

2558 **Poster Session**

Targeting innate immunity with BXCL701 in combination with pembrolizumab in patients with advanced solid cancers: Phase 2 basket study.

Ozgur Karakuzu, Apostolia Maria Tsimberidou, Veronica R. Holley, Abha Adat, Sapna Pradyuman Patel, Anil K. Sood, Anthony Paul Conley, Gabriele E Urschel, Diane I. Healey, Vincent O'Neill, Filip Janku; The University of Texas MD Anderson Cancer Center, Houston, TX; BioXcel Therapeutics, New Haven, CT

Background: BXCL701 is an oral competitive inhibitor of dipeptidyl peptidases (DPPs), primarily DPP8/9, which triggers the inflammasome to alert and prime immune cells, leading to induction of IL-18 and IL-1. BXCL701 therefore, can induce an innate immune reaction and tumor inflammation, bridging between innate and adaptive immunity, potentially leading to synergistic anticancer activity when combined with PD-1 antibody pembrolizumab. **Methods:** This is a phase 2, open-label, single-center study (NCT04171219) of oral BXCL701 0.3 mg BID on days 1-14 and intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle with a safety lead-in to evaluate RECIST/iRECIST response rate in patients with advanced solid cancers. After confirming safety and dose limiting toxicities (DLT) in the first 6 patients, additional patients are being enrolled to an immune checkpoint inhibitors (iCPI) nave cohort and iCPI pretreated cohort. Each cohort is planned to enroll 9 patients in the first stage, and if a partial (PR) or complete response (CR) is observed the cohort is expanded to a total of 17 patients in the second stage. The treatment is considered promising if at least 3 PRs or CRs are observed in a cohort of 17 patients. **Results:** As of February 11, 2021, 16 patients were treated; 5 patients (prostate cancer, endometrial cancer, liposarcoma, basal cell carcinoma, squamous cell carcinoma of unknown primary) were enrolled in the iCPI nave cohort and 11 patients (leiomyosarcoma [2], squamous cell carcinoma of unknown primary, triple negative breast cancer, uveal melanoma, melanoma, uterine myxoid sarcoma, pleomorphic sarcoma, colorectal cancer, anaplastic astrocytoma, prostate cancer) were enrolled to iCPI pretreated cohort. Among all 16 patients, there was 1 episode of grade 4 hypotension (recovered) and 1 episode of grade 5 hypotension attributed to BXCL701, which resulted in implementation of risk-mitigation strategies such as gradual dose escalation and blood pressure monitoring. In the CPI nave cohort, of 4 patients with available imaging, 1 had a PR (microsatellite stable endometrial cancer [-62%]) and 1 durable stable disease (SD -10%, basal cell carcinoma on therapy for 6+ months). In the CPI pretreated cohort, of 9 patients with available imaging, 1 had a PR (-31%, uveal melanoma) and 3 durable SD (-22%, pleomorphic sarcoma on therapy for 8+ months; +4%, squamous cell carcinoma of unknown primary on therapy for 6 months; +5%, uterine myxoid sarcoma on therapy for 6 months). **Conclusions:** BXCL701 in combination with pembrolizumab demonstrated encouraging signals of activity in selected difficult-to-treat cancers. Prespecified efficacy endpoints were met in the first stage and both cohorts will proceed to second-stage of the study Clinical trial information: NCT04171219. Research Sponsor: BioXcel Therapeutics.

2559 **Poster Session**

GS-3583, a novel FLT3 agonist Fc fusion protein, to expand conventional dendritic cells in healthy volunteers.

Nishanthan Rajakumaraswamy, Anees Dauki, Michelle R. Kuhne, Torsten Trowe, Jing He, Christopher Clarke, Brian Carr, Angela Worth, Anshu Vashishtha, Christian Schwabe, Ahmed A. Othman; Gilead Sciences, Inc., Foster City, CA; New Zealand Clinical Research, Auckland, New Zealand

Background: Conventional dendritic cells subtype 1 (cDC1) play a vital role in the priming and expansion of tumor specific CD8+ T cells and their recruitment to tumor microenvironment (TME). However, cDC1s are often underrepresented in the TME. Systemic administration of Fms-like tyrosine kinase 3 ligand (FLT3L), a hematopoietic growth factor that binds to FLT3 on myeloid and lymphoid progenitor cells, leads to expansion of cDC1s in the periphery which can then be recruited into the TME. We hypothesize that FLT3 pathway stimulation using GS-3583, a FLT3 agonist Fc fusion protein, has the potential to promote T cell mediated anti-tumor activity. **Methods:** This was a first-in-human placebo-controlled study of GS-3583 in healthy volunteers to evaluate the safety, PK, and PD of escalating single doses (ranging from 75μg to 2000μg) of GS-3583. The study was blinded to the subjects and the investigator. Each dose cohort enrolled 8-12 healthy subjects who received GS-3583 or placebo as single IV infusion at 3:1 ratio. Subjects were observed in the phase 1 unit for 15 days and then for 12 weeks as outpatients. As part of the PD evaluation, we investigated the changes in the number of cDC1s and cDC subtype 2 (cDC2) cells. **Results:** As of 8th Feb 2021, selected safety, PK and PD data from the first 3 cohorts were available. GS-3583 was well tolerated and all subjects had been discharged. To date, there have been no serious or grade 3 or higher adverse events. Preliminary PK analysis suggested dose-dependent increase in GS-3583 exposure (AUC and C_{max}). Preliminary PD analysis shows that administration of GS-3583 resulted in dose-dependent increases in cDC1/cDC2 cells that peaked at day 5 or day 8 and returned to baseline within three weeks of drug administration. **Conclusions:** GS-3583 was safe and well tolerated and induced dose dependent expansion of dendritic cells in the periphery. In patients with cancer, this increase in dendritic cells can be utilized to enhance anti-tumor responses to immuno-oncology therapies. Research Sponsor: Gilead Sciences, Inc.

Cohort	1	2	3	4
Subjects treated(A=active; P=placebo)	8(6A; 2P)	8(6A; 2P)	12(9A; 3P)	-
Age, yearsmedian (range)	32 (20, 38)	27 (23, 45)	22 (18, 45)	-
Male n (%)	5 (62.5%)	5 (62.5%)	8 (66.7%)	-
cDC1 peak cell count*median (Q1, Q3)	Day 5 69.6 (62.9, 89.2)	Day 5 169.0 (121.1, 215.1)	Day 8 76.2 (17.0, 97.1)	
cDC1, fold change from baseline*median (Q1, Q3)	Day 5 1.85 (1.38, 2.4)	Day 5 6.42 (5.62, 7.17)	Day 8 7.83 (3.83, 10.56)	-
cDC2 peak cell count*median (Q1, Q3)	Day 5 1346.0 (1124.8, 1395.1)	Day 5 2937.0 (1679.8, 3731.9)	Day 8 10637.4 (7496.6, 13602.8)	-
cDC2, fold change from baseline*median (Q1, Q3)	Day 5 1.20 (0.71, 1.85)	Day 5 7.61 (3.21, 8.03)	Day 8 15. 41 (7.76, 22.13)	-

* Data shown only from the subjects who received GS-3583; placebo data are excluded

Safety and efficacy of murine PVSRIPO plus anti-PD-1 immune checkpoint inhibitor (ICI) in a melanoma tumor model.

Lauren Neighbours, Zachary P McKay, Matthias Gromeier, Garrett Nichols, Andrea True Kelly, Daniel Corum, Michael Brown; Istari Oncology, Morrisville, NC; Duke University Medical Center, Durham, NC; Duke University Medical Center, Preston Robert Tisch Brain Tumor Center, Durham, NC

Background: Most patients with advanced melanoma (mel) fail/acquire resistance to ICI, including anti-(α) PD-1. PVSRIPO is a novel intratumoral immunotherapy derived from the Sabin type 1 attenuated poliovirus (PV) that targets CD155, widely expressed on solid tumors and antigen-presenting cells (APCs) of the tumor microenvironment. Therapy leads to direct tumor cell death and type I/III interferon-dominant innate inflammation, mediating priming and recruitment of tumor antigen-specific T cells. Inflammation-mediated upregulation of the PD-1/L1 IC suggests greater anti-tumor response could be achieved with PVSRIPO + αPD-1. The aim of this preclinical study was to evaluate the efficacy and safety of murine PVSRIPO (mRIPO) + αPD-1 in an aggressive mel tumor model (B16-F10.9-OVA in human-CD155 transgenic mice [C56Bl/6]). **Methods:** Mice were randomized to 4 groups (G) of 12: (G1 [control]: vehicle [v] + IgG; G2: v + αPD-1; G3: mRIPO + IgG; G4: mRIPO + αPD-1). Tumor cells (5 x 10^5) were implanted into the right (R) and left (L) flanks. When tumor volume (vol) was ~25 mm^3, 15 μL v or 1 x 10^7 $TCID_{50}$ mRIPO was injected into R (Day 1) and L (Day 4) tumors; αPD-1 or IgG (250 μg, 100 μL ip) was given on Days 1 and 4 and q 3 days until termination (Day 13). Weight, hematology, chemistry, and inflammatory cytokines were assessed pre/post-tumor implantation. Tumor vol was assessed every other day, with gross/histologic exam at termination. **Results:** 47 mice without health issues were euthanized as planned; 1 G1 animal required early euthanasia for tumor ulceration. Microscopic findings: increased mononuclear cell tumor infiltrates (G2 and G4); less severe L tumor growth necrosis in G2, G3, and G4 vs G1. There were no specific treatment-related changes in serum cytokines in G4. See the table below for summary of total tumor vol changes vs control; the most significant reduction was observed in G4. No tumor cells were observed via histopathology at Day 13 in R flanks of 1 mouse in G2; 3 in G3; and 8 in G4; and only G3 (n=1) and G4 (n=5) mice had no evidence of L flank tumor cells, with regression evident before L tumor mRIPO injection (ie, abscopal response). **Conclusions:** mRIPO + αPD-1 had the greatest overall anti-tumor response, and the combination was well tolerated. These results suggest combination therapy is not associated with untoward immune-mediated toxicity and highlight the potential for enhanced efficacy in injected and uninjected tumors. A phase 2 clinical trial of PVSRIPO ± αPD-1 in unresectable αPD-1 refractory mel is enrolling (LUMINOS-102, NCT04577807). Research Sponsor: Istari Oncology.

Geometric mean ratio (95% CI; p-value) of total tumor vol (R+L) relative to group 1/control.

Group	Day 3	Day 5	Day 9	Day 13
2	0.9 (0.7, 1.1); 0.4	1.0 (0.7, 1.3); 0.8	0.9 (0.6, 1.2); 0.3	0.7 (0.5, 1.1); 0.1
3	0.9 (0.7, 1.1); 0.2	0.9 (0.7, 1.1); 0.2	0.7 (0.5, 1.0); 0.08	0.6 (0.4, 0.9); **0.01**
4	0.9 (0.7, 1.1); 0.3	0.6 (0.5, 0.8); **0.001**	0.5 (0.3, 0.7); **<0.001**)	0.3 (0.2, 0.5); **<0.001**

2561 **Poster Session**

Resetting the tumor microenvironment to favor anti-tumor immunity after local ablation.

Corrine A. Nief, Júlia Sroda Agudogo, Alana Gonzales, Rebecca A. Previs, Smita K Nair, Nimmi Ramanujam; Duke University, Department of Biomedical Engineering, Durham, NC; Duke University, School of Medicine, Durham, NC; Division of Gynecologic Oncology, Duke Cancer Institute, Duke University Medical Center, Durham, NC; Duke University Medical Center, Department of Surgery, Durham, NC

Background: Percutaneous tumor ablation is a non-surgical method of tumor destruction that leaves necrotic tumor debris *in situ*. Tumor associated antigens released after ablation have the potential to initiate a systemic anti-tumor immune response, however the hostile tumor microenvironment hinders antigen presentation and T cell activity. We hypothesized that resetting the tumor microenvironment with oral sodium bicarbonate to decrease tumor acidity and low-dose cyclophosphamide to deplete pro-tumor immune cells would improve the ability of ablation to initiate anti-tumor immunity. **Methods:** Tumor growth, overall survival, and metastatic burden was assessed in orthotopic tumor models of triple-negative breast cancer (67NR, 4T1, and E0771). Tumor ablation was performed on palpable tumors using percutaneous ethanol injection (PEI) with 6% ethylcellulose to improve retention in the tumor. Surgical excision was used as a negative control to test the role of *in situ* tumor debris. Before ablation mice were placed on 200 mM of sodium bicarbonate (SB) in their drinking water and received a single intraperitoneal injection of 200 mg/kg of cyclophosphamide (CP). Mice surviving to 60 days after tumor implant without a primary tumor or signs of metastases were considered "cured" and re-challenged with 50e5 tumor cells in the contralateral mammary pad. T cell dependance was assessed with in vivo CD8 depletions. **Results:** The combination of PEI+SB+CP produced a potent anti-tumor response, curing a majority of mice (5/7 of E0771, 8/12 of 67NR, 7/12 of 4T1). No mice were cured using PEI alone, SB alone, CP alone, or any combination of two therapies (0/51 of E0771, 0/73 of 67NR, 0/75 of 4T1,). Re-challenge tumor growth was hindered in mice cured with PEI+SB+CP. Mice receiving PEI+SB+CP had significantly less metastases and lived longer than mice receiving surgical excision alone or surgical excision with SB+CP. Additionally the anti-metastatic response of PEI+SB+CP was undone when CD8+ T cells were depleted. **Conclusions:** Here the anti-tumor response of local ablation produced by PEI was enhanced by priming the tumor with low-dose CP and oral SB in metastatic breast cancer. These results suggest that tumor ablation with CP and SB can create a T cell dependent, personalized immune response to a tumor using only low-cost, easily accessible supplies, and the host's own tumor. Research Sponsor: National Institutes of Health.

2562 **Poster Session**

Phase 1 trial of the adenosine A_{2A} receptor antagonist inupadenant (EOS-850): Update on tolerability, and antitumor activity potentially associated with the expression of the A_{2A} receptor within the tumor.

Laurence Buisseret, Sylvie Rottey, Johann S. De Bono, Ariane Migeotte, Brant Delafontaine, Thubeena Manickavasagar, Chiara Martinoli, Noémie Wald, Maura Rossetti, Esha A. Gangolli, Erol Wiegert, Nicola McIntyre, Joanne J. Lager, Jean-Pascal H. Machiels; Institut Jules Bordet, Brussels, Belgium; Universitair Ziekenhuis Ghent, Ghent, Belgium; The Institute of Cancer Research and Royal Marsden Hospital, London, United Kingdom; Cliniques Universitaires Saint-Luc, Brussels, Belgium; Royal Marsden Hospital, London, United Kingdom; iTeos Therapeutics, Gosselies, Belgium; iTeos Therapeutics, Cambridge, MA; Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium

Background: Tumors produce high levels of extracellular adenosine which suppress anti-tumor immune responses. Blocking A_{2A} receptors, predominantly expressed on tumor-infiltrating immune cells, can reverse the immunosuppressive effect of adenosine. Inupadenant is a non brain-penetrant, potent and highly selective small molecule antagonist of the A_{2A} receptor that remains active even at the high adenosine concentrations found in tumors. **Methods:** This is the phase I portion of an ongoing first-in-human, clinical trial (NCT02740985) to evaluate safety/tolerability, pharmacokinetic, pharmacodynamic and anti-tumor activity of inupadenant in adult patients with solid tumors who have exhausted standard treatment options. In addition, tumor biomarkers, including adenosine-pathway markers by immunohistochemistry (IHC), are being evaluated. We present updated results of the dose escalation, new results from the monotherapy expansion and new analysis of tumor biomarkers. **Results:** Overall, 42 patients (21 patients in the dose escalation and an additional 21 patients in a monotherapy expansion) with a median of 3 prior regimens were treated as of the data cut off (DCO, 30Nov20).The dose levels investigated, along with the most frequent (>20%) treatment-emergent adverse events (TEAEs) across all dose levels are presented in the table. 7 AEs led to discontinuation; 2 (atrial fibrillation and myocardial infarction) were considered possibly study drug-related by the investigator. No dose reductions were required. Two partial responses (PRs) were reported: melanoma (NRAS-mutant; received prior immunotherapy), and prostate cancer (received antiandrogen and chemotherapy). At the DCO, both PRs were ongoing with a duration of response >230 days. 12 patients had stable disease (SD) as best response and SD >6 months was observed in 3 patients. Response and stable disease were associated with a higher number of cells expressing the A_{2A} receptor within the tumor at baseline, as measured by IHC. **Conclusions:** Inupadenant monotherapy was generally well-tolerated as of the DCO at a dose of 80 mg twice daily with initial evidence of clinical benefit, including 2 durable PRs in patients who have exhausted standard treatment options. Analysis of pre-treatment tumor biopsies has identified the A_{2A} receptor as a biomarker which may be associated with clinical benefit. Clinical trial information: NCT03873883. Research Sponsor: iTeos Therapeutics.

Most frequent TEAEs (>20%) in dose escalation and monotherapy expansion.

	Patients N (%)					
Preferred Term	20 mg QD (N=3)	40 mg QD (N=3)	40 mg BID (N=3)	80 mg BID (N=27)	160 mg BID (N=6)	Total (N=42)
Fatigue	1 (33.3)	2 (66.7)	1 (33.3)	9 (33.3)	4 (66.7)	17 (40.5)
Anemia	0 (0)	2 (66.7)	0 (0)	11 (40.7)	1 (16.7)	14 (33.3)
Decreased appetite	2 (66.7)	1 (33.3)	1 (33.3)	6 (22.2)	3 (50.0)	13 (30.9)
Constipation	2 (66.7)	1 (33.3)	0 (0)	7 (25.9)	1 (16.7)	11 (26.2)

2563 **Poster Session**

Tumor-selective activity of XTX202, a protein-engineered IL-2, in mice without peripheral toxicities in nonhuman primates.

Jennifer O'Neil, Wilson Guzman, Oleg Yerov, Parker Johnson, Manoussa Fanny, Justin Greene, Megan McLaughlin, Kurt Jenkins, Rebekah O'Donnell, Huawei Qiu, Benjamin Nicholson, William Avery, Ronan C. O'Hagan; Xilio Therapeutics, Waltham, MA

Background: High-dose recombinant human interleukin-2 (aldesleukin) elicits anti-tumor immunity and is approved for the treatment of renal cell carcinoma and melanoma based on durable complete remissions. However, use of aldesleukin is limited due to treatment-related life-threatening toxicities. Recent second-generation efforts to alleviate toxicities have largely focused on eliminating binding to IL-2Rα, often with half-life extension. We have determined that mice and non-human primates (NHPs) treated with a second generation IL-2 surrogate still experience characteristic dose-limiting toxicities, including vascular leak syndrome. To overcome these toxicities and improve the therapeutic index (TI) of IL-2 as an anti-tumor immunotherapy, we employed protein engineering to generate XTX202, a highly potent third generation masked IL-2. XTX202 is unmasked in the tumor microenvironment by proteolytic activation resulting in full restoration of binding to IL-2Rβ without binding to IL-2Rα. The current study characterizes the therapeutic index of XTX202 versus aldesleukin and a second generation IL-2 surrogate. **Methods:** XTX202 bioactivity was measured using STAT-5 phosphorylation in human PBMCs and reporter cell lines. Anti-tumor efficacy and peripheral immune activation were evaluated in mice bearing syngeneic tumor models. Safety was evaluated in rodents and Cynomolgus monkeys. XTX200, an unmasked half-life extended IL-2 that does not bind to IL-2Rα, was used as a surrogate second generation IL-2. **Results:** Masked XTX202 showed limited IL-2R-dependent STAT-5 signaling *in vitro*. Proteolytic activation of XTX202 resulted in $CD8^+$ T and NK cell activation and over 1000-fold reduction in Treg activation as compared to WT IL-2. XTX202 achieved potent tumor growth inhibition in syngeneic mouse models as a single agent with no evidence of toxicity or peripheral immune activation, thus demonstrating tumor selective activity. XTX202 efficacy in mice at 2 mg/kg dose was equivalent to that achieved with the MTD dose of 0.5 mg/kg of a second generation IL-2 surrogate. XTX202 was well tolerated in NHPs in a 4-week repeat dose study at doses up to 30 mg/kg QW whereas a second generation IL-2 surrogate was not tolerated beyond 0.7 mg/kg QW. Based on these data, XTX202 has a 10 fold improvement in TI vs second generation IL-2. Based on comparative efficacy studies with aldesleukin and literature NHP tolerability data, XTX202 is projected to have a $\geq$150 fold greater TI than aldesleukin. **Conclusions:** XTX202, a third generation, tumor-selective IL-2, inhibits tumor growth and is well tolerated in repeat dose studies in NHPs at high doses. GLP toxicity studies with XTX202 are underway and first-in-human studies are expected to initiate this year. XTX202 has the potential to be a best-in-class IL-2 immunotherapy by expanding the curative anti-tumor activity of IL-2 while minimizing dose-limiting toxicities. Research Sponsor: Xilio Therapeutics.

Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability–high tumors: A combined analysis of two cohorts in the GARNET study.

Dominique Berton, Susana N. Banerjee, Giuseppe Curigliano, Sara Cresta, Hendrik-Tobias Arkenau, Cyril Abdeddaim, Rebecca Sophie Kristeleit, Andrés Redondo, Charles A. Leath, Antonio Antón Torres, Wei Guo, Ellie Im, Thierry Andre; GINECO & Institut de Cancerologie de l'Ouest, Centre René Gaudducheau, Saint-Herblain, France; The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; Division of Early Drug Development for Innovative Therapies, IEO, European Institute of Oncology IRCCS, and University of Milano, Milan, Italy; IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy; Sarah Cannon Research Institute UK Limited, London, United Kingdom; Centre de Lutte Contre le Cancer-Centre Oscar Lambret, Lille, France; University College London Cancer Institute, UCL, London, United Kingdom; Hospital Universitario La Paz – IdiPAZ, Madrid, Spain; University of Alabama at Birmingham, Birmingham, AL; Miguel Servet University Hospital of Zaragoza, Zaragoza, Spain; GlaxoSmithKline, Waltham, MA; Sorbonne University and Saint-Antoine Hospital, Paris, France

Background: Dostarlimab is an investigational, humanized programmed death 1 (PD-1) receptor monoclonal antibody that blocks interaction with the PD-1 ligands, PD-L1 and PD-L2. GARNET (NCT02715284) is a phase 1 study assessing the antitumor activity and safety of dostarlimab monotherapy in patients with solid tumors. **Methods:** This multicenter, open-label, single-arm study is being conducted in 2 parts: dose escalation and expansion. Here we report on the 2 expansion cohorts that enrolled mismatch repairdeficient/microsatellite instabilityhigh (dMMR/MSI-H) patients. Cohort A1 enrolled patients with advanced or recurrent dMMR/MSI-H endometrial cancer (EC), and cohort F enrolled patients with advanced or recurrent dMMR/MSI-H or POLε-hypermutated non-EC solid tumors, mainly gastrointestinal (GI) tumors (99 [93.4%] had GI tumors, including 69 [65.1%] with colorectal cancer). Patients received 500 mg IV of dostarlimab every 3 weeks for 4 cycles, then 1000 mg IV every 6 weeks until disease progression or discontinuation. The primary endpoints were objective response rate (ORR) and duration of response (DOR) by RECIST v1.1. Here we report ORR and DOR, by individual cohort and as an overall population, in patients with dMMR tumors identified by immunohistochemistry testing. **Results:** For this interim analysis, an efficacy analysis was performed for the patients who had baseline measurable disease and $\geq$6 months of follow-up in the study (N = 209). The ORR was 41.6% (95% CI, 34.9%48.6%) for the combined A1+F dMMR cohorts (Table). Responses were durable, and median DOR has not been reached in either cohort (median follow-up: cohort A1, 16.3 months; cohort F, 12.4 months). A total of 267 patients were included in the safety population (all patients who received $\geq$1 dose; cohort A1, N = 126; cohort F, N = 141). Treatment-related adverse events (TRAEs) were consistent across tumor types. Overall, the most frequently reported any-grade TRAEs were asthenia (13.9%), diarrhea (13.5%), and fatigue (11.2%). The most common grade $\geq$3 TRAEs were anemia (2.2%), lipase increased (1.9%), alanine aminotransferase increased (1.1%), and diarrhea (1.1%). No deaths were attributed to dostarlimab. **Conclusions:** Dostarlimab demonstrated durable antitumor activity in patients with dMMR solid tumors, with consistent antitumor activity seen across endometrial and nonendometrial tumor types. The safety profile was manageable, with no new safety signals detected. Most TRAEs were low grade and were similar across cohorts. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

		Confirmed ORR (RECIST v1.1)	
dMMR solid tumors	N	n (%)	95% CI[a]
Cohort A1 (EC)	103	46 (44.7)	34.9–54.8
Cohort F (non-EC)	106	41 (38.7)	29.4–48.6
dMMR overall	209	87 (41.6)	34.9–48.6

[a]Exact, 2-sided 95% CI for the binomial proportion.

2565 **Poster Session**

Pembrolizumab in microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) cancers: Updated analysis from phase 2 KEYNOTE-158 study.

Michele Maio, Paolo Antonio Ascierto, Ludmila Manzyuk, Daniel Motola-Kuba, Nicolas Penel, Philippe A. Cassier, Giovanni Bariani, Ana De Jesus-Acosta, Toshihiko Doi, Federico Longo, Wilson H. Miller, Do-Youn Oh, Maya Gottfried, Ruixue Wang, Fan Jin, Kevin Glen Norwood, Aurelien Marabelle; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; Istituto Nazionale Tumori Istituto di Ricovero e Cura a Carattere Scientifico Fondazione Pascale, Naples, Italy; NN Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation; COMOP A.C., Clinical Investigation, Mexico City, Mexico; Centre Oscar Lambret, Lille, France; Department of Medical Oncology, Centre Léon Bérard, Lyon, France; Instituto do Càncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; National Cancer Center Hospital East, Kashiwa, Japan; Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRICYS), CIBERONC, Madrid, Spain; Jewish General Hospital and McGill University, Montréal, QC, Canada; Department of Internal Medicine, Seoul National University Hospital, and Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; Meir Medical Center, Tel Aviv, Israel; Merck & Co., Inc., Kenilworth, NJ; Gustave Roussy, Institut National de la Santé et de la Recherche Médicale U1015, Villejuif, France

Background: Approval of pembrolizumab for the treatment of unresectable or metastatic MSI-H/dMMR solid tumors that have progressed on prior therapy was supported by data from KEYNOTE-158 (NCT02628067). At the data cutoff of Dec 6, 2018, the ORR was 34.3% among 233 patients (pts) with MSI-H/dMMR solid tumors enrolled in all cohorts of KEYNOTE-158, 77.6% had duration of response (DOR) ≥24 mo, median PFS was 4.1 mo, and median OS was 23.5 mo. We present results from 351 pts enrolled in KEYNOTE-158 cohort K at the data cutoff of Oct 5, 2020. **Methods:** Cohort K of this phase 2, open-label study enrolled adults with any previously treated advanced noncolorectal MSI-H solid tumor, measurable disease per RECIST v1.1, and ECOG PS of 0–1. MSI-H/dMMR status was assessed locally from a tumor tissue sample and defined as ≥1 of 4 MMR proteins absent by immunohistochemistry or as ≥2 allelic loci size shifts of 5 microsatellite markers by PCR. Pts received pembrolizumab 200 mg Q3W for up to 35 cycles or until PD, unacceptable toxicity, investigator decision, or withdrawal of consent. The primary endpoint was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints were DOR and PFS per RECIST v1.1 by BICR, OS, and safety. Efficacy was assessed in all pts who received ≥1 dose of treatment with ≥6 mo follow-up; safety was assessed in all treated pts. **Results:** 351 pts were enrolled in KEYNOTE-158 cohort K across multiple tumor types, including endometrial (22.5%), gastric (14.5%), small intestine (7.4%), ovarian (7.1%), cholangiocarcinoma (6.3%), and pancreatic (6.3%). 41.0% had 1 prior line of therapy; 55.6% had ≥2 prior lines. Median time from first dose to database cutoff (Oct 5, 2020) was 37.5 (range, 0.2–55.6) mo; 16.0% were continuing treatment. The ORR among the 321 eligble pts was 30.8% (CR, 27; PR, 72); median DOR was 47.5 mo (Table). Treatment-related AEs occurred in 64.7% of pts (grade 3–5, 12.0%), led to discontinuation in 6.6%, and led to death in 3 pts (myocarditis, pneumonia, and Guillain-Barre syndrome). Immune-mediated AEs and infusion reactions occurred in 20.2% of pts (grade 3–4, 4.3%) and led to death in 2 pts with no other contributing factors (myocarditis [AE start, day 26; death, day 33] and Guillain-Barre syndrome [AE start, day 22; death, day 41]). **Conclusions:** Pembrolizumab demonstrated a high ORR (30.8%), durable clinical benefit, and a manageable safety profile in this heavily pretreated advanced MSI-H/dMMR noncolorectal pan-tumor population. Clinical trial information: NCT02628067. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	KEYNOTE-158 Cohort K N = 321
Confirmed ORR, % (95% CI)	30.8 (25.8 to 36.2)
Median DOR, mo (range)	47.5 (2.1+ to 51.1+)
≥24 mo, %	74.1
≥36 mo, %	70.1
Median PFS, mo (95% CI)	3.5 (2.3 to 4.2)
36-mo rate, %	24.0
Median OS, mo (95% CI)	20.1 (14.1 to 27.1)
36-mo rate, %	39.1

CI, confidence interval. + indicates no progressive disease by the time of last disease assessment.

2566 **Poster Session**

Efficacy and safety of HLX10, a novel anti-PD-1 antibody, in patients with previously treated unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors: A single-arm, multicenter, phase 2 study.

Shukui Qin, Jin Li, Haijun Zhong, Chuan Jin, Lili Chen, Xianglin Yuan, Qingxia Fan, Kehe Chen, Peiguo Cao, Jianjun Xiao, Da Jiang, Tao Zhang, Hongyu Zhang, Xicheng Wang, Wei Wang, Qingyu Wang; Chinese People's Liberation Army Cancer Center of Nanjing Bayi Hospital, Nanjing, China; Shanghai East Hospital, Shanghai, China; Department of Medical Oncology, Zhejiang Cancer Hospital, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, China; Affiliated Cancer Hospital of Guangzhou Medical University, Guangzhou, China; Taizhou First People's Hospital, Taizhou, China; Tongji Medical College, Huazhong University of Science and Technology, Hubei, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China; The Third Xiangya Hospital of Central South University, Changsha, China; Zhongshan City People's Hospital, Zhongshan, China; Department of Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; The Fifth Affiliated Hospital Sun Yat-sen University, Zhuhai, China; The First Affiliated Hospital/School of Clinical Medicine Guangdong Pharmaceutical University, Guangzhou, China; The First People's Hospital of Foshan, Foshan, China; Shanghai Henlius Biotech, Inc., Shanghai, China

Background: Microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) in cells render them susceptible to immune checkpoint blockages. This study aimed to evaluate the efficacy and safety of HLX10, a fully humanized monoclonal antibody against PD-1, in patients with unresectable or metastatic MSI-H/dMMR solid tumors who have progressed on or been intolerant to standard therapies. **Methods:** In this single-arm, open-label, multicenter, phase 2 study (NCT03941574), patients (18≤ age ≤75 years) with histologically/cytologically confirmed unresectable or metastatic MSI-H/dMMR solid tumors were recruited to receive 3 mg/kg HLX10 every two weeks intravenously for up to 2 years until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint was objective response rate (ORR) assessed by IRRC (evaluated every 6 weeks for the first 48 weeks and every 12 weeks thereafter) per RECIST v1.1. Secondary endpoints included ORR assessed by investigators, duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. All eligible patients who received at least one dose of HLX10 were included in the safety analyses. **Results:** As of Jan 9, 2021, 108 patients were enrolled and 68 with locally or centrally confirmed MSI-H were included in the main efficacy analysis population. Among the 68 patients, the median follow-up duration was 7.7 (range: 1.1–16.4) months and the median age was 53.0 (range: 23.0–72.0) years. MSI-H tumor types included colorectal cancer (n = 54), endometrial cancer (n = 5), gastric cancer (n = 4), breast cancer (n = 2), small intestine cancer (n = 2) and fallopian tube cancer (n = 1). IRRC and investigator assessed ORR were 38.2% (95% CI: 26.7–50.8%; 2 complete response) and 35.3% (95% CI: 24.1–47.8%) respectively in the main efficacy analysis population. Median DoR, PFS and OS have not been reached. 105 (97.2%) patients experienced treatment-emergent adverse events (TEAEs), most commonly anemia (34.3%), hypoproteinemia (27.8%) and increased aspartate aminotransferase (25.0%). 53 (49.1%) patients had grade 3 or worse TEAEs, most commonly anemia (8.3%), progressive disease (6.5%), increased γ- glutamyltransferase (5.6%) and intestinal obstruction (5.6%). 52 (48.1%) patients had immune-related adverse events (irAEs) while 10 (9.3%) had grade 3 or worse irAEs. 3 (2.8%) deaths (2 PD and 1 intestinal obstruction) that might be related to the study drug were reported. **Conclusions:** HLX10 provides encouraging antitumor activity with a manageable safety profile in patients with MSI-H/dMMR solid tumors who have progressed on or been intolerant to standard therapies. As an effective tissue-agnostic treatment, HLX10 possesses the potential to improve patients' clinical outcomes. Clinical trial information: NCT03941574. Research Sponsor: Shanghai Henlius Biotech, Inc.

2567 **Poster Session**

Multi-center phase 1 safety and efficacy study of nivolumab in renal transplant patients with metastatic malignancy.

John Raymond Zalcberg, Michael J. Boyer, Anne Elizabeth Taylor, Thean Hsiang Tan, Bronwyn Hockley, Rob Carroll; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Medical Oncology, Chris O'Brien Lifehouse, Camperdown, Australia; Royal Adelaide Hospital, Adelaide, SA, Australia; Royal Adelaide Hospital, Adelaide, Australia

Background: Organ Transplant Recipients (OTR) are generally excluded from trials of immune checkpoint inhibitors (ICI) due to the reported risk of allograft rejection. A recent systematic review of published case series includes only 65 cases. Transplant organ rejection rates of 41% are reported with cancer response rates of 39%. The majority of OTR treated with ICI have had reduction/cessation of immunosuppression (IS) prior to ICI. Isolated IS reduction is associated with organ rejection and therefore either IS manipulation alone and/or ICI could induce organ rejection episodes. **Methods:** Renal OTR with incurable cancer, for whom ICI would normally be used in the general population (without an organ transplant), were eligible if creatinine $<$ 180 umol/l, no donor specific HLA antibodies and ECOG $<$ 2. Treatment was with nivolumab (3mg/kg q 14 days for 5 doses, then 480 mg q 28 days), without manipulation of IS and pre-ICI-exposure alloimmune risk assessment. Treatment continued till progression, patient refusal, or graft rejection. Primary endpoint was rate of irretrievable renal graft rejection. **Results:** 15 patients (9 male:6 female; median age 66.6 years) were enrolled and treated with a median (range) 3(1-42) infusions and with median (range) follow-up of 128 (11-784) days. Tumour types included:1 melanoma; 2 renal tract; 1 hepatocellular carcinoma; 1 Merkel cell; 1 adenocarcinoma lung; 1 MSI high colorectal, 8 squamous cell carcinoma (SCC) head and neck. 2 patients experienced rejection; one at day 28 (2 infusions); one at day 36 (3 infusions). Both had SCC and have had a CR. One is on haemodialysis and alive at 2 years the other a creatinine 450 umol/l. Both rejections treated with steroid, plasma-exchange and anti-thymocyte-globulin (ATG). 1 patient (metastatic bladder cancer) experienced graft loss (at 300 days) due to ureteric-stent bleed and BK-nephritis indirectly related to nivolumab-this patient died of progressive disease at 65 days after nivolumab cessation. Median (range) progression free disease (PD) with $\geq$ 2 infusions was 300 (68-784+) days. There were 5 CR (1 MSI high colorectal, 4 SCC) median duration of response 13 months and 2 PR (1 SCC 1 bladder)- 1 without PD. **Conclusions:** In this interim analysis, rejection rates in OTR with incurable cancers treated with ICI was 2/15 (13%) when IS is maintained and there is pre exposure alloimmune assessment. The combined CR and PR rate was 7/15 (47%). Clinical trial information: 12617000741381. Research Sponsor: BMS.

2568 **Poster Session**

Phase I dose escalation of KD033, a PDL1-IL15 bispecific molecule, in advanced solid tumors.

Jason J. Luke, Anthony J. Olszanski, Igor Puzanov, Dan Lu, Adrian Hackett, Stella Martomo, Jeegar Patel, Olivier Schueller, Alessandro Mora, Miranda Schlitt, Linghui Li; UPMC Hillman Cancer Center, Pittsburgh, PA; Fox Chase Cancer Center, Philadelphia, PA; Vanderbilt University Medical Center, Nashville, TN; Kadmon Corporation, New York, NY; Kadmon, New York, NY; Kadmon Corporation, Cambridge, MA; Kadmon Corporation, LLC, Cambridge, MA

Background: IL-2 and IL-15 signal through the shared IL-2/15 $\beta\gamma$ receptor, but unlike IL-2, IL-15 does not expand regulatory T cells (Tregs), does not mediate activation-induced cell death and may have an improved therapeutic index. KD033 is a fusion antibody combining a fully human, high affinity anti-human Programmed Death Ligand 1 (PD-L1) IgG1 antibody with the human IL-15 receptor alpha (IL15Rα) sushi domain and human IL-15 (IL-15). KD033 (or its mouse cross reactive surrogate molecule, srKD033) has been extensively characterized in multiple *invitro* and *in vivo* nonclinical studies. The fusion of anti-PD-L1 antibody to IL-15 significantly increases the maximal-tolerated dose (MTD) of srKD033 in mice compared to free IL-15. In addition, srKD033 has exhibited increased efficacy in rejecting tumors in mice as compared to the combination of its individual components, anti-PD-L1 antibody and IL-15. **Methods:** This is a phase 1, open-label, multiple ascending dose, multi-center clinical trial being conducted in patients with metastatic or locally advanced solid tumors (NCT04242147). The primary objective is to determine the safety and tolerability and the MTD of KD033. Secondary objectives include characterization of PK and immunogenicity, evaluation of CD8 T and NK cell activation and assessment of best overall response and duration of response. KD033 is administered by IV infusion over 30 minutes every 14 days. Accelerated intra-patient dose escalation across the initial three dose levels, followed by 3+3 escalation thereafter, is investigating dose ranges from 3 μg/kg to 600 μg/kg. Efficacy evaluation is planned in an expansion cohort of patients with PD-1/L1 refractory tumors. **Results:** A total of 7 patients have received treatment. Three patients were dosed in Cohort 1 and four patients were dosed in Cohort 2. Through two dose escalation cohorts (3 μg/kg – 25 μg/kg), no dose-limiting toxicities have been reported. Grade 1-2 treatment-related toxicities, when observed, resolved within 24 hours with supportive management. 6 patients are evaluable for treatment response with one patient (adenoid cystic carcinoma) in the first cohort having stable disease for more than 6 months. **Conclusions:** KD033 has been well tolerated early in dose escalation with on-mechanism pharmacodynamics consistent with IL-15 agonism. Clinical trial information: NCT04242147. Research Sponsor: None.

2569 **Poster Session**

A phase 2 study of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable ormetastatic microsatellite instability-high/mismatch repair deficient solid tumors.

Jian Li, Ye Xu, Aimin Zang, Yunong Gao, Quanli Gao, Yanqiao Zhang, Dong Wang, Jianming Xu, Ying Yuan, Haiping Jiang, Jieer Ying, Chunmei Shi, Yanhong Deng, Jing Wang, Tianshu Liu, Yi Huang, Zhezhen Li, Huanli Wang, Shou Liu, Lin Shen; Beijing Cancer Hospital, Beijing, China; Fudan University Shanghai Cancer Center, Shanghai, China; Affiliated Hospital of Hebei University, Hebei, China; Henan Cancer Hospital, Henan, China; Department of Gastrointestinal Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China; Chongqing University Cancer Hospital, Chongqing, China; The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; The Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang, China; Cancer Hospital of The University of Chinese Academy of Sciences, Beijing, China; Fujian Medical University Union Hopsital, Fujian, China; The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Hunan Cancer Hospital, Hunan, China; Zhongshan Hospital, Fudan University, Shanghai, China; Hubei Cancer Hospital, Hubei, China; BeiGene (Shanghai) Co., Ltd., Shanghai, China

Background: Tislelizumab is an anti-programmed cell death protein 1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis. In early phase clinical studies, tislelizumab monotherapy was generally well tolerated and had antitumor activity in patients (pts) with solid tumors, including microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors such as colorectal cancer (CRC). **Methods:** This single-arm, multicenter, open-label, phase 2 study evaluated the efficacy and safety of tislelizumab monotherapy in adult Chinese pts with previously treated, locally advanced, unresectable or metastatic histologically confirmed MSI-H/dMMR solid tumors by central lab. Pts received tislelizumab 200 mg intravenously every 3 weeks until disease progression, unacceptable toxicity, or withdrawal. Radiological imaging was performed at 9 weeks then every 6 weeks for the first year of therapy and every 12 weeks thereafter. The primary efficacy analysis set was all pts who received any dose of tislelizumab with measurable disease per independent review committee (IRC) at baseline. The primary endpoint was IRC-assessed overall response rate (ORR; RECIST v1.1). Secondary endpoints included duration of response (DoR) and disease control rate. Using a binomial exact test, the null hypothesis of ORR=10% (historical rate) was rejected if 1-sided $p \leq 0.025$. **Results:** Between Sep 2018-Aug 2020, 80 pts were enrolled (median age 53 years; range 19-81 years) and 74 were included in the primary efficacy analysis set. At median study follow-up of 11.78 months, ORR by IRC was 45.9% (n=34/74; 95% CI 34.3, 57.9) in all tumor types (1-sided $p<0.0001$), including 4 complete responses (CR) and 30 partial responses (PR). Observed ORR by IRC was 39.1% (n=18/46; 95% CI 25.1, 54.6) in CRC pts and 57.1% (n=16/28; 95% CI 37.2, 75.5) in non-CRC pts. Of 74 pts, 53 (71.6%) had disease control and 39 (52.7%) achieved CR, PR or durable stable disease by IRC $\geq$24 weeks. Median DoR by IRC has not been reached; no disease progression was reported in the 34 responders (CR+PR), with 33 responders still on treatment (12-month DoR rate=100%). Treatment-emergent adverse events (TEAEs) $\geq$Grade 3 occurred in 47.5% (n=38/80) pts, of which 21.3% (n=17/80) were lab abnormalities. Immune-mediated TEAEs $\geq$Grade 3 were 5% (n=4/80). **Conclusions:** Tislelizumab achieved statistical significance and demonstrated clinically meaningful improvement in ORR in pts with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors. Treatment effect was consistent and durable across tumor types and endpoints. Tislelizumab was generally well tolerated and no new safety signals were identified. The data support tislelizumab as a new treatment option in this population. Clinical trial information: NCT03736889. Research Sponsor: This study is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jessica Jones, PhD, and Kirsty Millar, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

2570 **Poster Session**

Mega- and meta-analyses of fecal metagenomic studies in predicting response to immune checkpoint inhibitors.

Alya Heirali, Bo Chen, Matthew Wong, Pierre H.H. Schneeberger, Victor Rey, Anna Spreafico, Wei Xu, Bryan Coburn; University Health Network, University of Toronto, Toronto, ON, Canada; Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada; University of Toronto, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Toronto General Hospital, University Health Network, Toronto, ON, Canada

Background: A number of studies have demonstrated that the gut microbiome of responders to immune checkpoint inhibitors (ICI) is compositionally different compared to that of non-responders. However, differences in study design, patient cohorts and bioinformatic analyses make it challenging to identify bacterial species consistently associated with response to ICI across different cohorts and cancer types. **Methods:** We leveraged the statistical power of mega- and meta-analyses to identify bacterial species consistently associated with response to ICI using data from three published fecal metagenomic studies (Gopalakrishnan *et al., Science 2018;* Matson *et al., Science 2018;* Routy *et al., Science 2018)*. Metagenomic data was uniformly processed and analyzed using Metaphlan v2.0. We conducted a two-part modelling approach of bacterial species present in at least 20% of samples to account for both prevalence and relative abundance differences between responders/non-responders. **Results:** A total of 190 patients (n = 103 responders; n = 87 non-responders) were included from the three studies. Data from Routy *et al.*, was analyzed as subsets based on tumor type for a total of 4 analyzed cohorts. We identified five species including *Bacteroides thetaiotaomicron*, *Clostridium bolteae, Holdemania filiformis,Clostridiaceae bacterium JC118* and *Escherichia coli* that were concordantly significantly different between responders and non-responders using both meta- and mega-analyses. *B. thetaiotaomicron* and *Clostridium bolteae* relative abundance (RA) were independently predictive of non-response to immunotherapy when data sets were combined and analyzed using mega-analyses (AUC 0.59 95% CI 0.51-0.68 and AUC 0.61 95% CI 0.52-0.69, respectively). **Conclusions:** Despite inter-cohort heterogeneity in tumor type, treatment regimens, and sequencing modalities, meta- and mega analysis of published metagenomic studies identified generalizable bacterial species associated with ICI response or lack thereof. *B.thetaiotaomicron* and *C. bolteae* were predictors of non-response to ICI suggesting the clinical potential of narrow spectrum anti-biotics targeting non-response associated bacterial species to improve outcomes in ICI recipients. Research Sponsor: Princess Margaret Cancer Foundation, Tomcyzk AI and Microbiome Working Group.

2571 **Poster Session**

Phase 2 study of retifanlimab (INCMGA00012) in patients (pts) with selected solid tumors (POD1UM-203).

Michele Maio, Michael Schenker, Jacques Medioni, Slawomir Mandziuk, Margarita Majem, Gwenaelle Gravis, Mark J. Cornfeld, Sulabha Ranganathan, Yubing Yao, Howard Su-Hau Yeh, Tibor Csőszi; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; Centrul de Oncologie Sf. Nectarie, Oncologie Medicala, Craiova, Romania; Centre of Early Clinical Trials in Cancer Hôpital Européen Georges-Pompidou, Universite de Paris, Paris, France; Department of Clinical Oncology and Chemotherapy, Medical University of Lublin, Lublin, Poland; Medical Oncology Department, Hospital de Sant Pau, Barcelona, Spain; Department of Medical Oncology, Institut Paoli-Calmettes, Aix-Marseille Université, CRCM, Marseille, France; Incyte Corporation, Wilmington, DE; Covance Clinical Development Services, Princeton, NJ; Hetenyi Geza Korhaz, Onkologiai Kozpont, Szolnok, Hungary

Background: Checkpoint inhibitors (CPIs) are an effective treatment (tx) for many tumor types. Retifanlimab, an investigational humanized anti–PD-1 monoclonal antibody, has shown safety, pharmacology, and clinical activity consistent with the class. POD1UM-203 (NCT03679767) assessed efficacy and safety of retifanlimab in pts with selected solid tumors where CPI monotherapy is highly active. **Methods:** Eligible pts (≥18 y) had tx-nave metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (tumor proportion score ≥50%), cisplatin ineligible locally-advanced/metastatic urothelial cancer (UC) with PD-L1 expression (combined positive score ≥10%), unresectable/metastatic melanoma, or tx-nave locally advanced/metastatic clear-cell renal cell carcinoma (RCC). Measurable disease (RECIST v1.1) was required. ECOG PS >1 and prior PD-1/PD-L1 directed tx were exclusions. Retifanlimab was administered as an IV infusion at 500 mg every 4 wks over 30 min. Primary endpoint was investigator-assessed objective response rate (ORR). Secondary endpoints were duration of response (DOR), disease control rate (DCR), progression-free survival, overall survival, safety, and pharmacokinetics. **Results:** A total of 121 pts (35 melanoma, 23 NSCLC, 29 UC, 34 RCC) received ≥1 dose of retifanlimab and were included in the analyses. Median duration of tx was 169 d (range, 1–442). The efficacy cut-off for the primary analysis occurred once all pts had been followed for at least 6 mo from the time of initial tx. Confirmed RECIST v1.1 responses were observed in all tumor types (Table) and were consistent with published ORR for other CPIs; median DOR was not reached for any tumor cohort and tx was ongoing at the time of data cutoff for 17, 11, 9, and 15 pts with melanoma, NSCLC, UC, and RCC, respectively. The most common tx-emergent AEs (TEAEs, >10% incidence) were asthenia (17.4%), arthralgia (14.9%), decreased appetite (14.0%), pruritus (12.4%), rash (10.7%), and urinary tract infection (10.7%); majority of TEAEs were low grade (≤ grade 2) and none led to tx discontinuation. Immune-related AEs occurred in 23 pts (19.0%), most common (>1% incidence) were hypothyroidism (7.4%), rash (4.1%), hyperthyroidism (2.5%), and pruritus (1.7%).Immune-related AEs led to dose delay in 5 pts (4.1%), but none led to tx discontinuation and/or dose interruption. **Conclusions:** Retifanlimab demonstrated antitumor activity and was generally well-tolerated in pts with melanoma, NSCLC, UC, or RCC comparable with approved CPIs for these tumor types. These results support ongoing further development of retifanlimab. Clinical trial information: NCT03679767. Research Sponsor: Incyte Corporation Inc.

Efficacy summary.

	Melanoma n=35	NSCLC n=23	UC n=29	RCC n=34
ORR, n (%)	13 (37.1)	7 (30.4)	11 (37.9)	8 (23.5)
95% CI	21.5–55.1	13.2–52.9	20.7–57.7	10.7–41.2
DCR, %	54.3	65.2	55.2	64.7
95% CI	36.6–71.2	42.7–83.6	35.7–73.6	46.5–80.3
Median DOR 95% CI	NE	NE	NE	NE
NE, not estimable	NE–NE	1.9–NE	2.2–NE	2.8–NE

Efficacy of HX008 in high microsatellite instability/mismatch repair–defificient (MSI-H/dMMR) solid tumors: Results from a multicenter phase II open-label study.

Jing Huang, Yan Song, Suxia Luo, XianIi Yin, Enxiao LI, Hui Wang, Yifu He, Zhihui Liu, Qingxia Fan, Xinjun Liang, Yongqian Shu, Yunpeng Liu, Nong Xu, Shu Zhang, Zhixiang Zhuang, Jingdong Zhang, Xiaoge Kou, Fen Wang, Xiaodong Zhu, Shengmian Li; Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Henan Cancer Hospital, the Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; Hunan Cancer Hospital, Hunan, China; Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xian, China; Tianjin People's Hospital, Tianjin, China; Department of Oncology, The First Affiliated Hospital of USTC West District& Anhui Provicial Cancer Hospital, Hefei, China; Guangxi Medical University Cancer Hospital, Nanning, China; Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China; Hubei Cancer Hospital, Wuhan, China; Jiangsu Province Hospital, Jiangsu, China; Medical Oncology, The First Hospital of China Medical University, Shenyang, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Medical Oncology, Shandong Cancer Hospital, Jinan, China; The Second Affiliated Hospital of Soochow University, Suzhou, China; Liaoning Cancer Hospital, Shenyang, China; The First Affiliated Hospital of Xinxiang Medical College, Xinxiang, China; Peking University Shenzhen Hospital, Shenzhen, China; Fudan University Shanghai Cancer Center, Shanghai, China; The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Background: The subsequent treatment choices are limited for the patients with advanced solid tumors who had failed the standard therapies. PD-1 blockade monotherapy demonstrated robust antitumor activity in patients with MSI-H/dMMR. The aim of this study is to identify the efficacy and safety of HX008, an anti-PD-1 monoclonal antibody, in patients with advanced MSI-H/dMMR solid tumors. **Methods:** Eligible patients were age ≥18 years with histologically/cytologically confirmed advanced MSI-H/dMMR solid tumors, who have failed at least one line of standard systemic therapy. MSI-H/dMMR status was assessed centrally. Patients received HX008 200 mg once every 3 weeks until disease progression, unacceptable toxicity, or patient withdrawal. Radiologic imaging was performed 9 weeks after the first treatment, then every 6 weeks for the first year of therapy, and every 12 weeks thereafter. The primary end point was objective response rate (ORR) per RECIST1.1. **Results:** One hundred patients were enrolled from October 2018 to December 2020, with a median age of 53 (range 20-74) years. All of the patients were ≥ second-line patients. The most common cancer types were colorectal cancer (N=74) and gastric cancer (N=10). Median follow-up is 8.97 (range 0.03-25.53) months at the time of data cutoff. Among 86 patients who had reached the initial response evaluation, there were 8 CR, 33 PR, 24 SD, 17 PD and 4 NE. ORR was 47.67% (95%CI 36.79%-58.73%), and DCR was 75.58% (95%CI 65.13%-84.20%). ORR and DCR for the 66 colorectal cancer patients were 50% (95%CI 37.43-62.57%) and 75.76% (95%CI 63.64-85.46%). Median PFS was not reached (95%CI 6.18-NR) for all enrolled patients, while the 6-month and 12-month PFS rates were 62.66% (95%CI 50.98%-72.31%) and 52.70% (95%CI 39.96%-63.94%), respectively. Median OS was not reached. Treatment-related adverse events occurred in 77 patients (77%). Twelve patients (12%) had grade 3 or 4 treatment-related adverse events and there were no grade 5 treatment-related adverse events. The grade 3 or 4 treatment-related adverse events with incidence >1% included anemia (2%) and leukopenia (2%). Immune-related adverse events were observed in 15 patients (15%), including hypothyroidism in 9 patients (all were grade 1-2), and hepatitis, hyperglycemia, myocarditis, creatin kinase/creatin kinase MB increased, hypopigmentation of the vulva, rash, each in 1 patient. **Conclusions:** HX008 as a ≥second-line therapy showed promising efficacy and a manageable safety profile in patients with MSI-H/dMMR advanced solid tumors. Clinical trial information: NCT03704246. Research Sponsor: Taizhou Hanzhong Biomedical Co. LTD.

2573 **Poster Session**

An exploratory study of nivolumab (nivo) with or without ipilimumab (ipi) according to the percentage of tumoral CD8 cells in advanced metastatic cancer.

Apostolia Maria Tsimberidou, Alexandra Drakaki, Danny Khalil, Shivaani Kummar, F. Stephen Hodi, David Yoonsuk Oh, Christopher R. Cabanski, Michael Tezlaff, Theresa LaVallee, Marko Spasic, Leo Nissola, Lacey J. Kitch, Nicholas L. Bayless, Cheryl Selinsky, Jennifer C Ayran, Jill O'Donnell-Tormey, Vanessa M. Hubbard-Lucey, Ute Dugan, James Patrick Allison, Padmanee Sharma; The University of Texas MD Anderson Cancer Center, Houston, TX; University of California Los Angeles, Los Angeles, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Stanford University School of Medicine, Stanford, CA; Dana-Farber Cancer Institute, Boston, MA; University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Parker Institute for Cancer Immunotherapy, San Francisco, CA; University of Texas MD Anderson Cancer Center, Houston, TX; Cancer Research Institute, New York, NY; Bristol-Myers Squibb, Wallingford, CT

Background: Immune checkpoint inhibitors (ICIs) have demonstrated durable clinical responses and improved survival in patients (pts) across numerous indications. Despite this progress, the benefit of ICIs is limited to a minority of overall metastatic cancer patients. There is a critical need for biomarkers agnostic of tumor type to inform which pts will benefit from nivo alone versus ipi/nivo combination treatment. Both pre-treatment tumoral $CD8^+$ cells and recruitment of $CD8^+$ T cells in response to ICIs are associated with improved clinical outcomes in patients treated with anti-PD-1 therapy. [1,2,3,4] Here we report the final results of a prospective clinical study in which pts with varying advanced solid tumors were assigned to nivo, with or without ipi, based on the percentage of tumoral CD8 cells at the time of treatment. **Methods:** We performed a prospective, non-randomized, open-label, multicenter study in which pts with tumoral $CD8^+$ cells $\geq$ 15% ($CD8^+$ high) received nivo 360mg IV Q3W, followed by nivo maintenance 480mg Q4W. Pts with tumoral $CD8^+$ cells $<$ 15% ($CD8^+$ low) received nivo 360 mg IV Q3W, and ipi at 1 mg/kg IV Q3W for 2 doses and then Q6W for 2 doses, followed by nivo maintenance 480 mg IV Q4W until PD or intolerable toxicity. Primary endpoints were Disease Control Rate (DCR: CR, PR, or SD $\geq$ 6 months) and CD8 low to high conversion ($<$ 15% to $\geq$ 15%). Baseline and on-treatment tumor, blood and stool samples were collected for multiomic biomarker analyses. This study was not powered for formal statistical analysis. Up to 200 pts could be enrolled to allow for adaptive exploration of response and CD8 changes. **Results:** N = 79 pts were enrolled:7 in $CD8^+$ high arm (nivo) and 72 in $CD8^+$ low arm (ipi/nivo). The study enrolled a wide variety of primary solid tumors; the most common were gynecological (n = 15), prostate (12), and head and neck (7). DCR was 14% (1/7; 95% CI 1 - 44) and 24% (17/72; 95% CI 15 - 34) in the CD8 high and CD8 low arms, respectively. Of 39 pts in CD8 low arm with an on-treatment biopsy, 14 (36%; 95% CI 22 - 51) had CD8 conversion; 7/14 pts (50%) who converted had DCR. Immune-related AEs (irAEs) were consistent with known safety profile of both drugs. **Conclusions:** Ipi/nivo demonstrated clinical responses and increased CD8% in a range of cold tumors with low tumoral CD8 cells. There may be an association between increasing CD8% and response. Baseline high CD8% alone does not appear to be sufficient as a pan-cancer predictive biomarker of response to nivo monotherapy. CD8 conversion, response, and irAEs associated with circulating and stool-based biomarkers are under evaluation as composite biomarkers may improve their predictive value. Clinical trial information: 03651271. Research Sponsor: The Parker Institute for Cancer Immunotherapy.

2574 **Poster Session**

Assessment of cancer-specific microbiome signature of response to immune checkpoint inhibitors.

Michal Sarfaty, Christopher A. Desjardins, Paul Giardina, Kankana Bardhan, Swarna Pandian, Keith Halley, Elizabeth M. Halvorsen, Margaret K. Callahan, Michael A. Postow, Chung-Han Lee, Ritesh Kotecha, Daniel Kashani, Neha Ratna, Ashley Marie Regazzi, Matthew R. Henn, Matthew D. Hellmann, Gopa Iyer, Christopher B. Ford, Jonathan U. Peled; Memorial Sloan Kettering Cancer Center, New York, NY; Seres Therapeutics, Cambridge, MA

Background: Clinical and preclinical experiments suggest that the gut microbiome can affect outcome in cancer patients treated with immune checkpoint inhibitors (ICI). Most data to date has been in melanoma, so the relationship of the gut microbiome with treatment outcome in other cancers is poorly understood. Here, we evaluated the microbiome composition in correlation to ICI response in patients with metastatic lung, urothelial, or renal cancer, as well as metastatic melanoma. **Methods:** Fecal microbiome samples were obtained from patients with metastatic melanoma, lung, urothelial, or renal cancer immediately before ICI therapy was initiated. Bacterial genomic DNA was isolated and profiled by whole metagenome sequencing. Sequence data were analyzed using a custom implementation of MetaPhlAn2. Response to ICI was defined as partial or complete response or remaining on therapy for more than 6 months. **Results:** Samples were prospectively collected from 94 patients, including metastatic melanoma (n = 17), lung (n = 44), urothelial (n = 23), or renal cancer (n = 10). Treatment included anti-PD(L)1 monotherapy (n = 51), anti-PD1 + anti-CTLA4 combination therapy (n = 17), or a combination of anti-PD1 and chemotherapy (n = 26). Clinical response was observed in 58% of patients, including partial or complete response (45%) and on treatment for more than 6 months (55%, with 31% on treatment for more than 1 year). Although the variance in the composition of pretreatment microbiome samples did not explain response alone (R vs NR, PERMANOVA, p = 0.273), a significant portion of the variance in microbiome composition was explained by the interaction of cancer type and outcome (PERMANOVA, p = 0.014), suggesting a cancer-specific microbiome relationship. Notably, there was some similarity in the signature of NR across three cancer types (lung, urothelial and melanoma). One sample in this NR cluster was from a patient whose metastatic NSCLC was nonresponsive to pembrolizumab and carboplatin/pemetrexed. This microbiome sample was evaluated *in vivo* using subcutaneous MC38 and CT26 tumor models in germ-free mice. In contrast to mice colonized with stool from a healthy donor, mice colonized with stool from this patient yielded a nonresponsive result upon treatment with anti-PD1 or anti-PD-L1 in combination with anti-CTLA4. **Conclusions:** Analysis of the fecal microbiome composition from patients with metastatic lung, urothelial, renal cancer, and melanoma identified a cancer-specific signature of R and NR to ICI. Across three cancer types, a consistent signature of NR was identified and corroborated experimentally in preclinical models. Research Sponsor: Seres therapeutics, U.S. National Institutes of Health.

2575 **Poster Session**

CheckMate 8KX: Phase 1/2 multitumor preliminary analyses of a subcutaneous formulation of nivolumab (± rHuPH20).

Sara Lonardi, Iwona Lugowska, Christopher G. C. A. Jackson, Anne O'Donnell, Rastilav Bahleda, Marcelo Garrido, Loes Latten-Jansen, Matias Chacon, Habte Aragaw Yimer, Trixia Camacho, Srivani Konduri, Urvi Aras, Kinjal Sanghavi, Heather Vezina, Sonia Dolfi, Federica Alessi, R Donald Harvey, José Trigo, Aitana Calvo; Veneto Institute of Oncology (IOV)-IRCCS, Padua, Italy; Oddzial Badan Wczesnych Faz, Warsaw, Poland; Dunedin Hospital, Dunedin, New Zealand; Wellington Hospital, Wellington, New Zealand; Institut Gustave Roussy, Villejuif, France; Pontificia Universidad Católica de Chile, Santiago, Chile; Maastricht University Medical Center, Maastricht, Netherlands; Instituto Alexander Fleming, Buenos Aires, Argentina; Texas Oncology-Tyler, Tyler, TX; Bristol Myers Squibb, Princeton, NJ; Emory University School of Medicine, Atlanta, GA; Hospital Universitario Virgen de la Victoria, Málaga, Spain; Hospital General Universitario Gregorio Marañon, Madrid, Spain

Background: Immunotherapy has transformed cancer survival expectations. Nivolumab (NIVO), a programmed death-1 inhibitor, is approved for intravenous (IV) administration across multiple cancers. BMS is developing a subcutaneous (SC) NIVO formulation with a permeation enhancer, recombinant human hyaluronidase PH20 enzyme (rHuPH20), to allow for more rapid delivery and the potential to decrease treatment burden. We report the first data on pharmacokinetics (PK), pharmacodynamics, safety, and immunogenicity for SC NIVO + rHuPH20. **Methods:** CheckMate 8KX is a phase 1/2 study in checkpoint inhibitor-nave patients (pts) who were ≥ 18 years of age, ECOG PS 0–1, with metastatic/unresectable solid tumors and measurable disease. The primary objective was to describe SC NIVO PK; secondary objectives were safety and immunogenicity. Additional analyses compared exposures to historical IV NIVO (Zhao X, et al. *J Clin Oncol* 2020;31:302–309). In cycle 1, pts in Part A received SC NIVO 720 mg + rHuPH20, and pts in Part B received SC NIVO 720 mg, SC NIVO 960 mg + rHuPH20, or SC NIVO 960 mg. For cycles 2+, pts in Parts A and B received IV NIVO 480 mg every 4 weeks (Q4W). Pts still on study switched to Part C, SC NIVO 1200 mg + rHuPH20 until end of therapy. In Part D, pts received de novo SC NIVO 1200 mg + rHuPH20 Q4W. **Results:** Patient characteristics varied by age, weight, tumor type, and prior treatment. NIVO exposures increased with increasing SC dose (Table). For 960 mg and 1200 mg NIVO + rHuPH20, Cavg and Ctau were above geometric mean exposures for IV NIVO 3 mg/kg every 2 weeks (Q2W), and Cmax was below IV NIVO 10 mg/kg Q2W. In Part C (n = 28), 13 (46.4%) pts experienced any-grade TRAEs with no new/worsening grade 3+ TRAEs or TRAEs leading to discontinuation/death; 7 (25.0%) reported grade 1 local site reactions. In Part D (n = 36), 27 (75.0%) pts experienced any-grade TRAEs, 4 (11.1%) grade 3/4 TRAEs, 2 (5.6%) serious grade 3/4 TRAEs with 1 leading to discontinuation, and no treatment-related deaths; 10 (27.8%) reported grade 1 local site reactions. Anti-NIVO antibodies (Ab) were observed with SC NIVO but not associated with altered PK/safety, or neutralizing Ab. Exploratory biomarker data found increased CD8+ tumor-infiltrating lymphocytes and PD-L1 tumor expression in post-treatment biopsies, similar to IV NIVO. **Conclusions:** Exposures associated with SC NIVO + rHuPH20 doses investigated in CheckMate 8KX were well tolerated, with a safety profile consistent with IV NIVO. Data support evaluation of SC NIVO + rHuPH20 in a phase 3 study. Clinical trial information: NCT03656718. Research Sponsor: Bristol Myers Squibb, Professional medical writing assistance was provided by Katherine Groschwitz, PhD, and Jay Rathi, MA, of Spark Medica Inc, funded by Bristol Myers Squibb.

NIVO exposures by dose with rHuPH20.

Geometric mean NIVO concentration, μg/mL (range)	Ctau	Cavg	Cmax
NIVO 720 mg SC (n = 20[a])	22.2 (4.76–59.6)	36.6 (16.5–76.3)	54.8 (19.9–114)
NIVO 960 mg SC (n = 9)	39.5 (8.06–67.6)	62.2 (26.8–93.3)	84.8 (42.7–128)
NIVO 1200 mg SC (n = 25[b])	51.3 (18.4–96.5)	77.5 (39.1–141)	105 (40.0–245)

[a]n = 22 for Cmax [b]n = 26 for Cmax Ctau = concentration at the end of the dosing interval.

2576 **Poster Session**

Final results of a phase I RadVax trial of hypofractionated radiation combined with pembrolizumab in patients with metastatic solid tumors.

John Nicholas Lukens, Rosemarie Mick, Alexander Chan Chi Huang, Nicholas Han, Michael Farwell, Tara C. Mitchell, Ravi K. Amaravadi, Lynn Mara Schuchter, Abigail T. Berman, Mark H. O'Hara, Alisha Maity, David Miller, Andy Minn, Robert H. Vonderheide, E. John Wherry, Amit Maity; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; University of Pennsylvaina, Philadelphia, PA; Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; University of Pennsylvania Abramson Cancer Center, Philadelphia, PA; Abramson Family Cancer Research Institute, Philadelphia, PA; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA

Background: Many patients treated with anti-PD-1 therapy do not show a clinical response. Preclinical studies suggest that adding hypofractionated radiotherapy (HFRT) to anti-PD1 can increase the efficacy of immunotherapy through several mechanisms including increased antigen presentation. We conducted a prospective trial testing the combination of pembrolizumab and HFRT in patients with metastatic solid tumors. **Methods:** This prospective single-institution phase I trial tested pembrolizumab in combination with HFRT in patients with metastatic cancers (NSCLC, melanoma, pancreas, breast, others) and an ECOG performance status of 0-1. Melanoma and NSCLC patients were required to have progression of disease on anti-PD1, having received $\geq$ 2 doses of anti-PD1 and progression documented by RECIST v1.1. Patients were required to have an index lesion $\geq$1 cm that was amenable to HFRT and at least one other lesion that was not irradiated and could be followed for response using RECIST criteria. Pembrolizumab 200 mg IV every 3 weeks was administered beginning 1 week prior to the first fraction of radiation. The HFRT dose was 8 Gy x 3 fractions or 17 Gy x 1 fraction, determined by randomization during the Expansion phase. The primary objective was the safety of HFRT combined with pembrolizumab, with dose-limiting toxicity (DLT) defined as Grade $\geq$ 3 non-hematological toxicity related to the combination of Pembrolizumab and HFRT. The secondary objective was the radiographic response of metastatic lesions outside the radiation field as measured by RECIST. **Results:** 59 patients aged 27-90 years (median 60) were enrolled from March 2015 to December 2018 (24 in the Safety Phase and 35 in Expansion Phase). 40 patients (67.7%) had treatment-related AEs, of which 4 were grade 3 and none were grade 4. One patient experienced hepatitis, classified as DLT. While most patients did not have a radiologic response, in patients with metastatic melanoma, 7 of 16 (43.8%, exact 95% CI 19.8-70.1%) had an objective response to HFRT + pembrolizumab, including 3 complete and 4 partial responses. Responses are durable with 3/3 complete responders alive with no progression, and 3/4 partial responders alive with 2 having no evidence of progression. Among melanoma patients, only 2 of 7 (29%) responders received ipilimumab prior to enrollment, compared to 8 of 9 (89%) non-responders ($p = 0.035$). An increase in Ki67+ PD-1+ non-nave CD8 T-cells was observed in the blood 2 weeks after HFRT, but the magnitude did not correlate with likelihood of response. Responses were observed after either 17 Gy x 1 fraction or 8 Gy x 3 fractions, with no difference in response rate by fractionation. **Conclusions:** This study suggests that HFRT administered with concurrent pembrolizumab is associated with acceptable toxicity and that in patients with metastatic melanoma progressing on anti-PD-1 therapy, this approach yields an ORR of 44%. Clinical trial information: NCT02303990. Research Sponsor: Merck, U.S. National Institutes of Health.

2577 **Poster Session**

A first-in-human phase I dose escalation of YH001, an anti-CTLA-4 monoclonal antibody (mAb) in combination with toripalimab (anti-PD-1 mAb) in patients with advanced solid tumors.

Vinod Ganju, Adam Cooper, Bo Gao, Kate Wilkinson; Peninsula and Southeast Oncology, Frankston, VIC, Australia; St George Private Hospital, Kogarah, NSW, Australia; Blacktown and Westmead Hospital, Blacktown, NSW, Australia; Sydney Southwest Private Hospital & St George Private Hospital, Liverpool, NSW, Australia

Background: YH001 is a humanized anti -hCTLA-4 IgG1 mAb that relieves CTLA-4-mediated immunosuppression, and thereby enhances the T-cell-mediated antitumor immune response. Pre-clinical data have shown potent anti-cancer activity when combined with anti-PD-1 mAb. **Methods:** This is an ongoing phase 1 dose-escalation study. Patients (pts) with advanced solid tumors received YH001 by IV administration at 0.05 to 6.0 mg/kg for 1 cycle (21 days) then in combination with Toripalimab (anti-PD-1 mAb) at 240 mg Q3W for 4 cycles. An accelerated titration method followed by the standard 3+3 design was utilized to evaluate safety, tolerability and preliminary efficacy. **Results:** As of 31-Dec-2020 data cut-off, 10 pts were enrolled and treated at 0.05 mg/kg (n = 2), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3) and 1 mg/kg (n = 2). The median age was 62 years (range 46-74). Baseline ECOG scores were 0 (n = 8), 1(n = 2) with all pts progressed after a median of 2 prior lines of available standard therapy (range 1-4) including 1 pt progressed after immunotherapy of pembrolizumab. There were no dose limiting toxicities (DLT) observed. No severe adverse events (SAEs), Grade (G) 3 or above adverse events (AEs) and AEs leading to treatment discontinuation were reported. Twelve drug related AEs were all G1/2 events including 2 G2 AEs (1 rash maculopapular at 0.05mg/kg, 1 hypothyroidism at 0.1mg/kg), 10 G1 AEs (1 hypotension, 1 dry skin, 1 pruritus at 0.05mg/kg; 1 rash, 1 rash macular, 1 hyperthyroidism, 2 rash pruritus at 0.1mg/kg, 2 fatigues at 0.3mg/kg). Among 7 patients having imaging tumor assessment by RECIST v1.1, there were 4 SD, including 1 at 0.05 mg/kg with tongue carcinoma at week 8 assessment, 1 at 0.1 mg/kg with nasopharyngeal carcinoma at week 8 and 15 assessment, 2 at 0.3 mg/kg with gastroesophageal junction cancer and uterus leiomyosarcoma at week 8. **Conclusions:** YH001 combined with Toripalimab is safe and tolerable up to 1 mg/kg dose level. Updated safety and preliminary efficacy data will be presented. Clinical trial information: NCT04481009. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

2578 **Poster Session**

Phase I/II study of nivolumab plus vorolanib in patients with thoracic malignancies: Interim efficacy of the SCLC and primary refractory NSCLC cohorts, and safety data across all cohorts.

Selina K. Wong, Jennifer G. Whisenant, Christine M. Bestvina, Lynne D Berry, Taofeek K. Owonikoko, Rachel E. Sanborn, Philip Edward Lammers, Badi Edmond El Osta, Suresh S. Ramalingam, Jennifer W Carlisle, Conor Ernst Steuer, Hossein Borghaei, Giovanni Selvaggi, Yu Shyr, Heather A. Wakelee, Leora Horn, Katy Beckermann; Vanderbilt University Medical Center, Nashville, TN; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of Chicago Medical Center, Chicago, IL; Vanderbilt University, Nashville, TN; Emory University Winship Cancer Institute, Atlanta, GA; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; Baptist Cancer Center, Multidisciplinary Thoracic Oncology Department, Memphis, TN; Winship Cancer Institute of Emory University, Atlanta, GA; Fox Chase Cancer Center, Philadelphia, PA; Xcovery Holdings, Palm Beach Gardens, FL; Stanford Cancer Institute, Stanford, CA; Department of Medicine, Vanderbilt Ingram Cancer Center, Nashville, TN

Background: Combination strategies to improve the efficacy of single agent immune checkpoint inhibitors (ICIs) are increasingly being explored, with one strategy being the addition of vascular endothelial growth factor (VEGF) inhibition. Having shown promise in the treatment of hepatocellular carcinoma and renal cell carcinoma, NCT03583086 is a multi-institutional, phase I/II study of combination vorolanib and nivolumab in both nave and refractory thoracic tumors that progressed on at least one prior line of platinum-based chemotherapy. Though structurally similar to the tyrosine kinase inhibitor, sunitinib, vorolanib was designed to have a more favorable safety profile with comparable efficacy. Here we present safety data across all cohorts and interim efficacy analyses of the SCLC and NSCLC with primary resistance to ICI-based therapy cohorts, both of which have now completed enrolment. **Methods:** The maximum tolerated dose determined in phase I was vorolanib 200mg daily and nivolumab 240mg q2 weeks. Phase II uses a two-stage MinMax design across 5 cohorts with objective response rate (ORR) as the primary endpoint: NSCLC (ICI nave, primary refractory, and acquired resistance), SCLC, and thymic carcinoma. Primary refractory is defined as radiographic progression of disease within 12 weeks of ICI initiation. **Results:** As of January 2021, 75 patients have been enrolled across all cohorts. Stage 1 of the SCLC and primary refractory NSCLC cohorts have completed accrual at 18 and 15 patients, respectively. In the SCLC cohort, disease-control rate (DCR) was 7% and no objective responses were achieved among 14 evaluable patients. In the primary refractory NSCLC cohort, DCR was 57% and ORR 7% (1 partial response) among 14 evaluable patients. A total of 140 treatment-related adverse events (TRAEs) have been reported, 13 (9%) were grade 3 and there were no grade 4/5 events. Fatigue (9%), nausea (6%), diarrhea (6%), ALT elevation (5%), and AST elevation (5%) were the most common all grade TRAEs. The most common grade 3 TRAEs were ALT elevation and hypertension. **Conclusions:** This therapeutic strategy of nivolumab plus vorolanib appears to be a well-tolerated combination with a manageable safety profile. Adding VEGF inhibition may offer additional disease control in the setting of NSCLC with primary resistance to ICIs, but neither the SCLC or primary refractory NSCLC cohorts achieved the pre-determined target number of objective responses for progression to stage 2 of the study. Enrolment in the other 3 cohorts as well as exploratory correlatives are ongoing. Clinical trial information: NCT03583086. Research Sponsor: Bristol Myers Squibb, Xcovery.

2579 **Poster Session**

Phase Ib study of BI 836880 (VEGF/Ang2 nanobody) plus ezabenlimab (BI 754091; anti-PD-1 antibody) in patients (pts) with solid tumors.

Nicolas Girard, Martin Wermke, Fabrice Barlesi, Dong-Wan Kim, Francois Ghiringhelli, Jaafar Bennouna, Thierry Lesimple, Enriqueta Felip, David Berz, Jong-Seok Lee, Arnaud Jeanson, Celine Mascaux, Mark Voskoboynik, Piotr Serwatowski, Michael C. Burger, Harald Timotheus Landsteiner, Victoria Chen, Girish Jayadeva, Juergen Alt, Bjoern Hackanson; Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France; NCT/UCC Early Clinical Trial Unit, Universitätsklinikum Carl Gustav Carus, Dresden, Germany; Aix-Marseille University, CEPCM CLIP, Assistance Publique Hôpitaux de Marseille, Marseille, France; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Medical Oncology, Center Georges Francois Leclerc, Dijon, France; Thoracic Medical Oncology Functional Unit - Pneumology Department, Saint Herblain, France; Clinical Research Department, CLIP^2 and ARPEGO Network, Rennes, France; Medical Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Department of Internal Medicine, Beverly Hills Cancer Center, Los Angeles, CA; Aix-Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; Department of Pulmonology, University Hospital of Strasbourg, Strasbourg, France; Department of Medical Oncology, Alfred Hospital, Melbourne, Australia; Central Clinical School, Monash University, Melbourne, Australia; Dom Lekarski S.A., Szczecin, Poland; Dr. Senckenberg Institute for Neurooncology, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt, Germany; Division of Medicine/Clinical Operation, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria; Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; TA Oncology Medicine, Boehringer Ingelheim International GmbH, Ingelheim, Germany; Department of Internal Medicine III, University Medical Center, Mainz, Germany; Department of Hematology/Oncology, University Medical Center Augsburg, Augsburg, Germany

Background: In preclinical studies, the combination of anti-VEGF/Ang2 and anti-PD-1 therapy has been shown to promote an immunopermissive state, which is supportive of T-cell-mediated tumor cell destruction. BI 836880 is a humanized bispecific nanobody that targets VEGF and Ang2, and ezabenlimab (BI 754091) is an anti-PD-1 antibody. Phase I studies investigating each as monotherapies have reported safety and preliminary antitumor activity. This ongoing Phase Ib study is evaluating the combination of BI 836880 and ezabenlimab in pts with advanced solid tumors. In Part 1 (dose escalation), the combination was feasible in pts with advanced NSCLC, with a recommended Phase II dose (RP2D) of BI 836880 720 mg + ezabenlimab 240 mg IV q3w. Here, we report updated results from Part 2 (expansion phase), which is assessing the antitumor activity and safety of the RP2D. **Methods:** Seven cohorts are currently recruiting pts in Part 2: metastatic (m) NSCLC after checkpoint inhibitor (CPI) monotherapy (Cohort A); mNSCLC after chemotherapy (CT) + CPI (Cohort B); mSCLC after CT ± CPI (Cohort C); 1st and 2nd recurrences of glioblastoma (GBM; Cohort D); immunotherapy-resistant m-melanoma (Cohort E); hepatocellular carcinoma (HCC) after prior sorafenib or lenvatinib ± CPI (Cohort F); and previously untreated/unresectable HCC (Cohort G). Primary endpoint is objective response rate (complete response + partial response [PR]). **Results:** As of January 2021, 196 pts have received BI 836880 plus ezabenlimab (14 in Part 1, 182 in Part 2 [Cohort A, 26; B, 30; C, 19; D, 31; E, 32; F, 28; G, 16]). 134 (68%) pts were male, median age was 63 years and 102 (52%) had prior CPI use. Any grade and ≥G3 adverse events (AEs; any cause) were reported by 160 (82%) and 62 (32%) pts, most commonly (all%/≥G3%) hypertension (20/8), asthenia (20/3), diarrhea, decreased appetite, and nausea (all 11/1). 95 (48%) pts had a drug-related AE, most commonly hypertension and asthenia (both 11%). 6 pts had a G4 AE (non-related: hyperkalemia + cardiac arrest, laryngospasm, gastrointestinal perforation; drug-related: anaphylactic reaction, acute pancreatitis, transaminases increased); 8 pts had a G5 AE (non-related: general physical health deterioration, epilepsy, hemoptysis, cardio-respiratory arrest, hepatic failure, intracranial hemorrhage, COVID-19 pneumonia; drug-related tracheal hemorrhage). 30 (15%) pts had immune-related AEs (3% ≥G3), including hypothyroidism (3%). 11 (6%) pts had an AE leading to discontinuation. Overall, 145 pts were evaluable for response: 9 pts achieved confirmed PR (2 pts in Part 1 and 7 in Part 2 [NSCLC, n = 3; SCLC, n = 1; GBM, n = 1; melanoma, n = 1; and 2nd-line HCC, n = 1]), 87 pts had stable disease and 49 pts had progressive disease. 111 pts remain on treatment. **Conclusions:** BI 836880 plus ezabenlimab had a manageable safety profile. The combination showed preliminary antitumor activity in a range of tumor types. Clinical trial information: NCT03468426. Research Sponsor: Boehringer Ingelheim.

2580 **Poster Session**

Phase I open-label, dose escalation of YH003, an anti-CD40 monoclonal antibody in combination with toripalimab (anti-PD-1 mAb) in patients with advanced solid tumors.

Jermaine Coward, Afaf Abed, Adnan Nagrial, Ben Markman; ICON Cancer Care, South Brisbane, QLD, Australia; Linear Research, Nedlands, WA, Australia; Blacktown Hospital Cancer and Haematology Centre, Blacktown, NSW, Australia; Alfred Hospital, Melbourne, VIC, Australia

Background: YH003, a recombinant, humanized agonistic anti-CD40 IgG2 monoclonal antibody (mAb) specifically recognizes and agonizes CD40 on the antigen-presenting cells to enhance immune responses. Preclinical data have shown potent anti-cancer activity when combined with anti-PD-1 antibodies. **Methods:** This is an ongoing phase 1 dose-escalation study. Patients with advanced solid tumors receive YH003 by IV administration Q3W as monotherapy at 0.03 to 3.0 mg/kg for the first cycle (21 days) then in combination with Toripalimab at 240 mg Q3W for the 4 subsequent cycles in an accelerated 3+3 design. The safety, tolerability and preliminary efficacy data will be analyzed. **Results:** As of 31 Dec 2020 data cutoff, 9 patients (pts) were enrolled and treated at 0.03 mg/kg (n = 3), 0.1mg/kg (n = 3), and 0.3mg/kg (n = 3). The median age was 63 years (range 33-68). Baseline ECOG scores were 0 (7 pts) and 1 (2 pts) with a median of 2 prior lines therapy (range 1-7). 5 pts had received prior immunotherapy (PD-1/PD-L1 or PD-1+CTLA-4). As of data cutoff, no dose limiting toxicities (DLT) were observed. No Serious Adverse Event (SAE) or AEs leading to treatment discontinuation were reported. Four drug related AEs were reported including one Grade 1 (G1) choroidal thickening (related to YH003) at 0.03 mg/kg, one G1 fatigue (related to YH003) at 0.1 mg/kg, two G1 febrile episodes (one related to YH003 and the other related to combination treatment) at 0.3 mg/kg. Among 5 patients assessable for response, there were 2 SD (one with anti-PDL1 refractory Merkel cell carcinoma at 0.03 mg/kg and one with anti-PD1 refractory NSCLC at 0.1 mg/kg) and 1 PR with anti-PD1/anti-CTLA4 refractory ocular melanoma at 0.1 mg/kg. **Conclusions:** YH003 was well tolerated up to 0.3 mg/kg dose levels when combined with Toripalimab and has shown encouraging antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04481009. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

2581 **Poster Session**

Anlotinib enhanced penpulimab efficacy through remodeling of tumor vascular architecture and immune microenvironment in hPD-L1/hPD-1 humanized mouse model.

Yunlong Shan, Chongjin Zhong, Qi Ni, Mengying Zhang, Guangji Wang, Fang Zhou; China Pharmaceutical University, Nanjing, China

Background: Even though immune checkpoint inhibitor (ICI) such as anti-PD-1 mAb has emerged as effective treatment for tumor regression, the response rate of ICI monotherapy in solid tumor is low. Many studies have demonstrated that the efficacy of combination therapy of ICI and anti-angiogenesis was superior to monotherapy. Penpulimab (AK105), a humanized IgG1 mAb that blocks PD-1 binding to PD-L1, engineered to eliminate FcγR binding and ADCC/ADCP completely. Here, we explore a new combined therapy of penpulimab and anlotinib, an oral multi-targeted tyrosine kinase receptor inhibitor. **Methods:** MC38-hPD-L1 tumor-bearing B-hPD-1 humanized mouse model were conducted to investigate the effects of anlotinib (1 mg/kg, every day, p.o) or penpulimab (5 mg/kg, twice a week, i.p) alone or in combination. Immunofluorescence was applied to elucidate tumor vessel normalization. *In vivo* imaging was conducted to detect the distribution of AF647-labelled penpulimab after anlotinib treatment. Flow cytometry and other techniques were performed to investigate intratumoral immune cells. **Results:** After 3-week treatment, immunotherapeutic administration of anlotinib or penpulimab showed moderate inhibition of tumor growth (tumor volume: 66.5% and 58.4% of control group, respectively), while combined treatment of anlotinib with penpulimab significantly decreased tumor volume to 36.5% of control group. Tissue pathological and blood biochemical results showed no significant toxic and side effects. Immunohistochemistry revealed that anlotinib induced tumor vascular normalization, indicated by decreased $CD31^+$ area, increased α-SMA around tumor vessels and reduced $GLUT1^+$ area. Furthermore, anlotinib markedly enhanced the delivery of AF647-penpulimab into tumors. Combining anlotinib with penpulimab also promoted infiltration and activity of anti-tumoral immune cells by reducing the level of immune checkpoint TIM3 and increasing the IFNγ secretion from T cells. **Conclusions:** Our work provides a strong scientific rationale for the combination therapy of anlotinib and penpulimab to improve tumor microenvironment and immunotherapy, which highlights the clinical potential for this new combined therapy. Research Sponsor: None.

2582 **Poster Session**

Platform trial of ezabenlimab (BI 754091), an anti-PD-1 antibody, in patients (pts) with previously treated advanced solid tumors: Combination with BI 836880, a VEGF/Ang2-blocking nanobody.

Maen A. Hussein, Ivor John Percent, Johanna C. Bendell, Edward Arrowsmith, Hendrik-Tobias Arkenau, Quincy S. Chu, Aaron Richard Hansen, Damijan Erzen, Sheng Qiu, Anthony Lucarelli, Susanna Varkey Ulahannan; Florida Cancer Specialists, Lady Lake, FL and Sarah Cannon Research Institute, Nashville, TN; Florida Cancer Specialists, Port Charlotte, FL; Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; CHI Memorial Hospital, Chattanooga, TN; Sarah Cannon Research Institute and University College London Cancer Institute, London, United Kingdom; Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Boehringer Ingelheim GmbH, Ingelheim, Germany; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; Sarah Cannon Research Institute, Nashville, TN and University of Oklahoma Health Sciences Center-Stephenson Cancer Center, Oklahoma City, OK

Background: The combination of anti-PD-1 antibodies with other immunomodulatory or targeted therapies has the potential for synergistic effects. This open-label, Phase II platform trial is assessing ezabenlimab, an anti-PD-1 antibody, in combination with other agents. Here, we report preliminary data from Module C, which assesses ezabenlimab in combination with BI 836880, a humanized bispecific nanobody that targets vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang2). VEGF and Ang2 play key roles in tumor angiogenesis and have an immunosuppressive effect in the tumor microenvironment. Combining anti-VEGF/Ang2 with an anti-PD-1 therapy promotes an immunopermissive state supportive of T-cell-mediated tumor cell death. **Methods:** Pts are being enrolled into 5 cohorts: locally advanced/metastatic gastric or gastroesophageal adenocarcinoma with $\geq$1 prior treatment (anti-PD-[L]1 nave; Cohort 1); any advanced/metastatic solid tumor (excluding non-squamous NSCLC or melanoma) with prior anti-PD-(L)1 treatment, which progressed after achieving at least stable disease (SD) for $\geq$4 months (Cohort 2); advanced/metastatic solid tumors with no benefit from prior anti-PD-(L)1 treatment (SD or progressive disease [PD] in $<$ 4 months; Cohort 3); locally advanced/metastatic microsatellite stable (MSS) colorectal cancer with $\geq$1 prior treatment (anti-PD-[L]1 nave; Cohort 4); advanced MSS and mismatch repair-proficient endometrial carcinoma, which progressed after 1 line of chemotherapy (anti-PD-[L]1 nave; Cohort 5). Pts will receive BI 836880 720 mg and ezabenlimab 240 mg IV every 3 weeks. The primary endpoint is investigator-assessed objective response (complete response [CR] or partial response per RECIST v1.1). Safety is also being assessed. **Results:** As of Jan 2021, 29 pts have received ezabenlimab plus BI 836880; 26 pts remain on treatment. Cohorts 1/2/3/4/5 included 0/6/3/19/1 pts; median age 63 yrs; 20 (69%) pts were male. Overall, 22 (76%) pts experienced an adverse event (AE; any-cause), most commonly (all%/G3%) nausea (31/3), hypertension (28/7) and fatigue (21/0). No G4/5 AEs were reported; 5 (17%) pts experienced serious AEs. One pt had an immune-related AE (G1 rash). Eighteen (62%) pts had a drug-related AE, most commonly nausea (24%), vomiting, fatigue, and hypertension (all 14%). Three pts had infusion-related reactions (G1, n = 2; G2, n = 1) and 1 pt had an AE that led to treatment discontinuation (non-related G3 bile duct stone). Of 7 pts evaluable for response prior to cycle 3, 5 have SD (Cohort 2, n = 2; Cohort 4, n = 3), and 2 have PD (Cohorts 3 and 4, n = 1 each). Updated data will be presented. **Conclusions:** These preliminary data suggest that ezabenlimab in combination with BI 836880 has a manageable safety profile. Cohorts are continuing to recruit (approximately 30 pts per cohort). Clinical trial information: NCT03697304. Research Sponsor: Boehringer Ingelheim.

2583 **Poster Session**

AdvanTIG-105: Phase 1 dose-escalation study of anti-TIGIT monoclonal antibody ociperlimab (BGB-A1217) in combination with tislelizumab in patients with advanced solid tumors.

Sophia Frentzas, Tarek Meniawy, Steven Chuan-Hao Kao, Ruihua Wang, Yunxia Zuo, Hao Zheng, Wei Tan; Medical Oncology, Monash Health, Melbourne, Victoria, Australia, School of Medical and Health Sciences, Monash University, Melbourne, VIC, Australia; Edith Cowan University, Joondalup, Western Australia, Australia, School of Medicine, The University of Western Australia, Crawley, Western Australia, Australia, Department of Medical Oncology, Sir Charles Gairdner Hospital, Nedlands, WA, Australia; Chris O'Brien Life House, School of Medicine, University of Sydney, Sydney, NSW, Australia; BeiGene Ltd., Shanghai, China; BeiGene USA, Inc., San Mateo, CA

Background: Anti-programmed death 1 (PD-1) therapy has improved clinical outcomes for patients (pts) with advanced solid tumors but unmet needs remain. T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) is a co-inhibitory, immune checkpoint receptor. Ociperlimab (OCI; BGB-A1217) is a novel, humanized, monoclonal antibody that binds to TIGIT with high affinity and specificity. OCI has demonstrated competent binding with C1q and all Fcγ receptors and induces antibody-dependent cellular cytotoxicity. Preclinical studies demonstrated dual targeting with OCI and tislelizumab (TIS), an anti-PD-1 antibody, produces synergistic immune cell activation and enhanced antitumor activity. **Methods:** AdvanTIG-105 is a phase 1, open label, multicenter, dose-escalation study (NCT04047862) that assessed the safety and preliminary antitumor activity of OCI plus TIS in pts with advanced, metastatic, unresectable solid tumors, for which standard therapy was ineffective or unavailable. Eligible pts had an Eastern Cooperative Oncology Group performance score $\leq$1 and no prior therapy targeting TIGIT. Pts received OCI intravenously (IV) on Day 1 of Cycle 1 and TIS 200 mg IV on Day 8. Pts were monitored for dose-limiting toxicities (DLTs) until Day 28. If tolerated, OCI and TIS were administered sequentially on Day 29 and every 3 weeks (Q3W) thereafter. Pts received escalating doses of OCI (50-900 mg) plus TIS 200 mg. The study objective was determination of recommended phase 2 dose (RP2D) of OCI plus TIS. Study endpoints included assessment of adverse events (AEs), pharmacokinetics and antitumor activity. Data cut-off was October 12 2020. **Results:** 24 pts with various advanced solid tumors received OCI plus TIS. At baseline, pts had undergone a median of 2 prior treatment regimens; 9/24 (37.5%) pts had received prior immunotherapy. Median follow-up time was 17 weeks. No DLTs were observed. 20 pts had $\geq$1 treatment emergent AE (TEAE) and most TEAEs were grade $\leq$2; fatigue (6 pts) and diarrhea (4 pts) were most commonly reported. No pts had grade $\geq$4 TEAEs or TEAEs leading to death. There were 2 grade 3 immune related AEs (colitis and low cortisol). One pt on OCI 450 mg achieved partial response and 9 pts had stable disease. The longest duration of stable disease was 36 weeks (1 pt on OCI 150 mg). After administration, serum concentration of OCI decreased in a biphasic manner. Exposure to OCI increased proportionally with dose, and TIGIT receptor occupancy was sustained at $\geq$50 mg doses. **Conclusions:** OCI in combination with TIS was well tolerated across all doses in pts with advanced solid tumors. The RP2D was OCI 900 mg plus TIS 200 mg Q3W. Clinical trial information: NCT04047862. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Stephanie Pruden, BSc (Hons), of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

IFN-α, IFN-γ, IL-2 combined with TNF-α for predicting efficacy of PD-1 inhibitors combination therapy in patients with solid cancers.

Penghui Xing, Jinyan Zhang, Rongfeng Liu, Junyan Wang, Ming Ma, Lixing Wang, Wenjing Jiao, Junguo Shao, Yuxiang Wang, Hongtao He, Baoen Shan, Jian Shi; Department of Neurosurgery, Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Clinical Laboratory, Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Medical Oncology, Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Medical Oncology, The Fourth Hospital of Hebei Medical University, Shijia Zhuang, China; Department of Research Center, Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Radiation Oncology, Fourth Hospital of Hebei Medical University and Hebei Province Tumor Hospital, Shijiazhuang, China; Department of Medical, Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Research Center, Fourth Hospital of Hebei Medical University, Shjiazhuang, China

Background: PD-1 inhibitors have transformed the treatment landscape for patients (pts) with many advanced malignancies. Combination therapy with PD-1 inhibitors for cancer is a trend. However, Biomarkers for the efficacy of combination therapy remains unknown. In order for the benefited population to be screened out, biomarkers need to be established. we will conduct the following study, to explore the IFN-α, IFN-γ, IL-2 combined with TNF-α for predicting efficacy of PD-1 inhibitors combination therapy. **Methods:** Using postoperative without lesions as control group (n=7). Pts with lesions as the experimental group (n=66). 27 of 66 pts received chemoradiotherapy (group A), 39 of 66 pts received PD-1 inhibitors combined with therapy (group B). IFN-α, IFN-γ, IL-2, TNF-α in peripheral blood of all pts were measured using flow cytometry. **Results:** 1) There was significant difference in proportion above normal concentrations (ANCs) of IFN-α between two groups (57.1% vs 43.5%, $P<0.05$), but there was no significant difference in IFN-γ, IL-2 and TNF-α between two groups (IFN-γ 57.1% vs 52.2%, IL-2 14.3% vs 5.8%, TNF-α 42.9% vs 43.5%, $P>0.05$). 2) The normal ratios of IFN-α, IFN-γ and TNF-α in group B was significantly higher than that in group A (IFN-α 64.1% vs 51.9%, IFN-γ 59% vs 37%, TNF-α 69.2% vs 44.4%, $P<0.05$). The proportion ANCs of IFN-α, IFN-γ, and TNF-α were lower in group A (IFN-α 35.9% vs 63%, $P>0.05$; IFN-γ 41% vs 63%, $P<0.05$; TNF-α 30.8% vs 55.6%, $P<0.05$). However, the proportion ANCs of IL-2 detection was lower (7.4% vs 5.1%). 3) In group B, 21 of 39 pts were evaluable. ORR was 52.4% (11/21) and DCR was 85.7% (18/21). The proportion ANCs of IFN-α, IFN-γ and TNF-α in the pts with PR was higher than that with SD (IFN-α 37.5% vs 28.6%, IFN-γ 37.5% vs 28.6%, TNF-α 50% vs 38.8%, $P<0.05$). 4) We found that the coincidence rate of IFN-α+ IFN-γ and IFN-α+ IFN-γ+TNF-α was higher in group B (Table). **Conclusions:** Our results suggest that the proportion ANCs of IFN-α, IFN-γ, and TNF-α in the pts with lesions were lower than that without lesions, it may be the decrease of immune function with lesions. There was positive correlation between proportion ANCs of IFN-α, IFN-γ and TNF-α and efficacy in these pts. IL-2 was not used as a routine detection indicator. The coincidence rate of IFN-α, IFN-γ combined with TNF-α was higher, it may help predict the outcome of PD-1 inhibitors combination therapy in pts with solid cancers, and helpful to screen the benefit population. Further study is needed. Research Sponsor: None.

Coincidence rate of IFN-α, IFN-γ and TNF-α after treatment in different patients.*

	Non-coincidence rate (%)	Coincidence rate (%)
IFN-α+IFN-γ	14.8	85.2
IFN-α+IFN-γ (+)	15.4	84.6
IFN-α+IFN-γ (+SD)	0	100
IFN-α+IFN-γ (+PR)	0	100
IFN-α+IFN-γ+TNF-α	29.6	70.4
IFN-α+IFN-γ+TNF-α (+)	28.2	71.8
IFN-α+IFN-γ+TNF-α (+SD)	0	100
IFN-α+IFN-γ+TNF-α (+PR)	100	87.5

*IFN-α+IFN-γ, IFN-α+IFN-γ+TNF-α: group A; others: group B.

2585 **Poster Session**

A phase 1 dose-escalation study of a PD-L1xCD27 bispecific antibody CDX-527 in patients with advanced malignancies.

Rachel E. Sanborn, Rodolfo Eduardo Bordoni, Gini F. Fleming, Mustafa Khasraw, Thomas Hawthorne, Lawrence J Thomas, Tracey Rawls, Diane C. Young, Philip Golden, Tibor Keler, Michael Jay Yellin; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; Georgia Cancer Specialists, Marietta, GA; University of Chicago Medicine, Chicago, IL; Duke University Medical Center, Duke Cancer Institute, Durham, NC; Celldex Therapeutics, Inc., Hampton, NJ; Celldex Therapeutics, Inc., Needham, MA

Background: CDX-527 is a bispecific antibody (BsAb) targeting PD-L1 and CD27 that is designed to block immune checkpoint PD-L1/PD-1 interactions while providing immune costimulation through CD27 signaling. CD27 is a key immunostimulatory molecule that enhances T cell activation, effector function, and survival. Combining anti-PD-L1 and anti-CD27 mAbs synergize in preclinical studies, activating complementary cytotoxic and proliferative gene expression profiles, respectively. Clinical studies demonstrated the safety and biological activity of combining varlilumab, an agonist anti-CD27 mAb, with nivolumab or atezolizumab, along with modest clinical activity of the combinations. CDX-527 is a novel human BsAb containing a neutralizing, high affinity IgG1k PD-L1 mAb and the single chain Fv fragment (scFv) of an agonist anti-CD27 mAb genetically attached to the C-terminus of each heavy chain, thereby making CDX-527 bivalent for each target. Pre-clinical studies demonstrated enhanced T cell activation by CDX-527 and anti-tumor activity of a surrogate bispecific compared to individual mAb combinations. **Methods:** CDX527-01 is a phase 1 first-in-human, open-label, multi-center, dose-escalation (DE) and expansion study evaluating safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of CDX-527 in patient with advanced solid tumors that have progressed on standard-of-care therapy. The primary study objective is to characterize the safety and tolerability of CDX-527. CDX-527 is administered intravenously Q2W with doses ranging from 0.03 mg/kg up to 10.0 mg/kg or until the maximum tolerated dose. The first 2 cohorts of the DE phase initiate with single patients and subsequent DE cohorts will be conducted in 3+3 manner. Tumor-specific expansion cohorts may be enrolled to further characterize the safety, PK, PD, and efficacy of CDX-527. Tumor assessments are performed Q8W by the investigator per iRECIST. Biomarker assessments include characterizing the effects on peripheral blood immune cells and cytokines, and for the expansion cohorts, the impact of CDX-527 on the tumor microenvironment in paired tumor biopsies. **Results:** To date, 8 patients have received CDX-527 in doses ranging from 0.03 mg/kg to 1 mg/kg and 3 are still on treatment. There has been no drug related SAEs, DLTs or discontinuations due to an AE. Most common treatment related AEs were influenza-like illness, fatigue, and arthralgia (all at 25%). All drug related AEs have been grade 1 or 2. **Conclusions:** Preliminary results indicate that the novel anti-PD-L1xCD27 bispecific antibody CDX-527 up to and including the 1 mg/kg dose level has been well tolerated. Additional data will be presented, including the safety profile at higher dose levels along with clinical activity, as well as PK and PD data. Clinical trial information: NCT04440943. Research Sponsor: None.

2586 **Poster Session**

The predictive values of loss-of-function variants in histone methyltransferases for response to immune checkpoint inhibitors in solid tumors.

Naixin Liang, Yanling Niu, Xin Zhang, Tonghui Ma; Department of Thoracic Surgery,Peking Union Medical College Hospital,Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; Genetron Health (Beijing) Technology, Co. Ltd., Beijing, China

Background: Dysregulation of histone methyltransferases (HMTs) has been reported to play critical roles in cancer development. Previous studies showed that many HMTs were recruited to DNA damage sites where they posttranslationally modified chromatin to regulate chromatin-based DNA damage repair (DDR) activities. We hypothesized that loss-of-function (LOF) variants of HMTs may associate with genome instability and tumor mutational burden (TMB). Thus, we explored the associations of LOF variants in some HMTs with TMB and benefit from immune checkpoint inhibitors (ICIs) in solid tumors. **Methods:** An ICIs treatment cohort from the Memorial Sloan Kettering Cancer Center (MSKCC) was analyzed. The following solid tumor types were enrolled: NSCLC (n = 350), colorectal cancer (n = 110), bladder cancer (n = 215), breast cancer (n = 44), esophagogastric cancer (n = 126), head and neck cancer (n = 139), glioma (n = 117), melanoma (n = 320), and renal cell carcinoma (n = 151). We evaluated 15 HMTs (KMT2A, KMT2B, KMT2C, KMT2D, SETD2, SETD8, EZH1, EZH2, PRDM1, PRDM14, SMYD3, NSD1, WHSC1, WHSC1L1, and DOT1L). **Results:** The data revealed that LOF variants of *KMT2D*, *SETD2*, and *KMT2C* were more frequent in pan-cancer dataset. Furthermore, we found that LOF variants of 7 HMTs, including *KMT2A*, *KMT2B*, *KMT2C*, *KMT2D*, *NSD1*, *SETD2*, and *EZH2*, were associated with higher TMB ($P < 0.0001$). Then we analyzed the associations between LOF variants and overall survival (OS) after ICIs therapy. The results indicated that LOF variants of *KMT2A* (P = 0.0295), *KMT2B* (P = 0.0329), *KMT2C* (P = 0.0122), and *SETD2* (P = 0.0004) were significantly associated with prolonged median OS for all the enrolled patients. In this cohort, LOF variants of *KMT2A*, *KMT2B*, *KMT2C*, and *SETD2* were most common in bladder cancer, colorectal cancer, colorectal cancer, and renal cell carcinoma, respectively. Then we assessed the predictive values of these four genes for each type of cancer. It was noteworthy that *KMT2C* LOF variants were significantly correlated with longer median OS in colorectal cancer (P = 0.0171), but not in other cancer types. Surprisingly, we did not observe the predictive roles of LOF variants in *KMT2A*, *KMT2B*, and *SETD2* genes for response to ICIs therapy in any types of cancer. **Conclusions:** In pan-cancer dataset, we found that LOF variants of 4 HMTs, such as *KMT2A*, *KMT2B*, *KMT2C*, and *SETD2*, were correlated with better outcomes of ICIs treatment. However, for different types of cancer, only *KMT2C* LOF variants were associated with longer median OS in colorectal cancer, suggesting that it may be used as a predictive biomarker for ICIs efficacy in colorectal cancer. Because the sample sizes of patients with *KMT2A*, *KMT2B*, or *SETD2* LOF variants were small, we did not find the predictive values of LOF variants in these three genes for different types of cancer. Next, we will enroll more patients to address this question. Research Sponsor: None.

2587 **Poster Session**

Association of *KMT2C/D* loss-of-function mutations with tumor infiltrating lymphocytes and response to immune checkpoint inhibitors in solid tumors.

Ruiqi Liu, Yanling Niu, Xin Zhang, Tonghui Ma; Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China; Genetron Health (Beijing) Technology, Co. Ltd., Beijing, China

Background: Dysregulation of HMTs plays an important role in tumorigenesis. KMT2C and KMT2D are enzymatically active scaffold proteins that form the core of mammalian COMPASS complexes, which methylate the histone 3 lysine 4. Both KMT2C and KMT2D are involved in the regulation of gene expression. Therefore, we explored the associations of *KMT2C/D* loss-of-function (LOF) mutations with the expression of immune-related genes, the levels of tumor infiltrating lymphocytes (TILs), and response to immune checkpoint inhibitors (ICIs). **Methods:** *KMT2C/D* LOF mutations were defined as nonsense, frameshift, splice site variants within consensus regions, start lost, and stop lost/gained variants. An ICIs treatment cohort from the MSKCC was used for exploring the associations between *KMT2C/D* LOF mutations and ICIs efficacy. The RNA-Seq data obtained from the TCGA cohort was used for analysis of gene expression and the levels of TILs using *CIBERSORT*. **Results:** In MSKCC pan-cancer dataset, patients with *KMT2C/D* LOF mutations had a relatively longer median overall survival (OS) compared to those with non-LOF mutations, although the result did not reach statistical significance (P = 0.0832). Then we analyzed the predictive roles of *KMT2C/D* LOF mutations for each cancer type. The results showed that the predictive role of *KMT2C/D* LOF mutations for the clinical efficacy of ICIs therapy was only observed in colorectal cancer (P = 0.045). However, we did not find the associations of *KMT2C/D* LOF mutations with ICIs efficacy in bladder cancer, breast cancer, melanoma, glioma, head and neck cancer, renal cell carcinoma, NSCLC, and esophagogastric cancer. Consistently, analysis of TILs in colorectal cancer revealed that *KMT2C/D* LOF was associated with increased infiltration of several types of immune cells, such as CD8+ T cells (P = 0.0001), activated NK cells (P = 0.0001), M1 macrophage (P = 0.0005), M2 macrophage (P = 0.0115), and neutrophils (P = 0.0209). Meanwhile, regulatory T cells (Tregs) (P = 0.0048) and M0 macrophage (P = 0.0043) were dramatically decreased in *KMT2C/D* LOF group for colorectal cancer. Moreover, there were no significant relationships between *KMT2C/D* LOF and the levels of TILs in other cancer types. Our data also demonstrated that KMT2C and KMT2D could regulate the expression of more than 30 immune-related genes in colorectal cancer. **Conclusions:** Our data indicated that *KMT2C/D* LOF mutations were significantly correlated with better outcomes of ICIs therapy in colorectal cancer, suggesting it can be as a useful predictor for response to ICIs in colorectal cancer. Meanwhile, we found the associations of *KMT2C/D* LOF with the levels of TILs in colorectal cancer, but not in other cancer types, indicating that the efficacy of ICIs was consistent with the levels of TILs. Research Sponsor: None.

Risk of immunosuppression and hospitalization after checkpoint inhibitor therapy in patients with cancer and radiation therapy.

Kate E Lee, David Andrew Bender, Catherine S. Spina, Brigham Hyde, Adam S Faye, Simon Cheng; Columbia University Vagelos College of Physicians and Surgeons, New York, NY; Columbia University Medical Center, New York, NY; Decision Resources Group, Burlington, MA; Mount Sinai Hospital, New York, NY

Background: Immune checkpoint inhibitors (ICIs) are potent new cancer therapies but can cause serious immune-related adverse events. Radiation therapy (RT) also induces systemic immunologic effects, and data on the interaction and safety of combining ICIs and RT are limited. **Methods:** In this retrospective cohort study using a large medical claims database from 2010 to 2017, we ascertained the risk of immunosuppressive steroid therapy as well as the risk of hospitalization within 180 days of treatment with an ICI in patients with diagnoses of malignant melanoma or lung cancer. Patients were stratified by use of RT within 30 days before and after ICI therapy. ICIs included pembrolizumab, nivolumab, and ipilimumab, while immunosuppressive agents included oral prednisone and intravenous methylprednisolone. **Results:** 2020 patients (218 with RT, 1802 without RT) met inclusion criteria for prednisone analysis, while 3519 patients (361 with RT, 3158 without RT) met inclusion criteria for all other analyses. On univariable analysis, RT was not associated with need for prednisone or methylprednisolone (RR 1.2, 95%CI 0.8-1.9 and RR 1.2, 95%CI 0.7-2.1 respectively). When assessing hospitalization, RT was significantly associated with hospitalization following ICI therapy for certain cancer/drug combinations (RR 1.4, 95%CI 1.2-1.6, $p<0.001$ for lung cancer/PD-1 inhibitors, RR 2.0, 95%CI 1.0-3.5, $p=0.03$ for melanoma/ipilimumab). **Conclusions:** In patients treated with ICIs, receiving RT was not associated with a higher risk of requiring immunosuppressive steroid therapy as compared to not receiving RT. However, in those with ICIs, RT was associated with a higher risk of hospitalization as compared to no RT, though this may be a result of underlying differences in patent severity (more severe disease may require ICI and RT). Research Sponsor: Barry Neustein and Polyflex Inc. to the lung cancer research program in Radiation Oncology at Columbia University, Other Foundation, Louis V. Gerstner, Jr. Scholar Award.

Risk of corticosteroid treatment after ICI treatment across cancer type, ICI, and RT.[a,b]

	Oral Prednisone			IV Methylprednisolone		
	RT	No RT	Relative Risk (95% CI)	RT	No RT	Relative Risk (95% CI)
Melanoma PD-1 Inhibitors	13.6% (3/22)	10.7% (35/326)	1.3 (0.4, 3.8)	0.0% (0/33)	1.4% (7/501)	1.0 (0.1, 16.9)
Lung Cancer PD-1 Inhibitors	10.2% (18/176)	8.4% (96/1145)	1.2 (0.8, 2.0)	4.7% (12/257)	4.9% (78/1591)	1.0 (0.5, 1.7)
All Cancers PD-1 Inhibitors	10.6% (21/198)	8.9% (131/1471)	1.2 (0.8, 1.8)	4.1% (12/290)	4.1% (85/2092)	1.0 (0.6, 1.8)
Melanoma Ipilimumab	5.0% (1/20)	5.4% (18/331)	0.9 (0.1, 6.5)	2.8% (2/72)	1.3% (14/1066)	2.1 (0.5, 9.0)
Melanoma Ipi-Nivo Combo	40.0% (4/10)	32.2% (46/143)	1.2 (0.6, 2.8)	21.1% (4/19)	22.1% (44/199)	1.0 (0.4, 2.4)
All Cancers All ICIs	10.1% (22/218)	8.3% (149/1802)	1.2 (0.8, 1.9)	3.9% (14/362)	3.1% (99/3158)	1.2 (0.7, 2.1)

[a]No values were significantly different at $p<0.05$. [b]The patient populations for prednisone and methylprednisolone are not identical because the separate analyses required distinct inclusion criteria.

2589 **Poster Session**

Phase Ia/Ib dose-escalation study of IBI110 (anti-LAG-3 mAb) as a single agent and in combination with sintilimab (anti-PD-1 mAb) in patients (pts) with advanced solid tumors.

Cai Zhou, Yayi He, Shengxiang Ren, Wei Li, Jun Zhu, Jia Yu, Lei Wang, Anwen Xiong, Nong Xu, Chenyu Mao, Beiqing Pan, Ying Liu, Hui Zhou; Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; Shanghai Pulmonary Hospital, Shanghai, China; The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; Innovent Biologics, Inc., Shanghai, China

Background: Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor protein that functions to control T cell response, activation and growth. Dual inhibition of PD-1 and LAG-3 may improve anti-tumor effect synergistically. In this first-in-human dose-escalation study, we report the preliminary safety and anti-tumor activity of IBI110 ± sintilimab in pts with advanced solid tumors. **Methods:** Enrolled pts, ECOG PS 0-1, had locally advanced, recurrent or metastatic solid tumors for whom standard therapy had failed. Pts received escalating doses of IBI110 (0.01/0.1/0.3/1/3/10/20mg/kg) IV Q3W in phase Ia and escalating doses of IBI110 (0.3/0.7/1.5/3/5 mg/kg) in combination with sintilimab 200 mg IV Q3W in phase Ib. Crossover from mono to combo was allowed at progression. The objectives were safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of IBI110 alone or IBI110+sintilimab (per RECIST v1.1). **Results:** Phase Ia: 21 pts (median age: 62 yr [range 43-72]; ECOG PS: 0 [n = 11], 1 [n = 10]) were enrolled. Dose escalation has completed and no dose-limiting toxicity (DLT) was observed in all dose cohorts. The most common treatment-related adverse event (TRAE) was anaemia (19.0%). TRAEs ≥G3 included anaemia (4.8%), ascites (4.8%) and hepatic function abnormal (4.8%). By investigator-assessment, best response was 1 confirmed partial response (PR) (ovarian cancer, 3 mg/kg IBI110 single agent) and 5 stable disease (SD) in monotherapy. After crossing from mono to combo at progression, 5 pts were observed to have SD. Phase Ib: 12 pts (median age: 60 yr [range 33-72]; ECOG PS: 0 [n = 7], 1 [n = 5]) were enrolled. All dose cohorts in dose escalation except IBI110 5mg/kg+ sintilimab have completed DLT observation and no DLT was observed. The most common TRAE was AST increased (41.7%). TRAEs ≥G3 included hyperglycaemia (8.3%), bilirubin conjugated increased (8.3%) and hepatic function abnormal (8.3%). By investigator-assessment, best response was 2 PR (small cell lung cancer and endometrial cancer) and 6 SD. **Conclusions:** IBI110 alone or plus sintilimab has acceptable toxicity and shows preliminary antitumor activity. Clinical trial information: NCT04085185. Research Sponsor: Innovent Biologics, Inc.

2590 **Poster Session**

A phase I trial evaluating NBTXR3 activated by radiotherapy in combination with nivolumab or pembrolizumab in patients with advanced cancers.

Colette Shen, Jessica M. Frakes, Jiaxin Niu, Ari Rosenberg, Jared Weiss, Jimmy J. Caudell, Katherine LaRoque Jameson, Patricia Said, Tanguy Y. Seiwert; University of North Carolina at Chapel Hill, Chapel Hill, NC; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Banner MD Anderson, Phoenix, AZ; University of Chicago, Chicago, IL; University of North Carolina Hospitals, Chapel Hill, NC; Vanderbilt Univ. Med. Ctr., Nashville, TN; Nanobiotix, Paris, France; The University of Chicago Medicine, Chicago, IL

Background: Immune checkpoint inhibitors (ICIs) targeting PD-1 are an effective treatment for a variety of cancers. However, the majority of patients (pts) exhibit resistance to ICIs. Overcoming this resistance represents a major challenge in immuno-oncology. Emerging evidence suggests radiation therapy (RT) produces an immunomodulatory effect that may act synergistically with ICIs. However, RT dose and ultimate efficacy are limited by toxicity to surrounding healthy tissues. NBTXR3, a novel radioenhancer administered by direct intratumoral injection (ITI), is designed at the nanoscale to increase RT dose deposit within tumor cells and subsequent tumor cell killing, without increasing toxicity to surrounding healthy tissue. Preclinical data suggest NBTXR3/RT can trigger a local and systemic anti-tumor immune response and overcome anti-PD-1 resistance. NBTXR3/RT combined with anti-PD-1 may prime the immune system to increase the proportion of ICI responders, or convert ICI non-responders to responders. **Methods:** This is a multicenter, open-label, phase I trial [NCT03589339] to evaluate NBTXR3/RT/anti-PD-1 in 3 cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) amenable to HN re-irradiation, and metastases from any primary cancer eligible for anti-PD-1 (nivolumab or pembrolizumab) treatment specifically localized in the lung (2) or liver (3), respectively. Stereotactic body RT (SBRT) is delivered at tumor-site selective doses per standard practice. The primary objective is NBTXR3/RT/anti-PD-1 recommended phase 2 dose in each cohort. Secondary objectives are anti-tumor response (objective response rate), safety and feasibility of NBTXR3 injection. **Results:** Nine pts have been treated: 3 HNSCC, 4 lung, 2 liver. 7/9 pts were anti-PD-1 non-responders. Overall tumor regression was observed in 8/9 pts. NBTXR3/RT/anti-PD-1 resulted in tumor regression in 6/7 pts who had progressed on prior anti-PD-1. A complete response in the injected lymph node lasting over 1 year was observed in 1 anti-PD-1 nave pt. 2 SAEs related to anti-PD-1 and possibly related to NBTXR3 (G5 pneumonitis, G4 hyperglycemia) were observed in 1 anti-PD-1 nave HNSCC pt and considered DLTs. This pt also experienced 2 other SAEs related to anti-PD-1 (G4 diabetic ketoacidosis, G4 acute kidney injury). SBRT-related safety profile was as expected. Updated results will be presented. **Conclusions:** Data from this first-in-human phase I trial evaluating NBTXR3/RT/anti-PD-1 in pts with advanced cancers, show NBTXR3 ITI is feasible and well-tolerated. NBTXR3/RT/anti-PD-1 demonstrated promising signs of efficacy. Of particular interest, NBTXR3/RT can overcome ICI resistance in pts having progressed on prior anti-PD-1, supporting further development of NBTXR3 in combination with anti-PD-1 as well as other ICIs. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

2591 **Poster Session**

Overcoming resistance to anti-PD-1 with tumor agnostic NBTXR3: From bench to bed side.

Tanguy Y. Seiwert, Colette Shen, Jessica M. Frakes, Jiaxin Niu, Jared Weiss, Jimmy J. Caudell, Yun Hu, Hampartsoum B. Barsoumian, Juliette Thariat, Sylvie Bonvalot, Zsuzsanna Papai, Maria Angelica Cortez, Ping Zhang, Katherine LaRoque Jameson, Patricia Said, Sébastien Paris, James William Welsh; The University of Chicago Medicine, Chicago, IL; University of North Carolina at Chapel Hill, Chapel Hill, NC; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Banner MD Anderson, Phoenix, AZ; University of North Carolina Hospitals, Chapel Hill, NC; MD Anderson, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Centre Francois Baclesse, Caen, France; Institut Gustave Roussy, Villejuif, France; Honvédelmi Minisztérium Állami Egészségügyi Központ, Budapest, Hungary; Nanobiotix, Paris, France; Vanderbilt Univ. Med. Ctr., Nashville, TN

Background: Despite recent advances, resistance to immune checkpoint inhibitors (ICI), observed in over 80% of treated patients, is currently the main challenge in immuno-oncology. Intense efforts are being made to identify combination therapies that could improve ICI response rates. NBTXR3, a novel radioenhancer administered by direct intratumoral injection (ITI), is designed at the nanoscale to increase radiation therapy (XRT) dose deposit within tumor cells and subsequent tumor cell killing, without increasing toxicity to surrounding healthy tissue. Here we present evidence that NBTXR3 activated by XRT primes the immune system, producing an anti-tumor response, including activation of the cGAS-STING pathway, that overcomes anti-PD-1 resistance both in mice models and patients. **Methods:** Abscopal assays were conducted in immunocompetent mice. Anti-PD-1 sensitive or resistant tumor cell lines, were injected in both flanks of mice. Intratumoral injection of NBTXR3 (or vehicle) followed by XRT was performed in right flank (primary) tumors only. Some mice also received anti-PD-1 injections. Tumor growth was monitored, and tumor immune cell infiltrates analyzed by immunohistochemistry (IHC). Separately, in the phase II/III randomized Act.in.Sarc [NCT02379845] trial patients with locally advanced soft tissue sarcoma (STS) received either NBTXR3+XRT or XRT alone followed by tumor resection. Pre- and post-treatment tumor samples from patients in both groups were analyzed by IHC and Digital Pathology for immune biomarkers. The safety and efficacy (RECIST 1.1/iRECIST) of NBTXR3 plus stereotactic body radiotherapy (SBRT) in combination with anti-PD-1 is being evaluated in three cohorts of patients with advanced cancers [NCT03589339]. **Results:** Pre-clinical studies demonstrated that NBTXR3+XRT induces an immune response not observed with XRT alone and enhances systemic control. IHC showed significant increase of CD8+ T-cell infiltrates in both NBTXR3+XRT treated and untreated tumors compared to XRT alone. Similarly, increased CD8+ T-cell and decreased FOXP3+ Treg density (pre- vs post-treatment) was observed in tumor tissues from STS patients treated with NBTXR3+XRT. Furthermore, NBTXR3+XRT in combination with anti-PD-1 improved local and systemic control in mice bearing anti-PD-1 resistant lung tumors, as well as reduced the number of spontaneous lung metastases. Preliminary efficacy data from the first in human trial of NBTXR3+XRT in combination with anti-PD-1 showed tumor regression in the majority of patients (8/9). Of note, tumor regression was observed in 6/7 pts who had progressed on prior anti-PD-1. **Conclusions:** The clinical efficacy of NBTXR3+XRT has been demonstrated as a single agent. We now demonstrate that it potentiates anti-PD-1 treatment to overcome resistance mechanisms. These results highlight the potential of NBTXR3+XRT to positively impact the immuno-oncology field. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

2592 **Poster Session**

A phase 1/2 study of intratumoral INT230-6 alone (IT-01) or in combination with pembrolizumab [KEYNOTE-A10] in adult subjects with locally advanced, unresectable and metastatic solid tumors refractory to therapy.

Anthony B. El-Khoueiry, Jacob Stephen Thomas, Anthony J. Olszanski, Nilofer Saba Azad, Giles Francis Whalen, Diana L. Hanna, Matthew Ingham, Syed Mahmood, Lewis H. Bender, Ian B. Walters, Lillian L. Siu; University of Southern California, Los Angeles, CA; Division of Oncology, USC Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA; Fox Chase Cancer Center, Philadelphia, PA; Department of Oncology, Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD; University of Massachusetts Memorial Medical Center, Worcester, MA; Keck Hospital of USC, Los Angeles, CA; Columbia University Irving Medical Center, New York, NY; Intensity Therapeutics, Inc., Westport, CT; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Study IT-01 (KEYNOTE-A10) evaluates INT230-6, a novel formulation of cisplatin (CIS) and vinblastine (VIN) with an amphiphilic cell penetration enhancer designed for intratumoral (IT) administration, alone or in combination with pembrolizumab (PEM), an antibody to PD-1. INT230-6 dosing is set by a tumor's volume. In preclinical studies, INT230-6 increases drug dispersion throughout the tumor, allows drug diffusion into cancer cells and recruits dendritic, CD4 and CD8 T cells. The addition of PEM has been shown to improve these responses in models. Phase 1 data indicated INT230-6 alone induced tumor regression in both injected and non-injected lesions. Considering the large volume of drug injected and retained in the tumor, coupled with immune infiltration on biopsies, RECIST response methodology may not capture the benefit of INT230-6 treatment. **Methods:** IT-01 is an open-label phase 1/2 study, currently enrolling adult subjects with solid tumors in phase 2. INT230-6 was administered IT Q2W for 5 doses alone or with PEM 200mg Q3W. The study seeks to assess the safety and efficacy of IT INT230-6 alone and in combination with PEM. **Results:** 67 subjects have been enrolled (58 mono and 12 INT230-6 + PEM (3 started in mono, then received combo)) having a median of 3 prior therapies (0, 10). Median age was 60 (42, 85). 20+ cancer types were accrued; breast cancer and sarcoma were the most frequent. Over 500 image guided INT230-6 IT injections were given (253 to deep tumors) at doses of 0.3 to 172mL (86 mg CIS, 17.2 mg VIN) in a single session, which are higher amounts than typical IV doses. PK shows that 95% of INT230-6 active agents remain in the tumor. The most common ($>$ 20%) related TEAEs for INT230-6 alone were localized pain (57%), nausea (36%), fatigue (29%) and vomiting (24%); with grade 3 TEAEs ($>$ 1) of localized pain (5%) and anemia (3%). The safety in the combination was similar. There were no related grade 4 or 5 TEAEs. In evaluable monotherapy subjects (n = 43), the disease control rate (DCR) was 65% vs. 100% in PEM subjects (n = 5). Given the range of dose and entering tumor burden, an exploratory analysis of dose relative to tumor burden (TB) showed that subjects receiving a dose of INT230-6 $<$ 50% of their reported TB (n = 30) had a mOS of 3.5 months. While in subjects receiving a dose of INT230-6 to $\geq$50% of TB (n = 37), mOS has not yet been reached after a median follow up of 9.5 months (HR: 0.26 (0.13,0.51)). **Conclusions:** INT230-6 is well tolerated when administered IT as monotherapy and combined with PEM. Given the challenge in assessing overall response rate following IT delivery, an exploratory analysis suggests prolonged survival for subjects receiving an INT230-6 dose $\geq$50% of their tumor burden compares favorably to the $<$ 50% group and to literature accounting for prognostic factors (ECOG, LDH, # of metastatic sites). Clinical trial information: 03058289. Research Sponsor: Intensity Therapeutics, Inc.

2593 **Poster Session**

Nivolumab/ipilimumab primed immunotransplant in post-CAR-T and post-ASCT DLBCL.

Bailey Gleason Fitzgerald, Thomas Urban Marron, Dana Ostrowski, Jonah Shulman, Matko Kalac, Netonia Marshall, Joshua Brody; The Tisch Cancer Institute at Mount Sinai Health System, New York, NY; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Icahn School of Medicine At Mt Sinai/Beth Israel, New York, NY; Columbia Univ Presbyterian Hosp, New York, NY; Schrodinger, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY

Background: Patients with refractory diffuse large b cell lymphoma (DLBCL) have poor outcomes with $<$ 30% surviving for 12 months and especially poor outcomes for those who progress after chimeric antigen receptor T cells (CAR-T) or autologous stem cell transplant (ASCT). These therapies utilize lymphodepleting chemotherapy which induces homeostatic T cell proliferation. We have demonstrated these expanding T cells express high levels of PD1 and CTLA4. In pre-clinical models, addition of dual checkpoint blockade (DCB) with anti-PD1/anti-CTLA-4 to adoptive T cell transfer after lymphodepletion achieved a synergistic anti-tumor effect. Based on these studies, we developed a phase Ib/II study of Nivolumab/Ipilimumab primed immunotransplant for relapsed/refractory (R/R) DLBCL (NCT03305445). **Methods:** Phase Ib of the trial enrolled 6 patients with progressive disease following at least one line of standard therapy. Patients received two cycles of DCB with ipilimumab (1mg/kg) and nivolumab (3mg/kg) given at three-week intervals followed by immunotransplant (i.e. peripheral blood T cell harvest, lymphodepletion with fludarabine/cyclophosphamide, T cell reinfusion), followed by two further cycles of DCB and nivolumab maintenance. **Results:** Five patients received at least two cycles of DCB and the autologous T cell transfer, while one patient had progressive disease during initial DCB and required salvage chemotherapy. Treatment emergent AE (TEAE) occurred in 100% of patients. As expected with lymphodepleting chemotherapy, the most common TEAE were neutropenia (66.7% grade 1, 66.7% grade $\geq$ 3), fatigue (83.3%, 16.7%), fever (66.7%, 0%), and dyspnea (66.7%, 0.0%). One patient (16.7%) died during the intervention period (grade 5 TEAE), though relation to study drug is unclear. Three patients (50.0%) experienced clinical benefit with immunotransplant. One patient (a 58yo M with progression after seven lines of therapy including ASCT and CAR-T) is experiencing partial metabolic response after 4 months on protocol. One 77yo F with multiple prior lines of therapy including ASCT has experienced an extended complete metabolic response, currently 31 months post immunotransplant. A third (a 50yo F) experienced mixed radiographic response, and has not received subsequent therapy 30 months following immunotransplant. **Conclusions:** Nivolumab/Ipilimumab primed immunotransplant is well tolerated in patients with R/R DLBCL for whom there are few treatment options. Preliminary results demonstrate remissions in heavily pre-treated patients, including prior ASCT and CAR-T. Pre-clinical models in melanoma, non-small cell lung cancer, and T cell lymphoma all demonstrate synergy when DCB is administered with lymphodepletion and autologous T cell transfer. These data support further investigation of DCB-primed immunotransplant. Clinical trial information: NCT03305445. Research Sponsor: Bristol Myers Squibb.

2594 **Poster Session**

Safety, pharmacokinetics, pharmacodynamics profiles and preliminary antitumor activity of phase 1b/2a study of NT-I7, a long-acting interleukin-7, plus pembrolizumab in patients with advanced solid tumors: The phase 1b data report.

Aung Naing, Jean Fan, Byung Ha Lee, Debashree Basudhar, Shubham Pant, Marya F. Chaney, Cristina Laviada, Cynthia Rajan, Ngocdiep T. Le, Minal A. Barve; The University of Texas MD Anderson Cancer Center, Houston, TX; NeoImmuneTech, Inc., Rockville, MD; Merck & Co., Inc., Kenilworth, NJ; Mary Crowley Cancer Research, Dallas, TX; Mary Crowley Cancer Research Center, Dallas, TX

Background: NT-I7 (efineptakin alfa) is the first-in-class long-acting IL-7 which can increase the number and functionality of T cells in the peripheral blood (PB) of patients (pts). The combination of NT-I7 and pembrolizumab (pembro), a PD-1 Checkpoint Inhibitor (CPI), may augment and broaden the efficacy of CPIs. **Methods:** This is an open-label, phase 1b/2a study in pts with relapsed/refractory (R/R) advanced solid tumors. In the phase 1b (Dose Escalation), which followed the 3+3 design, pts received NT-I7 intramuscularly (IM) at 3 dose levels (DLs): 480, 960, and 1200 μg/kg every 6 weeks (Q6W) plus pembro 200 mg intravenously (IV) Q3W. The objectives of the phase 1b were to evaluate Dose Limiting Toxicity (DLT), determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D), and assess pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity. **Results:** As of 12 January 2021, 12 pts were enrolled in the phase 1b: DL1 (n=3), DL2 (n=3) and DL3 (n=6). Median age 58.0 years [43-77], ECOG PS 0 (50%), PS 1 (50%), median number of prior therapies 4 [1-8]. MTD was not reached. One DLT (Grade [G] 3 ALT increased) was reported in DL3. Treatment-related adverse events (AEs) occurred in 11 (91.7%) pts, 11 (91.7%) G1-2 and 4 (33.3%) G3; no G4 or G5 AEs reported. Common treatment-emergent AEs were injection site reaction (n=8, 66.7%), chills (n=7, 58.3%), nausea (n=6, 50%) and pyrexia (n=6, 50%). Preliminary PK analysis showed T_{max} = 24 hours and $T_{1/2}$ = 123 hours for NT-I7 at DL3. NT-I7 + pembro induced dose-dependent lymphocyte proliferation in the PB, with ~ 3-fold increase at DL3, and a corresponding decrease in neutrophil to lymphocyte ratio at 14 days after the 1st treatment. Importantly, increased number of T cells in the tumor microenvironment (TME) was also observed (Table). One pt with metastatic mucosal melanoma who had not responded to prior combination of nivolumab and ipilimumab had a rapid, confirmed partial response with 46% tumor reduction. Patient follow-up continues and updated data will be presented. The combination of NT-I7 1200 μg/kg IM Q6W + pembro 200 mg IV Q3W has been selected as the RP2D. **Conclusions:** The combination of NT-I7 + pembro was well tolerated in pts with R/R advanced solid tumors. NT-I7 + pembro significantly increased T cell numbers in both the TME and the PB, and there was encouraging antitumor activity with the combination in this pt population. These results support continued evaluation of NT-I7 in combination with pembro in pts with R/R advanced solid tumors. The phase 2a of the study is enrolling pts with either CPI-pretreated or CPI-nave solid tumors (NCT04332653). Clinical trial information: NCT04332653. Research Sponsor: NeoImmuneTech, Inc.

Increased lymphocytes in the TME on treatment (OT) compared to baseline (BL).

	% lymphocyte			
	Stroma		Tumor	
DL	BL	OT	BL	OT
DL2	2	7	0	<1
DL3	3	20	1	<1
DL3	13	16	<1	<1
DL3	15	20	6	20

2595 **Poster Session**

Phase II trial of MEDI0457 and durvalumab for patients with recurrent/metastatic HPV-associated cancers.

Van K. Morris, Amir A. Jazaeri, Shannon Neville Westin, Curtis Alvin Pettaway, Solly George, Ryan Huey, Michaela Onstad, Shi-Ming Tu, Jennifer Wang, Aaron Shafer, Benny Johnson, Lianchun Xiao, David J Vining, Ming Guo, Ying Yuan, Michael M. Frumovitz; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Virginia, Charlottesville, VA; University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas - MD Anderson Cancer Center, Houston, TX; Duke University Medical Center, Durham, NC; Department of Diagnostic Radiology, University of Texas M.D. Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Infection with human papillomavirus (HPV) types 16 or 18 drives oncogenesis for the majority of patients (pts) with cervical, anal, and some penile cancers via viral oncoproteins E6 and E7. While anti-PD1/PD-L1 antibodies have activity in pts with HPV-associated cancers, the majority do not derive benefit from these agents as monotherapy. MEDI0457, a therapeutic DNA vaccine containing plasmids for E6 and E7 oncogenes for HPV-16/18 and IL-12 adjuvant, has been shown to be safe and to provoke an immune response against the expressed antigens. We tested MEDI0457 with the anti-PD-L1 antibody durvalumab for pts with recurrent or metastatic HPV-associated cancers with the goal of improving anti-tumor activity. **Methods:** Pts with HPV-16/18 cervical cancer or rare (anal, penile, vaginal, or vulvar) HPV- associated cancers that were recurrent and/or metastatic following standard therapies were eligible. No prior immunotherapy was allowed. Pts received 7 mg of MEDI0457 intramuscularly (weeks 1, 3, 7, 12, and every 8 weeks thereafter) and durvalumab 1500 mg intravenously every 4 weeks starting at week 4. The primary endpoint was best overall response according to RECIST 1.1. Adverse events (AE) were assessed using CTCAE v4.03. A Simon two-stage phase 2 trial (Ho: $p < .15$; Ha: $p \geq .35$) using a one-sided alpha =.05 and beta =.20 was conducted. ≥2 responses were needed in both the cervical and non-cervical cohorts during the first stage in order for the trial to proceed. Median progression-free survival (PFS) and overall survival (OS) were estimated via Kaplan-Meier. **Results:** 41 pts were screened between 11/2018-10/2020. 21 pts (12 cervical, 7 anal, 2 penile) were treated. All 21 were evaluable for toxicity and 19 for response. Median age was 49 years (range, 29-75), and 18 (86%) were female. There were 17 squamous cell carcinomas (SCC) and 4 cervical adenocarcinomas. Grade ≥3 AEs occurred in 3 (14%) pts and included transaminitis, elevated lipase/amylase, hyponatremia, and neutropenia. No AE required study discontinuation. Overall response rate (ORR) was 21% (95% CI, 6-46%) and disease control rate (DCR) was 42% (95% CI, 20-67%). There was one patient with a complete response, 3 with partial response, and 4 with stable disease. All responses were noted among SCCs (1 cervical, 2 anal, 1 penile). Median duration of response among responders is 16 months (range, 11-27). Median PFS was 3.7 months (95% CI, 2.8-9.2), and median OS was 13.5 months (95% CI, 10.1-NA). 6-month PFS rate was 36% (95% CI, 20-65). **Conclusions:** The combination of MEDI0457 and durvalumab demonstrated acceptable safety/tolerability in pts with advanced HPV-16/18 cancers. Despite a clinically meaningful DCR, the low ORR among pts with cervical cancer led to study discontinuation for futility. Correlative studies are ongoing to characterize pts with prolonged disease control with study treatment. Clinical trial information: NCT03439085. Research Sponsor: AstraZeneca.

2596 **Poster Session**

Preliminary data from QUILT 3.055: A phase 2 multi-cohort study of N803 (IL-15 superagonist) in combination with checkpoint inhibitors (CPI).

John M. Wrangle, Mark M. Awad, Firas Benyamine Badin, Mark P Rubinstein, Paul Bhar, Chad Garner, Sandeep K. Reddy, Patrick Soon-Shiong; Johns Hopkins Univ School of Medcn, Baltimore, MD; Massachusetts General Hospital, Cambridge, MA; University of Kentucky, Lexington, KY; Department of Surgery, Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; ImmunityBio, Inc, Morrisville, NC; ImmunityBio, Culver City, CA; NantKwest, Inc, Culver City, CA

Background: There is currently a paucity of treatment options for checkpoint relapsed patients who have had an initial response but subsequently progress. N803, a novel IgG1 Fc-engineered IL-15-complexed protein may rescue checkpoint activity in a checkpoint independent manner via its selective enhancement of natural killer cell (NK) and CD8+ T cell number and function, without stimulation of T regs and MDSCs. **Methods:** QUILT 3.055, (NCT03228667) a phase 2b study of N803 plus investigator choice CPI in 11 tumor types: NSCLC, SCLC, Urothelial carcinoma, HNSCC, Merkel cell carcinoma, Melanoma (single PD-1/PD-L1 CPI or w/ ipilimumab), Renal cell carcinoma (RCC), Gastric cancer, Cervical cancer, Hepatocellular carcinoma, Microsatellite instability-high (MSI-H)/ mismatch repair deficient (dMMR) solid tumors, with a heterogeneous mix of prior therapies. We present interim data for 135 patients treated with CPI alone or in combination with chemotherapy as their most recent prior therapy. Trial inclusion required investigator assessed progression on last line of therapy, patients had either CR with relapse or partial response or stable disease for 6 months with progression as their most recent result of checkpoint therapy. Patients with hyperprogression or best initial response of progression were excluded. Subjects received N803 15mck/kg SC q 3 weeks in combination with the same checkpoint inhibitor on which they had their most recent progression. **Results:** Preliminary data from 135 patients (60% NSCLC) with treatment with checkpoint and N-803 following progression on the same checkpoint show CR 0%, PR 8%, Stable Disease 51%, Progression 29%, response unevaluable 12% to date. A PR or SD was seen in all subgroups. Median PFS 3.9 months (95% CI: 2.6,5.0). Median OS 13.8 months (95% CI: 11.8, 16.3) N-803 is well tolerated with grade 1-2 common N-803 treatment related adverse events (TRAE) were injection site reaction (68%), chills (32%) fatigue (26%), pyrexia (26%), flu-like illness (14%), nausea (12%) and no other individual AE $>$ 10%. Grade 3 N-803 TRAE were 12% but no individual grade 3 AEs were greater than 5%. **Conclusions:** N803 demonstrates low toxicity in patients previously treated with CPI and promising efficacy of cessation of progression and induction of response and durable stable disease in patients who had previously progressed on a CPI containing regimen in multiple tumor types and different CPIs. Clinical trial information: NCT03228667. Research Sponsor: ImmunityBio.

2597 **Poster Session**

Evaluating the role of immune-checkpoint inhibitor (ICI) combinations in patients (pts) with unselected cold tumors enrolled in early clinical trials (CT).

Omar Saavedra Santa Gadea, Alberto Hernando-Calvo, Roger Berche, Maria Vieito, Irene Brana, Ignacio Matos, Guzman Alonso, Vladimir Galvao, Analia Azaro, Honey Kumar Oberoi, Natassia Ann Wornham, Javier Ros, Juan Francisco Grau Béjar, Carmen García, Teresa Macarulla, Jaume Capdevila, Elena Elez, Josep Tabernero, Rodrigo Dienstmann, Elena Garralda; Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Vall d'Hebron University Hospital, Vall d'Hebrón Institute of Oncology, Barcelona, Spain; Hospital Univ Vall d'Hebron, Barcelona, Spain; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron Institute of Oncology, VHIO, Barcelona, Spain; Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Vall dHebron Institute of Oncology, Barcelona, Spain; Vall d'Hebron University Hospital, Barcelona, Spain; Vall dHebron University Hospital, Barcelona, Spain; Hospital Universitario Vall d'Hebron, Barcelona, Spain; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), UVic-UCC, Barcelona, Spain; Grupo Oncoclínicas, São Paulo, Brazil; Hospital Universitario Vall d'Hebron, Barcelona, Spain

Background: In order to improve the expected response rate (ORR) of less than 10% in cold tumors, several ICI combinations are being evaluated in clinical trials. However, most of these trials don't require any biomarker and pts are included based solely in histology. We aimed to assess the benefit of ICI combinations in pts with unselected cold tumors included in early CT. **Methods:** ICI nave pts with cold tumors treated from 2015 to 2021 with ICI combinations in early CT at VHIO were reviewed. Clinicopathological data and anti-tumor activity were extracted from a prospective database. ORR was defined as per RECIST v1.1 and clinical benefit rate (CBR) as complete/partial response (CR/PR) + stable disease (SD) for $\geq$ 4 months (m). Kaplan Meier estimates of progression-free survival (PFS) and overall survival (OS) were calculated and a Cox model according to LIPI (Lung Immune Prognostic Index = baseline LDH and derived neutrophil to lymphocyte ratio) was constructed. Immune-related adverse events (irAE) were classified as per CTCAE v.4.03. Hyperprogressive disease (HPD) was evaluated using RECIST v1.1 (Matos *et al,* 2020). **Results:** Out of 97 pts, median age was 62y, 61% had ECOG 0 and 29.8% had LIPI 0 (good prognostic score). Most pts had microsatellite stable (MSS) colorectal cancer (60.8%) or ovarian cancer (14.4%). Regimens included anti-PD1/L1 + another ICI in 69% (most commonly anti-LAG3 [26,8%] and CD40 agonist [20.9%]), anti-PD1/L1 + other molecule in 21.7% (most commonly SHP2 inhibitor [33.3%] and anti p53-HDM2 [28.5%]) and bispecific antibodies in 9.3% (anti-PD1/L1 + anti-LAG3 or CD137 agonist). No patient achieved a response. CBR was 15.3% (11 pts with MSS colorectal cancer, 2 ovarian cancer, 1 olfactory neuroblastoma, 1 paraganglioma). 33 pts (34%) presented irAE, 15 pts (15.5%) had irAE $\geq$ G2, 4 pts (4.1%) had G3 irAE (dry mouth, hypertransaminasemia, myocarditis and neutrophils count decreased) and 1 patient (1%) had G4 hyperglicemia. 58 pts (59.7%) had progressive disease (PD) as best response, 19 of these pts (32.7%) presented irAE. Overall, 20 pts (20.6%) met definition of HPD, representing 34.4% of pts with PD as best response. Median PFS for overall and CBR population were 1.9 m (CI95% 1.7-2.0) and 5.9 m (5.4-NR), respectively. Median OS for overall population was 7.6 m (5.9-9.5), with a trend for improved OS if LIPI good score vs. others (12.6 m vs. 6.2 m, hazard ratio 1.9, (CI 95% 1.1-3.3), p = 0.02). Among hyperprogressors, median OS was 5.33 m (3.39 - NR) and significantly worse LIPI scores (intermediate [1] or poor [2]) were observed as compared to pts with CBR (75% vs 53.3% p = 0.001). **Conclusions:** ICI combinations demonstrated very limited activity in pts with unselected cold tumors. However, the risk for irAE and HPD remain substantial. Further drug-biomarker co-development strategies are urgently needed to increase the risk benefit ratio for these pts. Research Sponsor: BBVA Foundation.

2598 **Poster Session**

A pan-cancer analysis of MUC family genes as potential biomarkers for immune checkpoint therapy.

Yang Li, Qianqian Duan, Yuan Tan; Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Jiangsu Simcere Diagnostics Co., Ltd., Nanjing, China; Jiangsu Simcere Diagnostics Co., Ltd., Jiangsu, China

Background: Mucin (MUC) is a family of high-molecular weight glycoproteins and increased mucin production occurs in many malignant tumors. Recent studies have found relationship between mutations of some MUC family genes and efficacy of immunotherapy. Here, we explored the associations of MUC family genes (MUC2, MUC3A, MUC4, MUC5B, MUC6, MUC12, MUC16, MUC17, MUC19) mutation with ICI response based on multidimensional data from multiple solid tumors. **Methods:** 15 solid tumor types of TCGA genomic data for 6138 patients was used to evaluate tumor mutational burden (TMB) differences between MUC family genes mutation group and wildtype group. TMB was calculated as the total count of nonsynonymous mutations in coding sequence. Neoantigens of 3039 samples across 11 solid tumor types were obtained from The Cancer Immunome Atlas. A pan-cancer immunotherapy cohort (Broad/Dana-Farber, Nat Genet 2018, N = 249) was used to explore the relationship between mutations of MUC family genes and its efficacy of immunotherapy. **Results:** The most common mutated MUC genes (frequency $>$ 5%) were MUC16 (25.3%), MUC17 (10.8%), MUC5B (10.5%), MUC4 (8.6%), and MUC2 (5.1%). The data between MUC mutation group and wild type group showed a significant difference ($P < 0.01$) in TMB. Median TMB across fifteen tumors in MUC mutation group and wild type group is 7.04 mutations per Mb and 2.07 mutations per Mb, separately. The TNB between two group is also showed a significant difference ($P < 0.01$). Median TNB across nine types tumor in MUC mutation group and wild type group is 121.5 neoantigens and 34.0 neoantigens, separately. A multivariable analysis across the pan-cancer cohort using Cox proportional-hazards regression demonstrated that KMT2C mutation was associated with better OS (hazard ratio, 0.66; 95%CI, 0.45-0.99; P = 0.042), adjusting for sex and cancer type. **Conclusions:** The results indicated that MUC family genes mutation was associated with a higher TMB and TNB. Analysis of immunotherapy cohort data showed MUC family was associated with better OS. These findings indicate that these genes mutation may serve as a predictive biomarker for ICI in solid tumor patients. Research Sponsor: None.

2599 **Poster Session**

Real-world pan-cancer landscape of frameshift mutations (FSM) and their role in predicting responses to immune checkpoint inhibitors (ICI) in patients (pts) with tumors with low tumor mutational burden (TMB).

Vaia Florou, Charalampos S. Floudas, Asaf Maoz, Abdul Rafeh Naqash, Gregory Hildebrand, Ethan Sokol, Garrett M. Frampton, Sonam Puri, Umang Swami, Breelyn A. Wilky, Peter Joel Hosein, Jonathan C. Trent, Gilberto Lopes, Wungki Park, Ignacio Garrido-Laguna; Huntsman Cancer Institute University of Utah, Salt Lake City, UT; Genitourinary Malignancies Branch, NCI, NIH, Bethesda, MD; Dana Farber Cancer Institute, Boston, MA; Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD; University of Kansas Medical Center, Kansas City, KS; Cancer Genomics Research, Foundation Medicine, Cambridge, MA; Foundation Medicine, Inc., Cambridge, MA; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; University of Colorado, Aurora, CO; University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; University of Miami-Sylvester Comprehensive Cancer Center, Jackson Memorial Hospital, Miami, FL; University of Miami Miller School of Medicine, Miami, FL; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY

Background: Pembrolizumab was recently approved in tumors with TMB $\geq$10 mut/Mb. FSM can complement TMB in predicting ICI responses. We obtained a real-world dataset of genomic alterations from 250,813 samples to examine the distribution of TMB and FSM across a variety of malignancies. We then conducted a multi-institutional retrospective review of pts treated with ICI. **Methods:** Database samples were sequenced by Foundation Medicine using hybrid capture genomic profiling to evaluate all classes of genomic alterations in at least 315 genes. The clinical cohort included pts with metastatic solid malignancies who received ICI and had undergone commercial next-generation sequencing (NGS). Pts were classified into four distinct groups: TMB-L ($<$ 10mut/Mb)/ FS-A (absent FSM), TMB-H ($\geq$10mut/Mb)/ FS-A, TMB-L /FS-P (present, $\geq$1 FSM) and TMB-H/FS-P. Progression-free survival (PFS), overall survival (OS), and response rate (RR) were compared between the groups. **Results:** 246,252 MSS and 4,561 MSI-High samples were segregated by histology and divided into four distinct groups based on the TMB and FSM. For the MSS cohort the distribution was: TMB-L/FS-A (N = 111,065, 45%), TMB-H/FS-A(N = 15,313, 6%), TMB-L /FS-P (N = 98,389, 40%) and TMB-H/FS-P (N = 21,485, 9%). In the ICI-treated clinical cohort, there were 230 pts in 12 histology groups; 212 had information on TMB and FSM. The most common primary sites were GI (N = 39), melanoma (N = 37), GU (N = 32) and H&N cancer (N = 21). 159 pts received single ICI and 53 dual ICI. 196 tumors were MSS, 11 MSI, and 5 unknown. Group distribution: TMB-L/FS-A 80 pts (38%), TMB-L/FS-P 57pts (27%), TMB-H/FS-A 36pts (17%), TMB-H/FS-P 39pts (18%). FS-P was associated with higher RR 23.81 vs. 12.8 % ($p = 0.02$). Regardless of TMB, the median PFS for FS-P vs. FS-A was 7.9 and 4.0 mo, respectively ($p < 0.01$). TMB-L/FS-P had superior PFS (5.1 mo) compared to TMB-L/FS-A (3.6 mo) group ($p < 0.01$). The 15-month PFS probability was 12% for TMB-L/FS-A vs. 38% for TMB-L/FS-P. No statistically significant difference was detected in OS between the groups. From the pan-cancer cohort, histologies with more than 40% of samples in the TBM-L/FS-P (MSS) group were: CRC, RCC, PDAC, biliary, breast, esophageal, and endometrial cancers. Additional genomic data will be presented. **Conclusions:** FSM are frequently found on commercial NGS testing in tumors that are MSS and TMB-L. The presence of FSM may complement TMB in predicting benefit from immunotherapy. If validated in additional cohorts, FSM presence could be utilized to identify pts that may benefit from ICI, particularly for tumors with low TMB. Research Sponsor: None.

2600 **Poster Session**

Association of KMT2C mutations with favorable outcomes with immune checkpoint inhibitors across multiple tumor types.

Chunling Liu, Qianqian Duan, Qin Zhang; The Affiliated Tumor Hospital of Xinjiang Medical University, Urumchi, China; Jiangsu Simcere Diagnostics Co., Ltd., Nanjing, China

Background: The KMT2 (lysine methyltransferase) family of histone modifying proteins play important roles in regulating developmental pathways, and mutations in the genes encoding these proteins have been strongly linked to many solid tumor cancers. Recently, there is emerging evidence that KMT2 family genes are involved in sensitivity to immune checkpoint inhibitors (ICIs) by modulating the immune environment. Here we explored the relationship between KMT2C mutation and its efficacy of immunotherapy. **Methods:** 1661 patients with next-generation sequencing (NGS) and immunotherapy data obtained from MSKCC clinical cohort were used to explore the association with KMT2C mutation and TMB and efficacy of ICIs. TMB was defined as the total number of somatic nonsynonymous mutations in the coding region. NGS data of 6624 pan-cancer patients who also detected MSI and PD-L1 expression from the Chinese clinical dataset were also analyzed relevance of mutation and these immune-related indicators. **Results:** In total, 9.81% (163/1661) patients in MSKCC cohort harbored KMT2C mutation. In the Chinese cohort, the KMT2C mutation ratio (11.19%, 741/6624) was similar to MSKCC. The TMB level of KMT2C mutation group in both MSKCC cohort and Chinese pan-cancer patient cohort was significantly higher than wild-type group ($P < 0.001$). A multivariable analysis across the pan-cancer cohort using Cox proportional-hazards regression demonstrated that KMT2C mutation was significantly associated with better OS (hazard ratio, 0.69; 95%CI, 0.52-0.90; $P = 0.006$), and association remained significant with bladder ($P = 0.039$), colorectal ($P = 0.024$), melanoma ($P < 0.001$) and renal ($P < 0.001$), adjusting for cancer age, sex, metastases or primary. In addition, in Chinese cohort, KMT2C mutation was associated with higher PD-L1 positive expression ($\geq 1\%$) ($P = 0.01203$) and MSI-H ($P < 0.001$). **Conclusions:** KMT2C mutation shows impressive association with efficacy of ICIs. Meanwhile, KMT2C-mutant group has a higher TMB, PD-L1 expression and MSI-H. These results indicated that KMT2C mutation may serve as a good potential biomarker of ICI benefit in patients with multiple cancer types. Research Sponsor: None.

2601 **Poster Session**

MSIFinder: A python package for detecting MSI status using random forest classifier.

Tao Zhou, Libin Chen, Jing Guo, Mengmeng Zhang, Huanhuan Liu, Yanrui Zhang, Huina Wang, Shanbo Cao, Haijun Wang, Feng Lou; AcornMed Biotechnology Co., Ltd., Beijing, China; Acornmed Biotechnology Co., Ltd., Beijing, China; The Second Affiliated hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Microsatellite instability (MSI) is a common genomic alteration in several tumors, such as colorectal cancer, endometrial carcinoma, and stomach, which is characterized as microsatellite instability-high (MSI-H) and microsatellite stable (MSS) based on a high degree of polymorphism in microsatellite lengths. MSI is a predictive biomarker for immunotherapy efficacy in advanced/metastatic solid tumors, especially in colorectal cancer (CRC) patients. Several computational approaches based on target panel sequencing data have been used to detect MSI; However, they are considerably affected by the sequencing depth and panel size. **Methods:** We developed MSIFinder, a python package for automatic MSI classification, using random forest classifier (RFC)-cbased genome sequencing, which is a machine learning technology. We included 19 MSI-H and 25 MSS samples as training sets. First, RFC model were built by 54 feature markers from the training sets. Second. The software was validated the classifier using a test set comprising 21 MSI-H and 379 MSS samples. **Results:** With this test set, MSIFinder achieved a sensitivity (recall) of 0.997, a specificity of 1, an accuracy of 0.998, a positive predictive value (PPV) of 0.954, an F1 score of 0.977, and an area under curve (AUC) of 0.999. We discovered that MSIFinder is less affected by low sequencing depth and can achieve a concordance of 0.993, while exhibiting a sequencing depth of 100×. Furthermore, we realized that MSIFinder is less affected by the panel size and can achieve a concordance of 0.99 when the panel size is 0.5 m (million base). **Conclusions:** These results indicated that MSIFinder is a robust MSI classification tool and not affected by the panel size and sequencing depth. Furthermore, MSIFinder can provide reliable MSI detection for scientific and clinical purposes. Research Sponsor: None.

Summary of classification performance of MSIFinder, mSINGS and MSIsensor.

Tools	Sen.	Spe.	Acc.	PPV	F1	AUC
MSIFinder	0.997	1.000	0.998	0.954	0.977	0.9999
msings	0.983	0.950	0.981	0.730	0.826	0.985
MSIsensor	0.959	0.944	0.958	0.586	0.723	0.985

Sen: Sensitivity; Spe: Specificity; Acc: Accuracy; PPV: positive predictive value; F1: F1 score; AUC: Area Under Curve.

2602 **Poster Session**

A cancer organogram test as a guide for oncology treatments in SOLID tumors: An analysis of 628 tests in 419 patients.

Astrid Margossian, Madison Pollastro, Annie Richardson, Payel Chatterjee, Mia Lints, Danielle Peretti, Rachele Rosati, Lauren Appleyard, Grace Durenberger, G. Adam Whitney, Hallie Swan, Shalini Pereira, Adam Diehl, Christopher J Kemp, Barbara Ann Goff, Kalyan Banda, William Proctor Harris, Elizabeth M. Swisher, Vijayakrishna K. Gadi, Carla Grandori; SEngine Precision Medicine, Seattle, WA; University of Washington Fred Hutchinson Cancer Research Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Washington Medical Center, Seattle, WA; Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA; University of Washington/ Seattle Cancer Care Alliance (SCCA), Seattle, WA; University of Washington School of Medicine, Seattle, WA; University of Illinois at Chicago College of Medicine, Division of Medical Oncology, Chicago, IL

Background: A CLIA-certified organoid based drug sensitivity assay (a cancer organogram) has been developed for all solid tumors. An actionable report of organogram sensitivities to endocrine, chemotherapy and targeted agents, produced a drug sensitivity score as a tool to inform therapy decision making. Objectives: To evaluate the success rate of organoid derivation, the organogram drug responses across cancer types and to analyze the impact of the organogram report on therapeutic decision making. **Methods:** From 2016 to 2020, 628 cancer organograms were performed, with 513 tumor samples from 419 cancer patients. Within 48 hours of collection, fresh samples of tumor cells obtained from core biopsies, surgical excisions, or fluids were cultured, the majority as 3D organoids. Drug screens were performed with a library of up to 220 drugs, and dose-response was evaluated across a range of concentrations for each drug. Organogram sensitivity was ranked as response in five categories based on SPM Score: Exceptional (SPM15/14), Good (13/12), Moderate to Low (11/9), and None(< 9). 118 drugs on average were tested per screen (range: 68-152), so in a total of 628 organograms, more than 70,000 individual drug trials have been performed. The median turnaround time was 28 days (range: 19.5-51.5). **Results:** Of the 513 collected samples, 314 were fresh specimens: 96 core biopsies, 151 surgical specimens, and 67 fluids (pleural effusions or ascites), with an organoid derivation success rate of 58.3%, 78%, and 88%, respectively. Overall success rate in organoid derivation was 70.2%. Samples with poor viability and low tumor cell count (22%) were rejected. The primary cancer types tested were ovarian (n = 92, 17.9%), breast (n = 73, 14.2%), colorectal (n = 70, 13.6%), pancreatic (n = 51, 9.9%), cholangiocarcinoma (n = 42, 8.1%), and other solid tumors (n = 185, 36%). Median age of patients was 56 years old (range: 5-83), most of them heavily pretreated. 20.45% of drugs screened had exceptional and good responses (SPM score 15-12) (SD: 17.92%). We reviewed genomic data from 374 third-party genomic reports. The most frequent genomic alterations found were *TP53* (n = 143, 38.2%), *BRCA1* and *BRCA2* (n = 47, 12.5%) *CDKN2A* (n = 42, 11.2%), *FGFR1/2/3/4* (n = 41, 10.9%), and *PIK3CA* (n = 38, 10.1%). Post-test treatment information is available for a subset of 61 patients. The treating physician made an organogram-guided therapeutic decision in 32/44 patients with post test treatment drugs scored (72%). **Conclusions:** The cancer organogram test has a high rate of success in generating an actionable report that identifies therapies for patients with limited therapeutic options, including those with no known genomic biomarkers. The organogram guided selection of therapeutics for a significant subset of patients, nearly 4 times the rate reported with genomic testing alone. Research Sponsor: Sengine Precision Medicine.

2603 **Poster Session**

Relationship between DICER1 mutations and immunotherapy biomarkers in solid tumors.

Jie Gao, Xia You, Taiyan Guo, Qin Zhang, Qianqian Duan, Chuang Qi; The Department of Hepatobillary Surgery, Peking University People's Hospital, Beijing, China; The Medical Department, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing Simcere Medical Laboratory Science Co., Ltd, The State Key Lab of Translational Medicine and Innovative Drug Development, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing, China

Background: Dicer1 functions as a tumor suppressor in mouse models. In humans, somatic mutations are associated with many cancers in adults, and patients with DICER1 syndrome with *DICER1* germline mutations are susceptible to childhood cancers. *DICER1* is the core caner-intrinsic CTL-evasion gene, especially positive correlate with innate anti-PD-1 resistance signature or IPRES signature and hERV expression which involved in sensitivity and resistance to ICIs. Nevertheless, the association between mutations in *DICER1* and the Chinese patients, the relationship between *DICER1* mutations with immunotherapy biomarkers are unknown. **Methods:** NGS and clinical data were collected from 10953 Western pan-cancer patients (TCGA cohort). A 539-gene panel targeted sequencing assay was performed on FFPE tumor samples from 3514 Chinese pan-cancer patients (Chinese cohort). Both *DICER1* mutation ratio and TMB were calculated on the two cohorts following the same criteria.DNA NGS testing (MSI-high vs low/stable (MSS)) in Chinese cohort were included. NGS data of 3514 patients who also detected PD-L1 expression from Chinese clinical dataset were analyzed to explore the association with mutation and PD-L1. The survival information was collected from 1661 pan-cancer patients to analyze the association between *DICER1* mutation and efficacy of immunotherapy (MSKCC cohort). **Results:** In total, 2.91% (319/10953) patients in TCGA harbored *DICER1* mutation; in the Chinese cohort, the *DICER1* mutation ratio (2.67%, 94/3514) was similar to TCGA. The top 5 mutant *DICER1*-associated cancer types in Chinese cohort were lung cancer, colon adenocarcinoma, liver cancer, uterine corpus endometrial carcinoma, melanoma. In both cohorts, TMB level of mutation group was significantly higher than wild-type group ($p < 0.001$). The ration of mutation group in MSI-H (50%) and MSI-L (23.53%) was significantly higher than wild-type group in Chinese cohort (2.17%) ($p < 0.001$). In addition, the ratio of PD-L1 positive expression ($\geq 1\%$) in mutation group (48.94%, 46/48) was significantly higher than wild-type in Chinese cohort (38.48%,1316/2104) ($p < 0.05$). The survival probability of mutation group was significantly longer than wild-type group in immunotherapy. **Conclusions:** The results indicated that *DICER1* mutation was associated with a higher TMB, MSI-H and PD-L1 expression level in Chinese patients. Patients with *DICER1* mutations may benefit more from ICIs. Research Sponsor: None.

2604 **Poster Session**

YAP1 mutation as a novel predictor of response to anti-PD-1/PD-L1 treatment in pan-cancers.

Wei-guo Xu, Jing Zhu, Lin Li, Dongsheng Chen, Qin Zhang, Qianqian Duan, Si Li, Mingzhe Xiao; Department of Respiratory and Critical Care Medicine, Mianyang Central Hospital, Mianyang, China; Mianyang Central Hospital, Mianyang, China; The Medical Department, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing Simcere Medical Laboratory Science Co., Ltd, The State Key Lab of Translational Medicine and Innovative Drug Development, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing, China; Jiangsu Simcere Diagnostics Co., Ltd., Nanjing, China

Background: YAP1 is the main downstream target of the Hippo pathway and acts as a transcriptional co-activator to regulate development processes. YAP1 amplification is a potentially useful biomarker for predicting treatment outcomes and identifying patients with a high risk of relapse who should be closely monitored in nonsurgical esophageal squamous cell carcinoma (ESCC). YAP1 overexpression has been identified in multiple solid cancers, which consistently correlated with unfavorable clinical outcomes. Previous work suggested that YAP1 alterations may enrich for responses to immune checkpoint inhibitors (ICI), validation of these findings in needed. **Methods:** Using 539-gene target-capture next generation sequencing, we analyzed the YAP1 mutation in 3547 tumor tissue or plasma ctDNA samples from different patients, and the public database of TACG was also compared. Data from MSK-IMPACT study (n = 1661, anti-PD-(L)1/CTLA-4 mono/ combined therapy) was retrieved and analysed. In survival analysis, Kaplan-Meier curves were compared by log-rank test, and the hazard ratio (HR) was determined through a multivariable Cox regression model. **Results:** In clinical cohort, the frequency of YAP1 mutation in 3547 tumor tissue or plasma ctDNA samples from different patients was 0.62 % (22 in 3547). Meanwhile, the frequency of YAP1 mutation in TCGA cohort was 0.90 % (99 in 10953). We further analyzed Kaplan-Meier curves from MSK-IMPACT study (n = 1661, anti-PD-(L)1/CTLA-4 mono/ combined therapy). In MSK-IMPACT cohort, mutation of YAP1 was associated with higher TMB (P = 0.022) and higher mutation count (P = 0.017) in pan-cancers. YAP1 mutation was associated with prolonged overall survival (OS) trend compared with YAP1 wt in pan-cancers (P = 0.15; HR, 2.209, 95% CI, 0.7109-6.8639). **Conclusions:** In our study, the frequency of YAP1 mutation was investigated in clinical and TCGA cohort, which might provide useful information to guide precision medicine. YAP1 mutation may serve as a novel predictor of response to anti-PD-1/PD-L1 treatment in pan-cancers via upregulating TMB and mutation count. Research Sponsor: None.

2605 **Poster Session**

Pan-cancer analysis of *CD274* (PD-L1) mutations in 314,631 patient samples and subset correlation with PD-L1 protein expression.

Richard S.P. Huang, Brennan Decker, Karthikeyan Murugesan, Matthew Hiemenz, Douglas A. Mata, Gerald Li, James Creeden, Shakti H. Ramkissoon, Jeffrey S. Ross; Foundation Medicine, Inc, Cambridge, MA; Foundation Medicine, Cambridge, MA

Background: The effects of non-amplification short variant (SV) mutations in *CD274 (PD-L1)* on PD-L1 protein expression and immune checkpoint inhibitor (ICPI) therapy are unknown. Here, we present a retrospective analysis of *CD274* mutations detected by comprehensive genomic profiling (CGP) and correlate these results with tumor-cell PD-L1 immunohistochemistry (IHC)-based expression assessment to better understand the relationship between mutations and protein expression of PD-L1. **Methods:** FoundationOne CGP was performed on hybridization-captured, adaptor ligation-based libraries using DNA and/or RNA extracted from 314,631 tumor samples that were sequenced for up to 406 cancer related genes and select gene rearrangements. PD-L1 IHC was performed on a subset of cases (n = 213) using the DAKO 22C3 PD-L1 IHC assay and scored with the tumor proportion score (TPS). **Results:** Overall, the prevalence of *CD274* SV mutations was low (0.3%, 1,081/314,631) with 577 unique variants. The most common *CD274* SV mutations were R260H (n = 51), R260C (n = 18), R125Q (n = 12), C272fs*13 (n = 11), R86W (n = 10), and R113H (n = 10). The prevalence of *CD274* mutations varied depending on tumor type with diffuse large B-cell lymphoma (1.9%, 19/997), cutaneous squamous cell carcinoma (1.6%, 14/868), endometrial adenocarcinoma (1.0%, 36/3740), unknown primary melanoma (0.9%, 33/3679), and cutaneous melanoma (0.8%, 32/3874) having the highest frequency of mutations. Ultraviolet exposure was likely a mechanism for *CD274* SV mutations in cutaneous tumors with high frequencies of ultraviolet mutational signatures (cutaneous squamous cell carcinoma [84.6%, 11/13], cutaneous melanoma [93.8%, 30/32], and unknown primary melanoma [100%, 32/32]), and microsatellite instability (MSI) was likely a mechanism for development of *CD274* mutations in non-serous endometrial adenocarcinoma. Of the R260H cases concurrently tested with PD-L1 IHC, most (81.8%, 9/11) had no PD-L1 expression, which contrasts to the five E237K cases where most (80%, 4/5) had PD-L1 expression. This difference in protein expression of these two mutations was significantly different (p = 0.036). It was notable that nearly all samples (88.9%, 16/18) with a clonal truncating variant (nonsense or frame shift indel) and PD-L1 testing showed a PD-L1 TPS score $\leq$1, whereas three of four samples with sub-clonal truncating variants had TPS scores $\geq$5. **Conclusions:** We defined the landscape of *CD274* mutations in a large cohort of tumor types that can be used as a reference for examining *CD274* mutations as potential resistance biomarkers for ICPI. Furthermore, we presented novel data on the correlation of *CD274* mutations and PD-L1 protein expression, providing important new information on the potential functionality of these mutations and can serve as a basis for future research. Research Sponsor: None.

2606 **Poster Session**

Investigating the various predictive values of *POLE/POLD1* mutations for response to immune checkpoint inhibitors (ICIs) in different solid tumors.

Yanling Niu, Tonghui Ma, Yanling Niu, Tao Li; Genetron Health (Beijing) Technology, Co. Ltd., Beijing, China; Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Hangzhou, Zhejiang, China, Hangzhou, China

Background: Both POLE and POLD1 encode the catalytic subunit of polymerase enzyme complexes involved in DNA replication and repair. The mutations of *POLE* and *POLD1* have been shown to be oncogenic and lead to DNA repair defects and elevated tumor mutation burden (TMB). And patients with *POLE/POLD1* mutations are more likely to benefit from ICIs therapy. Previous studies have shown that TMB has divergent predictive value for response to ICIs therapy in different cancer types. We hypothesized that the associations between *POLE/POLD1* mutations and ICIs efficacy are also varied in different solid tumors. Therefore, we explored the prediction values of *POLE/POLD1* mutations in some cancer types. **Methods:** The ICIs treatment cohort from Memorial Sloan Kettering Cancer Center (MSKCC) was selected to analyze the association of *POLE/POLD1* mutations with ICIs efficacy. TCGA cohort was enrolled for characterizing tumor infiltrating lymphocytes (TILs) with CIBERSORT. The patients were classified into two groups: *POLE/POLD1* mutations (Mut) and wildtype (WT). Overall survival (OS) after ICIs therapy was estimated with Kaplan-Meier method. **Results:** In MSKCC pan-cancer dataset, patients with *POLE/POLD1* mutations had significantly longer median OS after ICIs therapy (34.00 vs 19.00 months, P = 0.0143), indicating that *POLE/POLD1* mutations were associated with better immunotherapy outcomes. Then we analyzed the predictive roles in each cancer type. Notably, we found the associations of *POLE/POLD1* mutations with longer median OS in NSCLC (Undefined vs 12.00 months, P = 0.05) and esophagogastric cancer (27.00 vs 15.00 months, P = 0.05). However, the associations between *POLE/POLD1* mutations and ICIs efficacy were not observed in bladder cancer, melanoma, glioma, head and neck cancer, renal cell carcinoma, and colorectal cancer. Furthermore, our data showed that the median TMB was significantly higher in the Mut group for NSCLC (20.2 vs 6.9 muts/Mb, $P < 0.0001$) and esophagogastric cancer (21.4 vs 5.6 muts/Mb, $P < 0.0001$). In TCGA esophagogastric cancer cohort, *POLE/POLD1* mutations were correlated with decreased naive B cells (P = 0.0306) and increased activated memory CD4+ T cells (P = 0.0224). In TCGA NSCLC cohort, *POLE/POLD1* mutations were correlated with elevated gamma delta T cells (P = 0.0219). These data suggested that *POLE/POLD1* mutations were also involved in the infiltration of some immune cells. **Conclusions:** Although *POLE/POLD1* mutations were associated with better ICIs efficacy for all the enrolled patients, the prolonged OS was only found in the Mut group for NSCLC and esophagogastric. These data suggested that *POLE/POLD1* mutations may be a useful predictor for ICIs efficacy in these two types of cancer. Moreover, *POLE/POLD1* mutations were correlated with the level of TILs in NSCLC and esophagogastric. The finding was consistent with the efficacy of immunotherapy. Research Sponsor: None.

2607 **Poster Session**

Artificial intelligence-powered spatial analysis of tumor-infiltrating lymphocytes predicts survival after immune checkpoint inhibitor therapy across multiple cancer types.

Jeanne Shen, Taebum Lee, Jun-Eul Hwang, Yoon-La Choi, Se-Hoon Lee, Hyojin Kim, Jin-haeng Chung, Stephanie Bogdan, Maggie Huang, Tyler Raclin, George A. Fisher, Sergio Pereira, Seonwook Park, Minuk Ma, Donggeun Yoo, Seunghwan Shin, Kyunghyun Paeng, Chan-Young Ock, Tony S. K. Mok, Yung-Jue Bang; Department of Pathology, Stanford University School of Medicine, Stanford, CA; Department of Pathology, Chonnam National University Hospital, Gwangju, South Korea; Division of Hematology-Oncology, Department of Internal Medicine, Chonnam National University Medical School, Gwangju, South Korea; Department of Pathology and Translational Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Hematology and Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Pathology, Seoul National University Bundang Hospital, Seongnam, South Korea; Center for Artificial Intelligence in Medicine & Imaging, Stanford University School of Medicine, Stanford, CA; UC Davis Health, Davis, CA; Stanford University School of Medicine, Stanford, CA; Department of Medicine, Stanford University, Stanford, CA; Lunit Inc., Seoul, South Korea; State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong, China; Seoul National University College of Medicine, Seoul, South Korea

Background: Tumor infiltrating lymphocytes (TIL) are a potential tumor-agnostic biomarker for immune checkpoint inhibitor (ICI) therapy. We previously reported the clinical application of an artificial intelligence-powered spatial TIL analyzer, Lunit SCOPE IO, for predicting ICI treatment outcomes in advanced non-small cell lung cancer (NSCLC). Here, we expand the clinical application of Lunit SCOPE IO as a tumor-agnostic ICI biomarker across multiple cancer types. **Methods:** Lunit SCOPE IO was trained and validated with a 2.8 x 10^9 micrometer^2 area and 5.9 x 10^6 TILs from 3,166 H&E Whole-Slide Images (WSI) of multiple cancer types, annotated by 52 board-certified pathologists. The Inflamed Score (IS) was defined as the proportion of all tumor-containing 1 mm^2-size tiles within a WSI classified as being of the inflamed immune phenotype (high TIL density within cancer epithelium). We first evaluated the correlation between the IS and TMB, MSI-H, and immune cytolytic activity (*GZMA* and *PRF1*) across 22 cancer types from The Cancer Genome Atlas (TCGA, n = 7,467). Subsequently, the correlation between the IS and overall survival after ICI treatment was evaluated in a real-world dataset of patients with 9 different tumor types (n = 1,013), retrospectively collected from Stanford University Medical Center, Chonnam National University Hospital, Samsung Medical Center, and Seoul National University Bundang Hospital. **Results:** Lunit SCOPE IO accurately detected CE, CS, and TILs with an area under the receiver-operating-characteristic curve of 0.970, 0.949, and 0.925, respectively. In the TCGA pan-cancer cohort, Lunit SCOPE IO's IS correlated significantly with immune cytolytic activity (Spearman rho = 0.504, $p < 0.001$), TMB-high ($\geq$ 10 mutations/Mb, fold change 1.39, $p < 0.001$) and MSI-H (fold change 1.45, $p < 0.001$). The IS-positive proportions of microsatellite-stable (MSS) and TMB-low cases were 42.5% and 17.1%, using the thresholds of IS $\geq$ 20% and $\geq$ 50% as presumptive clinical cutoffs. In the real-world ICI clinical dataset (n = 1,013), an IS $\geq$ 20% correlated significantly with favorable overall survival after ICI treatment (cancer type-adjusted hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.59-0.83, $p < 0.0001$). Furthermore, this association remained significant after the exclusion of NSCLC patients (n = 519) (adjusted HR 0.68, 95% CI 0.53-0.86, $p = 0.0016$) indicating that the effect was not driven solely by one major tumor type. **Conclusions:** The Inflamed Score (IS), as evaluated by Lunit SCOPE IO, correlates with favorable overall survival after ICI treatment across multiple tumor types. AI-powered spatial TIL analysis of the tumor microenvironment may be able to detect a significant proportion of ICI responders, and offers promise as a new companion diagnostic, particularly in patients with MSS/TMB-low tumors. Research Sponsor: Lunit Inc.

2608 **Poster Session**

Awareness and utilization of tumor mutation burden (TMB) as a biomarker for administration of immuno-oncology (I-O) therapeutics by practicing community oncologists in the United States (U.S.).

Kristin M. Zimmerman Savill, Marjorie E. Zettler, Bruce A. Feinberg, Yolaine Jeune-Smith, Ajeet Gajra; Cardinal Health, Dublin, OH

Background: TMB, a measurement of the number of mutations carried by tumor cells, is emerging as a biomarker for the identification of patients who may benefit from certain I-O-based therapies. TMB-high (TMB-H) tumors, defined by the detection of $\geq$10 mutations/megabase (mut/Mb) in tumor cells using a tissue-based assay such as the FoundationOneCDx (F1CDx) assay (Foundation Medicine, Inc.), may be more likely to respond to some I-O therapies. Higher neoantigen loads of TMB-H tumors have been proposed to contribute to increased responsiveness of TMB-H tumors to certain I-O therapeutics. Pembrolizumab was approved by the FDA on June 16, 2020 for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H tumors, as determined by F1CDx, based on results from the KEYNOTE-158 trial (NCT02628067), which demonstrated that 50% of patients with TMB-H tumors had response durations of $\geq$24 months, with objective response rates in TMB-H vs. non-TMB-H patients of 29% and 6%, respectively (Marabelle et al, The Lancet Oncology, 2020). This survey-based study aimed to evaluate awareness and utilization of TMB as a biomarker for I-O therapeutics among practicing community oncologists in the U.S. **Methods:** Questions related to awareness and utilization of TMB as a biomarker for I-O therapeutics were developed by two medical oncologists (AG and BF) and presented to community oncologists in a web-based survey prior to virtual meetings held between October and November 2020. Descriptive statistics were used to analyze the results. **Results:** Of the 193 participating providers geographically distributed across the U.S., 15% reported being unaware of either the concept of TMB in I-O therapy or how to use the information clinically. 39% of these providers reported testing $\leq$25% of patients with advanced cancer for TMB, including 8% who do not test for TMB at all. Misconceptions regarding TMB identified among participating providers included the belief that high TMB is considered to be $>$ 5 mut/Mb among 20% of providers, that TMB is essentially the same as MSI-high among 8% of providers, and that there are no therapies with FDA approval based on TMB among 15% of providers. Further, 37% of the participants did not identify pembrolizumab as an agent approved for the treatment of solid tumors based on TMB-H status. **Conclusions:** These findings demonstrate that there is a knowledge gap regarding the definition of TMB, testing for TMB, as well as implementation of TMB status in clinical decision making. Education directed towards community oncology providers regarding TMB and its use as a predictive biomarker for I-O therapy may improve its utilization and adoption in solid tumors to improve patient outcomes. Research Sponsor: Cardinal Health.

2609 **Poster Session**

Comprehensive genomic and transcriptomic profiling (CGTP) to predict pembrolizumab (P) benefit in patients (pts) with advanced solid tumors (STs).

Dan Rhodes, Daniel H Hovelson, Malek M. Safa, Mark E. Burkard, Eddy Shih-Hsin Yang, William Jeffery Edenfield, Travis Reeder, Hana Vakil, Kat Kwiatkowski, Khalis Mitchell, Bryan Johnson, Scott A. Tomlins; Strata Oncology, Ann Arbor, NC; Strata Oncology, Ann Arbor, MI; Kettering Cancer Center, Kettering, OH; University of Wisconsin Carbone Cancer Center, Madison, WI; University of Alabama at Birmingham, Birmingham, AL; Prisma Health Greenville Memorial Hospital, Greenville, SC

Background: P is approved in many ST types, however predictive biomarkers and the proportion of pts who benefit vary widely. Biomarkers beyond PD-L1 immunohistochemistry and comprehensive genomic profiling (CGP) based tumor mutation burden (TMB) may improve benefit prediction. We determined if treatment data and CGTP collected in an ongoing observational trial (NCT03061305) could predict pan-ST P benefit. **Methods:** Eligible advanced ST pts had QC-passing TMB and expression data from multiplex PCR based tissue CGTP on FFPE tissue (StrataNGS and an investigational test) and documented P treatment $>$ 1 month. Real-world time to next treatment (TTNT) was defined as time in months from therapy start to new therapy start (after stopping initial therapy) or death. TMB and gene expression biomarker association with P TTNT was evaluated. Backward stepwise regression was performed to fit a multivariate Cox proportional hazards model; pts were assigned to four score groups (IRS 1-4) based on overlapping TTNT curves from 8 equal bins. P TTNT were compared between IRS groups by log-rank test. A chemotherapy (C) comparator cohort was established from C TTNT for pts in this cohort. Results were stratified by ST type, P mono vs. C combo, and TMB status. **Results:** 610 pts (254 [41.6%] NSCLC; 356 [58.4%] from 23 other ST types) with CGTP and P treatment were identified; P TTNT was highly correlated to overall survival (n=146; Pearsons r^2=0.75). By univariate analysis of TMB and 9 expression biomarkers, TMB, two independent *PD-L1* expression amplicons, and *PD-L2* expression were significantly associated with P TTNT (all $p \leq 0.002$). The most significant multivariate model included 5 variables, with 1) increasing TMB, *PD-L1*, and *PD-L2*, and 2) decreasing *TOP2A* (proliferation) and *GZMA* as P TTNT predictors. Median P TTNT, but not C TTNT (345 courses from 254 pts), differed significantly by IRS group (Table). Median P TTNT by IRS group did not significantly differ by non-small cell lung vs. other ST type or P mono vs. C combo (both $p > 0.05$); excluding TMB-high patients, median P TTNT was still significantly longer in IRS groups 3/4 vs. 1/2 (p = 5.0e-4). Across 19,623 total evaluable pts in NCT03061305, 12.2% were in IRS groups 3/4 and outside of P approved ST types/TMB-low. **Conclusions:** CGTP in an observational trial cohort demonstrated that TMB, *PD-L1* and *PD-L2* independently predicted pan-ST P benefit as assessed by OS-validated TTNT. A multivariate CGTP signature predicted P benefit relative to C across ST types. If further validated, such a signature may enable improved P benefit prediction. P versus C TTNT by IRS group. Clinical trial information: NCT03061305. Research Sponsor: Strata Oncology.

	P			C				
IRS Group	n	%	Median TTNT	n	%	Median TTNT	HR (95% CI)	p-val
1	73	12%	7	66	19%	7	0.97 (0.65–1.47)	0.894
2	138	23%	8.7	111	32%	7	0.71 (0.52–0.98)	0.037
3	233	38%	13	112	32%	7	0.51 (0.38–0.69)	1.1E-05
4	166	27%	>24	56	16%	6	0.26 (0.17–0.4)	2.9E-09
	610	100%		345	100%			

HR - hazard ratio; log-rank P-value.

2610 **Poster Session**

YAP1 transcription factor expression to define subsets of cancers with T-cell inflamed phenotype in a pan-tumor analysis across 33 tumor types.

Bhakti Dwivedi, Andrey Ivanov, Guojing Zhang, Fadlo Raja Khuri, Suresh S. Ramalingam, Haian Fu, Gabriel Sica, Taofeek K. Owonikoko; Emory University Department of Biostatistics and Bioinformatics, Atlanta, GA; Emory University, Atlanta; The Winship Cancer Institute of Emory University, Atlanta, GA; Winship Cancer Institute, Atlanta, GA; Winship Cancer Institute of Emory University, Atlanta, GA; Emory University, Atlanta, GA; Department of Pathology, Winship Cancer Institute, Emory University, Atlanta, GA; Emory University Winship Cancer Institute, Atlanta, GA

Background: Immune checkpoint blockade (ICB) has become an established treatment option for the majority of solid tumors. PD-L1 expression, tumor mutation burden (TMB) and mismatch repair (MMR) deficiency are established but suboptimal predictive markers to select patients for ICB therapy. The identification of better predictive biomarkers to complement existing biomarkers is an area of need. We previously identified Yes Associated Protein 1 (YAP1) gene expression as a marker of inflamed tumor phenotype in small cell lung cancer. We sought to elucidate the role of YAP1 as a tumor agnostic biomarker of inflamed tumor phenotype. **Methods:** We obtained the publicly available TCGA normalized RSEM expression data (version dated September 29, 2019) from the GDC legacy archive (https://portal.gdc.cancer.gov/legacy-archive) for this analysis. We used the shinySISPA method (https://bbisr.shinyapps.winship.emory.edu/shinySISPA/) to classify the primary tumor samples into YAP1 high or low on the basis of the normalized expression profile for YAP1 gene. The T-cell–inflamed gene expression profile score for each sample was calculated as weighted sum of the normalized expression values of the 18 genes (*PSMB10, HLA-DQA1, HLA-DRB1, CMKLR1, HLA-E, NKG7, CD8A, CCL5, CXCL9, CD27, CXCR6, IDO1, STAT1, TIGIT, LAG3, CD274, PDCD1LG2, CD276*) as originally published in the Patent filed under WO201609437 and validated as a predictor of clinical efficacy in patients treated with anti PD1 immunotherapy drug, pembrolizumab. **Results:** A total of 11283 samples from 33 different histologic tumor types contained in the TCGA database were included in this analysis. A small but meaningful subset of cases 271 (2%) were classified as YAP1 high with a wide range in proportion of YAP1 high tumors of 0.67% to 12.09% across the 33 histologic tumor types. Adrenocortical, cholangiocarcinoma, chromophobe RCC, DLBCL, and mesothelioma had a high rate of YAP1 high tumors ($>$ 10% of cases). Overall trend showed a higher median interferon gamma GEP score in YAP1 high versus YAP1 low tumors with a GEP score of 11.2 vs. 10.7 respectively. A minority of histologic tumor subtypes (HNSCC, clear cell RCC, sarcoma, uterine carcinosarcoma, testicular GCT, melanoma, mesothelioma and ovarian cancer) showed a reverse trend of lower GEP score in association with YAP1 high status. Ongoing validation of these findings in an independent cohort of clinical samples and correlation of YAP1 status with other predictive biomarkers (TMB, PD-L1 and MSS status) will be presented at the meeting. **Conclusions:** YAP1 is highly expressed in a small but meaningful subsets of cancers and is associated with the inflamed phenotype in the majority of cancers. YAP1 expression is most common in rarer tumor types and in histologic types where currently available biomarkers have not been shown to predict the benefit of ICB. Research Sponsor: U.S. National Institutes of Health.

2611 **Poster Session**

Therapeutic effect of DDR pathway with different functional annotations for immune checkpoint inhibitor.

Wei Nie, Hua Zhong, Fengcai Wen, Ding Zhang, Shiqing Chen, Baohui Han; Shanghai Chest Hospital, Shanghai, China; Shandong Provincial Chest Hospital, Shanghai, China; 3D Medicines, Shanghai, China; The Medical Department, 3D Medicines Inc., Shanghai, China; Department of Pulmonary, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China

Background: DNA damage response and repair (DDR) pathway-related gene mutations have been reported to predict the efficacy of immune checkpoint inhibitor (ICI). However, therapeutic effect of DDR pathway with different functional annotations is not fully studied. Here we explore the relationship of DDR pathway with different functional annotations and clinical outcomes in public cohorts of immunotherapy and chemotherapy. **Methods:** Genetic testing and clinical outcomes data were obtained from the public clinical cohorts across 10 tumor types. 232 DDR pathway-related gene were assigned to eight pathway according to the literature. Nine predictive models for the mutation pathogenicity were included in the analysis, of which at least five returned positive results were defined as deleterious mutations. All annotations were according to the American College of Medical Genetics (ACMG) standards and guidelines. To explore the association between DDR pathways and ICI, DDR pathway mutation is grouped. Patients, who harbored mutations in two or more DDR pathways and meanwhile had deleterious mutation in at least one DDR pathway, were enrolled in group A. Patients, who harbored deleterious mutations in only one DDR pathway or had only uncertain significance mutations, were enrolled in group B. Patients with no DDR gene mutations were enrolled in Group C. We analyzed relation of the group and survival outcomes in four public cohorts. **Results:** Of 4 clinical cohort analyzed, the group A treated with ICI has the best PFS or OS outcomes. However, the comparison of group B and group C is not coincide across different cohorts. Treatment is the key factor that influents the relation of DDR pathway mutations and clinical outcomes. As shown in POPLAR/OAK cohort, patients in group C has the best PFS (p=0.0381) or OS (p=0.0350) outcome when treated with chemotherapy, but patients in group A has the best PFS (p=0.0083) or OS (p=0.0222) outcome when treated with ICI. **Conclusions:** When treated with ICI, patients with at least one deleterious mutation and another deleterious or uncertain significance mutation has the best PFS or OS outcomes, but not for chemotherapy. Our study suggested that DDR pathway with deleterious mutations might be a potential predictive factor for immunotherapy. Research Sponsor: None.

Cohort	PFS sorting	OS sorting
Oak poplar-chemotherapy	C vs A vs B (p=0.0381)	C vs A vs B (p=0.0350)
Oak poplar-ICI therapy	A vs C vs B (p=0.0083)	A vs C vs B (p=0.0222)
MSKCC-NSCLC	A vs B vs C (p=0.0003)	
MSKCC cohort	A vs C vs B (p=0.0090)	
Mskccmbdata-mutations-mskcc.hg19		A vs B vs C (p<0.0001)

First-in-human, phase I study of PF-06753512, a vaccine-based immunotherapy regimen (PrCa VBIR), in biochemical relapse (BCR) and metastatic castration-resistant prostate cancer (mCRPC).

Karen A. Autio, Celestia S. Higano, Luke T. Nordquist, Leonard Joseph Appleman, Tian Zhang, Xinhua Zhu, Hani M. Babiker, Nicholas J. Vogelzang, Sandip Prasad, Michael Thomas Schweizer, Stephane Billotte, Joseph Binder, Nora Cavazos, Ruifeng Li, Kam Chan, Helen Cho, Michael Dermyer, Robert Hollingsworth, Kenneth Alan Kern, Daniel P. Petrylak; Memorial Sloan Kettering Cancer Center, New York, NY; University of British Columbia, Vancouver, BC, Canada; Urology Cancer Center and GU Research Network, Omaha, NE; University of Pittsburgh Medical Center, Pittsburgh, PA; Duke Cancer Institute, Duke University, Durham, NC; Northwell Health Cancer Institute, Lake Success, NY; University of Arizona Cancer Center, Tucson, AZ; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Atlantic Medical Center, Morristown, NJ; University of Washington, Seattle, WA; Pfizer Inc., New York, NY; Yale University Cancer Center, New Haven, CT

Background: Therapeutic vaccines targeting PC-associated antigens represent attractive approaches in combination with immune checkpoint inhibitors (ICI). Safety/antitumor activity of PF-06753512 (PrCa VBIR) was evaluated in a phase I, dose-escalation and expansion study in patients (pts) with BCR prior to ADT and in pts with mCRPC either prior to or after failure of novel hormone therapy. PrCa VBIR consists of: 1) priming immunization with a replication-deficient adenoviral vector (AdC68) expressing PSA, prostate-specific membrane antigen and prostate stem cell antigen; 2) boosts with plasmid DNA (pDNA) encoding the same antigens by IM electroporation; 3) ICI given subcutaneously, including anti CTLA-4 antibody tremelimumab (TRM) and anti PD-1 antibody sasanlimab (SSL). **Methods:** AdC68 ± ICI(s) were given on months (mos) 1 and 5 and pDNA ± ICI(s) on mos 2–4 and 6–8. After 8 mos, maintenance pDNA + ICI(s) were given every 1 or 2 mos. In Part A (6 escalation cohorts), pts with mCRPC received AdC68 (4 or 6x10e11 viral particles) + pDNA 5 mg ± ICIs (TRM alone 80 mg; TRM 40 or 80 mg + SSL 130 or 300 mg). In Part B (3 expansion cohorts), pts with mCRPC received AdC68 6x10e11 + pDNA 5 mg + TRM 80 mg + SSL 300 mg; pts with BCR received similar vector and pDNA + TRM 80 mg ± SSL 130 mg. Primary objectives: Assess overall safety (CTCAE v4.03), determine expansion dose. Secondary objectives: Anti-tumor activity (RECIST v1.1, Prostate Cancer Working Group 3, PSA 50 response) and immune response. (Note: Database remains open, some queries pending). **Results:** As of Sept 15, 2020, 91 pts were treated in dose-escalation (n=38) and expansion (n=53; BCR=35, mCRPC=18). Immune responses (ELISpot) were positive in some pts. Grade (G) 3 or 4 treatment-related adverse events (TRAEs) developed in 38.5% (35/91) of pts. G5 TRAEs occurred in 2 pts (n=1 G4 myasthenia gravis + G5 pulmonary embolism; n=1 G5 myocarditis). irAEs were more frequent in BCR compared to mCRPC. See the table for efficacy data. **Conclusions:** Vaccination with PrCa VBIR had a manageable safety profile. TRAEs increased when 2 ICIs were given. Some pts with BCR experienced durable PSA-50 responses without ADT; patients with mCRPC had few objective tumor responses, but had prolonged median rPFS. PrCa VBIR appears to stimulate antigen-specific immunity and results in noticeable antitumor activity, particularly in androgen sensitive disease. Clinical trial information: NCT02616185. Research Sponsor: Pfizer.

Efficacy

mCRPC (N)	PSA-50 n, (%)	ORR (%) [95% CI]	rPFS, mos, median [95% CI]
AdC68+pDNA+TRM 80+SSL 300 (32)	2 (6.3)	9.4 [2, 25]	9.2 [2, not reached]
BCR (N)	PSA-50 n, (%)	Duration of PSA-50 response, mos median (range)	
AdC68+pDNA+TRM 80 (20)	5 (25.0)*	10.2 (6.9 – 24.9)	
AdC68+pDNA+TRM 80 +SSL 130 (15)	4 (26.7)	3.9 (1.9 – 4.2)	

*Associated with G1 hypopituitarism in 1 pt.

2613 **Poster Session**

Long term results from a phase 1 trial of GEN-009, a personalized neoantigen vaccine, combined with PD-1 inhibition in advanced solid tumors.

Maura L. Gillison, Mark M. Awad, Przemyslaw Twardowski, Ammar Sukari, Melissa Lynne Johnson, Mark N. Stein, Richard Hernandez, Jessica Price, Kevin J. Mancini, Mara Shainheit, Vijetha Vemulapalli, Jessica Flechtner, Thomas A. Davis, Roger B. Cohen; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital, Cambridge, MA; City of Hope, Duarte, CA; Karmanos Cancer Institute, Wayne State University, Detriot, MI; Sarah Cannon Research Institute, Nashville, TN; Columbia University Medical Center, New York, NY; Genocea, Cambridge, MA; Genocea Biosciences, Waltham, MA; Genocea Biosciences, Cambridge, MA; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background: GEN-009 is an adjuvanted personalized cancer vaccine containing up to 20 neoantigens selected by ATLAS, an *ex vivo* bioassay screening autologous T cells for immune responses against both neoantigens as well as Inhibigens. Inhibigen-specific T cells suppress immunity and have been shown to accelerate tumor progression in mice and are avoided in GEN-009. In cohort A, all patients immunized in the adjuvant setting with GEN-009 monotherapy developed immune responses. Nearly all (99%) of selected peptides were immunogenic: *ex vivo* $CD4^+$ and $CD8^+$ fluorospot responses specific for 51% and 41% of immunized peptides, respectively. Seven of 8 patients continue without progression with a median follow up of 18 months. **Methods:** GEN-009 is being evaluated in patients (pts) with advanced cancer who received standard-of-care (SOC) PD-1 inhibitor as monotherapy or in combination therapy during vaccine manufacturing. Five vaccine doses were administered over 24 weeks in combination with a PD-1 CPI. Patients who progressed prior to vaccination received alternative salvage therapy followed by GEN-009 in combination. Peripheral T cell responses were measured by fluorospot assays in *ex vivo* and *in vitro* stimulation. **Results:** 15 pts received GEN-009 in combination with a PD-1 inhibitor; 1 patient received GEN-009 monotherapy. Median number of neoantigens per vaccine was 14 (5-18). GEN-009-related adverse events were limited to vaccine injection site reactions and mild myalgias or fatigue. Longitudinal evaluation of *ex vivo* T cell responses revealed that sequential vaccination with GEN-009 had an overall additive effect on the robustness of IFNγ secretion and responses were persistent for at least 6 months in some patients. Epitope spread was detected in CPI sensitive patients, but not in CPI refractory patients receiving salvage therapy. Three patients who responded to PD-1 inhibition followed by disease stabilization then demonstrated further reduction after GEN-009 vaccination that could represent vaccine effect. Eight of 9 CPI responsive patients are progression-free from 3 to 10 months after first vaccine dose. Four of 7 CPI refractory patients have experienced unexpected prolonged stable disease after vaccination of up to 8 months after vaccination. 2 of 2 patients with available samples lost all evidence of circulating tumor DNA including non-targeted neoantigens. **Conclusions:** Vaccination with GEN-009 in combination with anti-PD-1 CPI in patients with advanced solid tumors shows little additive toxicity. Preliminary data demonstrate induction of broad neoantigen-specific immune responses and epitope spreading in the presence of PD-1 CPI. Broad immunity against tumor specific targets and encouraging patient outcomes support further study. Clinical trial information: NCT03633110. Research Sponsor: Genocea Biosciences.

2614 **Poster Session**

Phase I trial to determine safety and immunogenicity of amplivant, a synthetic toll-like receptor 2 ligand, conjugated to two HPV16 E6 synthetic long peptides.

Frank M. Speetjens, Marij JP Welters, Marije Slingerland, Peggy de Vos van Steenwijk, Inge C.F.M. Roozen, Sanne Boekestijn, Nikki Loof, Gijs G Zom, Rob Valentijn, Willem-Jan Krebber, Cornelis JM Melief, Dmitri V Filippov, Hans Gelderblom, Sjoerd H van der Burg, Ferry Ossendorp; Leiden University Medical Center, Department of Medical Oncology, Leiden, Netherlands; Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, Netherlands; Department of Immunology, Leiden University Medical Center, Leiden, Netherlands; Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, Netherlands; ISA Pharmaceuticals B.V., Leiden, Netherlands; Leiden Institute of Chemistry, Leiden University, Leiden, Netherlands; Department of Medical Oncology, Oncode Institute, Leiden University Medical Center, Leiden, Netherlands

Background: Therapeutic vaccines based on synthetic long peptides (SLPs) have a great potential for immunotherapy of cancer patients as these SLPs include both human leukocyte antigen (HLA) class I and II epitopes and no patient selection for HLA types is required. The antigen-induced immune response can be strengthened with immune stimulating additives. Amplivant (AV) is a synthetic Toll-like receptor 2 ligand which can be directly conjugated to tumor peptide antigens. In preclinical studies, AV-conjugation to antigens led to both enhanced antigen presentation by dendritic cells and T-cell priming and caused superior induction of effective anti-tumor responses. Moreover, AV-conjugated SLPs showed a 100 times higher immune response compared to unconjugated SLP. The current study is a first-in-human trial to investigate safety and immunogenicity of AV-conjugated human papillomavirus (HPV)16-SLPs. **Methods:** A dose escalation phase I trial was performed in 24 patients with HPV16 positive (pre-) malignant lesions. AV was conjugated to two SLPs derived from the most immunodominant regions of the HPV16 E6 oncoprotein. Four dose groups (1, 5, 20 or 50 μg of each peptide) in 6 patients each were studied. The vaccine was injected three times intradermally in DMSO / water with a three-week interval. Adverse events (AE) were collected according to CTCAE v4.0 up to 26 weeks. Peptide-specific T-cell immune responses were determined in blood samples taken before and after vaccination using complementary immunological assays (proliferation assay, IFNγ-ELISPOT and cytokine bead array). **Results:** Toxicity after three AV-conjugated HPV16-SLP vaccinations was limited to CTCAE grade 1 or 2, with predominantly inflammation at the vaccination site and sometimes flu-like symptoms, which generally resolved within one day. Dose increase resulted from no AE in the lowest dose group to mild/moderate AE in all vaccinated persons in the highest dose group. In the lowest dose group, minor vaccine-induced T-cell responses were observed in three of six vaccinated persons. In the highest dose group, all patients displayed a strong HPV16-specific T-cell response after vaccination. The induced T-cell response against HPV16 lasted until the end of the trial. **Conclusions:** This first-in-human study showed that AV conjugated to SLPs can safely be used as an intradermal therapeutic vaccine. AV-conjugated HPV16-SLP was able to induce robust HPV16-specific T-cell immunity in patients treated for HPV16 positive (pre-) malignancies without any other vaccine adjuvant or formulation. Increase in dose resulted in both a higher number of mild adverse events as well as stronger T-cell immunity. Clinical trial information: NCT02821494. Research Sponsor: None.

2615 **Poster Session**

A phase 1b study of personalized neoantigen vaccine plus pembrolizumab in adults with advanced cancer.

Aaron Miller, Zeynep Kosaloglu-Yalcin, Luise Westernberg, Leslie Montero, Milad Bahmanof, Angela Frentzen, Ashmitaa Logandha Ramamoorthy Premlal, Jason Greenbaum, Gregory Seumois, Roxanne Habbaba, Amanda Natsuhara, Kim McConnell, Elaine Eng, Alessandro Sette, Bjoern Peters, Stephen Philip Schoenberger, Ezra E.W. Cohen; UCSD Moores Cancer Center, La Jolla, CA; La Jolla Institute for Immunology, La Jolla, CA

Background: Neoantigens (NeoAg) are key targets for personalized immunotherapy but efficient methods for their systematic identification and therapeutic targeting remain elusive. We developed a methodology to reliably identify and verify somatic alteration-derived neoantigens based on natural T cell responses against them which formed the basis of an individualized therapeutic vaccine strategy. **Methods:** This is a phase Ib study to assess the immunogenicity, safety and early clinical activity of personalized synthetic long peptides (PSLP) cancer vaccines in combination with pembrolizumab for patients with treatment refractory metastatic solid tumors or PSLP vaccine alone as an adjuvant treatment with patients with no evidence of disease (NED) that incorporates patient-specific NeoAg identified by an HLA-agnostic, functional T-cell assay (see table). **Results:** At the time of data cutoff, a total of 5 patients had been treated on ARM-A, 5 patients on ARM-C and 2 patients on ARM-D. AES possibly attributed to personalized vaccine (PSLP), or pembrolizumab, or both include: Grade 1: Arthralgia (1); Diarrhea (1); Fever (4); Fatigue (7); Generalized muscle weakness (1); Headache (2); Nausea (1); Confusion (1); Injection site reaction (5); Rash maculo-papular (3); Flu like symptoms (5); Myalgia (1); and Grade 2: Diarrhea (1); Fatigue (1); Hyperhidrosis (1); Hypothyroidism (1); Injection site reaction (1); Proteinuria (1); Renal and Urinary – other (1); and Grade 3: Colitis (1). For the 9 patients with at least 1 radiographic assessment at the time of analysis 6 had a best response of stable disease (SD) and 3 had progressive disease (PD). Immune monitoring of peripheral blood specimens consistently demonstrated that NeoAg-specific T cell responses were enhanced following administration of PSLP vaccine. On-treatment biopsies demonstrated immune-editing with the variant allele frequency of targeted mutations decreasing following administration of the PSLP vaccine. **Conclusions:** Taken together, these data meet the trial primary endpoint by demonstrating PSLP vaccines targeting NeoAg identified using the HLA-agnostic pipeline augment effector T cell function against these targets. Clinical trial information: NCT02287428. Research Sponsor: None.

ARM	PSLP	Adjuvant	Vaccinations	Pembrolizumab
A	5 NeoAg (max)	Montanide	3 doses SQ every 3 weeks	200 mg every 3 weeks
C	24 NeoAg (max)	Hiltonol	3 weekly IM doses then 6 doses every 3 weeks	200 mg every 3 weeks
D	24 NeoAg (max)	Hiltonol	3 weekly IM doses then 6 doses every 3 weeks	None

2616 **Poster Session**

A phase 1 study of an off-the shelf, multi-neoantigen vector (ADXS-503) in subjects with metastatic non-small cell lung cancer (NSCLC) progressing on pembrolizumab as last therapy.

Missak Haigentz, Suresh S. Ramalingam, Gregory James Gerstner, Balazs Halmos, Neil Morganstein, Surya Vangala, Megan Parsi, Victor Kabala, Dinesh Simkhada, Cristiane Metran, ANDRES A. GUTIERREZ, Jonathan Wade Goldman; Atlantic Health System Cancer Care, Morristown, NJ; Winship Cancer Institute of Emory University, Atlanta, GA; Illinois Cancer Care, Peoria, IL; Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY; Advaxis, Inc., Princeton, NJ; Advaxis Inc, Princeton, NJ; IQVIA Biotech, Missisauga, ON, Canada; Advaxis Inc, New Jersey, NJ; University of California, Los Angeles, CA

Background: ADXS-503 (A503) is an off-the-shelf, attenuated Listeria monocytogenes (Lm)-based immunotherapy bioengineered to elicit potent T cell responses against 22 tumor antigens commonly found in NSCLC (i.e., 11 hotspot mutations and 11 tumor-associated antigens, TAAs). Pembrolizumab (Pembro) is a programmed death receptor-1 (PD-1)- blocking antibody approved for the treatment of advanced lung cancer. A503 and Pembro have complementary mechanisms of immune activation and reversal of immune tolerance. **Methods:** A phase 1 study of A503 ± Pembro has been conducted in patients (pts) with metastatic squamous or non-squamous NSCLC. In dose-escalation part B, A503 was added-on to Pembro within 12 weeks of the first scan showing disease progression per RECIST criteria v1.1. Both, A503 (1 x10^8 CFU) and Pembro (200 mg) were infused by IV every 3 weeks until disease progression or limiting toxicity. The dose-escalation cohort has established safety, tolerability and immunogenicity of the combination therapy and it has been further expanded to evaluate efficacy (Goldman JW *et.al.*, SITC 2020). **Results:** Nine pts have been treated and evaluated in Part B. Pembro + A503 combo has been well tolerated and without immune related AEs. Of the nine evaluable pts, one has achieved partial response (PR) and 3 stable disease (SD), yielding an overall response rate (ORR) of 11% and disease control rate (DCR) of 44%. Two patients have had clinical benefit for over 12 months (i.e., one PR and one SD) and both of them had been on Pembro therapy for 2 years before enrollment. The two other pts with SD have sustained it for almost 6 months thus far. Seven pts have been evaluated for immunogenicity. In all pts there was a transient release of pro-inflammatory cytokines and proliferation of cytotoxic- and memory-CD8+ T cells. Seven evaluable pts had antigen-specific T cells within 1-2 weeks after starting therapy and 4/7 showed antigen spreading. **Conclusions:** ADXS-503 as an add-on therapy to Pembro at disease progression has been well tolerated and it has induced antigen specific-T cell responses and durable disease control in 44% of pts. Part B cohort is currently enrolling additional pts to further explore the potential reversal of Pembro resistance with ADXS-503. Clinical trial information: NCT03847519. Research Sponsor: ADVAXIS INC.

2617 **Poster Session**

A phase 1 open label trial of intravenous administration of MVA-BN-Brachyury vaccine in patients with advanced cancer.

Peter Joseph DeMaria, Katherine Lee-Wisdom, Ravi Amrit Madan, Fatima Karzai, Renee Nicole Donahue, Claudia Palena, Caroline Jochems, Charalampos S. Floudas, Julius Strauss, Jennifer L. Marte, Jason Redman, Houssein Abdul Sater, Borys Korchin, Tatiana Adams, Guenter Silbernagl, Cesar Pico-Navarro, Jeffrey Schlom, James L. Gulley, Marijo Bilusic; Genitourinary Malignancy Branch, NCI, NIH, Bethesda, MD; Genitourinary Malignancies Branch, NCI, NIH, Bethesda, MD; Laboratory of Tumor Immunology and Biology, NCI, NIH, 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; Bavarian Nordic GmbH, Martinsried, Germany

Background: Brachyury is a member of the T-box family of transcription factors which is overexpressed in several tumor types and has been associated with treatment resistance, epithelial to mesenchymal transition and metastatic potential. MVA-BN-Brachyury vaccine is a vector-based therapeutic cancer vaccine which demonstrated immunogenicity and safety in previous clinical trials. Preclinical studies suggested that IV administration of vaccines can induce superior CD8 + T-cell responses as compared with SC or IM routes. This is the first-in-human study to evaluate safety and tolerability of IV administration of this vaccine. **Methods:** Patients with metastatic or unresectable locally advanced malignant solid tumors were treated with MVA-BN-Brachyury vaccine in a phase 1, open-label, 3+3 dose-escalation study. Eligible patients received a total of three vaccine doses intravenously Q3W at $1x10^7$ (DL1), $1x10^8$ (DL2), or $1x10^9$ infections units (Inf.U) (DL3). Patients were admitted for 48 hours for observation after each dose and had imaging at baseline and 1 and 3 months after the last vaccine dose. Primary objective was to determine the safety and tolerability and establish the recommended phase 2 dose (RP2D). Immune assays were performed in the first 10 enrolled patients. **Results:** In 13 patients (10 chordoma, 1 small cell breast, 1 prostate, 1 colorectal cancer), no dose-limiting toxicities were observed. Right upper quadrant abdominal pain was the only grade 3 TRAE. All other TRAEs were grade 1 or 2; most common was cytokine release syndrome (four grade 2 and one grade 1. As of Feb 2021, 9 patients completed treatment and two planned restaging scans: 5 patients had PD (3 in DL1 and 2 in DL2), 3 had SD (2 in DL2 and 1 in DL3) and 1 had PR (DL3) as their best treatment response per RECIST 1.1. One patient with advanced sacral chordoma had significant reduction of ulcerated skin metastases after 2 doses, followed by 33% shrinkage at the end of trial. Two chordoma patients with SD reported significant pain improvement. Multifunctional Brachyury, CEA, and MUC1 specific T cells were increased after vaccination in in 60%, 67%, and 50% of patients, respectively. **Conclusions:** MVA-BN-Brachyury IV vaccine is safe across all tested dose levels and suggesting activity in chordoma at DL3 for which this vaccine was granted FDA orphan drug designation. Mild cytokine release syndrome (rigors, chills, fever and hypotension) has been observed in 5 patients and managed with IV fluids and steroids in 2 patients. A dose 1×10^9 Inf.U (DL3) was selected for RP2D based upon available safety data. Further research is pending to evaluate clinical benefit and immunogenicity. Clinical trial information: NCT04134312. Research Sponsor: U.S. National Institutes of Health, CRADA with Bavarian Nordic, Inc.

Long-term follow up of patients with mesothelioma treated with dendritic cell therapy in three phase I trials.

Daphne W Dumoulin, Robin Cornelissen, Koen Bezemer, Sara Baart, Joachim Aerts; Department of Pulmonary Medicine, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, Netherlands; Department of Pulmonary Medicine, Erasmus MC Rotterdam, Rotterdam, Netherlands; Department of Pulmonary Medicine, Erasmus University Medical Center, Rotterdam, Netherlands; Erasmus MC, Rotterdam, Netherlands

Background: Immunotherapy targeting PD-(L)1 has become indispensable in the treatment of many malignant tumors. Recently, checkpoint inhibition using anti-PD-1 in combination with anti-CTLA-4 was proved to be effective in patients with malignant pleural mesothelioma (MPM). However, the minority of patients benefit from this treatment. The lack of immunotherapy efficacy in the majority of patients with mesothelioma can be explained by the fact that mesothelioma is a tumor with an immune-desert phenotype, meaning a non-inflamed tumor characterized by low T-cell infiltration. By administration of dendritic cells (DCs), which were cultured, activated, and exposed to antigens ex-vivo, this immune-desert phenotype might be turned into an inflamed phenotype. Previously, we performed and published three phase I trials using activated DCs, which support this concept. Here, we report the long-term survival of the patients treated with DCs in these three phase 1 studies. **Methods:** We collected the survival data of the phase 1 trials using DC therapy in patients with MPM. In the first two trials, DCs loaded with autologous tumor lysate were used, while in the third allogeneic tumor lysate was used to load the DCs (Mesopher). **Results:** Between 2006 and 2015, in the three studies combined, 29 patients with MPM were treated with DC vaccination. At data cut-off, the median OS was 27 months (95% confidence interval (CI): 21 – 47 months). OS at 2 years was 55.2% (95% CI: 39.7%-76.6%), OS at 5 years was 20.7% (95% CI: 10.1%-42.2%). **Conclusions:** The long-term follow up of MPM patients treated with DC vaccination in the three separate phase 1 trials show a promising signal, with a 2-year OS of over 50% and a 5-year OS of over 20%. In addition, 2 patients are alive after 10 years of treatment. In our opinion, these findings show the potency of DC vaccination therapy in long-term activation of the immune system. DC vaccination therapy in patients with MPM is currently being investigated in a large, randomized phase II-III trial (NCT03610360) and in pancreatic cancer. Additional biomarker studies, as well as treatment combinations with for example ICI, could further improve the outcomes of DC-vaccination therapy. Clinical trial information: NCT02395679. Research Sponsor: Dutch Cancer Society (to KWF) and ZonMW (grant number 95104006).

Overall survival analysis based on the Kaplan Meier curves.

	Median OS (95% CI)	OS – 2 years (95% CI)	OS – 5 years (95% CI)
Overall	27 months (21 - 47)	55.2% (39.7% - 76.6%)	20.7% (10.1% - 42.2%)
Study 1	15 months (15 - Inf)	20.0% (5.8% - 69.1%)	10.0% (1.6% - 64.2%)
Study 2	26 months (20 - Inf)	60.0% (36.2 – 99.5%)	30.0% (11.6% - 77.3%)
Study 3	31 months (28 - Inf)	88.9% (70.6% - 100%)	22.2% (6.6% - 75.4%)

2619 **Poster Session**

Final report and long-term outcomes: Phase I trial of a HER2 intracellular plasmid-based vaccine in HER2+ advanced stage breast cancer.

Mary L. Disis, Yushe Dang, Andrew L. Coveler, Doreen Higgins, Jennifer Childs, Lupe G Salazar; University of Washington, Seattle, WA; Seattle Cancer Care Alliance/University of Washington, Seattle, WA

Background: Vaccination with the intracellular domain (ICD) of HER2 in pre-clinical models is both immunogenic and protective against the development of mammary tumors. This study (NCT00436254) was designed to examine the safety and optimal immunogenic dose of a DNA-based vaccine encoding the HER2 ICD in subjects with HER2+ breast cancer. **Methods:** Sixty-six patients with stage III or IV HER2 + breast cancer in remission or with stable bone only disease were enrolled into three vaccine arms: 1 (10mcg dose of plasmid), 2 (100mcg) and 3 (500mcg). Vaccines were administered i.d. monthly for three immunizations. Endpoints included safety and optimal dose. HER2 specific IFN-gamma immune responses were evaluated and DNA persistence at the vaccine site was assessed. Toxicity and clinical outcomes were followed for 10 years. **Results:** The majority of vaccine-related toxicity was grade 1 (89%) and grade 2 (11%) and was not significantly different between the three dose arms. All Arms developed HER2 ICD immunity after vaccination, however, patients in Arm 2 and Arm 3 had significantly better immune responses (of higher magnitude and at most time points) than patients in Arm 1 ($p=0.003$ and $p<0.001$, respectively) after adjusting for baseline factors. At 60 weeks, the number of patients who maintained the greatest fold-difference in HER2 ICD immune responses from their baseline was highest in Arm 2 (73%) when compared to Arm 1 (47%) and Arm 3 (45%). Associations between ICD responses and plasmid DNA persistence at the vaccine site were estimated via linear regression models. HER ICD immunity after the end of immunizations, relative to baseline, was significantly lower in patients with DNA persistence at week 16 compared to those without persistence ($p=0.02$). Patients at the highest dose demonstrated the greatest incidence of plasmid persistence (92%) as compared to 33% in Arm 1 and 10% in Arm 2. The median time of follow-up was 118.6 months (Arm 1), 99.7 months (Arm 2), and 73.5 months (Arm 3). The median OS and PFS has not been reached in any Arm and did not differ with respect to treatment arm (Log-rank p-value 0.36 for OS, and 0.63 for PFS). However, we observed a separation of Kaplan-Meier curves for OS from about 40 months and curves for PFS from about 30 months, and the separation maintained until the end of the study for Arm 2 versus Arm 1 and Arm 3. One patient in Arm 2 developed lymphocytic colitis 2.2 years from enrollment deemed possibly related to vaccination. **Conclusions:** An intermediate dose (100mcg) of vaccine was immunogenic and associated with persistence of immunity at 60 weeks. A randomized phase II trial of the HER2 ICD plasmid-based vaccine in the neoadjuvant setting is in development. Clinical trial information: NCT00436254. Research Sponsor: U.S. National Institutes of Health.

2620 **Poster Session**

A phase I clinical trial investigating the telomerase vaccine UV1 in combination with pembrolizumab in patients with advanced melanoma.

Yousef Zakharia, Steven O'Day, Wenche Rasch, Mohammed M. Milhem; University of Iowa and Holden Comprehensive Cancer Center, Iowa City, IA; John Wayne Cancer Institute Providence Saint John's Health Center, Santa Monica, CA; Ultimovacs ASA, Oslo, Norway; University of Iowa Hospitals and Clinics, Iowa City, IA

Background: UV1, a telomerase peptide-based vaccine, consists of 3 long peptides (15-30 aa) representing a 54 aa sequence in the catalytic unit of the reverse transcriptase subunit of telomerase (hTERT). UV1 contains both CD4 and CD8 epitopes, and immunogenicity is shown in 78% of HLA unselected patients (pts.) in prior studies. UV1 induced expansion of hTERT specific CD4+ T cells that might be relevant in tumors expressing telomerase, theoretically enabling enhanced checkpoint efficacy in pts. with insufficient spontaneously primed T cells. Reciprocally, checkpoint inhibitor may support the UV1-induced T cells and provide increased effector activity, as these cells may be restricted by intrinsic and tumor-induced suppressor mechanisms. **Methods:** UV1 was combined with standard of care pembrolizumab in pts. with advanced melanoma. The primary objective of this phase I, multicenter study (NCT03538314), was to evaluate safety and tolerability of UV1 in combination with standard pembrolizumab. Secondary objective was evaluation of response rate (RR) according to iRECIST. Pts. received, in a serial manner, adjuvant GM-CSF and UV1 (300μg) intradermally followed by pembrolizumab. The first 3 UV1/GM-CSF doses were given during week 1, and from week 2 in combination with pembrolizumab (Q3W). Two different doses of GM-CSF were investigated: 37.5μg (20 pts. cohort 1) and 75μg (10 pts. cohort 2). Totally 8 UV1/GM-CSF vaccinations per pt. were planned (14 weeks). **Results:** In total 30 pts. were enrolled; cohort 1 (N = 20); cohort 2 (N = 10). The abstract reports cohort 1 results. The majority of adverse events (AEs) reported was grade 1 or 2 (48%, 41%). Main AEs were fatigue (8%), injection site reaction (5%), diarrhea (4%) and pyrexia (3%). 18% and 30% of AEs were possibly/definitely related to UV1 or pembrolizumab, respectively. Three patients experienced SAE, one (inflammatory arthritis) was considered possibly related to UV1. No severe allergic reactions were observed. Pembrolizumab was continued after completion of UV1 treatment in 14 pts. for a mean of 8.2 months (range 3-21). Four pts. discontinued pembrolizumab due to PD, one for irAE and one for unknown reason. The RR was 60%, with 5 CRs, and the 1-year survival rate 85 %. **Conclusions:** Results from cohort 1 (N = 20) show that the treatment of UV1 together with pembrolizumab was safe and well tolerated in patients with advanced melanoma. Updated data with minimum 18 months follow-up will be presented at the conference. Cohort 2 results will be presented at a later stage. Clinical trial information: NCT03538314. Research Sponsor: Ultimovacs ASA.

Male /female	13/7
Median age (range)	70 (31-82)
ECOG 0/1	15/5
Stage IIIb, IIIc, IV	2 /8 /10
Elevated LDH	5
UV1/GM-CSF doses (pts.)	8 (17) 7 (2) 6 (1)
RR*	5 iCR (25%) 7 iPR (35%) 1 iSD (5%) 7 iUPD/iCPD (35%)
Survival rate*	80%
mPFS (1 yr.)	NR

*Median follow-up 18.3 months.

2621 **Poster Session**

Adverse effects of COVID-19 vaccination among cancer patients: Results from an Internet-based survey.

Brian Loew, Richard Tsai, John Hervey, Kathleen D. Hoffman, John Novack, Jennifer Johnson, Don S. Dizon, Stuart L. Goldberg; Inspire, Arlington, VA; Lifespan Cancer Institute and Brown University, Providence, RI; Hackensack Meridan School of Medicine, Nutley, NJ

Background: The rapid development of safe and effective vaccines against SARS-CoV-2 may stem the global COVID-19 pandemic. However, since individuals with cancer were under-represented during clinical vaccine trials, experience with COVID-19 vaccines among cancer patients is limited. **Methods:** An internet-based survey was conducted January 15 - February 10, 2021 among members of the Inspire online health community. The 63-item survey was emailed to members of the Inspire community who had opted-in for research. **Results:** Out of 19,152 respondents, 4895 (25%) self-reported a cancer diagnosis. Of these, 1337 (27%) were receiving active therapy. Cancer respondents were 66% female, 77% white, 44% college educated, with a median age range 55-65 years. 88% had solid tumors and 12% hematologic malignancies. 241 (5%) had prior COVID-19 and 148 (3%) thought they had had it but were not tested. Among cancer patients with COVID-19 approximately 30% reported ongoing late symptoms. At the time of survey, 1335 (27%) cancer patients had received a COVID-19 vaccine (Moderna 51% Pfizer-BioNTech 46%, Astra-Zeneca 3%, Other/unknown >1%). Following the first injection, 63% had local adverse events (AEs): injection site pain (51%), swelling (8%), redness (6%), and itching (4%). 34% reported systemic AEs including myalgia (32%), fatigue (18%), headache (12%), joint pain (5%), and chills (5%). 199 (15%) had received the second (booster) vaccination. 76% reported local AEs including pain (69%), swelling (14%), itching (8%), and redness (7%). 67% reported systemic AEs including fatigue (49%), myalgia (30%), headache (29%), chills (23%), fever (16%), joint pain (15%), and nausea (12%). AEs were comparable to the clinical trial results obtained from the general population (fda.gov/media/144245/download & 144434/download). **Conclusions:** In this internet-based survey drawn from the Inspire online health community 1335 cancer patients reported receiving COVID-19 vaccinations. By self-report the vaccines were well tolerated with AEs patterns mimicking clinical trial results conducted in the general population. These safety results should be reassuring to cancer patients although attention to COVID-19 vaccine efficacy is required (and will be studied during follow-up surveys). Research Sponsor: Inspire.

	Pfizer clinical trial	Moderna clinical trial	Cancer with Pfizer	Cancer with Moderna
First dose local AEs	79%	84%	58%	68%
First dose systemic AEs	59%	55%	36%	33%
Second dose local AEs	73%	89%	73%	79%
Second dose systemic AEs	70%	79%	60%	74%

Risk factors for immune mediated adverse events with immune checkpoint inhibitors.

Ari Pelcovits, Hetal Mistry, Rani Chudasama, Sarah Andrea, Humera Khurshid; Brown University, Providence, RI; Boston Medical Center, Boston, MA; Lifespan Biostatistics Core, Providence, RI; Rhode Island Hospital-The Warren Alpert Medical School of Brown University, Providence, RI

Background: Immune checkpoint inhibitors (ICIs) are associated with unique toxicity - immune-related adverse events (irAEs). irAEs are common, occurring in nearly 30 % of patients (pts) in clinical trials. Risk factors for irAEs remain largely unknown, with limited evidence to guide risk stratification for these pts. **Methods:** In this historical cohort study, we identified 400 pts receiving ICIs at our institution between 1/1/2015 - 12/31/2019 and followed them until progression, death, or study end date. Using modified Poisson and multinomial logistic regression we assessed irAEs (yes/no; none/grade 1-2/grade 3-4) as a function of independent risk factors in separate models. These included age, PDL-1%, steroid use in the 2 weeks (S2wks) prior to ICI, concurrent chemotherapy, combination ICI use, and pre-ICI creatinine (Cr) and absolute lymphocyte count. We constructed sample weights using sociodemographic and clinical factors to account for confounding by indication and mortality-related censoring. **Results:** 367 pts (median age: 68 yrs) had complete data for analysis comprising 55% men and 89% white. 111 (31%) experienced an irAE during the study period (median time to first event: 81 days). Risk was greatest for the youngest and oldest pts on ICI. In weighted models, Pts $\leq$59 yrs were 3 times as likely to experience an irAE relative to those aged 60-68 (95% CI: 1.18,7.41; Table). Additionally, for each 1 unit increase in Cr, risk of irAE increased by 19% (95% CI: 1.08,1.28). Precision of weighted estimates was impacted by limited pt comparability across factors of interest and overall sample size. While not statistically significant (RR: 2.04;95% CI:0.92,4.53) 70.6% of pts on combination ICIs experienced an irAE compared with 20.3% on one ICI. Similarly, while not statistically significant, 15.4% of pts with PDL-1 $>$49% experienced a grade 3/4 irAE compared with 7.7% of pts with PDL-1$<$1%. **Conclusions:** In this real-world analysis of irAEs, younger age and elevated creatinine were risk factors for development of irAEs. Further research leveraging larger data sources is needed to examine PDL-1% as a potential risk factor of irAE. Research Sponsor: None.

	irAE vs. No irAE[1] RR (95% CI)	Grade 1/2 irAE vs. No irAE[2] OR (95% CI)	Grade 3/4 irAE vs. No irAE[2] OR (95% CI)
Age (Ref: 60-68 yrs) 27-59 yrs	**2.95 (1.18,7.41)**	7.42 (0.83,66.10)	1.55 (0.31,7.83)
69-76 yrs	1.40 (0.77,2.57)	1.26 (0.51,3.12)	2.29 (0.56,9.44)
77-93 yrs	1.33 (0.71,2.50)	1.37 (0.55,3.44)	2.18 (0.66,7.30)
PDL-1 (Ref <1%)	1.36	1.22 (0.40,3.73)	2.67 (0.62,11.46)
1-49%	(0.70,2.64)		
>49%	2.27 (0.98,5.26)	5.08 (0.66 (38.96)	1.59 (0.38,6.59)
Initial Cr	**1.18 (1.08,1.28)**	**1.54 (1.05,2.27)**	0.92 (0.38,2.19)
Concurrent Chemotherapy (Ref: No)	0.73 (0.34,1.60)	0.77 (0.22,2.72)	0.42 (0.14,1.22)
S2wks (Ref: No)	1.00 (0.61,1.65)	0.69 (0.24,1.98)	1.90 (0.76,4.75)
Combination ICIs (Ref: One ICI)	2.04 (0.92,4.53)	2.27 (0.27,18.84)	7.08 (0.88,56.67)

[1]Weighted modified Poisson. [2]Weighted multinomial logistic.

2623 **Poster Session**

Safety, pharmacokinetics, efficacy, and preliminary biomarker data of first-in-class BI 765063, a selective SIRPα inhibitor: Results of monotherapy dose escalation in phase 1 study in patients with advanced solid tumors.

Stéphane Champiat, Philippe A. Cassier, Nuria Kotecki, Iphigenie Korakis, Armelle Vinceneux, Christiane Jungels, Jon Blatchford, Mabrouk M. Elgadi, Nicole Clarke, Claudia Fromond, Nicolas Poirier, Berangere Vasseur, Aurelien Marabelle, Jean-Pierre Delord; Gustave Roussy Cancer Campus, Department of Drug Development (DITEP), Villejuif, France; Centre Léon Bérard, Lyon, France; Institut Jules Bordet, Bruxelles, Belgium; Department of Oncology, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France; Departement of Medical Oncology, Centre Léon Bérard, Lyon, France; Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany; Boehringer Ingelheim (Canada) Ltd./Ltée, Burlington, ON, Canada; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim Am Rhein, Germany; OSE Immunotherapeutics, Paris, France; OSE Immunotherapeutics, Nantes, France; Institut Claudius Regaud IUCT-Oncopole, Toulouse, France

Background: BI 765063 is a humanized IgG4 monoclonal antibody antagonist of SIRPα (Signal Regulatory Protein α), which blocks the don't eat me signal of the SIRPα/CD47 axis, a critical innate immune checkpoint. SIRPα is expressed on myeloid cells. BI 765063 binds to the V1 SIRPα allele with high affinity and to the V2 SIRPα allele with low affinity. BI 765063 lacks SIRPγ binding to preserve T-cell activation. We report results of the completed BI 765063 monotherapy dose escalation in patients with advanced solid tumors. **Methods:** This study involves a step 1 dose escalation to determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD), then a step 2 dose-confirmation expansion at recommended phase 2 dose. In Step 1, BI 765063 ascending doses, given IV every 3 weeks, were tested using a Bayesian Logistic Regression Model (BLRM) approach with overdose control. The endpoints were safety, pharmacokinetics, receptor occupancy (RO) in peripheral $CD14^+$ monocytes and efficacy (RECIST 1.1). **Results:** Fifty patients (26 V1/V1, 24 V1/V2) received at least one dose of BI 765063. The most frequent tumors were ovarian (9), colorectal (8), lung (5), breast (4), melanoma (3), and kidney (3). No DLTs were reported up to the highest dose tested. MTD was not reached. The most frequent related adverse events were infusion related reaction (IRR) (46%), fatigue (12%), headache (10%), arthralgia and diarrhea (8% each). All related adverse events were mild to moderate, except one case of IRR Grade 3. No related anemia nor thrombocytopenia were observed. BI 765063 showed dose proportional exposure and full RO saturation in Cycle 1 after the fourth dose level. Clinical benefit was observed in 21/47 (45%) patients evaluable per RECIST 1.1. One patient with hepatocellular carcinoma (HCC) with liver and lung metastases and 7 prior lines of therapy showed a durable partial response maintained for 27 weeks treatment (ongoing). The baseline tumor biopsy of this patient showed high CD8 T-cell and macrophage infiltration. There was an increase in CD8 T-cell infiltration and activation on treatment. An increase in PD-L1 expression on tumor cells 2 weeks after first dosing was also observed. Analysis of paired tumor biopsies in other patients is ongoing. **Conclusions:** The first-in-class SIRPα inhibitor BI 765063 was well-tolerated, showed monotherapy activity, and sustained RO saturation. A durable partial response was observed in an advanced HCC patient. The on-treatment biopsy of the responder showed an increase in CD8 T-cell infiltration and activation. PD-L1 expression on tumor cells also increased. BI 765063 dose escalation in combination with ezabenlimab (anti-PD1 antibody) is ongoing. Clinical trial information: NCT03990233. Research Sponsor: OSE Immunotherapeutics; Boehringer Ingelheim.

2624 **Poster Session**

A phase 1/2 open-label study of KY1044, an anti-ICOS antibody with dual mechanism of action, as single agent and in combination with atezolizumab, in adult patients with advanced malignancies.

Manish R. Patel, Aung Naing, Howard A. Burris III, Chia-Chi Lin, Giuseppe Curigliano, Fiona Thistlethwaite, Anna Rachel Minchom, Paolo Antonio Ascierto, Filippo G. De Braud, Michael Cecchini, Wouter Hanekom, Richard C.A Sainson, Rosamund J Wilson, Sonia Quaratino; Sarah Cannon Research Institute, Florida Cancer Specialists, Sarasota, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; National Taiwan University Hospital, Taipei, Taiwan; Istituto Europeo di Oncologia, Milan, IRCCS and University of Milano, Milan, Italy; The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom; Drug Development Unit, Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; University of Milan, Fondazione IRCCS Istituto Nazionale del Tumori, Milan, Italy; Yale Cancer Center, New Haven, CT; Kymab Ltd., Cambridge, United Kingdom

Background: KY1044, is a fully human IgG1 anti ICOS antibody designed to stimulate Teffs and to deplete ICOS high Tregs in the tumor microenvironment. **Methods:** Patients with advanced/metastatic malignancies received escalating doses of KY1044 as a single agent and in combination with atezolizumab 1200 mg by IV infusion every 3 weeks until disease progression or unacceptable toxicity. Dose escalation was guided by a modified toxicity probability interval design. The primary objective was to determine safety, tolerability, and maximum tolerated dose. Cohorts that were tolerated were later enriched with more subjects. AEs were classified according to CTCAE v5 and efficacy measures performed according to RECIST v1.1 every 8 weeks for the first 16 weeks and then every 12 weeks. **Results:** As of 16-Dec-2020, a total of 103 patients have been enrolled in the study (38 patients as monotherapy in 6 cohorts at doses ranging from 0.8 to 240 mg and 65 in combination with atezolizumab in 5 cohorts at doses 0.8 – 80 mg). 63% and 55% of patients received $\geq$4 prior anti-cancer therapies in the single agent and combination cohorts, respectively. All cohorts were completed without DLTs during the first 21 days of treatment. In the KY1044 single agent cohorts, 47.4% of patients experienced treatment-related AEs (TRAEs), all were grades 1 or 2. In the combination cohorts, TRAEs were observed in 58% of patients. Most of the TRAEs were grade 1 or 2 apart from 8 TRAEs that were $\geq$grade 3 occurring in $<$8% of patients. Infusion-related reactions, pyrexia and lymphopenia were the most commonly occurring TRAEs in $\geq$10% of patients. TRAE leading to dose interruptions occurred in 1 patient in the single agent cohort and in 4 patients in the combination cohort. Only 1 patient discontinued treatment due to myositis that was considered related to the combination. Preliminary KY1044 PK data from 69 patients agree with the PK model predictions. Median treatment duration for all enrolled patients was 9 weeks. Treatment duration $\geq$16 weeks was observed in 24% (9/38) and 27% (17/64) patients in the single agent and combination cohorts, respectively. Five objective responses, including 1 CR in triple negative breast cancer (TNBC) and 4 PRs in TNBC, head and neck squamous cell carcinoma, penile and pancreatic cancer were observed. Four of the 5 responding patients were still on treatment at the data cut, with 3 patients on treatment for $>$43 weeks (range 45 to 66 weeks). **Conclusions:** KY1044 is well tolerated as single agent and in combination with atezolizumab. Objective responses have been observed in this phase 1 part of the study. The phase 1 expansion and phase 2 part of the study is ongoing. Clinical trial information: NCT03829501. Research Sponsor: Kymab.

2625 **Poster Session**

Real world experience with standalone immunotherapy regimens: Immune-related adverse events, healthcare utilization and cost among patients with commercial or Medicare Advantage insurance.

Krishna Soujanya Gunturu, Timothy Pham, Sonali Shambhu, Michael Jordan Fisch, John Barron, David Joseph Debono; Lahey Hospital and Medical Center, Burlington, MA; Healthcore, Wilmington, DE; HealthCore, Inc., Wilmington, DE; AIM Specialty Health, Chicago, IL; Anthem Inc, Indianapolis, IN

Background: Immunotherapy is a fast growing class of cancer therapy. We evaluated the rates of immune-related adverse events (irAEs), healthcare utilization, and costs up to 1 year post-index among patients using monotherapy (PD-1/PD-L1 inhibitor) and combination therapy (PD-1/PD-L1 with CTLA-4 inhibitors). **Methods:** We reviewed claims from the HealthCore Integrated Research Database (HIRD), which contains commercially insured/Medicare Advantage members and captures clinical, utilization, and cost measures. We analyzed both the monotherapy (M) and combination therapy (C) cohorts focusing on members with ≥ 6 months of baseline continuous medical and pharmacy coverage. Descriptive and multi-variate analyses were performed. **Results:** The C cohort had 904 and M had 9,084 patients, with mean ages of 58 and 64 years, respectively. Prominent cancer types were melanoma for C and lung for M. The most common incident irAEs (%) for C vs. M were: endocrinopathies (27.7, 14.7), hepatitis (17.1, 7.7), nephritis (21.0, 14.0), neuropathy (6.6, 7.0), followed by colitis, dermatitis, and myocarditis. After adjustment, C therapy showed greater risk of all-cause inpatient admissions (OR 2.27, 95% CI 1.93, 2.66), all-cause emergency department (ED) visits (OR 1.55, 95% CI 1.33, 1.81) and irAE-related visits (See table). Mean adjusted all-cause cost difference for C vs M was +$43,747 (95% CI $38,440, $49,427). In age ≥65 subset, 222 received C and 4,208 received M. C therapy patients had more irAE-related hospitalizations (45.3% vs. 57.7%, p=0.0004). Costs were similar to the main cohort. **Conclusions:** C therapy showed greater incident irAE rates, increased utilization and medical costs compared to M therapy. Limitations include less precise ascertainment of irAEs in claims data and generalizability only to those with commercial or Medicare Advantage insurance. Our study highlights the increased toxicity and cost tradeoffs involved in choosing combination immunotherapy over monotherapy. Research Sponsor: Anthem Inc.

	Monotherapy (n/mean/%/SD)	Combination Therapy (n/mean/%/SD)	OR/Adjusted Mean Difference (95% CI)	Adjusted p-value/ Unadjusted p-value*
All-cause				
Inpatient Stay, n (%)	5,028 (55.4%)	593 (65.6%)	2.27 (1.93, 2.66)	<0.0001
ED visit, n (%)	3,059 (33.7%)	374 (41.4%)	1.55 (1.33, 1.81)	<0.0001
Outpatient visit, n (%)	9,076 (99.9%)	902 (99.8%)	-	0.2274*
Total medical cost PMPM, mean (SD)	$26,741 ($55,623)	$67,877 ($237,854)	$43,747 ($38,440, $49,427)	<0.0001
irAE-related				
Inpatient stay, n (%)	3,826 (42.1%)	499 (55.2%)	2.17 (1.87, 2.53)	<0.0001
ED visit, n (%)	1,430 (15.7%)	205 (22.7%)	1.64 (1.36, 1.97)	<0.0001
Outpatient visit, n (%)	6,653 (73.2%)	729 (80.6%)	1.31 (1.09, 1.58)	0.0038
Total medical cost PMPM, mean (SD)	$7,837 ($30,841)	$22,626 ($165,487)	$19,224 ($14,911, $24,246)	<0.0001

2626 **Poster Session**

KY1044 to target the ICOS pathways inducing intratumoral Treg depletion and agonism of effector T cells: Preliminary pharmacodynamic markers from a phase 1/2 multicenter trial.

Chia-Chi Lin, Aung Naing, Manish R. Patel, Howard A. Burris III, Giuseppe Curigliano, Fiona Thistlethwaite, Anna Rachel Minchom, Paolo Antonio Ascierto, Filippo G. De Braud, Joseph Paul Eder, Matthew Wake, Cintia Cristina Palu, Anthea Louise Newton, Cecilia Deantonio, Wouter Hanekom, Richard C.A Sainson, Sonia Quaratino; National Taiwan University Hospital, Taipei, Taiwan; The University of Texas MD Anderson Cancer Center, Houston, TX; Sarah Cannon Research Institute, Florida Cancer Specialists, Sarasota, FL; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; Istituto Europeo di Oncologia, Milan, IRCCS and University of Milano, Milan, Italy; The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom; Drug Development Unit, Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom; Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; University of Milan, Fondazione IRCCS Istituto Nazionale del Tumori, Milan, Italy; Yale Cancer Center, New Haven, CT; Kymab Ltd., Cambridge, United Kingdom

Background: Inducible T-cell co-stimulator (ICOS) is an important co-stimulatory receptor on effector T cells (Teffs) that also promotes tumor growth due to its high expression on regulatory T cells (Tregs). KY1044 is a fully human IgG1 that targets ICOS, acting via a dual mode of action (MoA) by depleting $ICOS^{high}$ Tregs and stimulating $ICOS^{Low}$ Teffs. A Phase 1/2 clinical trial (NCT03829501) is currently assessing the safety and preliminary efficacy of KY1044, as a single agent and in combination with atezolizumab, in subjects with advanced relapsed/refractory malignancies. Using longitudinal blood samples and tumor biopsies, we aim to correlate KY1044 target engagement levels with pharmacodynamic (PD) properties (e.g. dual MoA) in the tumor microenvironment (TME) and the circulation. **Methods:** Phase 1 subjects were enrolled in dose escalation and enrichment cohorts to evaluate the effect of KY1044 as monotherapy (0.8 – 240 mg) Q3W and in combination (0.8 – 80 mg) with atezolizumab (1200 mg) Q3W. PBMCs, plasma and tumor biopsies were collected over the first 3 cycles to confirm target engagement and KY1044 MoA. The sample analysis included: immunohistochemistry (IHC) of tumor samples (ICOS, FOXP3 and CD8); circulating T cell immunoprofiling and receptor occupancy by chip-cytometry; PBMC and tumor sample pre- and post-treatment transcriptomic analysis; and the assessment of circulating cytokines (e.g. GM-CSF). **Results:** As assessed in PBMCs, full/prolonged ICOS target engagement on T cells was confirmed in subjects receiving a flat dose of 8 to 240 mg, while partial/transient saturation was observed at lower doses (0.8-2.4 mg). The target engagement was not affected by atezolizumab. The immune cell profiling showed changes in some populations, but there was no significant depletion of peripheral $ICOS^+$ cells. In contrast, pre- and post-treatment IHC analysis of $ICOS^+/FOXP3^+$ cells in tumor biopsies confirmed a KY1044-dose dependent reduction of $ICOS^+$ Tregs and maintenance of $CD8^+$ T cells in the TME. Together, this resulted in an increased intratumoral $CD8^+/ICOS^+$ Treg ratio at all doses, plateauing from subjects receiving a flat KY1044 dose of 8 mg. KY1044-dependent agonism was indirectly assessed by measuring circulating cytokine levels. A post-dosing transient induction of GM-CSF was evident in subjects dosed with KY1044 at the 0.8 and 2.4 mg dose, whereas minimal induction was observed at dose of 8 mg and higher. **Conclusions:** LongitudinalPDdata confirmed the expected KY1044 MoA, namely ICOS Treg depletion and increased CD8/ICOS Treg ratio in the TME as well as T cell co-stimulation. The observed PD responses are currently being further explored in a more homogenous patient population. Research Sponsor: Kymab.

2627 **Poster Session**

Association and prevalence of venous thromboembolism in cancer patients with COVID-19: A single healthcare system experience.

Aneesha Ananthula, Dat Tran, Katharine Thomas, Katie Lauren McLemore McQueen Amaker, Anh Nguyen, Soham Mahato, Brandon T Thrash, Andrew G Chapple, Suki Subbiah; Louisiana State University, New Orleans, LA; Section of Hematology/Oncology, LSU School of Medicine, New Orleans, LA

Background: There are increasing reports of thromboembolic complications in patients with COVID-19 infection. According to a meta-analysis of 28,173 patients, the prevalence of venous thromboembolism (VTE) in hospitalized COVID-19 patients ranges from 7.9% to 22.7% based on the severity of COVID-19. Cancer and anti-cancer therapies are known risk factors for thrombosis. Another study based on registry data reported the overall prevalence of VTE in hospitalized COVID-19 patients with cancer to be 14.5%. Our study aimed to assess the prevalence of VTE in cancer patients diagnosed with COVID-19 as well as the association between VTE and cancer in the setting of COVID-19 infection in a large predominantly urban healthcare system. **Methods:** We utilized a cohort data query tool in the electronic medical record at University Medical Center in New Orleans, Louisiana to identify patients >17 years of age with a hospital or clinic visit in the LCMC Health system between March 1, 2020 and December 31, 2020 which were considered the base population for the study. Cancer patients were identified via the cancer registry tool. Patients with COVID-19 were identified using the abnormal COVID-19 PCR test result search field. An encounter diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) was used to identify patients with VTE. Odds ratios, p-values, and corresponding confidence intervals (CI) were calculated using 2x2 contingency tables. **Results:** In our database, we identified 3,807 patients with a diagnosis of COVID-19 and 9,560 with a cancer diagnosis. 158,812 patients had neither COVID-19 nor cancer. There were statistically significant greater odds of developing VTE in all subgroups compared: COVID-19 alone vs neither (OR 2.43), cancer alone vs neither (OR 3.8), and COVID-19 and cancer vs neither (OR 10.65). **Conclusions:** COVID-19 and cancer are both risk factors for VTE. Based on our study, appears that cancer has the greater effect on VTE compared with COVID-19 infection. Also, there is possibly a synergistic effect between COVID-19 and cancer, which further increases the likelihood of VTE. This study is a preliminary analysis. Further investigation is warranted in the form of either variable adjusted analysis of the same data, individual chart review, or a prospective study. Research Sponsor: None.

Cohort [VTE n = prevalence%]	Odds ratio	CI	P value
COVID-19 [84 = 2.29%] vs none [1520 = 0.96%] *cancer excluded	2.43	1.95–3.04	<0.0001
Cancer [334 = 3.54%] vs none [1520 = 0.96%] *COVID-19 excluded	3.8	3.37–4.29	<0.0001
COVID-19 and cancer [14 = 9.33%] vs neither [1520 = 0.96%]	10.65	6.13–18.51	<0.0001

2628 **Poster Session**

Priming immunotherapy with radiotherapy (RT) in advanced non-small cell lung cancer (NSCLC) and head and neck squamous cell cancer (HNSCC): Interim analysis of phase II clinical trial.

Aasems Jacob, Alexander Kreimer, Jing Wei, Jianrong Wu, Lauren Corum, Ellen Reusch, Jerold Woodward, Donald Cohen, Subbarao Bondada, Val R. Adams, Rachael Morgan, Ronald C. McGarry, William H. St Clair, Mahesh R. Kudrimoti, Zin Myint, Susanne M. Arnold, John L. Villano; University of Kentucky, Lexington, KY

Background: Preclinical models demonstrate that combined RT with immune checkpoint inhibitor (ICI) results in specific CD8+ T-cell phenotype associated with a tumor-reactive population resulting in significant tumor response. Sequential treatment could allow radiation to release tumor antigens from immune inaccessible areas and provide robust anti-tumor immune response with ICI. We report an interim analysis of the phase II clinical trial evaluating the efficacy and safety of the combination. **Methods:** Advanced NSCLC and HNSCC patients who had initiated on FDA approved single-agent ICI were eligible. Patients were given SBRT (BED>100Gy) or 30 Gy fractionated RT delivered as a 3-dimensional dose to a single metastatic site within 14 days of the first ICI dose. Primary objective was 6-month PFS and secondary objectives were safety and tolerability, 1Y PFS and OS. This interim analysis was done after enrollment of 43 patients. **Results:** Between 10/2017 to 1/2021, 43 patients were enrolled, and 38 included in this analysis. Median age was 62 years; 26 patients were male. 9 patients received ICI for NSCLC as first-line, 7 for NSCLC second-line and 22 for HNSCC second-line. 24 patients received pembrolizumab and 14 nivolumab; 21 had SBRT and 17 fractionated RT. Median follow up duration was 11.8m (range: 2.7 - 31.4m) for patients without progressive disease (PD). 10 patients were off-study, 7 continuing treatment. 15 died and 26 had PD. 14 patients died of malignancy and cause of death for one patient was unknown. 6-month PFS was 49.19% with median PFS of 5.5 months. (table) Fifty-two grade-3-5 adverse events (AEs) were reported among 21 subjects. Most common were transaminitis (n=15), lymphopenia (n=8), and GI side effects (n=4). Treatment related AEs included 19 grade-3 events, and none were grade 4/5. Two grade-5 AEs were from PD (oral bleeding and unspecified). There were 20 grade-1/2 and 3 grade-3 immune related adverse events (IRAEs). No grade-4/5 IRAEs were reported. Two patients discontinued treatment due to grade 3 transaminitis. **Conclusions:** Interim analysis shows that 6m PFS was acceptable with majority of patients being second-line metastatic HNSCC who historically had mPFS of 2.1-2.3 months and mOS 7.7-8.4 months in Checkmate-141/KEYNOTE-040 trials. Hence, the combination is of further interest and accrual will continue to reach the goal. The combination therapy was tolerable without unexpected AEs. Majority of deaths were from disease progression. No treatment related grade 4/5 adverse events were reported. Two patients discontinued treatment due to grade-3 IRAE. Clinical trial information: NCT03313804. Research Sponsor: University of Kentucky Markey Cancer Center's Cancer Center Support Grant.

Median PFS, OS and survival probabilities in the study population.

	PFS	OS
Median follow-up duration	11.8m	11.5m
Median	5.5m	19.27m
Survival Probability		
6m	49.19%	77.68%
12m	32.20%	57.37%
24m	21.46%	40.16%

2629 **Poster Session**

The Tim3-galectin-9 interactions in the tumor microenvironment of nasopharyngeal cancer.

Dora Lai Wan Kwong, Ngar-Woon Kam, Wai Chun Tse, Sing Hei Lok, George Tsao, Victor Ho-Fun Lee; The University of Hong Kong, Hong Kong, China; Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

Background: The complex cell interactions within the tumor microenvironment (TME) have become a crucial point in cancer research. Yet, the cell interactions might not only depend on the frequency of immune cells, but also on the inter-individual distances as cells might interact via soluble factors and/or cell-cell contact. Accordingly, the mapping of TME has recently gained importance. The aim of this study is to investigate the alternations between galectin-9 (G9) and its natural immunosuppressive receptor, T cell immunoglobulin and mucin domain 3 (Tim3) in nasopharyngeal cancer (NPC). **Methods:** Using multiplexed quantitative immunofluorescence, we measured the levels of G9 and Tim3 in 95 NPC patients cancerous and 8 normal specimens in tissue microarray format. Cell densities and cell-to-cell distances were quantified. The interaction between G9-expressing tumor cell lines and T cells were also studied. **Results:** G9-expressing tumor cells were detected in all NPC cases and were significantly higher than normal tissue. Elevated G9 was associated with shorter overall survival (OS: 89% vs 70.5% at 7 years, p: 0.019). Incremental percentages of $Tim3^+$ cells were shown in top 10% cases strongly positive for G9-expressing tumor cells. The number of $Tim3^+$ cells was calculated at 15μm intervals from the nearest G9-expressing tumor cells, of which a significant difference of $Tim3^+$ cells was observed at the 0-15μm distance from G9-expressing cell in cancerous compared to normal tissues. Epithelial short distances were associated with a unfavourable prognosis. Observed short distance were hypothesized to represent $Tim3^+$ cells actively interacting with G9-expressing tumor cells. Accordingly, *In vitro* cocultured of G9-ovexpressing NPC cell lines induced Tim3 expression on T cells which suppressed the T-cell mediate cytotoxicity on tumor cells. **Conclusions:** Our findings indicate a specific pre-existing profile of $Tim3^+$ and G9-expressing tumor cells and demonstrated that $Tim3^+$ cells were mainly found intratumorally within 15μm of a NPC cell. The relevance of $Tim3^+$ and $G9^+$ distances reflect a potential marker of their functional interaction. Our results could have important implications for clinical therapeutic strategies. Since high G9 expression have poorer OS, they would deserve a different therapeutic strategy. Research Sponsor: Health and Medical Research Fund.

NPC (cases).

Total_G9-expressing tumor cells (Tc)	Top10% G9-expressing Tc	Tim3$^+$ within Top10% G9-expressing Tc	Tim3$^-$ within Top10%G9-expressing Tc	10-50% G9-expressing Tc	Tim3$^+$ within 10-50% G9-expressing Tc	Tim3$^-$ within 10-50% G9-expressing Tc
95	9	6	3	33	7	26
Cell densities (%)						
Tim3$^+$ cells within Top10% G9-expressing tumor cells	Tim3$^-$ cells within Top10% G9-expressing tumor cells	Tim3$^+$ cells within 10-50% G9-expressing tumor cells	Tim3$^-$ cells within 10-50% G9-expressing tumor cells			
30.62	69.38	19.54	80.46			
Distance to G9-expressing Tc (median; um)						
Tim3$^+$ cells	Tim3$^-$ cells					
7.62	11.34					

2630 **Poster Session**

Safety of AK117, an anti-CD47 monoclonal antibody, in patients with advanced or metastatic solid tumors in a phase I study.

Hui Kong Gan, Jermaine Coward, Anna Rachelle Austria Mislang, Rasha Cosman, Adnan Nagrial, Xiaoping Jin, Baiyong Li, Zhongmin Maxwell Wang, Kon Yew Kwek, Dennis Xia, Yu Xia; Austin Health, Heidelberg, VIC, Australia; ICON Cancer Care, South Brisbane, QLD, Australia; Adelaide Cancer Centre, Kurralta Park, SA, Australia; St Vincent's Hospital, Sydney, NSW, Australia; Blacktown Hospital Cancer and Haematology Centre, Blacktown, NSW, Australia; Akeso Biopharma, Inc., Zhongshan, China

Background: AK117 is a novel humanized IgG4 monoclonal antibody (mAb) targeting CD47, a macrophage immune checkpoint that allows tumor cells to evade immune destruction by phagocytic cells. CD47 is a target expressed in many cancers. However, the initial dose of anti-CD47 therapy may be limited by severe anemia due to ubiquitous CD47 expression on senescent red blood cells (RBCs). Here, we present encouraging preliminary AK117 safety and receptor occupancy (RO) data from an ongoing dose-escalation study in patients (pts) with advanced or metastatic solid tumors. **Methods:** This is a first-in-human, phase 1a/1b, multicenter, open label, single arm, dose escalation and dose expansion study of AK117 administered intravenously to adult pts with resistant/refractory advanced or metastatic solid tumors or lymphomas. In the dose escalation phase (phase 1a), an accelerated titration followed by a 3+3+3 design was used to assess the safety and tolerability of AK117 monotherapy (dose range 0.3 mg/kg to 45 mg/kg); and determine the maximum tolerated dose (MTD). AK117 was administered QW on a 28-day treatment cycle and dose limiting toxicity (DLT) observation period. Tumor assessments per RECIST v1.1 were performed once every 8 weeks (2 cycles). **Results:** As of 15 Feb 2021, 15 pts were enrolled in phase 1a with DLT evaluation of the 30 mg/kg cohort currently in progress. There were no DLTs up to 20 mg/kg QW AK117, inclusive. Five treatment-related adverse events (TRAEs) occurred in 4 subjects as shown in the table below. All pts with TRAEs continue to receive AK117, except the pt on 1 mg/kg AK117 who discontinued due to disease progression. G2 anemia and G1 thrombocytopenia occurred after Cycle 1 in a pt (liposarcoma, 10 mg/kg cohort), who had a medical history of anemia (hemoglobin 119 g/L at screening). No hematological TRAEs were seen in other pts, including those who received 20 mg/kg AK117 QW. There were no infusion-related reactions (IRRs) or grade ≥ 3 TRAEs. Target engagement in the periphery was confirmed by measuring CD47 RO of AK117 on RBCs and T lymphocytes. 100% RO on RBCs and T lymphocytes was achieved after the first dose and continued to Day 8 (prior to second dose) in the 10 mg/kg and 20 mg/kg cohorts. **Conclusions:** AK117 is safe and well-tolerated up to 20 mg/kg QW, inclusive, with no IRRs or severe TRAEs observed. There were no hematological TRAEs, except in a pt with baseline G1 anemia receiving 10 mg/kg AK117. Unlike other anti-CD47 therapies, AK117 does not require a lower priming' dose to prevent anemia. Safety evaluation of the 30 mg/kg dose level is in progress. Full and durable RO in the periphery was seen at 10 mg/kg and above. Further evaluation of AK117 in combination with AK104, an anti-PD-1/CTLA-4 bispecific antibody, shall commence imminently. Clinical trial information: NCT04349969. Research Sponsor: Akeso Biopharma, Inc.

Dose Level	AE	CTCAE Grade
1 mg/kg	Rash	1
3 mg/kg	Nausea	1
10 mg/kg (same pt)	Anemia	2
	Thrombocytopenia	1
20 mg/kg	Headache	1

2631 **Poster Session**

Phase 1 dose escalation study of MGC018, an anti-B7-H3 antibody-drug conjugate (ADC), in patients with advanced solid tumors.

Sekwon Jang, John D. Powderly, Alexander I. Spira, Ouiam Bakkacha, Deryk Loo, Gerry C. Bohac, Manish Sharma; Inova Schar Cancer Institute, Fairfax, VA; Carolina BioOncology Institute, Huntersville, NC; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; MacroGenics, Inc., Rockville, MD; START-Midwest, Grand Rapids, MI

Background: MGC018 is an investigational ADC with a duocarmycin payload linked to an anti-B7-H3 monoclonal antibody (mAb). B7-H3 is expressed on multiple solid tumors with limited normal tissue expression. It is hypothesized that MGC018 may exert activity against B7-H3-expressing tumors with an acceptable safety profile. Studies demonstrate that B7-H3 is a significant factor in progression and events of metastasis of multiple tumor types, including melanoma. **Methods:** This phase 1 study characterizes safety, maximum tolerated or maximum administered dose, pharmacokinetics, immunogenicity, and tumor response per RECIST v1.1 of MGC018 in a 3+3+3 dose escalation design in patients with advanced solid tumors. MGC018 was administered intravenously (IV) every 3 weeks. **Results:** The study enrolled 29 patients of multiple tumor types, which included 3 melanoma patients refractory to ≥2 prior lines of checkpoint therapy. The study completed 5 of 6 planned dose cohorts (0.5 mg/kg - 4 mg/kg) as of the data cutoff of 21 January 2021. The final cohort of 4 mg/kg has 3 patients with ongoing treatment and follow-up at the date of submission. Dosing MGC018 IV every 3 weeks resulted in minimal serum accumulation. At least 1 treatment emergent adverse event occurred in 29 patients (100.0%); most common (≥25%) were anemia, neutropenia, fatigue, hyperpigmentation, infusion related reaction, nausea, and palmar plantar erythrodysesthesia. Two dose-limiting toxicities occurred; one grade 4 neutropenia (2 mg/kg) and one grade 3 fatigue lasting 7 days (4 mg/kg). No febrile neutropenia was reported. The 3 melanoma patients had reductions in target lesion sum of 24.4%, 27.5%, and 35% (unconfirmed partial response) and remain on treatment as of the data cutoff. The recommended phase 2 dose was determined to be 3 mg/kg. **Conclusions:** Results to date demonstrate a manageable safety profile, with early evidence of clinical activity in pretreated metastatic melanoma. Cohort expansion is ongoing using a recommended phase 2 dose of 3 mg/kg IV every 3 weeks. The planned enrollment includes advanced metastatic castrate-resistant prostate cancer, melanoma, triple-negative breast cancer, and non-small cell lung cancer. Clinical trial information: NCT03729596. Research Sponsor: MacroGenics, Inc.

2632 **Poster Session**

Comparison of checkpoint inhibitor treatment-related cutaneous adverse events in racial and ethnic minority and Caucasian cohorts at Memorial Sloan Kettering Cancer Center.

Amaris Geisler, Dulce M. Barrios, Gregory Phillips, Rosa Nouvini, Mario E. Lacouture, Sarah Noor; CUNY School of Medicine, New York, NY; SUNY Upstate Medical University, Syracuse, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Stony Brook Univ Hosp, Woodbury, NY

Background: Immune-related cutaneous adverse events (irCAEs) are the most common and often the first toxicity of immune checkpoint inhibitors (CPIs). In the general population, irCAEs occur on average within 3.6 weeks of treatment initiation and most commonly manifest as maculopapular rash, lichenoid rash, and pruritus. Less is known about these irCAEs in racial and ethnic minority patients. The purpose of this study is to compare the irCAEs of cohorts of Caucasian and racial and ethnic minority patients at Memorial Sloan Kettering Cancer Center. **Methods:** Herein, we conducted a retrospective chart review of racial and ethnic minority patients treated with CPIs between 2012-2019 at Memorial Sloan Kettering Cancer Center. irCAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. These were compared to a Caucasian cohort matched by demographics and cancer therapy regimen. **Results:** One hundred ten racial and ethnic minority patients presented to dermatology for irCAEs. Our population consisted of 59 (53.6%) females and 51 (46.4%) males with a mean age of 59 (range 20-85). Of the patients who were seen by dermatology, 63/110 were Asian (57.3%) followed by 34/110 African American (30.9%), and 1 Native American. Twelve patients were of Hispanic ethnicity (10.9%), which included those of both African American and Caucasian race. The 110 patients that were evaluated by dermatology had 221 cutaneous adverse events. Rash (96, 43.4%), pruritus (40, 18.1%), and xerosis (23, 10.4%) were most frequently diagnosed (average time from treatment start to presentation was 125 days). Dermatology identified 87 (39.3%) grade 1, 103 (46.6%) grade 2, 30 (13.5%) grade 3, and 1 (0.4%) grade 4 events. There were 17 (15.5%) treatment interruptions, including 7 patients who required permanent discontinuation. In the Caucasian cohort, mean time to onset was 228 days (range 1-1500). Dermatology identified 48 (43.6%) grade 1, 44 (40.0%) grade 2, 18 (16.4%) grade 3, and 0 (0.0%) grade 4 events, with maculopapular rash (55, 50.0%) and pruritus (25, 22.7%) most frequently diagnosed. **Conclusions:** Our findings suggest that irCAEs occur frequently in cancer patients from racial and ethnic minority groups, with similar grade and morphology as Caucasian patients. When irCAEs develop in this population, the diagnosis occurred later than what has previously been reported, possibly due to these patients seeing MSK oncologists with an established dermatology consultation system and insight into how to manage these patients on their own. Prospective evaluation of underrepresented minorities receiving CPI therapy is warranted in order to identify risk factors and therapeutic strategies for these untoward events, so that optimal cancer care may be delivered. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

Proton pump inhibitor use (PPI) in patients treated with immune checkpoint inhibitors (ICI) for advanced cancer: Survival and prior therapy.

Marium Husain, Menglin Xu, Sandipkumar Patel, Andrew Johns, Madison Grogan, Mingjia Li, Gabrielle Lopez, Abdul Miah, Rebecca Hoyd, YunZhou Liu, Mitchell Muniak, Tyler Haddad, Gabriel Tinoco, Kari Lynn Kendra, Gregory Alan Otterson, Carolyn J Presley, Daniel Spakowicz, Dwight Hall Owen; The Ohio State University Medical Center, Columbus, OH; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; The Ohio State University, Columbus, OH; Ohio State University Wexner Medical Center, Columbus, OH; The Ohio State University Wexner Medical Center, Division of Hospital Medicine, Columbus, OH; Ohio State University, Columbus, OH; The Ohio State University Wexner Medical Center, Division of Medical Oncology, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH; The Ohio State University Wexner Medical Center, Columbus, OH; James Cancer Hospital, Columbus, OH; The Ohio State University Comprehensive Cancer Center, Department of Internal Medicine, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine & Department of Biomedical Informatics, Ohio State University, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, Ohio State University, Columbus, OH

Background: Emerging data suggest that concomitant medications (CM) influence response to ICI. CM impact the host microbiome which may mitigate tumor-immune responsiveness. PPI use in patients treated with ICI has been associated with worse survival. Few data exist regarding the effects of PPI use in terms of prior chemotherapy or in risk for immune related adverse events (irAE) (e.g., colitis). **Methods:** This retrospective study of patients with advanced cancer treated with ICI between 2011 and 2019 was conducted at The Ohio State University. Patients who received ICI as either single agent or combination were included. Clinical data was abstracted from chart review, including CM, toxicity, and survival. Overall survival (OS) was evaluated to date of death or last contact. Associations between OS and proton pump inhibitor (PPI) use were studied using log-rank tests and Cox regression analyses overall and by the groups of whether prior chemotherapy was administered and timing from chemotherapy to ICI. The associations between PPI and incidence of irAE (overall and colitis) were assessed by chi-square tests. **Results:** We identified 1,091 patients treated with ICI, of whom 415 (38%) received PPI at time of ICI. Most common cancers were NSCLC and melanoma; most common therapy was PD1/L1 (Table). PPI use was associated with shorter OS in patients treated as first line therapy (HR = 1.46, 95% CI = [1.11, 1.91], p=0.006) and in second line and beyond (HR = 1.30, 95% CI = [1.10, 1.53], p=0.002). PPI use was associated with shorter OS in patients treated with ICI for those without prior chemotherapy (HR = 1.47, 95% CI = [1.17, 1.86], p=0.001). When evaluated by timing from chemotherapy to ICI, PPI use was associated with shorter OS only in patients where last chemotherapy was $>$ 1 year from ICI (HR = 1.99, 95% CI [1.15, 3.45], p=0.014) but not for patients with chemotherapy within 1 year of ICI (HR = 1.01, 95% CI = [0.79, 1.29], p=0.960). The use of PPI was not associated with incidence of irAE (p=0.317) or colitis in particular (p=0.781). **Conclusions:** PPI use was associated with shorter survival in patients treated with ICI across a broad variety of cancers and in first line of therapy or beyond. In patients with recent chemotherapy ($<$1 year), PPI use was not associated with survival, which may be due to disruption of the microbiome by chemotherapy. Further study is needed to determine the impact of CM (e.g, PPI), on outcomes of patients treated with ICI. Research Sponsor: U.S. National Institutes of Health.

Patient Characteristics	No PPI	PPI	P value
N = 1091	676	415	
Age (mean (SD))	61.64 (13.73)	62.36 (11.88)	0.381
Female	280 (41.4)	164 (39.5)	0.577
ECOG PS (%)			0.026
0	254 (41.6)	130 (33.7)	
1	252 (41.2)	177 (45.9)	
2	91 (14.9)	61 (15.8)	
>2	14 (2.3)	18 (4.7)	
Immunotherapy (%)			0.602
PD1/L1	476 (70.4)	294 (70.8)	
CTLA4	116 (17.2)	78 (18.8)	
PD1/L1 + CTLA4	51 (7.5)	29 (7.0)	
Other	33 (4.9)	14 (3.4)	

2634 **Poster Session**

Initial findings of the first-in-human phase I study of AGEN2373, a conditionally active CD137 agonist antibody, in patients (pts) with advanced solid tumors.

Anthony W. Tolcher, Richard D. Carvajal, Anthony B. El-Khoueiry, Waldo Ortuzar Feliu, Hong Zang, Marek Ancukiewicz, Irina Shapiro, James Fredric Strauss; NEXT Oncology, San Antonio, TX; Columbia University Irving Medical Center, New York, NY; Norris Comprehensive Cancer Center, USC Keck School of Medicine, Los Angeles, CA; Agenus Inc, Lexington, MA; Mary Crowley Cancer Research Center, Dallas, TX

Background: CD137 is a member of the tumor necrosis factor receptor superfamily that functions as a potent co-stimulator of both adaptive and innate immune cells, thus making it an attractive target for cancer immunotherapy. The development of first-generation anti-CD137 antibodies has been hampered by limited clinical activity or dose-limiting hepatotoxicity. AGEN2373 is a novel, conditionally active CD137 agonist antibody designed to selectively enhance tumor immunity while mitigating side effects associated with systemic activation of CD137. Here we report the initial findings from the first-in-human evaluation of AGEN2373 in pts with advanced solid cancers. **Methods:** Pts received AGEN2373 on day 1 of a 28-day cycle (Q4W dosing), with cycles repeated until progression, intolerable toxicity or investigator/patient decision. Dose-escalation followed a standard 3+3 scheme, with planned dosing of 0.03, 0.06, 0.3, 1.0, 2.0, and 3.0 mg/kg. The primary objective was to determine the safety, tolerability, and dose-limiting toxicity (DLT) of AGEN2373 as monotherapy. Secondary objectives included pharmacokinetics (PK) and preliminary clinical activity. Adverse events (AEs) were reported per CTCAE v5.0 and DLTs evaluated within a 28-day window. For PK analyses, serum AGEN2373 concentrations determined using a validated bioanalytical assay and simultaneously analyzed by an NLME model. Antitumor activity was assessed using RECIST v1.1. **Results:** As of January 21 2021, 19 pts (median age 54.4 years, range 33-74; 11 men, 8 women; 7 with prior immunotherapy) have been treated with AGEN2373 Q4W at escalating doses from 0.03 – 2.0 mg/kg across 5 cohorts. Eleven pts (57.9%) experienced treatment-related AEs; none were grade 3 or higher. The most common events were fatigue (4 pts, 21.1%) and nausea (2 pts, 10.6%). No DLTs have been observed. Importantly, no drug-related elevations in liver transaminases (ALT, AST) or bilirubin beyond 1 grade have been seen. AGEN2373 PK were consistent with linear elimination. Prolonged disease stabilization as best response occurred in 5 pts (26.3%; range, 6-41 weeks); three of which were seen in heavily pretreated pts with metastatic leiomyosarcoma, including one who had progressed on prior combination checkpoint immunotherapy. Enrollment into the 3.0 mg/kg cohort is continuing. **Conclusions:** AGEN2373 demonstrates good tolerability in pts with advanced solid tumors, with a safety profile characterized by a lack of hepatotoxicity frequently observed with CD137-targeting antibodies. These findings underscore the suitability of AGEN2373 as a potential partnering agent for other immunomodulatory agents, including planned expansion as combination therapy with balstilimab (anti-PD-1). Clinical trial information: NCT04121676. Research Sponsor: Agenus Inc.

Late immune-related adverse events with immune checkpoint inhibitors.

Andrew Ip, Shuo Wang, Divya Cheruku, Kanchi Krishnamurthy, Melinda Weber, Brittany Sinclaire, Elli Gourna Paleoudis, Adil Alaoui, Shaked Iev-Ari, Michael T Serzan, Shari Adams, Jordan Kaufman, Sahil B. Parikh, Emily Tonti, Eric Muller, Aquino Williams, Jaeil Ahn, Andrew Pecora, Michael B. Atkins, Neil J. Shah; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Georgetown University, Washington, DC; Hackensack Meridian Health Mountainside Medical Center, Montclaire, NJ; John Theurer Cancer Center, Hackensack Univeristy Medical Center, Hackensack, NJ; Hackensack Meridian Health, Hackensack, NJ; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; MedStar Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC; Hackensack Meridian Health Mountainside Medical Center, Montclair, NJ; Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Immune Checkpoint Inhibitors (ICIs) are associated with unique immune-related adverse events (irAEs). IrAEs can occur at any timepoint of ICI treatment. Late irAEs are not well reported in the literature. Herein, we attempt to characterize irAEs that occur 6-month, one year and two years after ICI treatment initiation. **Methods:** We identified patients treated with ICIs (anti-CTLA-4, anti-PD(L)-1 either alone or in combination or with chemotherapy) across Hackensack Meridian Health hospital and MedStar Georgetown University Health systems from 12011 to 4/2018. Patients' baseline demographics, treatment history, and irAEs were collected from EHR. CTCAE V4.03 was used to grade irAEs. **Results:** We identified 1332 patients treated with 1443 unique ICIs. The ICI therapies were nivolumab 38% (543), pembrolizumab 23% (332), ipilimumab plus nivolumab 12% (180), ipilimumab 11% (161), Atezolizumab 3% (47) and others 13% (180). Tumor types were lung cancer 34% (496), melanoma 27% (389), GI cancers 6% (92), kidney cancer 6% (87), and other cancers 26% (379). The median age was 66 (21-87), age >75 37% (541), Caucasian 67% (970). We identified a total of 911 any grade irAEs among 37% (552) therapies. Among, 911 irAEs, grade 1-2, grade ≥3 and unknown grade irAEs were 39% (572), 12% (182) and 11% (157), respectively. The most common any grade irAEs were skin rash 22% (202), colitis 13% (120), and hepatitis 12% (108). 84% of all irAEs and 85% of ≥ Grade 3 irAEs occurred within 6 months of treatment initiation. Of the 350, patients on active treatment at six months, 37 % (132) and 7% (26) developed any grade and grade ≥3 irAEs, respectively. irAEs that had > 10% of their occurrences after six months were skin rash and colitis 14% each. Other common irAEs were hypothyroidism, hepatitis, joint pain, pruritis and pneumonitis at 7% each. Among 170 patients on active treatment at one year, 37% (62) and 7% (12) developed any grade and grade ≥3 irAEs respectively. irAEs with >10% incidence after one year of treatment were rash 19% and hepatitis 13%. **Conclusions:** Our RWE findings suggest although 85% irAEs occurs within the first six months of treatment, late irAEs can occur with ICI treatment. The incidence and pattern of late irAEs appears similar to early irAEs, (e.g., skin rash, colitis, hypothyroidism and hepatitis) with pneumonitis being a notable exception. It is uncertain if these results will be influenced by changing patterns of ICI use (e.g. different diseases and/or regimens) over time. Research Sponsor: U.S. National Institutes of Health.

Pattern of any grade, grade ≥ 3, and select irAEs over time.

	Any grade irAEs % (N=911)	Grade ≥ 3 irAEs % (N=182)	Any grade Colitis % (120)	Any grade Hepatitis % (108)	Any grade Rash % (202)	Any grade Pneumonitis % (54)
Less Than 3 months	72 (659)	75% (137)	72 (87)	86 (86)	80 (161)	67 (36)
4-6 months	12 (113)	10 (19)	11 (13)	12 (12)	10 (21)	15 (8)
7 -12 months	8 (70)	8 (14)	10 (12)	2 (2)	4 (8)	11 (6)
Over 1 year	5 (44)	5 (9)	4 (4)	2 (2)	4 (8)	6 (3)
Over 2 years	2 (18)	2 (3)	1 (1)	6 (6)	2 (4)	2 (1)

2636 **Poster Session**

Cardiovascular toxicity incidence following immune checkpoint inhibitors in randomized clinical trials: A systematic review and meta-analysis.

Camila Braganca Xavier, Carlos Diego Holanda Lopes, Guilherme Harada, Artur Katz, Denis Leonardo Fontes Jardim; Hospital Sírio-Libanês, São Paulo, Brazil

Background: Immune checkpoint inhibitors (ICIs) are widely used in oncology and may be associated with a variety of immune-related toxicities. Cardiovascular (CV) adverse effects (AEs) are underreported in randomized clinical trials (RCTs), and the real risk associated with ICIs use has yet to be defined. Therefore, we aimed to investigate the incidence and risk of cardiovascular toxicities in patients receiving ICIs, using an up-to-date meta-analysis of prospective RCTs. **Methods:** We conducted a systematic search of the literature from January 1st, 2010 until July 1st, 2020 to identify RCTs testing ICIs for solid tumors, either in monotherapy or in combination between them. Our initial search yielded a total of 21,249 relevant publications. For CV AEs incidence estimation, we included phase III RCTs testing PD-1, PD-L1, CTLA-4 inhibitors or any combination of these agents. For relative risk (RR) assessment, we included phase II or phase III RCTs testing the same agents and with placebo or best supportive care (BSC) as the comparator. Data were extracted by independent reviewers following *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) guidelines. CV AEs were categorized based on the *Common Toxicity Criteria* (CTCAE) and stratified by ICIs type. Analyses were conducted using random effects model. **Results:** After screening and eligibility assessment, a total of 21,118 patients (67 cohorts from 57 trials) were available for this meta-analysis. We categorized the cohorts by ICIs regimen as monotherapy with a PD-1 inhibitor (35 cohorts; 10,241 patients), PD-L1 inhibitor (12 cohorts; 3,755 patients), CTLA-4 inhibitor (11 cohorts; 4,135 patients), and combination therapy (9 cohorts; 2,987 patients). Incidence measures are described in the table. Deaths from any CV cause occurred in 0.20% of the patients (95%CI 0.10%; 0.20%). For RR analysis, we included 12 cohorts from 11 RCTs. Risk of experiencing all grade AEs was numerically higher among patients who received ICIs than placebo or BSC (RR 1.16; 95%CI 0.98; 1.37; p=0.09). When only grade 3-5 CV AEs were considered, ICIs were associated with increased risk (RR 1.36; 95%CI 1.06; 1.73; p= 0.01). Additional analyses were conducted to estimate the RR of individual CV AEs including arrhythmia, cardiac arrest, heart failure, stroke, hypertension, myocardial infarction, myocarditis, pericardial events, and thromboembolic events. None of the analysis identified a significant additional risk. **Conclusions:** This meta-analysis corroborates the preclinical rationale of worsen CV risk related to ICIs use. Research Sponsor: None.

ICI TYPE	ALL GRADE CV AEs (95% CI)	HIGH GRADE CV AEs (95% CI)
CTLA-4 inhibitor	8.30% (7.50%–9.10%)	4.80% (4.20%–5.50%)
PD-1 inhibitor	10.50% (10.00%–11.00%)	5.00% (4.50%–5.40%)
PD-L1 inhibitor	10.40% (9.50%–11,5%)	5.50% (4.80%–6.30%)
COMBINATION	15.87% (14.60%–17.20%)	6.30% (5.50%–7.20%)

2637 **Poster Session**

Infections in cancer patients treated with immune checkpoint inhibitors: Data from randomized trials.

Cinzia Solinas, Anna Maria Morelli, Andrea Luciani, Antonio Ghidini, Fausto Petrelli; Azienda Tutela della Salute Sardegna, Nuoro, Italy; ASL TO3, Rivoli, Italy; Oncology Unit, ASST Bergamo Ovest, Treviglio, Italy; ASST Bergamo Ovest, Treviglio, Italy

Background: Febrile neutropenia and infections are well studied complications of chemotherapy (CT) and some targeted agents employed in oncology. Less is known about the risk of infection associated with the use of immune checkpoint inhibitors (ICIs) in cancer patients. The present systematic review and meta-analysis was performed to address this question in patients diagnosed with solid tumors enrolled in randomized trials employing ICIs as experimental treatment. **Methods:** The Cochrane Library, EMBASE, and Pubmed databases were searched from inception through December 1^{st,} 2020. Randomized clinical trials comparing any ICI alone, with CT, or with other agents *vs* CT, placebo, or other agents in patients with solid tumors were included. Two independent reviewers used a standardized data extraction and quality assessment form. Discordant cases were discussed with a third independent investigator. The following information was extracted: baseline study characteristics, including the primary tumor, author, year of publication, type of trial, type of disease, and the type of therapy (experimental and control arms); and the incidence of any-grade (grades [G] 1–5), low-grade (G1–2), and high-grade (G3–4), fatal event (G5) infections, and type of event. Random or fixed-effect models were used according to the statistical heterogeneity. **Results:** 36 randomized clinical trials were deemed eligible. The total population reached 21451 patients. In the pooled analysis, the use of ICIs was associated with a similar risk of all-grade infections (relative risk, RR = 1.02; 95% CI 0.84–1.24; P = 0.85) compared to non-ICI treatments (G1-5 events: 9.6 *vs.* 8.3%). When the ICIs alone arms were compared to CT, the experimental arms were associated with a 42% less risk of all-grade infections (RR = 0.58, 95% CI 0.4–0.85; P = 0.01; N = 18 studies). Compared to CT, the combination of ICIs and CT increased the risk of all-grade infections (RR = 1.37, 95% CI 1.23–1.53; P $<$ 0.01; N = 13 studies) and severe infections (RR = 1.52, 95% CI 1.17–1.96; P $<$ 0.01; N = 12 studies). Fatal infections were similar in the experimental and control arms (0.5%). **Conclusions:** In patients with advanced solid tumors, when ICIs were administered with CT, the risk of all-grade and G3-5 infections was significantly increased. Compared to CT alone, ICIs were safer and their use should be recommended for frail patients. Further studies are required to identify high-risk patients and evaluate the need for CT dose reduction or prophylactic myeloid growth factors use. Research Sponsor: None.

2638 **Poster Session**

Age affects the efficacy of immune checkpoint inhibitors in patients with advanced cancer.

Yongjie Wang, Ronghua Yang, Dong Wang, Donghua Zhao, Peng Li, Mengjun Li, Yingxue Qi, Ningning Luo, Yaqing Wu, Qin Zhang; The Affiliated Hospital of Qingdao University, Qingdao, China; Qingdao University, Qingdao, China; The Medical Department, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing Simcere Medical Laboratory Science Co., Ltd, The State Key Lab of Translational Medicine and Innovative Drug Development, Jiangsu Simcere Diagnostics Co., Ltd, Nanjing, China

Background: Immune checkpoint inhibitors (ICIs), such as programmed death(ligand)1 (PD-(L)1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, have dramatic effects on treatment in patients with various malignancies. High tumor mutation burden (TMB) is predictive of clinical response to ICI in multiple cancer types. Although age-related immune dysfunction might induce difference on the efficacy of ICIs between younger and older patients, the potential effect of age on the efficacy of ICIs remains little known and controversial. Herein, we aimed to analysis the association between age and the efficacy of ICIs based on MSKCC cohort. **Methods:** We screened out 1661 patients having complete information with advanced cancer, whose tumors underwent next-generation sequencing (NGS) detection and who were treated with at least one dose of ICI in MSKCC cohort. All patients were divided into two groups according to age, the younger group (age $\leq$50-year old) and the older group (age $>$ 50-year old). We further analyzed the differences in overall survival (OS) and TMB between the two groups. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated via Cox regression model for OS and P-values were calculated via the Wilcoxon sign test for TMB. We analyzed the effect of age on ICI in lung cancer using the same way. **Results:** In 1661 patients with cancer in our study, 312 (19%) younger and 1349 (81%) older patients were found. The pooled HRs for OS was 1.28 (95% CI: 1.09-1.52) in younger group compared with older group. In 1661 patients with cancer, there was 350 (21%) patients with lung cancer, including 30 (9%) younger and 320 (91%) older patients. The pooled HRs for OS was 1.45 (95% CI: 0.95-2.23) in younger group compared with older group in lung cancer. In addition, TMB in older group was higher than in younger group and significant difference of TMB was found via the Wilcoxon sign test (p = 2.6e-10) between the two groups, especially in lung cancer (p = 1e-4). **Conclusions:** Our study assessed the impact of age on the efficacy of ICIs using the threshold of 50 years old for the first time and we founded that patients in older group had higher TMB and longer OS than younger group. Research Sponsor: None.

2639 **Poster Session**

Improving tolerability of pembrolizumab with weight based dosing: A meta-analysis.

Nabeela Khan Patail, Amna Falak Sher, Shenhong Wu; Stony Brook University Hospital, Stony Brook, NY; Stony Brook University School of Medicine, Stony Brook, NY

Background: Pembrolizumab, a PD-1 immune checkpoint inhibitor (ICI), has demonstrated significant clinical activity in various cancers. Despite a favorable toxicity profile, discontinuation due to adverse events including immune related adverse events (irAE) has been reported. We conducted a meta-analysis of published clinical trials to evaluate the tolerability of pembrolizumab in cancer patients. **Methods:** A systematic review was conducted of relevant studies from the databases of PubMed and abstracts presented at American Society of Clinical Oncology (ASCO) from June 2015 until September 2020. Eligible studies included prospective clinical trials that reported a discontinuation rate due to adverse effects. Incidence, relative risk and 95% confidence intervals (CI) were calculated by employing fixed or random effects models. **Results:** A total of 6,380 patients with a variety of hematologic and solid malignancies from 20 studies of pembrolizumab were included for analysis. The overall rate of pembrolizumab discontinuation due to adverse events was 8.2% (95% CI: 6.4-10.4%). The discontinuation rate of pembrolizumab was not significantly lower than the chemotherapy controls, with RR of 0.84 (95% CI: 0.58-1.12, $p = 0.33$). However, the discontinuation rate of pembrolizumab was significantly higher compared to placebo control with RR of 2.20 (95% CI: 1.36-3.54, $p < 0.001$), and significantly lower compared to ipilimumab with RR of 0.58 (95% CI: 0.34-0.99, $p = 0.04$) respectively. The discontinuation rate varied widely among different tumor types with the lowest rate of 0.8% (95% CI: 0.2-3%) in gastric cancer, and the highest of 13.5% (95% CI: 10.8-16.8%) in head and neck squamous cell carcinoma. Interestingly, the discontinuation rate varied with pembrolizumab dosing, with the fixed dosing of 200mg being 9.2% (95% CI: 6.9-12%) and the weight-based dosing being 6.5% (95% CI: 4.8-8.8%). The weight-based dosing was associated with a significantly lower discontinuation rate compared to controls with RR of 0.62 (95% CI: 0.47-0.81, $p < 0.0001$), while the fixed dosing had similar discontinuation rate with RR of 1.03 (95% CI: 0.89-1.20, $p = 0.67$). **Conclusions:** The tolerability of pembrolizumab may be comparable to chemotherapy in cancer patients and may vary with its dosing. Future studies are warranted to evaluate the impact of different dosing. Research Sponsor: None.

Pan-Canadian cohort of immune checkpoint inhibitor-induced insulin-dependent diabetes mellitus (CANDIED).

Thiago Pimentel Muniz, Daniel Vilarim Araujo, Kerry J. Savage, Tina Cheng, Moumita Saha, Xinni Song, Sabrina Gill, Jose Gerard Monzon, Debjani Grenier, Sofia Genta, Anna Spreafico, David Hogg; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Hospital de Base. Department of Medical Oncology., Sao Jose Do Rio Preto, Brazil; Division of Medical Oncology, Department of Medicine, The University of British Columbia, Vancouver, BC, Canada; Department of Oncology, University of Calgary, Calgary, AB, Canada; School of Medicine, University of British Columbia, Vancouver, BC, Canada; Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, ON, Canada; Division of Endocrinology & Metabolism, Department of Medicine, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada; Department of Medical Oncology, University of Manitoba, Winnipeg, MB, Canada

Background: Endocrine immune-related adverse events (irAEs) are frequent with immune checkpoint inhibitors (ICIs); however, ICI-related insulin-dependent diabetes mellitus (IDDM) is a rare but serious endocrine irAE. We describe the characteristics of patients who developed ICI-related IDDM across five academic Canadian cancer centres. **Methods:** In this multicentre, retrospective study, we included both patients who developed IDDM and patients with non-IDDM (NIDDM) or pre-DM who became insulin-dependent while on treatment with ICI. We collected data on primary tumor type, ICI regimen (single agent or combination), time to development of IDDM from ICI initiation, comorbidities, laboratory parameters at the time of IDDM diagnosis, tumor response and survival. A p value < 0.05 was considered statistically significant. **Results:** We identified 27 patients between July 2016 and August 2019. Median age was 60 (39-79) years, 20 (74%) were male, 15 (55%) had melanoma and 4 each (15%) non-small cell lung cancer (NSCLC) and renal cell carcinoma. Seven (26%) patients had prior NIDDM or pre-DM; 5 (18%) had an auto-immune disease (2 psoriasis, 2 inflammatory bowel disease, and 1 systemic lupus erythematosus). Laboratory parameters at presentation and management of IDDM are presented in the Table. Mean A1c was not statistically different between patients with or without prior NIDDM or pre-DM (8.4% vs. 8.6%; $p = 0.9$). All IDDM events were irreversible; 1 (4%) patient died of diabetic ketoacidosis. At time of IDDM diagnosis, 17 (63%) patients were receiving single agent anti-PD1 and 10 (37%) anti-PD1-based combinations (7 anti-CTLA-4, and 3 other compounds). Median time for development of IDDM from ICI initiation was 2.7 months (95% CI 0.2-5.3). Patients receiving combination ICI developed IDDM earlier than those treated with single agent (1.4 vs 4.8 months; $p = 0.05$). Amongst patients with metastatic disease (n = 24), 9 (38%) had a complete response and 7 (29%) had a partial response. Two patients (8%) were treated in the adjuvant setting; 1 (4%) received consolidation ICI. IDDM led to ICI discontinuation in 12 (44%) patients. After a median follow up of 21 months from ICI initiation, median survival was 30 months (95% CI NE) and was not reached in patients with melanoma and NSCLC. **Conclusions:** ICI-related IDDM is a rare and typically irreversible irAE that occurs early in the course of treatment and develops earlier with combination ICI. In this cohort, patients who developed ICI-related IDDM had a high tumor response rate and prolonged survival, especially melanoma and NSCLC patients. Prospective evaluation of autoantibodies to predict development of IDDM is ongoing. Research Sponsor: None.

Glucose, mean (SD)	33 μmol/L (15.6)
A1c (17 patients), mean (SD)	8.5% (1.9)
C-peptide decreased (12 patients)	8 (67%)
Diabetic ketoacidosis	14 (52%)
Management	
Insulin Replacement	27 (100%)
Hospital Admission	18 (67%)
Steroids	4 (15%)
Infliximab	1 (4%)

2641 **Poster Session**

Real-world outcomes of treatment with immune checkpoint inhibitors in unique patient cohorts: Elderly, non-caucasian race, poor performance status, obese, chronic viral infections, and autoimmune diseases.

Neil J. Shah, Shuo Wang, Aquino Williams, Melinda Weber, Brittany Sinclaire, Elli Gourna Paleoudis, Adil Alaoui, Shaked Iev-Ari, Shari Adams, Jordan Kaufman, Sahil B. Parikh, Emily Tonti, Eric Muller, Michael T Serzan, Divya Cheruku, Jaeil Ahn, Andrew Pecora, Andrew Ip, Michael B. Atkins; Memorial Sloan Kettering Cancer, New York, NY; Georgetown University, Washington, DC; Hackensack Meridian Health Mountainside Medical Center, Montclair, NJ; John Theurer Cancer Center, Hackensack Univeristy Medical Center, Hackensack, NJ; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Hackensack Meridian Health, Hackensack, NJ; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; MedStar Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC; Hackensack Meridian Health Mountainside Medical Center, Montclaire, NJ; Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC

Background: Immune Checkpoint Inhibitors (ICI) have revolutionized current cancer treatment. Nevertheless, outcomes data across various patient cohorts are lacking. To address this knowledge gap, we conducted a comprehensive analysis of real-world data (RWD) that included patient cohorts traditionally underrepresented in clinical trials. **Methods:** We identified patients (pts) treated with ICI (anti-CTLA-4, anti-PD(L)1 or their combination at 6 US academic and community hospitals from 1/2011 – 4/2018. Clinical data obtained from EHR and CTCAE V4.03 was used to define immune-related adverse events (irAEs). **Results:** A total of 1332 pts treated with 1443 unique ICI treatments were included in the cohort. The median age was 66 (21-87), Male 58% (827), Caucasian 70% (1004), African American (AA) 16% (232), other race 14% (207), ECOG PS 0,1 79% (1130), chronic viral infection 5% [hepatitis B (24), hepatitis C (32) and HIV (17)], with BMI $>$ 30 22% (287) and autoimmune disease (AID) 15% (215). Lung cancer (NSCLC) 34% (423), and melanoma 27% (389) were top 2 tumor types and nivolumab 38% (544), pembrolizumab 23% (332), and ipilimumab plus nivolumab 12% (180) were the most common ICI treatments. Overall survival (OS) was worse for patients with ECOG $\geq$2 (0.34 - 0.63) vs. ECOG 0,1 (1.27 - 1.73, P $<$0.001), and better with AID (1.21 - 2.63) vs. no AID (0.90 - 1.24, P=0.01) and Caucasian (1.02 - 1.45) vs AA (0.72 - 1.30, P=0.02). No difference in OS was noted for sex, other races, h/o chronic viral infection or obesity. We performed an analysis of OS and irAEs restricted to NSCLC patients (n=423); (N=447 unique ICI treatments); age $>$75 27% (120), AA 28% (124), Female 50% (224), ECOG PS $\geq$2 23% (104), BMI $>$30 15% (62), chronic viral infections 10% (44), and AID 14% (62). The ICI therapies were nivolumab 55% (245), pembrolizumab 23% (102), and atezolizumab 6% (27) and 16% (others). Data is contained in the table. **Conclusions:** Overall, in our RWD, OS appeared to be similar across above cohorts except poor OS for pts with ECOG $\geq$2. irAEs also appeared to be similar across cohorts except less with ECOG $\geq$2. In NSCLC cohort, we noted similar findings except less irAEs in Male cohort. Prospective studies are needed to confirm the above findings. Research Sponsor: U.S. National Institutes of Health.

NSCLC (N=447)	Overall survival Hazard Ratio	P value	Any grade IrAEs	P value univariate	Adj. P value multivariable
18-75 vs. Age > 75	0.90	0.5	29% vs. 40%	0.03	0.078
Male vs. Female	0.87	0.33	26% vs. 38%	0.01	0.046
Caucasian vs. AA	0.76	0.08	35% vs. 24%	0.08	N/A
No Chronic viral infections vs. Yes	1.19	0.48	31% vs 41%	0.23	N/A
No autoimmune disease vs. Yes	0.68	0.07	30% vs 45%	0.03	0.07
ECOG PS 0,1 vs. ECOG PS $\geq$2	1.96	0.01	36% vs. 20%	0.005	0.004
BMI 12 -30 vs. >30-60	1.10	0.60	30% vs. 36%	0.47	N/A

Maintenance immunosuppressive therapy with resumption of immune checkpoint inhibitor treatment to reduce recurrence of immune-mediated colitis.

Hamzah Abu-Sbeih, Fangwen Zou, Barbara Dutra, Mehmet Altan, Jennifer Leigh McQuade, John A. Thompson, Anusha Thomas, Yinghong Wang; University of Missouri, Kansas City, MO; Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, China; University of Texas Health Science Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Seattle Cancer Care Alliance, Seattle, WA

Background: Immune-mediated colitis (IMC) may limit immune checkpoint inhibitors (ICI) treatment. Current guidelines recommend consideration of resuming ICI when IMC symptoms subside to ≤ grade 1. We aimed to investigate the effect of maintenance immunosuppressive therapy (IST) on the outcome of IMC in patients who resume ICI therapy. **Methods:** We retrospectively studied patients who resumed ICI therapy after adequate treatment of IMC from March 2015 to June 2020 at MD Anderson Cancer Center. Relevant demographic, oncologic, and ICI data were collected and analyzed. Univariate logistic regression analysis was conducted to assess risk factors of IMC recurrence. **Results:** We included 102 patients with a median age of 61 years. 66% were males and 97% were Caucasians. 48 patients (47%) received IST maintenance in conjunction with ICI resumption and 54 patients did not. Symptoms of IMC recurred in 28 patients, 8 (17%) in the concurrent IST group and 20 (37%) in the other group. Compared to no concurrent IST group, patients on concurrent IST were more likely to have received combined ICI regimen (60% vs 41%, p = 0.003) and more initial ICI doses (9 vs 5 doses, p = 0.030). Concurrent IST group had significantly longer ICI treatment duration on resumption (72 vs 62 days, p = 0.023), more ICI resumed doses (5 vs 4 doses, p = 0.038), and lower IMC recurrence (17% vs 37%, p = 0.027). Patient who received more IST doses, both therapeutic and prophylactic, had lower rate of IMC recurrence (OR 0.72, p = 0.012; table). IST maintenance treatment (OR 0.34, p = 0.024) was associated with lower IMC recurrence rate after ICI resumption. Vedolizumab was the predominant IST used. Overall survival was comparable among the two groups (p = 0.934). **Conclusions:** Concurrent IST treatment with ICI resumption after IMC was associated with significantly lower IMC recurrence and more extended ICI treatment while reserving similar overall survival to patients without IST maintenance therapy. Future prospective randomized trial of concurrent IST is still merited for further clarification. Research Sponsor: None.

Univariate logistic regression analysis for risk factors of IMC recurrence.

Characteristic	OR (95% CI)	*P*
Initial ICI type		
CTLA-4	Reference	
PD-(L)-1	0.58 (0.15-2.18)	0.419
Combination	0.68 (0.19-2.34)	0.548
Use of IST for the initial IMC	0.86 (0.29-2.50)	0.776
Dose of IST for initial IMC	0.73 (0.46-1.17)	0.733
Corticosteroids duration for initial IMC	0.98 (0.96-1.02)	0.376
Total number of IST doses	0.72 (0.55-0.94)	0.012
IST Concurrent treatment	0.34 (0.13-0.87)	0.024
Concurrent treatment		
Infliximab	0.68 (0.19-2.47)	0.556
Vedolizumab	0.23 (0.07-0.74)	0.014
None	Reference	
Type of ICI resumed		
PD-(L)1	Reference	
CTLA-4 based	1.75 (0.71-4.68)	0.252
Median duration from last ICI to resumption	1.01 (0.99-1.02)	0.742

IST: immunosuppressive therapy.

2643 **Poster Session**

Outcomes of immune checkpoint inhibitor-mediated colitis: Multicenter cohort study.

Hamzah Abu-Sbeih, Tenglong Tang, David M. Faleck, Michael L. Dougan, Anna Olsson-Brown, Douglas Buckner Johnson, Dwight Hall Owen, David Engar Warner, Alexander B Philipp, Nick Powell, Ella Daniels, Jessica Philpott, Alison Margaret Weppler, David James Pinato, Yinghong Wang; University of Missouri, Kansas City, MO; The Second Xiangya Hospital, Central South University, Changsha, China; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital Cancer Center, Boston, MA; The Clatterbridge Cancer Centre, Wirral, United Kingdom; Vanderbilt University Medical Center, Nashville, TN; Division of Medical Oncology, Department of Internal Medicine, Ohio State University, Columbus, OH; Wake Forest Baptist Health, Winston-Salem, NC; Department of Medicine II, University of Munich, Munich, Germany; Imperial College London, London, United Kingdom; Chelsea and Westminster Hospital, Chelsa, United Kingdom; Cleveland Clinic, Cleveland, OH; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Surgery and Cancer, Imperial College, London, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitor (ICI)-mediated colitis (IMC) is a common and serious adverse event. Although small series have described the clinical presentation of IMC, large multicenter series that integrate clinical, endoscopic, and histologic findings are lacking. **Methods:** We retrospectively assessed patients who received ICI and had endoscopically confirmed IMC from 2010 to 2019. IMC was graded based on the CTCAE version 5.0 criteria. Multivariate logistic regression analyses were conducted to assess factors associated with recurrence of IMC symptoms and long duration of corticosteroids use ($>$ 70 days). **Results:** 675 patients were included. 387 patients were males (57%). Median age was 63 years. Melanoma was the most common cancer type (327; 48%). Most (365; 54%) patients received CTLA-4 inhibitor ICI, as monotherapy or in combination with PD-(L)1. Median time from ICI therapy to IMC was 62 days. IMC was grade 2 in 335 (50%) patients, Grade 3 in 181 (27%), and grade 4 in 16 (3%). 155 (23%) patients had mucosal ulceration on endoscopy, 91 of them had severe features (deep, large, or multiple ulcers); 336 (50%) patients had non-ulcerative inflammation. The rest had normal endoscopic findings with histologic inflammation. Most patients were admitted to the hospital for management of IMC (405; 60%) and 16 (3%) needed ICU-level of care. Treatment included corticosteroids in 577 (85%) patients (median duration 52 days), TNF inhibitor in 245 (36%), and vedolizumab in 90 (13%). 202 (32%) patients had recurrent IMC after resolution of symptoms. On multivariate logistic regression, factors associated with IMC recurrence and long ($>$ 70 days) duration of corticosteroid therapy were grade of IMC ($p = 0.049$), treatment with infliximab or vedolizumab ($p = 0.044$), presence of mucosal ulceration ($p = 0.034$), or features of active histologic inflammation ($p = 0.076$). Of note, patients with mucosal ulceration received infliximab or vedolizumab more frequently ($p < 0.001$). For patients with grade 2 IMC, mucosal inflammation on endoscopy and delay in performing endoscopy with time from IMC onset to endoscopy more than a month were associated with IMC recurrence and longer duration of corticosteroid use ($p = 0.029$ and $p < 0.001$, respectively). 16 (3%) patients had colonic perforation, 7 of them underwent surgical resection. No IMC-related death occurred. **Conclusions:** IMC is a clinically significant adverse event that can lead to premature termination of ICI therapy with high rates of hospital admission. Rarely, it results in colonic perforation requiring surgical intervention and ICU admission. Our data suggest that there is a utility of endoscopic and histologic evaluation in the prediction of worse outcomes from IMC. This finding is particularly important for grade 2 IMC as current guidelines do not recommend endoscopic evaluation for this group. Research Sponsor: None.

2644 **Poster Session**

Pancreatic volumes in immune checkpoint inhibitor-induced diabetes.

Rebecca Jeun, Sireesha Yedururi, Victor Lavis, Conor Best, Jeena Varghese, Ramona Dadu, Isabella Claudia Glitza, Sonali Thosani; Baylor College of Medicine, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitor-mediated insulin dependent diabetes (ICI-DM) is a rare and irreversible adverse event often presenting with life-threatening diabetic ketoacidosis (DKA). Pancreatic volume changes have been studied in classic Type 1 and Type 2 diabetes as a surrogate for functional β-cell mass. In this study, we investigate longitudinal changes in pancreatic volumes in patients who develop ICI-DM. **Methods:** Among patients with ICI-DM seen at our institution between 2014 and 2020, 20 patients who had serial CT scans of the abdomen and pelvis before and after ICI DM diagnosis were identified for inclusion in this study. Demographic data and clinical variables were obtained from the electronic medical record. Weight-adjusted pancreatic volumes were calculated from CT scans at three time points. The most recent CT scan prior to ICI initiation was used as baseline, the CT scan immediately prior to ICI DM diagnosis was used as a midpoint, and the most recent CT scan prior to the end of the study period was used as the final time point for comparison. **Results:** Median age was 63 years old (range 35 to 83). Renal cell carcinoma and melanoma were the most common cancer types. Male gender predominated (80%). 18/20 patients were on a PD-1 inhibitor with the remaining two on a PD-L1 inhibitor. After initiation of ICI therapy there was a variable response in pancreatic volumes prior to the diagnosis of ICI-DM with 20% patients experiencing a volume loss of $>$ 10% and 25% experiencing a volume gain of $>$ 10%. Volume loss nor volume gain prior to diabetes diagnosis was associated with presentation with DKA. 9/13 (69%) of patients who had pancreatic enzymes checked at diagnosis of ICI-DM had elevated levels. Pancreatic atrophy with a median volume loss of 41% was seen in all patients at a median of 14.9 months (range 3-77 months) after ICI-DM diagnosis. Most had more than 20% volume loss from baseline to most recent scan with no correlation in degree of volume loss with the time interval. There was no evidence of pancreatic ductal dilation, increased pancreatic fat nor any changes consistent with chronic pancreatitis. **Conclusions:** This study shows a variable response in pancreatic volumes after initiation of ICI in patients who progress to developing ICI-DM, though most had a significant decline in volume after the diagnosis of ICI-DM with long-term pancreatic atrophy. As β-cell mass is thought to comprise 1-2% of the pancreas, these findings may suggest both endocrine and exocrine compartment changes because of ICI-DM, though exocrine dysfunction has not been clinically described in this patient population. As these patients receive frequent imaging during treatment, fluctuations in pancreatic volumes with new or worsening hyperglycemia may portend the onset of ICI-DM and clinicians should have a low threshold to screen for this diagnosis as many will present with life-threatening DKA. Research Sponsor: None.

2645 **Poster Session**

Incidence of hepatitis associated with addition of immune checkpoint blockade to conventional solid tumor therapy: A meta-analysis of phase 3 randomized clinical trials.

Yu Fujiwara, Nobuyuki Horita, Ho Namkoong, Hirotaka Miyashita, Matthew Harrington, Matt D. Galsky; Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY; Chemotherapy Center, Yokohama City University Hospital, Yokohama, Japan; Division of Pulmonary Medicine, Department of Medicine, Keio University School of Medicine, Tokyo, Japan; Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Immune checkpoint blockade (ICB) has emerged as a promising treatment strategy for many solid tumors. Although safe for many patients, ICB causes immune-related adverse events (irAEs) including hepatitis, which may result in morbidity and treatment disruption. Severe hepatitis requires immunosuppression, including corticosteroids and mycophenolate mofetil. We conducted a meta-analysis of clinical trials to investigate the effect of adding ICB to conventional solid tumor therapy on the incidence of hepatitis. **Methods:** Phase 3 randomized clinical trials (RCTs) comparing ICB and conventional therapy to conventional therapy alone were chosen by database search on PubMed, Embase, Web of Science, and Cochrane Library. The odds ratios [OR] of any-grade and grade ≥3 hepatitis, elevated aspartate aminotransferase (AST), and elevated alanine aminotransferase (ALT) were calculated. Meta-analysis was conducted to determine the incidence of hepatitis, elevated AST, and elevated ALT among patients receiving ICB and those receiving conventional therapy alone. Subgroup analysis based on the mechanism of ICB (Cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitor, programmed cell death protein 1 [PD-1] inhibitor, and programmed death-ligand 1 [PD-L1] inhibitor) was also conducted. **Results:** A total of 29 randomized controlled trials (RCTs) enrolling 18,829 participants were analyzed. Incidence of hepatitis was derived from 24 RCTs enrolling 15,183 patients, and incidence of grade ≥3 hepatitis was derived from 22 RCTs enrolling 13,846 patients. Incidence of elevated AST was extracted from 18 RCTs, and incidence of elevated ALT was extracted from 20 RCTs. Addition of ICB to conventional therapy was associated with an increase in incidence of any-grade hepatitis (OR 2.54, 95% confidence interval [CI] 1.82-3.55) and grade ≥3 hepatitis (OR 4.22, 95% CI 2.51-7.11). The addition of ICB was also associated with an increase in incidence of elevated AST (any grade: OR 2.19, 95% CI 1.59-3.03; grade ≥3: OR 3.18, 95% CI 1.85-5.48) and elevated ALT (any grade: OR 2.08, 95% CI 1.47-2.92; grade ≥3: OR 2.41, 95% CI 1.40-4.14). Subgroup analysis based on the mechanism of ICB demonstrated increased incidence of grade ≥3 hepatitis associated with CTLA-4 inhibitor, PD-1 inhibitor, and PD-L1 inhibitor therapy (OR 2.78, 95% CI 1.26-6.14; OR 6.30, 95% CI 2.23-17.78; OR 4.73, 95% CI 1.83-12.23, respectively). No significant difference of heterogeneity was observed among subgroups ($I^2 = 0\%$, $p = 0.43$). **Conclusions:** Addition of ICB to conventional solid tumor therapy was associated with increased incidence of any-grade and severe hepatitis, and elevations of AST and ALT, regardless of the mechanism of ICB. Clinicians should weigh the risk of liver toxicity when considering addition of ICB therapy in patients with solid tumors. Research Sponsor: None.

2646 **Poster Session**

A first-in-human, multicenter, open-label, phase 1 study of ATOR-1017, a 4-1BB antibody, in patients with advanced solid malignancies.

Gustav J. Ullenhag, Jeffrey Yachnin, Ana Carneiro, Emma Elison, Malin Carlsson, Charlotte Astrid Russell, Karin Enell Smith; Akademiska Sjukhus, Uppsala, Sweden; Karolinska Institutet, Stockholm, Sweden; Lund University Hospital and Lund University, Lund, Sweden; Alligator Bioscience, Lund, Sweden

Background: ATOR-1017 is a human agonistic IgG4 antibody targeting the co-stimulatory receptor 4-1BB (CD137). It is developed to activate T cells and natural killer cells in the tumor environment, leading to immune-mediated tumor cell killing. This is a first-in-human, multicenter, phase 1 study (NCT04144842). **Methods:** In this study, ATOR-1017 is administered intravenously every 21 days as a single agent to patients with solid malignancies. ATOR-1017 is administered until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. The primary objective of the study is to determine the maximum tolerated dose, assessed by adverse events (AEs) and dose limiting toxicities (DLTs), and the recommended phase 2 dose. Secondary objectives include pharmacokinetics, immunogenicity and clinical efficacy, assessed with CT scans using response criteria for use in studies testing immunotherapeutics (iRECIST). The study uses a single cohort design for doses up to 40 mg, and thereafter a modified 3+3 design. **Results:** The first patient was dosed in December 2019; by 22 Jan 2021, twelve patients have been exposed to ATOR-1017. The following dose levels have been evaluated; 0.38 mg; 1.5 mg; 5 mg; 15 mg; 40 mg and 100 mg. Dose escalation is ongoing, and the 200 mg dose level is under evaluation. The maximum tolerated dose has not been reached. The following cancer types are included; ovarian cancer (n = 1), choroidal melanoma (n = 3), anal cancer (n = 1), cholangiocarcinoma (n = 1), gastrointestinal stromal tumor (n = 1), breast cancer (n = 1), pancreatic cancer (n = 1), adenoid cystic cancer (n = 1), malignant melanoma (n = 1), colorectal cancer (n = 1). Drug-related AEs were reported in 5 out of 12 patients; one patient experienced a grade 3, all others were grade 1 or 2. There have been two episodes each of chest pain (grades 2 and 3) and headache (grades 1 and 2). Single cases of pyrexia, upper abdominal pain, mouth ulceration, nausea, leukopenia, neutropenia, cytokine release syndrome (CRS), arthralgia, neck pain, and rash were also reported. No DLTs have been observed in the study to date. The median age of the patients were 48.5 years (range 34-76). Patients received a median of 2 prior lines of therapy (range 1-4). The median time on study were 15 weeks (range 0.14-51). Six patients are on study, and six patients have discontinued treatment. Reasons for discontinuation include; investigator decision (n = 1), confirmed disease progression (n = 1), withdrawal of consent (n = 1), death due to disease progression (n = 1) and other reason (n = 2). Preliminary PK data show dose-proportional kinetics up to 100 mg. Best response has been stable disease. **Conclusions:** ATOR-1017 is safe and well-tolerated up to 100 mg. Dose escalation continues and the current dose level is 200 mg. Clinical trial information: NCT04144842. Research Sponsor: Alligator Bioscience.

2647 **Poster Session**

Consensus disease definitions for the spectrum of neurologic immune related adverse events.

Amanda C Guidon, Leeann B Burton, Bart K Chwalisz, James M Hillis, Teilo Schaller, Kerry Lynn Reynolds, Neuro irAE Disease Definition Panel; Harvard Medical School, Boston, MA; Mass Eye and Ear Institute, Boston, MA; Project Data Sphere, Cary, NC; Massachusetts General Hospital Cancer Center, Boston, MA

Background: Expanding FDA-approved indications for immune checkpoint inhibitors in patients with cancer has resulted in both therapeutic success and immune related adverse events (irAEs). Neurologic irAEs (irAE-Ns) have an incidence of 1-12% and a high fatality rate relative to other irAEs. Lack of standardized disease definitions and accurate phenotyping leads to syndrome misclassification and impedes evidence-based treatments and research progress. The objectives of this study were to develop consensus guidance for an approach to irAE-Ns including disease definitions and severity grading. **Methods:** A working group of 4 neurologists drafted irAE-N consensus guidance and definitions, which were reviewed by the Neuro irAE Disease Definition Panel, consisting of neurologists, oncologists, neuro-oncologists and irAE subspecialists. A modified Delphi consensus process was used, with 2 rounds of anonymous ratings by panelists and 2 virtual meetings to discuss areas of controversy. Panelists rated content for usability, appropriateness and accuracy on 9-point scales in electronic surveys and provided free text comments. The working group aggregated survey responses and incorporated them into revised definitions. Consensus was based on numeric ratings using the RAND/UCLA Appropriateness Method with prespecified definitions. **Results:** Twenty-seven panelists from 15 academic medical centers voted on a total of 53 rating scales (6 general guidance, 24 central and 18 peripheral nervous system disease definition components, 3 severity criteria and 2 clinical trial adjudication statements); of these, 77% (41/53) received first round consensus. After revisions, all items received second round consensus. Consensus definitions were achieved for 7 core disorders: irMeningitis, irEncephalitis/Encephalomyelitis, irDemyelinating disease, irVasculitis, irNeuropathy, irNeuromuscular junction disorders and irMyopathy. For each disorder, 6 sub-classifications are described: disease subtype, diagnostic certainty, severity, autoantibody association, exacerbation of pre-existing disease or de novo presentation and present or absent concurrent irAE. **Conclusions:** These disease definitions standardize irAE-N classification. They are being incorporated into a multi-institutional registry that our group has initiated to study irAEs. Given consensus on their accuracy and usability from a representative panel group, we anticipate that they can be used broadly across clinical and research settings. Research Sponsor: Support from the non-profit Project Data Sphere.

2648 **Poster Session**

A risk stratification model for toxicities in phase 1 immuno-oncology (P1-IO) trials.

Alberto Hernando-Calvo, Abdulazeez Salawu, Marc Oliva Bernal, Daniel Vilarim Araujo, Zhihui (Amy) Liu, Rachel Chen, Lillian L. Siu; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Institut Català d'Oncologia Hospitalet. Institut Català d'Investigació Biomèdica de Bellvitge (IDIBELL), Spain, Barcelona, Spain; Hospital de Base. Department of Medical Oncology., Sao Jose Do Rio Preto, Brazil; Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Princeton University, Princeton, NJ

Background: Despite an exponential increase in the number of potential targets in the immuno-oncology (IO) field, lack of risk models to predict toxicities remains a challenge in early drug development. We proposed a risk stratification strategy and investigated whether different IO classes may be associated with incremental risk of toxicities. **Methods:** A systematic search for IO studies from 01/2014 to 10/2020 was conducted. Among the 12053 abstracts screened, 254 reporting phase I-IO trials were selected. Type of IO treatment (IO monotherapy [mono] vs IO combination [comb]), therapeutic class (e.g. IO, molecularly targeted agents [MTA]), and dose escalation method (rule-based, model-based and model-assisted) were collected. A risk scoring model was developed after expert consensus: treatment-related deaths (1:yes, 0:no), incidence of G3/G4 treatment related adverse events (TRAE) or treatment emergent adverse events (TEAE) (0 if 1-29%,1 if ≥30-49%, 2 if ≥50%), incidence of ≥G2 cytokine release syndrome (1:yes, 0:no), incidence of ≥G2 encephalopathy (1:yes 0:no) and incidence of dose-limiting toxicity (DLT) (0:no, 1:lab, 2:clinical). Risk categories were defined by summing all points (0 = low, 1-2 = intermediate, 3+ = high) and were correlated with type of IO treatment, therapeutic class and dose escalation method. **Results:** Of 254 P1-IO trials reviewed, 228 (90%) were scorable, 26 were not (25 due to lack of AE data). Up to 10/26 (38%) of non-scorable studies were cell therapies. Among the 228 scorable studies, 120 (53%) scored 0, 65 (28%) scored 1-2, 43 (19%) scored 3+; 24 (11%) and 125 (55%) did not provide no. of pts with G3/G4 TRAEs or TEAEs respectively. A significant association was observed between risk categories and therapeutic class ($p<0.001$) (see table). Additionally, IO-MTA and IO-IO were both associated with an increased risk of toxicity as compared to IO-mono (OR=3.91 (95%CI 1.7-9.2), p=0.002) and (OR=2.79 (95%CI 1.2-6.5), p=0.02) respectively. There was no association between dose escalation method and risk of toxicity (p=0.95), but 182 (92%) used rule-based methods. **Conclusions:** Our results suggest that different IO classes are associated with different risks of toxicity. This risk classification strategy may guide future clinical trial design. Additionally, standards for reporting toxicities in P1-IO trials are urgently needed. Research Sponsor: None.

IO class	N	Score = 0	Score = 1-2	Score = 3+
AntiPD-1/PD-L1 (mono)	20	11 (55)	7 (35)	2 (10)
AntiPD-1/PD-L1 (comb)	22	5 (23)	9 (41)	8 (36)
AntiCTLA-4	8	1 (13)	4 (50)	3 (37)
Co-stimulatory mAbs	12	4 (33)	4 (33)	4 (33)
Cytokines	18	3 (17)	7 (39)	8 (44)
BITE	4	0 (0)	0 (0)	4 (100)
Cell therapy (no conditioning)	13	11 (85)	2 (15)	0 (0)
Cell therapy (conditioning regimen)	8	1 (13)	3 (37)	4 (50)
Oncolytic virus	9	4 (44)	4 (44)	1 (11)
Vaccines	79	66 (83)	10 (13)	3 (4)
Other immunodulators	35	14 (40)	15 (43)	6 (17)

2649 **Poster Session**

Prevalence of hyperprogressive disease (HPD) mutations and correlations to immune-related biomarkers in a large pan-cancer Chinese cohort.

Shengli Yang, Xinyi Liu, Ting Bei, Mengli Huang; Department of Thoracic Surgery, Foshan First People's Hospital, Foshan, China; The Medical Department, 3D Medicines Inc., Shanghai, China; The Medical Department, 3D Medicines, Inc., Shanghai, China

Background: Immune checkpoint blockade (ICI) therapies have demonstrated inspiring clinical efficacy in multiple types of cancer. However, a subset of patients suffered rapid tumor growth after ICI treatment, which is known as hyperprogressive disease (HPD). Although the mechanism of HPD has not been fully elucidated, some genomic alterations, such as CDKN2A/CDKN2B loss and MDM2/MDM4 amplification were reported to occur in tumors with ICI-related HPD. We analyzed the prevalence of these four HPD mutations and their association with PD-L1 expression, TMB, and occurrence of driver gene mutations in a large pan-cancer Chinese cohort. **Methods:** Patients whose tumor tissues were subjected to molecular profiling using targeted next-generation sequencing from January 2017 – November 2020 were included. Single nucleotide variants (SNV), copy number variants (CNV), insertion/deletions (indels) and fusions were called. PD-L1 expression was stratified by CPS 5. Fisher's exact test were conducted to compare the frequencies of biomarkers and Mann-Whitney U test was used to compare the TMB level between the HPD mutations group and their wild-type counterpart. **Results:** 45,785 patients of 22 types of cancer were queried. Across all 22 cancers, CDKN2A loss and CDKN2B loss were most commonly seen in ESCA (23.3%, 19.8%), while with the lowest frequency in PRAD (0.18%, 0.18%). MDM2 gain and MDM4 gain occurred most frequently in SARC (14.6%) and BRCA (3.3%), respectively, with the lowest frequency in COAD (0.05%, 0.07%). PD-L1 positive (CPS$\geq$5) rates were similar in CDKN2A/B loss, MDM2/4 amp and wild-type groups in the whole cohort (26.1%, 25%, 27.7%). Enrichment of PD-L1 positivity was not observed in HPD-mutant groups in a specific cancer type. Compared with wild-type group, CDKN2A/B loss significantly correlated with higher TMB levels in NSCLC and SARC ($p < 0.05$) while MDM2/4 amp correlated with lower TMB levels in NSCLC, BTC, and STAD ($p < 0.05$). In NSCLC, SNV in EGFR, TP53, KEAP1, NFE2L2, STK11, PIK3CA, and SMARCA4 genes were significantly enriched in the CDKN2A/B loss group, while SNV in EGFR, RBM10, AR, KDR genes, and fusion in RET were significantly enriched in MDM2/4 amp group. **Conclusions:** HPD mutations were significantly associated with TMB level and occurrence of some driver genes, but were not correlated with PD-L1 expression. Our results revealed the immune-related molecular characteristics in tumors with HPD mutations, providing more insights into the exploration for mechanism of HPD. Research Sponsor: None.

2650 **Poster Session**

Pembrolizumab patient reported benefits: A perspective based on multiple tumors.

Elise Wu, Paivi H Miskala, Mohd Kashif Siddiqui, Pankaj Rai, Eva Hajdukova, Nathalie Erpelding, Jacqueline Vanderpuye-Orgle; Merck, North Wales, PA; Merck, Rockville, MD; Parexel International, Mohali, India; Parexel International, London, United Kingdom; HealthiVibe, Arlington, VA; Parexel International, Billerica, MA

Background: Pembrolizumab is a programmed death ligand receptor-1 (PD-L1) treatment indicated for multiple tumors. Patient-reported outcomes (PRO) benefit has only been reported at the tumor level, while a holistic review of PRO effects across tumor types has been missing. We performed a systematic review of PRO to assess the overall health-related quality of life (HRQoL) among cancer patients treated with pembrolizumab across multiple tumors. **Methods:** We systematically searched PRO evidence published from January 2014 to April 2020 across approved pembrolizumab indications using Embase, MEDLINE, and CENTRAL. Eligible studies were required to assess cancer patients treated with pembrolizumab (200 mg or 2mg/kg Q3W) and report PROs and/or HRQoL. The PRO evidence was summarized into three categories: short-term (≤Week 12), mid-term (Week 13-Week 24), and long-term (Week 25-Week 52). A clinically meaningful difference in HRQoL is defined as at least a 10 points improvement or deterioration relative to baseline; a change between ± 10 points is defined as stable. **Results:** We screened 1,262 citations, of which 16 publications reported EORTC QLQ-C30 data; 10 (9 trial-based studies; 1 observational study) of 16 publications reported global health status (GHS) mean change from baseline (CFB) across six indications. Within trial based studies in first-line setting (n=3 studies), the short-term, mid-term, and long-term GHS changes from baseline vary from 0.5 to 2.1, 1.2 to 8.4, and 1.6 to 2.5, respectively. For second-line plus setting (n=6 studies), GHS changes vary from -3.3 to 8.6, -1.0 to 10.9, and -0.9 to 9.2, respectively. Eight trial-based publications reported EORTC QLQ-C30 domain data as CFB. Short- or mid-term mean changes in functioning domain data showed improvement or stability in emotional, cognitive, role, and social functioning. Short-term deterioration in physical functioning was observed for 1 study, whereas physical functioning remained stable for other studies. For symptom domains, deterioration was not observed in any studies; mid-term improvement was reported by one study each in fatigue, dyspnea, and appetite loss; 2 studies reported mid-term improvement in pain. **Conclusions:** This is the first study that presented pembrolizumab PRO evidence at the product level. This study suggests that most pembrolizumab-treated patients maintained or improved HRQoL relative to baseline at pre-defined timepoints. This review's limitations include potential publication bias and lack of meta-analytic methods in reporting results. Nevertheless, these findings provide additional information about pembrolizumab's benefits to physicians and patients from a patient-centric perspective. Research Sponsor: Merck.

2651 **Poster Session**

Pseudoprogression and cancer immunotherapy: A seven year retrospective study of rate, temporal course, and predictive markers in an Irish tertiary referral center.

Kate McKendry, Fiona Desmond, Cian Ward, Austin G Duffy; Department of Medical Oncology, Dublin, GA, Ireland; Mater Misercordiae University Hospital, Dublin, Ireland; Mater Hospital, Dublin, Ireland; Mater Private, St Raphael's House, Dublin, Ireland

Background: Immunotherapy is a relatively new treatment strategy which has achieved unprecedented clinical efficacy in many advanced malignancies. However, the pattern of tumour response to immunotherapy is distinct from other therapies and poses major challenges to clinicians. One such challenge is pseudoprogression. The aim of this study was to assess the current management of patients on immunotherapy with radiological evidence of disease progression at first restaging imaging in an Irish cancer centre, and to determine the rate, time course, and predictive markers of pseudoprogression in those patients treated beyond progression (TBP). **Methods:** Patients treated with immunotherapy for metastatic malignancy in MMUH between March 2013 and September 2020 were retrospectively drawn. Inclusion required follow-up restaging imaging every 4-12 weeks for the duration of treatment. Patterns of response during immunotherapy were established from radiology reports and categorized as stable (SD), response (R), mixed disease (MD), or progressive disease (PD). Pseudoprogression was defined as progression/ mixed disease at first restaging compared to baseline followed by subsequent response/stable disease. **Results:** The cohort of 228 patients was comprised of 80 NSCLC, 74 melanoma, 25 RCC, 19 gynaecological, 14 gastrointestinal, 6 breast, 1 ESSCLC, and 9 other cancer patients. Median age was 61.16 (IQR 49.47-69.44). Therapeutic agents were anti-PD1 alone (176) or in combination with targeted therapy (6) or CTLA4 (13), CTLA4 alone (15), and anti-PD-L1 alone (13) or in combination with chemotherapy (5). At first restaging, the number (%) classified as SD, R, MD, and PD, respectively, was 29 (12.8), 62 (27.2), 16 (7), and 76 (33.3). Treatment was stopped prior to restaging in 44 (19.3) cases. Of the 92 patients with mixed/ progressive disease, 41 were TBP and 51 were not treated beyond progression (NTBP). Evidence of radiological progression and worsening performance status (PS) were the most common reasons given by clinicians for NTBP. Of those TBP, 20 had subsequent response/stable disease, occurring at a median of 105.50 (range 58.0-420) days after the initial restaging scan and giving an overall pseudoprogression rate of 8.8%. At one year, 100% of the pseudoprogression group was alive. The neutrophil-lymphocyte ratio (NLR) was significantly lower in the pseudoprogression group compared to those with true progression ($p = 0.006$). There was no significant difference in performance status between the two groups. **Conclusions:** Pseudoprogression on cancer immunotherapy is real but uncommon, with an overall incidence of 8.8%. It can occur any time up to 420 days after initial progression and indicates a high likelihood of $>$ 1 year survival. A low NLR may be a useful predictor of pseudoprogression but a technological solution is likely needed. Research Sponsor: None.

Proton pump inhibitors and antibiotics impact on toxicities and clinical outcomes in cancer patients treated with immunotherapy.

Haniel alves Araujo, Camila Motta Venchiarutti Moniz, Oddone Freitas Melro Braghiroli, Milena Perez Mak, Lucas Fernando Uratani, Ricardo Dahmer Tiecher, Priscila Muniz Moraes, Ingrid Barbosa, Veridiana Pires De Camargo, Maria Ignez Freitas Melro Braghiroli, Gilberto Castro, Paulo Marcelo Hoff, Maria Del Pilar Diz; Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, Brazil; Instituto D'Or de Pesquisa e Ensino, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; Instituto do Cancer do Estado de São Paulo (ICESP), São Paulo, Brazil; Instituto Do Cancer Do Estado De São Paulo, São Paulo, Brazil; Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil; Universidade de São Paulo, São Paulo, Brazil

Background: Gut microbiome dysbiosis impairs systemic immune responses and recent evidence suggests its critical role in patients (pts) treated with immune checkpoint inhibitors (ICI). Proton pump inhibitors (PPI) and antibiotics (ATB) may alter the microbiome and their impact on clinical outcomes and toxicities requires further investigation. **Methods:** This retrospective cohort included consecutive metastatic cancer pts treated with ICI with palliative intent. We reviewed pts' records, concomitant medication and toxicities graded by CTCAE 4.0. Pts with PPI or ATB exposure were analyzed according to previous use (pPPI and pATB, $\leq$60 days to ICI) and concomitant use (cPPI and cATB). We estimated median overall survival (mOS) and progression free survival (PFS) by Kaplan–Meier and used a Cox proportional-hazards model to adjust for differences in baseline characteristics. Toxicities and ATB/PPI interaction was calculated using Pearson Chi-square method. **Results:** We enrolled 216 pts with a median age of 59 years, mostly ECOG-PS 0 (34%) or 1 (58%). ICI employed were mostly anti-PD-1 (60.2%), anti-CTLA-4 (16.2%) and anti-PD-L1 (12.5%). Most frequent primary tumor sites were lung n = 39 (18.1%), gastrointestinal n = 34 (15.7%) and melanoma n = 33 (15.2%). Half of the pts (108) received ATB and 114 (52.8%) PPI. Compared to control, pPPI group n = 57 (26.4%) had shorter mOS (11.6m vs 19.7m, $p < 0.001$) and PFS (2.8m vs 8.5m, $p < 0.001$), but no statistically significant difference in toxicities grade $\geq$3 and/or leading to ICI discontinuation (36% vs 29.1%; p = 0.29). cPPI n = 100 (46.3%) depicted a negative impact on mOS (12.1m vs 17.0m; p = 0.01), PFS (4.3m vs 7.1m; p = 0.04) and augmented toxicities (42% vs 19%; $p < 0.001$). pATB n = 34 (15.7%) had shorter OS (6.9m vs 19.3m, $p < 0.001$) and PFS (3.2 vs 7.2m, p = 0.005) and higher incidence of toxicities (45.9% vs 28.1%; p = 0.04). cATB use n = 92 (42.6%) did not impact OS (12.1m vs 15.6m; p = 0.32) or PFS (5.5m vs 5.9m; p = 0.82), but had a higher incidence of toxicities: 37% vs. 24.2% (p = 0.05). Multivariate analyses confirmed that pATB therapy and pPPI respectively remained as independent prognostic variables associated with OS (HR 2.39; 95% CI, 1.60-3.59; P <.001 and HR 1.73; 95% CI 1.23-2.44; P = 0.002) and PFS (HR 1.72; 95% CI, 1.14-2.61; P = 0.01 and HR 2.36; 95% CI 1.67 - 3.34; $P < 0.001$) adjusted by performance status, age and line of treatment. **Conclusions:** These data suggest that concomitant use of PPI and ATB is associated with increased toxicities in ICI treated pts. pPPI and pATB can negatively impact OS and PFS and merit clinician's attention. Research Sponsor: None.

2653 **Poster Session**

Impact of pharmacodynamic biomarkers in immuno-oncology (IO) phase 1 clinical trials.

Abdulazeez Salawu, Rachel Chen, Alberto Hernando-Calvo, Daniel Vilarim Araujo, Marc Oliva Bernal, Zhihui (Amy) Liu, Lillian L. Siu; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Princeton University, Princeton, NJ; Princess Margaret Cancer Centre, Toronto, ON, Canada; Institut Català d'Oncologia Hospitalet. Institut Català dInvestigació Biomèdica de Bellvitge (IDIBELL), Spain, Barcelona, Spain; Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Pharmacodynamic biomarkers (PD) are considered fundamental for go/no-go decisions in phase 1 trials. Despite an increase in the availability of blood-based biomarker assays, the requirement of invasive non-diagnostic research tumor biopsies for trial eligibility remains common. In the immuno-oncology (IO) era, the impact of PD analysis for the confirmation of biologic activity and recommended phase 2 dose (RP2D) has not been investigated. **Methods:** Phase 1 studies from 01/2014 to 12/2018 were reviewed. Among 12053 abstracts screened, a total of 143 phase I-IO trials were identified. Characteristics of studies that included on-treatment PD biomarkers (tissue-derived, blood-based and radiomic) were extracted and analyzed. Outcomes from the biomarker data in terms of proof of mechanism/biologic activity and statistically significant correlation with clinical benefit (objective response or survival) were collected. Authors' statements on the influence of PD results on RP2D were also noted. **Results:** Out of 143 phase 1 IO trials, 107 (75%) were monotherapy. The most frequent IO evaluated were vaccines (41%), cell therapy (16%), immunomodulators (13%) and cytokines (7%). Of the 36 combination studies, 20 (61%) included a second IO drug while 16 (39%) included molecular-targeted agents. Only 18 of 143 studies (12%) did not report any PD data. Of the remaining 125 studies, tissue-derived PD (t-PD) biomarkers alone, blood-based PD (b-PD) biomarkers alone, both t-PD and b-PD biomarkers, and imaging biomarkers were tested in 3 (2%), 97 (78%), 25 (20%), and 7 (6%), respectively. Demonstration of proof of mechanism/biologic activity only were reported in 16/28 (57%), 80/122 (66%) and 4/7 (57%) of the t-PD, b-PD and imaging biomarker studies, respectively. Significant correlation with clinical benefit was reported in 2/28 (7%), 7/122 (6%) and 0/7 (0%) of the t-PD, b-PD and imaging biomarker studies, respectively; these involved 4 vaccines (1 in combination with PD1 blockade), 1 cell therapy and 1 oncolytic virus (in combination with CTLA4 blockade). Among 35 b-PD studies with negative results, 5 also performed t-PD biomarkers, all with negative results. Notably, 3 out of 10 t-PD studies with negative results reported concurrent positive b-PD results. Based on the published reports, authors stated that biomarker results helped with RP2D determination in 16/28 (57%) of t-PD and 78/122 (64%) of b-PD studies. **Conclusions:** Our results suggest that in the IO era, most studies perform PD analysis, with similar proportions of t-PD and b-PD showing proof of mechanism/biologic activity. IO PD biomarkers have limited correlation with clinical benefit. Many authors considered IO PD biomarkers to be relevant in RP2D decisions, but this needs confirmation by other measures of impact. With continued technological developments utilizing circulating biomarkers, b-PD may ultimately replace many t-PD tests in future IO studies. Research Sponsor: None.

2654 **Poster Session**

Impact of multidisciplinary severe immunotherapy complication service on outcomes for cancer patients receiving immune checkpoint inhibition.

Leyre Zubiri, Gabriel E. Molina, Meghan Mooradian, Sienna Durbin, Michael Dougan, Molly Thomas, Alexander Faje, Michelle Rengarajan, Amanda C Guidon, Steven T. Chen, Mazen Nasrallah, Minna Kohler, Meghan Sise, Tomas G Neilan, Daniel A Zlotoff, Aditya Bardia, Ryan J. Sullivan, Yevgeniy R. Semenov, Alexandra C Villani, Kerry Lynn Reynolds; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Division of Neuromuscular Medicine, Department of Neurology, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital, Harvard Medical, Boston, MA; Massachusetts General Hospital, Department of Dermatology, Boston, MA; Division of Oncology, Department of Medicine, Massachusetts General Hospital, Boston, MA

Background: The exponential increase in FDA-approved indications for immune checkpoint inhibitors (ICI) in cancer care has resulted in therapeutic success but also in the occurrence of immune-related adverse effects (irAEs) that can represent a significant clinical challenge. On October 3 2017, the Massachusetts General Hospital (MGH) implemented the Severe Immunotherapy Complications (SIC) Service, a multi-disciplinary care team for patients hospitalized with irAEs. The objectives of this study were to evaluate the impact of SIC Service on 1) healthcare utilization and 2) patients outcomes. **Methods:** Using pharmacy and hospital admission databases, a list of patients was identified that both received ICI for a malignancy and were hospitalized with severe irAEs in the period prior to initiation of the SIC service and after SIC initiation. The pre-SIC period was defined as an admission between 4/2/2016 through 10/3/2017, and the post-SIC period as an admission from 10/3/2017 through 10/24/2018. The rate of readmission after the index hospitalization was the primary outcome. Secondary outcomes included lengths of stay (LOS) for both initial irAE admissions and readmissions, use of corticosteroids and non-steroidal second-line immunosuppression, ICI discontinuation, and inpatient mortality in the pre- and post-SIC periods. **Results:** Among 1169 patients treated in the pre-SIC service intervention period; 127 were hospitalized for irAE. Among 1159 patients treated in the post-SIC intervention 122 were hospitalized for irAE. SIC Service implementation was associated with a significant reduction in irAE readmission rates (post-SIC 14.8% vs. pre-SIC 25.9%; odds ratio [OR], 0.46; 95% CI, 0.22-0.95; p=0.036). The length of stay, rates of corticosteroid use, second-line immunosuppression, and ICI discontinuation for irAE, as well as inpatient mortality rates were not significantly different before and after SIC Service implementation. **Conclusions:** This is the first study to report that establishing a highly subspecialized care team focused on irAEs can be associated with improved clinical outcomes for patients receiving ICI therapy. Such care teams may play an essential part in optimizing irAE care. Research Sponsor: None.

2655 **Poster Session**

Patients with steroid-refractory toxicity following immune checkpoint inhibitors: Frequent hospitalizations and long duration of illness.

Mia Bothwell, Aaron Cheng, Leyre Zubiri, Meghan Mooradian, Yevgeniy R. Semenov, Gayle C. Blouin, Erica Tavares, Jennifer Hutchinson, Leila Rostamnjad, Monica Jackson, Kerry Lynn Reynolds; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Massachusetts General Hospital, Department of Dermatology, Boston, MA; MGH Pharmacy, Boston; Division of Oncology, Department of Medicine, Massachusetts General Hospital, Boston, MA

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer with significantly improved outcomes, but these agents have a unique spectrum of toxicities known as immune-related adverse events (irAEs). The recommended treatment for non-endocrine toxicities is steroid based. However, a subset of patients (pts) is steroid-refractory and requires second-line immunosuppression. There is very little evidence regarding this population. In this retrospective study we report the 1) incidence 2) type of treatment used 3) natural history and 4) potential predictors of steroid-refractory irAE at a major academic medical center. **Methods:** The Research Patient Database Registry at Mass General Brigham was used to identify pts treated with an ICI from 1/5/2017 to 6/1/2019. Pharmaceutical records identified a subset of the cohort received a second-line immunosuppressive agent within a 15-month period after ICI. For pts with steroid-refractory irAE additional information was collected: demographics, ICI regimen, type/#/and severity of irAE, clinical characteristics, # of admissions, length of stay (LOS), amount and duration of steroid therapy, second line immunosuppression type, treatment discontinuation rates, response, and outcome of re-challenge. Multivariate logistic regressions were used to predict risk of refractory toxicity and study the association of different variables (age, sex, race, marital status, cancer and ICI types) with refractory toxicities. **Results:** We identified 61 pts (1.4%) with steroid-refractory irAEs (48 colitis, 4 myocarditis, 6 pneumonitis, 3 neurologic) out of the total ICI cohort (N=4,325). 60.7% received ICI monotherapy. 24.6% received ICI in the adjuvant setting. Median length of steroid duration was 68 days with max of 1135 days. Despite use of second line immunosuppression, 25.8% of pts were never able to discontinue steroids. Majority of pts (72.1%) had at least one hospitalization with median LOS of 7.5 days. 93.4% of pts permanently discontinued the ICI responsible for the irAE. Thirteen pts (21.3%) were later re-challenged with ICI and 7 (53.8%) of these developed a subsequent irAE. Anti-CTLA-4 therapy was associated with a 10-fold risk of refractory toxicity compared to PD-1 ($p<.05$). Best tumor response was complete response in 21.3% and partial response in 26.2%. Among different cancer types, melanoma was most strongly associated with refractory events (OR 2.97 in comparison to thoracic malignancy). **Conclusions:** Refractory toxicity is uncommon but leads to high rates of ICI discontinuation, frequent hospitalizations, and a long duration of illness with exposure to prolonged and high-doses of steroids. There is an urgent need for further investigation into predictive factors for steroid-refractory toxicity given that ICI is being used more frequently and in earlier lines of treatment. Research Sponsor: None.

TPS2656 **Poster Session**

Zanidatamab, an anti-HER2 bispecific antibody, plus chemotherapy with/without tislelizumab as first-line treatment for patients with advanced HER2-positive breast cancer or gastric/gastroesophageal junction adenocarcinoma: A phase 1B/2 trial-in-progress.

Keun Wook Lee, Young-Hyuck Im, Keun Seok Lee, Jae Yong Cho, Do-Youn Oh, Hyun Cheol Cheol Chung, Yee Chao, Li-Yuan Bai, Chia Jui Yen, In-Ho Kim, Sang Cheul Oh, Chia-Chi Lin, Jin Wang, Xin Wang, Huiyan Li, Yen-Yang Chen, Yoon-Koo Kang; 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; National Cancer Center, Goyang, South Korea; Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; Department of Oncology, Taipei Veterans General Hospital, Taipei City, Taiwan; China Medical University Hospital, China Medical University, Taichung, Taiwan; National Cheng Kung University Hospital, Tainan City, Taiwan; The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea; Korea University Guro Hospital, Seoul, South Korea; National Taiwan University Hospital, Taipei, Taiwan; BeiGene (Shanghai) Co., Ltd., Shanghai, China; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Asan Medical Centre, University of Uslan College of Medicine, Seoul, South Korea

Background: Zanidatamab is a novel HER2-targeted antibody that binds two distinct extracellular domains of HER2, allowing for multiple mechanisms of action including enhanced binding, clustering, receptor internalization and downregulation; this results in inhibition of ligand-dependent and -independent proliferation and potent activation of antibody-dependent cellular cytotoxicity. Zanidatamab monotherapy is well tolerated and has shown promising anti-tumor activity in patients (pts) with pre-treated advanced HER2-positive cancers, and was well tolerated in a Phase I trial (NCT02892123). Tislelizumab is an investigational anti-programmed death-1 (PD-1) antibody engineered to minimize binding of FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, which is a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy. Tislelizumab is well tolerated and has anti-tumor activity alone and in combination with chemotherapy in pts with advanced solid tumors. The highly immunogenic nature of HER2 tumors has led to the development of therapies combining anti-HER2 therapies with immune checkpoint blockade. **Methods:** This open-label, two cohort Phase 1B/2 study (NCT04276493) is designed to evaluate zanidatamab as a first-line therapy with chemotherapy in pts with HER2-positive metastatic breast cancer (mBC; cohort 1) or with chemotherapy + tislelizumab in pts with HER2-positive advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC; cohort 2). Weight-based dosing (cohorts 1a and 2a) and flat dosing (cohorts 1b and 2b) regimens of zanidatamab are being investigated. In cohort 1 (n = 20), pts with treatment-nave HER2-positive (IHC3+ or ISH amplified) mBC will receive intravenous (IV) zanidatamab 30 mg/kg (cohort 1a) or 1800 mg (cohort 1b), plus IV docetaxel 75 mg/m^2 once every 3 weeks (Q3W). In cohort 2 (n = 30), treatment-nave pts with HER2-positive (IHC3+ or IHC2+ with ISH amplification) advanced GC/GEJC will receive IV zanidatamab 30 mg/kg (cohort 2a), or 1800 mg (pts $<$ 70kg; cohort 2b) or 2400 mg (pts $\geq$ 70kg; cohort 2b), plus IV tislelizumab 200 mg and chemotherapy (CAPOX regimen: oral capecitabine 1000 mg/m^2 twice daily [days 1–14] and IV oxaliplatin 130 mg/m^2 [day 1]) Q3W. For cohort 2 there is a six pt safety lead-in phase, followed by dose expansion after approval by the safety monitoring committee. Primary endpoints are the safety profile and objective response rate. Secondary endpoints include duration of response, time to response, progression-free survival, disease control rate, and overall survival. Clinical trial information: NCT02892123. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Shannon Galgani, MSci, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS2657 **Poster Session**

SGNTGT-001: A phase 1 study of SEA-TGT, an effector-function enhanced monoclonal antibody (mAb), in advanced malignancies (trial in progress).

Elena Garralda, Rachel E. Sanborn, Anna Rachel Minchom, Diwakar Davar, Giuseppe Curigliano, Vincent Ribrag, Amitkumar Mehta, Francine M. Foss, Jasmine M. Zain, Andres Forero-Torres, Stephen M. Ansell; Hospital Vall d'Hebron, Barcelona, Spain; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; Drug Development Unit, Royal Marsden Hospital and The Institute of Cancer Research, London, United Kingdom; Hillman Cancer Center, Pittsburgh, PA; European Institute of Oncology, IRCCS and University of Milano, Milan, Italy; Gustave-Roussy Institute, Villejuif Cedex, France; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; Yale New Haven Hospital, New Haven, CT; City of Hope, Duarte, CA; Seagen Inc., Bothell, WA; Mayo Clinic, Rochester, MN

Background: T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is an inhibitory immune checkpoint receptor expressed on subsets of T cells and NK cells. SEA-TGT is an effector-function enhanced human mAb that targets TIGIT with pico-molar affinity and blocks TIGIT's interaction with CD155 and CD112. SEA-TGT was developed to have amplified binding to and engagement of Fcγ receptors. Enhanced effector function increases TIGIT+ T-regulatory cell depletion, enhances innate immune cell activation, and augments nave and memory CD8+ T-cell responses. Preclinically, SEA-TGT elicits superior anti-tumor immune responses compared to other TIGIT mAbs without effector-enhanced backbones, with curative anti-tumor activity as monotherapy and in combination with other immune-modulators. **Methods:** This phase 1, open-label, multicenter, dose-escalation/expansion study (NCT04254107) is assessing the safety, tolerability and preliminary activity of SEA-TGT monotherapy in up to 205 adults ($\geq$18 years) with histologically or cytologically confirmed relapsed, refractory, or progressive metastatic solid tumors (non-small cell lung, gastric/GE junction carcinomas, cutaneous melanoma, head and neck squamous cell carcinoma, bladder cancer, ovarian cancer or triple-negative breast cancer) or lymphomas (classical Hodgkin lymphoma, diffuse large B-cell lymphoma, or peripheral T-cell lymphoma, not otherwise specified). SEA-TGT will be infused on Day 1 of 21-day cycles. In Part A, the safety and tolerability of SEA-TGT will be assessed in ~25 subjects to identify the maximum tolerated dose and recommended phase II dose (RP2D). In Part B, the safety and antitumor activity of the RP2D will be assessed in ~180 subjects in disease-specific expansion cohorts. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities, and dose-level safety and activity. Secondary endpoints are objective response (OR) rates, duration of OR, complete response, progression-free survival, overall survival, PK, and antidrug antibodies. Exploratory biomarkers of SEA-TGT-mediated pharmacodynamic (PD) effects, PK-PD correlations, and correlative analyses of predictive and PD measurements with response, toxicity, and resistance will be explored. The study was opened April 2020 and is enrolling across sites in North America and Europe. Clinical trial information: NCT04254107. Research Sponsor: Seagen Inc.

TPS2658 **Poster Session**

A phase I, first-in-human clinical trial of the GDF-15 neutralizing antibody CTL-002 in subjects with advanced-stage solid tumors (ACRONYM: GDFATHER).

Ignacio Melero, Emiliano Calvo, Reinhard Dummer, Elena Garralda, Martin H. Schuler, Maria-Elisabeth Goebeler, Ralf C. Bargou, Tanja Gromke, Josep Tabernero, Egle Ramelyte, Maria De Miguel, Miguel F. Sanmamed, Maria E. Rodriguez-Ruiz, Petra Fettes, Kathrin Klar, Manfred Ruediger, Christine Schuberth-Wagner, Markus Haake, Joerg Wischhusen, Eugen Leo; Universidad de Navarra, Center for Applied Medical Research (CIMA), Pamplona, Spain; START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Hospital Madrid Norte Sanchinarro, Madrid, Spain; Skin Cancer Center, University Hospital of Zürich, Zürich, Switzerland; Hospital Universitario Vall d'Hebron, Barcelona, Spain; West German Cancer Centre, University Hospital Essen, Essen, Germany; Translational Oncology/Early Clinical Trial Unit (ECTU), Medizinische Klinik II, University Hospital Würzburg, Würzburg, Germany; Comprehensive Cancer Center Mainfranken, University Hospital Würzburg, Würzburg, Germany; University Hospital Essen, Essen, Germany; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), UVic-UCC, Barcelona, Spain; University Hospital Zurich, Zurich, Switzerland; START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Hospital Universitario HM Sanchinarro, Madrid, Spain; Department of Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain; Center for Applied Medical Research (CIMA), University of Navarra, Clínica Universidad de Navarra, Madrid, Spain; CatalYm GmbH, Planegg-Martinsried, Germany; CatalYm GmbH, Planegg/Munich, Germany; University of Wuerzburg, Department of Gynecology and Obstetrics, Würzburg, Germany; CatalYm GmbH, Munich, Germany

Background: Growth and differentiation factor 15 (GDF-15) is a TGF-β superfamily member physiologically expressed mainly in placenta and linked to feto-maternal tolerance. Under pathophysiologic conditions, prevention of excessive immune cell infiltration during tissue damage and cachexia induction have been ascribed to GDF-15. A recent study [Haake et al. AACR2020; Abstract #5597] elucidated a mechanism by which GDF-15 inhibits LFA-1 activation on CD8+ T cells, thus interfering with effector T cell recruitment to tissues. Importantly, several cancer entities secrete high levels of GDF-15, correlating with poor prognosis and reduced overall survival [reviewed in Front Immunol 2020 May 19;11:951]. To block this effect the GDF-15 neutralizing antibody CTL-002 was generated. In preclinical models CTL-002 demonstrated potent effector T cell shifting into tumor tissue by neutralizing GDF-15. **Methods:** This is a phase 1, first-in-human (FIH), two-part, open-label clinical trial of intravenous (IV) administration of CTL-002 given as monotherapy and in combination with an anti-PD-1 antibody in subjects with advanced-stage, relapsed/refractory solid tumors who relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy. Eligible subjects have exhausted all available approved standard treatments. Further key eligibility criteria include having received at least one prior anti-PD1/-PD-L1 treatment and having relapsed on or after it or having been refractory to it, and presenting with a biopsy-accessible tumor for serial biopsy taking. The trial is termed GDFATHER, for GDF-15 Antibody-mediaTed Effector cell Relocation. Main endpoints are safety of CTL-002 monotherapy and CTL-002 combination with an anti-PD-1 antibody, pharmacokinetics, pharmacodynamics (e.g. degree of GDF-15 neutralization achieved and change in immune-cell number and composition in the tumor tissue) as well as preliminary clinical efficacy (tumor mass reduction; anticachexia effect) In part A of the trial (dose escalation) up to 24 subjects will receive escalating doses of CTL-002 IV (0.3 – 20 mg/kg) in a mono-followed-by-combination-design with CTL-002 given as monotherapy and followed by combination with an anti-PD-1 checkpoint inhibitor. In part B (expansion) up to 5 cohorts with up to 25 subjects per cohort with defined tumor entities expected to be GDF-15 dependent will be treated to determine the recommended phase 2 dose (RP2D) and further evaluate safety and preliminary efficacy of CTL-002 monotherapy and the combination. The study was initiated in December 2020 and enrolled the first patient on Dec 09, 2020. Cohort 1 has been completed without DLT and enrollment for cohort 2 began in February 2021. Clinical trial information: NCT04725474. Research Sponsor: CatalYm GmbH.

TPS2659 **Poster Session**

A phase 1/2, open-label, dose-escalation, safety and tolerability study of NC410 in subjects with advanced or metastatic solid tumors.

Martin Gutierrez, Filip Janku, Linjie Tian, Jason J. Luke, Elaine Shum, John Shin, Ido Weiss, Linda N. Liu, Dallas Files, Solomon Langermann, Han Myint, Marijo Bilusic; John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX; NextCure Inc, Beltsville, MD; UPMC Hillman Cancer Center, Pittsburgh, PA; Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY; Mayo Clinic School of Graduate Medical Education, Rochester, MN; Amplimmune, Gaithesburg, MD; Amplimmune Inc, Gaithersburg, MD; Genitourinary Malignancies Branch, NCI, NIH, Bethesda, MD

Background: Leukocyte-Associated Immunoglobulin-like Receptor (LAIR)-1 and LAIR-2 are members of the Leukocyte Receptor Complex (LRC) (An & Brodsky, 2016). LAIR-1 is a co-inhibitory receptor expressed on several subsets of immune cells, and functions to delimit immune responses (Meyaard et al., 1997). LAIR-2 is a secreted protein with homology to the transmembrane protein LAIR-1 (Lebbink et al., 2008). In cancer, it is hypothesized that LAIR-1 expression on several subsets of leukocytes prevents optimal immune responses by limiting both innate and adaptive immune functionality. LAIR-1 serves to suppress anti-tumor immunity through the inhibition of stimulatory signaling pathways. Specifically, LAIR-1 is a checkpoint and adhesion receptor on T cells that limits T cell activation and increases adhesion to collagens (Meyaard, 2008). LAIR-2 is capable of blocking LAIR-1 functional interactions with ligands, resulting in improved immune function on multiple immune cell subsets. Dysregulation of LAIR-1 ligands in the tumor microenvironment results in excessive production of collagens and complement C1q as well as altered forms of collagens, that leads to immune inhibition through binding to LAIR-1+ immune cells. NC410 is a dimeric form of the LAIR-2 protein fused to a human Fc domain of the immunoglobulin (Ig) subtype IgG1. The rationale for developing NC410 as a cancer therapeutic is based on nonclinical data demonstrating LAIR-1 signaling blockade can improve the immune response. Because LAIR-2 binds to ligands shared with LAIR-1 with increased affinity, NC410 acts as a decoy receptor for LAIR-1 ligands releasing suppression from myeloid cells and T cells and promoting anti-tumor immunity. NC410 may also mediate remodeling of the tumor extracellular matrix, further contributing to anti-tumor activity. **Methods:** This is a multi-center, first in human, phase 1/2, open-label, single-armed study to determine the safety and tolerability, define maximum tolerated dose (MTD) and/or pharmacologically active dose, assess preliminary efficacy, and explore predictive and pharmacodynamic biomarkers of NC410 in subjects with advanced or metastatic solid tumors. Key eligibility criteria include measurable disease based on RECIST v1.1 and being able to consent for collection of biopsies at screening and on treatment. Phase 1 is a classic 3+3 dose escalation design to determine the safety, tolerability, DLT, MTD and recommended phase 2 dose (RP2D) (NCT04408599). Ongoing exploratory analyses include the assessment of predictive biomarkers associated with treatment benefit, and pharmacodynamic markers associated with study drug activity. Phase 2 is going to enroll ovarian, colorectal, NSCLC, H&N, and gastric carcinomas and other tumors depending on biomarker data available from the Phase 1 part of the study. Clinical trial information: 04408599. Research Sponsor: NextCure Inc.

TPS2660 **Poster Session**

A phase 1, first in human study of adenovirally transduced autologous macrophages engineered to contain an anti-HER2 chimeric antigen receptor (CAR) in subjects with HER2 overexpressing solid tumors.

Joshua Bauml, Natalie Sophia Grover, Amy Ronczka, Daniel Cushing, Michael Klichinsky, Debora Barton, Elizabeth Claire Dees; Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; University of North Carolina, Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Carisma Therapeutics, Philadelphia, PA; UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC

Background: Adoptive T cell therapies have led to remarkable advances among patients with hematologic malignancies, but not in those with solid tumors. Macrophages are actively recruited into, and abundantly present in the solid tumor microenvironment (sTME). Tumor- associated macrophages typically evince immunosuppressive behavior, but when engineered to be proinflammatory, may be an ideal vector to administer adoptive cellular therapy in solid tumors. Furthermore, insertion of a CAR confers on the macrophages the ability to selectively recognize and phagocytose antigen overexpressing cancer cells. Additionally, CAR macrophages reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and immune memory. Human Epidermal Growth Factor Receptor 2 (HER2) is overexpressed in many cancers, including but not limited to breast and gastroesophageal cancers (Table). CT-0508 is a cell product comprised of autologous monocyte-derived pro-inflammatory macrophages expressing an anti-HER2 CAR. Pre-clinical studies have shown that CT-0508 induced targeted cancer cell phagocytosis while sparing normal cells, decreased tumor burden and prolonged survival in relevant models. CT-0508 cells were safe and effective in a semi-immunocompetent mouse model of human HER2 overexpressing ovarian cancer. **Methods:** This is a FIH phase 1 study to evaluate safety, tolerability, cell manufacturing feasibility, trafficking, and preliminary evidence of efficacy of investigational product CT-0508 in approximately 18 subjects with locally advanced (unresectable) or metastatic solid tumors overexpressing HER2 who have failed available therapies including anti-HER2 therapies when indicated. Filgrastim will be used to mobilize autologous hematopoietic progenitor cells for monocyte collection by apheresis. The CT-0508 CAR macrophage product will be manufactured, prepared and cryopreserved from mobilized peripheral blood monocytes. The study is enrolling Group 1 subjects, who will receive CT-0508 infusion split over D1, 3 and 5. Subjects will be continually assessed for acute and cumulative toxicity. Dose limiting toxicities will be observed and addressed by a Safety Review Committee. Group 2 subjects will follow, and will receive the full CT-0508 infusion on D1. Pre and post treatment biopsies and blood samples will be collected to investigate correlates of trafficking, persistence, TME modulation, immune response and safety. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

HER2 positivity frequencies across tumor types.

Tumor	HER2 positive %*
Bladder	8–70
Breast	11.0–25.0
Cervical	2.8–3.9
Colorectal	1.6–5.0
Esophageal	12.0–14.0
Cholangiocarcinoma	6.3–9.0
Gallbladder	9.8–12.8
Gastric	7.0–34.0
Ovarian	26
Salivary mucoepidermoid	17.6
Salivary duct	30–40
Testicular	2.4
Uterine	3.0

*References available upon request.

TPS2661 **Poster Session**

Master protocol to assess safety and recommended phase 2 dose of next generation NY-ESO-1–specific TCR T-cells in HLA-A*02 patients with synovial sarcoma or non-small cell lung cancer (Substudies 1 and 2).

Adam Jacob Schoenfeld, Mehmet Altan, Taofeek K. Owonikoko, Sandra P. D'Angelo, Brian H. Ladle, Jonathan Christopher Noujaim, Kai He, David A. Liebner, Adrian G. Sacher, John B. A. G. Haanen, Jeffrey Yachnin, Chao H. Huang, Brian Andrew Van Tine, Aisha N. Hasan, Thomas H. Faitg, Emily Butler, Aiman Shalabi, Steven Attia, Dejka M. Araujo; Memorial Sloan Kettering Cancer Center, New York, NY; MD Anderson Cancer Center, Houston, TX; Emory University Winship Cancer Institute, Atlanta, GA; Johns Hopkins University, Baltimore, MD; Institut D'Hématologie-Oncologie, Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; The Ohio State University, Columbus, OH; Princess Margaret Cancer Centre, Toronto, ON, Canada; Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, Netherlands; Karolinska Institutet, Stockholm, Sweden; University of Kansas Medical Center, Kansas City, KS; Washington University in St. Louis, St. Louis, MO; GlaxoSmithKline, Philadelphia, PA; Mayo Clinic, Jacksonville, FL

Background: Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy using a genetically modified T-cell receptor (TCR) to improve recognition of cancer cells expressing NY-ESO-1/LAGE-1a. Next generation NY-ESO-1 TCR T-cell therapies, such as GSK3901961 and GSK3845097, integrate added genetic modifications to enhance anticancer activity. GSK3901961 co-expresses the CD8α chain to stabilize TCR-human leukocyte A (HLA) class I interactions on CD4+ T cells, improving T-cell persistence and helper functions such as Type 1 T-helper antitumor responses. GSK3845097 co-expresses a dominant negative transforming growth factor-β (TGF-β) type II receptor to reduce TGF-β pathway activation and maintain T-cell proliferation, cytokine production, and cytotoxicity in the tumor microenvironment. A first-time-in-human master protocol (NCT04526509) will evaluate safety, tolerability, and recommended phase 2 dose (RP2D) of these and possible subsequent therapies. Substudy 1 will assess GSK3901961 in patients (pts) with advanced non-small cell lung cancer (NSCLC) or synovial sarcoma (SS). Substudy 2 will assess GSK3845097 in pts with advanced SS. **Methods:** Each substudy includes a dose confirmation stage to assess RP2D and a dose expansion stage. Key inclusion criteria are age $\geq$18 y; measurable disease per RECIST v1.1; HLA-A*02:01, A*02:05, or A*02:06 positivity; NY-ESO-1/LAGE-1a tumor expression; advanced (metastatic/unresectable) SS with t(X;18) translocation and anthracycline-based therapy receipt/completion/intolerance (SS only); and Stage IV NSCLC, receipt of $\geq$1 prior line(s) of standard of care (SOC) therapy including programmed death receptor- or ligand-1 inhibitors, and SOC chemotherapy receipt/intolerance (Substudy 1 only). Key exclusion criteria are prior malignancy that is not in complete remission or clinically significant systemic illness; prior receipt of gene/NY-ESO-1–specific therapy or allogenic stem cell/solid organ transplant; central nervous system metastases (SS only); and actionable genetic aberration and receipt/failure of $\geq$3 systemic therapy lines (Substudy 1 only). Primary endpoints are safety (adverse events) and tolerability (dose-limiting toxicities). Secondary endpoints include investigator-assessed overall response rate, duration of response, and maximum expansion/persistence and phenotype of infiltrating transduced T cells. Exploratory endpoints include laboratory parameters, overall survival, and anti-GSK3901961 or -GSK3845097 titers as applicable. Analyses will be descriptive. The substudies are enrolling. Funding: GSK (209012; NCT04526509). Editorial support was provided by Eithne Maguire, PhD, of Fishawack Indicia, part of Fishawack Health; funded by GSK. Previously presented at AACR 2021 (CT219). Clinical trial information: NCT04526509. Research Sponsor: GlaxoSmithKline (209012).

TPS2662 **Poster Session**

A phase 1 study to evaluate chimeric antigen receptor (CAR) T cells incorporating a chlorotoxin tumor-targeting domain for patients with MMP2+ Recurrent or progressive glioblastoma (NCT04214392).

Behnam Badie, Michael E Barish, Ammar Chaudhry, Massimo D'Apuzzo, Stephen J. Forman, Jana Portnow, Shirong (Sean) Wang, Julie A Ressler, Jennifer Simpson, Julie Kilpatrick, Paige McNamara, Jamie Wagner, Suzette Blanchard, Dongrui Wang, Christine Brown; City of Hope National Medical Center, Duarte, CA; City of Hope, Duarte, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; City of Hope Medical Center, Duarte, CA; MD Anderson, Houston, TX

Background: Glioblastoma (GBM) is the most common and most aggressive primary brain tumor. Around 294,900 new cases are diagnosed globally with 241,000 deaths each year. The 5-year survival is only 5%. Median overall survival from first recurrence is only 5-8 months. There is no established standard of care for recurrent GBM. City of Hope (COH) has developed and optimized a CAR T cell therapy utilizing the chlorotoxin peptide (CLTX) as the CAR's tumor recognition domain against GBM. CLTX-CAR T cells specifically and broadly target GBM through recognition of a receptor complex including membrane-bound matrix metalloprotease 2 (MMP-2). CLTX-CAR T cells do not exhibit off-tumor recognition of normal human or murine cells and tissues in preclinical models. In *in vitro* studies, COH evaluated patient-derived brain tumor (PBT) cell lines for CLTX binding and expression of IL13Rα2, HER2 and EGFR, three targets of CAR T cell trials for GBMs. Strong CLTX binding to tumor cells was observed in of the majority of primary GBM lines, independent of these other antigens. In preclinical studies using *in vivo* mouse models, a single intratumoral (ICT) injection of CLTX-CAR T cells (1×10^6 CAR+ T cells) exhibited robust anti-tumor activity against ffLuc+ PBT106 tumors orthotopically-engrafted in NSG mice. Overall, when compared to mice treated with mock-transduced Tn/mem (no CAR) T cells, the CLTX(EQ)28ζ/CD19t+ T cells reduced tumor burden and significantly increased survival. Taken together, these preclinical findings support the potential safety and efficacy of CLTX-CAR T cells, and provide the rationale for clinical testing of this therapy. As cellular heterogeneity intrinsic to GBM likely contributes to resistance to therapy and limited response rates, CLTX-CAR T cells may provide greater tumor eradication in a higher proportion of patients with GBM. **Methods:** This study is a phase 1, single center, safety and maximum tolerated dose (MTD) finding study of CLTX-CAR T cells for subjects with MMP2+ recurrent or progressive GBM. A safety lead-in of 3−6 participants receiving CLTX-CAR T cells by ICT delivery will be completed first. Subsequently, subjects would receive cells administered through both ICT and intraventricular (ICV catheters) (i.e. dual delivery) in two dose schedules. Subjects will be evaluated for safety and tolerability, and may continue to receive treatment until disease progression. Time to progression, overall survival, and disease response by Response Assessment in Neuro-Oncology (RANO) criteria, will be evaluated and descriptively compared to historical data. The study is actively enrolling patients. Clinical trial information: NCT04214392. Research Sponsor: U.S. National Institutes of Health.

TPS2663 **Poster Session**

Phase I study of adoptive immunotherapy for advanced MUC1* positive breast cancer with autologous T cells engineered to express a chimeric antigen receptor, huMNC2-CAR44 specific for a cleaved form of MUC1 (MUC1*).

Jennifer M. Specht, David G. Maloney, Cecilia Yeung, Vicky Wu, Cynthia Bamdad; University of Washington, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; Minerva Biotechnologies, Waltham, MA

Background: Chimeric antigen receptor (CAR) T cell therapy targeting CD19 results in marked tumor regression for patients with CD19+ malignancies. It would be ideal to extend the success of CAR-T cell therapy to epithelial cancers. MUC1* is a post-translationally modified/cleaved form of mucin 1 (MUC1) that is frequently expressed on breast tumors, functions as a growth factor receptor, and a promising antigen for CAR-T cell therapy. Minerva Biotechnologies developed a CAR (huMNC2-CAR44) which recognizes MUC1* and does not bind to full-length or MUC1* negative cells. huMNC2-CAR44 product consists of autologous T cells transduced with a lentiviral vector encoding humanized MNC2-scFv (MUC1* targeting head), sequences from CD8 ? leader, hinge and transmembrane domains, 4-1BB and CD3ζ domains. **Methods:** NCT04020575 is a phase I study evaluating the safety of adoptively transferred autologous T cells genetically modified to express huMNC2-CAR44 in patients with metastatic MUC1* positive breast cancer. After screening, leukapheresis is performed, CD8+ and CD4+ T cells are selected, transduced with huMNC2-CAR44, expanded, and antigen stimulated *in vitro*. Lymphodepletion with cyclophosphamide and fludarabine is followed by infusion of huMNC2-CAR44 CAR-T cells in escalating doses (3.3×10^5 CAR+ T cells/kg – 1×10^7 CAR+ T cells/kg). Key inclusion criteria include metastatic breast cancer of known ER, PR and HER2 status, MUC1* membrane expression $>$ or = 30% with 2+ staining by IHC, measurable or evaluable disease, receipt of standard systemic therapies known to confer benefit, age $>$ 18, informed consent, adequate organ function, and KPS $>$ or = 60%. Patients with active autoimmune disease, uncontrolled infection, anticipated survival $<$ 3 months, and/or untreated CNS metastases are not eligible. The primary objective is to identify the maximum tolerated (MTD) dose of huMNC2-CAR44 T cells by CTCAE v5 and Lee criteria. Secondary objectives include persistence and phenotype of adoptively transferred huMNC2-CAR44 T cells and preliminary antitumor activity. Exploratory objectives include trafficking of huMNC2-CAR44 T cells to tumor sites, effector function of huMNC2-CAR44 T cells *in vivo*, association between tumor MUC1* expression and huMNC2-CAR44 T cell persistence and response, change in tumor immune microenvironment by multiplex IHC in pre- and post-treatment tumor biopsies. Dose escalation is completed using a "3+3" design. Once the MTD has been determined, up to 15 more patients will be enrolled in each of 3 expansion cohorts (Luminal, HER2 positive, and TNBC) to inform future huMNC2-CAR44 T cell trials. Study is open to screening and enrollment in dose escalation. Up to 69 patients may be enrolled in dose escalation and expansion phases. Clinical trial information: NCT04020575. Research Sponsor: Minerva Biotechnologies, Other Foundation.

TPS2664 **Poster Session**

A phase 1 study of RTX-321, an engineered red blood cell as an artificial antigen-presenting cell expressing HLA-A*02 with the HPV-16 E7 peptide and 4-1BB ligand with membrane-bound IL-12 for the treatment of HPV 16-positive cancers.

Johanna C. Bendell, Alexander I. Spira, Ramez Nassef Eskander, Ezra E.W. Cohen, Geoffrey Kuesters, Christopher Plescia, Karen Campbell, Tiffany Chen, Omid Hamid; Sarah Cannon Research Institute/ Tennessee Oncology PLLC, Nashville, TN; US Oncology Research/Virginia Cancer Specialists, Fairfax, VA; UC San Diego Moores Cancer Center, San Diego, CA; University of California, San Diego, San Diego, CA; Rubius Therapeutics, Cambridge, MA; The Angeles Clinic and Research Institute, Los Angeles, CA

Background: High-risk strains of HPV (HPV 16/18) have been associated with the development of multiple cancers, and the associated viral antigens are validated targets from immunotherapy approaches. We engineered red blood cells into allogeneic, off-the-shelf, artificial antigen-presenting cells (aAPCs) that express a human papillomavirus (HPV) 16 E7 peptide bound to human leukocyte antigen (HLA)-A*02:01, the costimulatory molecule 4-1BB ligand (L), and the cytokine interleukin (IL)-12 on the cell surface. This aAPC, RTX-321, activated HPV specific T-cells and promoted effector function *in vitro*. In animal models using a murine surrogate system, this aAPC approach resulted in robust antigen-specific T-cell expansion, NK cell expansion, tumor control, memory formation and antigen spreading, which led to a broad and robust antitumor immune response. The presence of 4-1BBL and IL-12 induced minimal toxicities in these models due to restriction of the biodistribution of the aAPC to the vasculature and spleen. RTX-321 is a potential *in vivo* cellular immunotherapy for treating HPV 16-positive cancers including cervical, head and neck and anal cancers. **Methods:** The RTX-321-01 study is a phase 1 multi-center, dose-escalation study of RTX-321 administered intravenously every 3 weeks in HLA-A*02:01-positive patients with relapsed or refractory HPV 16-positive cancers of the cervix or anal canal, or squamous cell cancers of the head and neck (HNSCC). Patients with cervical cancer or HNSCC will undergo testing for the presence of the HPV 16 virus or provide confirmation from archival tumor tissue prior to enrollment. Patients with anal cancer will not be required to have prospective determination of HPV 16-positive status prior to enrollment given the high incidence in this indication (approximately 80-85 percent of anal cancers). Approximately 18 patients will be enrolled across dose level cohorts to identify the recommended phase 2 dose (RP2D) of RTX-321, followed by RP2D expansion cohorts in specific indications. The starting dose is 1 billion ($1x10^9$) cells administered intravenously every 3 weeks (Q3W) and the dose will escalate by half-log increments, following a Bayesian logarithmic regression model (BLRM) with overdose control. Translational studies will investigate the activation and expansion of HPV16 E7 antigen-specific responses as well as broad innate and adaptive responses in multiple peripheral blood samples over the first 3 cycles of therapy as well as in optional paired tumor biopsies. At this time, the study is open and enrolling patients in the first dose escalation cohort (NCT04672980). Clinical trial information: NCT04672980. Research Sponsor: Rubius Therapeutics.

TPS2665 **Poster Session**

Identification of a microbiome signature predicting immune checkpoint inhibitor outcomes across multiple cancer types in the MITRE study.

Philippa Gail Corrie, Sarah Joanne Welsh, Grant D. Stewart, Gary Doherty, Kevin Vervier, Anne Neville, Christine Parkinson, Kate Fife, Guy Faust, Kamalram Thippu Jayaprakash, Thomas R. Geldart, Ewan Brown, Matthew Wheater, Jenny Penelope Nobes, David Bruce, Nikos Demiris, Katy Marie Dalchau, David Adams, Mat Robinson, Trevor Lawley; Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Cambridge University Hospitals, Cambridge, United Kingdom; University of Cambridge, Cambridge, United Kingdom; Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Microbiotica Ltd, Cambridge, United Kingdom; Cancer Research UK Cambridge Institute, Cambridge, United Kingdom; Oncology Department, Leicester, United Kingdom; Queen Elizabeth Hospital, Kings Lynn, United Kingdom; Royal Bournemouth Hospital, Bournemouth, United Kingdom; Western General Hospital, Edinburgh, United Kingdom; University Hospital Southampton, Southampton, United Kingdom; Department of Clinical Oncology, Norwich, United Kingdom; Cambridge Cancer Trials Centre, Cambridge, United Kingdom; Wellcome Sanger Institute, Cambridge, United Kingdom

Background: The gut microbiome is implicated as a biomarker of response to immune checkpoint inhibitors (ICIs), based on preclinical mouse models and preliminary observations in limited patient series. Furthermore, early reports suggest faecal microbial transfer may have therapeutic potential, converting ICI non-responders to responders. So far, identification of specific responsible bacterial taxa has been inconsistent between published studies, which limits future application. By culturing and metagenomic sequencing of stool sample bacteria, our group has identified a unique microbiome signature, which appears to be predictive of response to ICIs across all key published series as well as our own melanoma patient series (Robinson M *et al*, J Immunother Cancer 2020;8(suppl 3):A404). Because the patient numbers in all published series remain low, we are now further exploring and validating this microbiome signature in a larger scale study across several different cancer types. **Methods:** MITRE (Microbiome Immunotherapy Toxicity and Response Evaluation) is a UK NIHR portfolio multi-centre prospective study funded jointly by Cancer Research UK and Microbiotica (NCT04107168). Up to 1800 patients receiving ICIs will be recruited over a 5-year period. In the first stage, 300 patients with advanced melanoma (cohort 1: anti-PD1 monotherapy, cohort 2: anti-PD1+anti-CTLA-4 combination), renal cancer (cohort 3: anti-PD(L)1+kinase inhibitor, cohort 4: anti-PD1+anti-CTLA-4 combination) and non-small cell lung cancer (cohort 5: anti-PD(L)1 monotherapy, cohort 6: anti-PD(L)1+chemotherapy+anti-angiogenic) are being recruited, 50 patients to each cohort. A cohort-specific, simulation-based power calculation will then be performed, guiding subsequent recruitment. Stool and blood are collected prior to treatment, at 3, 6 and 12 months, or disease progression (whichever is sooner), as well as after any grade >3 immune-related adverse events. Patients collect and freeze their own stool samples which are cultured and subjected to shotgun metagenomic sequencing. Plasma, whole blood, buffy coat, RNA and PBMCs are being stored, for correlative studies. Any tumour, or organ biopsies, taken prior to and during treatment are also being collected. Clinical data collection includes treatment, disease response (using RECIST criteria) and toxicity. The primary outcome measure is 1 year progression-free survival. Patients are also asked to invite a household member to be part of the study control group. Recruitment started in July 2020. The Covid-19 pandemic hindered recruitment last year, but the protocol was amended to incorporate a Covid-19 substudy (to document testing, infection and vaccination) and adapt processes for remote trial delivery as much as possible. As of February 2021, 7 sites have opened, 17 patients and 5 household controls have been recruited. Clinical trial information: NCT04107168. Research Sponsor: Cancer Research UK, Pharmaceutical/Biotech Company.

TPS2666 **Poster Session**

Phase I/Ib study with INT-1B3, a novel LNP-formulated micro-RNA (miR-193a-3p mimic) therapeutic for patients with advanced solid cancer.

Nuria Kotecki, Frans Opdam, Debbie Robbrecht, Michiel Strijbos, Karlijn Kroon, Michel Janicot, Sanaz Yahyanejad, Bryony Telford, Marion van den Bosch, Farshid Alemdehy, Thijs de Gunst, Harm den Boer, Rogier M. Vos, Laurens van Pinxteren, Roel Schaapveld; Institut Jules Bordet, Bruxelles, Belgium; NKI-AVL, Amsterdam, Netherlands; Erasmus MC, Rotterdam, Netherlands; GZA Hospitals Sint-Augustinus, Wilrijk, Belgium; InteRNA Technologies, Utrecht, Netherlands

Background: MicroRNAs (miR) are naturally-occurring small non-coding RNA molecules involved in the regulation of gene expression and their dysregulation plays a fundamental role in several pathological conditions including cancer. The miR-193a-3p acts as a tumor suppressor and is downregulated in many cancer types. INT-1B3 is a novel lipid-nanoparticle (LNP) formulated 1B3, a 22-nucleotide double stranded chemically-modified miR-193a-3p mimic. INT-1B3 showed significant tumor growth inhibition in a large panel of human and syngeneic tumor models. It directly targets tumor cells and the tumor microenvironment by specific modulation of multiple signaling pathway components. Furthermore, in syngeneic mice models for e.g. TNBC (4T1) and HCC (H22), INT-1B3 was able to modulate the immune tumor microenvironment by turning cold' tumors into hot' tumors *via* upregulation of cytokines (e.g., IL-2 and IFN-g), decreasing immunosuppressive cells/Treg (e.g., CD4+ /LAG3+ and CD3+ /FoxP3+) and triggering cytotoxic CD8+ T cell-mediated long-term memory immune protection against re-challenge with tumor cells. These preclinical results suggest potential clinical benefit in a broad range of cancer indications, and a reduced potential to develop drug resistance due to its multi-targeted mode of action. **Methods:** This is a 2-part, multi-center, open-label, multiple ascending dose, first-in-human, clinical study to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of INT-1B3 in the treatment of patients with advanced solid tumors. The phase 1 part follows a hybrid' 3+3 study design in all-comer' cancer patients enrolled and treated in cohorts to define the recommended phase 2 dose (RP2D). Upon completion of the dose escalation phase of the study, 2 expansion cohorts are planned to further confirm the safety, tolerability, and preliminary efficacy of the RP2D of INT-1B3 in patients with hepatocellular carcinoma and triple negative breast cancer. Major eligibility criteria include evaluable disease according to RECIST 1.1 and no more than one prior line of anti-PD-1/PD-L1 therapy. Patients will receive INT-1B3 *via* 60-min i.v. infusions twice a week in 21-day cycles. The first patient was enrolled on January the 14th 2021. Clinical trial information: NCT04675996. Research Sponsor: InteRNA Technologies BV.

TPS2667 **Poster Session**

Phase 1/2 study of the novel SUMOylation inhibitor TAK-981 in adult patients (pts) with advanced or metastatic solid tumors or relapsed/refractory (RR) hematologic malignancies.

Arkadiusz Z. Dudek, Dejan Juric, Afshin Dowlati, Erlene Kuizon Seymour, Jordi Rodon Ahnert, Bingxia Wang, Dennis Huszar, Allison J. Berger, Sharon Friedlander, Alejandro Gomez-Pinillos, Igor Proscurshim, Anthony J. Olszanski; University of Minnesota, Department of Medicine, Division of Hematology, Oncology, and Transplantation, Minneapolis, MN, Regions Cancer Care Center, HealthPartners, Saint Paul, MN; Massachusetts General Hospital Cancer Center, Boston, MA; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; Wayne State University School of Medicine and Karmanos Cancer Institute, Detroit, MI; Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA; Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA

Background: SUMOylation, a posttranslational modification analogous to ubiquitination, attaches a small, ubiquitin-like modifier (SUMO) to target proteins. SUMOylation plays a central role in regulating type I interferon (IFN-I)-dependent innate response and functions to constrain the innate immune response, which can impair tumor immune surveillance. TAK-981 is a first-in-class, small-molecule inhibitor of SUMO-activating enzyme subunit 2 (SAE2). Inhibition of SAE2 by TAK-981 disrupts SUMOylation, thereby allowing innate immune system activation. In *ex vivo* assays, TAK-981 increased phagocytic activity of monocyte-derived macrophages, increased natural killer cell cytotoxicity, and induced markers of dendritic cell activation and maturation via IFN-I signaling. In syngeneic mouse models, TAK-981 resulted in antitumor activity, including complete remissions, and a sustained, protective antitumor immune response. **Methods:** This first-in-human study of single-agent TAK-981 comprises two parts. Phase 1 primary objectives are to determine safety and tolerability, and to select a recommended phase 2 dose (RP2D); secondary objectives are to assess preliminary antitumor activity, characterize pharmacokinetics (PK), and explore pharmacodynamic (PD) biomarkers. This phase will enroll ~70 pts with untreatable locally advanced or metastatic solid tumors or RR lymphoma. The phase 2 primary objective is to evaluate preliminary efficacy at the RP2D in ~132 pts with non-squamous non-small cell lung cancer, cervical cancer, microsatellite-stable colorectal cancer, or CD20+ RR diffuse large B-cell lymphoma or follicular lymphoma. Pts receive TAK-981 via a 1-hour intravenous infusion on days 1, 4, 8, and 11 in 21-day cycles until unacceptable toxicity, pt withdrawal, or death. Dose escalation is proceeding from 3 mg, guided by an adaptive 3+3 design combined with Bayesian logistic regression modelling with overdose control, plus consideration of other safety, clinical, PK, and PD data. The RP2D will be based on the maximum tolerated dose (MTD) or on a biologically effective dose (BED) that is $\leq$MTD. The BED is defined as a dose at which there is evidence of drug-target engagement and inhibition of SUMOylation, plus: induction of cytokines/chemokines and/or IFN-I signature in tumor or blood; evidence of increased T cell infiltration in tumor; or antitumor activity. PK/PD modeling in the BED range is ongoing and will be used in RP2D determination. Clinical trial information: NCT03648372. Research Sponsor: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

TPS2668 **Poster Session**

Association of combined phase I/II study of a novel bicyclic peptide and MMAE conjugate BT8009 in patients with advanced malignancies with Nectin-4 expression.

Meredith McKean, Gerald Steven Falchook, Johanna C. Bendell, Babar Bashir, Neil Palmisiano, Roshawn Watson, Mary-Anne McKenna, Carly Campbell, Dominic Paul Smethurst, Phil Jeffrey, Julius Kirui, Hendrik-Tobias Arkenau, Elisa Fontana; Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN; Sarah Cannon Research Institute at HealthONE, Denver, CO; Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN; Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA; Bicycle Therapeutics, Lexington, MA; Bicycle Therapeutics, Cambridge, United Kingdom; Sarah Cannon Development Innovations, Nashville, TN; Sarah Cannon Research Institute, United Kingdom, London, United Kingdom

Background: BT8009 is a Bicycle Toxin Conjugate (BTC), a novel class of chemically synthesized molecules, comprising a bicyclic peptide targeting Nectin-4 tumor antigen, linked to cytotoxin (monomethyl auristatin E [MMAE]) via a valine-citrulline (val-cit) cleavable linker. Nectins (Nectin-1, -2, -3, and -4) and nectin-like molecules (Necl) are Ca2+ independent immunoglobulin-like cell adhesion molecules. Recent studies have shown the importance of Nectin-4 in several human cancers, including lung, ovarian, breast and bladder cancer; however, the precise roles and clinical relevance of Nectin-4 in tumors remain largely unknown. The Nectin-4 targeted enfortumab vedotin, linked to MMAE via a val-cit linker, is highly active in late-stage bladder cancer and demonstrates notable additional clinical activity as a single agent and in combination with pembrolizumab[1]. Skin toxicities, bone marrow suppression, peripheral neuropathy and diabetes have been associated with enfortumab, with some of these toxicities already noted with MMAE-bearing antibody therapies. We anticipate a similar toxicity profile for BT8009 in clinical studies. BT8009 exhibited a favorable preclinical profile and was effective in a range of cell-derived xenograph tumor models. **Methods:** Study BT8009-100 (NCT04561362) will evaluate safety and tolerability of weekly and every other week BT8009 administration, alone and in combination with q4w nivolumab. Determination of both a realistic phase 2 dose and a sequence will also be key to further exploration of safety and efficacy signals, along with an early examination of the role of baseline immunohistochemistry-ascertained levels of tumor Nectin-4. Patients will be recruited with advanced solid tumors associated with Nectin-4 expression after exhausting SOC options (i.e., bladder, breast, pancreatic, head and neck, gastric, esophageal and ovarian). Patients must have available tumor tissue, acceptable hematologic and other critical organ function and be willing to participate. Appropriate ethical and regulatory approvals and advice will be in place and adhered to. Exclusion criteria include uncontrolled brain metastases, uncontrolled hypertension, concomitant CYP3A4 inhibitors and significant history of autoimmune disease for the nivolumab cohorts. PK serial collections will be taken on D1 through D15. Radiologic tumor assessments for response per RECIST will be taken every two months. 1. Enfortumab Vedotin. FDA_data. 761137Orig1s000MultiDisciplineR.pdf (fda.gov). Clinical trial information: NCT04561362. Research Sponsor: Bicycle Therapeutics.

TPS2669 **Poster Session**

Trial in progress: A phase 1b study of sotorasib, a specific and irreversible KRAS^{G12C} inhibitor, as monotherapy in non-small cell lung cancer (NSCLC) with brain metastasis and in combination with other anticancer therapies in advanced solid tumors (CodeBreaK 101).

David S. Hong, John H. Strickler, Marwan Fakih, Gerald Steven Falchook, Bob T. Li, Greg Andrew Durm, Timothy F. Burns, Suresh S. Ramalingam, Sarah B. Goldberg, Tammy Lo, Kristen Marrone, Catherine A. Shu, David R. Gandara, Neelesh Soman, Haby Adel Henary, Ramaswamy Govindan; The University of Texas MD Anderson Cancer Center, Houston, TX; Duke University School of Medicine, Durham, NC; City of Hope Comprehensive Medical Center, Duarte, CA; Sarah Cannon Research Institute, Denver, CO; Memorial Sloan Kettering Cancer Center, New York, NY; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Winship Cancer Institute of Emory University, Atlanta, GA; Yale School of Medicine, New Haven, CT; Nuvance Health, Norwalk, CT; Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Columbia University Medical Center, New York, NY; University of California Davis Comprehensive Cancer Center, Sacramento, CA; Translational Medicine, Amgen Inc., Thousand Oaks, CA; Amgen Inc., Thousand Oaks, CA; Washington University School of Medicine, St. Louis, MO

Background: Kirsten rat sarcoma viral oncogene homolog(*KRAS*) p.G12C mutation is an oncogenic driver mutation in several solid tumors. Sotorasib is a specific, irreversible, small molecule inhibitor of KRAS^{G12C} that has demonstrated durable clinical benefit in NSCLC, with mild and manageable toxicities. The combination of sotorasib with other anticancer therapies may enhance antitumor efficacy. This master protocol is designed to evaluate safety, tolerability, pharmacokinetics (PK), and efficacy of multiple sotorasib combinations in patients (pts) with *KRAS*p.G12C mutated solid tumors. Herein, we overview 1 monotherapy and 11 combination cohorts. **Methods:** This is a phase 1b, open-label study evaluating sotorasib alone and in combination regimens (Table) in pts with advanced *KRAS* p.G12Cmutated solid tumors. Dose exploration will evaluate the safety and tolerability of sotorasib alone and in combination regimens; dose expansion will then verify the safety and tolerability profile of sotorasib regimens and assess antitumor efficacy. Key eligibility criteria include locally-advanced or metastatic solid tumor with *KRAS* p.G12C mutation identified through molecular testing in pts who have received $\geq$1 lines of prior systemic therapy. Primary endpoints include dose-limiting toxicities and treatment-emergent or treatment-related adverse events. Secondary endpoints include PK profile of combination regimens and efficacy (eg, objective response, disease control, duration of response, progression-free survival, and duration of stable disease assessed per RECIST 1.1). Enrollment began in December 2019 and is ongoing. Clinical trial information: NCT04185883. Research Sponsor: Amgen Inc.

Advanced tumor types	Treatment arms
NSCLC with brain metastasis	Sotorasib monotherapy
NSCLC	Sotorasib + TKI
	Sotorasib + anti-PDL1 therapy
	Sotorasib + chemotherapeutic regimen
	Sotorasib + anti-PD1 therapy
Colorectal cancer	Sotorasib + anti-VEGF therapy + chemotherapeutic regimen
All solid tumors	Sotorasib + MEK inhibitor ± EGFR inhibitor
	Sotorasib + anti-PD1 therapy
	Sotorasib + SHP2 inhibitor
	Sotorasib + anti-EGFR therapy ± chemotherapeutic regimen
	Sotorasib + CDK inhibitor
	Sotorasib + mTOR inhibitor

CDK = cyclin-dependent kinase; EGFR = epidermal growth factor receptor; MEK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; PD1 = programmed cell death protein-1; PDL1 = programmed death-ligand 1; SHP2 = Src homology region-containing protein tyrosine phosphatase 2; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

TPS2670 **Poster Session**

A phase 1 dose-escalation study of intravenously (IV) administered TAK-676, a novel STING agonist, alone and in combination with pembrolizumab in patients (pts) with advanced or metastatic solid tumors.

Gerald Steven Falchook, Jason J. Luke, James F. Strauss, Xin Gao, Patricia LoRusso, PEI JYE VOON, Cong Li, Michael Shaw, Richard C. Gregory, Kristin Horn, John Gibbs, Neil Lineberry, Kate Stumpo, Karim Malek, Anthony J. Olszanski; Sarah Cannon Research Institute at HealthONE, Denver, CO; Cancer Immunotherapeutics Center, University of Pittsburgh, Pittsburgh, PA; Mary Crowley Cancer Research Center, Dallas, TX; Massachusetts General Hospital, Boston, MA; Yale Cancer Center, New Haven, CT; University Health Network, Toronto, ON, Canada; Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA; Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA

Background: Immuno-oncology therapies, including immune checkpoint inhibitors (CPIs), are revolutionizing cancer treatment. However, primary and secondary resistance to CPIs remains a significant challenge. CPI resistance has been associated with reduced interferon (IFN) signaling, altered antigen presentation, and an immunosuppressive tumor phenotype. Stimulating innate immune cells to develop a proinflammatory tumor environment that activates IFN signaling and downstream adaptive antitumor immune mechanisms is predicted to overcome such resistance. Stimulator of Interferon Genes (STING) is a key mediator of type 1 IFN-dependent innate immune modulation. Most STING agonists evaluated clinically have required intratumoral administration, which has significant logistical challenges and excludes many pts whose tumors are not accessible for injection. TAK-676 is a novel STING agonist under clinical investigation as an IV administered systemic therapy in pts with solid tumors. **Methods:** The primary objective of this study is to determine the safety and tolerability of TAK-676 alone and in combination with pembrolizumab. Secondary objectives are to: determine the pharmacologically active dose and recommended phase 2 dose; characterize TAK-676 pharmacokinetics; assess preliminary antitumor activity; and assess STING agonism gene signature induction. An exploratory objective is to assess immune cell activation and clinical response. The study comprises a single-pt safety lead-in with single-agent (SA) TAK-676 0.1 mg IV, followed by dose escalation using Bayesian Logistic Regression Model design. Dose escalation will start in the combination arm when $\geq$2 dose levels in the SA arm have been evaluated and considered safe. In both arms, pts will receive TAK-676 on days 1, 8, and 15 in 21-day cycles for up to 1 year. In the combination arm, pts will also receive pembrolizumab 200 mg IV on day 1 of each cycle. Adult pts with histologically confirmed advanced or metastatic solid tumors who have no standard therapeutic options or are intolerant to them, with an Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and $\geq$1 Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1- evaluable lesion are eligible; pts with tumors that have relapsed, are refractory or nave to anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) therapy are eligible for the combination arm. Planned enrollment is ~76 pts; recruitment is ongoing. Clinical trial information: NCT04420884. Research Sponsor: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

TPS2671 **Poster Session**

Trials in progress: A phase 1, open-label, dose-escalation, pharmacokinetic, safety and tolerability study of the selective TAM kinase inhibitor PF-07265807 in patients with advanced or metastatic solid tumors.

Vivek Subbiah, Mark M. Awad, Adil Daud, Martin Gutierrez, Jessica Dreger McDermott, Sai-Hong Ignatius Ou, Tomoko Hirohashi, Kim Ingram, Colleen Oliver, Derek Smith, Lance Wollenberg, James L. Abbruzzese; The University of Texas MD Anderson Cancer Center, Houston, TX; Lowe C, Dana-Farber Cancer Institute, Boston, MA; University of California, San Francisco, San Francisco, CA; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; University of Colorado, Aurora, CO; University of California Irvine, Irvine, CA; Pfizer, New York, NY; Pfizer, Boulder, CO; Duke University Medical Center, Durham, NC

Background: MERTK is a receptor tyrosine kinase from the tumor-associated macrophage kinase (TAMK) family that regulates key aspects of immune homeostasis and responses to infection. MERTK inhibition may lower the threshold for immune activation thereby promoting anti-tumor activity. Agents with some degree of MERTK inhibitory activity have been investigated in the clinic, but are limited by poor potency in patients (pts) and significant off-targets effects. PF-07265807 (ARRY-067) is a selective small-molecule inhibitor of the TAMKs MERTK and AXL. In preclinical models, PF-07265807 monotherapy shows antitumor activity that results in long-term cures and resistance to tumor re-challenge when combined with anti-programmed cell death protein 1/programmed death-ligand 1 (anti-PD-1/PD-L1) antibodies. This first-in-human study will evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumor activity of PF-07265807 in pts with selected advanced or metastatic solid tumors. This study will also explore the potential utility of PF-07265807 in combination with anti-PD-1/PD-L1 antibodies. **Methods:** This is a phase 1, open-label, multi-center, dose-escalation study (NCT04458259) to evaluate the safety, PK and tolerability of PF-07265807. Eligible participants will be adult pts with selected advanced or metastatic solid tumors who are intolerant or resistant to standard therapy. Other key eligibility criteria: measurable disease by RECIST 1.1 or non-measurable disease; Eastern Cooperative Oncology Group performance status 0–2; adequate bone marrow, renal and liver function; and resolved acute effects of any prior therapy. Successive cohorts of pts will receive escalating doses of PF-07265807 starting from 25 mg QD. Each cycle will be 21 days in duration (14 days on/7 days off). Study drug treatment will continue until disease progression or unacceptable toxicity, whichever occurs first. For dose escalation, a Bayesian logistic regression model will be used to model the relationship of dose-limiting toxicities (DLTs) to PF-07265807 dose. This model, along with escalation with overdose control, will guide the dose escalation of PF-07265807 after the completion of the DLT observation period (first two cycles of treatment, i.e. 42 days) of each cohort, until determination of the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D). After the MTD/RP2D is identified, the safety and efficacy of combined PF-07265807 and anti-PD1/PD-L1 treatment will be explored. Primary endpoints: incidence of DLTs, treatment-emergent adverse events and laboratory abnormalities. Secondary endpoints: PK parameters of PF-07265807, objective response rate and duration of response. The study began enrolling pts in September 2020 and is still recruiting. Clinical trial information: NCT04458259. Research Sponsor: Pfizer.

TPS2672 **Poster Session**

Phase 1, first-in-human trial of JTX-8064, an anti-LILRB2/ILT4 monoclonal antibody, as monotherapy and in combination with anti-PD-1 in adult patients with advanced solid tumors (INNATE).

Kyriakos P. Papadopoulos, Nehal J. Lakhani, Timothy A. Yap, Allison L Naumovski, Karen S Brown, Ben Umiker, Lara McGrath, Weidong Zhang, Edward Stack, Gosia Riley, Nancy Mota, Christina Tasillo, Haley Laken, Elizabeth G. Trehu, Johan Baeck; START-San Antonio, San Antonio, TX; START Midwest, Grand Rapids, MI; The University of Texas MD Anderson Cancer Center, Houston, TX; Jounce Therapeutics, Cambridge, MA

Background: Leukocyte Immunoglobulin-like receptor B2 [LILRB2; immunoglobulin-like transcript 4 (ILT4)] is an immunoinhibitory protein expressed on the surface of myeloid cells and is a therapeutic target of interest in immuno-oncology. Published data showed that antagonism of LILRB2 resulted in the repolarization of human macrophages from an M2 (suppressive) to M1 (pro-inflammatory) phenotype, and enhancement of anti-tumor immunity in a mouse model (Chen 2018). JTX-8064 is a novel humanized IgG4 monoclonal antagonist antibody that selectively binds LILRB2 and prevents it from binding its ligands, classical and non-classical MHC I molecules. By blocking the ability of LILRB2 to bind HLA-A/B and/or HLA-G, a marker of immunotolerance on cancer cells, JTX-8064 has been shown to enhance pro-inflammatory cytokine production in macrophages (Cohen 2019). Additionally, blocking HLA-A/B-LILRB2 binding with JTX-8064 may augment antigen presentation and has been shown to lead to enhanced T cell activation and IFNg production (McGrath 2021). Using an ex vivo tumor explant model, we observed an IFNg-associated pharmacodynamic response in tumor tissue treated with JTX-8064 and a PD-1 inhibitor (PD-1i) that was not observed with PD-1i alone. Biomarkers were identified that predicted this JTX-8064 driven response (Hashambhoy-Ramsay 2020). It is hypothesized that JTX-8064 is a novel macrophage immune checkpoint inhibitor that may overcome mechanisms of resistance to PD-1i in tumors not responsive to JTX-8064 or PD-1i alone. **Methods:** The primary objectives of this open-label, phase 1, first-in-human, multicenter trial are to determine the safety and tolerability, and the recommended phase 2 dose (RP2D) of JTX-8064 as a monotherapy and in combination with a PD-1i, JTX-4014 (a Jounce investigational agent) or pembrolizumab, in patients with advanced solid tumors (NCT04669899). The INNATE study will consist of 4 stages: 1) JTX-8064 monotherapy dose escalation, 2) JTX-8064 dose escalation in combination with a PD-1i, 3) JTX-8064 monotherapy in indication-specific expansion cohorts and 4) JTX-8064 in combination with a PD-1i in indication-specific expansion cohorts. Stages 1 and 2 will employ an innovative interval i3 + 3 design with Bayesian decision framework to guide dose escalation. Safety, pharmacokinetic and receptor occupancy data will be considered during dose escalation. INNATE will assess pharmacodynamic and potential predictive biomarkers of response, and the expansion cohorts will explore multiple patient populations, including PD-(L)1i sensitive and PD-(L)1i-resistant (primary or acquired) patients to address current unmet medical needs. Enrolment in INNATE began in January 2021. Clinical trial information: NCT04669899. Research Sponsor: Jounce Therapeutics.

TPS2673 **Poster Session**

A phase 1, multicenter, open-label, dose-escalation, safety, pharmaco-dynamic, pharmacokinetic study of Q702 with a cohort expansion at the RP2D in patients with advanced solid tumors.

Angela Tatiana Alistar, Anthony B. El-Khoueiry, Devalingam Mahalingam, Monica M. Mita, Hwankyu Kang, Yeong-In Yang, Jiye Ahn, Jeongjun Kim, Baejung Choi, Yeejin Jeon, Chunwon Jung, Borami Jeon, Jaeseung Kim, Kiyean Nam; Atlantic Health System, Morristown, NJ; University of Southern California, Los Angeles, CA; Northwestern University, Chicago, IL; Cedars-Sinai Medical Center, Los Angeles, CA; Qurient Co. Ltd, Seongnam-Si, South Korea

Background: Immune checkpoint inhibitors directly targeting T cell activation have been successfully used in the treatment of various malignancies, nevertheless, the durable ORRs are low for certain indications. The low ORRs have been attributed to the immune suppressive tumor microenvironment (TME), composed of innate immune suppressive components such as tumor associated macrophages (TAM) and myeloid-derived suppression cells (MDSC). The potential contributions of innate immune modulation to anti-tumor immunity, suggest the need for the novel strategies to elicit a more efficient/robust immune response against the targeted malignant cells. Axl, Mer and CSF1R receptor tyrosine kinases play vital roles in promoting an immune suppressive TME by affecting TAM and MDSC populations and by decreasing antigen presentation on tumor cells. Q702 is a novel Axl/Mer/CSF1R inhibitor, able to modulate the TAM and MDSC population leading to CD8+ T cell activation and to increase antigen presentation of the tumor cells in syngeneic animal models. Q702, as a monotherapy, shows significant tumor growth inhibition in multiple syngeneic tumor models, and demonstrates synergistic effects with anti-PD-1 treatment particularly in high myeloid containing tumor models. Interestingly, intermittent administration of Q702 monotherapy demonstrates a more favorable immune cell population changes, possibly through preventing immune exhaustion secondary to negative feedback with continuous activation. These results suggest that Q702 monotherapy or in combination with existing therapies have a good potential to become a novel treatment strategy for patients with advanced solid tumors.
Methods: A Phase 1, Multicenter, Open-label, Dose-Escalation, Safety, Pharmacodynamic, Pharmacokinetic Study of Q702 with a Cohort Expansion at the RP2D in Patients with Advanced Solid Tumors. (NCT04648254) is open and recruiting patients at 4 US investigative sites. Patients with histologically or cytologically confirmed advanced or metastatic solid tumors, that have progressed following SOC or for which there is no SOC which confers clinical benefit are being enrolled in this study. The study follows a standard dose escalation. The study will enroll up to 78 patients. The primary endpoint is to establish safety, PK profile and define the recommended phase 2 dose. The secondary and exploratory endpoints include establishing pharmacokinetic/pharmacodynamic relationship, potential biomarkers and preliminary anti-tumor activity. Clinical trial information: NCT04648254. Research Sponsor: Qurient Co. Ltd.

TPS2674 **Poster Session**

Phase 1 first-in-human study of ABBV-184 monotherapy in adult patients with previously treated acute myeloid leukemia or non-small cell lung cancer.

Abraham Avigdor, Pierre Peterlin, Junichiro Yuda, Mor Tal Moskovitz, Nashat Y. Gabrail, Yakir Moshe, Bruno Quesnel, William R Henner, Edward B. Reilly, Donghui Huang, Maria Kovalenko, Apurvasena Parikh, Stacy Jaryno, Rachel S Leibman, Kevin J Freise, Esma Saada-Bouzid, Toshio Shimizu; Institute of Hematology, Sheba Medical Center, Ramat Gan, Israel, and Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel; Centre Hospitalier et Universitaire (CHU) de Nantes, CHU Hotel-Dieu, Nantes, France; National Cancer Center Hospital East, Kashiwa, Japan; Rambam Health Care Campus, Haifa, Israel; Gabrail Cancer Center, Canton, OH; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; CHU Lille, Service des Maladies du Sang, Lille, France; AbbVie, Inc, North Chicago, IL; AbbVie, Inc, Redwood City, CA; Centre Antoine Lacassagne, University Côte d'Azur, Nice, France; National Cancer Center Hospital, Tokyo, Japan

Background: Survivin, a member of the inhibitor of apoptosis protein family, is an attractive therapeutic target in cancer, due to its broad expression in solid tumors and hematologic malignancies but limited expression in normal tissues. Elevated survivin expression is associated with an increased invasive phenotype and worse clinical outcomes. ABBV-184 is a first-in-class T-cell receptor (TCR)/anti-cluster of differentiation 3 (CD3) bispecific molecule. It is composed of a soluble TCR that binds to a survivin-derived peptide bound to the class I MHC allele HLA-A2:01 expressed on tumor cells and to the CD3 receptor on T cells. Preclinical data have demonstrated that treatment with ABBV-184 results in T-cell activation, proliferation, and redirected cytotoxicity of HLA-A2:01–positive target cell lines. This first-in-human trial evaluates ABBV-184 monotherapy in patients with previously treated acute myeloid leukemia (AML) or non-small cell lung cancer (NSCLC). **Methods:** Patients ($\geq$18 years, Eastern Cooperative Oncology Group performance status $\leq$2, HLA-A2:01 restricted genotype) with relapsed or refractory AML or NSCLC are currently enrolling in this phase 1 multicenter, open-label trial (NCT04272203), which includes parallel dose-escalation and dose-expansion phases for both diseases. Primary objectives are to determine the recommended phase 2 dose (RP2D) of ABBV-184 (dose escalation) and to assess its preliminary efficacy (dose expansion). Secondary objectives include safety, tolerability, pharmacokinetics (PK), and immunogenicity assessments (dose escalation and dose expansion) and duration of response (dose expansion). Patients will receive intravenous infusion of ABBV-184 once weekly. Dose escalation of ABBV-184 is guided by a Bayesian optimal interval design and the RP2D will be determined on the basis of clinical safety, PK, and pharmacodynamic data. For patients with AML, disease assessment is performed according to modified European LeukemiaNet-International Working Group criteria. For patients with NSCLC, response will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and immune RECIST. Treatment can continue until disease progression or intolerable toxicity. Biomarker assessments will include longitudinal profiling of peripheral blood immune cells and cytokines, analysis of HLA-A2 and survivin levels on AML bone marrow blasts and NSCLC tumor biopsies, and retrospective correlations of biomarker data with antitumor activity. Enrollment initiated in Sep 2020, with 7 patients enrolled as of Jan 2021. Clinical trial information: NCT04272203. Research Sponsor: AbbVie, Inc.

TPS2675 **Poster Session**

A phase I study of AK119, an anti-CD73 monoclonal antibody, in combination with AK104, an anti-PD-1/CTLA-4 bispecific antibody, in patients with advanced or metastatic solid tumors.

Ben Markman, Amy Hsin-Chieh Hsieh, Jermaine Coward, Matteo S. Carlino, Sophia Frentzas, Xiaoping Jin, Baiyong Li, Zhongmin Maxwell Wang, Kon Yew Kwek, Yu Xia; Alfred Hospital, Melbourne, Australia; Icon Cancer Centre, Windsor Gardens, SA, Australia; ICON Cancer Care, South Brisbane, QLD, Australia; Westmead Hospital, Sydney, NSW, Australia; Monash Health, Melbourne, VIC, Australia; Akeso Biopharma, Inc., Zhongshan, China

Background: AK119 is a humanized IgG1 monoclonal antibody (mAb) that selectively binds to and inhibits the ectonucleotidase activity of CD73, a cell surface enzyme that converts adenosine monophosphate (AMP) into adenosine. Adenosine has been shown to facilitate tumor-mediated evasion. CD73 inhibition may therefore reduce adenosine accumulation and promote anti-tumor immunity. AK104 is a recombinant humanized IgG1 bispecific antibody that simultaneously binds to programmed cell death protein 1 (PD-1) and cytotoxic T- lymphocyte-associated antigen protein 4 (CTLA-4). Preliminary data from phase I and II studies suggest that AK104 has encouraging anti-tumor activity in selected tumor types and an improved safety profile compared to the co-administration of anti-PD-1 plus anti-CTLA-4 mAbs. Preclinical studies show that CD73 inhibition synergistically increases the anti-tumor activity of PD-1 and CTLA-4 immune checkpoint inhibitors (ICIs). Published early clinical data suggests that anti-CD73 therapy in combination with ICIs produces improved clinical outcomes. Thus, AK119 plus AK104 is postulated to have synergistically enhanced anti-tumor activity compared to the administration of anti-CD73 monotherapy or ICIs alone. **Methods:** This is a phase 1a/1b, first-in-human, multicenter, open-label study in patients with advanced solid tumors that are refractory to standard therapies. The primary objective is to assess safety, tolerability and dose limiting toxicity; and to determine the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) of AK119 in combination with AK104. Secondary objectives are to evaluate antitumor activity, PK and AK119 immunogenicity. The dose-escalation phase will evaluate 5 dose levels of AK119 (1mg/kg to 40 mg/kg Q2W IV) in combination with 6mg/kg AK104 Q2W IV using a 3+3+3 study design. Eligible pts will receive a single dose of AK119 on C0D1 of a 14-day lead-in period. Thereafter, from C1D1 pts will receive AK119 in combination with AK104 on a 28-day cycle, until unacceptable toxicity, confirmed progressive disease, subject withdrawal, or for a maximum of 24 months. The lead-in period is only applicable for dose-escalation cohorts. Any dose-escalation cohort not exceeding the MTD may be expanded to a maximum of 18 subjects with selected solid tumor types for further evaluation of safety, PK/ PD, immunogenicity, and preliminary anti-tumor activity. Cohort 1 is currently in progress with the first patient enrolled in January 2021. For the dose-expansion phase, cohorts of pts with advanced/metastatic pancreatic cancer or MSS/pMMR colorectal cancer will be enrolled. Cohorts of other tumor types may be added based on emerging pharmacodynamic and anti-tumor response data. Clinical trial information: NCT04572152. Research Sponsor: Akeso Biopharma, Inc.

TPS2676 **Poster Session**

A phase 1b study of nivolumab in patients with autoimmune disorders and advanced malignancies (AIM-NIVO).

Ecaterina Elena Dumbrava, Michael L. Dougan, Sarthak Gupta, Laura Cappelli, Tamiko R. Katsumoto, Osama E. Rahma, Jeane Painter, Yinghong Wang, Maria E. Suarez-Almazor, Pankti Reid, Sarah F. Wesley, David A Hafler, Clifton O. Bingham, Blake M Warner, Lorinda Chung, Patrick Alexander Ott, Harriet M. Kluger, Arezou Khosroshahi, Hussein Abdul-Hassan Tawbi, Elad Sharon; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital Cancer Center, Boston, MA; National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD; Johns Hopkins School of Medicine, Baltimore, MD; Stanford University School of Medicine, Stanford, CA; Dana-Farber Cancer Institute, Boston, MA; Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Chicago, Chicago, IL; Columbia University Vagelos College of Physicians and Surgeons, New York, NY; Yale School of Medicine, New Haven, CT; Johns Hopkins University School of Medicine, Baltimore, MD; National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD; Stanford University School of Medicine, Palo Alto, CA; Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT; Emory University, Atlanta, GA; National Cancer Institute, Bethesda, MD

Background: Nivolumab is an anti-PD1 monoclonal antibody approved for treatment of an increasing number of solid tumors and hematological malignancies. However, patients (pts) with history of autoimmune disorders are excluded from the majority of clinical trials testing immune-checkpoint inhibitors (ICI) such as anti-PD1/anti-PD-L1 antibodies. Consequently, the risks of flare ups, worsening of pre-existing autoimmune disorders or risk of de-novo immune related adverse events (irAEs) in pts with dysfunctional immune systems and tumor types who otherwise stand to benefit from ICI therapy are largely unknown, posing a challenge for oncologists. We are conducting a phase Ib study to test the hypothesis that nivolumab can be safely administered to pts with varying severity of Dermatomyositis, Systemic Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Inflammatory Bowel Disease, Multiple Sclerosis and other autoimmune disorders (AIM-Nivo). **Methods:** AIM-Nivo is an open-label, multi-center ongoing phase Ib study with nivolumab 480mg IV every 28 days in pts with autoimmune diseases and advanced malignancies (NCT03816345). The study has autoimmune disease-specific cohorts overseen by a multidisciplinary group of experts. The primary objective is to assess the overall safety and toxicity profile of nivolumab in pts with autoimmune disorders and advanced malignancies. Secondary objectives are to evaluate the antitumor efficacy; the impact of nivolumab on the autoimmune disease severity indices; and to explore potential biomarkers of response, resistance, or toxicity for each of the autoimmune disease-specific cohorts. Key overall inclusion criteria include age $\geq$18 years, histologically confirmed advanced or metastatic malignancies in which ICI are approved or have shown clinical activity. Key overall exclusion criteria include prior therapy with anti-PD-1/PD-L1 antibodies. Specific eligibility criteria are defined for each disease-specific cohort. For each autoimmune disorder, severity level of the disease as defined by disease-specific severity indices will be assessed, and up to a total of 12 pts will be included in each disease cohort at each severity level (max 36 pts per cohort). Primary endpoints are dose-limiting toxicities, adverse events (AEs) and serious AEs. Continuous monitoring of toxicity will be conducted. Key secondary endpoints are best objective response per RECIST1.1; progression free and overall survival; and cohort specific tumor tissue, blood, and non-tumor tissue-based biomarkers. The AIM-Nivo trial opened in May 2019 and is enrolling pts through the National Cancer Institute Experimental Therapeutics Clinical Trials Network (ETCTN), Early Drug Development Opportunity Program (EDDOP), and Create Access to Targeted Cancer Therapy for Underserved Populations (CATCH-UP) sites. Clinical trial information: NCT03816345. Research Sponsor: U.S. National Institutes of Health.

TPS2677 **Poster Session**

An open-label phase 1b/2 study of surufatinib in combination with tislelizumab in subjects with advanced solid tumors.

Arvind Dasari, John S. Kauh, Christopher Tucci, Shivani Nanda, Marek K. Kania, Jennifer W Carlisle, Andrew Scott Paulson; The University of Texas MD Anderson Cancer Center, Houston, TX; Hutchison MediPharma (US) Inc., Florham Park, NJ; Hutchison MediPharma, Florham Park, NJ; Hutchison MediPharma International Inc, Florham Park, NJ; Winship Cancer Institute of Emory University, Atlanta, GA; Baylor Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, TX

Background: Surufatinib (S) is an inhibitor of VEGFR1, 2, & 3; FGFR1; and CSF-1R. In two phase 3 randomized trials (SANET-ep; NCT02588170 & SANET-p; NCT02589821) S demonstrated a manageable safety profile and statistically significant efficacy. Patients (pts) with extrapancreatic neuroendocrine tumors (epNETs) achieved a median progression free survival (PFS) of 9.2 v 3.8 months (mo) (hazard ratio [HR] 0.334; $p<0.0001$), and pts with pancreatic NETs (pNETs) achieved a median PFS of 10.9 v 3.7 mo (HR 0.491; $p=0.0011$), with S v placebo, respectively. S was recently approved for the treatment of pts with epNET in China. Tislelizumab (T) is a humanized immunoglobulin G4 anti-PD-1 monoclonal antibody engineered to minimize binding to Fc-gamma-receptor on macrophages. T is approved in China in combination with chemotherapy for squamous non-small cell lung cancer and has conditional approval for Hodgkin's lymphoma and locally advanced or metastatic urothelial carcinoma with PD-L1 high expression. The objective of this study is to evaluate the safety and efficacy of combination therapy with S and T, which may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor activity.
Methods: This study (NCT04579757) will include pts, $\geq$18 years of age, with advanced metastatic solid tumors, who have an Eastern Cooperative Oncology Group performance status of 0 or 1 and have progressed on or are intolerant to standard therapies. The primary objective of part 1 (dose escalation) will be to evaluate the safety and tolerability of S and T to determine the recommended phase 2 dose of the combination. The starting dose in part 1 will be 250 mg of S, orally, daily, and 200mg of T, intravenously, every 3 weeks. The dose of S will be escalated during part 1, while the dose of T will remain fixed. Endpoints include dose limiting toxicities, treatment emergent adverse events, serious adverse events, adverse events leading to discontinuation, electrocardiograms, clinical laboratory abnormalities and vital signs. Antitumor activity will be evaluated as a secondary objective. Six to 12 pts will be enrolled. The primary objective of part 2 (dose expansion) will be to evaluate the objective response rate (ORR) of S in combination with T per RECIST v1.1. The endpoint will be ORR at 12 weeks. Key secondary endpoints include PFS, disease control rate, duration of response, safety endpoints, and PK parameters. Approximately 95 pts with indications of interest will be enrolled: colorectal cancer, neuroendocrine tumors (thoracic and gastroenteropancreatic), small-cell lung cancer, gastric cancer, and soft tissue sarcoma (undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma). Enrollment in the United States is open and ongoing, and enrollment in Europe is planned for fourth quarter 2021. Clinical trial information: NCT04579757. Research Sponsor: Hutchison MediPharma Limited.

TPS2678 **Poster Session**

Combination of atezolizumab and pirfenidone in second-line and beyond NSCLC: A phase I/II study.

Takefumi Komiya, Jun Zhang, Prakash C. Neupane, Kathan Mehta, Chao Hui Huang; Hematology/Medical Oncology, Parkview Cancer Institute, Fort Wayne, IN; University of Kansas Medical Center, Kansas City, KS; University of Kansas Cancer Center, Westwood, KS; Univ of Kansas Cancer Ctr, Kansas City, KS

Background: Checkpoint inhibitors (CPI) targeting the PD1/PD-L1 axis significantly improved patient outcomes in stage IV non-small cell lung cancer (NSCLC). However, these patients will eventually develop resistance and progression. There is a need to identify novel treatment options. Poor response to PD-L1 antibody was correlated with increase in cancer-associated fibroblasts (CAF), which is known to interact with cytotoxic T cells (CTLs) by suppressing their function in a manner similar to regulatory T cells (Tregs). Production of cytokines by CAFs leads to impaired antitumor immunity by impairing CTL function (TGF beta) and prevent recruitment/mobilization of CTLs into tumors. These effects suggesting that CAF can be a therapeutic target in lung cancer resistant to checkpoint inhibitors. Pirfenidone (P) is approved to treat pulmonary fibrosis with anti-fibrotic effect by blocking the differentiation of fibroblasts into CAFs and suppress the production of TGF beta and TGF beta-induced signaling pathways/collagens. Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (CD80), both of which function as inhibitory receptors expressed on T cells. We proposed a phase I/II trial to test the combination of atezolizumab (A) with P in patients with recurrent non-small cell lung cancer (NSCLC) after progression with CPI. The primary objective of phase I is to determine the maximum tolerated (MTD) dose of P in combination with A and assess the safety and tolerability of this combination. The secondary objective is to determine the efficacy of AP in all NSCLC participants treated in this study. Exploratory objectives include the measurement of circulating levels of TGF beta and research in expression of CAF related proteins. **Methods:** The initial phase I will enroll 3 patients using P at 801 mg po TID. A will be at 1200mg iv every 3 weeks. If there is $\leq$ 1 DLT, the study will proceed to phase II If there are 2- 3 DLT, P will be reduced to 534 mg TID. If there is $\leq$ 1 DLT, then this dose will proceed to phase II. If there is 2-3 DLT, then the study will be terminated. The phase II will enroll 16 patients to assess efficacy. Main inclusion criteria are patients with recurrent NSCLC after progression with first-line therapy CPI with or without chemotherapy, measurable disease, ECOG 0-2, and adequate organ function. Clinical trial information: NCT04467723. Research Sponsor: Genentech.

TPS2679 **Poster Session**

Immune Resistance Interrogation Study (IRIS): A prospective comprehensive multi-omic analysis in patients with intrinsic and acquired resistance to immunotherapy.

Sofia Genta, Ming Sound Tsao, Ben X Wang, Aaron Richard Hansen, Trevor John Pugh, Mathieu Lupien, Bryan Coburn, Javier Diaz-Mejia, Marcus O. Butler, Philippe L. Bedard, Albiruni Ryan Abdul Razak, Sevan Hakgor, Vanessa Speers, Heidi Wagner, Laura Tamblyn, Troy Ketela, Dax Torti, Nikolina Radulovich, Lillian L. Siu, Anna Spreafico; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; Princess Margaret-University Health Network, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre / University Health Network, Toronto, ON, Canada; Toronto General Hospital, University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada, Toronto, ON, Canada; Tumor Immunotherapy Program, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Ontario Institute for Cancer Research, Toronto, ON, Canada; Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Immune checkpoint inhibitors (ICI) have demonstrated efficacy in a wide variety of cancers. Nevertheless, only a small proportion of patients derive a durable benefit. Mechanisms underlying primary and acquired resistance are still incompletely understood. They comprise tumor-intrinsic factors such as genomic and transcriptomic changes; upregulation of immunosuppressive subsets; T cell exhaustion; and promotion of an immune-tolerant tumor microenvironment. The collection of tumor biopsy at disease progression (PD) is challenging both in clinical and research settings as this often occurs at the time of treatment discontinuation. However, the analysis of these samples can lead to novel strategies to prevent or reverse immune resistance. Thus, the current approach to begin a profiling study with patients at the time of PD on ICI enables access and interrogation of such samples. **Methods:** IRIS is a prospective, investigator-initiated trial at the Princess Margaret Cancer Centre that aims to extensively characterize the genomic, transcriptomic, epigenetic and immunophenotypic profiles of tumors with primary versus acquired resistance to ICI-based therapy. Primary resistance is defined as PD at the first on-treatment imaging, whereas acquired resistance is defined as PD occurring after an initial partial or complete response or following disease stability lasting $\geq$6 months. Additional objectives include the evaluation of radiomic parameters on standard radiological imaging, investigation of fecal microbiome, generation of patient-derived organoids and facilitation of data and sample sharing with the research community. The planned samples size is 100 patients. A one-time fresh tumor biopsy, blood and stool samples and archival tissue (when available) are collected at the time of PD on ICI (baseline) from all the participants. Longitudinal blood samples are obtained every 2-3 months (around the time of tumor imaging) until PD in patients receiving a subsequent treatment. Subjects who are not amenable for therapy undergo blood collections at the time of further PD. Molecular characterization of tumor samples includes: DNA/RNA sequencing, Assay of Transposase Accessible Chromatin (ATAC)-sequencing, Cellular Indexing of Transcriptomes and Epitopes (CITE)-sequencing, multiplexed immunohistochemistry and flow cytometry. Results of NGS performed on the first biopsy core are returned to patient and physician. Key eligibility criteria include diagnosis of solid tumor, progression to ICI as the most recent line of treatment and disease amenable to core needle biopsy. The IRIS trial, activated in October 2020, is currently open to enrollment. As of January 2021, 21 patients have been enrolled and a total of 92 tissue cores, 42 blood and 20 stool samples have been collected. Clinical trial information: NCT04243720. Research Sponsor: Princess Margaret Cancer Center institutional founding.

TPS2680 **Poster Session**

Personalized DNA neoantigen vaccine in combination with plasmid IL-12 and pembrolizumab for the treatment of patients with advanced hepatocellular carcinoma.

Mark Yarchoan, Edward Gane, Thomas Urban Marron, Sarah Rochestie, Neil Cooch, Joann Peters, Ildiko Csiki, Alfredo Perales-Puchalt, Niranjan Sardesai; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Auckland City Hospital, Auckland, New Zealand; Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Geneos Therapeutics, Plymouth Meeting, PA; City of Hope, Duarte, CA

Background: Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death. Immune checkpoint inhibitors targeting PD-1 have limited activity in HCC as monotherapy, with response rates ranging from 14-17%. Tumor neoantigens derived from tumor-specific mutations can be incorporated into personalized therapeutic cancer vaccines to prime T cell responses, potentially enhancing responses to anti-PD1 therapy. DNA vaccines have been shown to elicit strong CD8 and CD4 T cell responses in preclinical and clinical trials. In preclinical studies, DNA-encoded neoantigen vaccines have shown induction of CD8 T cells against 50% of predicted high affinity epitopes with the ability to impact tumor growth. GNOS-PV02 is a personalized DNA vaccine, encoding up to 40 patient-specific neoantigens. In the GT-30 trial, it is used in combination with INO-9012 (plasmid-encoded IL-12) and pembrolizumab for the treatment of advanced HCC. **Methods:** The GT-30 trial (NCT04251117) is a single-arm phase I/II clinical trial to assess the safety, immunogenicity, and preliminary efficacy of GNOS-PV02 in combination with INO-9012 and pembrolizumab in patients with advanced HCC. Twenty-four patients are anticipated to be enrolled. Patients are recruited upon diagnosis or during first-line treatment with tyrosine kinase inhibitors (TKI). Tumors are biopsied for exome and transcriptome sequencing. The tumor specific vaccine is designed, optimized and manufactured during first-line therapy. Each vaccine encodes up to 40 neoantigens, which includes all detected neoantigens for the majority of HCC patients. After progression or intolerance with first-line therapy, patients can commence trial therapy with concurrent personalized vaccine and pembrolizumab. GNOS-PV02 + INO-9012 are administered Q3w for the first 4 doses and Q9w thereafter until disease progression. Pembrolizumab is delivered Q3w until disease progression. Immunogenicity of each of the vaccine epitopes will be determined by ex vivo ELISpot and flow cytometry. Clinical activity is assessed by RECIST1.1 at baseline and every 9 weeks. Serial biopsies will be obtained at 9 weeks and upon disease progression to evaluate changes in the exome, transcriptome and changes to the tumor microenvironment. Clinical trial information: NCT04251117. Research Sponsor: Geneos Therapeutics.

TPS2681 **Poster Session**

Phase I study investigating the safety of stereotactic body radiotherapy (SBRT) with anti-PD-1 and anti-IL-8 for the treatment of multiple metastases in advanced solid tumors.

Lilit Karapetyan, Adam C. Olson, William E. Gooding, Riyue Bao, Steven J. Chmura, Jason J. Luke; UPMC HCC, Pittsburgh, PA; Department of Radiation Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; University of Pittsburgh Cancer Institute, Pittsburgh, PA; UPMC Hillman Cancer Center, Pittsburgh, PA; Department of Radiation and Cellular Oncology The University of Chicago Medicine, Chicago, IL

Background: Anti-PD-(L)1 immunotherapy improves outcomes for patients across various cancers; however, many patients do not benefit. Previous studies combining multi-site SBRT with anti-PD1 have confirmed feasibility and revealed induction of interferon signaling by SBRT. Elevated levels of serum IL8 (sIL8) associate with lack of response to anti-PD1 and we have observed that elevated IL8 is strongly associated with lack of response to immunotherapy and SBRT combinations. Overcoming IL8 induced epithelial-mesenchymal transitioning and trafficking of myeloid derived suppressor cells in tumor microenvironment therefore represents a promising strategy to overcome resistance. BMS-986253 is a fully human neutralizing antibody that binds to sIL8. The combination of BMS-986253 and nivolumab was safe in patients with advanced solid tumors. The present study aims to evaluate safety and preliminary efficacy of combining BMS-986253 with nivolumab and SBRT in patients with advanced solid tumors, Melanoma (MEL) and Renal Cell Carcinoma (RCC). **Methods:** This is a phase 1 open label single arm study (CT.gov: NCT04572451) which will include safety and efficacy cohorts. Patients will receive SBRT in 1-4 tumor lesions, in 3 or 5 fractions, at the total of 30 or 45 or 50 Gy based on the irradiated organ site. This will be followed by intravenous (IV) nivolumab (480mg q4 weeks (W)) and IV BMS-986253 (2400mg q2W) within seven days of completing SBRT. In the initial safety portion of the clinical trial, we will include 30 patients with advanced/metastatic solid tumors in order to evaluate safety. The primary endpoint of dose limiting toxicity will be assessed by continual Bayesian monitoring. The toxicities will be attributed to combination of SBRT/Immunotherapy as opposed to individual components. The secondary objective of the study is efficacy with an endpoint of objective response rate (ORR) as assessed by RECIST v1.1 in Mel and RCC. We will include 20 patients with MEL and RCC and compare against a historical benchmark of 20% ORR as sufficient signal of activity for further study. ORR will be assessed for association with serum IL-8 levels and radiation-induced changes in peripheral blood T cell populations. Clinical trial information: NCT04572451. Research Sponsor: Bristol Myers Squibb.