3000 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Pilot study on outcome and antitumor efficacy of an autologous cancer cell vaccine applied in patients with advanced solid tumors. *First Author: Eglys Gonzalez Marcano, UniFontis, Sickte, Germany*

Background: In the last decade cancer immunotherapy has emerged as the most promising anti-tumor approach. The most commonly used immunotherapies are vaccines and checkpoint inhibitors. An autologous cell vaccine is made with the patient's own tumor cells processed in vitro, which may elicit a cytotoxic T-lymphocytic immune response against tumor cells antigens, resulting in tumor cell death. We performed a pilot study to evaluate the clinical relevance and general outcome of an autologous vaccine as a treatment in different types of cancer. **Methods:** A total of 31 patients (n=31) with advanced solid tumors and the lack of standard treatments were treated with an immunotherapy protocol consisting of 6 intradermal doses of the vaccine, given the first two doses at day 1 and 2, and the rest every two weeks. All patients signed an informed consent form. Response evaluation was assessed by PET/CT identified as metric (iRECIST) response and in some cases tumor markers where available. **Results:** Out of 31 patients treated, 2 patients suffered from pancreatic cancer, 2 from sarcoma, 1 from lung cancer, 13 from breast cancer, 2 from ovarian cancer, 1 from prostate cancer, 1 from cholangiocarcinoma, 4 from colorectal cancer, 1 from non-Hodgkin lymphoma, 1 from gastric cancer, 1 from laryngeal and hypopharyngeal cancer, 1 from fallopian tube cancer, 1 from peritoneal cancer. Side effects related to the therapy were rare including light redness in the area of injection and in one case inflammation of the tumor area. 26 patients were evaluated for metric response and 5 for tumor marker response assessment. For tumor marker follow up 9.6 % had a SD of $>$ 3 month and 6.5 % a PD. For metric follow up 12.9 % had a CR, 6.5 % a PR, 25.8 % a SD of $>$ 3 month and 38.7 % a PD. **Conclusions:** This study have confirmed an anti-tumor response in the majority of patients treated, with none to very low side effects and a good quality of life during the treatment. To obtain more detailed and significant data on the efficacy of this therapy, a further controlled clinical phase study should be performed. Research Sponsor: None.

3001 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Oral DNA vaccination targeting VEGFR2 combined with anti-PDL1 avelumab in patients with progressive glioblastoma: Safety run-in results—NCT03750071. *First Author: Wolfgang Wick, National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: VEGFR2 overexpression in glioblastoma serves as a target for VEGFR2 primed T cells using VXM01 DNA vaccine encoding for VEGFR2. VXM01 is delivered in a bacterial Ty21a carrier suitable for oral administration. A previous phase I/II study in 14 patients with progressive glioblastoma showed that detection of VEGFR2 specific T cells as well as altered intra-tumoral immunity is correlated with prolonged overall survival, one partial response was reported with VXM01 alone. Three patients received nivolumab in addition to VXM01, which resulted in one complete and one partial clinical response. Based on these findings, a trial combining VXM01 and avelumab was designed. **Methods:** A multicentre, open-label phase I/II study (*EudraCT* 2017-003076-31) in progressive glioblastoma includes 30 patients (24 non-resectable, 6 resectable) previously treated with temozolomide/radiotherapy. VXM01 is administered on day 1, 3, 5, 7 followed by boostings q4w. Avelumab 800mg is given intravenously q2w. Treatment continues up to week 48 followed by a 2 year observation period. The safety run-in phase of dose groups treated with VXM01 10^6 or 10^7 CFU plus avelumab was completed with 9 patients. Safety evaluation by the Data Safety Monitoring Board was performed after 3 and 9 patients treated for at least 5 weeks. Endpoints include safety and tolerability, objective response rate (ORR), clinical response using immune-response assessment in Neurooncology criteria (iRANO), and immunological assays like ELISpot, FACS, TCR-sequencing and tumor stainings. **Results:** No treatment-related toxicities were observed. Three partial responses with tumor reductions of 58, 81 and 95% to baseline were reported in 9 patients according to iRANO. Two of these patients are progression-free $>$ 6 months. Significant VEGFR2 specific T cell responses were measured in several patients, and pre-existing intra-tumoral T cells are positively associated with the effectiveness of the immunotherapy combination. **Conclusions:** VXM01 in combination with avelumab was safe and produces detectable peripheral VEGFR-2 specific immune responses. Three patients had an objective response. Clinical trial information: NCT03750071. Research Sponsor: Vaximm Gmbh.

3002 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

A phase I combination study of vigil and atezolizumab in recurrent/refractory advanced-stage ovarian cancer: Efficacy assessment in BRCA1/2-wt patients. *First Author: Rodney Paul Rocconi, University of South Alabama, Mobile, AL*

Background: Recent studies have shown poor clinical outcomes and limited survival advantage to checkpoint inhibitors (CIs) in advanced stage ovarian cancer (OvC). Vigil is a personalized precision vaccine constructed from autologous tumor tissue transfected with a DNA plasmid encoding GM-CSF and bi-shRNA-furin thereby creating TGFβ expression control and enhancing immune activation. Phase 1 and 2 trials in OvC demonstrate safety, functional immune activation and clinical response benefit. Combining Vigil with CIs may broaden responsiveness of immunotherapy in OvC. **Methods:** This is a randomized, 3-part safety Phase 1 study of Vigil in combination with Atezolizumab in recurrent OvC patients. Part 2 is a randomized, intra-patient crossover study of Vigil first (VF) or Atezolizumab first (AF) for two cycles followed by sequence of the combination of the two agents. Vigil (1×10^6 or 1×10^7 cells/ml) or Atezolizumab (1200mg) were administered 1x every 21 days each cycle until progression or untoward adverse event. We now report the preliminary results of part 2 of the study. **Results:** Twenty-one patients were randomized (1:1) to VF (n = 11) or AF (n = 10), groups were similar in demographics. Grade 3/4 toxic events occurred in 17% of AF patients compared to 3% in VF patients. Median OS of VF patients (n = 11) was not reached vs. AF (n = 10) 10.8 months suggested modest advantage to VF (HR 0.33, one-sided p 0.097). However, the subset analysis of BRCA1/2 wild type (wt) demonstrated more significant overall survival benefit in VF (n = 7) median OS not reached vs. AF (n = 7) 5.2 months (HR 0.12, one-sided p 0.015). **Conclusions:** The combination of Vigil immunotherapy and checkpoint inhibitor atezolizumab in recurrent OvC demonstrated safety and suggest a lower toxicity profile and a significant OS advantage in recurrent *BRCA1/2*-wt OvC patients treated with Vigil first followed by the combination of Vigil and Atezolizumab. Clinical trial information: NCT03073525. Research Sponsor: None.

Group	N (VF/AF)	1-year OS rate (VF/AF)	Median OS (months) (VF/AF)	HR	p-value
ITT	21 (11/10)	90.9% vs 49.2%	NR vs 10.8	0.33 (95% CI: 0.064,1.7)	0.097
BRCA1/2-wt	14 (7/7)	100% vs 22.9%	NR vs 5.2	0.12 (95% CI: 0.018, 0.81)	0.015

3003 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Safety and tolerability of MEDI0562 in combination with durvalumab or tremelimumab in patients with advanced solid tumors. *First Author: Jonathan Wade Goldman, David Geffen School of Medicine, UCLA, Santa Monica, CA*

Background: We report safety and tolerability of MEDI0562, a humanized $IgG1_\kappa$ OX40 monoclonal antibody (mAb), in combination with durvalumab (durva; anti-PD-L1 mAb) or tremelimumab (treme; anti-CTLA-4 mAb) in patients (pts) with previously treated advanced solid tumors. **Methods:** In this phase 1, open-label study (NCT02705482), adult pts received escalating doses of MEDI0562 (2.25, 7.5 or 22.5 mg/kg) every 2 wks (Q2W) in combination with durva (1500 mg/kg) or treme (75 or 225 mg/kg) Q4W, until confirmed disease progression or unacceptable toxicity. Tumor assessments were performed Q8W with immune-related Response Evaluation Criteria in Solid Tumors. **Results:** In total, 27 and 31 pts received MEDI0562 + durva or treme, across 5 dose combination cohorts (3 + 3 design), with a maximum tolerated dose of 7.5 mg MEDI0652 + 1500 mg durva and maximum administered dose of 10 mg MEDI0562 + 225 mg treme. Median duration of exposure was 12.0 (range 2.0–80.9) and 8.0 (range 2.0–42.0) wks, respectively. Two (22.5 mg MEDI10562 + durva) and 3 (2.25 mg MEDI0652 + 225 mg treme, 22.5 mg MEDI0562 + 75 and 225 mg treme) dose limiting toxicities were observed. For MEDI0562 + durva and MEDI0562 + treme groups respectively, treatment-emergent adverse events (TEAEs) were reported in 96.3% and 100% of pts; most common TEAEs were fatigue (55.6%) and pruritus (45.2%), Gr 3/4 TEAEs occurred in 74.1% and 67.7%; and MEDI0562-related AEs were reported in 20 (74.1%) and 24 (77.4%) pts. Six TEAEs in each group led to MEDI0562 discontinuation (22.2% and 19.4%, respectively), 2 led to death (renal failure [7.5 mg MEDI0562 + durva], multiple organ dysfunction syndrome [22.5 mg MEDI0562 + 225 mg treme]). Three response evaluable pts had PR (11.5% [7.5 and 22.5 mg MEDI0562 + durva, n = 26]). Median overall survival was 17.4 and 11.9 mos for MEDI0562 + durva and MEDI0562 + treme, with stable disease seen in 9 pts from each group, 34.6% vs 29.0%, respectively. Serum exposure of MEDI0562 increased dose proportionally. Post treatment serum antidrug antibody (ADA) was detected in 20 pts from MEDI0562 + durva and MEDI0562 + treme (74.1% and 71.4%, respectively). The impact of ADA on MEDI0562 pharmacokinetics was seen at all doses. Mean percentage of Ki67+CD4+ and Ki67+CD8+ memory T cells increased, while mean percentage of OX40+CD4+ memory T cells decreased following the first dose of MEDI0562 + durva or treme. **Conclusions:** The safety profile of MEDI0562 in combination with durva or treme was similar between groups. Clinical activity was observed with MEDI0562 + durva in pts with advanced solid tumors. Clinical trial information: NCT02705482. Research Sponsor: AstraZeneca.

3004 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

A phase I, first-in-human, open-label, dose-escalation study of MGD013, a bispecific DART molecule binding PD-1 and LAG-3, in patients with unresectable or metastatic neoplasms. *First Author: Jason J. Luke, University of Pittsburgh, Hillman Cancer Center, Pittsburgh, PA*

Background: MGD013 is an investigational, first-in-class, Fc-bearing bispecific tetravalent DART molecule designed to bind PD-1 and LAG-3 and sustain/restore the function of exhausted T cells. MGD013 demonstrates ligand blocking properties consistent with anti-PD-1 and anti-LAG-3 benchmark molecules, and improves T cell responses beyond that observed with benchmark or component antibodies alone or in combination. **Methods:** This study characterizes the safety, tolerability, dose-limiting toxicities, maximum tolerated dose (MTD), PK/PD, and antitumor activity of MGD013 in patients (pts) with advanced solid and hematologic malignancies. Sequential single-pt cohorts were treated with escalating flat doses of MGD013 (1-1200 mg IV every 2 weeks), followed by a 3+3 design. Tumor-specific expansion cohorts are being treated at the recommended Phase 2 dose of 600 mg. **Results:** At data-cutoff, 50 pts (46% checkpoint-experienced) were treated in Dose Escalation, and 157 pts (32% checkpoint-experienced) in Cohort Expansion. No MTD was defined. Treatment-related adverse events (TRAEs) occurred in 146/207 (70.5%) pts, most commonly fatigue (19%) and nausea (11%). The rate of Grade $\geq$ 3 TRAEs was 23.2%. Immune-related AEs were consistent with events observed with anti-PD-1 antibodies. Mean half-life was 11 days; peripheral blood flow cytometry analyses confirmed full and sustained on-target binding during treatment at doses $\geq$ 120 mg. Among 41 response-evaluable [RE] dose escalation pts, 3 confirmed partial responses [cPRs] (triple negative breast cancer [TNBC], mesothelioma, gastric cancer) per RECIST 1.1 were observed, while 21 pts had stable disease [SD]. Among select expansion cohorts, PRs have been observed in epithelial ovarian cancer (n=2; both cPRs, and 7 with SD among 15 RE pts) and TNBC (n=2; 1 cPR, 1 unconfirmed PR [uPR], and 5 with SD among 14 RE pts). In a cohort of pts with HER2+ tumors treated with MGD013 in combination with margetuximab (investigational anti-HER-2 antibody), 3 PRs have been observed (breast [n=2], colorectal [n=1]; 1 cPR, 2 uPRs) and 2 pts with SD among 6 RE pts. Objective responses have been observed in several pts after prior anti-PD-1 therapy. Investigations into potential correlative biomarkers including LAG-3 and PD-1 are ongoing. **Conclusions:** MGD013, a novel molecule designed to coordinately block PD-1 and LAG-3, has demonstrated an acceptable safety profile and encouraging early evidence of anti-tumor activity. Clinical trial information: NCT03219268. Research Sponsor: MacroGenics, Inc.

3005 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

PROCLAIM-CX-072: Analysis of patients with advanced solid tumors receiving long-term treatment with CX-072, a PD-L1 probody therapeutic, as a single agent or in combination with ipilimumab. *First Author: Fiona Thistlethwaite, The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom*

Background: Monotherapy with immune checkpoint inhibitors (ICIs) has demonstrated efficacy in many cancers. Combining ICIs PD-L1 + CTLA-4 enhanced efficacy but worsened toxicity vs monotherapy; therefore, CTLA-4 dose modifications are often needed, despite a dose-response effect having been shown for efficacy. CX-072 is an investigational PD-L1 PROBODY therapeutic that is preferentially activated in the tumor microenvironment (TME); localized activation may reduce immune-related AEs (irAEs). PROCLAIM-CX-072-001 identified 10 mg/kg Q2W (Mono10) as the recommended monotherapy dose. Here we provide data for Mono10 and for dose escalation of CX-072 in combination with IPI (Combo), with a focus on long-term ($\geq$6 mo) therapy. **Methods:** Mono10 was evaluated in multiple tumor types. Combo doses evaluated were CX-072 0.3–10 mg/kg and IPI 3–10 mg/kg Q3W. Patients (pts) with $\geq$6 mo treatment duration ($\geq$6M-TD) were compared to those with $<$ 6 mo of treatment ($<$ 6M-TD) as of November 30, 2019. **Results:** Disease control rates (DCR = CR+PR+SD) were 41% for Mono10 (n = 47 of 114; 10 PRs) and 37% for Combo (n = 10 of 27; 1CR + 4 PRs (1CR and 3PRs at 3 mg/kg IPI [IPI3]). Additional results are shown in the table. No treatment-related adverse events (TRAEs) led to death. The most common reason for discontinuation (dc) in all groups was disease progression. **Conclusions:** CX-072 monotherapy demonstrated durable responses consistent with activation of the PROBODY therapeutic in the TME. The safety profile supports the tolerability of CX-072 as monotherapy and when combined with IPI3. CX-072 + IPI3 demonstrated activity in heavily pretreated pts with various tumors. The safety profile of the combination of CX-072 with IPI3 compares favorably to historical data (grade $\geq$3 TRAEs 55% and leading to dc in 36%; Larkin J, et al. *N Engl J Med.* 2015;373:23-34). CX-072 + IPI3 is being explored in a phase 2 study in 2L melanoma Clinical trial information: NCT03993379. Research Sponsor: CytomX Therapeutics, Inc.

	Mono10 < 6M-TD (n = 86)	Mono10 ≥6M-TD (n = 28)	Combo < 6M-TD (n = 21)	Combo ≥6M-TD (n = 6)
Median follow-up (wk)	14.5	46.4	13.0	83.6
Median age (y)/no. prior treatments	60/2	60/2	56/3	55/4
PD-L1+ expression (%)	42	54	24	17
ECOG PS 0 (%)	33	57	43	33
Grade ≥3 TRAEs (%)	9	14	33	33
G3+ irAEs (%)	3	0	29	0
Treatment related serious AEs (%)	5	7	33	17
TRAEs leading to dc (%)	2	0	19	0

3006 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Durvalumab and tremelimumab in combination with FOLFOX in patients with RAS-mutated, microsatellite-stable, previously untreated metastatic colorectal cancer (MCRC): Results of the first intermediate analysis of the phase Ib/II MEDETREME trial. *First Author: François Ghiringhelli, Department of Medical Oncology, Center GF Leclerc, Dijon, France, Dijon, France*

Background: Single agent PD-1/L1 inhibition are not effective in metastatic colorectal cancer (MCRC) with microsatellite stable tumors. However, signal of efficacy was shown using combo therapy of anti-PD-L1 and anti CTLA-4 in multitreated patients. FOLFOX regimen could induced immunogenic cell death and elimination of myeloid derived suppressor cells (MDSCs) thus leading to a potential positive effect on antitumor immune response. **Methods:** This is a single arm exploratory investigator-initiated trial planned to include 57 pts to receive mFOLFOX6 (6cycles) in combination with durvalumab (150mg/q2W) and tremelimumab (75mg/q4W). After 6 cycles of chemotherapy, patients are treated with durvalumab untils progression. Primary endpoint is 6 months' progression-free survival rate. Secondary endpoints are response rate, tolerability and translational research evaluating tissue and blood immune parameter. Upon Simon's design an efficacy intermediate analysis was planned after the 16th patient has passed 6 months. **Results:** As of 1st of January 2020 the 55/57 pts were enrolled and treated with the MEDETREME regimen at 8 French sites. The intermediate efficacy analysis was conducted on the 1st of January after a median of 13.4 months of treatment. The following adverse events were noted: asthenia (81.25%), neuropathy (87.5%), diarrhea (56.25%) and neutropenia (62.5%). Notable grade 3/4 (CTC AE 4.03) include asthenia (18.75%) diarrhea (12.5%) neutropenia (50%) and elevated blood pressure (25%). Most of adverse events were related to chemotherapy. It has been noted one cytolysis grade 3, one thyroid dysfunction grade 3 and one hypophysitis grade 3 related to immunotherapy. Median PFS was not reached. Progression free survival at 6 months was observed in 10/16 pts (62,5%) given 5 CR, 5 PR and 4 SD. Updated translational data will be presented at the meeting. **Conclusions:** The interim safety analysis has supported safety and efficacy of the MEDITREME regimen in first- line MCRC. Finally, results will be presented after maturation of follow up. Clinical trial information: NCT03202758. Research Sponsor: Astra-Zeneca.

3007 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Association of LRP1B pathogenic genomic alterations with favorable outcomes with immune checkpoint inhibitors across multiple tumor types. *First Author: Landon Carter Brown, Duke Cancer Institute, Durham, NC*

Background: Low-density lipoprotein receptor-related protein 1b (LRP1b) is a putative tumor suppressor and one of the most frequently altered genes in cancer. Our prior single-center work suggested that *LRP1B* alterations may enrich for responses to immune checkpoint inhibitors (ICI) in solid tumors including prostate cancer; however, validation of these findings is needed. **Methods:** We conducted a multicenter, retrospective analysis of patients with *LRP1B* alterations (on tissue-based next-generation sequencing panels) treated with ICI at Duke, Johns Hopkins (JHU), and University of Michigan (UM). The primary objective was to assess the association between objective response rate (ORR) to ICI and pathogenic *LRP1B* alterations, defined as deletions or truncating alterations, when compared with *LRP1B* variants of undetermined significance (VUS), defined as missense mutations not predicted to be pathogenic in COSMIC. Missense changes with a COSCMIC FATHMM score of $>$ 0.8 were categorized separately as likely pathogenic. Summary statistics, ORR, progression free survival (PFS), and overall survival (OS) were calculated. **Results:** 101 patients (44 Duke, 35 JHU, 22 UM) with *LRP1B* alterations were treated with ICI. Median age was 61 (range 32-82). The most common tumor types by alteration (pathogenic or likely pathogenic/VUS%) were lung (33/47%), GI (17/13%), prostate (11/7%), sarcoma (2/9%), melanoma (11/0%), and others (26/24%). 93% of patients received single-agent PD-(L)1 inhibition. The ORR for patients with either pathogenic/likely pathogenic alterations, or VUS alterations was 57% and 18%, respectively. After excluding MSI-high or TMB-high ($>$ 10 mut/Mb) tumors, ORR was 14/25 (56%) and 6/36 (17%), respectively. Pathogenic or likely pathogenic *LRP1B* alterations were associated with longer PFS (HR 0.39, 95% CI 0.24-0.63) and OS (HR 0.58, 95% CI 0.36-0.95). **Conclusions:** This multicenter study shows impressive and durable objective response rates to ICI for patients harboring pathogenic *LRP1B* alterations when compared to those with *LRP1B* VUS, independent of TMB/MSI status. Further mechanistic insights and prospective validation studies are warranted. Research Sponsor: None.

	Pathogenic or likely pathogenic (n = 46)	VUS (n = 55)
CR n, (%)	1 (2%)	2 (4%)
PR n, (%)	25 (54%)	8 (15%)
SD n, (%)	11 (24%)	16 (29%)
PD n, (%)	8 (17%)	24 (44%)
NE n, (%)	1 (2%)	5 (9%)
Median PFS (95% CI)	14.1 mo (6.4-26.3)	3.4 mo (2.8-4.8)
Median OS (95% CI)	23.0 mo (11.0-27.3)	8.9 mo (8.0-18.0)
TMB-high n, (%)	23 (50%)	19 (35%)
MSI-high/MSI available n, (%)	5/45 (11%)	1/43 (2%)

3008 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Correlation of pathogenic POLE mutations with clinical benefit to immune checkpoint inhibitor therapy. *First Author: Benjamin Garmezy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mutations in DNA polymerase epsilon (*POLE*) may induce DNA replication errors, increasing neoantigen load and potentially enhancing clinical benefit to immune checkpoint inhibitors (ICI). We present a clinicopathologic analysis of patients (pts) with advanced cancers harboring *POLE* mutations and their response to ICI therapy at MD Anderson Cancer Center. **Methods:** We used targeted exome sequencing via CLIA-certified next generation sequencing assays to identify pts with *POLE*-aberrant tumors and their co-occurring mutations. The pathogenicity of each *POLE* mutation was annotated utilizing InterVar and ClinVar databases. Chi-square analysis was performed. **Results:** Tumors from 12,947 pts were analyzed and 448 (3.5%) pts had a mutation or copy number variation in *POLE* (3.5%), comparable to the TCGA PanCancer Atlas (4.0%). Clinical data were available for 293 pts; the most common cancers were colorectal (14.7%), non-small cell lung (13.7%), cholangiocarcinoma (13.3%) and melanoma (10.2%). There were 267 unique co-mutations, including *KRAS* (23.0%), *ARID1A* (21.5%), *BRCA2* (18.7%), *ATM* (18.4%), *CDKN2A* (17.5%), *BRAF* (15.3%), *EGFR* (15.3%), *ATRX* (12.6%), *CREBBP* (11.7%), *APC* (11.3%), *ATR* (11.0%), *BRCA1* (11.0%) and *CDK12* (10.4%). *POLE* variants were annotated in all pts: pathogenic/likely pathogenic (n = 34, 11.6%), benign/likely benign (61, 20.8%), and variant of unknown significance (198, 67.6%). 104 (35.8%) of 293 pts with *POLE* mutations received PD-1/L1 inhibitors as monotherapy or in combination. 93 (88.4%) of 104 pts were evaluable for response: Radiological CR 4.3% (n = 4), PR 26.9% (n = 25), SD 22.6% (n = 21), PD 46.2% (n = 43), for a clinical benefit rate (CR + PR + SD) of 53.8%. Pathogenic status of *POLE* mutation was associated with clinical benefit to PD-1/L1 inhibitors ($p = 0.04$). TMB ($p = 0.44$), PD-L1 ($p = 0.11$), and MSI ($p = 0.66$) status were not associated with pathogenic status. MSI-H status was not over-represented in pts with ICI clinical benefit ($p = 0.36$). **Conclusions:** Pathogenic *POLE* mutations were associated with clinical benefit to ICI therapy. Further studies are warranted to validate *POLE* mutations as a predictive biomarker. Multiple co-occurring DNA damage response mutations were found, which may contribute to ICI clinical benefit. Research Sponsor: None.

3010 Poster Discussion Session; Displayed in Poster Session (Board #74), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Combined PD-1 inhibition (Pembrolizumab) and CCR5 inhibition (Maraviroc) for the treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC): First results of the PICCASSO phase I trial. *First Author: Georg Martin Haag, Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany*

Background: Checkpoint inhibition using PD-1/PD-L1 inhibitors does not show clinically relevant activity in MSS/pMMR (Mismatch Repair Proficient) colorectal cancer. Previous work showed that inhibition of CCR5 (C-C chemokine receptor type 5) leads to a macrophage re-polarization towards M1 macrophages within the tumor microenvironment which directly affects immune cell infiltrates. The current phase I trial explores a combined modification of the innate immune system (by CCR 5 blockade) and the adaptive immune system (by PD-1 inhibition) in the treatment of MSS CRC. **Methods:** 20 patients with metastatic MSS/pMMR colorectal cancer with failure of fluoropyrimidines, oxaliplatin, irinotecan, VEGF antibodies and EGFR antibodies (in ras WT patients) received pembrolizumab 200 mg q21d and maraviroc 300 mg bid cont. for 8 cycles, followed by pembrolizumab monotherapy for a maximum of 24 additional cycles. Imaging was performed every nine weeks (RECIST and irRECIST criteria). Primary endpoint was the feasibility rate (rate of patients receiving the protocol treatment during the core treatment without special event: treatment-related Grade $\geq$ 3 immune-related abnormalities, treatment-related Grade $\geq$ 4 AEs or any toxicity-related premature withdrawal of treatment). Secondary endpoints included safety/toxicity, ORR, PFS and OS. **Results:** 20 patients were enrolled. The median number of applied cycles was 3.5 for pembrolizumab and 3.5 for maraviroc. Two patients completed the core treatment period with pembrolizumab and started maintenance treatment. The feasibility rate was 94.7% (90% CI 77.4 to 99.7%), with one patient experiencing a special event. Except this grade 4 event (hyperglycemia) no $\geq$ 3 treatment-related toxicities were observed. According to irRECIST criteria one patient showed a partial response and one a stable disease as best response, resulting in an irDCR of 10.5%. Median PFS according to irRECIST was 2 months (CI 95%, 2 to 3), median OS 9 months (CI 95%, 6 to 20). **Conclusions:** Therapy with pembrolizumab and maraviroc was feasible and showed a beneficial toxicity pattern. Clinical activity in MSS CRC patients was limited, however prolonged disease stabilizations were observed in single patients and overall survival was higher than expected in this heavily pretreated population. Clinical trial information: NCT03274804. Research Sponsor: Merck Sharp & Dohme.

3011 Poster Discussion Session; Displayed in Poster Session (Board #75), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Interim subgroup analysis for response by PD-L1 status of CLASSICAL-Lung, a phase Ib/II study of pepinemab (VX15/2503) in combination with avelumab in advanced NSCLC. *First Author: Michael Rahman Shafique, Department of Thoracic Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Antibody blockade of semaphorin 4D (SEMA4D, CD100) promotes tumoral dendritic cell and CD8+ T cell infiltration and reduces function and recruitment of immunosuppressive myeloid cells. Importantly, these mechanisms to overcome immune exclusion and suppression have been shown to complement immune checkpoint therapies in preclinical models. Pepinemab is an IgG4 humanized monoclonal antibody targeting semaphorin 4D. The CLASSICAL-Lung clinical trial tests the combination of pepinemab with avelumab to couple T cell activation via checkpoint inhibition with beneficial modifications of the immune microenvironment via pepinemab. **Methods:** This phase 1b/2, single arm, first-in-human study is designed to evaluate the safety, tolerability and efficacy of pepinemab with avelumab in 62 patients (pts) with advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC), including immunotherapy-naïve (ION) pts and pts whose tumors progressed following immunotherapy (IOF). **Results:** Among 21 evaluable ION pts, 5 experienced partial response (PR), 3 pts had clinical benefit $\geq$ 1 year, and the disease control rate (DCR) is 81%. Pts enrolled in this study were observed to have lower PD-L1 expression relative to prior single agent studies (likely due to approval of pembrolizumab for first line therapy). We, therefore, performed subgroup analysis for response by PD-L1 status. The objective tumor response (ORR) in the PD-L1 negative and low population ($<$ 80% TPS by Dako 73-10 assay) appears to be approximately 2-2.5 fold greater with combination therapy than with historical single agent immune checkpoint controls. Notably, 97% of pts who experienced PR or SD were reported to have tumors with negative or low PD-L1 expression. Among 29 evaluable IOF pts, the combination resulted in 59% DCR, including 2 PR and 7 patients with durable clinical benefit of $\geq$ 23 weeks. Biomarker analysis of pre- and on-treatment biopsies confirmed increased $CD8^+$ T cell density correlating with response. Surprisingly, analysis of myeloid-derived suppressor cells (MDSCs) revealed a relative paucity of these cells in pretreatment NSCLC biopsies as compared to other cancer indications such as HNSCC. **Conclusions:** This trial is nearing completion with only 5 of 62 subjects remaining on study. Preliminary data suggest the combination is well tolerated and shows signs of increased antitumor activity, particularly in PD-L1 negative or low tumors. Updated clinical response data and immunophenotypic analyses will be presented. Clinical trial information: NCT03268057. Research Sponsor: Vaccinex, (Rochester, NY), and from Merck KGaA as part of the alliance between Merck KGaA, (Darmstadt, Germany) and Pfizer, Inc, (New York, NY, USA).

3012 Poster Discussion Session; Displayed in Poster Session (Board #76), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Long-term follow-up of anti-CD19 CAR T-cell therapy for B-cell lymphoma and chronic lymphocytic leukemia. *First Author: Kathryn Cappell, National Institute of Health, Bethesda, MD*

Background: T cells expressing anti-CD19 chimeric antigen receptors (CARs) can cause complete remissions of relapsed lymphoma. We conducted the first clinical trial of anti-CD19 CAR T cells to show responses against lymphoma. This CAR was later developed as axicabtagene ciloleucel. Here, we aimed to assess the long-term durability of remissions and the long-term adverse effects after anti-CD19 CAR T-cell therapy. **Methods:** Between 2009 and 2015, we treated 43 patients with anti-CD19 CAR T cells preceded by conditioning chemotherapy of cyclophosphamide plus fludarabine (NCT00924326). Three patients were re-treated for a total of 46 CAR T-cell treatments. Twenty-eight patients had aggressive lymphoma (diffuse large B-cell lymphoma or primary mediastinal B cell lymphoma), eight patients had low-grade lymphoma (five with follicular lymphoma and 1 each with splenic marginal zone lymphoma, mantle cell lymphoma, and unspecified low-grade non-Hodgkin lymphoma), and seven patients had chronic lymphocytic leukemia (CLL). Patients were treated in three cohorts that differed in the CAR T-cell production process and conditioning chemotherapy dose. **Results:** Of the 43 treated patients, 63% had chemotherapy-refractory lymphoma. Patients had received a median of 4 previous lines of therapy. The median CAR^+ T cell dose per kilogram was 2X10^6. The overall remission rate was 76% with 54% complete remissions (CR) and 22% partial remissions (PR). Patients with CR had higher median peak blood CAR levels (86 CAR^+ cells/μL) than those who did not have CR (16 CAR^+ cells/μL, $P = 0.0041$). Long-term adverse effects were rare except for B-cell depletion and hypogammaglobulinemia, which both improved over time. **Conclusions:** This is the longest follow-up study of patients who received anti-CD19 CAR T cells. Anti-CD19 CAR T cells cause highly durable remissions of relapsed B-cell lymphoma and CLL, and long-term adverse effects of anti-CD19 CAR T cells were rare and usually mild. Clinical trial information: NCT00924326. Research Sponsor: U.S. National Institutes of Health.

	All Patients	Aggressive lymphoma (n = 28)	Low-grade lymphoma (n = 10)	CLL (n = 8)
Median CAR^+ T cell dose per kg	2 X 10^6	2 X 10^6	3 X 10^6	3.5 X 10^6
Chemotherapy refractory (%)	63%	89%	20%	25%
Median prior lines of therapy (Range)	4 (1 to 12)	4 (2 to 12)	4 (1 to 7)	4 (1 to 7)
Overall Response (%)	76%	68%	90%	88%
Complete Response (%)	54%	50%	60%	63%
Median duration of complete response in months (Range)	58 (6 to 113)	50 (6 to 83)	60 (19 to 113)	70 (18 to 99)
Median event-free survival 45 evaluable treatments	60 (1-114)	15 (1 to 85)	66 (1-114)	41 (5-101)

3013 Poster Discussion Session; Displayed in Poster Session (Board #77), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Safety and efficacy results of GC027: The first-in-human, universal CAR-T cell therapy for adult relapsed/refractory T-cell acute lymphoblastic leukemia (r/r T-ALL). *First Author: Xinxin Wang, Gracell Biotechnologies Co., Ltd., Shanghai, China*

Background: Patients with r/r T-ALL usually have high relapse and mortality rates. Due to shared common surface antigen and potential contamination by malignant cells, development of autologous CAR-T therapies for r/r T-ALL has been lagged, regardless of the costly and lengthy process of autologous CAR-T production. Through targeting CD7, a common T cell antigen highly expressed in >95% T-ALL samples, universal CAR-T product GC027 has been developed using lentivirus and CRISPR/Cas9 system with demonstrated anti-leukemia ability in a murine xenograft model. **Methods:** Preliminary safety, anti-leukemic activity and expansion kinetics of GC027 are being evaluated in a single-arm, open-label, multi-center, prospective study for treating adult patients with r/r T-ALL. To date, a total of 5 patients (age 19-38 yrs, median 24 yrs) were enrolled with marrow tumor load 4-80.2% (median prior lines 5). All 5 pts have received a 6-day enhanced preconditioning chemotherapy followed by a single infusion of GC027. No patient was bridged to HSCT. Adverse events, disease response, and expansion kinetics were evaluated in this study. **Results:** As of Feb. 6, 2020, 5 pts had received a single dose of GC027, including 1 at $0.6x10^7$/kg, 3 at $1x10^7$/kg, 1 at $1.5x10^7$/kg. 3 pts achieved MRD negative complete responses (MRD- CR) at D28 evaluation and remained MRD- at follow-up re-evaluations (161, D118, 61, respectively) without bridging to HSCT. 1 pt just achieved D28 MRD- CR at time of submission. 1 pt achieved MRD+ CR at D14, but his disease progressed at D29 and deceased due to relapse. In all 4 pts with MRD- CR, peak expansions of GC027 in peripheral blood were observed between week 1-2, analyzed by flow cytometry and Q-PCR. Grade 3 cytokine release syndrome (CRS) occurred in 4 pts and Grade 4 CRS occurred in 1 pt (ASBMT Consensus Grading). CRS symptoms were manageable and resolved after treatment and supportive care. None developed neurotoxicity or GvHD. One had prolonged cytopenia due to fungal infection and required antifungal therapy. **Conclusions:** With a single infusion of GC027, 80% of the patients had robust CAR-T cell expansion and achieved persistent MRD- CR without using any biologics as part of the preconditioning therapy or bridging to HSCT. The first-in-human, universal CAR-T therapy for r/r T-ALL, GC027 has demonstrated superior clinical efficacy and induced deep response in patients with acceptable safety profile. The trial enrollment is ongoing and updated data will be presented at the meeting. Clinical trial information: ChiCTR1900025311. Research Sponsor: Gracell Biotechnologies Co., Ltd.

3014 Poster Discussion Session; Displayed in Poster Session (Board #78), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Feasibility and preliminary safety and efficacy of first-in-human intraperitoneal delivery of MCY-M11, anti-human-mesothelin CAR mRNA transfected into peripheral blood mononuclear cells, for ovarian cancer and malignant peritoneal mesothelioma. *First Author: Christina M. Annunziata, Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: MCY-M11 is a mesothelin-targeting chimeric antigen receptor (CAR) therapy made by a non-viral, mRNA-based platform, for rapid (< 1 day) CAR manufacturing. We are conducting a phase I dose escalation trial in ovarian cancer and malignant peritoneal mesothelioma (MPM) (NCT03608618). **Methods:** MCY-M11 are fresh, non-expanded, autologous peripheral blood mononuclear cells (PBMCs) transfected by flow electroporation with mRNA encoding a human anti-mesothelin CAR. Following a 3+3 design, patients are treated in dose level (DL) escalating cohorts (DL1 1.0×10^7, DL2 5.0×10^7, DL3 1.0×10^8, DL4 5.0×10^8 cells/dose), in one cycle of weekly x 3 doses, intraperitoneal (ip) without preconditioning chemotherapy. **Results:** By January 2020, CP-M11-101 study successfully completed DL1 and DL2 without safety concerns. Based on 11 patients treated in DL1, DL2 and DL3, ip infusion of MCY-M11 is safe and well tolerated. No infusion-related adverse events and no dose limiting toxicities (DLTs) have occurred. No neurotoxicity has been observed. Most reported treatment-related adverse events have been Grades 1-2 per NCI CTCAE. One patient in DL3 presented with G2 pericarditis, fever and transient neutropenia clinically assessed as related SAEs, that resolved without further complications. These events were assessed as on-target off-tumor effects and possibly G1 cytokine release syndrome (CRS). Two unrelated SAEs (G2 confusion in a patient in DL2; G3 enterocutaneous fistula in a patient in DL3) were reported. These 2 patients have been replaced as they did not complete the evaluation period (3 weekly infusions and the DLT 43 day follow up). There have been no treatment-related discontinuations or deaths. Three patients in DL2 showed stable disease (SD) by RECIST 1.1 at the end of the DLT period. Of them, 1 completed the study and did not participate in additional follow up, 1 remained in SD 6 months, and 1 remained in SD 2 months. In DL3, 1 patient remains in SD at 2 months, and evaluation is pending for the other 2 patients. Enrollment is ongoing. **Conclusions:** Feasibility of 1-day manufacturing of MCY-M11 for ip delivery is demonstrated. Treatment has been safe. Initial SD observed in DL2 and DL3 with one-cycle infusions is encouraging and supports exploration of additional strategies such as the addition of preconditioning chemotherapy and multiple cycles to increase efficacy. Clinical trial information: NCT03608618. Research Sponsor: MaxCyte Inc.

3015 Poster Discussion Session; Displayed in Poster Session (Board #79), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Early safety from a phase I, multicenter, open-label clinical trial of talimogene laherparepvec (T-VEC) injected (inj) into liver tumors in combination with pembrolizumab (pem). *First Author: J. Randolph Hecht, David Geffen School of Medicine, University of California, Los Angeles, CA*

Background: T-VEC is a genetically modified, oncolytic HSV-1 designed to selectively replicate within tumors and produce GM-CSF to enhance systemic antitumor immunity. The safety and efficacy of T-VEC in treatment of advanced melanoma has been demonstrated as monotherapy and in combination with checkpoint inhibitors (Andtbacka *JCO* 2015, Chesney *JCO* 2017, Ribas *Cell* 2017). T-VEC has also demonstrated tolerable safety for intrahepatic inj (Hecht *JCO* 2018). This phase 1b, multicenter, open-label, dose escalation study (NCT02509507) evaluates the safety of intrahepatic inj of T-VEC in combination with intravenous (IV) pem in patients (pts) with hepatocellular carcinoma (HCC) or liver metastases (mets). **Methods:** The primary objective is to assess the maximum tolerated concentration (MTC) of T-VEC inj into liver tumors based on the incidence of dose-limiting toxicities (DLTs). DLT rate was evaluated with the mTPI up-and-down design. Eligible pts were ≥ 18 years, had progressive HCC or breast cancer, colorectal cancer, gastroesophageal cancer, melanoma, non-small cell lung cancer, or renal cell cancer liver mets, with measurable liver tumors suitable for inj. This dose escalation study comprised 2 groups: A (non-HCC) and B (HCC). T-VEC was given initially at 10^6 plaque-forming units (PFU)/mL followed by up to 4 mL of 10^7 PFU/mL (cohort 5) or 10^8 PFU/mL (cohort 6) every 21 (±3) days (Q21D). Inj volume was based on lesion size. Pem (200 mg) was given IV Q21D. **Results:** Here we report on three cohorts: A5 (10^7 PFU/mL T-VEC + pem), A6 (10^8 PFU/mL T-VEC + pem), and B5 (10^7 PFU/mL T-VEC + pem). Twenty-nine pts were treated: 7 in A5, 17 in A6, 5 in B5. Median age was 61 years (range: 30, 76). Median number of inj was 4 and median treatment duration was 88 days. One DLT of cholestatic hepatitis was observed out of 6 DLT evaluable pts in cohort A5. No DLTs were observed in cohort A6 and B5. MTC was 10^8 PFU/mL in non-HCC patients; exploration of MTC in the HCC population is ongoing. Treatment-emergent adverse events (TEAEs) were consistent across cohorts. The most common treatment-emergent treatment-related adverse events (TETRAE) were pyrexia (79.3%), chills (37.9%), and nausea (37.9%). Eight pts (27.6%) had grade 3/4 TEAEs: 2pts (6.9%) related to the combination therapy and the rest not related to treatment. No fatal AEs were observed. **Conclusions:** T-VEC intrahepatic inj in combination with IV pem at standard doses has thus far been demonstrated as feasible and tolerable to continue further investigation. Clinical trial information: NCT02509507. Research Sponsor: Amgen Inc.

3016 Poster Discussion Session; Displayed in Poster Session (Board #80), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Pharmacodynamic, safety, and efficacy results of a phase I/II trial of intratumoral INT230-6 alone (IT-01) or in combination with pembrolizumab (PEM) (Keynote A10) in patients with advanced solid tumors. *First Author: Jacob Stephen Thomas, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: INT230-6 is comprised of cisplatin (CIS), vinblastine (VIN) and an amphiphilic penetration enhancer which facilitates dispersion throughout tumors and diffusion into cancer cells when given IT. Preclinical experiments show strong synergy with a PD1 antibody. **Methods:** Solid tumors pts that progressed on standard treatment were enrolled. INT230-6 dose was set by tumor volume, injected Q2weeks x 5. Escalation occurred by increasing number of tumors injected, loading per tumor, and total dose. In another arm, PEM (200mg IV Q3weeks) was combined with INT230-6. Patients were monitored for safety weekly while on INT230-6. Blood and tumors were assessed for PK and PD. **Results:** 46 pts (17 unique cancer types) were enrolled in the monotherapy arm and 4 pts in the PEM combo arm with a median of 3 prior treatments. Doses from 0.3 ml up to-160 ml of INT230-6 (80 mg CIS and 16mg of VIN) were injected. PK results indicate 95% of the drugs are retained in the tumor when compared to historical IV dosing. No dose limiting toxicity was reported. Two pts experienced drug-related SAE's of tumor pain. The most frequent treatment-related AEs were: pain at injected site (48%), fatigue (40%) and nausea (33%). Most AE's were grade 1 and 2, 17% were grade 3, and none ≥ grade 4. Several injected and non-injected tumors had > 30% decreases in diameter. Assessments revealed substantial reductions in tumor volume (> 50%). Stable pts had a median increase of 50% in circulating CD4 and CD8 T-cells, while PD subjects showed decreases in circulating T-cells ($p < 0.05$). Dose-response suggests that monotherapy subjects receiving > 50% of tumors injected at dose/tumor volume ratio of > 1:4 (target dosing), predicts for prolonged SD with 88%(7/8) having SD ≥ 4mo, correlating with reduced tumor viability on IHC, and increase in tumor-infiltrating lymphocytes (TIL's). **Conclusions:** Proof of concept was demonstrated that INT230-6 delivers high drug doses into the tumor without systemic exposure and typical cytotoxic AEs. Systemic and local immune activation was observed. INT230-6 was safe and well tolerated in > 175 deep tumor injections with tumor burden reduction in injected and non-injected tumors (an abscopal effect). Patients who received target dosing often had prolonged disease control post treatment. Updated safety, response and biomarker data from the monotherapy and PEM combo arm will be presented. Clinical trial information: 03058289. Research Sponsor: Intensity Therapeutics.

3017 Poster Discussion Session; Displayed in Poster Session (Board #81), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Phase I/II study to evaluate systemic durvalumab + intraperitoneal (IP) ONCOS-102 in patients with peritoneal disease who have epithelial ovarian (OC) or metastatic colorectal cancer (CRC): Interim phase I clinical and translational results. *First Author: Dmitriy Zamarin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Metastasis to the peritoneal cavity is associated with end-stage disease in many cancers, including OC and CRC, both of which exhibit poor responses to checkpoint inhibitors. Locoregional treatment with oncolytic viruses may be used to improve the efficacy of checkpoint inhibitors at both treated and distant tumor sites. This study evaluates the combination of IP-administered ONCOS-102, an oncolytic adenovirus encoding for granulocyte macrophage colony stimulating factor (GMCSF), with systemic durvalumab, an anti PD-L1 antibody, in patients with peritoneal disease who have histologically confirmed OC or metastatic CRC and have failed prior standard therapies. **Methods:** This ongoing Phase 1/2, open-label study (NCT02963831) evaluates safety and antitumor/biologic activity of durvalumab (1500 mg IV, every 4 weeks x 12) + ONCOS-102 (IP, weekly x 6); cyclophosphamide is given pre first ONCOS-102 dose. Phase 1 uses a 3+3 design to evaluate the ONCOS-102 dose (1 or 3 x 10^{11} VP) to be given with durvalumab. Phase 2 evaluates the activity of the combination using Simon's 2-stage MINIMAX design. Safety, response rate by RECIST 1.1, and immunological effects in tumors were evaluated for Phase 1; the current abstract reports on the phase 1 results. **Results:** Enrollment opened 7 Sep 2017; data cutoff, 1 Nov 2019. There were 17 patients treated in Phase 1: 8 CRC, 9 ovarian; 94% female; median age, 56 [37-77] years; ECOG PS0, 47%; ECOG PS1, 53%. There were no DLTs. Grade 3 treatment-related AEs included hypokalemia (n = 2); anemia, myocarditis, increased GGT, and influenza like illness (n = 1 each). There were 4 deaths due to PD. One patient had durable confirmed partial response and remains on treatment $>$ 1 year; 4 patients had stable disease as best overall response. Two patients remained on treatment at data cutoff. Analysis of pre- and on-treatment tumor biopsies revealed changes in the tumor-infiltrating immune cells and PD-L1 expression, including an increase in tumor-infiltrating CD8 T cells in 5 of 11 evaluable patients. **Conclusions:** Combination of durvalumab and IP ONCOS-102 was safe, and no DLTs were observed. Preliminary analyses demonstrate evidence of biologic and clinical activity. Phase 2 enrollment is ongoing. Clinical trial information: NCT02963831. Research Sponsor: Ludwig Institute for Cancer Research, Cancer Research Institute, Pharmaceutical/Biotech Company.

3018 Poster Discussion Session; Displayed in Poster Session (Board #82), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Impact of radiotherapy on risk of adverse events in patients receiving immunotherapy: A U.S. Food and Drug Administration pooled analysis. *First Author: Mitchell Steven Anscher, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Immune checkpoint inhibitors (ICIs) are widely used in the treatment of multiple advanced malignancies. Radiotherapy (RT) has been used in combination with ICIs to activate tumor-specific T cell responses, and RT also promotes non-specific acute and chronic inflammatory responses both locally and systemically. More than 50% of patients receive RT at some point during their course of cancer therapy, and relatively little information is available pertaining to the impact of RT, if any, on the risk of adverse events (AEs) in patients receiving ICIs. **Methods:** Pooled data from prospective trials of ICIs submitted to the FDA in initial or supplemental BLAs or NDAs through 12/2019 were included (N=66). Trials from applications that were withdrawn or not approved were not included. Patients were subdivided by whether or not radiotherapy was administered at any time during the course of their cancer treatment. AEs common to both ICI treatment and RT were identified to focus on the following reactions: neutropenia, thrombocytopenia, colitis, hepatitis, pneumonitis, and myocarditis. Descriptive statistics were used to examine AEs associated with the use of radiation and ICIs. **Results:** A total of 25,836 patients were identified, of which 9087 (35%) received RT and 16,749 (65%) did not. Radiation was associated with similar rates of AEs overall with numerically higher hematologic toxicities and pneumonitis and numerically lower colitis, hepatitis and myocarditis (Table). Patients receiving RT were more likely to experience Grade 3-5 hematologic toxicities compared to those not receiving RT. **Conclusions:** To our knowledge, this is the largest report of AE risk associated with the use of radiation and ICIs. Our results show that the incidence of hematologic toxicity and pneumonitis in patients receiving RT may be slightly higher. Analysis to determine comparability of baseline demographic characteristics, comprehensive AE profile, and timing of RT is underway. Research Sponsor: None.

Description of toxicity in patients treated with ICI with or without RT.

	Incidence -risk All Grades (%)		Grades 3-4 (%)		Grade 5 (%)	
Toxicity	**RT (n=9,087)**	**No RT (n=16,749)**	**RT**	**No RT**	**RT**	**No RT**
Neutropenia	8.4	5.8	6.0	3.9	0	0
Thrombocytopenia	6.9	3.8	3.6	1.4	0	0.01
Pneumonitis	5.0	3.1	1.0	0.9	0.13	0.11
Colitis	2.0	3.0	1.2	1.7	0	0.01
Hepatitis	0.6	0.9	0.4	0.7	0	0.02
Myocarditis	0.03	0.06	0.01	0.05	0.02	0.02

3020 Poster Discussion Session; Displayed in Poster Session (Board #84), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

The preliminary efficacy and safety data of KN046 in patients failed on prior immune checkpoint inhibitors therapy. *First Author: Hongyun Zhao, Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China*

Background: KN046 is a bispecific antibody that blocks PD-L1 and CTLA-4 by interaction with PD1 and CD80/CD86. KN046-CHN-001 (NCT03529526) is a, dose escalation and expansion phase Ia/Ib clinical trial in China. Here we reported safety, tolerability and preliminary efficacy in patients failed on prior immune checkpoint inhibiters (ICIs) treatment. **Methods:** Patients progressed on ICIs (including but not limited to antibodies targeting PD-1, PD-L1, OX40, et al) with pathologically confirmed solid tumor, ECOG 0-1, measurable lesion per RECIST v1.1, no immune-related adverse events (IRAEs) led to ICIs discontinuation, were enrolled and received intravenous KN046 treatment across four dose levels including 3.0 mg/kg (n = 3) and 5.0 mg/kg (n = 20) Q2W; and 5.0 mg/kg (n = 4), 300.0 mg flat dose (n = 2) Q3W. Safety and tolerability were assessed per NCI-CTCAE v5.0. Treatment-emergent AEs (TEAEs) and IRAEs were decided by investigators. Efficacy was evaluated by investigators per RECIST 1.1 every 6 weeks. **Results:** Twenty-nine who progressed on prior ICIs therapy were enrolled (25anti-PD-1 antibody; 3 anti-OX40 antibody; and 1 anti-CD137 antibody) and were included in the current analysis. Among 29 patients, 19 were nasopharyngeal cancer (NPC) and 9 were non-small cell lung cancer (NSCLC). The median duration of the exposure of KN046 was 12 weeks (range 2 to 40). Eleven patients remained on the treatment and 18 discontinued due to disease progression (n = 13), AE (n = 1), death (n = 1) and others (n = 3). Twenty-six (89.7%) patients experienced TRAEs of all grades and 2 (6.9%) experienced grade$\geq$3 TRAEs (1 grade 3 anemia and 1 grade 3 infusion-related reaction). The most common ($\geq$10%) TRAEs were pruritus (8, 27.6%), rash (8, 27.6%), asthenia (6, 20.7%), fatigue (6, 20.7%), pyrexia (5, 17.2%), infusion related reaction (4, 13.8%), alanine aminotransferase elevation (3, 10.3%) and white blood cell count elevation (3, 10.3%). Eleven (37.9%) patients experienced irAEs (with no grade$\geq$3). Objective responses were occurred in 3 (12.0%, 25 evaluable) patients, disease control rate was 52.0% (10 stable disease). Median progression free survival was 2.69 (95%CI 1.31,5.52) months. Median overall survival was not reached. PFS rates for 3 and 6 Months were 41.0% (95%CI 18.5, 62.5) and 21.9% (95%CI 4.6, 47.3). OS rates for 6 and 9 months were88% (95%CI 57.2, 97.1) and 58.7% (95%CI 8.3, 89.2), respectively. **Conclusions:** Overall, KN046 showed a favorable safety profile and promising clinical benefit in advanced solid tumor patients who failed on prior ICIs therapy. Clinical trial information: NCT03529526. Research Sponsor: Alphamab (Australia) Co Pty Ltd.

3021 Poster Session (Board #85), Fri, 8:00 AM-11:00 AM

Envafolimab (KN035) in advanced tumors with mismatch-repair deficiency. *First Author: Lin Shen, Peking University Cancer Hospital & Institute, Beijing, China*

Background: KN035 is a novel fusion protein of humanized anti-PD-L1 single domain antibody and human IgG1 Fc formulated for subcutaneous injection. This open-label phase II study evaluated the safety and antitumor activity of KN035 in patients with advanced microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) cancer. **Methods:** The study included patients aged $\geq$18 years with previously treated MSI-H/dMMR colorectal cancer (CRC) or other advanced solid tumors. MSI-H/dMMR status was assessed centrally for CRC and gastric cancer (GC) and locally for other tumors. KN035 was administered at 150 mg once weekly until progression, unacceptable toxicity, or withdrawal. Tumor assessments were every 8 weeks. The primary endpoint was the objective response rate per RECIST v1.1 by independent radiology review. The primary efficacy population (PEP) included patients with CRC who failed fluoropyrimidine (F), oxaliplatin (O), and irinotecan (I) plus those with advanced GC who had failed at least one prior systemic treatment. This was a planned interim analysis performed after the first 50 patients in the PEP had at least two on-study tumor assessments (PEP_i). **Results:** As of December 17, 2019, 103 patients with MSI-H/dMMR advanced cancers were enrolled at 25 centers in China. The PEP_i included 39 patients with CRC and 11 with GC, with a median follow-up of 7.5 months. The overall population included 65 patients with CRC (24 had prior therapy with F and O or I), 18 with GC, and 20 with other tumors, with a median follow-up of 6.7 months. The confirmed objective response rate was 30% (95% CI: 17.9%, 44.6%) in the PEP_i, 54.2% (95% CI: 32.8%, 74.4%) in the CRC patients who had prior therapy with F and O or I, and 34.0% (95% CI: 24.9%, 44.0%) in the overall population. Of patients who had an objective response at the interim analysis, 80% of those in the PEPi, 84.6% of CRC patients who had prior therapy with F and O or I, and 85.7% of those in the overall population were still responding at the time of data cutoff. Median progression-free survival was 6.6 months in both the PEP_i and the overall population. Median overall survival was not reached in either population. Fourteen (13.6%) patients had grade 3–4 treatment-related adverse events. No grade 5 treatment-related adverse events, pneumonitis, or colitis were reported. Local injection-site reactions, all grade 1 or 2, were reported in nine patients. **Conclusions:** Envafolimab demonstrated durable antitumor activity with a manageable safety profile in patients with previously treated advanced MSI-H/dMMR cancer. Clinical trial information: NCT03667170. Research Sponsor: 3D Medicines (Sichuan) Co. Ltd.

3022 Poster Session (Board #86), Fri, 8:00 AM-11:00 AM

Tumor microenvironment associated with increased pretreatment density of activated PD-1+ LAG-3+/− TIM-3− CD8+ T cells facilitates clinical response to axicabtagene ciloleucel (axi-cel) in patients (pts) with large B-cell lymphoma. *First Author: Jerome Galon, HalioDx, Marseille, France*

Background: Axi-cel is a US and EU-approved autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy for pts with relapsed/refractory large B cell lymphoma after ≥ 2 prior therapies. In ZUMA-1 (NCT02348216), the objective response rate was 83% (58% complete response rate; Locke et al. *Lancet Oncol*. 2019). T cell-related biology (Immunosign 21; Immunoscore) measured pretreatment in the tumor microenvironment (TME) was associated with response to axi-cel (Rossi et al. AACR 2018. #LB-016; Rossi et al. AACR 2019. #CT153). This expanded analysis characterized the pretreatment TME immune contexture and examined associations between immune cell subsets and response. **Methods:** In ZUMA-1, pts received axi-cel at a target dose of 2.0×10^6 CAR T cells/kg. Archival pretreatment tumor biopsy samples were analyzed by multiplex immunohistochemistry (Brightplex). Two panels were developed and applied to assess T cell (CD3, CD8, FoxP3, PD-1, LAG-3, TIM-3) and myeloid cell (CD11b, CD14, CD15, LOX1, S100A9, CD68) subsets (n = 14 total). The association between T cell and myeloid cell subset density, prespecified immune scores (Immunosign 21; Immunoscore), and objective response was evaluated. T test values were based on Brightplex analysis. **Results:** Pretreatment tumor biopsy samples from 18 pts were analyzed (14 objective responders and 4 nonresponders). The pretreatment TME comprised all major myeloid and T cell subsets, with diverse distribution across samples analyzed. The median TME density of monocytes (CD11b+ CD15− CD14+; 1215 cells/mm^2) and macrophages (CD68+; 530 cells/mm^2) was greater than that of the total CD8+ T cell subset (312 cells/mm^2). The pretreatment Immunosign 21 and Immunoscore scores associated positively with the density of all major T cell subsets and some myeloid subsets. The density of activated CD8+ T cells (PD-1+ LAG-3+/− TIM-3−) was most significantly associated with clinical response versus other T cell subsets. The density of nonactivated CD8+ T cells (PD-1− LAG-3− TIM-3−) and exhausted CD8+ T cells (PD-1+ LAG-3+ TIM-3+) were not significantly associated with response. Additional characterization of the immune contexture and correlative analysis of cell subsets will be presented. **Conclusions:** These results suggest that a TME associated with increased density of activated PD-1+ LAG-3+/− TIM-3− CD8+ T cells, measurable pretreatment, facilitates clinical response in pts post–axi-cel. Research Sponsor: Kite, a Gilead Company.

3023 Poster Session (Board #87), Fri, 8:00 AM-11:00 AM

Product characteristics and pharmacological profile of KTE-X19 in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) in the phase II registrational ZUMA-2 trial. *First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ZUMA-2 is a Phase 2 study evaluating KTE-X19, an autologous anti-CD19 CAR T cell therapy, in pts with R/R MCL (1 – 5 prior therapies, including a BTK inhibitor). In the primary efficacy analysis of ZUMA-2 (N = 60), the objective response rate was 93% (67% complete responses) and was generally comparable among high risk pts (Wang et al. ASH 2019 #754). CAR T cell levels in blood were associated with objective response (including minimal residual disease [MRD] negativity) and toxicity. Here, we describe a comparative analysis of KTE-X19 pharmacology profile in higher vs lower risk pts in ZUMA-2. **Methods:** Product attributes, CAR T cell and serum cytokine levels in blood, and their associations with clinical outcomes, were analyzed using previously described methods (Locke et al. *Mol Ther* 2017). MRD (10^{-5} sensitivity) was assessed by next-generation sequencing. Pharmacology data are reported for all 68 pts treated with KTE-X19 (2×10^6 cells/kg). **Results:** Manufactured KTE-X19 products showed a slight bias to CD8 and effector memory/effector phenotype. Median CD4/CD8 ratio was 0.7 (range, 0.04 – 3.7); T cell phenotypes included naive (median, 24.5%; range, 0.3 – 80.7), central memory (median, 12.8%; range, 2.3 – 51.6), effector memory (median, 24.5% (range, 0.8 – 70.3) and effector (median, 28.7%; range, 2.8 – 65.2). MRD negative (n = 24/29) vs positive pts (n = 5/29) at 1 mo post KTE-X19 had increased median cytokine levels, including IL-15, IL-2, IFN-γ, IL-10, and IL-6, peaking in serum within 7 days post treatment. Pts who were MRD negative by 1 mo post treatment also had increased median peak levels of Granzyme B and soluble PD-L1. Six pts developed Grade 4 neurologic events (NE), including 1 cerebral edema case; 3 had concurrent Grade 4 cytokine release syndrome. These pts had higher peak cytokine levels vs pts without Grade 4 NE, with lack of reversion to baseline by Day 28 of serum IL-6 and sVCAM-1. Peak CAR T cell in blood and serum cytokine levels were generally comparable in higher vs lower risk pts defined as *TP53* mutated (n = 6/36) vs unmutated (n = 30/36), or high vs low Ki-67 proliferation index (PI; ≥ 30% [n = 40/49] and < 30% [n = 9/49]), consistent with the comparable clinical efficacy of KTE-X19 in these subgroups. **Conclusions:** PD profile of KTE-X19 associated with efficacy (MRD status at 1 mo) and treatment-related NE. In contrast to approved therapies, KTE-X19 showed comparable pharmacology and clinical outcomes in pts with higher vs lower risk MCL defined by *TP53* mutation or Ki-67 PI. Clinical trial information: NCT02601313. Research Sponsor: Kite, a Gilead Company.

3024 Poster Session (Board #88), Fri, 8:00 AM-11:00 AM

Assessing readmission after axicabtagene ciloleucel immunotherapy. *First Author: Paula Perkins, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Axicabtagene ciloleucel (axi-cel) is an FDA approved CD19 targeted CAR-T for patients (pts) with diffuse-large-B cell lymphoma (DLBCL) after 2 lines of treatment. Pts are monitored inpatient for minimum 7 days after CAR-T infusion but remain at risk of complications after discharge that can lead to readmission. We report our institutional experience on the rate and etiology of readmissions after initial discharge. **Methods:** In this retrospective study, readmission was defined as an inpatient stay greater than 48 hours while under the auspice of the Immunotherapy service. Cytokine release syndrome (CRS) and neurotoxicity (NT) were graded based on the Lee and CTC v.4 criteria, respectively. Logistic regression models were used to study the association between clinical factors and readmission. **Results:** 44 pts received axi-cel. Median age was 62 (25-79). 33 pts (75%) had primary refractory disease and 14 (30%) had prior transplant. Pts had median 3 lines (2 -9) of treatment before axi-cel. Median time from most recent treatment to leukapheresis was 10 weeks (0.5-109). 22 pts (48%) received bridging therapy between leukapheresis and lymphodepletion (LD). Median duration of initial planned admission was 7.5 days (6-16). Incidence of CRS was 88% (all grades) and 12% (grade 3/4). Median time to start of CRS was 3 days (0-13). Incidence of NT was 61% (all grades) and 16% (grade 3/4) and median time to NT was 6 days (3-14). 6 pts (14%) were readmitted after initial hospitalization (1 had 2 readmissions). Median day of readmission was 13 (9-25). Median duration of subsequent hospitalization was 5 days (2-31). Reasons for readmission were: infection (2), CRS (2), GI bleed (1), progressive disease (PD) (1) and NT (1). 4 of 6 pts had no CRS or NT before readmission. 2 of the 4 were readmitted on days 9 and 13 for NT. The other 2 pts were readmitted for infection and GI bleed. 1 pt had grade 2 CRS and grade 2 NT during first admission and was readmitted on day 25 for PD. Last pt had grade 2 CRS and grade 3 NT during first admission with discharge day 13, readmission day 14 through day 17 with recurrent NT and second readmission day 30 for infection. 3 of 6 pts had ICU admissions during second admissions. There was no association between pre- and post- CAR-T variables and risk of readmission in multivariable models. **Conclusions:** Readmissions after discharge from initial planned hospitalization for axi-cel are not uncommon. This data supports our current policy of close monitoring until at least a month after CAR-T therapy and supports the requirement of a full-time caregiver until discharge from the Immunotherapy service. Research Sponsor: None.

3026 Poster Session (Board #90), Fri, 8:00 AM-11:00 AM

First-in-human clinical trial of the autologous CD7-CART for relapsed/refractory ACUTE lymphoblastic leukemia/lymphoma. *First Author: Mingzhi Zhang, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China*

Background: CD7 represents a potential target for T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL). We developed CD7 nanobody derived chimeric antigen receptor T-cells (CD7-CART), and established a non-gene editing strategy by anchoring CD7 in the ER and/or Golgi to overcome the CART fratricide. **Methods:** This single-arm, open-label, phase I study is to investigate CD7-CART cell manufacturing feasibility without contamination of malignant T cells, and the safety and efficacy of the CART on patients with CD7 positive relapsed/refractory T-ALL/T-LBL. 3 subjects, identified as both CD4 and CD8 negative T-ALL or T-LBL were enrolled. CART cells were manufactured by using CD4+/CD8+ sorted T cells from leukapheresis. All patients (Pts) were pretreated with Flu/Cy prior to CART infusion. 1x10^6/kg CART cells were given to case 2 and 3, while 1.5x10^6/kg to case 1. **Results:** Case 1 was diagnosed as refractory ALL with myeloid differentiation, who had received intensive chemotherapy and allogeneic hematopoietic stem cell microtransplantation. Case 2 was diagnosed as ALL (T/B mixed type) but relapsed with CNS involvement, and received radiotherapy in addition to intensive chemotherapy. Prior to CART infusion, case 2 had no abnormal B cells but 17.69% of abnormal early T cellsfrom BM. Case 3 had stage VI of T-LBL, which recurred after multi-cycle chemotherapy of BFM-90 regimen and autologous SCT. After CART treatment, no neurotoxicity was observed in all pts. Case 1 had grade 3 CRSwhile case 2 and 3 had grade 1, although increased IL-6 was detected in all pts. Significant CART expansion and persistence were observed in case 2 and 3, and MRD negative CR was confirmed on day 28 in both pts. The number of generalized lymphadenopathy, lymph node size, and the degree of metabolism were all significantly reduced in case 3. Case 1 had only moderate CART expansion, but abnormal early T cells from BM decreased from 70.03% to 19.57% on day 30. After CART infusion, the number of peripheral abnormal T cells became either undetectable in case 2 and 3, or significantly decreased in case 1. Interestingly, CART had unsustained effect on normal T cells in all pts. As of Feb-10-2020, case 1 has 5 months of OS, including 3 months of PFS. Case 2 and 3 has reached 2 and 1 months of PFS and is still in remission. **Conclusions:** CD7-CART cells can be manufactured without contamination of malignant T cells. CD7-CART therapy is well-tolerated and has great therapeutic potential for relapsed/refractory CD7 positive T cell malignancies. Clinical trial information: NCT04004637. Research Sponsor: National Key R&D Program of China (2016YFC1303403).

3027 Poster Session (Board #91), Fri, 8:00 AM-11:00 AM

Successful tumor-infiltrating lymphocyte (TIL) growth from uveal melanoma (UM) using a three-signal (3.0) method. *First Author: Meredith Pelster, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Metastatic UM is a rare cancer with poor response rates to systemic therapy. Adoptive transfer of patient-specific TIL may represent the best strategy for treatment. TIL are harvested from primary or metastatic tumors and initially expanded in culture with high dose IL-2 prior to undergoing rapid expansion protocol and therapeutic administration. Here, we report improved rates of initial expansion using a previously described TIL 3.0 method which utilizes dual agonistic antibodies to TCR and 4-1BB (Urelumab) for stimulation, respectively, with high dose IL-2, compared to the traditional method. **Methods:** Between 2006 and 2019, patients were consented for TIL harvest from either primary or metastatic UM tumors. Demographics, clinical features, and outcomes of the TIL initial expansion were collected. Success rates, number of cells expanded, and days in culture for the two methods were analyzed using partially overlapping samples t-tests and z-tests. **Results:** There were 85 harvests and expansions from 76 patients using the traditional method and 32 expansions from 30 patients using TIL 3.0. Initial TIL expansion was successful in 97% of TIL 3.0 harvests compared to 35% for the traditional method ($p < 0.001$). More TIL were expanded with TIL 3.0 compared to the traditional method (291.3 million cells vs. 88.6 million cells, $p < 0.001$), and fewer days were required in culture (18.5 vs. 29.0, $p < 0.001$). Both primary UM harvests and metastatic harvests were more successful with TIL 3.0 (90% vs. 12% for primary, $p < 0.001$, and 100% vs. 42% for metastatic, $p < 0.001$). **Conclusions:** Expansion of UM tumors via the TIL 3.0 method led to successful growth in 97% of harvests. Therapeutic administration to patients with TIL 3.0 is under active investigation. Research Sponsor: U.S. National Institutes of Health, Other Government Agency.

	Traditional (n=85)	TIL 3.0 (n=32)
Age, years, median (range)	54.0 (28-68)	58.5 (28-72)
Gender		
Male, n (%)	45 (59%)	17 (57%)
Female, n (%)	31 (41%)	13 (43%)
TIL source		
Primary UM, n	25	10
Metastatic UM, n	60	22
Primary UM features		
Largest basal diameter, mm, median (range)	13.9 (8.5-20.5)	13.4 (10.0-18.1)
Apical dimension, mm, median (range)	8.9 (3.8-14.6)	8.9 (2.3-14.6)
Gene expression profile	5 (20%)	3 (30%)
Class 1A, n (%)	5 (20%)	0 (0%)
Class 1B, n (%)	9 (36%)	5 (50%)
Class 2, n (%)	6 (24%)	2 (20%)
Unknown, n (%)		
Metastatic harvest location		
Liver, n (%)	18 (30%)	7 (32%)
Lung, n (%)	6 (10%)	3 (14%)
Skin/soft tissue, n (%)	30 (50%)	10 (45%)
Other, n (%)	6 (10%)	2 (9%)

3028 Poster Session (Board #92), Fri, 8:00 AM-11:00 AM

Association of lymphocyte to monocyte ratio with clinical response and survival in patients with relapsed, aggressive non-Hodgkin lymphoma treated with axicabtagene ciloleucel CAR-T. *First Author: Abdullah S. Al Saleh, Mayo Clinic, Rochester, MN*

Background: Chimeric antigen receptor T-cell (CAR-T) therapy induces complete remission (CR) in 30-40% of patients with non-Hodgkin lymphoma (NHL). However, for patients who do not achieve CR as their first response, predictors for achieving CR as best response can guide management between careful observation or early intervention. Increased absolute lymphocyte count to absolute monocyte count ratio (ALC/AMC) predicts better response rates and survival in NHL patients receiving chemotherapy and/or autologous stem cell transplant. We evaluated the prognostic impact of ALC/AMC in CAR-T therapy for NHL. **Methods:** This was a retrospective review of patients who received CAR-T for NHL from June 2016-August 2019. ALC/AMC was assessed at the start of lymphodepletion (LD) chemotherapy. The receiver operator curve (ROC) was used to determine the best cutoff for ALC/AMC in predicting CR at 3 months. Event-free survival (EFS) was defined from time of CAR-T infusion to relapse or death, whichever occurred first. Overall survival (OS) was defined from time of infusion to death of any cause. **Results:** Forty-seven patients received axicabtagene ciloleucel, with a median follow-up of 14 months. By ROC, ALC/AMC > 0.8 before LD chemotherapy was predictive of achieving CR at 3 months. Baseline characteristics were similar between the high (n = 30) and low (n = 17) ALC/AMC groups. Patients with an ALC/AMC > 0.8 at the time of LD chemotherapy were more likely to achieve CR at 3 months (46% vs. 12%, p = 0.01), 6 months (52% vs. 0%, $p < 0.0005$), and 12 months (42% vs. 0%, p = 0.01). Correspondingly, the EFS and OS were significantly shorter in patients with ALC/AMC$\leq$0.8 vs. those > 0.8 (median EFS: 2 vs. 13 months, $P < 0.0001$) and (median OS: 15 months vs. not reached, P = 0.03), respectively. Association between ALC/AMC ratio and EFS and OS remained consistent in multivariate Cox models after adjusting for other prognostic variables, including abnormal lactate dehydrogenase and increased ferritin level at infusion day. **Conclusions:** ALC/AMC > 0.8 before lymphodepletion chemotherapy is a strong predictor for complete remission as well as improved event-free and overall survival for axicabtagene ciloleucel in NHL. Research Sponsor: None.

3029 Poster Session (Board #93), Fri, 8:00 AM-11:00 AM

A prospective phase I trial of dendritic cell-based cryoimmunotherapy in metastatic castration-resistant prostate cancer. *First Author: Liv Cecilie Vestrheim Thomsen, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway*

Background: Dendritic cell (DC)-based cryoimmunotherapy (CryoIT) was used to treat metastatic castration-resistant prostate cancer in a Phase I clinical trial. Primary objective was safety of treatment. Secondarily, clinical, radiological and immunological treatment responses were investigated. **Methods:** In 18 patients cryoablation by a freeze-thaw process under general anesthesia was performed, followed by intratumoral autologous immature DC injection. In the last 9 patients checkpoint inhibition of either CTLA-4 or PD-1 was added. Subjects had minimum 46 weeks follow-up. Adverse events (AEs) and blood analyses were registered at all visits. Disease progression was determined by three imaging modalities according to (i)RECISTv1.1 and progression-free survival (PFS) by Kaplan-Meier method. Circulating tumor cells (CTC/7.5 mL, CellSearch) and ultradeep T-cell receptor (TCR) b-chain sequences (TCRSafe) were enumerated. Patients were separated by CTC into none (n=10), 1-4 (n=4) and $\geq$ 5 (n=4). Health related quality of life (HRQoL) measured by EORTC-QLQ C30 questionnaire were answered at inclusion, and 10, 22 and 46 weeks post CryoIT. Scores were calculated according to the EORTC manual. **Results:** Subjects progressing within 22 weeks had higher PSA (p=0.03). AE profile of the total cohort (n=18) was comparable with interim reports (n=13); of 20 possible DC-related AEs one was severe (urinary retention) and 19 mild-to-moderate, and spread independent of treatment regime. Maximum tolerated dose of DC was not reached. By 46 weeks, imaging showed 6 patients partial response or stable disease. Median PFS was 150 days in total cohort. Pretreatment CTC counts $\geq$5 indicated higher progression rates and recurring CTC. Ultradeep TCR-sequencing showed more prevalent and higher expressed (>5-fold) new TCR clonotypes at 2-6 weeks in men without progression. Participants reported high and stable HRQoL scores throughout the study. However, presence of CTC was associated with worse HRQoL scores at week 10 (p=0.031) and 22 (p=0.005). **Conclusions:** DC treatment seems safe and well tolerated, also combined with checkpoint inhibitors. Effect is indicated in subjects with moderate pre-treatment PSA levels. Immune responses are suggested by higher number of novel TCR clonotypes in men with non-progressive disease. Clinical trial information: NCT02423928. Research Sponsor: Alden Cancer Therapy II, Centre for Cancer Biomarkers CCBIO, University of Bergen, Bergen, Norway.

3030 Poster Session (Board #94), Fri, 8:00 AM-11:00 AM

Ongoing, first-in-human, phase I dose escalation study of the investigational CD47-blocker TTI-622 in patients with advanced relapsed or refractory lymphoma. *First Author: Krish Patel, Swedish Cancer Institute, Seattle, WA*

Background: CD47 is an immune checkpoint that binds signal regulatory protein alpha (SIRPα) and delivers a "do not eat" signal to suppress macrophage phagocytosis. Cancer cells frequently overexpress CD47 to escape immune surveillance. TTI-622 is a fusion protein consisting of the CD47-binding domain of human SIRPα linked to the Fc region of human IgG4. TTI-622 acts as a decoy receptor, preventing CD47 from delivering its inhibitory signal and enabling macrophage activation and anti-cancer activity via pro-phagocytic signals present on cancer cells. Unlike many CD47-blocking antibodies, TTI-622 does not bind to human erythrocytes and thus may not cause anemia in patients. **Methods:** In phase 1A, patients with advanced relapsed or refractory lymphoma received IV TTI-622 once per week with dose increased based on traditional 3+3 escalation. Dosing was on a mg/kg basis with the third and subsequent weekly doses approximately 2-fold higher than the first 2 doses (e.g., 0.05, 0.05, and 0.1 mg/kg for weeks 1, 2 and 3). Blood samples were obtained for PK analysis and assessment of CD47 receptor occupancy (RO) on peripheral T cells. **Results:** At data cut-off, 19 patients (11 M, 8 F) of median age 62 years (range, 24-86) with the following lymphomas: DLBCL 10; HL 6; and TCL, MCL and FL, 1 each, with a median of 3 prior therapies (range, 1-8) were enrolled. No DLTs have been observed in 5 dose levels (0.05 to 4.0 mg/kg). Grade $\geq$3 related neutropenia occurred in 2 patients; other related AEs occurring in 2 patients each included abdominal pain, fatigue, and nausea; no patients experienced a related SAE. Acute, post-dose platelet decreases occurred transiently and generally were Grade 1- 2; no related Grade $\geq$3 thrombocytopenia or anemia AEs have been observed. Preliminary PK data indicate a dose-proportional increase in exposure and a T1/2 of approximately 4-5 days following repeat infusions (Week 6). Preliminary biomarker data reveal approximately 60% RO at the end of the first infusion of 2 mg/kg and more sustained 24-hour RO at 1 and 2 mg/kg vs $\leq$ 0.8 mg/kg. To date, 1 patient with stage 4 non-GCB DLBCL (5 prior therapies) initially achieved PR by Wk 8 and CR by Wk 36, with response ongoing. **Conclusions:** TTI-622 is well tolerated at doses up to 4 mg/kg per week. Preliminary data indicate dose-dependent increases in PK exposure and target engagement with 1 DLBCL patient having achieved a durable, ongoing CR. Dose escalation is ongoing and additional safety, PK, biomarker and response data will be available at the time of meeting presentation. Clinical trial information: NCT03530683. Research Sponsor: Trillium Therapeutics Inc.

3031 Poster Session (Board #95), Fri, 8:00 AM-11:00 AM

Modulation of inhibitory signals in CAR T cells leads to improved activity against glioblastoma. *First Author: Khaled Sanber, Center for Cell and Gene Therapy, Department of Medicine, Baylor College of Medicine, Houston, TX*

Background: Early clinical trials have demonstrated the safety of chimeric antigen receptor (CAR) T cells targeting glioblastoma (GBM), however, their efficacy remains limited by multiple obstacles including the immunosuppressive tumor microenvironment. Adoptively transferred CAR T cells remain susceptible to inhibition via the engagement of co-inhibitory receptors on their surface such as PD1, BTLA, CTLA4 and LAG3. The subsequent recruitment of Src homology region 2 containing protein tyrosine phosphatase 2 (SHP2) by these receptors to the immune synapse may represent a common mechanism of T cell inhibition, as SHP2 can de-phosphorylate key signaling molecules that mediate T cell activation (including CD28 and CD3ζ). We hypothesized that SHP2 deletion will simultaneously offset the effects of multiple co-inhibitory receptors, thereby improving the anti-tumor activity of CAR T cells. **Methods:** Electroporation of sgRNA/Cas9 ribonucleoprotein complexes into human T cells was used to knockout (KO) SHP2. Retroviral vector transduction was used to express a clinically-utilized second generation CAR (with a CD28 endodomain) targeting HER2. The phenotype of wild-type (WT) and $SHP2^{KO}$ CAR T cells was evaluated with mass cytometry and flow cytometry. Their anti-tumor function was tested *in vitro* using the xCELLigence assay (an impedance-based cytotoxicity assay), and *in vivo,* in an orthotopic xenograft mouse model of GBM. **Results:** Efficient and reproducible depletion of the SHP2 protein in human T cells was verified using western blotting. The Inference of CRISPR Efficiency (ICE) Assay confirmed efficient editing of the PTPN11 gene encoding SHP2. An anti-HER2 CAR was efficiently expressed in the $SHP2^{KO}$ T cells. SHP2 deletion did not significantly affect CAR T cell expansion, proliferation or baseline phenotype. However, following co-culture with HER2+ LN229-GBM cells, the CD8+ central memory (CCR7+ CD45RA-) and effector memory (CCR7- CD45RA-) subsets were enriched to a greater extent in the $SHP2^{KO}$ CAR T cells. The pattern of cytokine co-expression varied between donors in a single-cell analysis comparing $SHP2^{KO}$ to WT CAR T cells after encountering LN229 cells. Functionally, $SHP2^{KO}$ CAR T cells derived from the majority of healthy donor and patient peripheral blood eliminated LN229 cells more rapidly *in vitro.* In an orthotopic mouse model of GBM, $SHP2^{KO}$ CAR T cells showed better early control of established LN229 xenografts and improved survival in comparison to WT CAR T cells. **Conclusions:** SHP2 deletion in CD28ζ.CAR T cells improves their anti-tumor activity. Research Sponsor: Stand Up to Cancer, Other Foundation.

3032 Poster Session (Board #96), Fri, 8:00 AM-11:00 AM

CYAD-101: An innovative non-gene edited allogeneic CAR-T for solid tumor cancer therapy. *First Author: Hans Prenen, University Hospital Antwerp, Edegem, Belgium*

Background: In contrast to autologous CAR-T cell therapies, allogeneic donor-derived CAR-T cells can be banked and used in a timely fashion overcoming the critical time delay of just in time autologous cell manufacture. CYAD-101 is an allogeneic CAR-T that uses a non-gene edited peptide-based technology (TIM) to control graft versus host disease (GvHD) combined with a NKG2D-based CAR. Pre-clinical studies confirmed that CYAD-101 maintained CAR-directed anti-tumor activity in the absence of the induction of GvHD. Clinical grade CYAD-101 cells were produced for the phase 1 alloSHRINK trial (NCT03692429). **Methods:** A bank of clinical grade CYAD-101 cells was generated through two production runs using a single donor apheresis. Together, the bank generated > 53 billion CYAD-101 cells suitable for the entire dose escalation segment and short expansion phase of the trial (15 patients in total). Both runs showed high consistency with the CYAD-101 product generated composed mainly of $CD4^+$ T cells (>85%) with a transduction level of > 92%, low relative expression of CD69/CD25 and largely absent expression levels of PD-1/LAG-3. The CYAD-101 cells were predominantly (>80%) $CD45RA^-$/ $CD62L^-$/ $CD27^-$ suggestive of an effector memory T cell population. **Results:** Upon co-culture with target K562 cells, CYAD-101 readily produced IFN-γ that was blocked by a NKG2D blocking antibody confirming specificity of the CAR. CYAD-101 cells showed in vitro cytotoxicity against tumor cells and produced an array of Th1 (IFN-γ, IL-2 and TGF-β) and Th2 (IL-4, IL-5) cytokines. Importantly, minimal IFN-γ was produced upon TCR stimulation while stimulation with a non-TCR mitogen (PMA + ionomycin) lead to high levels of IFN-γ. Together, these data show that clinical grade CYAD-101 cells were able to functionally respond through the CAR but showed minimal TCR-driven activation. Fifteen refractory metastatic CRC patients who had previously failed at least one line of oxaliplatin—containing therapy were treated with three doses of CYAD-101 cells given on Day 3 of three successive FOLFOX chemotherapy cycles. Updated clinical results continue to demonstrate an encouraging clinical activity (2 patients with partial response and 9 with stable disease) and the absence of GvHD in the context of CYAD-101 cell engraftment. **Conclusions:** These early clinical results demonstrate the safety and tolerability of a non-gene edited predominantly $CD4^+$ CAR-T therapeutic approach. The initial observations of clinical activity in metastatic CRC patients warrants the continued development of this therapy. Clinical trial information: NCT03692429. Research Sponsor: Celyad SA.

3034 Poster Session (Board #98), Fri, 8:00 AM-11:00 AM

Safety and efficacy of optimized tandem CD19/CD20 CAR-engineered T cells in patients with relapsed/refractory non-Hodgkin lymphoma. *First Author: Yajing Zhang, Chinese PLA General Hospital, Beijing, China*

Background: Chimeric antigen receptor T (CAR T) cells targeting CD19 have been used to achieve breakthroughs in the treatment of hematological malignancies, however, a high recurrence rate is the main obstacle to durable remission following CAR T cell therapy. **Methods:** As an open-label and single-arm phase I/IIa trial (ClinicalTrials.gov number, NCT03097770), we screened 99 patients with r/r B-NHL—including DLBCL, PMBCL, CLL/SLL, MCL, TFL and FL—according to the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue, and a total of 87 patients received an infusion of one dose tandem CD19/CD20 CAR-engineered T cells on day 0 in the range of 0.5×10^6-10×10^6 cells per kilogram of body weight after conditioning chemotherapy. The primary objective was to evaluate the safety and tolerability of CAR T cells. Efficacy, progression-free survival (PFS) and overall survival (OS) were evaluated as secondary objectives. Our clinical trials is registered with ClinicalTrials.gov, NCT03097770. Safety was assessed by CTCAE Version 5.0, and clinical response by PET-CT referred to standard international criteria. The trial remains open, and recruitment to extension cohorts with alternative endpoints is underway. **Results:** Between May 11, 2017, and Jan 31, 2020, 99 patients were enrolled and 87 received tandem CD19/CD20 CAR-engineered T cells across phases I/IIa. As of the cutoff date, 74 assessable patients were followed up for a median of 13.5 months (IQR 33.2 - 3.3), 62 (84%) had an objective response, and 55 (74%) had a complete response. The median progression-free survival and overall survival were all not reached. Cytokine release syndrome (CRS) occurred in 62 patients (71%), with 61% grade 1 or 2 and 10% grade 3 or more. CAR-T-cell-related encephalopathy syndrome (CRES) of grade 3 occurred in 2 patients (2%) . Three treatment-related deaths (2 in pulmonary infection and 1 in deposition of CART cells in pulmonary alveoli). **Conclusions:** In this study, optimized tandem CD19/CD20 CAR-engineered T cells induced a potent and durable anti-tumour response with controllable CRS and CRES. Clinical trial information: NCT03097770. Research Sponsor: National Natural Science Foundation of China.

3035 Poster Session (Board #99), Fri, 8:00 AM-11:00 AM

Efficacy of SCRI-CAR19x22 T cell product in B-ALL and persistence of anti-CD22 activity. *First Author: Rebecca Alice Gardner, Seattle Children's Hospital, Seattle, WA*

Background: Loss of CD19 expression is a major cause of limited durable B-ALL remission following CD19 CAR T cells, which might be overcome by utilization of dual CD19xCD22 CAR T cell targeting. **Methods:** A Phase I trial (NCT03330691) of SCRI-CAR19x22 was developed using dual transduction of lentiviral vectors encoding for either a CD19- or CD22-specific CAR T cell construct, both with 4-1BB co-stimulation. Manufacturing was performed in a closed G-Rex system with IL-7, IL-15 and IL-21. After lymphodepletion, CAR T cells were infused at 1 or 3 X 10^6 CAR T cells/kg dose levels. Leukemic response and CAR T cell persistence were evaluated by flow cytometry. **Results:** Products were successfully manufactured in all 28 enrolled subjects with 7.92 average days in culture (range of 7-11 days) and consisted of an average CD8:CD4 ratio of 3.09 (range 0.19 to 8.9). The cellular product CAR composition was 29% CD19, 31% CD22 and 39% CD19 and CD22 targeting. 13 subjects had prior exposure to CD19 or CD22 targeting therapies with diverse expression of CD19 and CD22 on the leukemic blasts. No dose limiting toxicities occurred in the 27 infused subjects. The recommended phase 2 dose is 3 x 10^6 CAR+ cells/kg. CRS was present in 80% of subjects, with 85% of CRS being grade 2 or less, and a peak grade of 3 (n = 3). Mild neurotoxicity occurred in 38%, with a single grade 3 event. 84.6% obtained a CR, of which 95% were MRD negative. Of the 4 subjects who did not achieved a CR, 2 had a pre-existing CD19 negative population and one had previously received CAR T cells and rejected SCRI-CAR19x22. There have been 4 relapses with varying CD19 and CD22 expression as follows: 1 CD19-CD22-, 1 CD19+CD22+, and 2 CD19-CD22+. The in vivo engraftment of CAR T cells peaked most frequently between day +7 and +14 and was predominated by the CD19 CAR+ T cells. **Conclusions:** We demonstrate manufacturing feasibility and safety of SCRI-CAR19x22. While initial efficacy is demonstrated, CD22 activity is poor due to limited expansion of the CD22 CAR-containing components and subjects with pre-existing CD19 negative leukemia fared poorly. Development of a revised CD22 CAR that exhibits a reduction tonic signaling is underway, with plans to explore the new construct in the context of a dual-targeting CD19xCD22 CAR T cell product. Clinical trial information: NCT03330691. Research Sponsor: Philanthropy.

3036 Poster Session (Board #100), Fri, 8:00 AM-11:00 AM

In vitro and in vivo characterization of MDNA11: A long-acting "beta-only" IL-2 superkine in syngeneic mice tumor models and nonhuman primates. *First Author: Moutih Rafei, Université de Montréal, Montréal, QC, Canada*

Background: Use of IL-2 (Proleukin) remains limited due to its short half-life, toxicity, and its ability to preferentially activate Tregs resulting in unwanted immune suppression. Approaches to reduce binding to CD25 (IL2α), such as pegylation techniques, also results in reduced affinity to CD122 (IL2β). To bypass these limitations, we engineered MDNA11, an IL-2 Superkine containing core mutations to diminish binding to CD25 while increasing affinity to CD122. To increase half-life, MDNA11 was fused to an albumin scaffold, which is known to allow accumulation at the tumor site. **Methods:** MDNA11 was evaluated using *in vitro* and *in vivo* studies that included: IL-2 signaling in human PBMCs, Biacore binding analyses, PK studies in mice, and efficacy studies in syngeneic tumor models with or without immune checkpoint inhibitors (ICIs). In addition, dose-range finding studies in cynomolgus monkeys (NHP) were performed to characterize the safety and PK/PD profiles of MDNA11. **Results:** MDNA11 displayed enhanced STAT5 signaling in human NK and naïve CD8 T-cells with diminished Treg activity. In mice, the terminal half-life of MDNA11 was 24-fold longer than IL-2. As a result, MDNA11 triggered effective tumor growth control, as monotherapy or in combination with ICI, in multiple tumor models in spite of q1wk dosing for two weeks. MDNA11 administration to mice with pre-established CT26 colon cancer resulted in tumor-free animals and induced strong memory response and protection against subsequent re-challenges. MDNA11 also inhibited the growth of B16F10 melanomas, which translated into a durable increase in tumor infiltrating CD8 T-cells. When tested in NHP, MDNA11 led to increased circulating CD8 T-cells lasting for almost 14 days with limited effects on Tregs and eosinophils (the latter being a source of IL-5 causing vascular leak syndrome). High doses resulted in mild side effects that were transient and reversible even following repeated dosing. **Conclusions:** The long-acting MDNA11 Superkine has superior potency over IL-2 at activating naïve CD8 T-cells and NK cells, while exhibiting diminished Treg activation. This molecule potently inhibited tumor growth and induced durable regression and long-term memory response. Studies in NHP showed prolonged proliferation of immune effector cells lasting almost two weeks post-MDNA11 administration. The sum of these data underscores the potency of MDNA11 to trigger the host's immune response to control or eradicate established tumors. Research Sponsor: Medicenna Therapeutics.

3037 Poster Session (Board #101), Fri, 8:00 AM-11:00 AM

A randomized phase I/IIa study to evaluate the safety and efficacy of SNK01 (non-genetically modified autologous natural killer cells with enhanced cytotoxicity) plus pembrolizumab in patients with stage IV non-small cell lung cancer. *First Author: Eo Jin Kim, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Despite the increased promise of checkpoint inhibitors in the treatment of lung cancer, the overall response rate is approximately 30% with up to 30% moderate to severe side effects. Natural killer (NK) cells have recently been implicated in antitumor response to immune checkpoint inhibitors. SNK01 is a novel non-genetically modified autologous natural killer cell therapy with enhanced cytotoxicity which has been found to have tumoricidal effects against several lung cancer cell lines. **Methods:** 18 patients with Stage IV NSCLC (PD-L1+, EGFR-, ALK-) who all failed prior frontline platinum-based therapy were randomized 2:1 to Pembrolizumab every three weeks +/- 6 weekly infusions of SNK01 at either 2×10^9 or 4×10^9 cells per infusion. Primary endpoint is safety and secondary endpoints are objective response rate (ORR), progression-free survival (PFS), overall survival (OS), time to progression (TPP), and quality of life (QoL). **Results:** 14 patients have been enrolled up to date and 9 have completed treatment. Median age is 69 (52-73). Two patients discontinued treatment prior to receiving their first dose of SNK01 due to Grade 3 toxicity to Pembrolizumab. Three patients have completed therapy with Pembrolizumab alone and all had progressive disease. Three patients have completed Pembrolizumab with 2×10^9 SNK01 and three patients have completed Pembrolizumab with 4×10^9 SNK01. Of patients receiving full combination therapy, there have been no adverse events or any reported toxicity while overall QoL has been improved. The week 9 overall response rate in the combination group is 66% using iRECIST (3/6 cPR, 1/6 PR). All remaining planned patients are currently being enrolled and a full update will be presented. **Conclusions:** These preliminary results demonstrate that combination therapy with Pembrolizumab and SNK01 is very safe and even appears to reduce checkpoint associated toxicity while increasing overall tumor response compared to Pembrolizumab monotherapy alone in Stage IV NSCLC patients who have failed prior platinum-based treatment. Research Sponsor: NKMAX.

3038 Poster Session (Board #102), Fri, 8:00 AM-11:00 AM

Phase I study of CRISPR-engineered CAR-T cells with PD-1 inactivation in treating mesothelin-positive solid tumors. *First Author: Zhenguang Wang, Molecular & Immunological Department, Bio-therapeutic Department, Chinese PLA General Hospital, Beijing, China*

Background: Our previous phase I study with MPTK-CAR-T (mesothelin-directed 28ζ CAR-T cells with PD-1 and TCR disruption by CRISPR-Cas9 system) demonstrated feasibility and safety of CRISPR-mediated PD-1 inactivation in CAR-T cells, and suggested the natural TCR is beneficial for the proliferation of CAR-T cells in solid tumors. Based on these observations, we initiated a pilot dose escalation study to investigate mesothelin-directed CAR-T cells with only PD-1 disruption by CRISPR (termed as GC008t) in patients with mesothelin-positive advanced solid tumors (NCT03747965). **Methods:** On the data cut-off date (Jan 20, 2020), nine patients (6 pancreatic cancers, 2 ovarian cancers, 1 colorectal cancer) were treated (5 received ≥12 numbers of therapy), three in cohort 1 ($0.1\text{-}0.2 \times 10^7$/kg), four in cohort 2 ($0.5\text{-}1.0 \times 10^7$/kg), two in cohort 3 ($2.5\text{-}5 \times 10^7$/kg). Eight of the 9 patients received lymphodepletion regimen of cyclophosphamide and nab-paclitaxel with or without gemcitabine. Four of the 9 patients received repeat infusions of GC008t per protocol. **Results:** Comparable proliferation capacity was observed *in vitro* between the MPTK-CAR-T and the GC008t products. The mean PD-1 surface expression in cell products was 0.5% (range, 0.2%-0.9%). GC008t infusions were well tolerated with no observed on-target/off-tumor toxicity, autoimmune activity. Only two patients in cohort 3 developed grade 1 CRS with fever and rash. Circulating GC008t expanded with a peak at day 7-14 and became undetectable by qPCR beyond 1 month. The mean peak levels of circulating CAR-T cells between GC008t and MPTK-CAR-T at similar dose level were not statistically significant. Failure of GC008t engraftment after repeat infusion was observed in 2 out of 4 patients. The best response of the 7 evaluable patients was stable disease in 4 and partial response in 2 patients (dosed $\geq 1 \times 10^7$/kg) with PFS of 80 and 160 days. **Conclusions:** Phase I trial of GC008t further establishes that genetic inactivation of PD-1 in CAR-T cells by CRISPR is feasible and safe. The expansion and persistence of CAR-T cells with PD-1 disruption is not improved significantly even in the setting of natural TCR and lymphodepletion. Future endeavors are needed to improve the clinical efficacy of CAR-T therapy in the treatment of solid tumor. Clinical trial information: NCT03747965. Research Sponsor: National Natural Science Foundation of China;National Key Research and Development Program of China;Strategic Priority Research Program of the Chinese Academy of Sciences.

3039 Poster Session (Board #103), Fri, 8:00 AM-11:00 AM

Safety and efficacy of chimeric antigen receptor T cells modified to target mesothelin and express PD-1 antibodies in patients with relapsed/refractory solid cancers in a phase I trial. *First Author: Juemin Fang, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China*

Background: The limitations of chimeric antigen receptor T cells (CAR-T) in solid tumors are immunosuppressive tumor microenvironment and difficult infiltration to tumor. In order to reduce on-target off-tumor toxicities and circumvent the immune-suppressive tumor microenvironment(TME), we modified autologous CAR-T to be specific for mesothelin (MSLN) on cancer cells and secrete PD-1 antibodies (aPD1-MSLN-CAR T cells). Here, we report the safety and efficacy of aPD1-MSLN-CAR T cells in 10 patients with relapsed/refractory solid cancers in this single-arm, open-label, first-in-human phase I pilot study (ClinicalTrial.gov: NCT03615313). **Methods:** aPD1-MSLN-CAR T cells were prepared from peripheral blood mononuclear cells and engineered using PiggyBac Transposon System to target MSLN and secrete PD-1 antibodies. 10 patients with mesothelin positive relapsed/refractory solid cancers after failure to standard therapies were treated with aPD1-MSLN-CAR T cells for two or more cycles until disease progression or intolerable toxicity. The dose escalation of CAR T cells was designed to be 5×10^6/kg, 5×10^7/kg, and 1×10^8/kg, respectively. Adverse events were evaluated according to CTCAE-V4.03 and clinical response was assessed by RECIST 1.1. CAR expression was analyzed using quantitative real-time polymerase chain reaction. PD-1 antibodies were detected by ELISA. Serum IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α were measured using flow cytometry. **Results:** The most common adverse events were mild fatigue and fever. Abdominal pain was also observed in 1 patient. Grade 1 and 2 cytokine release syndromes were observed without neurologic symptoms in 10 patients. After aPD1-MSLN-mRNA-CAR T cells treatment, 2 patients (20%) achieved partial response (PR), 4 (40%) remained stable (SD), and the rest 4 (40%) patients developed disease progression (PD). The median PFS was 97 days [95% CI (13, 180)] estimated by Kaplan-Meier method. **Conclusions:** These findings lend support that the combination of modified CAR T cells targeting MSLN with PD1 inhibition for solid tumors is safe. Modified CAR-T cells expressing PD-1 antibodies maybe an option to improve CAR-T efficacy as a result of refined TME. Clinical trial information: NCT03615313. Research Sponsor: Funding from Shanghai Tenth People's Hospital.

Characteristics and clinical responses.

Characteristics	NO.
Mean Age, years	54.5 (39, 67) years
Male/ Female	2/8
Ovarian cancer	6
Rectal cancer	2
Gallbladder cancer	2
PR	2(20%)
SD	4(40%)
PD	4(40%)
PFS, days	97 [95% CI (13, 180)]

3040 Poster Session (Board #104), Fri, 8:00 AM-11:00 AM

Final results of controlled IL-12 monotherapy in adults with grade III or IV gliomas. *First Author: E. Antonio Chiocca, Brigham and Women's Hospital, Boston, MA*

Background: Interleukin-12 (IL-12), a master regulator of the immune system, results in anti-tumor responses in preclinical models, but safe use requires tightly controlled production. This phase 1 trial (NCT02026271) is the first to evaluate the safety and tolerability of Ad-RTS-hIL-12 (Ad) under transcriptional control with veledimex (V) in adults with grade III or IV gliomas. **Methods:** Multicenter, phase 1, open-label, 3 + 3 dose escalation study of Ad (a single intratumoral injection, 2×10^{11} viral particles, Day 0) with oral V dosing (Days 0 to 14) of 10, 20, 30, and 40 mg in subjects with rGBM. **Results:** 38 subjects were treated (resection group: V 10 mg (n = 6); 20 mg (n = 15); 30 mg (n = 4); 40 mg (n = 6); and, stereotactic group: V 20 mg, n = 7). The adverse event profile of Ad+ V, was predictable and controllable, with the main adverse reactions (ARs) being mild to moderate. All ARs were manageable and reversible upon withholding V. We observed increased peak (mean ± SEM) serum recombinant IL-12 and downstream endogenous IFN-g: V 10mg 21.4 ± 11.7 pg/mL and 14.6 ± 7.1 pg/mL; V 20 mg 25.8 ± 7.1 pg/mL and 57.0 ± 26.5 pg/mL; V 30 mg 65.7 ± 45.5 pg/mL and 60.7 ± 50.0 pg/mL; V 40mg 108.8 ± 41.0 pg/mL and 167.5 ± 70.9 pg/mL, V 20mg (stereotactic) 25.1 ± 7.2 pg/mL and 69.8 ± 48.5 pg/mL, respectively. In the V 20 mg cohort, there was an increase in tumor-associated T cells ($CD3^+CD8^+$%) from pre-Ad (mean ± SEM) 0.6 ± 0.4 to biopsy (~5 mons) 6.3 ± 5.0 and production of IFN-g 97.2 ± 85.3 pg/g (n = 2). Median overall survival (mOS) in the V 20 mg cohort (resection, n = 15) was 12.7 mons (mean follow-up, 13.1 mons). Subjects with unifocal disease (n = 6) who received low-dose (≤ 20mg total) dexamethasone during active dosing (Days 0-14) had an mOS of 17.8 mons. Tumor response data will be presented. **Conclusions:** Results of Controlled IL-12 in rGBM are promising, with V-dependent and proportional increases in IL-12 and IFN-g resulting in immune activation, with a favorable safety profile and encouraging survival. The 20 mg V dose is the recommended phase 2 *dose*. Controlled IL-12 is being evaluated in a monotherapy substudy (n = 36, V 20 mg) and two combination studies with immune checkpoint inhibitors for rGBM. Clinical trial information: NCT02026271. Research Sponsor: Ziopharm Oncology.

3041 Poster Session (Board #105), Fri, 8:00 AM-11:00 AM

Selective targeting of HER2-overexpressing solid tumors with a next-generation CAR-T cell therapy. *First Author: Jenny Mu, Arcellx, Inc., Gaithersburg, MD*

Background: Conventional chimeric antigen receptor T cell (CAR-T) therapies have achieved limited clinical success in the treatment of solid tumors, in part due to the challenges of identifying tumor antigen(s) that are uniquely expressed on tumor cells. The dearth of such targets requires that current CAR-T therapies be re-engineered to preferentially target tumor cells thereby mitigating potential on-target off-tumor toxicity to normal cells. Herein we describe a novel cell therapy platform comprising Antigen Receptor Complex T (ARC-T) cells that are readily activated, silenced, and reprogrammed *in vivo* by administration of a novel tumor-targeting soluble protein antigen-receptor X-linker (sparX). The formation of the ARC-T, sparX, and tumor complex is required for the ARC-T to kill the tumor. Because ARC-T activity is entirely dependent on the dose of sparX administered, therapeutic doses of sparX may be defined that preferentially target cells over-expressing a target antigen and thus limit coincident kill of normal cells expressing lower levels of target antigen. **Methods:** We have created a library of sparX that bind different cell surface antigens, including HER2. The HER2 sparX was tested as both monovalent and bivalent constructs *in vitro* by assessing ARC-T cell activation, cytokine release and target cell cytotoxicity. *In vivo* efficacy models utilized NSG mice and incorporated tumor volume measurements and histopathologic assessments to evaluate tumor clearance. **Results:** *In vitro* studies demonstrate that co-culture of ARC-T cells, sparX-HER2 and HER2-expressing target cells drives T cell activation, expansion, cytokine secretion and cytotoxicity of target cells in a dose-dependent manner. Furthermore, by affinity tuning the HER2 binding domain and bivalent formatting of sparX-HER2, we achieved selective killing of HER2-overexpressing breast cancer cells with minimal effect on cells expressing HER2 levels representative of normal tissues. *In vivo* proof-of-principal studies with ARC-T/sparX-HER2 similarly demonstrate complete eradication of HER2-overexpressing solid tumor cells. **Conclusions:** These results demonstrate that a single intravenous dose of ARC-T cells can traffic to a solid tumor site and induce tumor eradication upon systemic administration and co-localization of tumor-targeting sparX in a mouse model. Bivalent formatting of sparX-HER2 further enabled ARC-T sensitivity to target antigen density to avoid the on-target off-tumor toxicity that has hindered conventional monovalent CAR-T treatments. Research Sponsor: Arcellx, Inc.

3043 Poster Session (Board #107), Fri, 8:00 AM-11:00 AM

Correlating immune toxicity, blood cell counts, and overall survival in cancer patients receiving immune therapy. *First Author: Rong Lu, UT Southwestern Medical Center, Dallas, TX*

Background: Baseline circulating white blood cell differential counts have been proposed as possible markers of response to Immune therapy (ICI) and immune toxicity (irAE), but have not been validated for clinical practice. **Methods:** 214 patients with various cancers receiving ICI had clinical lab results and overall/organ specific irAE analyzed. Absolute lymphocyte (ALC), eosinophil (AEC) and neutrophil (ANC) counts <7 days of starting and 3-12 weeks after ICI were correlated with survival and development of irAE. The association between overall irAE and cell count changes was evaluated using multivariate logistic regression, adjusting for patients' age, gender, race, and including all 3 types of cell count changes in one model. The association between overall survival and cell counts changes was tested using multivariate Cox proportional hazard model, adjusting for age, gender, race, and overall irAE (yes/no). **Results:** The combination of MEDIAN rise or fall in ALC, ANC and AEC after ICI combined with development of irAE was associated with altered overall survival (OS). Higher statistically significant (p=<0.05) OS was seen in patients with AEC↑/irAE+(n=94; median OS 14.9 months), ANC↓/irAE+(60; 17.9 mo), ALC↑/irAE+(65; 11.5 mo), ALC↓/irAE+(92; 12.2 mo). Lower OS was seen with ANC↑/irAE-(21; 5.4 mo), ALC↑/irAE-(9; 5.8 mo), ALC↓/irAE-(24; 6.1 mo). All these relationships were unchanged if patients were grouped into ANY rise during the 3-12 weeks rather than median. After multivariable adjustment for age/sex/race there was statistically significant association between higher baseline ALC and development of any irAE (p=0.05) and grade ≥2 irAE (p=0.02). No association was seen between overall toxicities and ANC or AEC. Organ-specific irAE's with statistically significant associations included pneumonitis:↓AEC (p=0.05), hepatitis:↓ANC (p=0.05), hypothyroidism:↓ANC (p=0.02), colitis:↑ALC (p=0.02). Skin rash, hypophysitis and adrenalitis were not associated with any cell count changes. **Conclusions:** In patients with cancer receiving immune therapy, the predictive value of serial monitoring in ALC, AEC and ANC is greatly enhanced by the addition of irAE detection. irAEs appear to be a greater predictor of survival than changes in blood counts. In contrast to prior reports we found ANC/ALC/AEC in isolation were less reliable in predicting improved survival. Lack of standardized methods of assessing irAE's confound identifying strong associations with clinical lab-derived cell counts. Research Sponsor: None.

3044 Poster Session (Board #108), Fri, 8:00 AM-11:00 AM

Association of reinvigoration of circulating anti-telomerase CD4 Th1 response in cancer patients with anti-PD-1 response. *First Author: Emeline Orillard, University Hospital Jean Minjoz, Besançon, France*

Background: Increasing evidence highlights the crucial roles played by CD4+ Th1 cells in cancer immunity and immunotherapy (Spitzer et al., Cell 2017, Borst et al., Nat rev Immunol 2018). Here, we investigate the relevance of circulating CD4 Th1 response against shared tumor-associated antigens (TAA) in cancer patients treated by anti-PD-1 immunotherapy. **Methods:** A total of 46 advanced cancer patients (pts) including 32 pts with non-small cell lung cancer (NSCLC), 14 pts with melanoma, were enrolled (ITHER trial NCT02840058). Patients were treated with anti-PD-1 therapy as standard of care (26 pts with nivolumab and 20 pts with pembrolizumab). Peripheral blood mononuclear cells were collected before and after treatment at 1 and 3 months. The presence of circulating TAA-specific Th1 response was measured by IFNy ELISPOT assay using a mixture of 15mer peptides derived from telomerase (TERT) (Laheurte et al., Oncoimmunology 2016 and Br J C 2019). **Results:** At the baseline, the anti-TERT Th1 response was observed in 37% of pts. After anti-PD-1 therapy, *de novo* induction and/or amplification of pre-existing anti-TERT Th1 response was found in 26 % of pts (12/46). Whereas, a decrease of this response was documented in 15% of pts (7/46).The presence of anti-TERT Th1 response in peripheral blood during anti-PD-1 treatment was associated with a prolonged progression free-survival (PFS) as compared to the immune non responder pts (14.4 vs 2.6 months respectively, p = 0.006, HR 0.39 [0.2;0.76]). Similar observation was made for the overall survival (OS) (22.3 vs 12.3 months respectively, p = 0.04 HR 0.45 [0.21;0.96]). Notably, *de novo* reinvigoration of peripheral anti-TERT Th1 response after anti-PD-1 therapy was associated with a better clinical outcome as compared to the group of pts with decreased immune response after treatment (Median OS not reached vs 5.8 months). In contrast, no association with anti-PD-1 response was observed neither with circulating anti-NY-ESO-1 or with anti-viral Th1 response, concurrently measured in these patients. **Conclusions:** The reinvigoration of circulating CD4 Th1 against telomerase in patients treated by anti-PD-1 is associated with a better clinical outcome. These results underline the potential interest of monitoring circulating antitumor CD4 Th1 response for immune checkpoint inhibitors management. Research Sponsor: None.

3045 Poster Session (Board #109), Fri, 8:00 AM-11:00 AM

Novel biomarker panel based on cellular and soluble checkpoint proteins for PD-1/PD-L1 blockade treatment efficacy. *First Author: Hiroki Nagai, Valley Hospital, Paramus, NJ*

Background: Although anti-PD-1/PD-L1 therapy has become one of the standard treatments for advanced cancers, its low treatment efficacy (10-30%) has remained a major issue. We sought to perform a detailed immune profiling of cells and soluble proteins in order to characterize key regulators and signaling molecules and identify therapeutic targets and biomarkers that may improve treatment efficacy and diagnosis. **Methods:** This observational study enrolled 49 advanced cancer patients treated with PD-1/PD-L1 blockade monotherapy. Treatment response was assessed by RECIST 1.1. PBMC and plasma samples were collected at baseline and every 6 weeks following initial treatment. Immune profiling of PBMC was done by multi-parametric flow cytometer, and t-SNE analysis was used to identify key immune subtypes. Soluble proteins were evaluated by LUMINEX assays. Cut-off values were determined by ROC curve analysis. **Results:** Three unique subtypes of immune cells were identified. The population of $CD11c^{+}HLA\text{-}DR^{low}CD80^{+}CD86^{-}$ $CD274^{+}$ cells (regDC) at baseline was significantly higher in patients with progressive disease (PD, n=28) than in patients showing clinical benefit (non-PD, n=21; p=0.030). The higher regDC population also correlated with higher levels of IL-8, IL-10, CXCL1, CXCL5, and CXCL11 in plasma. The population of $CD4^{+}CD25^{+}CD62L^{+}$ T cells (Treg) was also higher in PD patients ($p<0.001$). A unique subtype of $CD4^{+}CD28^{-}$ T cell, however, was higher in non-PD patients ($p<0.001$). For the soluble proteins, the levels of sLAG-3 and sGITR in plasma correlated with better clinical outcome in low regDC patients (p=0.004 and 0.044, respectively). The combined biomarker panel (cellular and protein markers) yields high sensitivity (90.5 %) and specificity (82.1 %) for predicting treatment efficacy. Disease control rate (DCR) and median progression free survival (PFS) are shown in the Table. **Conclusions:** To our knowledge, this pilot study is the first to detect three immune cell subtypes, regDC, Treg and $CD4^{+}CD28^{-}$ cells, associated with clinical outcome in the treatment of PD-1/PD-L1 blockade. Profiling of immune cell subtypes and soluble immune checkpoint proteins can serve to identify therapeutic targets and biomarkers for treatment efficacy. We will report the data with further enrollment. Research Sponsor: None.

	DCR (%)	p value	PFS (days)	p value
High/low regDC	13.3 /55.9	0.011	74 vs 178	0.010
High/low Treg	13.7 /85.0	<0.001	69 vs 407	<0.001
High/low $CD4^{+}CD28^{-}$ T cell	81.3 /24.2	<0.001	561 vs 74	<0.001
Our model outcome favorable/unfavorable	79.2 /8.0	<0.001	500 vs 67	<0.001

3046 Poster Session (Board #110), Fri, 8:00 AM-11:00 AM

Plasma next-generation sequencing (NGS) in advanced non-small cell lung cancer (aNSCLC) patients (pts) treated with immune checkpoint inhibitors (ICIs): Impact of *STK11* and *TP53* mutations on outcome. *First Author: Alberto Pavan, Medical Oncology 2, Istituto Oncologico Veneto IOV-IRCCS, Padua, Italy*

Background: ICIs revolutionized aNSCLC treatment. The next challenge lays on the search for predictive markers. Detection of multiple tumor-related genetic alterations through NGS in cell free DNA is a promising tool, provided the limited availability of tumor tissue in most cases. **Methods:** Between January 2017 and October 2019, aNSCLC pts consecutively referring to our Institution were prospectively screened with plasma NGS while included in two clinical trials: VISION (NCT02864992) and MAGIC trial, an observational study. In VISION trial NGS was performed in plasma (Guardant360 test) and tissue (Oncomine Focus Assay). In MAGIC Myriapod NGS-IL 56G Assay was used. Aim of the study was to evaluate the impact of *STK11*, *KRAS* and *TP53* mutations (muts) on outcome of ICI-treated pts, with overall survival (OS) as primary endpoint. A control group of pts not receiving ICIs was also analyzed. **Results:** A total of 235 NSCLC pts were enrolled and received ICIs. 93 pts were analyzed in plasma at the time of beginning ICIs: median OS was 18.9 m (95% CI: 13.7-24.1) and median immune-related progression free disease (irPFS) 3.8 m (95% CI: 2.5-5.1). 49 (52.7%), 22 (23.7%) and 8 (8.6%) pts carried *TP53*, *KRAS* and *STK11* pathogenic alterations, respectively. *STK11* mutated pts showed a trend for worse OS compared with wildtype counterpart (14.9 m, 95% CI: 6.5-23.3, *versus* 20.3, 95% CI: 13.4-27.2, p = 0.192) *KRAS* muts had no impact on outcome. Pts with *TP53* or *STK11/KRAS* co-mut (n = 3) had worse OS (12.3 m, 95% CI: 9.2-15.4; HR = 3, 95% CI: 1.6-5.8, p = 0.001 and 5.9 m, 95% CI: 1.4-7.6; HR = 2.9, 95% CI: 1.4-6.3, p = 0.007) and worse irPFS (2.8 m, 95% CI: 1.7-3.9, HR = 1.8 95% CI: 1.1-3.1, p = 0.03 and 1.2 m, 95% CI: 0.9-1.5, HR = 2.2 95% CI: 1.2-4.1, p = 0.01). Number of muts negatively impacts pts' OS (HR = 1.2, 95% CI: 1.1-1.3, p = 0.02) and was higher among *TP53* mutated pts ($p <$ 0.001, Mann-Whitney test). In multivariate analysis, *TP53* and *STK11/KRAS* retained significance. A control group of pts not receiving ICIs was analyzed (n = 101): median OS was 16.8 m (95% CI: 13-20.6). Nor *STK11* (n = 10), nor *STK11/KRAS* (n = 6) had impact on OS (HR = 1.8, 95% CI: 0.7-4.7, p = 0.267 and 1.4, 95% CI: 0.7-3.0, p = 0.293) while the presence of *TP53* muts (n = 41) was associated with shorter OS (11.4 m, 95% CI: 7.3-15.5; HR = 2.2, 95% CI: 1.2-4.2, p = 0.009). **Conclusions:** NGS performed in plasma might be used to detect predictive markers. *TP53* muts in plasma at baseline had prognostic value, while *STK11/KRAS* muts were associated with worse outcome to ICIs. Research Sponsor: None.

3047 Poster Session (Board #111), Fri, 8:00 AM-11:00 AM

Changes in lymphocyte/monocyte ratio, prognostic marker to predict overall survival in patients with advanced cancer treated with immune checkpoint inhibitor. *First Author: Sandip H. Patel, The Ohio State University Comprehensive Cancer Center, Department of Internal Medicine, Division of Medical Oncology, Columbus, OH*

Background: Immunosuppressive factors within the tumor microenvironment (TME) pose a barrier to response to treatment with immune checkpoint inhibitors (ICI). Monocytes alter the TME to promote cancer progression through local immune suppression and angiogenesis. Peripheral blood lymphocyte-to-monocyte ratio (LMR) may reflect the interaction between host immunity, represented by lymphocytes, and the tumor microenvironment, represented by monocytes. A low LMR in the peripheral blood may serve as a surrogate biomarker and has been associated with poor prognosis in various cancers; however, its role has not been well defined in the era of treatment with ICI. **Methods:** We retrospectively evaluated 1034 patients with advanced cancer treated with ICI from 2011 to 2017. We calculated LMR as ratio of absolute lymphocyte/monocyte counts at baseline and median of 21 days after first cycle of ICI (on-treatment LMR) and considered low if < 2. Overall survival (OS) was calculated from the initiation of ICI to date of death or censored at last follow-up. Median OS with 95% confidence intervals (CI) was estimated using the Kaplan-Meier method. Log rank test was used for group comparison. **Results:** 536 pts (52%) with LMR $<$ 2 at baseline had shorted median OS compared to 498 (48%) with LMR$\geq$2 (median OS 8.4 months vs 17.8 months, $p < 0.001$). Of 1034 pts with baseline LMR, 837 had follow up LMR evaluable. In patients with baseline and on-treatment LMR, those with baseline LMR < 2, who had on treatment LMR $\geq$2, had OS of 16.8 months (95% CI 10.3-23.5) compared to median OS 8.0 months (95% CI 6-9.4) for patients with on treatment LMR < 2 after first cycle of ICI, $p < 0.001$. Patients with baseline LMR$\geq$2, who had on treatment LMR $\geq$ 2, had median OS of 23 months (95% CI 19.7-28.9), but median OS was 9.4 months (95% CI 7.1-11.1) for patients with on-treatment LMR < 2 after first cycle of ICI, $p < 0.001$. **Conclusions:** We observed a statistically significant association between not only baseline LMR but also change in LMR from baseline after first cycle of ICI and overall survival in cancer patients treated with ICI. The role of LMR at baseline and on-treatment LMR should be evaluated in further studies incorporating known additional prognostic factors for ICI therapy. Research Sponsor: None.

LMR ratio (Baseline)	LMR ratio (After first cycle of Immunotherapy)	Number of Patients (%)	Median Overall Survival (Month) and 95% CI	p value
< 2		536 (52%)	8.7 (7.4-9.9)	< 0.001
	< 2	341	8 (6-9.4)	<
	≥2	90	16.8 (10.3-23.5)	0.001
≥2		498 (48%)	17.8 (15.7-21.6)	
	< 2	108	9.4 (7.1-11.1)	<
	≥2	298	23 (19.7-28.9)	0.001

3048 Poster Session (Board #112), Fri, 8:00 AM-11:00 AM

Neutrophil-lymphocyte score: A novel prognostic scoring system that utilized the dynamic change of neutrophil, lymphocyte, and albumin and its comparison to other indices. *First Author: Songzhu Zhao, Center for Biostatistics, The Ohio State University, Columbus, OH*

Background: Indications for immune checkpoint inhibitor (ICI) in cancer care are expanding rapidly. There is increasing need for accurate decision tool to better guide treatment. We have constructed a new prognostic scoring system, neutrophil-lymphocyte score (NRS), based on the nonlinear dynamic change of neutrophil to lymphocyte ratio (NLR) in relation to survival over the first cycle of ICI treatment. We compared this novel system to existing indices such as NLR, lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), Advanced Lung Cancer Inflammation Index (ALI), and Systemic Immune-inflammation Index (SII). **Methods:** This is a retrospective analysis of 837 patients at Ohio State University from 2011-18. Neutrophil (ANC), lymphocyte (ALC), platelet (plt), monocyte (AMC), albumin (alb), and body mass index (BMI) were collected at baseline. Repeat labs were collected at cycle 2. NLR = ANC/ALC, ALI = BMI x alb / NLR, LMR = ALC/AMC, SII = platelet x NLR, PLR = plt/ALC. NLR Ratio = baseline NLR / repeat NLR. Based on the association between NLR and the overall survival, we assigned 1 point (p) for baseline NLR < 0.7, 6p for 0.7 to < 2, 5p for 2 to < 3, 4 p for 3 to < 4, 3 for 4 to 5, 2p for 5 to < 9, and 1p for $\geq$9. We also assigned 1p for NLR ratio < 0.6, 2p for 0.6 to < 0.8, 3p for 0.8 to < 1.2, 5p for 1.25 to < 1.4, 3p for 1.4 to < 1.6, and 2p for $\geq$1.6. NLS = sum of these 2 scores . NLS_A = NLS*alb. Time-dependent receiver operator characteristic (ROC) curves with integrated time-dependent area under the curve (TD AUC) values were used to evaluate the predictive accuracy of each index for survival. **Results:** For baseline and repeat values, all indices were statistically significant ($P < 0.001$) in predicting survival. Baseline integrated TD AUC were: ALI 0.704, NLR 0.692, SII 0.663, LMR 0.645, and PLR 0.612. All of the repeat indices at cycle 2 had higher prognostic value than their baseline counterparts. Integrated TD AUC for indices at cycle 2 were: ALI 0.740 (with baseline BMI), NLR 0.729, SII 0.694, LMR 0.671, and PLR 0.652. NLS_A was a composite score based on the dynamic change of NLR from cycle 1 to 2 and the treatment alb with integrated TD-AUC at 0.754. **Conclusions:** Indices constructed from ANC, ALC, AMC, Plt, alb, and BMI can be obtained inexpensively and provide great prognostic value for pts on ICI. We have constructed a novel scoring system (NLS_A) and demonstrated its improvement over the current prognostic indices. Studies with a larger cohort are needed to further improve and validate this system. Research Sponsor: Research support provided by the REDCap project and The Ohio State University Center for Clinical and Translational Science grant support (National Center for Advancing Translational Sciences, Grant UL1TR002733). Dr. Owen is a Paul Calabresi Scholar suppo.

3049 Poster Session (Board #113), Fri, 8:00 AM-11:00 AM

Clinical value of noninvasive biomarkers reflecting a collagen-rich stroma in metastatic melanoma patients treated with anti-PD1 therapy. *First Author: Christina Jensen, Biomarkers & Research, Nordic Bioscience, Herlev, Denmark*

Background: Poor response to anti-PD1/PD-L1 remains a clinical challenge in a subgroup of patients with metastatic melanoma. Recent evidence strongly suggests that these poor responses are associated with TGF-β signaling and CD8+ T-cell excluded tumors characterized by a collagen-rich peritumoral stroma that blocks the interaction between T cells and tumor cells. In the pursuit of identifying non-invasive biomarkers associated with a T-cell excluded phenotype and predict resistance/response to immune checkpoint inhibitor therapy, we evaluated the association between blood-based biomarkers measuring type III collagen formation and cross-linking and survival outcomes in metastatic melanoma patients treated with anti-PD1 therapy. **Methods:** 107 patients with metastatic melanoma who started anti-PD1 monotherapy between May 2016 – March 2019 entered in a prospective real-life study (nivolumab n = 62, pembrolizumab n = 45). Type III collagen formation (PRO-C3) and type III collagen formation and cross-linking (PC3X) were measured with ELISAs in pre-treatment serum. Biomarker levels were associated to Disease Control Rate (according to RECIST v.1.1) by Mann-Whitney test and correlated to survival outcomes by Kaplan-Meier and Cox regression analyses. **Results:** PRO-C3 was significantly elevated in patients with progressive disease compared to the combined group of patients with complete response, partial response and stable disease (p = 0.046). High PRO-C3 and PC3X ($> 75^{th}$ percentile) prior to treatment were significantly associated with poor overall survival (PRO-C3: HR = 2.4, p = 0.008; PC3X: HR = 2.2, p = 0.019) and progression free survival (PRO-C3: HR = 1.91, p = 0.016; PC3X: HR = 1.94, p = 0.013). The median overall survival was 417 and 511 days in biomarker high patients compared to 1269 and 1269 days in biomarker low patients, for PRO-C3 and PC3X, respectively. **Conclusions:** Biomarkers quantified in a pre-treatment liquid biopsy reflecting excessive collagen formation and cross-linking were associated with poor response and survival outcomes in metastatic melanoma patients treated with anti-PD1 therapy. This supports an association between collagen formation and resistance to anti-PD1 therapy. Furthermore, if validated, these non-invasive collagen biomarkers may have potential for guiding patient stratification for immune checkpoint inhibitor therapy and combination therapies. Clinical trial information: NTR7015. Research Sponsor: The Danish Research Foundation, Erasmus Medical Center.

3050 Poster Session (Board #114), Fri, 8:00 AM-11:00 AM

TCR clonality and Treg frequency as predictors of outcome in stage III NSCLC treated with durvalumab. *First Author: Sally CM Lau, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: Novel blood-based biomarkers evaluating T-cell receptor (TCR) clonality as well as the frequency/activation of immune populations hold significant potential for predicting response and elucidating the biology of anti-tumor immunity in stage 3 NSCLC treated with durvalumab. In this study, we sought to characterize clinical and immunologic predictors of durable response to therapy with a specific focus on TCR clonality and peripheral immune populations. **Methods:** Stage 3 NSCLC patients undergoing chemoradiation (CRT) and durvalumab were prospectively recruited and underwent baseline and serial blood collections. TCR repertoire analysis was performed on cfDNA using hybrid-capture TCR sequencing and TCR diversity estimated using Shannon's entropy index. Viably preserved peripheral blood mononuclear cells (PBMC) were analyzed by high-dimensional flow cytometry using validated panels to evaluate T/B/NK-cell, Treg and myeloid populations. Correlations between cell populations were examined using linear and cox regression. **Results:** 134 stage 3 NSCLC patients who received durvalumab had a median PFS was 15.4 months, with worse PFS in patients with PD-L1 1-49% (HR 2.4, p = 0.03) and PD-L1 $<$ 1% (HR 2.6, p = 0.03). Smoking and *EGFR/ALK* mutations were not predictors of PFS. Immune profiling was performed in a pilot of 19 patients. Baseline TCR diversity did not associate with clinical factors or outcome. However, lack of clonal expansion after CRT indicated by a higher Shannon's index was significantly associated with increased frequency of Tregs after durvalumab ($p < 0.05$). In turn, this elevation in Tregs was associated with significantly reduced PFS in *EGFR/ALK* wt patients (p = 0.03) and a trend towards reduced PFS in the overall cohort (HR 5.2, p = 0.1). **Conclusions:** Clonal expansion of T cells after CRT may influence the likelihood of an anti-tumor immune response following PD-L1 blockade in stage 3 NSCLC. Similarly, expansion of peripheral Treg populations is associated with increased likelihood of disease recurrence. Further characterization of TCR clonality, minimal residual disease and T cell subpopulations using serially collected blood is ongoing. Research Sponsor: This study is performed under the auspice of the LIBERATE study, which is an institutional liquid biopsy program at the University Health Network supported by the BMO Financial Group Chair in Precision Cancer Genomics (Chair held by Dr. Lillian Siu), Ontario Institute of Cancer Research, Tumor Genomics Laboratory Grant.

3051 Poster Session (Board #115), Fri, 8:00 AM-11:00 AM

Sequential monitoring of circulating stromal cells from blood is predictive of progression in NSCLC patients undergoing anti-PD-L1 therapy after definitive chemoradiation therapy. *First Author: Daniel Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Cancer Associated Macrophage-Like cells (CAMLs) are a recently described circulating stromal cell common in the peripheral blood of patients with solid tumors. In non-small cell lung carcinoma (NSCLC), patients with CAMLs ≥50μm after completion of chemoradiation therapy (CRT) have been shown to have worse progression free survival (PFS). However, with the recent addition of anti-PD-L1 therapies in conjunction with CRT as standard of care, it has never yet to be evaluated whether CAMLs remain predictive for monitoring progression in NSCLC patients post anti-PD-L1 therapy. **Methods:** A 2 year single blind prospective study was undertaken to test the relationship of ≥50μm CAMLs to PFS based on imaging in lung patients before and after induction of CRT and PD-L1. We recruited 104 patients with pathologically confirmed unresectable NSCLC Stage II (n = 14), Stage III (n = 83), Stage IV (n = 3), and locally recurrent disease (n = 4). Baseline (BL) blood samples were taken prior to start of therapy. A second time point blood sample (T1) was taken at the end of radiotherapy (~40 days). A third time blood sample (T2) was taken after induction of anti-PD-L1 therapy (e.g. Imfinizi, Keytruda, etc.). Blood was filtered by CellSieve filtration and CAMLs were quantified. Analysis by CAML size of $<$ 49 μm or ≥50 μm was used to evaluate PFS hazard ratios (HRs) by censored univariate & multivariate analysis. **Results:** CAMLs were found in 87% of samples averaging 2.9 CAMLs/7.5mL sample. At BL, CAMLs ≥50 μm had similar PFS to patients with $<$ 50 μm CAMLs (HR = 1.1 95%CI 0.6-1.95 p = 0.8661). However, after CRT (T1), patients with CAML size ≥50 μm had worse PFS (HR = 3.2, 95%CI 1.8-5.8 p = 0.0002). After induction of anti-PD-L1 therapy (T2), patients with ≥50 μm CAMLs also had worse PFS (HR = 2.8 95%CI 1.5-5.4 p = 0.0037). CAML size at BL was not accurate at predicting progression within 24 months; however ≥50 μm CAMLs after CRT or after 1 cycle of anti-PDL1 therapy was 71% accurate at predicting progression of disease. **Conclusions:** Our data suggests that in NSCLC, ≥50 μm CAMLs after completion of CRT or appearing after induction of anti-PD-L1 therapy appears to predict progressive disease. If validated, additional studies are needed to determine if CAMLs can serve as a significantly prognostic blood based marker for predicting survival in NSCLC patients early in the treatment regime. Research Sponsor: U.S. National Institutes of Health.

3052 Poster Session (Board #116), Fri, 8:00 AM-11:00 AM

Tumor methylation patterns to measure tumor fraction in cell-free DNA. *First Author: Colin Melton, GRAIL, Inc, Menlo Park, CA*

Background: Cell-free DNA (cfDNA) tumor fraction (TF), the proportion of tumor molecules in a cfDNA sample, is a direct measurement of signal for cfDNA cancer applications. The Circulating Cell-free Genome Atlas study (CCGA; NCT02889978) is a prospective, multi-center, observational, case-control study designed to support development of a methylation-based, multi-cancer detection test in which a classifier is trained to distinguish cancer from non-cancer. Here we leveraged CCGA data to examine the relationship between cfDNA containing tumor DNA methylation patterns, TF, and cancer classification performance. **Methods:** The CCGA classifier was trained on whole-genome bisulfite sequencing (WGBS) and targeted methylation (TM) sequencing data to detect cancer versus non-cancer. 822 samples had biopsy WGBS performed; of those, 231 also had cfDNA targeted methylation (TM) and cfDNA whole-genome sequencing (WGS). Biopsy WGBS identified somatic single nucleotide variants (SNV) and methylation variants (MV; defined as methylation patterns in sequenced DNA fragments observed commonly in biopsy but rarely [$<$ 1/10,000] in the cfDNA of non-cancer controls [n = 898]). Observed tumor fragment counts (SNV in WGS; MV in TM), were modeled as a Poisson process with rate dependent on TF. TF and classifier limits of detection (LOD) were each assessed using Bayesian logistic regression. **Results:** Across biopsy samples, a median of 2,635 MV was distributed across the genome, with a median of 86.8% shared with ≥1 participant, and a median of 69.3% targeted by the TM assay. TF LOD from MV was 0.00050 (95% credible interval [CI]: 0.00041 - 0.00061); MV and SNV estimates were concordant (Spearman's Rho: 0.820). MV TF estimates explained classifier performance (Spearman's Rho: 0.856) and allowed determination of the classifier LOD (0.00082 [95% CI: 0.00057 - 0.00115]). **Conclusions:** These data demonstrate the existence of methylation patterns in tumor-derived cfDNA fragments that are rarely found in individuals without cancer; their abundance directly measured TF, and was a major factor influencing classification performance. Finally, the low classifier LOD (~0.1%) motivates further clinical development of a methylation-based assay for cancer detection. Clinical trial information: NCT02889978. Research Sponsor: GRAIL.

3053 Poster Session (Board #117), Fri, 8:00 AM-11:00 AM

Rechallenging with immune checkpoint inhibition after a treatment-limiting immune-related adverse event. *First Author: Richard Lee O'Neal, University of Kentucky, Markey Cancer Center, Greenville, KY*

Background: Immune checkpoint inhibition (ICI) with cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), or programmed death ligand-1 (PD-L1) blockade can be associated with the development of immune related adverse events (irAE), many of which can be treatment-limiting. Due to an absence of randomized controlled trials, the current approach in regards to ICI discontinuation versus rechallenging remains controversial. **Methods:** We assessed all patients who had received ICI at a single academic institution from 5/2015 to 1/2019, identifying those who had delays in their treatment. Retrospective chart review was performed to determine type of ICI, type and grade of irAE, treatment of irAE, and recurrence and grades of irAE if ICI was resumed, as well as to assess overall survival (OS). **Results:** 562 patients received ICI (lung cancer [232, 41%], melanoma [66, 12%], kidney cancer [43, 8%], bladder cancer [27, 5%], and other cancers [194, 34.5%]) from 5/2015 – 1/2019. Of these, 121 (22%) had a treatment-limiting irAE (most commonly dermatitis [24%], colitis [17%], pneumonitis [14%], and hepatitis [12%]). Of the patients who had ICI held, 80/121 (66%) were eventually rechallenged, while 41/121 (34%) discontinued permanently. When rechallenged with ICI, 47/80 (59%) had no further treatment-limiting irAEs, 16/80 (20%) had a recurrence of the same irAE, and 17/80 (21%) developed a different irAE. Of those who were rechallenged, only 17/80 (21%) ultimately had to discontinue because of a second irAE. At a median follow up time of 12.1 months, median OS was not reached in those patients who experienced a treatment limiting irAE and was 8.1 months in those who did not (hazard ratio [HR] for death, 0.33; 95% CI 0.23 – 0.48; $p < 0.001$). At 12 months from initiation of ICI, 77.0% of patients who had a treatment-limiting irAE were alive, compared to 39.6% of those who did not have an event. Restarting ICI after a treatment-limiting irAE was not associated with a change in OS (HR 0.66 [95% CI 0.27 – 1.66], p = 0.38). **Conclusions:** Patients who discontinued ICI secondary to irAEs had relatively low rates of recurrent toxicity when rechallenged with treatment. These patients were just as likely to develop a new toxicity as a recurrence of the original irAE, and relatively few had to discontinue permanently. Development of a treatment-limiting irAE was associated with improved OS compared to those who did not. This study suggests that rechallenging with ICI may be safe in selected patients, though this did not have an impact on OS. Research Sponsor: None.

3054 Poster Session (Board #118), Fri, 8:00 AM-11:00 AM

An open-label, phase I trial of BI 754091 alone and in combination with BI 754111 in Asian patients (pts) with advanced solid tumors. *First Author: Yoon-Koo Kang, Asan Medical Center, Seoul, South Korea*

Background: Dual blockade of immune checkpoint molecules, PD-1 and LAG-3, may enhance the anti-tumor response versus PD-1 blockade alone. This Phase I trial investigated BI 754091, an anti-PD-1 antibody, as monotherapy and in combination with BI 754111, an anti-LAG-3 antibody, in Asian pts with advanced solid tumors. **Methods:** This trial comprised 3 parts. Parts 1 and 2 (dose escalation) were in pts with unresectable/metastatic solid tumors. In Part 1, pts received BI 754091 240 mg intravenously (iv), every 3 weeks (q3w); in Part 2, pts received BI 754091 240 mg in combination with BI 754111 (400 mg, 600 mg or 800 mg iv, q3w). Dose escalation was guided by a Bayesian logistic regression model, with overdose control. The primary endpoint in Parts 1 and 2 was maximum tolerated dose (MTD) of BI 754091 alone or in combination with BI 754111, based on dose-limiting toxicities (DLTs) in Cycle 1. In Part 3, BI 754091 240 mg plus BI 754111 600 mg q3w was assessed in 4 expansion cohorts. Cohorts A–C included pts with: A) gastric/esophagogastric junction cancer; B) esophageal cancer; C) hepatocellular cancer; all had received ≥1 line of prior systemic therapy and no prior anti-PD-(L)1 therapy. Cohort D included pts who had received prior anti-PD-(L)1 therapy for the tumor types in Cohorts A–C. The primary endpoint in Part 3 was objective response (confirmed complete response or partial response [PR] per RECIST 1.1). **Results:** In Part 1, 6 pts received BI 754091 240 mg. In Part 2, 9 pts received BI 754091 240 mg plus BI 754111 (400 mg/600 mg/800 mg; n = 3 per cohort). No DLTs were reported in Parts 1 and 2. In Part 3, 121 pts were treated (97 [80%] male, median age 61 years [range 23–80]); Cohorts A/B/C/D included 33/33/20/35 pts. All-grade adverse events (AEs) and treatment-related AEs (TRAEs) were experienced by 96 (79%) and 47 (39%) pts, respectively. The most commonly reported AEs (all/≥G3) were pyrexia (21%/0%), decreased appetite (17%/2%), anemia (11%/6%), and nausea (9%/0%). 36 (30%) pts reported immune-related AEs, most commonly hypothyroidism, in 7 (6%) pts. Confirmed PR was observed in 6 pts (5%; Cohort A/B, n = 4/2) and 35 (29%) pts had stable disease (Cohort A/B/C/D, n = 9/11/10/5). **Conclusions:** MTD was not reached for BI 754091 monotherapy or for BI 754091 in combination with BI 754111. The recommended dose for the combination was determined as BI 754091 240 mg plus BI 754111 600 mg q3w. Treatment was well tolerated and consistent with that observed in the global trial. Preliminary anti-tumor activity was seen. Clinical trial information: NCT03433898. Research Sponsor: Boehringer Ingelheim.

3055 Poster Session (Board #119), Fri, 8:00 AM-11:00 AM

Evolving development of PD-1 therapy: Cetrelimab (JNJ-63723283) from monotherapy to combination with erdafitinib. *First Author: Victor Moreno, START Madrid-FJD, Fundación Jiménez Díaz University Hospital, Madrid, Spain*

Background: Cetrelimab (CET) is an investigational checkpoint inhibitor (CI). In part 1 of a first-in-human (FIH) trial (LUC1001; NCT02908906), pts with advanced solid tumors with ≥1 prior treatment received CET 80–800 mg Q2W or 480 mg Q4W. Response rates and safety profiles were similar to other CIs. Based on preclinical and clinical data, a phase 1/2 study (NORSE; NCT03473743) of CET + erdafitinib (ERD) in metastatic urothelial carcinoma (mUC) + FGFR alterations (alt) was initiated and is ongoing. **Methods:** In LUC1001 Part 2, pts with nonsmall cell lung cancer (NSCLC), melanoma (MEL), or MSI-H/dMMR colorectal cancer (CRC) received CET IV 240 q2w. Overall response rates (ORR = % complete response + partial response [PR] confirmed) were assessed as per RECIST v1.1. Adverse events (AEs) were assessed for all patients receiving CET IV 240 q2w in parts 1 and 2. **Results:** As of July 1, 2019, 122 pts with NSCLC (n=30); MEL (n=50); or CRC (n= 42) had been treated in Part 2. Median age ranged from 58 to 64 yrs (overall range, 23–86 yrs). Duration of treatment was 8.1 mos (range, 0.0-24.7) for NSCLC; 5.5 mos (range, 0.0-25.0) for MEL; and for 3.0 mos (0.0-16.1) for CRC. ORR was 37% in NSCLC; 53% in PD-L1+ NSCLC (≥50% by IHC), 28% in MEL; 32% in non-uveal MEL, 14% in CRC and 24% in centrally confirmed MSI-high CRC. In all CET IV 240 q2w treated pts in the FIH study (N= 162), treatment-related grade ≥3 and serious AEs were reported in 15% and 12% of pts, respectively. All grade and grade ≥3 immune-related (ir) AEs were reported in 41% and 8% of pts, respectively Most common ir AE: hypothyroidism (8%), asthenia (6%), diarrhea (4%), rash (4%), hyperthyroidism (4%), dyspnea (3%), pruritis (3%) and pneumonitis (3%). There was 1 treatment-related death due to myasthenia gravis. In the phase 1 combination study (NORSE), pts with mUC + FGFR alt (n=17) received fixed-dose CET IV 240 q2w + ERD 6mg, 8 mg or 8mg + up titration (UpT) to 9 mg to establish the RP2D for the combination as CET + ERD 8mg + UpT. In the RP2D group (n=10), 60% had treatment-related grade ≥3 AEs. ORR (all confirmed PR) was 50% in the all treated response-evaluable group (n=16). **Conclusions:** CET is a CI with efficacy and safety profiles in advanced solid tumors similar to approved CIs. In NORSE phase 1, CET+ERD demonstrated antitumor activity in mUC with an acceptable safety profile. NORSE phase 2 is evaluating this combination as first-line therapy in pts with mUC with FGFR alt. References: Rutkowski, et al J Clin Oncol.2019; 37 (8 suppl): 31-31. Moreno, et al. ASCO-GU Genitourinary Cancers Symposium. February 13-15, 2020. San Francisco, CA. Clinical trial information: NCT02908906 and NCT03473743. Research Sponsor: Janssen Research and Development.

3056 Poster Session (Board #120), Fri, 8:00 AM-11:00 AM

A phase I study of ALX148, a CD47 blocker, in combination with standard anticancer antibodies and chemotherapy regimens in patients with advanced malignancy. *First Author: Laura Quan Man Chow, University of Washington, Seattle, WA*

Background: CD47 is a myeloid checkpoint upregulated by tumor cells to evade the host immune response. ALX148 (A) is a fusion protein comprised of a high affinity CD47 blocker linked to an inactive immunoglobulin Fc region. ALX148 enhances innate and adaptive immune responses against cancer and has previously been shown to be well tolerated in combination with the checkpoint inhibitor (CPI), pembrolizumab (P), and trastuzumab (T) in a range of solid tumors (ASCO 2019 #2514). ALX148 safety and activity in combination with T or P and standard chemotherapy regimens are reported in patients (pts) including head and neck squamous cell cancer (HNSCC) and HER2 positive gastric/gastroesophageal cancer (GC). **Methods:** Pts with advanced malignancy were administered AP or AT. Patients with ≥2L HNSCC progressed on platinum therapy received AP, while those with untreated advanced disease received AP+5FU (FU)+platinum. Pts with ≥2L GC progressed on T+FU+platinum received AT +/- ramucirumab (ram)+paclitaxel (pac). Safety, response, pharmacokinetic and pharmacodynamic (PD) markers were assessed. Data are reported as of 21, Jan. 2020. **Results:** Patients received AP (n=52); AP+FU+platinum (n=1); AT (n=30); or AT+ram+pac (n=3) as of data cutoff. Eighty-two pts experienced any adverse event (AE). Fifty-seven pts administered AP or AT regimens reported mostly low grade ALX148 treatment related (TR) AEs, the most common being fatigue (18%), AST increase (11%), platelets decreased (10%), ALT increase (8.5%), anemia (8.5%), and pruritus (8.5%). Pts receiving AP+FU+platinum or AT+ram+pac reported no TRAEs as of data cutoff. Anticancer activity was observed in response-evaluable pts. AP: HNSCC CPI-naïve (n=10) 40% ORR, mPFS 4.6 [95% CI:0.5; 7.5], mOS not reached with 14.4m median follow-up; AP: HNSCC CPI-experienced (n=10) 0% ORR, mPFS 2.0 [95% CI:0.9;3.6], mOS 7.4 [95% CI:3.1;NC]; and AT: GC (n=20) 20% ORR, mPFS 2.2 [95% CI:1.9;5.4], mOS 8.1 [95% CI:3.4;12.8]. Full peripheral CD47 target occupancy and increased infiltrating immune cells in tumor biopsies were seen. Exploratory analysis of biomarkers associated with response is ongoing. **Conclusions:** Initial data suggests ALX148 demonstrates excellent tolerability in combination with anti cancer antibodies and standard chemotherapy. Clinical activity in pts with advanced CPI naïve HNSCC (including PD-L1 negative) and GC compares favorably with historic controls. Final data from AP and AT cohorts and initial data from chemotherapy combination cohorts will be presented. Clinical trial information: NCT03013218. Research Sponsor: ALX Oncology Inc.

3058 Poster Session (Board #122), Fri, 8:00 AM-11:00 AM

Anti-CTLA-4 probody BMS-986249 alone or in combination with nivolumab in patients with advanced cancers: Initial phase I results. *First Author: Martin Gutierrez, Hackensack University Medical Center, Hackensack, NJ*

Background: Blockade of the CTLA-4 pathway with ipilimumab (IPI) ± nivolumab (NIVO; anti–PD-1) is an effective treatment for a variety of cancers. To optimize the risk-benefit profile of CTLA-4–directed therapy, a Probody therapeutic technology platform (Pb-Tx, CytomX Therapeutics) was used to generate BMS-986249, a peptide-masked version of IPI that is unmasked by tumor-associated proteases. Pb-Tx may localize CTLA-4 activity to the tumor, minimize systemic toxicity, and allow for higher doses of anti–CTLA-4 ± anti-PD-1. In preclinical studies, BMS-986249, given at similar doses, showed comparable intratumoral and reduced peripheral pharmacodynamic activity relative to IPI (Engelhardt, AACR 2020). Here, we present the initial results of the first-in-human phase 1/2 study of BMS-986249 ± NIVO in pts with advanced (adv) cancers (NCT03369223). **Methods:** During dose escalation, pts received BMS-986249 at or above the approved doses of the parent molecule using a Q4W or Q8W dosing schedule as monotherapy (240–2400 mg Q4W or 1600 mg Q8W; ≈ 3–30 mg/kg vs approved 3 mg/kg Q3W IPI) or in combination (240–1200 mg Q4W or 800 mg Q8W) + NIVO 480 mg Q4W. Safety and pharmacokinetics (PK) were evaluated. Efficacy is being assessed in the dose-expansion phase. **Results:** As of December 7, 2019, 82 anti–CTLA-4 naive pts with various adv cancers received BMS-986249 ± NIVO (mono, n = 39; combo, n = 43). Median age 60 (25–78) y; 95% pts had prior systemic therapy. TRAEs occurred in 59% of pts (Gr 3/4, 23%) with mono and 74% of pts (Gr 3/4, 30%) with combo. Diarrhea was the most common any-Gr TRAE (mono, 23%; combo, 21%) and Gr 3/4 TRAE (mono, 15%; combo, 7%). Rates of Gr 3/4 TRAEs increased with higher doses of BMS-986249 but were substantially reduced with Q8W schedule (eg, 800 mg Q4W, 18%; 1600 mg Q4W, 60%; 1600 mg Q8W, 9%). Most TRAEs resolved, no Gr 5 TRAEs occurred. The peptide-masked intact probody accounted for most (73%) of the systemic BMS-986249-related species; elimination of the probody indicated involvement of both catabolism and cleavage processes. **Conclusions:** BMS-986249 ± NIVO displayed a clinically manageable safety profile, allowing assessment of comparably higher BMS-986249 dose intensity (240-1200 mg; ≈ 3-15 mg/kg) + NIVO (480 mg Q4W, full dose) than that tested with IPI + NIVO. The types of TRAEs were consistent with CTLA-4 blockade, and the overall data align with the proposed Pb-Tx mechanism of action. The preclinical and clinical data support the ongoing randomized BMS-986249 + NIVO expansion in pts with adv melanoma, in addition to other adv tumors. Clinical trial information: NCT03369223. Research Sponsor: Bristol-Myers Squibb.

3059 Poster Session (Board #123), Fri, 8:00 AM-11:00 AM

Phase Ib clinical study of CBP501, cisplatin, and nivolumab administered every three weeks in patients with advanced refractory tumors: Efficacy in dose-escalation and expansion cohorts. *First Author: Marc Ryan Matrana, Ochsner Cancer Institute, New Orleans, LA*

Background: CBP501 is a 12-amino acid G2 checkpoint abrogator and calmodulin-modulating peptide that increases platinum influx into tumor cells and induces tumor immunogenic cell death. CBP501 also suppresses platinum-induced release of cytokines by macrophages, lowers cancer stem cell populations, and reduces migration, invasion, and epithelial-mesenchymal transition of tumor cells. We report safety and efficacy outcomes from dose-escalation and expansion cohorts of a Phase Ib study of CBP501 combined with cisplatin and nivolumab (NCT03113188). **Methods:** An open-label Phase I trial was conducted using a 3+3 design: CBP501 and cisplatin were dosed simultaneously by 1h infusion Q3W at 4 different combined dose levels (CBP501: 16 or 25 mg/m^2; cisplatin: 60 or 75 mg/m^2) in the dose-escalation cohort. Nivolumab (240 mg) was dosed on the same day as a 1h infusion following CBP501/cisplatin. CBP501 and cisplatin were fixed at 25 and 60 mg/m^2, respectively, in the expansion cohort. Eligible patients had pathologically confirmed, locally advanced or metastatic solid tumors, age ≥18 years, ECOG PS 0-1, life expectancy > 3 months. The dose-expansion cohort had pretreated metastatic exocrine pancreatic cancer or microsatellite stable colorectal cancer (CRC). Scans were performed every 6 weeks while on study, then every 3 months. **Results:** The most common related adverse events (AEs) were infusion-related reaction (rash, itching, hives; n = 32/37 [Gr 1, n = 4; Gr 2, n = 28]; 86%) and anemia (n = 19/37 [Gr 1/2, n = 10; Gr 3, n = 9]; 51%). There were no additional safety signals other than those known for each agent. At January 9, 2020 (interim analysis), efficacy was evaluable in 17/19 patients in the dose-escalation cohort. Unconfirmed partial response was seen in 18% (3/17; 1 pancreatic, 1 colorectal, 1 cholangiocarcinoma), with > 3 months stable disease (SD) in 41% (7/17), disease control in 41% (7/17), and > 8 months overall survival (OS) in 53% (9/17). In the expansion cohort, efficacy was evaluable in 8/13 patients with pancreatic cancer: > 4 months SD was 50% (4/8), median progression-free survival 4.2 months, and median OS 5.9 months (6/8 ≥3rd line). The CRC cohort median OS for all CRC patients (n = 10) including the dose-escalation cohort (n = 5) was 17.5 months (10/10 ≥3rd line). **Conclusions:** The triple-drug combination is reasonably tolerable with preliminary signs of efficacy in refractory solid tumors, including those in which cisplatin and nivolumab have limited single-agent activity. Clinical trial information: NCT03113188. Research Sponsor: CanBas Co., Ltd.

3060 Poster Session (Board #124), Fri, 8:00 AM-11:00 AM

Characteristics and outcomes of real-world (RW) patients (pts) with microsatellite instability-high (MSI-H) solid tumors treated with pembrolizumab monotherapy (P) after FDA approval. *First Author: Tamara Snow, Flatiron Health, New York, NY*

Background: The first tumor-agnostic, biomarker-based FDA approval in oncology was P in May 2017 for pts with MSI-H or mismatch repair (MMR) deficient tumors. 1 yr overall survival (OS) was >70% for colorectal cancer (CRC) and >60% for non-CRC in P-treated MSI-H clinical trial pts (Le 2019; Marabelle 2019). As tumor-agnostic therapies are a new paradigm, it is important to assess their use and effectiveness in routine clinical practice. We examined characteristics and outcomes of RW pts with MSI-H solid tumors who received P after May 2017. **Methods:** Pts with MSI-H solid tumors who received P after May 2017 were selected from the Flatiron Health-Foundation Medicine (FH-FMI) clinico-genomic database, a nationwide de-identified EHR-derived database linked to comprehensive genomic profiling (CGP) data. Pts with 2+ visits in the FH network from 01/2011-09/2019 with CGP prior to P use were included. Clinical characteristics were assessed at first P use. Time to treatment discontinuation (TTD) and OS from first P use were estimated with Kaplan-Meier analyses of all pts and the largest tumor types. **Results:** 33,395 pts had a solid tumor tested for MSI by CGP, of which 557 (1.7%) were MSI-H (median age 68 yrs; 34% male). 129 MSI-H pts across 33 tumor types received first P after May 2017. CRC (N=36) and Endometrial cancer (N=39) were most common. 52 pts (40%) had a concurrent MMR alteration (MLH1, MSH2, MSH6 or PMS2); median TMB was 32.2 mut/mb (IQR 20.9-47.5). Median number of therapies prior to P was 1; median time from CGP to first P use was 3 mos. Table shows OS and TTD. **Conclusions:** In this RW study, P use was observed across 33 MSI-H tumor types. Median OS exceeded 1 yr across all pts and in CRC, Endometrial, and Other cohorts. 1 yr OS rate was consistent with P trial outcomes. Further study should evaluate whether effectiveness differs across diseases, MSI testing method, or other genomic attributes to improve treatment selection. Research Sponsor: Flatiron health Inc.

OS and TTD in P-treated, pantumor MSI-H pts.

	N	Median TTD, mos [95% CI]	Median OS, mos [95% CI]	N at risk at 12-mos	12-mos OS, % [95% CI]
All Pts	129	5.5 [4.1-7.6]	NR [14.6-NR]	38	62.7 [53.3-73.7]
CRC	36	4.5 [2.8-9.2]	NR [12.9-NR]	9	71.8 [55.0-93.7]
Endometrial	39	6.2 [3.0-11.0]	NR [11.0-NR]	13	58.4 [42.9-79.5]
Other*	54	6.1 [2.8-8.2]	17.3 [9.9-NR]	16	60.3 [46.7-78.0]

*Tumors included (largest to smallest N): Gastric, Occult/Unknown Primary, Prostate, Esophageal/Gastroesophageal Junction, Breast, Hepatobiliary, Small Intestine, Non-Small Cell Lung, Pancreatic, Ovarian

3061 Poster Session (Board #125), Fri, 8:00 AM-11:00 AM

A first-in-human phase I study in patients with advanced and/or refractory solid malignancies to evaluate the safety of ATOR-1015, a CTLA-4 x OX40 bispecific antibody. *First Author: Jeffrey Yachnin, Karolinska Institutet, Stockholm, Sweden*

Background: ATOR-1015 is a human CTLA-4 x OX40 targeting IgG1 bispecific antibody developed to be a next generation CTLA-4 antibody with enhanced immune activation and tumor-directed activity for improved efficacy and reduced toxicity. **Methods:** The primary objective of the study is to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) in patients with advanced solid malignancies. Safety and tolerability of ATOR-1015 are assessed by adverse events (AEs), vital signs, ECG, laboratory evaluations and physical examinations. Secondary objectives include pharmacokinetics (PK), immunogenicity and clinical efficacy. Clinical efficacy is assessed using Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST). The study is designed with single patient cohorts for doses below 100 mg followed by a modified 3+3 design (NCT03782467). Intra-patient dose escalation is allowed. ATOR-1015 is administered intravenously every other week as a single agent until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. **Results:** From March 2019 to February 2020, 15 patients have been exposed to ATOR-1015. The median age of the patients is 52 years (range 40-72). The following cancer types have been included: colorectal cancer (n=8), uveal melanoma (n=2), pancreatic cancer (n=2), ovarian cancer (n=2), and cholangiocarcinoma (n=1). Patients received a median of 6 prior lines of therapy (range 3-16). Dose levels from 0.043 mg to 200 mg have been evaluated and declared safe. Dose escalation is ongoing, and 400 mg is under evaluation. The median time on study was 8 weeks (range 2.1-34.3). Four patients are on study and eleven patients have discontinued treatment. Reasons for discontinuation include clinical deterioration (n=7), death due to disease progression (n=2), confirmed disease progression (n=1) and investigator´s decision (n=1). Six of the 15 patients experienced drug-related AEs which were grade 2 or less. Infusion-related reactions (IRR) were reported in four patients. One of those four also had abdominal pain and mediastinal burning sensation. The IRR symptoms were predominantly rash. One patient had vitiligo, and one had rash. No dose-limiting toxicities have occurred. Preliminary PK data show dose-proportional kinetics up to 200 mg. **Conclusions:** The dosing of ATOR-1015 has been safe and well-tolerated up to 200 mg. Dose escalation continues and the current dose level under evaluation is 400 mg. Clinical trial information: NCT03782467. Research Sponsor: Alligator Bioscience AB.

3062 Poster Session (Board #126), Fri, 8:00 AM-11:00 AM

Phase Ia dose escalation of IBI318, a first-in-class bispecific anti-PD-1/PD-L1, in patients with advanced tumors. *First Author: Rui-hua Xu, Sun Yat-sen University Cancer Centre, Guangzhou, China*

Background: With the proven success of PD-1 and PD-L1 monoclonal antibodies, exploiting antibody based immune checkpoint strategies has potential to reduce disease burden and improve patient survival outcome. IBI318, as a first-in-class anti-PD-1/PD-L1 bispecific antibody, could provide more potent anti-tumor activity and more durable response. Here we report preliminary results from an ongoing phase 1a/1b study of IBI318 in advanced tumors. **Methods:** In the dose escalation of Phase 1a, patients with advanced and/or refractory solid tumors or hematological malignancies were enrolled to receive IBI318. Dose escalation was from 0.3 mg to 600 mg (8 cohorts) via an accelerated titration followed by a modified toxicity probability interval-2 design with a 28-day dose-limiting toxicity (DLT) observation period. Patients without DLT will receive IBI318 every two week (Q2W). Tumor assessments were performed every 6 weeks. **Results:** As of Jan 10, 2020, 15 pts who had failed at least one line of treatment had been enrolled (1 pt each in 0.3 mg, 1 mg, 3 mg and 10 mg; 3 pts in 30 mg; 3 pts in 100 mg, 3 pts in 300 mg and 2 pts in 600 mg) for dose escalation and received at least 1 dose of treatment. Median duration of treatment was 6.1 (range: 2.1-24.7) weeks. IBI318 had been well tolerated with no DLT from 0.3mg to 300mg group. 11 of 15 pts had treatment related AEs (TRAEs) and the most common (≥10%) TRAEs were pyrexia (20.0%, G1/2) and infusion-related reaction (20.0%, G1/2). 1 patient in 300 mg had an immune-related AE (G2 arthritis). No ≥G3 TRAE had been observed. 12 pts had at least one on-study tumor assessment. 3 of 9 pts receiving dose level ≥10mg had achieved partial response (1 confirmed, 1 pending confirmation and the other PD after the first PR scan). A total of 10 pts discontinued treatment due to disease progression (8) and AE (2, G4 lung infection and G4 upper gastrointestinal hemorrhage, both were not related to treatment). **Conclusions:** IBI318 has shown an acceptable safety profile. Preliminary efficacy results are promising in advanced cancer patients. The study is currently ongoing at dose level of 600 mg Q2W. Clinical trial information: NCT03875157. Research Sponsor: Innovent Biologics, Inc.

3063 Poster Session (Board #127), Fri, 8:00 AM-11:00 AM

Safety of BI 754111, an anti-LAG-3 monoclonal antibody (mAb), in combination with BI 754091, an anti-PD-1 mAb, in patients with advanced solid tumors. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: LAG-3, an immune checkpoint receptor involved in T-cell regulation, is frequently co-expressed with PD-1. LAG-3 and PD-1 signaling contributes to immune cell exhaustion and reduces the immune response to tumor cells. Dual inhibition of PD-1 and LAG-3 may reactivate the T-cell response better than blockade of either individual pathway. Here, we report combined safety data from 4 trials investigating BI 754111, an anti-LAG-3 mAb, in combination with BI 754091, an anti-PD-1 mAb, in patients with advanced solid tumors. **Methods:** Data from 2 phase I dose-escalation/expansion trials, 1 phase I imaging trial, and 1 phase II trial were included. Eligible patients had advanced and/or metastatic solid tumors with measurable disease and an Eastern Cooperative Oncology Group performance status ≤1. Patients received BI 754111 (intravenously [iv], 4–800 mg) in combination with BI 754091 (iv, 240 mg fixed dose) every 3 weeks (q3w). Patients remained on treatment until progressive disease or unacceptable toxicity. In each trial, safety was assessed by incidence and severity of adverse events (AEs), and graded according to Common Terminology Criteria for AEs, version 5. **Results:** Overall, 321 patients were treated with BI 754111 in combination with BI 754091 (200 [62%] male; median age, 63 years [range 18–88]). Median treatment exposure was 85 days (range 9–625). Of these patients, 282 (87.9%) had any AE (G≥3 in 99 [30.8%]). 285 patients received the 600 mg recommended phase II dose of BI 754111 plus BI 754091 240 mg q3w. Median treatment exposure in these patients was 74 days (range, 8–590). The table shows the 3 most common AEs and 4 most common immune-related AEs, and their frequency. 21 (7.4%) patients had AEs leading to study drug discontinuation, most commonly infusion-related reactions (IRRs) in 6 (2.1%) patients. Serious AEs (all-cause) occurred in 77 patients (27.0%), most commonly pleural effusion in 6 (2.1%) and deep vein thrombosis in 4 (1.4%) patients. 2 patients (0.7%) experienced an AE resulting in death (cardiac tamponade and acute kidney injury, both related to underlying diseases). **Conclusions:** The combination of BI 754111 and BI 754091 had a manageable safety profile, similar to other checkpoint inhibitors. Clinical trial information: NCT03156114, NCT03433898, NCT03697304, NCT03780725. Research Sponsor: Boehringer Ingelheim.

N (%)	All grades (N = 285)	Grade ≥3 (N = 285)
Any AEs	**247 (86.7)**	**88 (30.9)**
Fatigue	65 (22.8)	4 (1.4)
Pyrexia	53 (18.6)	1 (0.4)
Nausea	47 (16.5)	2 (0.7)
Any immune-related AEs	**60 (21.1)**	**16 (5.6)**
IRRs	14 (4.9)	3 (1.1)
Hypothyroidism	9 (3.2)	0
Rash maculopapular	7 (2.5)	2 (0.7)
Hyperthyroidism	7 (2.5)	1 (0.4)

3064 Poster Session (Board #128), Fri, 8:00 AM-11:00 AM

Results of a first-in-human phase I study of SRF231, a fully human, high-affinity anti-CD47 antibody. *First Author: Amita Patnaik, START, San Antonio, TX*

Background: CD47 is a transmembrane protein that acts as a "Don't Eat Me" signal to evade immune recognition. It is overexpressed in multiple cancer subtypes and is associated with poor prognosis. SRF231 is an investigational, fully human, high-affinity CD47-targeting antibody that delivers an activating signal to myeloid cells and displays favorable preclinical characteristics regarding its receptor occupancy/tumor exposure/efficacy relationship. **Methods:** In a Phase 1 study, SRF231-101 (NCT03512340), patients with advanced solid and hematologic malignancies who had failed standard therapy were enrolled in dose escalation cohorts (accelerated single-patient followed by standard 3+3) to establish the preliminary safety of SRF231 as a monotherapy and identify a dose and schedule suitable for expansion. In addition to collection of safety data, clinical outcomes were evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and SRF231 pharmacokinetic (PK) and pharmacodynamic (receptor occupancy) analyses were performed. **Results:** As of January 11, 2020, a total of 46 patients were enrolled, 25 in every-3-week intravenous (IV) dosing schedules and 21 in weekly IV dosing schedules. Weekly dosing schedules also explored the use of a 1.0 mg/kg initiation dose. Other than one patient with recurrent follicular lymphoma, all patients had recurrent/refractory solid tumors. The most common treatment emergent adverse events across dosing schedules were low-grade fatigue (43%), headache (35%), and pyrexia (30%). On every-3-week dosing schedules, 2 dose-limiting toxicities (DLTs) were observed: Grade 3 febrile neutropenia and Grade 3 hemolysis, both at a 12.0 mg/kg dose level. On weekly dosing schedules, 3 DLTs were observed: Grade 4 thrombocytopenia (6.0 mg/kg), Grade 4 amylase and lipase increased (4.0 mg/kg with initiation dose), and Grade 3 fatigue (4.0 mg/kg). The maximum tolerated dose was 9.0 mg/kg on an every-3-week and 4.0 mg/kg on a weekly schedule. Receptor occupancy was maintained at > 90% throughout the dosing period with a 4.0 mg/kg weekly dose schedule. Out of 37 patients who were response evaluable by RECIST, there were no complete or partial responders, although prolonged stable disease has been observed. **Conclusions:** Preliminary data from a Phase 1 study of SRF231, an anti-CD47 antibody, demonstrate that SRF231 may be administered safely and doses of 4.0 mg/kg weekly maintain > 90% receptor occupancy throughout the dosing period. Updated safety data, clinical outcomes, and PK/pharmacodynamic data will be presented. Clinical trial information: NCT03512340. Research Sponsor: Surface Oncology, Inc. Cambridge, MA, USA.

3065 Poster Session (Board #129), Fri, 8:00 AM-11:00 AM

A phase Ib study of TQ-B2450 plus anlotinib in patients with advanced solid tumor. *First Author: Ying Cheng, Jilin Cancer Hospital, Changchun, China*

Background: Anlotinib, an antiangiogenic multi-target tyrosine kinase inhibitor, significantly improved clinical outcomes in solid tumors. TQ-B2450 is an engineered anti-programmed death-ligand 1 antibody. This onging phase 1b study aimed to assess the safety and effect of TQ-B2450 plus anlotinib in advanced solid tumors. **Methods:** This phase 1b study, which included a dose-escalating phase and an expansion phase, enrolled patients with advanced solid tumor who failed in or had no standard treatment between June 2019 and January 2020.Eligible patients were firstly assigned into sequential dose-escalating cohorts including 10mg and 12mg anlotinib plus TQ-B2450 following the conventional 3+3 design. If the starting dose of 10mg anlotinib led to ≥2 dose-limiting toxicities (DLTs), 8mg anlotinib would be administered. After the dose-escalating phase, eligible patients were enrolled into the expansion cohort. The primary outcomes were safety and objective response rate. **Results:** In the dose-escalating phase, three eligible patients received 10mg anlotinib plus TQ-B2450 had no DLTs in the first cycle, neither did three patients with 12mg anlotinib plus TQ-B2450. Then the expansion phase started, sixteen patients received 12mg anlotinib plus TQ-B2450. Finally, a total of 22 patients were included (6 small cell lung cancers [SCLC], 8 non-small cell lung cancers [NSCLC], 2 colorectal cancers, 2 breast cancers, 2 ovarian cancers, 1 thymic carcinoma and 1 cervical cancer). Ten ≥3 grade adverse events were observed (Table). Seventeen patients underwent at least once effect evaluation. One SCLC patient with 10mg anlotinib plus TQ-B2450 had confirmed partial responses (PR). Four patients with 12mg anlotinib plus TQ-B2450 had unconfirmed PR (2 SCLC and 2 NSCLC). And 9 patients had stable disease, 3 patients had progression disease. **Conclusions:** 12mg anlotinib plus TQ-B2450 showed an acceptable safety profile and promising response in advanced solid tumors. Clinical trial information: NCT03897283. Research Sponsor: None.

The ≥3 grade adverse events.

≥3 grade adverse events	10mg anlotinib plus TQ-B2450, n=3	12mg anlotinib plus TQ-B2450, n=19
Hypertriglyceridemia	1	4
Dyspnea	1	
Pericardial effusion	1	
Oropharyngeal and gingival pain		1
Decreased lymphocyte count	1	
Elevation of γ-glutamyltransferase	1	

3066 Poster Session (Board #130), Fri, 8:00 AM-11:00 AM

Assessing the effect of immunosuppressive agents for immune-related adverse event management on tumor response. *First Author: Pankti Reid, University of Chicago, Chicago, IL*

Background: High grade immune-related adverse events (irAEs) to cancer immune checkpoint inhibitors (ICI) require considerable immunosuppression (IS) with high-dose steroids and steroid-sparing IS (SSIS) for steroid-dependent cases. T lymphocyte-specific IS has generally been avoided or used with significant caution due to the fear that these agents may negatively impact ICI efficacy. We sought to determine whether T cell-specific IS agents, such as calcineurin inhibitors (CNIs), have an adverse effect on tumor control when compared to other immunomodulatory drugs (IMDs). **Methods:** We retrospectively analyzed clinical annotations of adult patients treated with ICIs for malignancy from 1/1/2000-12/31/2019, highlighting patients who were managed with SSIS, specifically those most commonly used for autoimmune disease therapy. Topical IS use was excluded. Patients were categorized as tumor responders or non-responders, and irAEs were graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Progression-free survival (PFS) was assessed via Kaplan-Meier curve. **Results:** 1331 unique individuals were prescribed ≥1 ICIs, with 526 prescribed systemic steroids (39.5%) and 90 (6.8%) patients prescribed SSIS agents, 25 patients with >1 SSIS: mycophenolate (39), methotrexate (26), leflunomide (5), azathioprine (3), rituximab (24), tocilizumab (3), infliximab (8), etanercept (1), adalimumab (1), golimumab (1) and CNIs (18): cyclosporine, tacrolimus. IMDs hydroxychloroquine (6) and sulfasalazine (5) were also prescribed. The objective response rate was 50.0% in the CNI group compared to 45.5% in the IMD cohort and 45.4% in the irAE group (CTCAE grade matched) with steroids alone without any SSIS. Median PFS were compared between CNI cohort (5.4 months, range 1.3-34 months) to IMD (1.1 months, range 0.4-6.4, p=0.02) and steroid alone (2.4 months, range 0.69-17.7, p=0.48). Multiple regression analysis identified irAE presence as an independent correlates to tumor response (p=0.02). **Conclusions:** T cell-specific IS should not be excluded from irAE treatment algorithm as we observed that PFS was comparable to immunomodulators and similar efficacy was observed compared to steroids alone. Rapid identification and management of irAEs can help mitigate morbidity but there are virtually no reliable clinical trials to guide irAE management with SSIS. These findings support the need for larger, prospective evaluation of immunosuppression use for high grade irAE therapy. Research Sponsor: None.

3067 Poster Session (Board #131), Fri, 8:00 AM-11:00 AM

Fecal microbiota transplantation (FMT) for immune checkpoint inhibitor induced–colitis (IMC) refractory to immunosuppressive therapy. *First Author: Yinghong Wang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ICIs are efficacious treatment for several advanced malignancies. IMC can limit their use, and can be refractory to medical treatment (immunosuppression) with significant morbidity. Gut microbiome alteration affects IMC development. We sought FMT as a novel therapy for IMC refractory to immunosuppressive therapy. **Methods:** 15 patients who received FMT for IMC after failure of immunosuppressive therapy were included (6/2017-1/2020). FMT was performed via colonoscopy with healthy donor's stool. **Results:** Median age was 55 years with 67% males. 5 patients received PD(L)-1, one CTLA-4 and 9 on combination. Majority had genitourinary cancers followed by melanoma. Median time from ICI to IMC was 75 days. 14 patients had grade 3-4 diarrhea and 9 had grade 3-4 colitis. Endoscopy showed mucosal inflammation in 12 patients and normal mucosa in 3 patients. IMC was refractory to 2-3 doses of infliximab or vedolizumab after corticosteroids prior to FMT. Median time from IMC onset to FMT was 75 days. 13 patients received one . 11 patients achieved clinical response within 10 days of FMT (7-14). Symptom remission was maintained for a median follow-up of 13 months. 6 patients resumed non ICI cancer treatments after FMT. 4 patients had persistent symptoms; 2 continued on vedolizumab, 1 had total colectomy, and 1 transferred to hospice. 4-8 weeks after FMT, endoscopic remission was achieved in 64% of the 11 patients who responded to FMT. No adverse events were reported. **Conclusions:** FMT treatment was successful in 73% of patients with for IMC refractory to immunosuppressive therapy. Controlled clinical trials are warranted to confirm our conclusion. Research Sponsor: None.

Characteristics of FMT (n = 15).

Characteristic	Data (N=15)
Median days from IMC onset to FMT (IQR)	75 (58-127)
Median time from FMT to symptom improvement– days (IQR)	10 (7-14)
Resumed cancer treatment after FMT—no (%)	6 (40)
Symptom improvement after FMT—no (%)	11 (73)
Endoscopic remission achieved—no (%)	7 (64)
Histology remission achieved—no (%)	5 (45)

3068 Poster Session (Board #132), Fri, 8:00 AM-11:00 AM

Circulating tumor DNA dynamics as prognostic and predictive biomarkers of response to pembrolizumab in patients with virally-related tumors (VRT) treated within the INSPIRE study. *First Author: Marc Oliva Bernal, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: We previously showed a correlation between circulating tumor DNA (ctDNA) dynamics and response to pembrolizumab in a cohort of mixed tumors treated in the INSPIRE study (Yang et al, ESMO 2019). We investigated the prognostic and predictive value of ctDNA dynamics in patients (pts) with VRT. **Methods:** Pts with VRT (HPV+ squamous cell carcinoma (SCC), EBER+ nasopharyngeal carcinoma (NPC) and MCPyV+ Merkel carcinoma (MC)) and a control cohort of non-VRT (HPV- head and neck SCC) treated with single-agent pembrolizumab were selected for the analysis. ctDNA was assayed at baseline and start of cycle 3 using a pt-specific amplicon-based NGS assay (Signatera). Samples were considered ctDNA positive if ≥2 of 16 pt-specific targets met the qualifying confidence score threshold. Whole exome sequencing (WES) performed in baseline tumor tissue; presence of HPV, EBV and MCPyV in tumor determined through bioinformatic analysis of WES data (VirusFinder, *PMID23717618*). Changes in tumor size (mm) and response data using RECIST 1.1 were collected. Progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier method. **Results:** Twenty pts with VRT (HPV+ head and neck = 8, cervical = 2 and anal = 2 SCC; EBER+NPC = 2; MC = 6) and 11 pts with non-VRT were included. Median follow-up: 11 months (0,5-11). Treatment response: VRT 6 responders (CR + PR + SD > 18weeks) and 14 non-responders (SD < 18 weeks + PD); non-VRT 3 responders and 8 non-responders. Median OS and PFS for all pts were 10.61 and 3.2 months, respectively. No differences in PFS (p = 0.60) nor OS (p = 0.66) were observed among responders between VRT and non-VRT. Among non-responders, VRT had significantly higher OS but not PFS when compared to non-VRT (HR 0.30, p = 0.01 and HR 0.82 p = 0.62, respectively). VRT had quantitatively higher ctDNA at baseline vs non-VRT (Mean 7.9 vs 0.4 ng, p < 0.001). ΔctDNA (Change in ctDNA between baseline and cycle 3) strongly correlated with changes in tumor measurements and response by RECIST 1.1 (Spearman Rho = 0.75) and was associated with survival regardless of viral status (Table). **Conclusions:** ΔctDNA strongly correlated with changes in tumor response and survival in both VRT and non-VRT. Higher baseline ctDNA was found in VRT. Correlation with circulating viral DNA and radiomics analyses is on-going. Research Sponsor: None.

Variable	HR[1] for PFS	p-value	HR[1] for OS	p-value
VRT vs non-VRT	1.1	0.8	0.6	0.3
ΔctDNA continuous	1.6[2]	**0.01**	1.5[2]	**0.03**
ΔctDNA up vs. down	4.1	**0.003**	4.1	**0.007**

1. Hazard Ratio. 2. Per unit increase in ΔctDNA

3069 Poster Session (Board #133), Fri, 8:00 AM-11:00 AM

Using autoantibody signatures to predict immunotherapy discontinuation in melanoma patients. *First Author: Iman Osman, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY*

Background: Immune checkpoint inhibitors (ICIs), e.g., ipilimumab (IPI) and/or nivolumab (NIVO), produce durable survival benefit in a substantial proportion of melanoma patients but can also induce severe immune-related adverse events (irAEs) requiring treatment discontinuation. There is no biomarker to predict irAEs in ICI-treated melanoma patients. Given the similar clinical manifestation between irAEs and autoimmune disorders, we hypothesized that a subset of patients possess a subclinical baseline predisposition to developing irAEs that is characterized by specific autoantibodies (autoAbs). **Methods:** Pre-treatment melanoma patient sera from the CheckMate-238 Phase III trial of adjuvant IPI vs. NIVO were used for autoAb profiling with HuProt proteomic arrays (CDI Labs). The outcome of interest is to predict toxicity events that caused treatment discontinuation. For each treatment arm, we allocated patients to training and testing datasets in a 3:1 ratio. We calculated the area under the curve (AUC) of the receiver operating characteristic curve to select a probability threshold, which was applied to the testing dataset to assess accuracy, sensitivity, and specificity. Functional enrichment among autoAb protein targets was assessed using Metascape. **Results:** There were 707 irAEs among 597 patients (IPI = 423, NIVO = 174), of which 355 required treatment discontinuation (IPI = 287, NIVO = 68). In the training sets, we identified a 170 autoAbs signature consisting of 102 autoAbs for IPI treatment and 68 autoAbs for NIVO treatment. In the independent testing set, the signatures showed AUC of 0.85 (0.78, 0.92), 82% sensitivity, 78% specificity, and overall accuracy of 81% to predict IPI discontinuation, and AUC of 0.87 (0.74, 0.99), 75% sensitivity, 97% specificity, and overall accuracy of 88% to predict NIVO discontinuation. Enrichment of nuclear lumen-associated protein targets was identified among autoAb signatures that predict IPI or NIVO discontinuation. **Conclusions:** The identified signature within a large Phase III trial cohort highlights the potential utility of pre-treatment autoAbs for prediction of patients at high risk of developing irAEs in the adjuvant setting necessitating treatment termination. We are currently validating and refining toxicity-associated autoAb signatures with the goal of developing a Clinical Laboratory Improvement Amendments (CLIA)-certified assay to enable clinicians to optimize immunotherapy delivery and patient selection. Research Sponsor: P50 CA225450 NYU Melanoma SPORE, P30 CA016087: Cancer Center Support Grant; R01CA231295.

3070 Poster Session (Board #134), Fri, 8:00 AM-11:00 AM

Spatial analysis of tumor immune microenvironment (TIME) in patients treated with Bintrafusp alfa. *First Author: Houssein Abdul Sater, National Cancer Institute, Genitourinary Malignancies Branch, Bethesda, MD*

Background: Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of TGF-βRII receptor (TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. In preclinical models, bintrafusp alfa treatment promoted CD8+ T cell and NK cell activation, and both immune cell (IC) populations were required for optimal bintrafusp alfa mediated tumor control. However, the effect of bintrafusp alfa on TIME in humans has not been reported. **Methods:** In this unplanned interim analysis of a biomarker expansion cohort (NCT 02517398), patients (pts) with advanced non-small cell lung cancer (NSCLC) underwent paired biopsies (bx) before and on treatment with bintrafusp alfa (~ 50 days apart). The objective was to evaluate frequency and localization of tumor infiltrated ICs by IHC. Out of 12 pts, 7 had matched (Pre vs Post) tumor-containing specimens sufficient for multiplex immunofluorescence (MxIF) analysis of TIME. Four pts were excluded as Post bx histology for 3/12 [2 PR (partial response), 1 SD (stable disease)] was negative for tumor (necrosis or fibrosis) and 1/12 did not have a Post bx performed. **Results:** TIME study shows CD8 T cell infiltrates were increased in Post compared to Pre bx (median 161 vs 62/mm^2; interquartile range [IQR] 65–396/mm^2 vs 31–135/mm^2; p = 0·04). While M2 macrophages were also increased (median 800 vs 367/mm^2; IQR 776–1131/mm^2 vs 171–831/mm^2; p = 0·04), the ratio of M1/M2 was reversed in pts with SD (↑) compared to pts with PD (↓). Other ICs such as CD4, T-regs, NK cells and M1 macrophages were not changed. On average compared to baseline, M2 macrophages were > 2 fold closer to every other IC in pts with PD, but > 2 fold further from any IC in pts with SD. Tregs were relatively closer to other IC in PD pts. Linear Discriminant Analysis was also performed and results indicate that differential IC densities (mainly M1 macrophages and CD4 T cells) do perform as classifiers between long (> 5 months) and short (< 5 months) term responses. **Conclusions:** This study suggests that bintrafusp alfa not only can enhance intratumoral effector IC infiltrates (CD8) but also has a modulating effect on the spatial distribution of both M1/M2 macrophages within the NSCLC TIME. The differential proximity of M2 macrophages to other IC infiltrates and changes in M1/M2 ratios in association with response suggests that an M1/M2 macrophage balance is directly involved in response and/or resistance to bintrafusp alfa. Given the limited number of patients in this cohort, we intend to study effects of bintrafusp alfa in a larger cohort of patients. Clinical trial information: 02517398. Research Sponsor: None.

3071 Poster Session (Board #135), Fri, 8:00 AM-11:00 AM

Preliminary dose escalation results from a phase I/II, first-in-human study of MGC018 (anti-B7-H3 antibody-drug conjugate) in patients with advanced solid tumors. *First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC*

Background: Antibody-drug conjugates (ADCs) are cancer agents that have a cytotoxic payload linked to a monoclonal antibody (mAb) that target cancer cells. ADCs offer increased cytotoxic activity while reducing normal tissue exposure. B7-H3 is expressed on multiple solid tumors with limited normal tissue expression. MGC018 is an investigational ADC with a duocarmycin payload linked to an anti-B7-H3 mAb. It is hypothesized that MGC018 has activity against B7-H3 expressing tumors with an acceptable safety profile. **Methods:** This study evaluates safety, dose-limiting toxicities (DLT), and maximum tolerated dose (MTD) of MGC018 in a dose escalation 3+3+3 design. In addition, pharmacokinetics, immunogenicity, and tumor response using RECIST v1.1 are evaluated. Cohort expansion will enroll at the MTD to assess safety and tumor response. **Results:** The study is enrolling Cohort 3 (6 total cohorts planned) in dose escalation. 20 patients (pts) were enrolled as of Feb 03, 2020. At least 1 treatment related adverse event (TRAE) occurred in 16 pts (80.0%). The most common TRAEs were neutropenia/decreased neutrophil count (35%); fatigue, lymphopenia/decreased lymphocyte count (30.0%); palmar plantar erythrodysaesthesia (PPE), skin hyperpigmentation (25.0%); pruritis, nausea, chills, infusion related reaction (20.0%); and vomiting, pyrexia, maculopapular rash (15.0%). Eleven pts (55.0%) experienced TRAEs ≥ Grade 3; events were decreased lymphocyte count/lymphopenia (n = 6), decreased neutrophil count/neutropenia (n = 3), PPE (n = 2), and maculopapular rash (n = 2). Three related serious adverse events occurred in 3 unique pts: pneumonitis in a pt with concurrent bacterial pneumonia, non-infectious gastroenteritis, and stasis dermatitis in a pt with chronic venous insufficiency. One DLT has occurred (Grade 4 neutropenia). No febrile neutropenia was observed. Target lesion decrease was noted in 1 pt each with small cell lung cancer (-6.3%), non-small cell lung cancer (-23.8%), and metastatic castrate-resistant prostate cancer (mCRPC) (-29.4%) with PSA change from 82.8 ng/ml to 57.1 ng/ml. One mCRPC pt with bone only disease had substantial improvement on bone scan and PSA decrease from 60 ng/ml to 4.7 ng/ml. **Conclusions:** Results to date demonstrate a manageable safety profile with early evidence of clinical activity. Continued dose escalation and clinical investigation of MGC018 is ongoing. Clinical trial information: NCT03729596. Research Sponsor: MacroGenics, Inc.

3073 Poster Session (Board #137), Fri, 8:00 AM-11:00 AM

A signal-seeking trial of olaparib and durvalumab in homologous repair-deficient tumors: A sub-study of the cancer molecular screening and therapeutics (MoST) program. *First Author: Anthony M. Joshua, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Data on the utility of a PARP inhibitor in combination with a checkpoint inhibitor remain limited, particularly in the histology agnostic setting with homologous recombination deficiency (HRD). This study evaluated the clinical activity of the combination of olaparib and durvalumab with the primary study endpoint of progression-free survival (PFS) at 6 months (PFS6m). **Methods:** This was a phase II, single-arm, signal-seeking study of the MoST program. Patients were recruited into two cohorts based on HRD genes, agnostic to histology: (1) BRCA 1/2 deficient tumours, excluding breast, prostate, ovarian cancers, and (2) other HRD related genes. Molecular testing was performed using in-house and commercial panels on archival tumour tissue centrally adjudicated by a molecular tumour board. All patients were treated with olaparib 300mg bid for 1 month, followed by combination with durvalumab 1500mg q4 weekly for 13 cycles. Olaparib treatment was then continued until disease progression. **Results:** Between Nov 2017-Feb 2019, 48 patients were enrolled (16 to BRCA 1/2 cohort 1 and 32 to HRD related genes cohort 2). Most common tumour sites were bone/soft tissue (15%, N=7), pancreas (13%, N=6) and stomach (8%, N=4). Overall best response in cohort 1 was PR (25%, N=4) and SD 4 (25%, N=4), and cohort 2 was PR (6%, N=2) and SD (56%, N=18). Median PFS was 3.65m (Cohort 1) and 3.56m (Cohort 2) respectively. PFS6m was 35% (Cohort 1) and 38% (Cohort 2) respectively. PDL1 status was not predictive of olaparib and durvalumab benefit. The most common grade 3/4 adverse events were anemia (11%%, N=4), abdominal pain (9%, N=3), increased lipase (9%,N=3), increased amylase (9%, N=3), dyspnea (6%, N=2), Hyperglycemia dyspnea (6%, N=2), Pancreatitis dyspnea (6%, N=2) and hematuria (6%, N=2). **Conclusions:** Olaparib and durvalumab show promising activity in a histology agnostic setting, particularly in BRCA deficient tumours. Further research is needed to identify biomarkers that correlate with treatment benefit. Results from longer clinical follow-up and additional biomarker analyses will be presented. Clinical trial information: ACTRN12617001000392. Research Sponsor: Department of Health, Australia.

3074 Poster Session (Board #138), Fri, 8:00 AM-11:00 AM

Statin treatment improves response to anti-PD1 agents in patients with malignant pleural mesothelioma and non-small cell lung cancer. *First Author: Luca Cantini, Clinical Oncology, Polytechnic University of Marche, AOU Ospedali Riuniti, Ancona, Italy*

Background: After progression to standard chemotherapy, only a small proportion of malignant pleural mesothelioma (MPM) and non-small cell lung cancer (NSCLC) patients (pts) benefit from anti-programmed cell death (PD-1) treatment. Combination strategies might improve response. In pre-clinical models, statins showed vaccine adjuvant activities and synergized with anti-PD1 agents. In this multi-center study, we evaluated the impact of baseline statin treatment in MPM and NSCLC pts. **Methods:** We separately examined MPM and NSCLC pts treated with anti-PD1 monotherapy after progression to standard chemotherapy at two European academic institutions. As control cohort, MPM pts treated with first-line chemotherapy were also examined. Pts receiving statins at start of treatment were compared with those who did not. Objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were analyzed. **Results:** A total of 287 patients were examined. Twenty-seven out of 80 (34%) MPM and 36 out of 130 (20%) NSCLC pts received statins at start of anti-PD1 treatment. The most common statins were simvastatin, atorvastatin and rosuvastatin. In MPM pts, statin use was associated with improved ORR (22% versus 5%, $P = 0.05$), longer PFS (median 6.7 versus 2.4 months, hazard ratio (HR) 0.42, 95% confidence interval (CI) 0.23–0.77, $P < 0.01$), and longer OS (median not reached versus 6.0 months, HR 0.43, 95% CI 0.21–0.85, $P = 0.01$). In NSCLC pts, statin use was associated with improved ORR (40% versus 22%, $P = 0.04$), longer PFS (median 7.8 versus 3.6 months, HR 0.59, 95% CI 0.37–0.97.2, $P = 0.03$) but similar OS (median 13.1 versus 10.1 months, HR 0.79, 95% CI 0.49–1.28, $P = 0.30$). At multivariate analyses, after adjusting for ECOG performance status (PS) and histological subtype, the impact of statins remained significant for ORR, PFS and OS in MPM and for PFS in NSCLC. Conversely, no association between statin use and outcomes was found in 77 MPM pts treated with first-line chemotherapy. **Conclusions:** This study shows that statin use at start of anti-PD1 treatment improves response to anti-PD1 agents in MPM and NSCLC pts who progressed to standard chemotherapy in routine clinical practice. This association could not be found in MPM pts treated with first-line chemotherapy, thus suggesting a synergy between statins and anti-PD1 agents. Prospective studies are needed to confirm whether the combination of statin and anti-PD1 therapy could improve outcome in pts with poorly immunogenic thoracic malignancies. Research Sponsor: None.

3075 Poster Session (Board #139), Fri, 8:00 AM-11:00 AM

Interrogation of neoantigen-specific CD8 T cells in peripheral blood following PD-L1 blockade in patients with metastatic urothelial carcinoma (mUC). *First Author: Jeppe Sejerø Holm, Technical University of Denmark, Kgs. Lyngby, Denmark*

Background: Proliferation of CD8 T cells can be detected in the blood of cancer patients (pts) following a single dose of immune checkpoint blockade (ICB) and tends to be more robust in responding pts. Furthermore, tumor mutational burden (TMB) is seen to predict outcome to ICB across cancers. Mutation-derived neoepitopes presented on the tumor cell surface is believed to be recognized by T cells and are thus critical for tumor clearance. However, the capacity to mount a neoantigen T cell response and the kinetics in relation to ICB remain poorly understood. **Methods:** 24 pts with mUC were treated with atezolizumab (anti-PD-L1) 1200mg q3w on IMVigor 210 at MSKCC and included in here. Pt-specific neoepitopes were predicted based on whole-exome and RNA sequencing of pre-treatment archival tumors using the MuPeXI platform. Using DNA-barcode labelled pMHC multimers, we investigated CD8 T cell recognition of mutation-derived neoepitopes by screening pt PBMC samples pre- and post-treatment with atezolizumab (n = 85 PBMC samples). The kinetics of neoepitope-specific CD8 T cells were assessed for association with durable clinical benefit (DCB; defined as progression free survival $>$ 6 mo). **Results:** Neoepitope peptide libraries of between 200-587 peptides were generated per pt (mean = 260 peptides per pt). 31 out of a combined 56 possible pt HLA types across the cohort were utilized for T cell analyses (mean four HLAs per pt). MHC multimer-based screening of pt PBMCs revealed detection of neoepitope-specific CD8 T cells in 22 of 24 pts pre-treatment (range one to 14 neoepitope responses) and 21 of 22 pts post-treatment (up to 273 weeks after trial start; one to 19 neoepitope responses). There were large inter- and intra-patient variations of neoepitope-specific CD8 T cell responses during treatment with the largest increases occurring at the 3-wk, post-treatment initiation timepoint. We observed that pts with DCB tend to raise a broader neoantigen T cell response than patients without DCB. 38% of pts without DCB and 67% of pts with DCB exhibited an increase in neoepitope-specific CD8 T cell responses within 3 wks of treatment initiation. **Conclusions:** Using high-throughput screening, pt-specific neoepitope reactive CD8 T cells could be detected pre- and post-treatment in pts with mUC treated with atezolizumab. Phenotypic characterization of neoepitope reactive CD8 T cells is ongoing. These data may help elucidate the dynamics and characteristics of the T cells of highest relevance to the ICB-induced, anti-tumor immune response. Research Sponsor: Ludwig Grant, Other Foundation.

3076 Poster Session (Board #140), Fri, 8:00 AM-11:00 AM

Checkpoint inhibitor treatment-related cutaneous adverse events in skin of color patients at Memorial Sloan Kettering Cancer Center. *First Author: Amaris Geisler, CUNY School of Medicine, New York, NY*

Background: The advent of immune checkpoint inhibitors (CPIs) for the management of advanced malignancies has led to unintended consequences of nonspecific immune activation. Cutaneous immune related adverse events (irCAEs) are the most common and first to manifest, on average within 3.6 weeks of treatment initiation. irCAEs may require CPI treatment dose reduction or discontinuation and negatively impact patient quality of life. There is substantial variability in the reporting of these toxicities and inadequate reporting in skin of color patients (SOC), who are often underrepresented in oncology clinical trials. The purpose of this study is to characterize irCAEs in SOC cancer patients. **Methods:** A single center retrospective analysis of electronic medical records from 2009-2020 was conducted. SOC was defined as African American, Hispanic, Native American/Pacific Islander, or Asian. irCAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. **Results:** Of 1459 SOC patients that presented to our institution and received CPIs during the study period, 175 (12%) presented to dermatology for irCAEs [African American (56, 32%); Asian (98, 56%); Hispanic (20,11%); Native American (1, 0.5%)]. Patients' toxicities were stratified by CPI mechanism: anti-PD-1/L1 (139, 79%), combination of anti-PD-1/L1 plus anti-CTLA-4 (29, 17%), and anti-CTLA-4 therapy (7, 4%). Of 376 irCAEs, pruritus (62, 16%), xerosis (42, 11%), maculopapular rash (40, 11%), and cutaneous hyperpigmentation (36, 10%) were most frequently diagnosed. There were 86 (23%) grade 1, 93 (25%) grade 2, and 18 (5%) grade 3 events. Average time from CPI-treatment initiation to irCAE onset was 6.5 months (SD 7.9). Fifteen (9%) patients required CPI dose reduction or discontinuation due to skin toxicity. Topical corticosteroids (133, 76%) were the most frequently used treatment for all irCAEs. **Conclusions:** Our findings suggest that irCAEs occur frequently in SOC cancer patients. Furthermore, a 6.5-month delay in time to diagnosis highlights a need for increased surveillance of these cutaneous toxicities in darkly pigmented skin. Generally, SOC patients present unique diagnostic and management challenges due to differences in skin biology and propensity toward hyperpigmentation; however, in SOC *cancer* patients, the mechanisms of oncologic immunotherapy must be considered in developing successful treatment strategies and management of dermatologic health in this population. Research Sponsor: None.

3077 Poster Session (Board #141), Fri, 8:00 AM-11:00 AM

Novel blood-based biomarker predicting severe toxicity in melanoma anti-CTLA-4 immunotherapy treatment. *First Author: Vylyny Chat, New York University School of Medicine, New York, NY*

Background: Immune checkpoint inhibition (ICI) has improved clinical outcomes of metastatic melanoma (MM). However, 65-80% of treated patients experience immune-related adverse events (irAEs), urging for the availability of personalized and easy-access clinical biomarkers. We have previously shown that germline genetics related to host immunity affects ICI response and MM survival. In this study, we investigated if germline immune-related expression quantitative trait loci (ieQTLs) may predict ICI-induced irAEs in MM. **Methods:** Through a comprehensive interrogation of a healthy twin-cohort expression dataset (MuTHER), we identified 40 ieQTLs most significantly associated with the expression of 382 immune-related genes. These germline variants were genotyped using the MassARRAY system in anti-CTLA-4-treated MM patients, collected as part of a multi-institutional collaboration. Using multivariable logistic regression models, we tested the association of 40 ieQTLs with irAEs in a discovery cohort of 97 MM patients followed by a validation in additional cohort of 97 anti-CTLA-4 treated patients. **Results:** We found rs7036417 significantly associated with severe anti-CTLA-4 irAEs in the discovery (OR = 6.18; 95%CI = 1.61-23.74; p = 0.007) and validation (OR = 6.73, 95%CI = 1.42-31.86; p = 0.02) cohorts. Pooled analysis showed that carriers of two rs7036417 alternate alleles (TT) have a 6-fold increased risk of developing severe irAEs (OR = 6.11; 95% = 2.26-16.56;p = 0.0003). This association was not observed with ICI response or survival. The alternate allele of rs7036417 is associated with higher expression of *SYK* (spleen-associated tyrosine kinase), suggesting that elevated SYK contributes to developing severe irAEs. **Conclusions:** We report that rs7036417, an ieQTL in *SYK*, associates with an increased risk of severe irAEs, independent of ICI efficacy. *SYK* plays an important role in B-cell/T-cell expansion and increased pSYK has been reported in patients with rheumatoid arthritis or systemic lupus erythematosus. Based on our data, the over-expression of SYK likely explains the biological mechanisms of the association between rs7036417 and anti-CTLA4 irAEs. These findings propose a novel blood-based baseline biomarker stratifying the patients at increased risk of severe irAEs, with a clinical effect substantially surpassing those observed for currently available predictors. Our ongoing studies are currently investigating SYK eQTL as a novel target in toxicity-reducing therapies. Research Sponsor: U.S. National Institutes of Health.

3078 Poster Session (Board #142), Fri, 8:00 AM-11:00 AM

Success and failure of additional immunosuppressants in steroid-refractory pneumonitis related to immune checkpoint blockade. *First Author: Jason Beattie, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Severe immune related adverse events (irAEs) with immune checkpoint blockade are uncommon but can be fatal. Steroids are the most common initial treatment for most non-endocrine irAEs, but some patients are or become refractory to steroids. When steroids are not effective, there is limited data to guide management strategies, particularly in the context of pneumonitis. **Methods:** All patients at MSK treated with immune checkpoint blockade from 2013-2020 were queried for receipt of an immunosuppressant (e.g. TNF antagonists, mycophenolate mofetil, cyclophosphamide) beyond steroids. Patient records were then manually reviewed to identify patients who received such therapy for management of immunotherapy-related pneumonitis. **Results:** Among 5363 patients treated with immune checkpoint blockade, 364 (6.8%) received an additional immunosuppressant for an irAE, including 28 (0.5% of all patients treated) patients treated for pneumonitis. Most of these pneumonitis events (19/28, 68%) were grade 3 or higher. Agents used included mycophenolate mofetil (7/28; 25%), TNF antagonists (23/28; 82%), and cyclophosphamide (1/28; 3.5%); more than one medication was used in 3 patients (11%). The indications were primary non-response to steroids (n = 16, 57%) and recrudescence after initial response to steroids (n = 12, 43%). At 90 days from initiation of the additional immunosuppressant, 13/28 (46%) patients were alive with improvement or resolution of pneumonitis while 15/28 (54%) had died. Survival with resolution/improvement was more common in patients treated for recrudescence vs primary non-response (67% vs 25%, p = 0.05). **Conclusions:** Outcomes with additional immunosuppressants in the setting of steroid-refractory immune-related pneumonitis are poor, but resolution can occur in some cases. A deeper understanding of the mechanistic underpinnings of irAEs is needed to more effectively tailor immunosuppressant therapies, particularly in severe pneumonitis events. Research Sponsor: None.

3079 Poster Session (Board #143), Fri, 8:00 AM-11:00 AM

Preliminary results of sintilimab plus different dose of IBI305 (anti-VEGF monoclonal antibody) in patients with advanced hepatocellular carcinoma: A phase Ib study. *First Author: Wen Zhang, Department of Medical oncology, Cancer Hospital, CAMS, Beijing, China*

Background: The study aimed to evaluate the safety and efficacy of sintilimab, a PD-1 blockade, plus IBI305, a biosimilar candidate of bevacizumab, in patients (pts) with advanced hepatocellular carcinoma (HCC). **Methods:** Adults with histocytologically confirmed advanced or metastatic HCC were enrolled in this two-part study. Part 1 was dose escalation trial, with initial dose of sintilimab 200 mg plus IBI305 7.5 mg/kg, q3w (low-dose group). If tolerable, IBI305 was escalated to 15 mg/kg (high-dose group). In part 2 for extension, at least 20 pts were enrolled to each tolerable dose group. **Results:** As data cutoff (Jan. 7, 2020), 50 pts were enrolled, 29 in low-dose group and 21 in high-dose group. 41 patients were systemic treatment naïve. The median treatment cycle was 4 (range: 1-19) in low-dose group and 11 (range: 1-16) in high-dose group. Most TRAEs were G1-2 with the most common being hypertension (28.0%) and pyrexia (26.0%). Totally, the grade 3 or more TRAEs were occurred in 6 (12.0%) pts, including hypertension occurred in 2 (4%) pts. The objective response rate (ORR) per RECIST v1.1 was 24.1% (95%CI: 10.3 - 43.5) in low-dose group, and 33.3% (95% CI:13.3 - 59.0) in high-dose group. As with the cutoff date, the median PFS has not been reached and the 6-month PFS rates were 60.5% (95%CI 36.1, 78.0) and 75.8% (95% CI: 47.3, 90.2), respectively. **Conclusions:** The combination of sintilimab and IBI305 showed promising efficacy and favourable safety profile in advanced HCC in both low-dose and high-dose groups. The preliminary result of this study warrant further exploration of dose selection for anti-VEGF/VEGFR agent when combined with PD-1/PD-L1 antibody. Clinical trial information: NCT04072679. Research Sponsor: Innovent Biologics, Inc.

Antitumor activity in both groups.

	Sintilimab 200 mg + IBI305 7.5 mg/kg Total (N=29)	Sintilimab 200 mg + IBI305 15 mg/kg Total (N=21)
Number of subjects having at least one radiological assessment [a]	29	18
CR, n	0	0
PR, n	7*	6**
SD, n	15	9
PD, n	7	3
ORR (95%CI), %	24.1 (10.3 - 43.5)	33.3 (13.3 - 59.0)
DCR (95%CI), %	75.9 (56.5 - 89.7)	83.3 (58.6 - 96.4)

[a]: three subjects had no radiological assessment till data cutoff and were excluded from the table. Number of subjects having at least one radiological assessment is used for the denominator of percentage in this table. * Seven patients were confirmed by RECIST v1.1. ** Five patients were confirmed by RECIST v1.1.

3080 Poster Session (Board #144), Fri, 8:00 AM-11:00 AM

Influence of antibiotic therapy (ATB) on oncological outcomes of metastatic non-small cell lung cancer (mNSCLC) patients treated with chemo-immunotherapy (CIT). *First Author: James Clark, Department of Surgery & Cancer, Imperial College London,, London, United Kingdom*

Background: ATB exposure is proven to worsen response and survival in immunotherapy recipients. However, its influence on outcomes from CIT is currently undefined. **Methods:** We conducted a retrospective, multi-centre observational study including 77 mNSCLC patients who received pembrolizumab, pemetrexed and carboplatin CIT as first-line therapy for mNSCLC, between December 1, 2018 and January 1, 2020 in 3 academic referral centres in Europe and in the United States. We documented ATB exposure in the 30 days prior to CIT commencement (pATB) or concurrently (cATB) until CIT cessation. Outcome measures included overall (OS) and progression-free survival (PFS) calculated from commencement of CIT, and overall response rates (ORR) defined by Response Evaluation Criteria in Solid Tumors (v1.1). **Results:** We enrolled 77 patients, 41 of whom were female (n = 53%) with adenocarcinoma (n = 73, 95%), performance status (PS) 0-1 (n = 69, 90%) PD-L1 Tumour Proportion Score < 50 (n = 57, 74%). Median OS was 16.4 months (95%CI 8.4-24.4), median PFS was 6.7 months (95%CI 5.7-7.6). ORR was 48% including 1 complete (1%) and 36 partial responses (47%). Eleven patients (14%) received pATB, with penicillin/cephalosporins (p/c, n = 7, 63%) for <7 days (n = 10, 90%). Thirty-five patients (45%) received cATB with p/c (n = 11, 40%) for <7 days (n = 28, 80%). Most common indication for ATB was peri-procedure prophylaxis in pATB (n = 7, 63%) and suspected febrile neutropenia in cATB (n = 14, 40%). pATB ($p = 0.004$) but not cATB ($p = 0.85$) predicted for worse OS (19.6 vs 6.5 months, Hazard Ratio [HR] 2.9 95%CI 1.3-6.3). Neither pATB nor cATB predicted for PFS or ORR ($p > 0.05$). Multivariable analyses confirmed pATB (HR 2.3 95%CI 1.1-5.5, p = 0.05) to predict for OS independent of PD-L1 status, PS and cATB. pATB+/- groups were balanced with regards to age, gender, PS nor PD-L1 status ($p > 0.05$). **Conclusions:** Whilst cATB does not compromise outcome from CIT, this study reproduces the detrimental effects observed for pATB exposure in immunotherapy recipients. Mechanistic verification of the immune-biologic foundations underlying this association is urgently warranted. Research Sponsor: None.

3081 Poster Session (Board #145), Fri, 8:00 AM-11:00 AM

Targeting HER2 in combination with anti-PD-1 and chemotherapy confers a significant tumor shrinkage of gastric cancer: A multi-institutional phase Ib/II trial of first-line triplet regimen (pembrolizumab, trastuzumab, chemotherapy) for HER2-positive advanced gastric cancer (AGC). *First Author: Sun Young Rha, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Combining anti-PD-1 agent and trastuzumab has shown synergy in HER2 positive preclinical cancer models. We first report the result of a multi-institutional phase Ib/II trial of triple combination (pembrolizumab, trastuzumab, and chempotherapy) as first line therapy for HER2 positive AGC. (PANTHERA trial; NCT02901301). **Methods:** Pembrolizumab 200mg IV D1, Trastuzumab 6mg/kg (after 8mg/kg load) D1, Capecitabine 1000mg/m^2 bid D1-14, and Cisplatin 80mg/m^2 D1 every 3 weeks was selected as recommended phase II dose. The primary endpoint for phase II was ORR per RECIST v1.1. Secondary endpoints included PFS, OS, DoR, safety, and molecular analysis by targeted NGS. **Results:** Total of 43 patients were treated with median follow up of 16.1 months, and 11 pts remained on the treatment (treatment duration range: 1.4 to 24 months). There was significant tumor shrinkage of 95.3% with 54.6% median depth of response, with 76.7% ORR (CR 16.3%, PR 60.5%, conversion surgery 4.6%), and 97.7% DCR. Median PFS was 8.6 months (95% CI 7.2-22.0) and median OS was 18.4 months (95% CI 17.9-NA). Subsequent chemotherapy was given to 83.3% of 30 progressed pts. There were no MSI-H/dMMR or EBV-positive pts. PD-L1 status (57.1% of pts $\geq$ CPS 1 and 14.3% of pts $\geq$ CPS 10 among 35 pts), metastatic organ or baseline tumor burden was not related to the survival. Treatment-related AE ($\geq$G3) occurred in 32 pts (74.4%) including 17 pts (39.5%) with neutropenia G3-4. Immune-related AEs ($\geq$G3) occurred in 4 pts (10%). Ninety-six tumor tissues from 32 pts (paired tumor tissues from 25 pts) were analyzed with targeted NGS. TMB (median 12.7 mut/MB with range of 9.45-16.71) was not related to the PD-L1 expression or survival. **Conclusions:** First-line triplet regimen (Pembrolizumab, Trastuzumab, and Chemotherapy) confers a significant tumor shrinkage for HER2 positive AGC, regardless of PD-L1 status. Phase III Keynote-811 study (NCT03615326) is ongoing based on the protocol of this study. Clinical trial information: NCT02901301. Research Sponsor: MSD, Pharmaceutical/Biotech Company.

Response and survival of PANTHERA Trial (cut-off date: 12-31-2019).

Tumor Shrinkage rate	ORR	DCR	PFS	OS	DoR	6-months PFS
95.3%	76.7%	97.7%	8.6 months (95% CI 7.2-22.0)	18.4 months (95% CI 17.9-NA)	10.8 months (95% CI 7.2-NA)	76.7% (95% CI 65.1-90.5)

3082 Poster Session (Board #146), Fri, 8:00 AM-11:00 AM

Association of a STK11/KEAP1-mutation gene expression signature in lung adenocarcinoma with immune desertion in squamous cell carcinomas and mediation by NFE2L2 deregulation. *First Author: Damian Tobias Rieke, Department of Hematology and Oncology - Charité Universitätsmedizin Berlin, Berlin, Germany*

Background: KEAP1 and STK11 mutations are associated with resistance to immune checkpoint inhibition (ICI) in non-small cell lung cancer (NSCLC). Mechanisms are currently unknown. **Methods:** We examined mutation, methylation, copy number and gene expression data from the cancer genome atlas (TCGA) lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LSCC), head and neck squamous cell carcinoma (HNSCC) and cervical carcinoma (CESC) data sets as well as public single cell gene expression data from a HNSCC cohort. Pathway annotations were performed using gene set enrichment analysis. A previously published cohort of NSCLC patients treated with ICI was analyzed for the predictive value of NFE2L2 mutations on PFS. **Results:** Annotation of STK11 and KEAP1 mutant LUAD revealed identical gene set enrichment for mitochondrial metabolism and downregulation of the STING-pathway, immune checkpoints, and interferon signaling. A STK11/KEAP1-mutation derived gene expression signature was established in LUAD and found to be driven by NFE2L2-regulated genes. This gene expression signature was independently predictive of immune desertion in LSCC, CESC and HNSCC and associated with STING-pathway downregulation in single cell sequencing analyses in HNSCC. KEAP1 and STK11 mutations were less frequent in LSCC, CESC and HNSCC but NFE2L2 mutations were identified in 15, 6 and 5%, respectively. NFE2L2 mutant SCC exhibited upregulation of the 15-gene- signature as well as immune desertion. In NSCLC, NFE2L2 mutations were associated with significantly worse PFS with ICI. **Conclusions:** Alterations of KEAP1, STK11, NFE2L2 and other related genes are linked to NFE2L2 target gene upregulation and immune desertion in LUAD, CESC, LSCC and HNSCC alike. The NFE2L2 pathway should be investigated clinically as a putative negative predictive biomarker for ICI and a potential therapeutic target. Research Sponsor: None.

3083 Poster Session (Board #147), Fri, 8:00 AM-11:00 AM

Prevalence of human leukocyte antigen-B27 supertype in the context of positively charged neoepitopes and association with PD-L1 as an immune escape mechanism. *First Author: Charlene Marie Fares, Department of Medicine, Division of Hematology/Oncology, UCLA, Los Angeles, CA*

Background: Recent evidence suggests efficacy of immune checkpoint blockade may be influenced by human leukocyte antigen (HLA)-B. HLA-B27 supertype has an electronegative binding pocket which favorably binds and displays neoepitopes harboring positively charged amino acids (AAs). Based on immune surveillance, we postulate that B27 tumors that have favorable neoepitopes should face negative selective pressure, and B27 tumors with favorable neoepitopes that develop could be more likely to upregulate immune escape mechanisms. Here we evaluate the relationship between prevalence of B27 and positively charged neoepitopes and assess association between positively charged neoepitopes and expression of PD-L1. **Methods:** TCGA datasets from head and neck squamous cell (HNSC), lung squamous cell (LUSC), and melanoma (SKCM) patients were evaluated. HLA alleles were determined with OptiType and supertype was based on 2008 criteria. Nonsynonymous mutations were annotated with Ensembl VEP and VAtools. pVAC-Seq using NetMHCpan algorithm predicted neoepitopes 9 AAs in length. Favorable B27 neoepitopes were defined as those having new positively charged AA substitutions (H/K/R) from negative or uncharged wildtype AAs. RNA-seq data for the PD-L1 gene were normalized on transcripts per million and log2 transformed. Linear regression tests were performed between PD-L1 gene expression values and fraction of nonsynonymous mutations resulting in neoepitopes with new positively charged AAs in patients with B27. **Results:** Data from 497 HNSC, 494 LUSC, and 468 SKCM patients were analyzed. B27 was observed in 20.1%, 23.2%, and 26.5% of HNSC, LUSC, and SKCM patients, respectively, with a significant difference seen between HNSC and SKCM by chi-square test (χ^2 = 5.14, p = .023). Of new charged AAs resulting from nonsynonymous mutations, 76.3% in HNSC, 74.0% in LUSC, and 72.0% in SKCM were positively charged ($p < .05$ between all histologies, paired t-tests). In B27 patients, association between PD-L1 gene expression and fraction of neoepitopes with new positively charged AAs was seen in HNSC (r = 0.25 p = .036) and SKCM (r = 0.30 p = .007), but not LUSC (r = -0.12 p = .296). **Conclusions:** With increasing fraction of positively charged neoepitopes, a decrease in prevalence of B27 was observed, suggesting improved binding and immune elimination of tumors with favorable neoepitopes. In B27 tumors that develop despite having favorable neoepitopes, upregulation of PD-L1 could be a putative mechanism to evade immune detection. Research Sponsor: None.

3084 Poster Session (Board #148), Fri, 8:00 AM-11:00 AM

Rapid expansion of M-MDSCs and association with high levels of plasma TSLP and primary resistance to PD-1 inhibitors in metastatic NSCLC. *First Author: Sally CM Lau, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: Elevated frequency of peripheral myeloid cell populations has consistently been associated with poor response to immune checkpoint inhibitors (ICI) in metastatic non-small cell lung cancer (mNSCLC). The mechanisms underlying this relationship remains poorly understood. Thymic stromal lymphopoietin (TSLP), a cytokine involved in T-cell maturation, has been implicated in a complex feedback loop leading to tumor growth and expansion of myeloid populations. We hypothesized that TSLP levels directly correlate with the presence and expansion of myeloid derived suppressor cell (MDSC) populations and sought to explore their association with response to PD-1 inhibitors in mNSCLC. **Methods:** mNSCLC patients treated with ICIs underwent baseline and serial blood collection. Peripheral blood mononuclear cells (PBMC) were analyzed by high-dimensional flow cytometry using validated panels to evaluate T/B/NK-cell, Treg and myeloid populations. Plasma cytokines including TSLP were analyzed using ELISA and Luminex assays. Cox and logistic regressions were utilized to correlate biomarkers with progression-free survival (PFS), overall survival (OS) and radiographic response. **Results:** 30 mNSCLC patients treated with single-agent ICI were included in the analysis. TSLP level was significantly associated with expansion of monocytic(M)-MDSCs in response to ICI treatment (p=0.02). M-MDSC frequency after a median of 20 days of ICI treatment was significantly associated with progressive disease (PD), reduced PFS and OS (all $p<0.05$) whereas no correlation was seen with baseline M-MDSC frequency. Patients with a doubling of M-MDSCs (n=11) after treatment had a primary PD rate of 64% vs 24% (OR 7.0, p=0.04) and significantly worse median PFS (2.5 vs 7.8 months, HR 2.6 p=0.04). **Conclusions:** Early expansion of circulating M-MDSCs after treatment with PD-1 inhibitors is associated with elevated baseline TSLP levels and primary disease progression following ICI therapy in mNSCLC. These findings suggest that elevated TSLP and early expansion of myeloid populations may represent an important mechanism of primary resistance to PD-1 inhibitors in mNSCLC. Research Sponsor: None.

3085 Poster Session (Board #149), Fri, 8:00 AM-11:00 AM

A phase I/II study of GB1275, a first-in-class oral CD11b modulator, alone, and combined with pembrolizumab in specified advanced solid tumors or with chemotherapy in metastatic pancreatic cancer (KEYNOTE-A36). *First Author: Drew W. Rasco, START, San Antonio, TX*

Background: GB1275 is a first-in-class CD11b modulator that reduced myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs) at the tumor site, repolarized M2 immunosuppressive TAMs to an M1 phenotype, and increased tumor infiltration of activated CD8+ T cells in preclinical models. When combined with an anti-PD-1 antibody or chemotherapy, these immunomodulatory effects translated into potent anti-tumor effects and prolonged survival in orthotopic PDAC models [Panni RZ, et al. Sci Transl Med. 2019 Jul 3;11(499)]. This ongoing first-in-human study consists of dose escalation of GB1275 monotherapy (Regimen A), GB1275 + pembrolizumab (Regimen B), and GB1275 + nab-paclitaxel + gemcitabine (Regimen C), followed by Phase 2 expansion in newly diagnosed metastatic pancreatic, MSS colorectal, and PD-L1-positive gastric/GEJ cancers. Here we report interim results of the dose escalation portion of the trial. **Methods:** The dose escalation phase is based on a standard oncology phase 1, 3+3 design. Cohorts of 3 to 6 patients (pts) with histologically confirmed locally advanced/metastatic pancreatic, esophageal, gastric, MSS colorectal, prostate, or breast cancer were sequentially assigned to ascending dose levels of GB1275 taken orally twice daily (BID) in 1 of 3 regimens: Regimen A was initiated first; Regimen B commenced after completion of the first two cohorts of Regimen A, and Regimen C will be initiated when Regimen A is completed. Dose escalation was based on assessment of safety including dose-limiting toxicity (DLT). Serial blood and tumor samples were collected for pharmacokinetic (PK) and biomarker analyses. **Results:** As of January 21, 2020, 13 pts were treated, with 3 each in Regimen A (GB1275 100mg, 200 mg and 400 mg BID) dose levels and 4 in Regimen B with GB1275 100 mg BID + pembrolizumab. No DLTs have been reported. GB1275 treatment-related adverse events were reported in 5 pts; all were Grade 1 in severity. Preliminary PK analyses showed a mean elimination half-life of ~7 hours. Reduction in peripheral MDSCs was observed in the majority of pts with serial samples. Biomarker analysis in serial tumor tissue is ongoing. **Conclusions:** Preliminary data show minimal treatment-related toxicities with the studied regimens. PK data support BID dosing. Dose escalation is ongoing. Updated data will be presented. Clinical trial information: NCT04060342. Research Sponsor: Gossamer Bio, Inc.

3086 Poster Session (Board #150), Fri, 8:00 AM-11:00 AM

The spatial localization of CD163+ tumor-associated macrophages predicts prognosis and response to therapy in inflammatory breast cancer. *First Author: Christophe Van Berckelaer, Translational Cancer Research Unit, GZA Hospitals & CORE, University of Antwerp, Antwerp, Belgium*

Background: The mechanisms contributing to the aggressive biology of inflammatory breast cancer (IBC) are under investigation. A specific immune response seems to be an important driver, but the functional role of infiltrating immune cells in IBC remains unclear. Tumor-associated macrophages (TAMs) are associated with worse outcome, while CD8+ cytotoxic T cells demonstrate anti-tumor properties in breast cancer. In this study, we assessed spatial associations between CD163+ TAMs, CD8+ cells and cancer cells in IBC, using deep-learning and ecological statistics. **Methods:** We collected clinicopathological variables, evaluated PDL1-positivity (SP142, Ventana) and scored TILs according to the TIL working group guidelines on H&E slides for 144 IBC patients. Immunostainings for CD8 and CD163 (Hematoxylin-DAB) were done according to validated protocols. All slides were digitized, underwent virtual multiplexing and were evaluated in Visiopharm to quantify the number of DAB+ immune cells. Each immune cell was located using XY coordinates and spatial interactions were examined using a Morisita Horn Index (MHI). Tumor cell coordinates were collected using a deep-learning algorithm applied to the CD8-stained slide. This algorithm was trained in 18 images with more than 150.000 iterations (Deeplabv3+). **Results:** Complete pathological response (pCR) after neo-adjuvant chemotherapy was achieved by 30.6% (n= 30/98) of the patients with initially localized disease. Besides PDL1-postivity (*P*= .03), infiltration with CD8+ T cells (*P*= .02) and TAMs (*P*= .01) also predicted pCR. However, a likelihood ratio test showed no difference between a model using CD8+ cells, TAMs or TILs. Interestingly, the colocalization of CD163+ and CD8+ cells (MHI >0.83) was associated with pCR (*P*= .01) and remained significant in a multivariate model (OR: 3.18; 95% CI: 1.04 – 10.6; P= .05) including TIL score, PDL1-positivity and hormone receptor (HR) status. Furthermore, a shorter disease-free survival (DFS) was associated with HR-status, no pCR and the colocalization of TAMs near tumor cells (HR: 3.3; 95% CI: 1.6 – 7.1; P= .002) in a multivariate model. The density of TAMs was not associated with outcome. **Conclusions:** The impact of TAMs on clinical outcome appears to depend on the spatial arrangement. The number of TAMs solely was not associated with outcome, but patients with more TAMs in proximity of the tumor cells had a worse DFS. Surprisingly, the clustering of TAMs near CD8+ cells was associated with pCR independent of the number of TAMs or TILs. Research Sponsor: Research Foundation - Flanders (FWO).

3087 Poster Session (Board #151), Fri, 8:00 AM-11:00 AM

Discovery of a novel shared tumor antigen in human lung cancer. *First Author: Diane Tseng, Stanford University, Palo Alto, CA*

Background: While there has been much attention on mutation-associated neoantigens in tumors, there is less known about non-mutated tumor antigens that are shared across individuals. Understanding tumor-infiltrating T cell recognition of shared tumor antigens is important for understanding cancer immune recognition and escape, and may reveal novel targets for therapy. **Methods:** We have established a novel approach for discovering shared tumor antigens in human lung cancer. This approach involves identifying candidate T cell receptor (TCR) alpha/beta pairs that are predicted to exhibit specificity for shared tumor antigens in the context of a given human leukocyte antigen (HLA). We then screen the T cell receptor for binding to yeast display libraries of peptide-HLA. The Mark Davis lab at Stanford has previously developed an algorithm that groups T cell receptors into antigen specificity groups based on shared motifs within the TCR complementarity-determining region 3 (CDR3) sequences. Leveraging a dataset of over 700K CDR3 sequences from 178 HLA-typed non-small cell lung cancer (NSCLC) patients, we have found up to 4,300 antigen specificity groups after applying stringent cutoffs. We sequenced TCR alpha/beta pairs from 15 patients with lung adenocarcinoma (n = 4,705). **Results:** We identified an antigen specificity group enriched in tumor compared to adjacent uninvolved lungs. Antigen screening of the T cell receptor belonging to this specificity group using an A02 yeast display libraries led to the identification of a dominant peptide after four rounds of enrichment. We functionally validated that the peptide derived from the protein TMEM161A stimulated Jurkat cells expressing the TCR alpha/beta receptor of interest. We show that full-length TMEM161A protein is processed and presented into a peptide that stimulates primary T cells expressing the TCR alpha/beta receptor. We observe that a peptide from Epstein-Barr virus (EBV) protein LMP2 also stimulated the same TCR alpha/beta receptor. We have show that TMEM161A RNA and protein are overexpressed in human lung cancer compared to adjacent uninvolved lungs. **Conclusions:** We have demonstrated a novel approach toward antigen discovery and identified a shared tumor antigen TMEM161A in human lung cancer. Research Sponsor: Lung Cancer Research Foundation, Conquer Cancer Foundation of the American Society of Clinical Oncology, Ellie Guardino Cancer Foundation Award from the Stanford Cancer Institute.

3088 Poster Session (Board #152), Fri, 8:00 AM-11:00 AM

Effect of Kaiso on immune signaling of breast cancer exosomes. *First Author: Windy Marie Dean-Colomb, Lousiana State University School of Medicine, New Orleans, LA*

Background: Exosomes are communication vesicles that act as mediators of intracellular transfer of genetic information, an important role in intercommunication between tumor cells and immune cells. However, the mechanism underlining this cell-cell communication is not well understanding, particularly in African American breast cancer patients. Recently, our lab has demonstrated that Kaiso, a novel bi-modal transcription factor is highly expressed in African American breast cancer and notably, high Kaiso expression correlates with breast cancer aggressiveness and the disparity in survival outcomes of breast cancer patients of African American compared to European American patients. However, the differential expression and biological consequences of Kaiso in immune signaling of breast cancer exosomes has not been studied yet. Herein we demonstrate the biological role of Kaiso in immune signaling in breast cancer exosomes. **Methods:** In this study we utilized Nanostring immune profiling technology along with multiple *in vitro* and *in vivo* assays were used to study the role of Kaiso in breast cancer immune escape. **Results:** Nanostring pan cancer immune profiling demonstrated that European American breast cancer exosomes exhibited higher expression of TILs markers, T cell activation markers and $CD8^+$T Cells markers compared to African American ($p < 0.05$, FDR), while we observed an increase in the expression of the anti-phagocytic molecule CD47 in breast cancer patient exosomes of African American compared to European American patients. In addition to that CD47 and SIRP-α (Signal Regulatory Protein) are highly expressed in Kaiso-scrambled MDA-MB-231 cells (sh-Scr) and exosomes, whereas THBS1, which is a regulator of CD47 expression and is regarded as angiogenesis inhibitor is significantly increased in sh-Kaiso MDA-231 cells and exosomes. Additionally, we observed that Kaiso directly binds methylated sequences in the promoter region of CD47 and THBS1 by ChIP assay. Furthermore, in vivo sh-Kaiso cells injected into athymic mice exhibited delayed tumor formation after four weeks with smaller tumor size as compared to sh-SCR cells ($p < 0.05$), and we observed higher expression of THBS1 with lower expression of CD47 and SIRP-α molecules by IHC and exosomes isolated from *in vivo* tumors ($p < 0.05$), indicating that Kaiso is associated with macrophage mediated immune escape. **Conclusions:** These findings demonstrate the important role of kaiso in immune signaling through exosomes which may be related with more aggressive cancer phenotype in breast cancer, especially in African Americans. Research Sponsor: DOD.

3089 Poster Session (Board #153), Fri, 8:00 AM-11:00 AM

Immune profiling and clinical outcomes in patients treated with ramucirumab and pembrolizumab in phase I study JVDF. *First Author: Roy S. Herbst, Yale University, New Haven, CT*

Background: In Study JVDF (NCT02443324), we combined ramucirumab (VEGFR2 antagonist) and pembrolizumab (PD-1 antagonist) to simultaneously target the tumor microenvironment and immune checkpoints in patients with advanced non-small cell lung cancer (NSCLC), gastric or gastroesophageal junction adenocarcinoma (G/GEJ), urothelial carcinoma (UC) or biliary tract cancer (BTC). We reported that this combination was associated with increased antitumor activity in patients with PD-L1 positive tumors by immunohistochemistry (IHC) compared with PD-L1 negative tumors.1) Here we explore the association between baseline gene expression profiles and clinical outcomes. **Methods:** JVDF was a nonrandomized phase 1a/b trial that treated patients with intravenous ramucirumab at 8 mg/kg on days 1 and 8 (G/GEJ, BTC) or 10 mg/kg on day 1 (G/GEJ, NSCLC, UC) plus pembrolizumab (200 mg day 1) every 3 weeks.[1] Baseline tumor samples from 53 patients across 7 study cohorts were analyzed with the NanoString PanCancer Immune Profiling Panel for RNA expression and the DAKO PD-L1 IHC 22C3 pharmDx assay for PD-L1 protein expression. Clinical outcomes included progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). **Results:** Across cohorts, PD-L1 gene expression was correlated with increased IFNγ gene expression and immune-related gene signatures (T effector, T cell-inflamed (TIS)), and trended with PD-L1 protein expression. Expression of immune checkpoint-related genes and myeloid-derived suppressor cell /regulatory T cell markers was increased in the NSCLC TPS$\geq$50% PD-L1 IHC subgroup (N=8), while no clear pattern of expression was observed in other cohorts. Higher T effector and TIS scores appeared associated with better survival and response in NSCLC cohorts (mean TIS: 1.21$\pm$0.80 in responders (N=7) vs -0.13$\pm$0.57 in non-responders (N=7); p=0.004), and a trend was observed in G/GEJ cohorts (mean TIS: -0.18$\pm$0.30 (N=5) vs -0.39$\pm$0.21 (N=13); p=0.207). Of note, partial responses and stable disease were also observed in NSCLC and G/GEJ patients with a low baseline inflammatory signature score. Additional analyses are ongoing and will be presented. **Conclusions:** Baseline PD-L1 gene and protein expression tends to correlate with immune-related gene expression, and an inflamed tumor microenvironment may be associated with better clinical outcomes with ramucirumab and pembrolizumab. However, interpretation is limited by lack of control arm and sample size.1) Herbst et al. Lancet Oncol. 2019 Aug; 20 (8): 1109-1123. Clinical trial information: NCT02443324. Research Sponsor: Eli Lilly and Company.

3090 Poster Session (Board #154), Fri, 8:00 AM-11:00 AM

Relationship of infusion duration to safety, efficacy, and pharmacodynamics (PD): Second part of a phase I-II study using VSV-IFNβ-NIS (VV1) oncolytic virus in patients with refractory solid tumors. *First Author: Jaime R. Merchan, University of Miami, Miami, FL*

Background: VV1 (Voyager V1) is derived from VSV, an RNA virus with low human seroprevalence, engineered to replicate selectively in and kill human cancer cells. In Part 1 of this study, we demonstrated the safety of intratumoral VV1 and dose-response, using serum IFNβ as a biomarker; we observed viral replication in tumor and concomitant lymphocyte/neutrophil trafficking (SITC 2018). 2 other studies suggested greater efficacy and higher IFNβ levels with IV administration. Longer infusion durations were reported to mitigate infusion reactions (IRRs) for another oncolytic. **Methods:** We studied 3 different infusion durations of VV1 monotherapy at the recommended phase 2 IV dose (1.7×10^{10} $TCID_{50}$) in patients with advanced solid tumors. Endpoints included safety, preliminary anti-tumor activity, viral titers, IFNβ PD and shedding. Patients received IV VV1 once on D1 and were monitored for DLT over 21 days with efficacy assessments every 6 weeks. IRRs were classified using Lee 2014 criteria for CRS as either constitutional symptoms only (G1) or involving hypotension (G2). **Results:** 18 patients were treated at 30, 60 and 180-minute durations (n = 7, 5 and 6, respectively). No DLTs, deaths or G3-4 related IRR AEs were observed. Most pts were female (67%), white (100%), with ECOG PS 0 (61%) and median 4 lines of prior systemic therapy (range 1-14) for colorectal (CRC; 56%), squamous cell carcinoma (11%), pheochromocytoma (11%), sarcoma (11%) or other (11%) cancers. The table shows results (number of patients) by infusion duration. **Conclusions:** There was no difference in safety between the 3 infusion durations, while efficacy and PD markers suggested better anti-tumor effect with 30-minute infusion. VV1 is safe for caregivers, with no viral shedding. Part 3 of this study will now treat CRC patients with VV1 in combination with a checkpoint inhibitor (avelumab). A 5-arm phase 2 basket study in combination with cemiplimab is proceeding with 30-minute infusions. Clinical trial information: NCT02923466. Research Sponsor: Vyriad.

Duration (mins)	N	IRR G1	IRR G2	Total IRRs	RECIST PR/SD	IFNβ > 150 pg/mL	Shedding
30	7	4	3	7	5	4	0
60	5	4	1	5	3	0	0
180	6	2	3	5	1	0	0

3091 Poster Session (Board #155), Fri, 8:00 AM-11:00 AM

Impact of relacorilant, a selective glucocorticoid receptor antagonist, on the immunosuppressive effects of endogenous cortisol. *First Author: Andrew Greenstein, Corcept Therapeutics, Menlo Park, CA*

Background: Cortisol, an endogenous glucocorticoid receptor (GR) agonist, controls a broad transcriptional program that affects T-cell activation, pro-inflammatory cytokine secretion, and immune cell trafficking. By selectively antagonizing GR, relacorilant may reverse the immunosuppressive effects of cortisol in solid tumor cancers. **Methods:** Immune cells and GR expression were assessed by IHC and calculated based on The Cancer Genome Atlas (TCGA) data. Human PBMCs were stimulated with αCD3+IL-12 +/- cortisol or cortisol + relacorilant. EG7 tumor-bearing mice were treated with anti-PD1 (RMP1-14) ip Q5D +/- relacorilant QD. Whole blood mRNA was measured via Nanostring, hematology was performed using standard complete blood count assays, and cytokines were assessed by immunoassays in study NCT02762981. **Results:** GR expression was observed in human tumor and immune cells. Its abundance was positively correlated with tumor infiltration of T_H2, Treg, and PDL1$^+$ cells ($P<$ .001) and negatively correlated with T_H1 cells ($P<$ .001). In PBMCs, cortisol inhibited, and relacorilant restored, CD8$^+$ T-cell activation ($P<$ .001) and pro-inflammatory cytokine secretion (TNFα $P=$ .006, IFNγ $P<$ .05). In the EG7 syngeneic model, relacorilant increased αPD1 efficacy ($P=$ .007) and decreased circulating IL-10 ($P<$ .002). In patients with advanced solid tumors, relacorilant + nab-paclitaxel systemically suppressed the expression of canonical GR-controlled genes (*ptgs2* $P<$ .001) and genes encoding candidate-immunomodulatory drug targets (*cxcl8*, *ptger4*, *ido1;* $P<$ .001). In a small subset of patients (n = 11), sustained clinical response was associated with increased T-cell count ($P=$ .06) and IFNγ ($P=$ .03), as well as decreased Tregs ($P=$ .06) and IL-10 ($P=$ .03). **Conclusions:** Evidence of T-cell activation by relacorilant was observed in PBMCs, syngeneic mouse tumors, and patients with sustained response in a Phase 1 study. This supports the hypothesis that relacorilant can reverse immune suppression by endogenous cortisol in solid tumor cancers. Clinical studies with immune checkpoint inhibitors and relacorilant are planned. Research Sponsor: Corcept Therapeutics.

3092 Poster Session (Board #156), Fri, 8:00 AM-11:00 AM

A phase I study of mRNA-2752, a lipid nanoparticle encapsulating mRNAs encoding human OX40L, IL-23, and IL-36γ, for intratumoral (iTu) injection alone and in combination with durvalumab. *First Author: Manish R. Patel, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL*

Background: mRNA-2752 is a novel mRNA-based therapeutic agent encoding OX40L T cell co-stimulator, IL-23 and IL-36γ pro-inflammatory cytokines. Here we present findings from a first-in-human study of iTu mRNA-2752 in solid tumor patients as monotherapy or in combination with durvalumab (durva). At the time of presentation, data will encompass the monotherapy escalation MTD/RDE along with the supporting translational work, and the available data in combination. **Methods:** iTu mRNA-2752 was administered every 2 weeks for up to 7 doses as monotherapy or in combination with durva in patients with advanced solid malignancy or lymphoma. Biomarker analyses include measurement of IL-23, IL-36γ and pro-inflammatory cytokine proteins in pre- and post-treatment tumor biopsies and plasma. PD-L1 immunohistochemistry was used to further characterize baseline status and changes to the TME with treatment. **Results:** As of 20 December 2019, 23 solid tumor patients have been treated either with mRNA-2752 alone (n = 14) or in combination (n = 9) and has been well tolerated with no dose limiting toxicities or related grade 3/4 toxicities. Of the 17 patients evaluated per RECIST and iRECIST, 1 had a PR (iRECIST), 6 had SD, and 10 had PD. The patient with a PR (52% tumor reduction) received 0.5 mg mRNA-2752 with durva, and had aPD-1/L1 naïve squamous-cell bladder carcinoma. Tumor shrinkage was observed in an additional 5 patients in injected and/or uninjected lesions in both monotherapy and combination. Preliminary biomarker data showed increased IL-23 and IL-36γ protein expression after 6-24 hours, and increased levels of downstream cytokines IL-22 and IL-6, respectively. Pro-inflammatory cytokines (e.g. IFN-γ, TNF-α) were also significantly increased at 1 day and 1-week post-treatment. Significant increases in PD-L1 expression predominantly in tumor-associated immune cells were observed after first dose and persisted up to 29 days after treatment. **Conclusions:** iTu mRNA-2752 given as monotherapy and in combination with durva is tolerable at all dose levels studied, and administration can be associated with tumor shrinkage. Analyses of tumor and plasma biomarkers suggest a sustained immunomodulatory effect of treatment that includes elevated IFN-γ, TNF-α, and PD-L1 levels. These data support the ongoing testing of the mRNA-2752/durva combination in the dose escalation part of the study. Clinical trial information: NCT03739931. Research Sponsor: Moderna Tx. Inc.

3093 Poster Session (Board #157), Fri, 8:00 AM-11:00 AM

Clinical activity of MCLA-128 (zenocutuzumab), trastuzumab, and vinorelbine in HER2 amplified metastatic breast cancer (MBC) patients (pts) who had progressed on anti-HER2 ADCs. *First Author: Erika Paige Hamilton, Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN*

Background: MCLA-128 (zenocutuzumab), a HER3 pathway inhibitor, is a humanized bispecific full-length IgG1 antibody targeting both HER2 and HER3 with enhanced ADCC activity. The unique Dock & Block mechanism inhibits HER3 from interacting with its ligands and targets HER2 at a different epitope than trastuzumab, blocking HER2/HER3 dimerization and downstream PI3K/AKT/mTOR signaling. In MBC, HER3 overexpression and/or HER3 ligand upregulation are important drivers leading to trastuzumab resistance, indicating a role for MCLA-128. Preclinical activity was seen in HER2+ breast models when MCLA-128 was combined with trastuzumab. Furthermore, single agent MCLA-128 showed consistent antitumor activity in heavily pretreated HER2+ MBC pts. A phase 2, open-label study explored the MCLA-128/trastuzumab plus vinorelbine triplet in an MBC population. **Methods:** This open-label trial planned for up to 40 evaluable women with HER2+/amplified MBC progressing on up to 5 anti-HER2 lines including trastuzumab, pertuzumab and an anti-HER2 ADC. Pts received MCLA-128 (750 mg, 2h IV), trastuzumab (8 mg/kg loading, then 6 mg/kg) and vinorelbine (25 mg/m^2, D1 and 8), q3w. A safety run-in of MCLA-128 + trastuzumab ± chemotherapy was performed. Disease control rate (DCR; RECIST 1.1, per investigator), best overall response (BOR), overall response rate (ORR), safety, and PK are evaluated. Data cutoff was 14Nov2019. **Results:** 28 pts with a median 3 lines (range 2-5) of anti-HER2 therapy (metastatic setting) and 3 (range 1-6) metastatic sites, received a median of 5 (range 1-17) MCLA-128 cycles. Among 26 pts evaluable for efficacy, 20 patients had CR/PR/SD as BOR; DCR was 77% (90%CI: 60-89) with 1 confirmed CR and 4 PRs (2 unconfirmed). Common related AEs (all grades; G3-4) were neutropenia/neutrophil count decrease (61%; 46%), diarrhea (61%; 4%), asthenia/fatigue (46%; 0), nausea (29%; 0). No clinically significant LVEF decline was seen. At the end of cycle 1, mean trough levels of MCLA-128 was 19.1 μg/mL, and mean terminal half-life was 112 h (n = 8-11). Data on the primary endpoint, clinical benefit rate at 24 weeks, and biomarkers will be provided. **Conclusions:** The triplet MCLA-128-based combination is active in heavily pretreated pts with HER2+/amplified MBC. The regimen is safe and well tolerated with a manageable AE profile mostly related to the chemotherapy component. Clinical trial information: NCT03321981. Research Sponsor: Merus NV.

3094 Poster Session (Board #158), Fri, 8:00 AM-11:00 AM

A phase I, open-label, multicenter, single-dose escalation and multi-dose study of a monoclonal antibody targeting CEACAM1 in subjects with selected advanced or recurrent malignancies. *First Author: Roni Shapira, Chaim Sheba Medical Center, Tel Hashomer, Israel*

Background: The carcinomembryonic antigen cell adhesion molecule 1 (CEACAM1, CD66a) is a member of the CEA gene family. CEACAM1 interacts homophilically and heterophilically with CEACAM5, and is involved in various anti-proliferative activities. CEACAM1 is expressed on a variety of epithelial and hematological cells, including multiple types of cancer and activated lymphocytes. High CEACAM1 expression in some tumor types is known to be associated with poor disease prognosis. Recently it was demonstrated CEACAM1 is co-expressed on exhausted lymphocytes with other immune checkpoints such as TIM-3 and may regulate downstream activity. CM24 is a novel humanized α-CEACAM1-specific antibody with nM affinity to the N terminal domain of CEACAM1, which blocks intercellular CEACAM1 interactions. **Methods:** The primary objective was to test the safety and tolerability of CM24 in adult patients with advanced or recurrent cancer. Secondary objectives included assessment of CM24 PK and PD profiles, anti-tumor response and the recommended Phase 2 dose. Patient received IV infusion of CM24 at 7 dose levels ranging between 0.01 and 10 mg/kg in a cycle of 4 doses administered q2wks followed by a 6-week observation only period and additional 6 cycles. **Results:** 27 patients (median pretreatment of 4 prior regimens; range 2-8, 11 colorectal, 7 melanoma, 4 ovarian, 3 gastric, 2 NSCLC; 13 males, 14 females, mean age of 60 years), were included. Treatment with CM-24 was overall well-tolerated without DLTs up to 10 mg/kg. The most frequent AE was grade 1-3 increased alanine aminotransferase (7 subjects) and the most severe AE was grade 3/4 increase in gamma-glutamyltransferase (4 subjects). Drug-related AEs were observed in 63% of the subjects with grade 3-5 occurred in 3.7%. Eight subjects (29.6%) had stable disease as the best overall response. Median overall survival was 4 (3.4, 8.0) and 6.2 (2.7, 10.2) months for the 3 and 10 mg/kg doses, suggesting dose response. Cmax, AUC and t1/2 increased with increasing dose with the longest t1/2 of 11.2 days obtained at 10mg/kg. The average target occupancy of CM24 at 3mg/kg and 10mg/kg were 75% and 93%, respectively. **Conclusions:** PK and target-mediated drug disposition analysis suggest that doses higher than 10mg/kg are needed for target saturation at a q2 week regimen while a q3 week regimen is less optimal. A phase 1/2 clinical trial testing CM24 in combination with anti-PD-1 therapy in patients with NSCLC including assessment of CEACAM1 expression is warranted. Clinical trial information: NCT02346955. Research Sponsor: Merck Sharp & Dohme Corp.

3095 Poster Session (Board #159), Fri, 8:00 AM-11:00 AM

Gut microbiome to predict efficacy and immune-related toxicities in patients with advanced non-small cell lung cancer treated with anti-PD-1/PD-L1 antibody-based immunotherapy. *First Author: Taiki Hakozaki, Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan*

Background: The gut microbiome (GM) plays an important role in shaping systemic immune responses. Preclinical and clinical data suggest that GM influences anti-PD-1/PD-L1 or -CTLA-4 Antibody (Ab)-mediated anti-cancer responses. Furthermore, there is strong evidence that antibiotics (ATB) worsen clinical outcomes based on multiple retrospective and one prospective studies using immune checkpoint inhibitor (ICI). However, whether GM profiling, at baseline or post-ATB, could represent a biomarker of response in advanced non-small cell lung cancer (NSCLC) during ICI therapy remains unknown. **Methods:** We prospectively collected baseline (pre-ICI) fecal samples and clinical data Japanese patients (pts) with NSCLC treated with anti-PD-1/PD-L1 Abs in first or second-line therapy. We performed a 16S rRNA V3-V4 sequencing of gene amplicons of fecal microbes. Amplicon sequence variants were generated with dada2 R package. Diversity analysis was performed with phyloseq R. Differential abundance analysis was performed with both LEfSe and DESeq2 methods. Clinical endpoints were progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and immune-related adverse events (irAE). **Results:** 70 fecal samples were analyzed. Median OS and PFS in all patients were 16.1 and 5.2 months, respectively. 16 pts (23%) were exposed to ATB 1 month prior to ICI initiation. Pts on ATB had lower α-diversity at baseline and underrepresentation of *Clostridiales* and *Ruminococcaceae UCG 13*. When analyzing ATB-free pts, lower α-diversity was observed in non-responders. In addition, *Ruminococcaceae UCG 13* was enriched in patients with OS $>$ 12 months, favorable ORR, and PFS $>$ 6 months. *Clostridiales* order was also enriched in patients with OS $>$ 12 months. Compositional GM differences were also observed between the patients who experienced clinically significant ($\geq$grade 2) irAE; *Lactobacillaceae* and *Raoultella* were enriched in pts who had no significant irAE. **Conclusions:** We demonstrated the negative influence of ATB on GM composition and identified differential bacteria repertoire in pts experiencing favorable clinical outcomes or low grade irAE. Our data pave the way to the development of diagnosis tools aimed at identifying gut dysbiosis to predict resistance or irAE during ICI for NSCLC. Research Sponsor: This work was supported by JSPS KAKENHI Grant Number JP19K16820.

3096 Poster Session (Board #160), Fri, 8:00 AM-11:00 AM

A phase I dose-escalation and expansion study of intratumoral CV8102 as single-agent or in combination with anti-PD-1 antibodies in patients with advanced solid tumors. *First Author: Thomas Eigentler, Department of Dermatology, University Hospital Tübingen, Tübingen, Germany*

Background: CV8102 is a non-coding, non-capped RNA that activates the innate (via TLR7/8, RIG-I) and adaptive immunity dose-dependently. CV8102 injected intratumorally (i.t.), as a single agent or combined with systemic anti-PD-1 antibody (Ab) led to tumor growth inhibition in animal models and showed synergism with PD-1 blockade. **Methods:** An open-label, cohort-based, dose escalation and expansion study in patients with advanced cutaneous melanoma (cMEL), cutaneous squamous cell carcinoma (cSCC), head and neck squamous cell carcinoma (hnSCC) or adenoid cystic carcinoma (ACC) is ongoing investigating i.t. CV8102 as single agent and in combination with anti-PD-1 antibodies. [NCT03291002]. **Results:** As of December 2019, 23 patients in the cohort A (single agent) and 13 patients in cohort C (combination with anti-PD-1 Ab) were exposed to at least one dose of CV8102 at dose levels of 25-600 μg (single agent) and 25-450 μg (combination). No dose limiting toxicities (DLTs) were observed within the first two weeks of study drug treatment. Most frequent TEAEs were G1/2 fatigue, fever, chills and headache. 4 (17%) patients (pts) in cohort A and 3 (23%) pts in cohort C experienced related G3 TEAEs that were manageable with supportive treatment (liver enzyme increases (3), abscess at injection site (1), hypertension (1), asymptomatic elevation of pancreatic enzymes (2)). In cohort A, 2 cMEL patients experienced an objective response according to RECIST 1.1 (1 CR in a PD-1 naïve pt and 1 PR in a PD-1 refractory pt) and 2 further pts (cMEL, hnSCC) showed SD with shrinkage of tumor lesions. **Conclusions:** CV8102 i.t. was well tolerated without dose limiting toxicities to date and showed evidence of single agent activity. Updated results on safety, efficacy and serum biomarkers will be presented. Clinical trial information: NCT03291002. Research Sponsor: CureVac AG.

3097 Poster Session (Board #161), Fri, 8:00 AM-11:00 AM

Immune activation in first-in-human anti-macrophage antibody (anti-Clever-1 mAb; FP-1305) phase I/II MATINS trial: Part I dose-escalation, safety, and efficacy results. *First Author: Petri Bono, Terveystalo Finland and University of Helsinki, Helsinki, Finland*

Background: The scavenger receptor CLEVER-1 mediates the clearance of "unwanted" self-components and is highly expressed on tumor associated macrophages (TAMs). CLEVER-1 expression is associated with immunotherapy resistance and poor survival in several cancers. Pre-clinical studies demonstrate that CLEVER-1 inhibition increases TAM pro-inflammatory cytokine secretion and antigen presentation reactivating CD8 T cell responses with robust anti-tumor activity. Targeting CLEVER-1 could therefore overcome the immunosuppressive tumor microenvironment and has led to the development of FP-1305, a humanized anti-CLEVER-1 IgG4-antibody. **Methods:** The MATINS (Macrophage Antibody To INhibit immune Suppression) trial is a multicenter first-in-human phase I/II study (NCT03733990) to assess the tolerability, safety and preliminary efficacy of FP-1305 in patients (pts) with advanced cancers including immunotherapy-refractory melanoma, cholangiocarcinoma, hepatocellular carcinoma, ovarian cancer, colorectal (CRC), and pancreatic ductal adenocarcinoma. Part 1 consisted of a dose escalation phase; 30 pts (median age 65, range 30-81) were enrolled to examine 5 dose levels (0.1, 0.3, 1.0, 3.0, 10 mg/kg), to determine the optimal dose of FP-1305 for Parts 2 and 3. Two-stage time-to-event continual reassessment method (TITE-CRM) was utilized for the dose escalation in Part 1. Pts received 1-8 cycles (median 3) of FP-1305 Q3w. FP-1305 was well tolerated without dose-limiting toxicities. A consistent increase in blood NK cells, CD8/CD4 T cell ratio, B cells and a decrease in regulatory T cells was demonstrated. FP-1305 dosing led to the activation ($CD25^+$) and Th1 skewing ($CXCR3^+$) of T cell populations including increase in effector CD8 T-cells with downregulation of several inhibitory immune checkpoint molecules (PD-1, PD-L1, CTLA-4, and LAG3). Increased circulating IFNγ levels were detected, with the highest levels in a heavily pretreated metastatic, microsatellite stable (MSS) colorectal cancer patient leading to a partial tumor response (-52%). FP-1305 is the first macrophage checkpoint inhibitor candidate promoting immune switch with promising tolerability and clinical anti-tumor activity. FP-1305 represents a novel treatment option to provoke immune response especially in non-inflamed tumors. Full safety, pharmacokinetic and efficacy results of MATINS trial (Part 1) will be presented for the first time in a final late breaking abstract. Clinical trial information: 2018-002732-24. Research Sponsor: Faron Pharmaceuticals.

3098 Poster Session (Board #162), Fri, 8:00 AM-11:00 AM

First-in-class microbial ecosystem therapeutics 4 (MET4) in metastatic solid cancer patients treated with immunotherapy: MET4-IO. *First Author: Daniel Vilarim Araujo, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Therapeutic augmentation of the intestinal microbiome to improve immunotherapy outcomes is an active area of investigation. Microbial Ecosystem Therapeutics (METs) are consortia of human-derived bacteria designed to be reproducible, scalable and safe alternatives to fecal transplant. MET4 is a first-in-class consortium of taxa associated with immune checkpoint inhibitor (ICI)-responsiveness. Here we describe preliminary results of MET4-IO, an interventional trial assessing the safety and ecological effects of MET4 in ICI recipients. **Methods:** MET4-IO is a randomized investigator-initiated trial, evaluating MET4 in solid cancer patients treated with ICI. MET4-IO involves 3 cohorts of 65 total patients: Group A, a safety cohort of 5 patients already on ICI; Group B, patients starting ICI, randomized 3:1 to receive MET4 or not; Group C, patients on ICI who experience radiological progression but not clinical deterioration, randomized 1:1 to receive MET4 or not. Stool and blood samples are collected at baseline and 4-5 additional time-points. For this interim analysis, 16S rRNA gene sequencing was performed on fecal specimens. Shannon diversity, relative abundance (RA), number and fold-change of MET4 taxa $>$ RA 0.01 were assessed and compared to controls. **Results:** As of January 26, 2020, 21 patients were enrolled (A = 5,B = 12,C = 4), and 15 (71%) received MET4. The mean age was 65.9 years, 40% were females, 52% had head and neck cancer and 19% melanoma. Sixteen patients (76%) were treated with an anti-PD1 agent as monotherapy and 5 with a combination of anti-PD1 and anti-CTLA4 antibodies. G3-4 toxicities (CTCAEv5.0) attributed to ICI were observed in 13% vs. 17% of MET4 exposed and control patients, respectively. Three patients (20%) experienced toxicities attributed to MET4, all grade 1 except G2 dyspepsia in 1 patient. A greater number of MET4-associated taxa were detectable in MET4 recipients than controls ($p < 0.01$), with a trend towards higher cumulative RA ($p = 0.10$). No significant change in Shannon diversity after MET4 was observed, however controls were more likely to lose diversity overtime than MET4 recipients ($p = 0.05$). Colonization with MET4 varied by recipient and by taxon. *Bifidobacterium*, *Collinsella* and *Enterococcus* were significantly more common and abundant in MET4 recipients than controls. **Conclusions:** In this cohort, MET4 treatment was safe and associated with higher MET4-associated taxa in recipients than controls. Further analyses including peripheral blood immunophenotyping are ongoing. Clinical trial information: NCT03686202. Research Sponsor: University Health Network, Pharmaceutical/Biotech Company.

3099 Poster Session (Board #163), Fri, 8:00 AM-11:00 AM

Open-label, phase I study evaluating feasibility and safety of subcutaneous IMP321 (LAG-3Ig fusion protein, eftilagimod alpha) combined with avelumab in advanced stage solid tumor entities: Results from stratum D of the INSIGHT platform trial. *First Author: Thorsten Oliver Goetze, University Cancer Center Frankfurt, Institut für Klinisch-Onkologische Forschung and IKF Klinische Krebsforschung GmbH am Krankenhaus Nordwest, Frankfurt, Germany*

Background: Stratum D of the INSIGHT study investigates the feasibility and safety of s.c. application of IMP321 (eftilagimod alpha) combined with the PD-L1 inhibitor avelumab in advanced stage solid tumors. The MHC class II agonist IMP321 activates antigen-presenting cells followed by CD8 T-cell activation. The addition of avelumab aims at enhancing activity by combining IMP321's activating effects on immune cells with the release of immune inhibitory effects caused by interruption of the PD-1/PD-L1 axis. **Methods:** This investigator-initiated phase I trial consists of four strata: intratumoral (A) or intraperitoneal IMP321 (B); s.c. IMP321 with SOC (C) or with PD-L1 inhibition (D). This abstract focuses on Stratum D. Patients (pts) receive 800mg avelumab i.v. q2w along with s.c. IMP321 injections (6mg IMP321 in cohort 1 and 30mg IMP321 in cohort 2). 12 pts are planned in stratum D: 6 pts in cohort 1 and 6 pts in cohort 2. Primary endpoint is safety. **Results:** So far, 8 pts have been enrolled (6 in cohort 1 and 2 in cohort 2). In 6 pts (cohort 1) treated for different tumor indications (gastric, gallbladder, colon cancer, pleural mesothelioma), no dose limiting toxicities occurred. 3 serious adverse events (SAEs) (1 acute kidney injury grade 5 in 1 pt, 2 preileus grade 3 in 1 pt) were reported, none of them was related to any of the study drugs. In total, 34 adverse events (AEs; grade 1-2, 21; grade 3, 12; no grade 4; grade 5, 1) have been documented in 5 pts. Most common grade 1-2 AEs were pain, nausea, and injection site reaction in 50%, 33%, and 17% of the pts. Most common grade 3 AEs were nausea/vomiting, preileus/ileus, and ascites in 33%, 33%, and 17% of the pts. One AE grade 5 (acute kidney injury) was reported. 4 AEs grade 1-2 were possibly or definitely related to IMP321 (injection site reaction 2x; fever; lipohypertrophy), 6 AEs grade 1-2 were possibly or definitely related to avelumab (nausea 2x; chills; fever; dyspnea; lipohypertrophy). All AEs grade 3-5 were unrelated to any of the study drugs. Of the 8 pts enrolled so far, 4 had disease progression (acc. to RECIST 1.1), 1 partial response, 1 stable disease with some extent of tumor shrinkage, and 2 have not had tumor assessment yet. **Conclusions:** Combination treatment with avelumab 800mg and IMP321 6mg is safe and well tolerated. Cohort 2 will be presented at the meeting. Clinical trial information: NCT03252938. Research Sponsor: Immutep.

3100 Poster Session (Board #164), Fri, 8:00 AM-11:00 AM

Initial results from a phase II study (TACTI-002) in metastatic non-small cell lung or head and neck carcinoma patients receiving eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab. *First Author: Enriqueta Felip, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Eftilagimod alpha (efti) is a soluble LAG-3 protein that binds to a subset of MHC class II molecules to mediate antigen presenting cell (APC) activation and then CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment with efti may lead to stronger anti-tumor responses than observed with pembrolizumab alone. We hereby report initial results of a phase II trial (NCT03625323). **Methods:** A predefined number of patients (pts) are recruited into this 3-cohort trial irrespective of PD-L1 expression; part A: 1st line, PD-X naïve NSCLC; part B: 2nd line, PD-X refractory NSCLC and part C: 2nd line PD-X naive HNSCC. The study has a Simon's 2-stage design, with objective response rate (ORR) as primary endpoint. Secondary endpoints include disease control rate, progression free and overall survival, PK, PD and immunogenicity. Additional pts (N2) will be recruited for each part if pre-specified thresholds for ORR are met. Up to 109 pts will be enrolled. Efti is administered as 30 mg subcutaneous injection every 2 wks for 8 cycles and then every 3 wks for 9 cycles with pembrolizumab (200 mg intravenous infusion every 3 wks for up to 2 yrs). The study was approved by ethic committees and institutional review boards. **Results:** Between 04 Mar 19 and 31 Jan 2020, 48 pts were enrolled and evaluated for safety and exposure. The median age was 66 yrs (range 48-84) and 73 % were male. The ECOG was 0 in 50 % and 1 in 50 % of pts, respectively. Pts received a median of 5 (7) and in total 311 (413) pembrolizumab (efti) administrations, respectively. Three pts (6.3 %) discontinued study treatment due to AEs. The most common ($>$ 10%) adverse events (AEs) being cough (31 %), asthenia (23 %), decreased appetite (19 %), fatigue (19 %), dyspnea (17 %), diarrhea (15 %) and constipation 13 %). From part A all pts (n = 17) were evaluated. Eight pts (47 %) had a partial response (iPR) and six (35 %) had stable disease according to iRECIST representing an ORR (DCR) of 47 % (82 %). irPRs were observed in all different PD-L1 groups ($<$ 1%; $\geq$ 1 % $\leq$49 %; $\geq$ 50 %). Ten (10; 59 %) pts are still on therapy (8+ months). In part C stage 1 15/18 pts are evaluable and six (40 %) had an iPR to date. **Conclusions:** Efti in combination with pembrolizumab is safe and shows encouraging antitumor activity in all comer PD-L1 1st line NSCLC and 2nd line HNSCC. Stage 2 has opened for both parts. Clinical trial information: NCT03625323. Research Sponsor: Immutep S.A.S.

3101 Poster Session (Board #165), Fri, 8:00 AM-11:00 AM

A phase I study to evaluate the T-cell engager AMV564 alone and in combination with pembrolizumab in subjects with advanced solid tumors. *First Author: Alexander Starodub, Riverside Peninsula Cancer Institute, Newport News, VA*

Background: Overcoming the immune-suppressive tumor environment induced by myeloid-derived suppressor cells (MDSC) is a major challenge in immune therapy. CD33 signaling in immature myeloid cells promotes expansion of MDSC and production of immune-suppressive factors. AMV564 is a bivalent, bispecific T-cell engager that binds CD3 and CD33. Preferential binding of AMV564 to areas of high CD33 density enables selective targeting of MDSC. Ex vivo data (Cheng 2017; *Blood*;130:51) and an ongoing clinical trial in acute myeloid leukemia (NCT03144245) demonstrate the ability of AMV564 to deplete MDSC while sparing monocytes and neutrophils. **Methods:** In this 3+3 dose escalation study, patients with advanced solid tumors receive AMV564 once daily via subcutaneous (SC) injection for 2 out of 3 wks per cycle, alone or in combination with pembrolizumab (200 mg every 3 wks). Key objectives are to evaluate AMV564 safety, identify a maximum tolerated or recommended phase 2 dose, and evaluate PK, immunophenotype of myeloid and T cell compartments, and preliminary efficacy. **Results:** Eleven patients have been enrolled: 8 monotherapy (3 at 15 mcg/d, 5 at 50 mcg/d) and 3 combination (5 mcg/d). Tumor types include ovarian (n = 2), small bowel, gastroesophageal junction, endometrial, rectal, penile, urothelial, squamous cell carcinoma (skin), appendiceal, and non-small cell lung. AMV564 was associated with grade (G) 1-2 injection site reactions and G1-2 fevers, which were manageable with acetaminophen and diphenhydramine, as well as G2 weight gain and G3 anemia. No dose-liming toxicity has been observed in any cohort. Three monotherapy patients (15 mcg/d) were evaluable for efficacy with $\geq$1 on-treatment scan; 2 had SD and 1 PD per RECIST 1.1 criteria. T cell activation, as shown by redistribution from the periphery (margination), was apparent in the first week of dosing for most patients. Compensatory myelopoiesis led to initial expansion of MDSC which were then depleted by AMV564. Increased cytotoxic T cell activation and T-helper (Th) 1 response was evidenced by increased T-bet positive CD4 and CD8 cells and controlled or decreased regulatory T cells. In some patients, effector memory CD8 cell populations (Tem and Temra) were expanded. **Conclusions:** AMV564 is safe and tolerable when administered SC at doses of 15 mcg/d alone and 5 mcg/d in combination with pembrolizumab. AMV564 depleted MDSC populations and altered T cell profiles consistent with activation of cytotoxic T cells and a Th1 response. Clinical trial information: NCT04128423. Research Sponsor: Amphivena Therapeutics.

3102 Poster Session (Board #166), Fri, 8:00 AM-11:00 AM

An increase in serum choline levels to predict progression-free survival (PFS) in patients (pts) with advanced cancers receiving pembrolizumab. *First Author: Geoffrey Alan Watson, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Recent work from our laboratory demonstrated that T cell-derived acetylcholine induces vasodilation and increases T cell migration to infected tissues in response to viral infection (Cox et al. Science 2019). Choline acetyltransferase catalyzes the production of acetylcholine from choline and acetyl-CoA, however acetylcholine is challenging to quantify due to its extremely short half-life while choline is stable. This study is the first reported attempt to correlate serum choline levels in patients (pts) with advanced solid tumors receiving pembrolizumab with treatment outcomes. **Methods:** Blood samples were collected pre-treatment in 106 pts treated with pembrolizumab 200 mg IV Q3W in the investigator-initiated INSPIRE study (NCT02644369). Of these, 81 pts had on-treatment blood samples collected at week 7 (pre-cycle 3). Serum choline was analyzed with an HPLC-tandem mass spectrometry assay. PD-L1 staining was performed in baseline tumor tissues using 22C3 antibody and scored using modified proportion score. Tumor mutational burden (TMB) was calculated based on number of nonsynonymous mutations detected using whole exome sequencing. Multivariable Cox models were used to assess the impact of choline on PFS and OS, while adjusting for cohort, PD-L1 expression and TMB. **Results:** This pan-cancer group of 106 pts (median age 55, 62% females) comprised of 5 cohorts: squamous cell carcinoma of the head and neck = 19 pts, triple negative breast cancer = 22, high grade serous ovarian cancer = 21, melanoma = 19, mixed solid tumors = 32. With a median follow-up of 11 months, the median PFS = 1.9 months and median OS = 13.9 months for the entire cohort. In univariable analysis adjusted by cohort, baseline serum choline levels in 106 pts did not correlate with PFS or OS. However, an increase in serum choline level at week 7 compared to pre-treatment (D choline) in 81 pts was significantly associated with a better PFS (aHR 0.49, 95% CI 0.28-0.85, p = 0.01), and a trend towards a better OS (aHR 0.57, 95% CI 0.32-1.03, p = 0.064). In multivariable analysis, D choline remains significantly associated with an improved PFS (p = 0.0087) after adjustment for cohort, PD-L1 and TMB. **Conclusions:** This is the first exploratory report of serum choline levels in pan-cancer pts receiving pembrolizumab. The association between improved PFS and D choline suggests a possible role for the cholingeric system in the regulation of antitumor immunity. Further nonclinical and clinical studies are required to validate this finding. Research Sponsor: Merck.

3103 Poster Session (Board #167), Fri, 8:00 AM-11:00 AM

Single vector multiplexed shRNA provides a non-gene edited strategy to concurrently knockdown the expression of multiple genes in CAR T cells. *First Author: David Edward Gilham, Celyad, Mont-Saint-Guibert, Belgium*

Background: Engineered T cells expressing chimeric antigen receptors (CAR) are now delivering clinically relevant results in patients with advanced hematological malignancies. One critical area for future development is to modulate gene expression thereby endowing the engineered T cell with specific desired features that enhance anti-tumor activity. **Methods:** Short-hairpin RNA (shRNA) were cloned individually or multiplexed within micro-RNA scaffolds that enabled the co-expression of the individual shRNA with a CAR and a selectable marker all driven by a PolII promoter within a single retroviral vector. Primary human T cells transduced with the CAR-shRNA vectors were selected, expanded in vitro, subjected to negative selection to eliminate any remaining TCR^+ cells and examined for target gene expression and functional activity. **Results:** A 500bp DNA fragment incorporating a shRNA-specific for CD3ζ cloned into a retroviral vectoreffectively knocked down expression of CD3ζ in transduced BCMA-specific CAR T cells. The consequent reduction of cell surface TCR expression resulted in minimal cytokine production upon TCR stimulation in vitro providing a potential allogeneic CAR T approach. These CAR T cells showed no demonstrable evidence of GvHD induction when infused in NSG mice yet maintained BCMA-specific CAR activity in KMS-11 and RPMI-8226 established myeloma models. Initial studies further confirmed that two shRNA could be expressed from a single retroviral vector to modulate the expression of multiple genes. Further engineering of the microRNA framework reduced the size of the transgene load to 394bp while enabling the expression of up to 4 shRNA within a single vector. shRNA specific for CD3ζ, beta-2-microglobulin, CD52 and diacylglycerol kinase alpha were engineered into the framework downstream of a CD19-CAR. Transduced Jurkat cells showed concurrent knockdown of the respective gene products at the mRNA and protein levels. **Conclusions:** A first-in-human clinical trial evaluating the first-generation single shRNA-vector in the context of a BCMA-targeting CAR as a non-gene edited approach to allogeneic CAR T cell therapy will be initiated in 2020. The proof of principle study here shows that multiple shRNAs are active within a single viral vector thereby avoiding the need for bespoke individual clinical reagents to target multiple genes. The multiplexed shRNA vector system is now in further development to explore whether this strategy can enhance the therapeutic potential of CAR T cells. Research Sponsor: Celyad SA.

3104 Poster Session (Board #168), Fri, 8:00 AM-11:00 AM

Combination therapy with DPX-Survivac, intermittent low-dose cyclophosphamide (CPA) and pembrolizumab for the treatment of advanced and metastatic solid tumors: Early safety and efficacy results from a phase II basket study. *First Author: Henry Jacob Conter, William Osler Health System, Brampton, ON, Canada*

Background: DPX-Survivac is a targeted T cell therapy against tumors expressing survivin. The robust and durable survivin specific T cells induced by DPX-Survivac have been shown to infiltrate tumors and are associated with clinical response in blood and solid tumors. In nonclinical studies, treatment with DPX-Survivac increases PD-L1 and PD-1 expression providing the rationale for combination with anti-PD1/L1. This study investigates if enhanced clinical benefits can be achieved in a subset of solid tumor indications with different response rates to pembrolizumab single agent therapy. **Methods:** Subjects with survivin-expressing advanced, recurrent HCC, NSCLC, bladder and MSI-H tumors are enrolled to single arm, non-randomized cohorts that each utilizes a Simon 2-stage design. The primary objectives are to determine the ORR by RECIST 1.1 and safety profile of treatment with DPX-Survivac/CPA and pembrolizumab. Secondary objectives are DoR, DCR, PFS, and OS as measured by iRECIST. Exploratory analyses will look at T cell kinetics and infiltration of the tumor along with extensive biomarker analyses to further support the mechanism of action of DPX-Survivac when combined with pembrolizumab. **Results:** Thirty subjects across HCC (N = 5), NSCLC (12), bladder (6) and MSI-H (7) tumors that express survivin were enrolled for this analysis. The median number of prior lines of therapies was 2 [0 to 10]; 16/30 previously received and progressed on or after CPI therapy. As of the data cutoff, 10 subjects had at least 1 on-treatment scan. Six of 10 subjects (60%) demonstrated target lesion regressions with 3 achieving PR by RECIST (2 bladder, 1 MSI-H [endometrial]) and 3 achieving SD (2 with prior CPI), all are ongoing. Twenty-one of 30 subjects remain on treatment. Nine subjects have discontinued treatment: 5 subjects due to early progression, 2 due to unrelated AEs, and 2 withdrew consent. Treatment has been well tolerated with no immune-related AEs and 2 related SAEs reported. The majority of AE have been grade 1-2 injection site reactions. DPX-Survivac treatment induced a robust survivin-specific T cell response and tumor immune infiltration which are being evaluated for potential correlation with clinical response. **Conclusions:** DPX-Survivac/CPA with pembrolizumab is well tolerated and shows early signs of clinical efficacy and disease control in advanced and metastatic solid tumors. Clinical trial information: NCT03836352. Research Sponsor: IMV Inc.

3105 Poster Session (Board #169), Fri, 8:00 AM-11:00 AM

A phase I, dose-escalation study of ADG106, a fully human anti-CD137 agonistic antibody, in subjects with advanced solid tumors or relapsed/refractory non-Hodgkin lymphoma. *First Author: Li Zhang, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: ADG106 is a fully human agonistic anti-CD137 monoclonal IgG4 antibody, targeting a unique epitope of CD137 with novel mechanism of actions for CD137 agonism, CD137 ligand antagonism and potent cross-linking *via* FcgRIIb. This phase 1 study was conducted to assess its safety, tolerability, pharmacokinetic (PK) profile, immunogenicity and preliminary efficacy. **Methods:** Eligible patients with age 18 to 75, ECOG ≤1, measurable lesion received intravenous infusion of ADG106 every 3 weeks for a maximum of 24 months. Accelerated titration was applied in 0.1mg/kg dose level and traditional Fibonacci 3+3 method was applied in 0.5, 1.5, 3.0, 5.0 and 10.0 mg/kg dose levels. A dose-expansion cohort will be started for dose levels that have been proved tolerable and with evidence of clinical or biological activity. **Results:** Data cutoff at Jan 17 2020, 15 patients [5 adenoid cystic carcinoma (ACC), 5 non-small cell lung cancer (NSCLC), 3 nasopharyngeal carcinoma, 1 malignant pleural mesothelioma and 1 follicular lymphoma] were enrolled and received treatment: 0.1mg/kg (n = 1), 0.5mg/kg (n = 3), 1.5mg/kg (n = 5), 3mg/kg (n = 3), and 5mg/kg (n = 3). Of these 15 patients, 6 with ongoing treatment, 9 discontinued (8 progression disease, 1 lack of clinical benefit). Medium treatment duration was 2 cycles (range 2-8). No dose limiting toxicities were observed. Seven (47%) patients experienced treatment-related AEs (TRAEs): rash (13%), pruritus (13%), nausea (7%), pyrexia (7%), hemoptysis (7%), mouth ulceration (7%), vomiting (7%), chest discomfort (7%), LDH increased (7%). All TRAEs were grade 1, no grade ≥3 occurred. One serious adverse event (anemia, not related) was observed. Pharmacokinetic analysis of ADG106 showed a half-life ranging from 5~10 days, with dose-dependent increase of systemic exposure. Treatment induced anti-drug antibodies were developed in 3 (20%) patients. No objective response was observed among the 14 evaluated patients. Disease control rate was 57% (8 stable disease), tumor shrinkage was observed in 3 (21%) patients (2 ACC, 1 NSCLC). **Conclusions:** ADG106 is safe and tolerable at doses up to 5 mg/kg in solid tumors and non-Hodgkin lymphoma. The dose expansion cohorts have started at selected doses. Clinical trial information: NCT03802955. Research Sponsor: None.

3106 Poster Session (Board #170), Fri, 8:00 AM-11:00 AM

Deep learning-based predictive imaging biomarker model for EGFR mutation status in non-small cell lung cancer from CT imaging. *First Author: Abhishek Mahajan, Tata Memorial Centre, Mumbai, India*

Background: Deep learning based radiogenomic (DLR) models present a promising performance in assisting lung cancer care. The purpose of this study was 1) To develop and validate DLR signatures to predict the EGFR mutation, 2) To assess the incremental value of these DLR signatures in comparison to the traditional clinical and semantic features. **Methods:** 223 patients were selected from two phase III randomized trials in patients with advanced non-squamous NSCLC with *EGFR*-sensitizing mutation and EGFR wild type who were planned to receive palliative therapy (trial 1: gefitinib or gefitinib plus pemetrexed and carboplatin and trial 2: pemetrexed maintenance and erlotinib maintenance). Our method is an end-to-end pipeline that requires only the manually selected tumour region in a CT image without precise tumour boundary segmentation or human-defined features. Two deep convolutional neural networks with 3D U-Net architectures are trained to segment lung masses and nodules from 3D regions of the CT image. The primary end point was EGFR prediction using Radiomics and DLR pipeline. We also compared the performance of combination of models in predicting the mutational status. **Results:** A total of 223 patients (mean age, 54.18 years; age range, 28–80 years) were included in this study. There were 121 (54.3%) patients with EGFR mutation and 102 (45.7%) patients who were EGFR wild type. On multivariate logistic regression analysis, Clinical variable and CT semantic features that were found to be significantly associated EGFR mutation were tumor stage, smoking status, pure solid texture, presence of non-tumor lobe nodule, and average enhancement. For predicting EGFR mutation, ROC curve plotted with clinical variables model, CT semantic variables model, Radiomics model, DLR model showed an AUC value of 0.70, 0.73, 0.94, 0.72 respectively. Clinical variables and semantic features were added to the radiomics predictive model and deep learning predictive model independently, showed further improvement in the accuracy for either model from AUC 0.94+/-0.02 to 0.96+/-0.02 and from AUC 0.72+/-0.02 to 0.82+/-0.04 respectively. **Conclusions:** The radiomics and DLR model by machine-learned information, extracted from CT images without precise manual segmentation, could predict EGFR mutation with very high accuracy. This AI based model can be used as non-invasive and easy-to-use surrogate imaging biomarker for EGFR mutation status prediction. Clinical trial information: CTRI/2018/10/022102. Research Sponsor: DBT-BIRAC research grant.

3107 Poster Session (Board #171), Fri, 8:00 AM-11:00 AM

GEN-009, a neoantigen vaccine containing ATLAS selected neoantigens, to generate broad sustained immunity against immunogenic tumor mutations and avoid inhibitory peptides. *First Author: Roger B. Cohen, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Tumor-specific neoantigens provide personalized targets for immunotherapy. Vaccines against epitopes predicted by *in silico* approaches very rarely induce $CD4^+$ and $CD8^+$ *ex vivo* T cell responses regardless of formulation. ATLAS selects neoantigens for vaccine inclusion using *ex vivo* screening of all patient-specific mutations to identify pre-existing $CD4^+$ or $CD8^+$ T cell responses and to exclude Inhibigens, which are inhibitory peptides that suppress immunity and accelerate tumor progression. The Inhibigen burden correlates with patient outcomes in observational studies and rapid tumor progression in mouse models. **Methods:** GEN-009-101 is a phase 1/2a study testing safety, immunogenicity and clinical activity in immune responsive tumors. After next-generation tumor sequencing and ATLAS testing of autologous leukocytes, up to 20 stimulatory synthetic long peptides adjuvanted with poly-ICLC comprise each personalized vaccine. Eight vaccinated patients have been followed for sustained immunological responses and clinical outcomes. **Results:** The 40 doses given across patients have induced only mild local discomfort and no DLT. Vaccination has generated immune responses against 99% of administered peptides, with both $CD8^+$ and $CD4^+$ responses in *ex vivo* fluorospot assays. To date, no patients have developed recurrent disease. Broad immunity develops as early as Day 29 and is sustained for over 12 months. Immune response against individual peptides is correlated with peptide concentration (OR = 1.26, $p \leq 0.0001$) but not with other classifiers such as GRAVY index (Grand Average of Hydropathy), tumor type, injection site or sex. The Inhibigen burden prior to treatment again correlates with disease progression. **Conclusions:** GEN-009 identifies tumor specific immune targets from the individual patient's tumor mutagens. Initial clinical data show that ATLAS antigen selection may be critical to the induction of broad, rapid and sustained immunity against tumor specific neoantigens. Clinical vaccination with PD-1 blockade is in process. Clinical trial information: NCT03633110. Research Sponsor: None.

		ATLAS Neoantigens		Post-vaccination Response		
Pt	Tumor type	Stimulatory	Inhibitory	*ex vivo* CD4/CD8	IVS CD4/CD8	Total Positive
1	NSCLC	6	0	10% / 40%	100% / 20%	100%
2	Urothelial	16	4	50% / 38%	63% / 50%	100%
3	Melanoma	199	41	6% / 38%	100%/100%	100%
4	Urothelial	18	1	100%/69%	85%/31%	100%
5	NSCLC	16	9	55% / 45%	100%/64%	100%
6	Urothelial	24	104	77%/15%	77%/62%	100%
7	Urothelial	14	4	38%/75%	88%/63%	100%
8	SCCHN	15	15	89%/11%	78%/33%	89%

3108 Poster Session (Board #172), Fri, 8:00 AM-11:00 AM

Evidence of intratumoral localization, activation, and immunomodulatory effect of CX-072, a probody therapeutic targeting PD-L1, in a phase I/II trial. *First Author: Susan Lyman, CytomX Therapeutics, Inc., South San Francisco, CA*

Background: PROBODY therapeutics (Pb-Tx) are masked antibodies designed to be selectively activated in the tumor microenvironment by tumor-associated proteases and to remain largely inactive in normal tissue. CX-072, a Pb-Tx directed against PD-L1, is designed to reduce the potential for immune-associated adverse events in normal tissues while maintaining anti-tumor activity. CX-072 is being investigated in PROCLAIM-CX-072 (NCT03013491), a first-in-human phase 1/2 trial. CX-072 is administered as monotherapy or in combination with ipilimumab to patients with metastatic or recurrent solid tumors or lymphomas for which approved PD-1/-L1–based therapy is not available. We present the updated results of a tissue-based biomarker program designed to assess activation, localization, and mechanism of action of CX-072 in patient tumors. **Methods:** Tumor biopsies were collected during the screening phase, and also 3–5 days after the first or third dose of 0.3–30 mg/kg CX-072. Tumor-associated protease activity was measured by tissue zymography. Intratumoral CX-072 activation was measured using capillary immunoelectrophoresis, and PD-L1 levels were measured by an ultrasensitive ELISA. Intratumoral CD8 expression was analyzed using immunohistochemistry. Intact and total CX-072 in plasma were measured by LC-MS/MS. **Results:** Twenty-six of 30 (87%) evaluable predose biopsies had detectable levels of relevant protease activity. Intratumoral activation of CX-072 was quantifiable in 3 of 8 (38%) biopsies from patients treated with CX-072 at 3 mg/kg and in 12 of 12 (100%) biopsies from patients treated with $\geq$10 mg/kg. In contrast, CX-072 remained predominantly in the intact form in circulation. The molar ratio of activated intratumoral CX-072 to total intratumoral PD-L1 ranged from ~14x to > 100x in patients dosed at 10 mg/kg, and the calculated tumor receptor occupancy for these patients was $\geq$99%, congruent with quantitative systems pharmacology model predictions. An increase in $CD8^+$ T cells and elevation of cytotoxic T-cell markers was observed in the tumors of 11 of 18 (61%) CX-072 monotherapy patients, consistent with inhibition of the PD-L1 pathway. **Conclusions:** These results demonstrate that the Pb-Tx CX-072 behaves as designed in patients. Clinical trial information: NCT03013491. Research Sponsor: CytomX Therapeutics, Inc.

3109 Poster Session (Board #173), Fri, 8:00 AM-11:00 AM

MR1 in combination with tumor mutational burden and PD-1/PD-L1 expression as a potentially novel clinical predictor for T cell exhaustion and immune checkpoint inhibitor response. *First Author: Mark Farha, University of Michigan Medical School, Ann Arbor, MI*

Background: Immune checkpoint inhibitors (ICIs) restore T cell function by reversing T cell exhaustion. Variable response to ICIs warrants the development of precise predictive biomarkers, which is challenging due to difficulty in capturing the interplay of factors involved with tumor cell immune recognition. High intratumoral expression of MR1, the MHC-I related protein basally expressed on cancer cells, may drive T cell exhaustion through presentation of cancer-specific antigens. Here, we construct a database to study the relationship between MR1, tumor mutational burden (TMB), the PD-1/PD-L1 axis and T cell exhaustion across 8,975 sequenced tumors and 27 cancer types. **Methods:** RNA Seq by expectation maximization (RSEM) values from the TCGA were collected and normalized along with expression data for markers of interest (Table). TMB was defined as the number of non-synonymous somatic mutations per sample. For each cancer, 5 cohorts were created based on ascending mean expression levels of MR1, PD-1, PD-L1, and increasing TMB. For each cancer, an "immunogenicity score" for these factors was computed, and its relationship with T cell exhaustion signatures was assessed via linear regression. Data is presented as adjusted R^2 and p-value. **Results:** While PD-1 and T cell exhaustion marker expression were correlated across cancers, the "immunogenicity score" (IS) correlated with exhaustion markers specifically in cancers with FDA-approved ICIs. Excluding MR1 from the score weakened the correlation with EOMES and TBET expression (Table). Each component of the score analyzed independently failed to show a statistically significant correlation for both EOMES and TBET expression. **Conclusions:** In this cross-cancer analysis, we support the hypothesis that presentation of metabolic intermediates in cancer cells via MR1 may drive T cell exhaustion. Also, the novel "immunogenicity score", which incorporates MR1 into standard biomarkers for response to ICIs may convey the global picture of cancer cell recognition by the immune system and warrants further investigation as a tool for predicting clinical response. Research Sponsor: None.

		IS		IS minus MR1		MR1		TMB		PD-L1		PD-1	
	Exhaustion Marker	R^2	p	R^2	p	R^2	p	R^2	p	R^2	p	R^2	p
FDA-Approved ICI	EOMES	**0.24**	**0.05**	0.17	0.08	0.04	0.24	0.08	0.86	0.09	0.16	**0.29**	**0.03**
	TBET	**0.56**	**0.001**	0.32	0.02	0.13	0.12	0.08	0.97	**0.29**	**0.03**	**0.55**	**0.002**
Non-FDA approved ICI	EOMES	0.02	0.27	0.09	0.14	0.08	0.98	0.03	0.47	0.06	0.20	**0.58**	**0.001**
	TBET	0.11	0.12	0.16	0.08	0.07	0.75	0.04	0.49	0.14	0.10	**0.76**	**1.33x10^-5**

3110 Poster Session (Board #174), Fri, 8:00 AM-11:00 AM

SBT6050, a HER2-directed TLR8 therapeutic, as a systemically administered, tumor-targeted human myeloid cell agonist. *First Author: Heather Metz, Silverback Therapeutics, Seattle, WA*

Background: Solid tumors are replete with myeloid cells which, when activated, drive potent anti-tumor responses. Clinical development of systemically administered myeloid cell agonists, however, has been hindered by acute toxicities due to peripheral activation of the targeted cell types. Intratumoral administration, the route of delivery typically used for innate immune/myeloid cell agonists, is limited by tumor accessibility and a dependence on abscopal responses. A systemically delivered myeloid cell agonist with tumor-localized activity has the potential to overcome challenges encountered with other innate immune/myeloid cell agonists in clinical development. **Methods:** SBT6050 is a novel therapeutic comprised of a potent toll-like receptor (TLR) 8 agonist payload conjugated to a HER2-directed monoclonal antibody. Delivery of the payload into the endosome of human myeloid cells, where TLR8 resides, requires the co-engagement of HER2 on tumor cells and Fc gamma receptor on human myeloid cells. Thus, SBT6050 is designed for systemic delivery and tumor-targeted activation of human myeloid cells. **Results:** Studies with human immune cells show that SBT6050 potently induces, in a HER2-dependent manner, multiple anti-tumor immune activities due to its direct activation of myeloid cells and the subsequent induction of T and NK cell cytolytic activity. SBT6050 is designed to activate human myeloid cells only in the presence of HER2-positive tumor cells with moderate (2+ by IHC) or high (3+ by IHC) expression levels. Tumor-localized activity has been demonstrated in mouse models using a SBT6050 mouse surrogate. Systemic delivery results in robust single agent efficacy in multiple mouse tumor models, even those engineered to lack T cells, without accompanying peripheral cytokine production. Trastuzumab and SBT6050 bind to distinct epitopes on HER2 and enhanced activity is observed when the two agents are combined. **Conclusions:** SBT6050 is a systemically administered, tumor-targeted myeloid cell agonist that demonstrates single agent efficacy in multiple mouse tumor models without peripheral cytokine production. A first-in-human study with SBT6050 is expected to begin this year for patients with HER2-expressing solid tumors. Research Sponsor: Silverback Therapeutics.

3111 Poster Session (Board #175), Fri, 8:00 AM-11:00 AM

A pilot study of Bruton's tyrosine kinase inhibitor ibrutinib alone and in combination with PD-1 inhibitor nivolumab in patients with metastatic solid tumors. *First Author: Brooke Benner, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Myeloid-derived suppressor cells (MDSC) are expanded in cancer and promote immune suppression. We have shown that ibrutinib inhibits migration and immunosuppressive function of MDSC. Moreover, the combination of ibrutinib and a PD-L1 inhibitor has been found to have synergistic anti-tumor effects in a multiple solid tumor mouse models. Therefore, we conducted a pilot study testing the combination of ibrutinib and nivolumab in patients with metastatic solid tumors. **Methods:** Sixteen patients with advanced solid tumors were recruited to this trial. Ibrutinib was dosed as an oral single agent, starting 7 days prior to cycle 1 of nivolumab and given until cycle 1, day 8 of nivolumab. Nivolumab was administered intravenously on days 1 and 15 on 28-day cycles. Patients had blood samples collected prior to initiation of ibrutinib, day 1 of cycle 1, day 8 of cycle 1, day 1 of cycle 2, and at the time of disease progression. From these specimens, we measured circulating MDSC levels, other circulating immune subsets, T cell proliferation, and cytokines/chemokines levels. Circulating MDSC levels were measured by mass spectrometry. T cell function was evaluated by CFSE to monitor proliferating cells by dye dilution and cytokine/chemokine levels were measured with a U-PLEX assay. Data were analyzed using two-tailed, paired Student's *t*-tests to assess statistical significance. **Results:** An increase in circulating MDSC (22% to 28%; SD 9.158) levels was observed following 7 days of single-agent ibrutinib compared to baseline. However, in combination therapy, MDSC levels decreased (19%; SD 13.17) prior to cycle 2. Despite increasing levels of circulating MDSC, T cell function improved throughout the study. Furthermore, plasma levels of chemokines associated with MDSC recruitment and migration significantly decreased with ibrutinib treatment (IL-12, CCL2, CCL3, and CCL4). Of the 16 patients, four achieved a partial response and four achieved stable disease. Median progression free survival was 3.5 months and median overall survival was 11.5 months. **Conclusions:** The combination of ibrutinib and nivolumab was well tolerated, demonstrated early signs of immune modulation, and showed preliminary signs of promising clinical activity in patients with metastatic solid tumors. Clinical trial information: NCT03525925. Research Sponsor: Pelotonia IRP.

3112 Poster Session (Board #176), Fri, 8:00 AM-11:00 AM

A phase II, open-label study of tomivosertib (eFT508) added on to continued checkpoint inhibitor therapy in patients (pts) with insufficient response to single-agent treatment. *First Author: Anthony B. El-Khoueiry, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Despite the broad activity of checkpoint inhibitors across tumor types, primary or secondary resistance after initial response represents a major challenge. Tomivosertib (T), a potent and highly selective inhibitor of the immunosuppressive kinases MNK-1 and 2, blocks expression of checkpoint proteins PD-1, PD-L1, and LAG-3 as well as immunosuppressive cytokines IL-6 and IL-8. In preclinical models, T was shown to trigger an anti-tumor immune response and enhance the activity of checkpoint inhibitors in a T-cell dependent manner. In prior clinical studies, T had an acceptable safety profile as a single agent and in combination with anti-PD-L1 agent avelumab. **Methods:** Patients experiencing insufficient response (progression or stable disease for 12 weeks or more) to any FDA-approved checkpoint inhibitor in any approved indication were eligible. T at 200 mg oral (PO) BID was added to the existing checkpoint inhibitor until disease progression or unacceptable toxicity was noted. **Results:** 39 pts (23 male, 16 female) were enrolled across seven cancer types. Median age was 68 (range 42-85). Median prior therapies were 2 (range 1-6). The most common cancers were lung (N = 17), urothelial (N = 6), renal (N = 5) and head and neck (N = 5). 36 pts continued on anti PD-1 antibody (Pembrolizumab and Nivolumab, 18 each) and 3 on anti PD-L-1 antibody (Durvalumab 2, Atezolizumab 1) . The most common grade 3/4 treatment related adverse events occurring in more than 1 pt were alanine aminotransferase increase (2), blood creatine phosphokinase increase (2) and maculo-papular rash (2). 7 patients discontinued treatment (18%) due to adverse events attributable to either drug. Three partial responses (PR) per RECIST 1.1 were observed in pts with previous progression on checkpoint inhibitor therapy, one each in NSCLC (1/17), gastric (1/1) and renal cancer (1/5). 7 NSCLC pts (41%) were progression free for $\geq$ 24 weeks. All NSCLC patients entered the study with progression by RECIST 1.1 on single agent checkpoint inhibitor prior to adding T. **Conclusions:** The addition of T to existing checkpoint therapy was well tolerated and manifested clinical activity including objective responses in pts with progression on existing checkpoint inhibitor. A Progression Free Survival rate at 24 weeks of 41% was noted in NSCLC patients. Additional studies evaluating the addition of T to checkpoint inhibitor therapy after progression on anti PD-1 or PD-L-1 therapy are planned. Clinical trial information: NCT03616834. Research Sponsor: eFFECTOR Therapeutics.

3113 Poster Session (Board #177), Fri, 8:00 AM-11:00 AM

Characterization of NRG1 gene fusion events in solid tumors. *First Author: Sushma Jonna, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: *NRG1* fusions are actionable genomic alterations detected across tumor types. The *NRG1* gene encode for neuregulin, which serves as a ligand for ERBB3 and ERBB4 receptors and activates downstream signaling through the MAPK and PI3K pathways. Here, we update the detection of *NRG1* gene fusions across tumor types and further describe fusion characteristics. **Methods:** Samples submitted for clinical molecular profiling that included RNA-sequencing (Archer Dx or Caris MI transcriptome) were retrospectively analyzed for *NRG1* fusion events. All *NRG1* fusions with $\geq$ 3 junction reads were identified for manual review and for characterization of fusion class, intact functional domains, domain prediction, breakpoints, frame retention and co-occurring alterations by NGS. **Results:** A total of 82 *NRG1* fusion events (0.2% of 44,570) were identified. Among the fusions identified, the distribution across tumor types was as follows: non-small cell lung cancer (NSCLC, 54%), breast cancer (11%), ovarian cancer (7%), pancreatic cancer (7%), cholangiocarcinoma (6%), colorectal cancer (5%), and other (10%). Forty-two unique fusion partners were identified, the most common being *CD74* (23%), *ATP1B1* (9%), *SLC3A2* (7%), *RBPMS* (6%) and *SDC4* (4%). Almost half (47%) of all fusion events are expected to include the transmembrane domain contributed by the *NRG1* fusion partner. Lung and pancreatobilliary cancers had the highest rates of transmembrane domain retention from their fusion partners (63.6% and 54.5%, respectively). In all other tumor groups, most fusion partners lacked transmembrane domains. In 15% of cases, the chimeric transcripts are predicted to lead to increased expression of NRG1. The most commonly reported breakpoints in *NRG1* occur in exon 6 and exon 2. While fusions with the *NRG1* breakpoint at exon 2 retain the immunoglobulin (Ig) domain and all downstream portions (including EGF-like domain), those at exon 6 do not contain the Ig portion and result in shorter chimeric proteins. The breakpoints in all *CD74:NRG1* fusions, the most common fusions in NSCLC, occur at exon 5 or 6 and cause truncation of domains upstream of the EGF-like domain. In *ATP1B1:NRG1* fusions, the most common fusions in pancreatobilliary cancers, the breakpoints are at exon 1 or 2 and retain the Ig domain. **Conclusions:** *NRG1* fusion products are diverse across tumor types, but the significance of these variations is not clear. The biological and clinical implications of retaining certain domains of *NRG1* (such as the Ig domain) and of fusion partners warrants further investigation. Research Sponsor: None.

3114 Poster Session (Board #178), Fri, 8:00 AM-11:00 AM

An in vivo model to evaluate donor-dependent cytokine release in response to single-agent or combination immune-oncology therapies. *First Author: Kyle Draheim, The Jackson Laboratory, Sacramento, CA*

Background: Although immune-oncology therapies such as checkpoint inhibitor, bi-specific antibody and CAR-T cell therapies are successfully used for cancer therapy, they can have very severe adverse effects such as cytokine release syndrome (CRS). The animal models and in vitro human PBMC assays presently in use do not reliably predict CRS in patients. Currently, the only widely accepted predictors of CRS are cancer burden and therapeutic dose. Despite this, most pre-clinical assays that evaluate CRS do not incorporate cancer cells and the safety of drug combinations has not been widely explored. A predictive assay that identifies patient/cancer/therapy combinations at risk for developing CRS upfront in addition to treatment efficacy would improve the safety of immune-oncology drug development. **Methods:** We have developed sensitive in vivo humanized mouse models for quantitating CRS that are rapid, reproducible and able to show variation among PBMC donors. The NSG mouse and its derivatives are engrafted with cancer cells and human PBMCs. Mice are then dosed with checkpoint inhibitors or bi-specific antibodies as a single therapy or in combination. Cytokine release is evaluated 2-6 hours post dosing. This assay can be modified to also evaluate efficacy by using luciferase labeled cancer cells and monitoring tumor burden using the Xenogen IVIS imaging system. **Results:** For all therapy groups, each cytokine tested (including human IFN-γ, IL-2, IL-6, IL-10 and TNF) was upregulated 2-6 hours after drug treatment, but different PBMC donors had various cytokines release levels. Cytokine release levels correlated with a dose response, PBMC engraftment levels and tumor burden. We can demonstrate additive and synergistic cytokine release in the combination treated groups and compare efficacy versus single agents. Our in vivo method was able to determine CRS missed in the in vitro testing method. **Conclusions:** We have developed a rapid, sensitive and reproducible novel in vivo PBMC humanized mouse model that can differentiate human PBMC donors based on individual safety response to single agent and combination therapeutics of immune checkpoint inhibitors and bispecific T-cell-engaging antibodies. Additionally, this assay can utilize luciferase labelled cell lines to measure treatment efficacy. Using this assay, we can potentially evaluate both cytokine release and efficacy of current immune-oncology therapies as single agents and in combination. This assay has immediate utility in current and future drug development. Research Sponsor: None.

3115 Poster Session (Board #179), Fri, 8:00 AM-11:00 AM

Association between immune and tumor gene signatures with response or resistance to tislelizumab monotherapy or in combination with chemotherapy in gastroesophageal adenocarcinoma. *First Author: Jianming Xu, Department of Gastrointestinal Oncology, The Fifth Medical Center, General Hospital of People's Liberation Army, Beijing, China*

Background: Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated clinical benefit as a single agent and in combination with chemotherapy for patients (pts) with gastroesophageal adenocarcinoma (GEA), including gastric, gastroesophageal junction (G/GEJ), and esophageal adenocarcinoma (EAC). Immune- and tumor-transcriptomic features of response and resistance to tislelizumab were assessed from data collected in two monotherapy studies (NCT02407990, CTR20160872) and one tislelizumab plus chemotherapy study (NCT03469557). **Methods:** Gene expression profiling (GEP), using the 1392-gene HTG EdgeSeq panel, was performed on baseline tumor samples from 103 pts with GEA receiving monotherapy and 13 receiving combination therapy. Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures (GS). Differential gene signature (DEG) analysis was performed between responders and nonresponders (NRs) using Wilcoxon rank-sum test; GS associated with survival were evaluated using Cox proportional hazards model. **Results:** Of the 76 pts with available GEP data, 64 (n=51 G/GEJ; n=13 EAC) had evaluable responses. Across these pts with GEA, tislelizumab demonstrated antitumor activity (Table). In pts treated with monotherapy, DEG showed IFNγ GS (*IFNG*, *CXCL9*, *CXCL10*, *HLA-DRA*, *IDO1*, *STAT1*) scores were positively correlated with response (P=0.03) as well as progression-free (HR=0.5, 95% CI: 0.27–0.93) and overall survival (HR=0.44, 95% CI: 0.21–0.89). Monotherapy NRs could be clustered into distinct GEP subgroups. Compared with responders, two NR subgroups had lower IFNγ GS (P=0.002, 0.047) along with either higher epithelial-mesenchymal transition (EMT; P=0.027), and angiogenesis (P=0.002) or cell cycle (CC; P=0.097) GS expression. A third NR subgroup showed higher CC GS scores compared with responders (P=0.015), despite high IFNγ GS levels. Unlike tislelizumab monotherapy, responders to combination therapy showed higher CC GS expression versus NRs (P=0.089). **Conclusions:** While higher IFNγ GS was associated with clinical benefit with monotherapy, elevated EMT/angiogenesis and CC GS levels may indicate resistance. The effects of these signatures in pts treated with combination therapy may vary. Both immune- and tumor-intrinsic factors may be considered for validation in a phase 3 study (NCT03777657). Research Sponsor: BeiGene, Ltd.

	Monotherapy (n=53)	Combination (n=11)
Median follow-up, mo	14.3	16.3
ORR, %	13.2	54.5

3116 Poster Session (Board #180), Fri, 8:00 AM-11:00 AM

Investigating the tumor immune infiltrate for populations that predict immune-related adverse events (irAEs) in patients receiving PD-1 inhibitors. *First Author: Steven Michael Blum, Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA*

Background: The mechanistic relationship between clinical benefit and immune-related adverse events (irAEs) in response to immune checkpoint inhibitors (ICIs) remains unclear, with several clinical studies reporting that irAEs are biomarkers of responses. Single-cell RNA sequencing (scRNAseq) analysis of tumors from patients with advanced melanoma before and after treatment with ICIs have identified immune cells that correlate with response to ICIs. We sought to evaluate if these populations were also associated with irAEs. **Methods:** A published scRNAseq data set generated with the Smart-Seq2 protocol (Sade-Feldman M, et al. Cell 2018.) was re-analyzed, stratified by two definitions of irAEs: (1) toxicity requiring systemic immunosuppression (prednisone $>$ 10mg/day) or (2) systemic immunosuppression and/or endocrinopathy. Unbiased single-cell analysis was performed, followed by sub-clustering of T cell populations. The percentage of cells in each cluster was determined on a per sample basis. **Results:** 13,184 immune cells from 39 samples collected from 25 patients were re-analyzed. 27 samples were from patients who did not respond to ICIs, while 12 samples came from responding patients. 21 samples came from patients who required immunosuppression, 5 samples from patients with isolated thyroiditis, and 13 samples from patients who met neither irAE criteria. Unsupervised scRNAseq analyses focused on ICI efficacy re-capitulated published associations between response and populations that included B-cells ($p < 0.01$) and TCF7 expressing T-cells ($p < 0.01$). While these cell populations were not associated with either definition of toxicity, we observed a non-Treg CD4 expressing T cell population (0.8-10.5% cells/sample) that positively correlated with either definition of toxicity ($p < 0.05$) but not efficacy. **Conclusions:** In a patient cohort with advanced melanoma, tumor-infiltrating immune cell populations associated with response to ICI therapy were not associated with irAEs. This suggests that biomarkers of ICI response may not function as biomarkers of irAEs, and ongoing analysis will seek to validate this result. Understanding the differences between ICI response and irAEs may identify new therapeutic targets for maximizing efficacy while mitigating toxicity. Research Sponsor: U.S. National Institutes of Health.

3117 Poster Session (Board #181), Fri, 8:00 AM-11:00 AM

Validation of an immunomodulatory gene signature algorithm to predict response to neoadjuvant immunochemotherapy in patients with primary triple-negative breast cancer. *First Author: Toshiaki Iwase, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A 101-gene algorithm established as a molecular subtyping method for triple-negative breast cancer (TNBC) includes assignment of an immunomodulatory (IM) subtype based on genes active in immune cell processes. Recently, we isolated the IM concept to an independent 27-gene algorithm and its predictive ability for immunotherapy response was demonstrated in lung cancer. The objective of this study was to validate the predictive accuracy of the IM subtype as determined by the 27-gene algorithm for pathological complete response (pCR) compared with PD-L1 immunohistochemistry (IHC) staining in TNBC. **Methods:** We obtained RNA sequencing data from pretreatment core needle biopsies in 55 patients with stage I-III primary TNBC who received neoadjuvant immunotherapy (durvalumab with weekly nab-paclitaxel followed by ddAC) in phase I/II trial (NCT02489448). The 27-gene algorithm was used to determine IM positivity using a cutoff point previously validated from 71 lung cancer biopsy patients treated with immunotherapy. Results from the algorithm and PD-L1 IHC (antibody, SP263) were compared with pCR. Predictive accuracy of both methods was determined by diagnostic indicators. In cases positive for the IM subtype and pCR, we analyzed the immune microenvironment by deconvoluting the immune infiltration using a computational algorithm. **Results:** Of the 55 patients, 25 (45%) had pCR. Compared with previous subtyping methods, the 27-gene algorithm showed stronger predictive value (odds ratio, 4.125; 95% CI, 1.36-13.47; $P < 0.015$). For PD-L1 IHC, the odds ratio was 2.63 (95% CI, 0.82-9.21; $P = 0.11$). The positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for PD-L1 IHC were 0.55, 0.68, 1.43, and 0.54, respectively. For the 27-gene algorithm, these metrics were 0.65, 0.69, 2.09, and 0.51, indicating its superior accuracy for predicting pCR. The computational algorithm showed that the IM subtype and pCR were negatively associated with a macrophage-enriched microenvironment. CD4+ T cells and dendritic cells were significantly increased among the baseline immune cell population in IM-positive patients. **Conclusions:** We conclude that 27-gene algorithm is a clinically applicable and a possible predictive marker for response to neoadjuvant immunochemotherapy for patients with primary TNBC. Our immune microenvironment results suggest that antigen-presenting immune cells have a crucial role in immunochemotherapy response. Research Sponsor: Astra Zeneca.

3118 Poster Session (Board #182), Fri, 8:00 AM-11:00 AM

Significance of meflin-positive cancer-associated fibroblasts in predicting response to immune checkpoint inhibitors in non-small cell lung cancer. *First Author: Yuki Miyai, Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan*

Background: Tumor immunity is regulated by complex interactions between cancer and immune cells, which also involves other components of the tumor microenvironment (TME). Recently, cancer-associated fibroblasts (CAFs), a major constituent of the TME, have emerged as important regulators of tumor immunity. Specifically, for example, α-smooth muscle actin or leucine-rich repeat containing 15-positive CAFs have been shown to be crucial for the suppression of tumor immunity. However, a comprehensive picture of how other CAF subset(s) are involved in tumor immunity is still lacking. Here, we show the involvement of a CAF subset highly expressing Meflin, which was recently identified as a marker of cancer-restraining CAFs in pancreatic cancer (Mizutani et al., Cancer Res, 2019), in the response of non-small cell lung cancer (NSCLC) patients to immune checkpoint inhibitors (ICIs). **Methods:** A sample cohort of 122 subjects with NSCLC who had received ICI monotherapy with nivolumab, pembrolizumab, or atezolizumab was identified at the Department of Respiratory Medicine at Nagoya University Hospital. We selected 92 eligible patients, collected formalin-fixed paraffin-embedded tumor tissues, and prepared 4–μm-thick slides for the analysis of Meflin expression by RNA-in situ hybridization assay, followed by the evaluation of treatment response of 88 patients using the iRECIST criteria. We assessed the number of Meflin-positive CAFs and divided the patients into Meflin-High (20% and more CAFs express Meflin) and -Low groups. The cut-off value was obtained by the ROC analysis. Primarily, objective response rate (ORR) was compared between Meflin-High and –Low groups. Overall survival (OS), and progression free survival (PFS) were also assessed. **Results:** Patients who started to receive ICIs till the end of March 2019 were enrolled and followed-up until the end of 2019. Analysis of the tumor tissues revealed that 24 (40.7%) of 59 Meflin-High patients responded to the ICI monotherapy. In contrast, none (0%) of 29 Meflin-Low patients showed any significant response (p-value: 0.0000174). Meflin-High groups showed statistically significant prolongations in both OS and PFS with the hazard ratios of 0.3114 [0.1591-0.6094] and 0.3997 [0.2290-0.6976], respectively. **Conclusions:** This retrospective observation indicated that the high infiltration of Meflin-positive CAFs may shape tumor-suppressive immune response and increase the sensitivity to ICIs, which differs from those of other CAF subsets. Research Sponsor: the Ministry of Education, Culture, Sports, Science and Technology, Japan.

3119 Poster Session (Board #183), Fri, 8:00 AM-11:00 AM

Deep learning-based immune phenotype analysis reveals distinct resistance pattern of immune checkpoint inhibitor in non-small cell lung cancer. *First Author: Chan-Young Ock, Lunit Inc., Seoul, South Korea*

Background: Resistance pattern and biological mechanism of immune checkpoint inhibitor (ICI) has been poorly understood. Sine suggested resistance mechanisms would be either innate resistance caused by lack of immune recruitment or acquired immune evasion after durable response of ICI treatment, we hypothesized that resistance pattern of tumor microenvironment would be distinct according to duration of ICI response in non-small cell lung carcinoma (NSCLC). In the current study, we applied deep-learning-based classification of three immune phenotypes (3IP): *inflamed*, *excluded*, and *desert*, to objectively assess the immunologic status of tumor microenvironment. **Methods:** Deep-learning algorithm of H&E Whole-Slide Images (WSI), called Lunit-SCOPE, was trained with 1,824 H&E WSI of NSCLC from Samsung Medical Center (SMC). WSI was divided into patches and each patch (~10 high-power fields) was classified as *inflamed*, *excluded* and *desert*, based on both quantity and localization of immune cells. Among NSCLC patients treated with ICI in SMC, 87 paired treatment-naïve (Pre, patch N = 15,415) and post-progression (Post, patch N = 18,197) tumor tissues were analyzed for Lunit-SCOPE. **Results:** In 87-paired samples, proportions of excluded and desert phenotypes were increased in post-progression tumor tissues (excluded; Pre 26.8% versus Post 32.5%, desert; Pre 19.5% versus Post 25.3%). Focused on 29 patients classified as inflamed in treatment-naïve, proportion of immune phenotypes of post-progression were clearly different according to duration of response, divided by median progression-free survival (PFS) of 3.7 m. Patients with rapid progression without ICI response (PFS $<$ 3.7 m) turned into desert type (46.2%), whereas durable responder (PFS $\geq$ 3.7 m) either still remained on inflamed phenotype (42.9%) or turned into excluded phenotype (21.4%). Patients who remained on inflamed phenotype had favorable overall survival after progression on ICI, compared to turned into desert type (median survival not reached versus 6.6 m, P= 0.0296). **Conclusions:** Resistance patterns of ICI are distinct according to duration of response in patients with inflamed phenotype. Rapid progressor turns off immune into desert phenotype whereas most durable responder keeps immune recruitment into tumor microenvironment, which needs tailored strategy to overcome ICI resistance. Research Sponsor: Lunit Inc.

3120 Poster Session (Board #184), Fri, 8:00 AM-11:00 AM

Deep-learning analysis of H&E images to define three immune phenotypes to reveal loss-of-target in excluded immune cells as a novel resistance mechanism of immune checkpoint inhibitor in non-small cell lung cancer. *First Author: Sehhoon Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Discovery of predictive biomarker to enrich the responder of immune checkpoint inhibitor (ICI) in PD-L1-low ($<$ 50%) non-small cell lung cancer (NSCLC) is still challenging. Recent study showed that loss of heterozygosity (LOH) of *HLA* led to immune evasion. In the current study, we hypothesized that 3 immune phenotype (3IP): *inflamed*, *excluded* and *desert* would be reliably classified by deep-learning algorithm of H&E image, called Lunit-SCOPE, which would dictate the responder in PD-L1-low NSCLC patients and discover a unique resistance pathway in *excluded* phenotype. **Methods:** Lunit-SCOPE was trained with 1,824 H&E Whole-Slide Image (WSI) of NSCLC from Samsung Medical Center (SMC). WSI was divided into patches (~10 high-power fields) which was classified for 3IP, based on both quantity and localization of immune cells. The 3IP was trained and optimized by considering clinical outcome of 119 NSCLC patients with PD-(L)1 inhibitor (training cohort, patches = 25,897), and validated in 62 patients enrolled in LC-biomarker study (NCT03578185, validation cohort, patches = 8,929). Tumor Proportion Score (TPS) of PD-L1 22C3 immunohistochemistry was assessed by pathologists. Tumor Mutational Burden (TMB) was calculated as number of nonsynonymous alterations throughout whole-exome and *HLA* LOH was called by LOHHLA algorithm. **Results:** Interactive analysis to classify 3IP in training cohort showed that 8,726 (33.7%), 10,965 (42.3%), and 6,206 (24.0%) patches were classified as *inflamed*, *excluded*, and *desert*, respectively. In validation cohort, median progression-free survival (mPFS) of *inflamed* phenotype was 10.1 m, significantly prolonged compared to either *excluded* phenotype (3.0 m, P= 0.0053) or *desert* phenotype (1.4 m, P= 0.0011). *Inflamed* phenotype independently dictated favorable ICI outcome in PD-L1-low (TPS $<$ 50%, mPFS of *inflamed*: 14.3 m vs *excluded/desert*: 1.4 m, P= 0.0233) as well as in PD-L1-high (TPS$\geq$50%, 10.1 m vs 4.2 m, P= 0.0361), respectively. *Excluded* phenotype had higher TMB compared to *inflamed* phenotype had (median 177 vs 107), and *HLA* LOH was also enriched in *excluded* phenotype (31.0%) compared to *inflamed* (17.6%) and *desert* (16.7%) phenotypes. **Conclusions:** Lunit-SCOPE based 3IP classification can predict ICI outcome especially in PD-L1-low ($<$ 50%) patients. *Excluded* phenotype showed poor ICI outcome even with high TMB, partially explained by *HLA* LOH resulting in loss-of-target, as a novel resistance mechanism of ICI. Research Sponsor: Lunit Inc.

3121 Poster Session (Board #185), Fri, 8:00 AM-11:00 AM

Gene signature of antigen processing and presentation machinery (APM) as highly predictive of response to checkpoint blockade in lung cancer and melanoma. *First Author: Jeffrey C. Thompson, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Treatment of non-small cell lung cancer (NSCLC) with immune checkpoint blockade (ICB) has resulted in striking clinical responses, but only in a subset of patients (pts), underscoring the need to identify genomic and molecular determinants of immune evasion. Limited data exist on the potential role of alterations in HLA Class I antigen processing and presentation machinery (APM) in mediating response to ICB. **Methods:** We conducted a retrospective cohort study analyzing transcriptional profiles from pre-treatment tumor samples of chemotherapy-refractory advanced NSCLC pts treated with ICB. RNA was analyzed using the AmpliSeq transcriptomic platform. An APM signature was generated utilizing 8 genes associated with antigen processing (*B2M, CALR, NLRC5, PSMB9, PSME1, PSME3, RFX5, HSP90AB1*) and was examined for its association with response to therapy and progression-free and overall survival (PFS, OS). The APM signature was then evaluated in two independent melanoma cohorts treated with ICB. **Results:** We analyzed pre-treatment tumor samples from 51 advanced NSCLC pts treated with ICB, median age 64 (range 31-92), smokers (n = 43), adenocarcinoma (n = 31). There were 23 responders and 28 non-responders. The APM signature was significantly higher in responders compared to non-responders (average z-score 2.69 vs. -2.49, p = 0.0001). An APM score above the median value for the entire cohort was significantly associated with improved PFS (HR 0.24, 95% CI, 0.12-0.47, log-rank = 0.001) and OS (HR 0.34, 95% CI, 0.18-0.67, log-rank = 0.005). The APM score was significantly correlated with the well-validated T-cell-inflamed resistance gene expression profile (GEP) score (R^2 = 0.32, p $<$ 0.0001). However, the APM score demonstrated improved ability to predict response to ICB relative to the GEP score with AUCs of 0.83 and 0.69, respectively. In an independent cohort of 14 high-risk resectable stage III/IV melanoma pts treated with neoadjuvant anti-PD1 therapy, upregulation of genes involved in antigen processing was associated with improved disease free survival (HR: 0.08, 95% CI, 0.01-0.50, p = 0.0065). In an additional independent melanoma cohort of 28 metastatic pts treated with ICB, a higher APM score was associated with improved overall survival (HR 0.31, 95% CI, 0.09-0.89, log-rank = 0.044). **Conclusions:** Our data demonstrate that defects in antigen presentation may be an important feature in predicting outcomes to ICB in both lung cancer and melanoma. Research Sponsor: U.S. National Institutes of Health.

3122 Poster Session (Board #186), Fri, 8:00 AM-11:00 AM

A machine learning-based approach for the inference of immunotherapy biomarker status in lung adenocarcinoma from hematoxylin and eosin (H&E) histopathology images. *First Author: Cory Batenchuk, Verily Life Sciences, South San Francisco, CA*

Background: The current standard work-up for both diagnosis and predictive biomarker testing in metastatic non-small cell lung cancer (NSCLC), can exhaust an entire tumor specimen. Notably, gene mutation panels or tumor mutation burden (TMB) testing currently requires 10 tissue slides and ranges from 10 days to 3 weeks from sample acquisition to test result. As more companion diagnostic (CDx)-restricted drugs are developed for NSCLC, rapid, tissue-sparing tests are sorely needed. We investigated whether TMB, T-effector (TEFF) gene signatures and PD-L1 status can be inferred from H&E images alone using a machine learning approach. **Methods:** Algorithm development included two steps: First, a neural network was trained to segment hand-annotated, pathologist-confirmed biological features from H&E images, such as tumor architecture and cell types. Second, these feature maps were fed into a classification model to predict the biomarker status. Ground truth biomarker status of the H&E-associated tumor samples came from whole exome sequencing (WES) for TMB, RNAseq for the TEFF gene signatures or reverse-phase protein array for PD-L1. Digital H&E images of NSCLC adenocarcinoma for model development were obtained from the cancer genome atlas (TCGA) and commercial sources. **Results:** This approach achieves $>$ 75% accuracy in predicting TMB, TEFF and PD-L1 status, offers a way to interpret the model, and provides biological insights into the tumor-host microenvironment. **Conclusions:** These findings suggest that biomarker inference from H&E images is feasible, and may be sufficiently accurate to supplement or replace current tissue-based tests in a clinical setting. Our approach utilizes biological features for inference, and is thus robust, interpretable, and readily verifiable by pathologists. Finally, biomarker status inference from a single H&E image may enable testing in patients whose tumor tissue has been exhausted, spare further tissue use, and return test results within hours to enable rapid treatment decision-making to maximize patient benefit. Research Sponsor: Verily Life Sciences.

3123 Poster Session (Board #187), Fri, 8:00 AM-11:00 AM

Extrachromosomal DNA (ecDNA) carrying amplified oncogenes as a biomarker for insensitivity to pembrolizumab treatment in gastric cancer patients. *First Author: Jason H. Christiansen, Boundless Bio, Inc., La Jolla, CA*

Background: In the KEYNOTE-059 study, the anti-PD-1 checkpoint inhibitor pembrolizumab was shown to have a modest overall response of 11.6%. Common predictors of response including, high microsatellite instability (MSI-H), PD-L1 expression, tumor mutational burden (TMB) and tumor inflammation signature (TIS), were not individually sufficient for patient selection. Recent pancancer studies have highlighted a unique population of cancer patients whose tumors appear to be driven by oncogene amplifications on extrachromosomal DNA (ecDNA). These ecDNA-driven tumors are aggressive and characterized by high levels of genomic instability. We sought to understand if tumors that possess ecDNA may represent a subset of the patient group that is non-responsive to anti-PD-1 therapy. **Methods:** We determined the ecDNA status of gastric cancer patients (N = 108) using whole genome sequencing (WGS) from the TCGA Pan-cancer dataset These patients had been previously subtyped for EBV status, genomic stability (GS), microsatellite instability (MSI), and chromosomal instability (CIN). Patients that were ecDNA+ were re-classified into a set regardless of gastric subtype. Additionally, TMB, TIS, and PD-L1 expression levels were collected. **Results:** 32% of gastric cancer patients were positive for ecDNA signatures and mutually exclusive from the 23% of MSI-H patients. We found that ecDNA positive tumors had statistically significantly lower TIS than all other groups (p-value < 0.05) except CIN tumors (p-value = 0.09). The ecDNA positive tumors also had lower PD-L1 expression than all but GS tumors. Only MSI-H showed statistically significantly higher TMB scores compared to every other group (p-value < 0.001), no difference in TMB scores were observed between every other pair of groups. **Conclusions:** Patients whose tumors are ecDNA positive represent a unique population that display signatures for non-response to checkpoint inhibitor therapy, including MSS, low TIS, and PD-L1 expression. Thus, the determination of tumor ecDNA status may have utility as an additional patient selection strategy for checkpoint inhibitor therapy. As ecDNA are not limited to gastric cancers, this study highlights the importance of the development of a clinical diagnostic test for ecDNA status and the need for further research on ecDNA biology, its impact on immunotherapy response, and potential ecDNA-directed therapeutics Research Sponsor: Boundless Bio, Inc.

3124 Poster Session (Board #188), Fri, 8:00 AM-11:00 AM

The prevalence of HLA LOH across 10 cancer types in Chinese patients. *First Author: Jian'An Huang, The First Affiliated Hospital of Soochow University, Suzhou, China*

Background: Recognition of tumor neoantigen is the key to generating immune response. The expression and integrity of human leukocyte antigen (HLA) are the prerequisites for neoantigen presentation, and loss of heterozygosity in HLA (HLA LOH) may facilitate immune evasion. However, the incidence of HLA LOH in Chinese cancer patients is unknown. **Methods:** In this study, 45 samples sequenced with both 1021-gene panel and whole-exome sequencing(WES) were used to evaluate the consistency of HLA LOH in the two testing strategies. The prevalence of HLA LOH analysis was performed in 1546 advanced patients across 10 diverse cancer types and 114 early-stage lung cancer patients who had undergone tumor profiling using 1021-gene panel. Exon 2, exon 3 and bilateral introns of *HLA-A/B/C* genes were well covered in 1021-gene panel. HLA LOH were analysis using LOHHLA algorithm (McGranahan, et al. 2017). **Results:** In the HLA LOH analysis of 45 samples, the consistency of 1021-gene panel and WES was 95.6% (43/45). Among the 1660 samples, 1.3% (21) were detected as HLA homozygous at all of the three site. HLA LOH was found in 45.1% (697/1546) of all the advanced patients, range from 24.1% to 59.7%. In colorectal cancer, the HLA LOH ratio of MSS samples was significantly higher than that of MSI-H samples (46.2%, 61/132 vs 16.7%, 3/18 p =0.0214). For NSCLC, the proportion of HLALOH in early-stage (I-IIIa) lung adenocarcinoma and lung squamous cell carcinoma was 25.7% (18/70) and 65.9% (29/44), respectively, consistent with the report. However, advanced (IIIa-IV) lung adenocarcinoma and lung squamous cell carcinoma were 49.4%(168/340) and 58.7%(179/305), respectively. The reason for the difference between early-stage lung adenocarcinoma and advanced lung adenocarcinoma needs further study. In 43.8% of cases (326/744), LOH occurred simultaneously in HLA-A, B and C,suggesting that the Class I locus was often lost together. **Conclusions:** We can use multi-gene panel for HLA LOH analysis, provided that the relevant regions are well captured. The prevalenceof HLA LOHpresent differences among cancer types.Understanding these distributions may provide more information for immunotherapy research. Research Sponsor: None.

HLA statusacross 10 cancer types in advanced patients.

Cancer types	Percent with HLA LOH
Breast cancer	42.1% (53/126)
Cervical cancer	59.7% (43/72)
Colorectal cancer	43.8% (70/160)
Endometrial cancer	23.8% (10/42)
Gastric and esophageal cancers	39.6% (57/144)
Kidney cancer	32.1% (25/78)
Liver cancer	24.1% (19/79)
Non-small-cell lung cancers	53.7% (347/645)
Ovarian cancer	38.2% (52136)
Pancreatic cancer	32.8% (21/64)

3125 Poster Session (Board #189), Fri, 8:00 AM-11:00 AM

CIMAC-CIDC tissue imaging harmonization. *First Author: Guray Akturk, Icahn School of Medicine at Mount Sinai, New York City, NY*

Background: The Cancer Immune Monitoring and Analysis Centers Cancer Immunology Data Commons (CIMAC-CIDC) network is a NCI Cancer Moonshots initiative to provide state-of-the-art technology and expertise for immunotherapy clinical trials. Multiplex tissue immunostaining is an integral assay provided that examines density and spatial distribution of immune cells and markers in tissues, for their prognostic or predictive value. Two approaches were evaluated for sensitivity, specificity, and reproducibility and subsequently harmonized: chromogenic-based Multiplex Immunohistochemical Consecutive Staining on Single Slide (MICSSS) and Multiplex Immunofluorescence (mIF) based tyramide signal amplification system. **Methods:** Harmonization was performed across CIMACs (Mount Sinai, Dana Farber Cancer Institute, MD Anderson Cancer Center) in multiple steps to prove that comparable data can be generated independent of site and platform. Goals: 1) harmonize image analysis platforms alone using tissues pre-stained with single chromogenic IHC for CD3 (membrane), Ki67 (nuclear), and CD68 (cytoplasmic), 2) compare image acquisition platforms, 3) streamline Antibody (Ab) clones and assess PD-L1 detection in relation to CLIA- assays, 4) harmonize staining protocols, image acquisition, and analysis platforms on 2 test head and neck tumor samples using MICSSS and mIF, 5) validate harmonization results with a tissue microarray on 27 tissues representing multiple tumors. For last steps, each CIMAC used their platforms for PD-L1, PD-1, CD3, CD8, and pan-cytokeratin (PanCK) staining on one of three consecutive slides from serial sections and compared densities of each marker. **Results:** Variables as PD-1 Ab clone, positive control reference tissues, sigma value for nuclear segmentation, and use of machine-learning based cell classifier were found to be key to produce accurate, reliable, comparable data. After visual quality control assessment and comparisons of each Region Of Interest (ROI), an overall inter-site Spearman correlation coefficient of ≥ 0.85 was achieved per marker within each tissue and across tissue types (expect pan-Cytokeratin, ≥ 0.7), with average coefficient of variation ≤ 0.1. **Conclusions:** These results show for the first time that two platforms can deliver harmonized data, despite differences in protocols, platforms, reagents, and analysis tools. Data resulting from retrospective and prospective CIMAC-CIDC analyses may be used with confidence for statistical associations with clinical parameters and outcome. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

3127 Poster Session (Board #191), Fri, 8:00 AM-11:00 AM

VCAN accumulation and proteolysis as predictors of T lymphocyte-excluded and permissive tumor microenvironments. *First Author: Philip Emmerich, University of Wisconsin Carbone Cancer Center, Madison, WI*

Background: Immune checkpoint inhibitors (ICIs) represent a major advance for treating solid tumors. However, only a minority of patients (pts) benefit from these therapies and markers that predict response have been elusive. Versican (VCAN) is an immunosuppressive proteoglycan in the tumor microenvironment (TME), which releases an immunostimulatory N-terminal fragment versikine (Vkine) when cleaved by ADAMTS proteases. We have demonstrated in colorectal cancers (CRC) that a low VCAN/high Vkine (VCAN proteolytic predominant [VPP]) phenotype correlates with increased tumor-infiltrating $CD8^+$ T lymphocytes (TILs). Here we examine the accumulation of VCAN as a marker of immune exclusion and its proteolysis as a marker of an immune-permissive TME. **Methods:** Immunohistochemistry for VCAN, Vkine and CD8+ was performed on samples from 1662 pts across breast (BC), CRC, endometrial cancer, pancreatic adenocarcinoma (PDAC), esophageal cancers and neuroendocrine tumors (NETs), across stages of disease (I-IV) and with diverse prior treatments. Stromal intensities of VCAN and Vkine staining quantified in collaboration with blinded surgical pathologists using a 0-3+ scale. 0/1+ were considered "low" for both VCAN and Vkine, whereas 2/3+ were considered "high". The number of $CD8^+$ TILs were counted using 400x magnification, the equivalent of a high power field (hpf). **Results:** Across the entire cohort VCAN phenotypes were diverse (VCAN high/Vkine low, 21%; VCAN high/Vkine high, 23%; VCAN low/Vkine low, 29%; VCAN low/Vkine high (VPP), 27%). Consistent with VCAN accumulation as a marker of T cell exclusion, VCAN low cancers had increased TILs compared to VCAN high (4.8 vs 18.3 TILs/hpf, $p < 0.001$). Low VCAN was identified in 85% esophageal, 79% NET (including small cell lung cancer [SCLC]) 72% endometrial, 47% MSI-H CRCs, 28% triple-negative BC and only 22% MSS CRC, 18% PDAC, 17% ER+ BCs. The VPP subgroup had the highest TILs per hpf across tumors. VPP was identified in 47% of esophageal, 45% endometrial, 41% NETs (including SCLC), 24% MSI-H CRCs, and only 9% MSS CRC, 7% ER+ BCs, 3% triple-negative BCs, and 0% of PDAC (n = 131 PDAC pts). **Conclusions:** VCAN accumulation correlates with T lymphocyte exclusion, while VCAN proteolysis predicts an immune permissive phenotype. VCAN accumulation and proteolysis are now incorporated into ICI clinical trials as a potential marker of response. Future studies will clarify the role of these biomarkers in predicting benefits of immuno-oncology treatment strategies. Research Sponsor: Funk Out Cancer, Bowlin for Colons.

3128 Poster Session (Board #192), Fri, 8:00 AM-11:00 AM

The HLA Ligand Atlas: A novel immuno-oncology resource for T-cell antigen discovery. *First Author: Ana Marcu, University of Tübingen, Cluster of Excellence iFIT (EXC 2180) "Image-Guided and Functionally Instructed Tumor Therapies", Tübingen, Germany*

Background: The human leukocyte antigen (HLA) complex regulates the adaptive immune response by showcasing the intracellular and extracellular protein content to the immune system, which is the basis for T cell-dependent tumor rejection. Therefore, a comprehensive map of the entirety of both HLA class I- and class II-presented peptides from various benign tissues is a highly sought after resource, as it enables the definition of tumor-association on the immunologically pivotal level of the HLA ligandome. **Methods:** Human tissue samples were snap frozen *post mortem* during autopsy. The study was approved by the local IRB. HLA ligands were immunopurified and characterized using an Orbitrap Fusion Lumos mass spectrometer coupled to an Ultimate 3000 RSLC Nano UHPLC System. Data acquisition was performed as technical triplicates in data-dependent mode, and data were analyzed using the containerized, computational pipeline MHCquant. **Results:** In this work, we describe the HLA Ligand Atlas, a comprehensive collection of matched HLA class I and class II ligandomes from 29 non-malignant tissues and 13 human subjects (208 samples in total), covering 38 HLA class I, and 17 HLA*DRB alleles and comprising 48,381 HLA class I and 16,146 HLA class II peptides. Nearly 50% of HLA ligands have not been previously described. The HLA Ligand Atlas is publicly available as a raw data resource, but also in the form of a user-friendly web interface that allows users to quickly formulate complex queries against the data set. Both downloadable data and the query interface are available at www.hla-ligand-atlas.org. **Conclusions:** This data set provides a valuable tool for research in diverse fields such as systems biology, general immunology, autoimmune disease and organ transplantation. Most importantly, the HLA Ligand Atlas provides essential information for translational applications in immuno-oncology. The knowledge of HLA ligands from benign tissues strongly supports the informed design of proteogenomic HLA-dependent target discovery approaches. Research Sponsor: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy - EXC 2180 – 390900677; Deutsche Forschungsgemeinschaft (DFG) SFB 685 "Immunotherapy: Molecular Basis and Clinical Application"; funded by ERC Ad.

3130 Poster Session (Board #194), Fri, 8:00 AM-11:00 AM

Machine learning-based identification of predictive features of the tumor micro-environment and vasculature in NSCLC patients using the IMpower150 study. *First Author: Amaro Taylor-Weiner, PathAI, Boston, MA*

Background: IMpower150 is a phase 3 study measuring the effect of carboplatin and paclitaxel (CP) combined with atezolizumab (A) and/or bevacizumab (B) in patients with advanced nonsquamous NSCLC, testing the hypothesis that anti-PD-L1 therapy may be enhanced by the blockade of VEGF. Here, we apply a machine-learning based approach to quantify the tumor micro-environment (TME) and vasculature and identify associations with clinical outcome in IMpower150. **Methods:** Digitized H&E images were registered onto the PathAI research platform (n=1027). Over 200K annotations from 90 pathologists were used to train convolutional neural networks (CNNs) that classify human-interpretable features (HIFs) of cells and tissue structures from images. Blood vessel compression (BVC) indices were calculated using the long versus short axes for each predicted blood vessel. HIFs were clustered to reduce redundancy, and selected features were associated with progression free survival (PFS) within each arm (ABCP, ACP, and BCP) using Cox proportional hazard models. **Results:** We used the trained CNNs to generate 4,534 features summarizing each patient's histopathology and TME. After association with survival and correction for multiple comparisons we identified clusters that were significantly associated with survival in at least one arm. Among patients receiving treatments that target PD-L1 (ABCP and ACP), high lymphocyte to fibroblast ratio (LFR) was associated with improved PFS (HR=0.64 (0.51, 0.81), $p < 0.001$) and showed no significant association with PFS among patients treated with BCP alone (HR=1.13 (0.85, 1.51), p=0.4). Among BCP treated patients, a higher average BVC within the tumor tissue was associated with improved PFS (HR=0.67 (0.50,0.90), p=0.01) and worse PFS among patients treated with ACP (HR=1.50 (1.10,2.06), p=0.009). **Conclusions:** We developed a deep learning-based assay for quantifying pathology features of the TME and vasculature from H&E images. Application of this system to Impower150 identified an association between high LFR and improved PFS among patients receiving PD-L1 targeting therapy, and between low BVC and improved PFS among patients receiving BCP. These findings support the importance of the TME and vasculature in determining response to PD-L1 and VEGF-targeting therapies. Research Sponsor: Genentech.

3131 Poster Session (Board #195), Fri, 8:00 AM-11:00 AM

Effect of chemokine signaling signatures on resolving discrepancy between TMB and checkpoint expression. *First Author: Christopher Szeto, ImmunityBio, Inc, Santa Cruz, CA*

Background: Tumor mutation burden (TMB) and *PD1/L1* expression are independent biomarkers for immune checkpoint blockade therapy, as seen in the Checkmate227 trial. Here we explore whether chemokine activity, an intermediate step between neoantigen presentation and immune-infiltration, can resolve this lack of association between existing biomarkers. We further use this novel biomarker to corroborate recent findings from Crowther et al. for a role of MHC class 1-related gene (*MR1)* downregulation in immune evasion. **Methods:** 1,395 clinical samples from the NantHealth database with matched tumor:normal whole exomes and deep whole-transcriptomic sequencing (> 200M reads) were available for analysis. The most common indications in the cohort were Breast (18%), Colon (9.8%), Lung (7.8%), Soft-tissue/Sarcomas (7.7%), and Pancreatic (6.1%). TMB was calculated by counting non-synonymous exonic mutations as per Rizvi, 2015. Immune-infiltration and chemokine signaling were inferred from RNAseq expression of published immune-cell-specific genesets (Bindea, 2013) and chemokine ligands (Nagarsheth, 2017) respectively. Significant associations between TMB, chemokine activity, immune-infiltration, and checkpoint expression were analyzed by ranksums test and corrected for multiple-hypothesis testing using Benjamini-Hochberg adjustment. **Results:** As expected, TMB and *PD1/L1* mRNA expression were not correlated in this cohort (r = 0.08 and r = 0.07 respectively). 36.3% of patients classified as highly immune-infiltrated by unsupervised clustering of immune-cell scores, and this subgroup significantly overexpressed all 11 targetable checkpoint genes analyzed including *PD1*, *PDL1, CTLA4, IDO1,* and *VISTA* (adj. p 9.7e-68 to 4e-168). There was no association between immune-infiltrated samples and TMB (t = 0.9, p = 0.35). Twice as many patients classified as chemokine-active (70.0%) and there was significant agreement between immune-infiltrated and chemokine-active patients (OR = 34.8, p = 6.5e-81). Interestingly, there was a weak but significant association between high chemokine-activity and increased TMB (t = 3.3, p = 0.001). Within patients that were chemokine-active but lacked immune-infiltration, *MR1* expression was significantly depleted (t = -10.7, p = 1e-26). **Conclusions:** Chemokine signatures can help resolve discordance between TMB and checkpoint expression. Analysis of discordance between chemokine-active but immune-depleted tumors may aid in identifying targets for converting from cold to hot tumor microenvironments. Research Sponsor: ImmunityBio, Inc.

3134 Poster Session (Board #198), Fri, 8:00 AM-11:00 AM

Personalized neoantigen/cancer testis antigen nanovaccine (PVAC) in combination with PD-1 monoclonal antibody and/or antiangiogenic treatment in patients with metastatic solid tumors. *First Author: Jia Wei, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: T-cell targeting of mutation-derived epitopes (neoantigens) has been demonstrated to drive anti-tumor responses. Nanotechnology has been reported to enhance immune responses of vaccines. Moreover, immunizing patients against such neoantigens, in combination with checkpoint inhibitor (CPI) and/or antiangiogenic drugs may elicit greater anti-tumor responses. **Methods:** Patient-specific mutation-containing neoantigens were selected on the basis of tumour-specific mutations whole-exome sequencing (WES) and RNA sequencing. Cancer testis antigens were obtained according to immunohistochemical staining and HLA-binding affinity prediction. Personalized neoantigen/cancer testis antigen nanovaccine (PVAC) is an amphiphiles nanovaccine loaded with personalized vaccine encoding multiple neoantigens designed to induce neoantigen specific T cells responses. Patients will receive PVAC in combination with PD-1 monoclonal antibody and/or antiangiogenic drugs. Primary end points include safety and tolerability. **Results:** 13 microsatellite stability (MSS) patients, which had relapsed from standard treatments, are enrolled in this study. 5 patients (1 gastric cancer, 1 liver cancer, 1 cervical carcinoma, 1 soft tissue sarcoma, 1 renal carcinoma) received PVAC in combination with PD-1 mAb, and another 8 patients (3 gastric cancer, 2 colon cancer, 1 NSCLC, 1 renal carcinoma) received PVAC in combination with PD-1 mAb and antiangiogenic therapy. No DLTs were reported. Five patients developed grade 1 and one patients developed grade 2 subcutaneous indurations in the injection sites, which collected with nanovaccine. One patient had grade 2 rash caused by anti-angiogenic drug. No drug related SAEs have been observed. There are 1 CR, 6 PR, 4 SD and 2 PD. Neoantigen specific T cell responses have been detected by IFN-γ ELISpot from PBMCs. **Conclusions:** PVAC is safe and well tolerated. Clinical responses have been observed in combination with PD-1 mAb and antiangiogenic drugs and neoantigen-specific T cell response have been observed after vaccination. Clinical trial information: ChiCTR1900022986. Research Sponsor: the National Natural Science Foundation of China.

3135 Poster Session (Board #199), Fri, 8:00 AM-11:00 AM

ESR1 mutations provide novel targets for breast cancer immunotherapy. *First Author: Jonathan Goldberg, Dana–Farber Cancer Institute, Boston, MA*

Background: Estrogen receptor (ER)-positive breast cancer is not considered immunogenic. Standard treatment is endocrine therapy to include aromatase inhibitors (AI). However, constitutively activating mutations in estrogen receptor alpha (*ESR1*) emerge with treatment making tumors resistant to AI therapy. While these mutations represent a pathway of resistance, they also represent potential neoepitopes that can be targeted with immunotherapy. Here we characterize the role of *ESR1* mutations as novel targets for breast cancer immunotherapy. **Methods:** Immunogenic epitopes derived from mutated *ESR1* (i.e. D538G, Y537S and E380Q) were identified in silico using the Immune Epitope Database and by determining overlapping peptides. In vitro T2 binding assays were used to measure the affinities of these peptides to HLA class-I, specifically HLA-A*0201. Dissociation assays were employed to characterize the stability of the peptide-HLA complex. Peptide-HLA-A*0201 tetramer staining was used to determine the expansion potential of peptide-specific cytotoxic T lymphocytes (CTL) from peripheral blood of healthy females. Cytotoxicity assays were used to determine the ability of peptide-specific CTLs to lyse cells presenting mutated ESR1-derived peptides. **Results:** We identified 22 nonameric and decameric peptides derived from the most common ESR1 mutations; 10/22 demonstrated high affinity (i.e. IC50 $<$ 500nM) binding to HLA-A*0201. The 3 highest predicted peptides demonstrated low IC50 values (13 nM, 19.5 nM and 56.6 nM), indicating very tight binding to HLA-*0201. *In vitro* assays confirmed high affinity binding for 10 of the 22 *in silico*-predicted peptides with an average fold change of 1.52 compared to non-pulsed T2 cells, and a median dissociation half-life of 6.45 hours. Tetramer staining of peptide specific CTLs from normal donor peripheral blood mononuclear cells showed relatively high expansion frequencies, with the highest three frequencies noted for D538G (1.04%), Y537S (0.49%) and V392I (0.27%). Using 4-hour *in vitro* cytotoxicity assays, in comparison with non-pulsed T2 cells, there was significantly higher lysis of peptide pulsed T2 cells that were cocultured with matching peptide-specific CTL: D538G (67.1 % vs 36.9%, $P < 0.001$), Y537S (59.5% vs 37.5%, $P < 0.01$), and E380Q (36.3% vs 7.8%, $P < 0.001$). **Conclusions:** These data confirm the immunogenicity of epitopes derived from the most common ESR1 mutations. Further investigation of these peptides as part of novel immunotherapies, to include vaccine strategies is warranted. Research Sponsor: Parker Institute for Cancer Immunotherapy.

3136 Poster Session (Board #200), Fri, 8:00 AM-11:00 AM

A shared tumor-antigen RNA-lipoplex vaccine with/without anti-PD1 in patients with checkpoint-inhibition experienced melanoma. *First Author: Carmen Loquai, Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany*

Background: Cancer vaccines are considered unsuitable for patients with advanced tumours and have not been clinically successful. **Methods:** Lipo-MERIT is an ongoing phase 1/2 trial (NCT02410733) with melanoma FixVac, a liposomal RNA vaccine targeting four non-mutant shared tumour-associated antigens (TAAs) (MAGE-A3, NY-ESO-1, tyrosinase, TPTE). Patients with stage IIIB-C and IV melanoma are eligible. The trial comprises 7 dose escalation and 3 dose expansion cohorts, the latter with FixVac alone or combined with anti-PD1. Eight doses of FixVac are administered i.v. weekly/bi-weekly followed by optional continued monthly treatment. This abstract summarizes the findings of an exploratory interim analysis (cut-off JUL2019) of 89 patients. **Results:** 42 of 89 patients had measurable disease at baseline and were eligible for assessment of best objective overall response. All but one patient were stage IV and had undergone previous lines of treatment, 41 patients were checkpoint-inhibitor (CPI)-experienced, and 35 had been exposed to both anti-CTLA4 and anti-PD1 therapy. In the vaccine monotherapy group (n = 25) three patients experienced a partial response (PR) and 7 patients had stable disease (SD). An additional patient showed a complete metabolic remission of metastatic lesions based on [^{18}F]-FDG PET/CT imaging. In the group of patients treated with melanoma FixVac and PD1 blockade, 6 of 17 patients developed a PR. Patients with PR showed induction of poly-epitopic and strong CD4$^+$ and CD8$^+$ T cell immunity against the vaccine antigens. The number of antigen-specific cytotoxic T cells in some responders reached up to low 2-digit percentages of circulating CD8$^+$ T cells and was maintained at high levels by continued vaccination. Overall, 75% of the 50 patients tested by *ex vivo* IFNg ELISpot analysis and all 20 patients tested by IFNg ELISpot after *in vitro* stimulation showed vaccine-induced immune responses against at least one vaccine antigen. Typically, antigen-specific T cells ramped up within the first 4-8 weeks to single-digit and low double-digit percent fractions of circulating CD8$^+$ T cells. Immune responses were of effector memory phenotype and their strength and frequency did not depend on disease status at baseline (measurable *versus* non-measurable disease), on vaccine dose or on treatment (FixVac alone *versus* in combination with anti-PD1). **Conclusions:** FixVac alone and in combination with anti-PD1 mediates durable objective responses in pre-treated, CPI experienced patients with advanced progressing melanoma. Clinical trial information: NCT02410733. Research Sponsor: BioNTech RNA Pharmaceuticals GmbH.

3137 Poster Session (Board #201), Fri, 8:00 AM-11:00 AM

Personalized viral-based prime/boost immunotherapy targeting patient-specific or shared neoantigens: Immunogenicity, safety, and efficacy results from two ongoing phase I studies. *First Author: Charles G. Drake, Herbert Irving Comprehensive Cancer Center, New York, NY*

Background: Neoantigens are key targets of a tumor-specific immune response and CD8 T cells targeting neoantigens drive clinical benefit in patients (pts) treated with checkpoint inhibitors. **Methods:** Two Phase I studies are being conducted to assess the safety, immunogenicity, and early clinical activity of a viral-based neoantigen-targeting prime/boost immunotherapy aimed at maximizing the CD8 T cell response. Both studies use a chimpanzee adenovirus prime followed by increasing doses of repeat boosts with a self-amplifying mRNA in combination with IV nivolumab +/- SC ipilimumab. In the first study, GO-004, patient-specific neoantigens are predicted using Gritstone's EDGE model and incorporated into both prime/boost vectors. In GO-005, shared neoantigens derived from common driver mutations (including several from *KRAS*) are encoded in off-the-shelf prime/boost vectors. **Results:** To date, 12 pts have been treated: 6 pts with GEA, NSCLC, or MSS-CRC (GO-004) and 6 pts with NSCLC, MSS-CRC, or PDA (GO-005) with all pts receiving IV nivolumab and 5 pts also receiving SC ipilimumab. Nine pts continue to receive study treatment. No DLTs have been observed. Treatment-related AEs are reversible and include Grade 1/2 fever (7/12), injection site reactions (4/12), fatigue (3/12), diarrhea (2/12), hypotension (2/12), pruritus (2/12), skin reactions (2/12), anorexia (1/12), dyspnea (1/12), hyponatremia (1/12), infusion-related reactions (1/12), myalgia (1/12), and asymptomatic Grade 3 CK elevation (1/12). At the time of analysis, 8 of 12 pts with $\geq$ 1 radiographic assessment have a best response of stable disease (SD) (3) and progressive disease (PD) (4), and one pt with no evaluable disease at baseline continues on study $>$ 8 months. In GO-005, 1 pt with SD has a 20% reduction in tumor dimensions that correlates with a decrease in ctDNA. In 4 pts in GO-004 analyzed to date, all pts showed substantial neoantigen-specific CD8 T cell responses to multiple neoantigens after priming which increase further in 2 of 3 pts analyzed after subsequent boosts. In GO-005, 1 of 3 pts showed a robust KRAS G12C-specific CD8 T cell response. Induced T cells express IFNg and granzyme B, consistent with an effector response. **Conclusions:** Taken together, these early data support the tolerability of a viral-based prime/boost immunotherapy, demonstrate marked immunogenicity, and are consistent with potential clinical activity. Additional pts and data at higher dose levels will be presented. Clinical trial information: NCT03639714, NCT03953235. Research Sponsor: Gritstone Oncology, Inc.

3138 Poster Session (Board #202), Fri, 8:00 AM-11:00 AM

Multi-antigen active specific immunotherapy induced long-term remission and prevent colorectal cancer relapse. *First Author: Juan Pablo Marquez-Manriquez, CICS USA, Seattle, WA*

Background: Clinical effective multi-antigen active immunotherapy for colorectal cancer (CRC) is still limited and most studies have failed. We consider this is because the targets in some of the studies are not oncogenic drivers. This is especially important for patients that progressed to standard of care treatment. Also, most of the studies with Immune checkpoint inhibitors (ICH) have failed in CRC but potentially may impact and provide better outcomes if used as combination therapies. We treated CRC patients with progressive disease in a pilot study n = 15 and found clinical responses that correlate with the CD8, delayed-type hypersensitivity (DTH) and Th1 parameters. After patients achieved remission we used the same peptides to prevent relapse with clinical and statistics significance. **Methods:** N = 15 CRC patients were enrolled in this pilot trial after approval for the ethic IRB committee from CICS Mexico. Patients were treated with an intradermal vaccine every week for four weeks, every two weeks four times in axillary and inguinal lymph nodes (LN) areas, and finally subcutaneously every month six times in the sites with tumor activity. Previously to the treatment we perform Granzyme B ELISPOT, ELISA, DTH and CT scan as initial controls. We delivered intradermal four peptides from sixteen peptides predicted from four proteins such as Fascin-1, Ape-1, VCP and RCAS1. **Results:** 86% of the patients had an objective clinical responses and 14% stable disease. All the patients had a correlation with the immunological assays as following. 58% of patients had an increased in the CD8 cells demonstrated by Granzyme B; DTH reactions were gradually increasing and by the first month of treatment the DTH were positive for Fascin-1 (78%), Ape-1 (85%), VCP (95%) and RCAS1 (83%) peptides. The more immunogenic peptides by ELISA were Fascin-1 A ($P = 0.001$), Fascin-1 D ($P = 0.005$), Ape-1 C ($p = 0.001$), VCP A ($P = 0.003$), RCAS1 A ($p = 0.001$) and RCAS1 B ($P = 0.01$). **Conclusions:** The treatment was effective with CR and SD responses. Once we validate this data we are planning a clinical study combining the treatment with low dose of ICH. Currently all the patients with CR are now under relapse prevention. We are still treating the patients with SD until disease progression. Importantly we believe that this data may impact the PFS and OS in CRC patients who have Karnoksky $>$ to 80% despite progressive disease to standard of care. Research Sponsor: Sonora Cancer Research Center Foundation from Ciudad Obregon, Sonora, Mexico.

3139 Poster Session (Board #203), Fri, 8:00 AM-11:00 AM

Safety and tolerability of intratumorally administered OH2, an oncolytic herpes simplex virus 2, in patients with advanced solid tumors: A phase I dose escalation clinical study. *First Author: Jing Huang, 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*

Background: There have been limited reports concerning treatment outcomes of oncolytic viruses in solid tumors other than melanoma. OH2 is a genetically engineered oncolytic herpes simplex virus type 2 designed to selectively amplify in tumor cells and express GM-CSF to enhance tumor-specific immune responses. **Methods:** We conducted an open-label, single-center, phase 1 study. Eligible pts were 18-75 years of age; had histologically confirmed advanced solid tumor; had progressed after standard systemic treatments. Pts were required to have tumor(s) deemed safe to inject, with a longest diameter of at least 0.5cm. Other eligibility criteria included measurable lesion as per RECIST v1.1; ECOGPS score of 0-1 and adequate organ functions. A 3+3 dose-escalation strategy was used in the study and 3 dose levels (10^6, 10^7 and 10^8 CCID50/mL) of OH2 were assessed. OH2 was administered intratumorally every 3 weeks for the first cycle and every 2 weeks.Treatment may continue afterwards in ptswith potential clinical benefit at the discretion of the investigators. The primary objective was the safety and tolerability of OH2 injection as defined by the dose limiting toxicities (DLTs) within the first 3 weeks of therapy, and the maximum tolerated dose (MTD). Secondary objectives included efficacy and immunogenicity of OH2. **Results:** 11 pts were enrolled between April 17, 2019 and November 4, 2019. The median follow-up duration was 8.36 months (95%CI: 5.64-11.08). OH2 was well-tolerated as no DLTs were reported and no MTD reached. Before the end of the DLT assessment period,1 pt withdrew consent, and 1 pt died of arrhythmia unrelated to OH2, with negative OH2 DNA copies in serum, urine and saliva samples. Most treatment-related adverse events (TRAEs) observed were of grade 1-2, except that 1 pt in the 10^8 CCID50/mL group developed grade 3 fever. The most common TRAEs were fever (n =5) and blood bilirubin level increase (n = 4). There were no grade 4 or 5 TRAEs. One pt(rectal cancer) had PR and 2 (appendix cancer and ovarian cancer) had SD as per RECIST v1.1. One patient (esophageal cancer) achieved iPR as per iRECIST criteria. The duration of follow-up for the 2 responders were 9.70 months and 8.36 months, respectively, and both had ongoing responses. Notably, regression of a non-injected lesion was observed in 1 patient. **Conclusions:** OH2 had a favorable safety profile with no DLTs and MTD. The dose expansion study in selected tumor types is currently underway. Clinical trial information: NCT03866525. Research Sponsor: Wuhan Binhui Biotechnology Co., Ltd.

3140 Poster Session (Board #204), Fri, 8:00 AM-11:00 AM

Inhaled corticosteroid use and risk of pneumonitis in patients treated with immune checkpoint inhibitors. *First Author: Mingjia Li, The Ohio State University Wexner Medical Center, Division of Hospital Medicine, Columbus, OH*

Background: The identification of risk factors for immune-related adverse events (irAEs) is an important area of research. Among irAEs, pneumonitis carries one of the highest morbidities. There is a lack of strong predictors for pneumonitis in patients (pts) treated with ICI. We sought to identify predictors for the development of pneumonitis, and whether the use of inhaled corticosteroids (ICS) at time of ICI could be protective. **Methods:** Pts with advanced cancer treated with ICI from 2011 and 2018 were included in this retrospective study. Pneumonitis attribution to ICI was determined by treating physician at time of diagnosis. Time to pneumonitis was defined as days from the start of ICI to pneumonitis diagnosis. Pts who never had pneumonitis were censored at the time of last follow up or death. Predictors of pneumonitis were assessed by univariate Cox proportional hazard models at a significance threshold of alpha = 0.05. **Results:** A total of 837 pts were identified, and 30 (3.6%) pts developed any grade pneumonitis (12 grade 2, 14 grade 3, 1 grade 4, 3 grade 5) after receiving ICI (Table). Pts with age ≥65 years (y) had increased risk of developing pneumonitis over pts with age < 65y (HR 2.1, 95 CI: 1.02-4.4, p=0.041). 82 (9.7%) of the total cohort were on inhaled corticosteroid (ICS) at time of ICI, and 9 (11%) developed pneumonitis. Rather than being protective, pts on ICS had higher risk of pneumonitis (HR 4.2, 95 CI: 1.9-9.2, p=0.001). Pts with lung cancer had an increased risk for pneumonitis compared to pts with other cancers (HR 3.2, 95 CI: 1.5-6.4, p =0.003). Other risk factors included performance status, smoking history, line of therapy, or prior treatment including radiation were not statistically significant. **Conclusions:** Rather than a protective effect of ICS, our analysis found a higher risk of pneumonitis in pts treated with ICS. We confirmed an increased risk of pneumonitis for lung cancer pts compared to pts with other cancers, and higher risk of pneumonitis in pts age >65y. We hypothesize that the increased inflammatory status in chronic lung inflammation may predispose pts to pneumonitis that was not ameliorated by ICS. Future study is needed in prospective cohorts to further clarify the underlying inflammatory mechanism. Research Sponsor: Research support provided by the REDCap project and The Ohio State University Center for Clinical and Translational Science grant support (National Center for Advancing Translational Sciences, Grant UL1TR002733). Dr. Owen is a Paul Calabresi Scholar suppo.

	Pt Count	Pneumonitis Count		Pt Count	Pneumonitis Count
Age <65y	483 (58%)	12 (2.5%)	on ICS	82 (9.8%)	9(11%)
Age ≥65y	354(42%)	18 (5.1%)	Not on ICS	755 (92.2%)	21 (2.8%)
Cancer Types					
Melanoma	310 (37%)	7 (2.3%)			
Lung Cancers	209 (25%)	14 (6.7%)			
Renal Cell	73 (9%)	2 (2.7%)			
Other	245 (29%)	7 (2.8%)			

3141 Poster Session (Board #205), Fri, 8:00 AM-11:00 AM

Response criteria for intratumoral immunotherapy in solid tumors: itRECIST. *First Author: Gregory V. Goldmacher, Merck & Co., Inc., Kenilworth, NJ*

Background: The approval of intratumoral (IT) immunotherapy for metastatic melanoma and the active development of numerous novel IT drugs have created a need for standardized evaluation of response to this unique treatment strategy. The Response Evaluation Criteria in Solid Tumors (RECIST) is not suitable for assessing responses separately for injected and noninjected tumors. Building on RECIST concepts, we propose an IT immunotherapy RECIST (itRECIST) to capture data and assess local and systemic responses in a standardized fashion for clinical trials involving IT immunotherapies. **Methods:** itRECIST will address the unique needs of IT immunotherapy trials but, where possible, aligns with RECIST 1.1 and iRECIST. It does not dictate which lesions to inject but provides guidelines for collecting data and assessing response as treatment evolves. **Results:** itRECIST enables overall response assessment, separate response assessments in injected and noninjected lesions, and continued assessment following modifications of therapy at initial progression. At baseline, lesions are classified into 4 categories: target injected, target noninjected, nontarget injected, and nontarget noninjected. After baseline, lesions can be reclassified from noninjected to injected if the investigator decides to change the lesions to inject, but target and nontarget designations never change. Overall response at each assessment is based on target lesion response (injected and noninjected), nontarget lesion response, and absence/appearance of new lesions. Noninjected lesion response is determined by comparing tumor burden with baseline and nadir values. Injected lesion assessment is based on visit-to-visit changes in the lesions injected during treatment and on a combined assessment once the patient is off treatment. A new response category is defined to capture progression that would be "confirmed" per iRECIST even though injected lesions are responding and therapy continues. Multiple examples have been created to aid in training and adoption. **Conclusions:** itRECIST is an important step toward a standardized method of response assessment for this promising and evolving therapeutic modality. The proposed guidelines can be adopted into trial protocols and routine clinical practice without the need for complex additional assessments by treating physicians. Until there is evidence to support wider use, itRECIST is intended only to support standardized collection of data and to facilitate exploratory analysis. Authors G.V.G. and A.D.K. contributed equally to this work. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

3142 Poster Session (Board #206), Fri, 8:00 AM-11:00 AM

Analysis of mutation detection of POLD1/pole in pan-cancer. *First Author: Gao Yang, Xiangya Hospital, Central South University, Changsha, China*

Background: Previous studies proved that mutation of *POLD1* and *POLE* elevates base-substitution mutations and lead to the elevation of tumor mutation burden (TMB). Other signature needs to explore to identify driver mutations in these two genes. **Methods:** Using gene-panel target-capture next generation sequencing, we analyzed the TMB and *POLD1/POLE* mutation in 17383 tumor tissue or plasma ctDNA samples from different patients. **Results:** Tumor mutation burdens were calculated of all the 17383 samples. According to the present research and our panel, we use 10 and 100 Mut/Mb to define hypermutation and ultra-hypermutation. Samples with hypermutation possessed 18.8% (n = 3268) and ultra-hypermutation possessed 0.3% (n = 58). In unselected, hypermutation and ultra-hypermutation group, *POLD1* or/and *POLE* mutations were identified in 3.5% (n = 625), 56.1% (n = 32) and 87.9%(n = 372) samples. There were 0.5% (n = 81), 17.0% (n = 73) and 87.7%(n = 51) identified more than one mutation. These results showed that *POLD1* or/and *POLE* mutations were enriched in samples with high TMB. We screened every known *POLE* and *POLD1* driver mutations. There were 22 ultra-hypermutation samples identified these mutations, including A456P(3), P286R(10), V411L(6), M444K(1), S459F(1) in *POLE* and R1016H(1) in *POLD1*. Interestingly, all of them were identified in microsatellite stable (MSS) samples , which suggest that driver mutation may enriched in MSS samples. These already known driver mutation was not detect in 24 high-level microsatellite instability (MSI-H) and ultra-hypermutation samples. We further analyzed 10 *POLD1/POLE* mutations in other 5 MSS and ultra-hypermutation samples. *POLE* L424V was a pathogenic germline mutation but not defined as a driver mutation clearly before. *POLE* P286C had not been biochemically characterized but had different residue with P286R in the same position. Others had not been biochemically characterized (R232H, A234T, V945M, S1064I, Y467H in *POLD1*, D462N and R749Q, E1956D in *POLE*). These mutations were potential driver mutations and further research need to be support. **Conclusions:** We found that not only *POLD1* or/and *POLE* mutations were enriched in samples with high TMB, but also driver mutations were enriched in microsatellite stable tumors. Further researches need to continue to identify more driver mutations of *POLD1* and *POLE*. Research Sponsor: None.

3143 Poster Session (Board #207), Fri, 8:00 AM-11:00 AM

Percutaneous hepatic injection of rose bengal disodium (PV-10) in metastatic uveal melanoma. *First Author: Sapna Pradyuman Patel, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PV-10 is a small molecule autolytic immunotherapy in clinical development for treatment of solid tumors. When administered by intralesional (IL) injection, PV-10 can produce immunogenic cell death that may induce a T cell-mediated immune response against treatment refractory and immunologically cold tumors. Given this mechanism of action and clinical data that metastatic uveal melanoma (MUM) generates low response rates to immune checkpoint blockade (CB), we investigated treatment of MUM with percutaneously-delivered PV-10. **Methods:** This open-label Phase 1 basket study (NCT00986661) is evaluating the safety, tolerability, and preliminary efficacy of intralesional PV-10 in patients (pts) with solid tumors of the liver. PV-10 is injected into one or more designated hepatic tumor(s) with a maximum sum of diameters ≤4.9 cm. Response assessments using 2D EASL criteria are performed at Day 28, then every 3 months. Pts with additional injectable tumors are eligible to receive further PV-10 after Day 28. Pts can receive standard of care CB immunotherapy during treatment with PV-10. **Results:** As of February 1, 2020, the initial cohort of 15 pts with MUM to the liver was fully enrolled. Pts had received at least 1 IL injection of PV-10, with an average of 2 hepatic lesions injected per pt (range 1-4). Of these, 4 pts were refractory to prior CB. Three pts received PV-10 alone, 3 received PV-10 + anti-PD-1 and 9 received PV-10 + anti-PD-1 + anti-CTLA-4. Adverse events (AEs) were consistent with established patterns for PV-10 and CB: AEs attributed to PV-10 were transient and included 3 cases of Grade 3/4 transaminitis that resolved within 72 hrs, injection site pain, photosensitivity, and pink discoloration of skin, urine or feces; AEs attributed to CB included nausea, decreased WBC, and fatigue. Response assessments on 24 injected tumors were: 2 complete response (8%), 7 partial response (29%) and 11 stable disease (46%), per 2D EASL. Among the 4 CB-refractory pts, median overall survival (OS) was 9.2 months (range 5.3 - 11.4 months, with 2 pts alive at 5.3 months each), while among the 11 CB-naïve pts OS was undefined (range 0.5 - 21.9+ months, with 1 death at 7.9 months). Pts receiving PV-10 alone (1 CB-refractory, 2 naïve) achieved a median OS of 7.9 months with one CB-naïve pt alive with partial overall response at 21.9 months. **Conclusions:** Response indicative of regression or stabilization in a majority (83%) of injected lesions is encouraging in a disease of major unmet need. Enrollment and follow-up for safety, duration of response and survival are ongoing. Clinical trial information: NCT00986661. Research Sponsor: Provectus Biopharmaceuticals.

3144 Poster Session (Board #208), Fri, 8:00 AM-11:00 AM

Immune-mediated adverse events following concomitant radiotherapy and immunotherapy in patients with melanoma and Merkel cell carcinoma: A preliminary report from an evolving retrospective registry. *First Author: Nikolaos Andreatos, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: Radiotherapy (RT) potentiates immune-mediated responses against tumor antigens, an effect that is enhanced by checkpoint inhibitors (CPIs) and may hold therapeutic promise. However, the mechanisms underlying this abscopal effect can theoretically increase the rate of immune-mediated adverse events (irAEs). We estimated the incidence of irAEs in a single-institution cohort treated with concomitant RT and immunotherapy. **Methods:** We retrospectively screened 731 patients that received RT and CPIs at our institution. Patients diagnosed with melanoma or Merkel cell carcinoma (MCC) who underwent RT concurrently or within 30 days of CPI administration were eligible. A radiation period (RP) comprised the interval between the first and last treatment days (≤90 days); a patient could contribute multiple RPs. Data on new irAEs diagnosed within 3 months after RT and relevant demographic and clinicopathologic variables were collected; univariate analysis was performed with the chi-squared test. **Results:** 35 patients (23 male, 12 female) contributed 43 RPs; mean age was 65.5 years (range: 39-90). Five had MCC, and 30 had melanoma (24 cutaneous, 1 uveal and 5 urogenital melanomas). PD-1 inhibitors were most commonly employed (22 RPs), followed by ipilimumab-nivolumab (14 RPs), ipilimumab (4 RPs), and avelumab (3 RPs). CPIs were administered concurrently with RT in 32 RPs and sequentially in 11 RPs. Fourteen RPs comprised intracranial radiation. Importantly, 45.7% of patients (16/35) experienced irAEs, which manifested within a month of RT in 25.7% (9/35). Four patients experienced grade ≥3 irAEs leading to hospitalization; one died of respiratory failure after developing pneumonitis. On univariate analysis, no significant association between tumor type, CPI regimen, concurrent RT, intracranial vs. extracranial RT, and irAE incidence was noted. A trend for increased irAEs within the ipilimumab-nivolumab group was observed ($p = 0.27$). **Conclusions:** Almost half of patients developed new irAEs following RT, with 25% (4/16) of cases warranting hospitalization; these incidence rates appear to exceed rates from historical data and raise concerns about the additive toxicity of CPIs and RT. Comparison to non-RT cohorts and survival analyses are ongoing. Research Sponsor: None.

TPS3145 Poster Session (Board #209), Fri, 8:00 AM-11:00 AM

ZW25, 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. *First Author: Do-Youn Oh, Seoul National University Hospital, Seoul, South Korea*

Background: ZW25 is a novel HER2-targeted antibody that binds two distinct extracellular domains of HER2, allowing for multiple mechanisms of action, including activation of ADCC and inhibition of ligand-dependent and -independent cellular growth. ZW25 is well tolerated and showed single-agent antitumor activity in patients (pts) with advanced HER2-positive cancers. Previous reports suggested that tislelizumab, an investigational anti-PD-1 antibody engineered to minimize binding of FcgR on macrophages in order to abrogate antibody-dependent phagocytosis, was generally well tolerated and had antitumor activity alone and in combination with chemotherapy in pts with advanced solid tumors. Combining HER2-targeted agents with chemotherapy has resulted in improved survival; 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 is designed to evaluate ZW25 plus chemotherapy ± tislelizumab as first-line therapy in pts (n≈50) with HER2-positive metastatic breast cancer (mBC; cohort 1) or advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC; cohort 2). In cohort 1, pts with HER2-positive (IHC3+ or ISH amplified) mBC must be treatment-naïve for metastatic disease and will receive intravenous (IV) ZW25 30 mg/kg plus docetaxel 75 mg/m^2 IV once every 3 weeks (Q3W). In cohort 2, treatment-naïve pts with HER2-positive (IHC3+ or IHC2+ with ISH amplification) advanced GC/GEJC will receive ZW25 30 mg/kg plus tislelizumab 200 mg IV and chemotherapy (CAPOX regimen: capecitabine 1000 mg/m^2 twice daily and oxaliplatin 130 mg/m^2 IV) Q3W. A safety lead-in phase is designed for the first six pts in cohort 2, followed by dose expansion after a safety monitoring committee review. Primary endpoints are the safety/tolerability 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: Registered, NCT number pending will provide as soon as available. Research Sponsor: BeiGene, Ltd.

TPS3146 Poster Session (Board #210), Fri, 8:00 AM-11:00 AM

Bgb-A425, an investigational anti-TIM-3 monoclonal antibody, in combination with tislelizumab, an anti-PD-1 monoclonal antibody, in patients with advanced solid tumors: A phase I/II trial in progress. *First Author: Jayesh Desai, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: While immune surveillance plays a critical role in preventing tumor proliferation and metastasis, tumors develop resistance mechanisms to suppress and/or escape the immune system. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and programmed cell death protein-1 (PD-1) function as immune checkpoint receptors on tumor-infiltrating lymphocytes. Overlap in expression and function suggests TIM-3 and PD-1 cooperate to maximize effector T-cell exhaustion, leading to a decreased antitumor immune response. Although blockade of TIM-3 alone is unlikely to result in an efficacious antitumor immune response, combined TIM-3/PD-1 blockade may enhance the antitumor properties of anti-PD-1 therapies alone. BGB-A425 is an investigational IgG1-variant monoclonal antibody against TIM-3. Tislelizumab, an anti-PD-1 antibody, was engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. This phase 1/2 study will assess the safety/tolerability, pharmacokinetic (PK) profile, and antitumor activity of BGB-A425 in combination with tislelizumab in patients with advanced solid tumors. **Methods:** This is an open-label phase 1/2 study (NCT03744468) of BGB-A425 in combination with tislelizumab in patients with histologically/cytologically confirmed advanced, metastatic, unresectable solid tumors. Phase 1 will determine the recommended phase 2 dose (RP2D) for combination treatment; phase 2 will assess the antitumor effects of the combination in select tumor types. In phase 1, up to 42 patients will be enrolled into sequential cohorts of increasing doses of intravenous (IV) BGB-A425 in combination with tislelizumab 200 mg IV, based on a 3+3 study design. During Cycle 1, patients will receive BGB-A425 alone on Day 1 followed by tislelizumab alone on Day 8. If no dose-limiting toxicities are observed, patients will receive both BGB-A425 and tislelizumab sequentially on Day 29 and every 21 days thereafter. Once the RP2D is determined, the combination therapy will be evaluated in up to 120 patients with select tumor types in phase 2. Safety/tolerability profile and RP2D determination (phase 1) and objective response rate per RECIST v1.1 (phase 2) are primary objectives; secondary objectives include antitumor activity, PK profile, and immunogenicity of combination therapy. Clinical trial information: NCT03744468. Research Sponsor: BeiGene, Ltd.

TPS3147 Poster Session (Board #211), Fri, 8:00 AM-11:00 AM

A phase I study of CD40 agonist ABBV-927 plus OX40 agonist ABBV-368 with or without the PD-1 inhibitor budigalimab in patients with advanced solid tumors. *First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC*

Background: CD40 is a key costimulatory molecule for both the innate and adaptive immune systems that is essential for T-cell activation and proliferation. OX40 is a costimulatory molecule that is involved in enhancing nascent immune responses and concomitantly acts to suppress regulatory T-cell activity. ABBV-927 and ABBV-368 are potent agonistic antibodies against CD40 and OX40, respectively. This open-label, Phase 1 study will evaluate the doublet combination of ABBV-927 and ABBV-368 and the triplet combination of ABBV-927, ABBV-368, and the programmed cell death protein-1 (PD-1) inhibitor budigalimab in patients with advanced solid tumors. **Methods:** For this study (NCT03893955), patients must be ≥18 y with an Eastern Cooperative Oncology Group performance status of 0-1. Patients must have an advanced solid tumor that has progressed on standard therapies. Disease-specific cohorts will include patients with non-small cell lung cancer (NSCLC) and triple-negative breast cancer (TNBC). Patients with NSCLC must have previously received a PD-1/PD-ligand 1 inhibitor and a platinum-based therapy and no more than one prior immunotherapy. Patients with TNBC must not have received immunotherapy. Patients with uncontrolled central nervous system metastases will be excluded. The recommended Phase 2 dose (RP2D) will first be identified with ABBV-927 + ABBV-368 in patients with solid tumors (Arm A) and will be expanded in disease-specific cohorts including TNBC. The RP2D of ABBV-927 + ABBV-368 + budigalimab will be identified in patients with NSCLC (Arm B). The primary endpoints are determination of the RP2D of ABBV-927 + ABBV-368, the RP2D of ABBV-927 + ABBV-368 + budigalimab, and overall response rate; duration of response, progression-free survival, safety, and pharmacokinetics are secondary endpoints. Screening began on 21 May 2019, and enrollment is ongoing. Clinical trial information: NCT03893955. Research Sponsor: Abbvie, Inc.

TPS3148 Poster Session (Board #212), Fri, 8:00 AM-11:00 AM

A phase II open-label multicenter study to assess the efficacy and safety of AFM13 in patients with relapsed or refractory CD30-positive peripheral T-cell lymphoma or transformed mycosis fungoides: The REDIRECT study design and rationale. *First Author: Cassandra Choe-Juliak, Affimed Inc, NY, NY*

Background: AFM13 is a tetravalent, bispecific (anti-CD30/anti-CD16A) recombinant antibody being developed for the treatment of CD30-positive T-cell malignancies and Hodgkin lymphoma. AFM13 selectively kills CD30-positive tumor cells by engaging and activating natural killer cells and macrophages. AFM13 was well tolerated at doses of 0.01 to 7 mg/kg and showed clinical activity in patients with relapsed/refractory (R/R) Hodgkin lymphoma in a Phase 1 study. In an ongoing biomarker Phase 1b/2a study in patients with R/R CD30-positive lymphomas with cutaneous involvement, 4 of 8 patients responded (at different doses) including one CR. Based on these findings, this Phase 2 study (REDIRECT) has been initiated. **Methods:** This is a Phase 2, open-label, multicenter global study investigating the efficacy and safety of AFM13 in patients with R/R CD30-positive peripheral T cell lymphoma (PTCL) or transformed mycosis fungoides (TMF). AFM13 is administered at 200 mg weekly via an intravenous infusion until disease progression, unacceptable toxicity, investigator discretion or withdrawal of consent. Cohorts A and B include PTCL patients with ≥10%, and ≥1% to <10% CD30 expression by IHC, respectively. Cohort C includes patients with TMF who express ≥1% CD30. Eligible PTCL patients must have received at least 1 prior line of systemic therapy and, if diagnosed with systemic anaplastic large cell lymphoma, must have failed or be intolerant to brentuximab vedotin. Eligible patients with TMF must have received at least 1 prior line of systemic therapy and have exhausted systemic therapies with regular approval for their disease. This global trial started enrollment in Oct 2019. The primary endpoint is objective response rate as confirmed by an Independent Review Committee for all cohorts. The study will also assess investigator-measured efficacy parameters, safety, PK, immunogenicity and QOL. Disease assessment will be done at screening and every 8 weeks for the first 3 assessments, then every 12 weeks thereafter, regardless of any treatment/cycle delays that may occur. ClinicalTrials.gov identifier: NCT04101331. References: Reusch U et al. *mAbs.* 2014;6(3):728-739. Rothe A et al. *Blood.* 2015;125(26):4024-4031. Clinical trial information: NCT04101331. Research Sponsor: Affimed GmbH.

TPS3149 Poster Session (Board #213), Fri, 8:00 AM-11:00 AM

KITE-439: A phase I study of HPV16 E7 T cell receptor-engineered T cells in patients with relapsed/refractory HPV16-positive cancers. *First Author: Kedar Kirtane, Moffitt Cancer Center, Tampa, FL*

Background: Human papillomavirus 16 (HPV16) is the most prominent subtype across invasive head and neck cancers, as well as cervical cancer and other anogenital cancers (Saraiya M, et al. *J Natl Cancer Inst.* 2015). The HPV16 E7 (E7) viral antigen is important for the survival of HPV-positive tumor cells but is absent from normal human tissue, making it an attractive target for anti-cancer therapy. Preclinical efficacy has been observed with MHC class I-restricted T cell receptor (TCR)-engineered T cells targeting E7 on HPV16-positive tumor cells (Jin BY, et al. *JCI Insight.* 2018). This Phase 1, first-in-human, open-label, multicenter study (NCT03912831) will evaluate the safety and efficacy of KITE-439, an autologous TCR-engineered T cell therapy targeting E7, in HLA-A*02:01–positive patients with relapsed/refractory HPV16-positive cancers. **Methods:** A single-patient dose-escalation schema will be used in Phase 1A of the study, enrolling up to 30 patients. Phase 1A will evaluate safety and inform the recommended dose of KITE-439 for Phase 1B. Approximately 45 patients with squamous cell cancer of the head and neck, cervical cancer, and other HPV16-positive tumors will be included in Phase 1B. Patients in Phase 1A and Phase 1B may receive optional bridging therapy followed by cyclophosphamide and fludarabine conditioning chemotherapy. Patients will then receive an infusion of KITE-439 at 1×10^6 up to 1×10^8 TCR-transduced T cells/kg along with daily subcutaneous IL-2 therapy for a maximum of 14 doses post-infusion. The primary endpoint for Phase 1A is the incidence of adverse events defined as dose-limiting toxicities. The primary endpoint for Phase 1B is investigator-assessed objective response rate per modified RECIST v1.1 criteria (Eisenhauer EA, et al. *Eur J Cancer.* 2009). Secondary endpoints for Phase 1B include duration of response, progression-free survival, overall survival, and safety. Patients ≥ 18 years must be HLA-A*02:01–positive and have relapsed/refractory HPV16-positive cancer, an ECOG PS of ≤ 1, and adequate bone marrow and organ function. Key exclusion criteria include a history of stroke, myocardial infarction, or symptomatic deep vein thrombosis/pulmonary embolism, known infection with human immunodeficiency virus, detectable hepatitis C, or detectable hepatitis B. This study is currently open and accruing patients. Clinical trial information: NCT03912831. Research Sponsor: Kite, a Gilead Company.

TPS3150 Poster Session (Board #214), Fri, 8:00 AM-11:00 AM

Phase I trial of drug resistant immunotherapy: A first-in-class combination of MGMT-modified γδ t cells and temozolomide chemotherapy in newly diagnosed glioblastoma multiforme. *First Author: Lawrence S. Lamb, Incysus Therapeutics, New York, NY*

Background: Temozolomide (TMZ) transiently upregulates GBM-specific stress-induced NKG2D ligands that are targeted by innate immune effector cells. Leveraging this effect is problematic, however, due to the lymphodepleting effects of TMZ.Genetic modification of *ex vivo* expanded and activated with an MGMT-expressing lentivector allows simultaneous chemotherapy and γδ T cell therapy that targets the tumor when NKG2DL are maximally expressed. We have termed this Drug Resistant Immunotherapy (DRI). Patient-derived xenograft mouse models of both primary and recurrent GBM treated with DRI have shown a significant survival advantage that were otherwise impervious to either cell therapy or TMZ. These preclinical findings and associated safety data provide the rationale to initiate a Phase I trial of DRI in primary GBM. **Methods:** This first in human study will evaluate the safety and optimal dosing frequency of the DRI with TMZ (NCT04165941).Eligibility criteria include the following: GBM eligible for resection, ≥18y, adequate organ and marrow function, and KPS≥70. Six to 12patients with newly diagnosed GBM are being enrolled in a 3 + 3 design into 1 of 2 fixed dose levels (DL) of DRI. Following tumor resection and immediately prior to induction chemo/radiotherapy, an apheresis product is collected and γδ T cells expanded in Zoledronic Acid (Novartis) and rhIL-12 (Miltenyi) and transduced with a P140K-MGMT lentivector (Miltenyi Lentigen, Gaithersburg, MD), harvested, and cryopreserved. At initiation of maintenance phase TMZ therapy, patients receive 150mg/m^2 intravenous TMZ concurrently with intracranial injection of 1 x 10^7 γδ T cells (DL1) delivered through a Rickham reservoir previously inserted into the tumor cavity at resection. The patient then receives 4 daily doses of oral TMZ followed by 24d rest. Treatment cycles escalate from 1 to 3 (DL2) DRI doses following a safety observation period and absence of dose limiting toxicity. Maintenance TMZ treatment will continue for 6 cycles. Safety evaluations consist of routine laboratory analyses, clinical measurements (physical exams, vital signs), neurological function and evidence DRI γδ T cell related toxicity. Peripheral blood will be obtained for comprehensive immuno-phenotyping and T cell function analysis. Clinical benefit of DRI will be characterized by evaluating responses (CR, PR, SD and PD) and determining progression-free, median, and overall survival. As of February 2020, enrollment into DL 1 is ongoing. Clinical trial information: NCT04165941. Research Sponsor: Incysus Therapeutics, Inc.

TPS3151 Poster Session (Board #215), Fri, 8:00 AM-11:00 AM

A phase Ia/Ib, open-label first-in-human study of the safety, tolerability, and feasibility of gene-edited autologous NeoTCR-T cells (NeoTCR-P1) administered to patients with locally advanced or metastatic solid tumors. *First Author: Bartosz Chmielowski, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Neoepitopes (neoE) derived from private tumor-exclusive mutations represent compelling targets for personalized TCR-T cell therapy. An ultra-sensitive and high-throughput process was developed to capture tumor mutation-targeted CD8 T cells from patient blood. NeoTCRs cloned from the captured CD8 T cells, when engineered into fresh CD8 and CD4 T cells, effected killing of patients' autologous tumor cells in vitro. These observations have been leveraged for the development of a fully personalized adoptive T cell therapy (NeoTCR-P1). A Phase 1 clinical trial testing NeoTCR-P1 in subjects with solid tumors is ongoing (NCT03970382). **Methods:** During the initial trial phase, escalating doses of NeoTCR-P1 T cells administered without and with IL-2 in the regimen, and following conditioning chemotherapy, will be evaluated in subjects with advanced or metastatic solid tumors (melanoma, urothelial cancer, colorectal cancer, ovarian cancer, HR^+ breast cancer, and prostate cancer). The objective of the Phase 1a study is to establish a recommended Phase 2 dose. Primary endpoints include the incidence and nature of DLTs and overall process feasibility. The proliferation, persistence, and trafficking of NeoTCR-T cells will be characterized. In the expansion trial phase, preliminary anti-tumor activity of NeoTCR-P1 will be assessed in selected tumors. The combination of NeoTCR-P1 dosing plus nivolumab will be tested in a Phase 1b study. Conclusion: This is the first clinical study of an autologous, fully personalized adoptive T cell therapy directed against private tumor-exclusive mutations, generated without using recombinant viral vectors. Clinical trial information: NCT03970382. Research Sponsor: PACT Pharma.

TPS3152 Poster Session (Board #216), Fri, 8:00 AM-11:00 AM

Quilt-3.064: An open-label phase I study of PD-L1 t-haNK in subjects with locally advanced or metastatic solid cancers. *First Author: Tara Elisabeth Seery, Chan Soon Shiong Institute for Medicine, El Segundo, CA*

Background: Tumor cells can escape immunosurveillance through upregulation of PD-L1, which inhibits the proliferation and antitumor activity of T cells. T cells genetically altered to express chimeric antigen receptors (CARs) that recognize tumor-associated antigens have mediated potent responses in patients with hematologic cancers, but have shown limited efficacy in solid tumor cancers and can be associated with severe toxicity, ie, cytokine release syndrome (CRS). Like T cells, NK cells can be genetically modified to express CARs that can specifically recognize and lyse cancer cells. Unlike T cells, NK cell cytotoxicity does not require prior sensitization and is not HLA-restricted, making NK cells an attractive choice for clinical immunotherapy. In addition to their innate cytotoxicity, NK cells mediate antibody-dependent cellular cytotoxicity (ADCC) via expression of CD16. PD-L1 t-haNK is an off-the-shelf, human, allogeneic, NK cell line engineered to express a CAR targeting PD-L1. It can be easily and continuously expanded in culture and preclinical in vitro and in vivo studies have demonstrated effective PD-L1 CAR–mediated antitumor activity against $PD\text{-}L1^+$ MDSCs. PD-L1 t-haNK has also been engineered to express the high-affinity variant of the Fcγ receptor (FcγRIIIa/CD16a 158V), and thus has enhanced CD16-targeted ADCC capabilities, particularly when combined with a monoclonal antibody. As such, a dual-targeted NK approach may be more effective at potentiating antitumor activity and reversing suppression in multiple cancers that express PD-L1 in the tumor microenvironment. **Methods:** This is a dose-escalation study of PD-L1 t-haNK in subjects with locally advanced or metastatic solid cancers, regardless of PD-L1 expression. Dose escalation will involve a standard 3 + 3 design. The primary objectives are to determine safety, maximum tolerated dose (MTD), and designate a recommended phase 2 dose. Secondary objectives include estimates of preliminary efficacy by objective response rate, progression-free survival, and overall survival. Subjects in Cohort 1 will receive $\sim 2 \times 10^9$ PD-L1 t-haNK cells twice per week and assessed for dose-limiting toxicities (DLTs). If no DLTs occur, the dose may increase to $\sim 4 \times 10^9$ cells twice per week in Cohort 2. Dose expansion will occur when the MTD has been determined. PD-L1 t-haNK is administered by IV infusion in an outpatient setting. Enrollment in Cohort 1 has been completed ($N = 6$, > 100 doses total) without DLTs or CRS. Enrollment into Cohort 2 began December 2019. Clinical trial information: NCT04050709. Research Sponsor: NantKwest.

TPS3154 Poster Session (Board #218), Fri, 8:00 AM-11:00 AM

Alliance A151804: Establishment of a national biorepository to advance studies of immune-related adverse events. *First Author: David E. Kozono, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune-related Adverse Events (irAEs) are rare but serious sequelae of treatment with immuno-oncology (IO) therapeutics. These therapeutics, including monoclonal antibodies targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have had transformative effects on outcomes for patients (pts) with advanced cancers. Although most pts tolerate the therapies well, a few experience irAEs ranging in severity up to life-threatening. These irAEs involve diverse organs including the heart, kidney, liver and lung, and gastrointestinal, musculoskeletal, central and peripheral nervous systems. Because of the relatively low incidence and wide variety of irAEs due to various immunotherapies for multiple tumor types, establishment of an efficient centralized repository for acquisition and organized distribution of well-annotated biospecimens is vital for translational studies that improve understanding of the molecular pathogenesis and treatment of these significant toxicities. **Methods:** This multi-institutional study is open at sites across the National Clinical Trial Network to pts who received $\geq$ 1 IO therapeutics (e.g., CTLA-4, PD-1 or PD-L1 inhibitor) and experienced 1) $\geq$ 1 serious (grade 3–5) adverse events that are likely immune-related, 2) rare infection or 3) tumor hyperprogression. IrAEs of interest include myocarditis, colitis, hepatitis, nephritis, myositis, pneumonitis, meningitis/encephalitis, dermatitis, endocrinopathies and neuropathy. Pts may be on an NCTN or non-NCTN IO trial or be receiving standard-of-care therapy. Registration must occur $\leq$ 72 hours after confirmation of the irAE event. Clinical data are collected at registration, 1 month after registration and for up to 1 year. Biospecimens (tumor blocks, biopsies of inflammatory tissues used to establish irAE diagnosis, and serial blood samples for isolation of plasma, serum and peripheral blood mononuclear cells) are collected at 1-2 timepoints. Stool samples are collected from pts experiencing colitis. Imaging data are collected for pts with hyperprogression or pneumonitis. Goal accrual is 240 pts. Biospecimens and data will be made available to investigators following future submission and approval of proposals. Support: U10CA180821, U10CA180882, U24CA196171; U10CA180820 (ECOG-ACRIN); U10CA180888 (SWOG); U10CA180868 (NRG); https://acknowledgments.alliancefound.org; Clinical trial information: NCT04242095. Research Sponsor: U.S. National Institutes of Health.

TPS3155 Poster Session (Board #219), Fri, 8:00 AM-11:00 AM

A phase I study of AK112, a bispecific antibody that targets PD-1 and VEGF co-expressing T cells, in patients with advanced solid tumors. *First Author: Jermaine Coward, Icon Cancer Care, Brisbane, Australia*

Background: AK112 is a humanized IgG1 bispecific anti-PD-1/VEGF antibody. VEGF blockade potentiates PD-1 inhibition by, *inter alia*, opposing the immunosuppressive effects of VEGF-A, which include suppression of dendritic cell activity and enhancement of checkpoint molecule expression on CD8+ T cells and proliferation of regulatory T cells. Combination therapies involving PD-(L)1 and VEGF inhibitors have been approved for the treatment of selected patients with metastatic non-small cell lung carcinoma, advanced renal cell carcinoma and advanced endometrial carcinoma. A supplemental Biologics License Application has been submitted for an anti-PD-L1 + anti-VEGF combination for the first-line treatment of unresectable hepatocellular carcinoma. Given the strong correlation between VEGF and PD-1 expression in the tumor microenvironment, the simultaneous blockade of these 2 targets by AK112 as a single agent might achieve higher target binding specificities and synergistically produce enhanced antitumor activity compared to co-administration of anti-PD-(L)1 and anti-VEGF therapies. **Methods:** This is a Phase 1a/1b, first-in-human, multicenter, open-label study in patients with advanced or metastatic solid tumor that is refractory/relapsed to standard therapies. The primary objective is to assess safety, tolerability and DLTs; and to determine the Maximum Tolerated Dose (MTD) or Maximum Administered Dose of AK112. Antitumor activity, PK and immunogenicity of AK112 will be studied as secondary objectives. As exploratory endpoints, tumor tissue samples may be evaluated for PD-L1 expression, mRNA expression profile and biomarkers (e.g. CD8+, FoxP3, Granzyme B, apelin and EPHB4). PD-1 receptor occupancy on circulating T-cells and serum VEGF level may also be measured as indications of target engagement. The dose-escalation phase will evaluate 5 dose levels of AK112 (up to 20 mg/kg Q2W IV) using a 3+3+3 study design. Additional subjects (up to 18 subjects) may be enrolled at any dose level not exceeding the MTD for additional PK, PD and safety evaluations to determine the optimal dose level for the dose-expansion phase. Cohorts 1 and 2 have been completed and enrollment to Cohort 3 began in January 2020. The dose-expansion phase will be performed in patients with selected advanced solid tumors who had no prior exposure to drugs targeting T-cell co-stimulation or immune checkpoint pathways. Clinical trial information: NCT04047290. Research Sponsor: Akeso BioPharma, Inc.

TPS3156 **Poster Session (Board #220), Fri, 8:00 AM-11:00 AM**

A phase II study of olaparib in combination with pembrolizumab in patients with previously treated advanced solid tumors with homologous recombination repair mutation (HRRm) and/or homologous recombination repair deficiency (HRD): KEYLYNK-007. *First Author: Timothy A Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The anti-PD-1 antibody pembrolizumab (pembro) has improved clinical outcomes in multiple previously treated advanced solid tumors. The poly (ADP-ribose) polymerase (PARP) inhibitor olaparib (ola) has shown antitumor activity as monotherapy in previously treated advanced cancers with *BRCA1*/*BRCA2* mutations (BRCAm), other HRRm, and ovarian cancer with HRD phenotype. Antitumor activity of PD-(L)1 plus PARP inhibition was reportedly higher than expected with either agent alone in patients (pts) with recurrent ovarian cancer regardless of BRCAm or HRD status and in pts with BRCAm breast cancer. KEYLYNK-007 (NCT04123366) evaluates antitumor activity and safety of ola plus pembro in pts with advanced solid tumors with HRRm and/or HRD. **Methods:** This phase 2, nonrandomized, multicenter, open-label study plans to enroll ~300 pts aged ≥18 y with histologically/cytologically confirmed, previously treated, advanced solid tumors with HRRm and/or HRD per Lynparza HRR-HRD assay (Foundation Medicine, Inc., Cambridge, MA, USA) and ECOG PS 0-1. Pts will be grouped by biomarker status: (1) BRCAm; (2) HRRm without BRCAm; (3) HRD positive without HRRm (loss of heterozygosity score ≥16 per Lynparza HRR-HRD assay). Pts will receive ola 300 mg BID + pembro 200 mg IV Q3W (35 cycles) until PD, unacceptable AEs, intercurrent illness, investigator decision, withdrawal, or pregnancy. Tumor imaging assessment by blinded independent central review (BICR) per RECIST v1.1 or Prostate Cancer Working Group (PCWG)-modified RECIST v1.1 for prostate cancer will occur Q9W for 12 mo, then Q12W until PD, start of new anticancer treatment, withdrawal, pregnancy, or death. AEs will be monitored throughout the study and for 30 days after final dose (90 days for serious AEs) and graded by NCI CTCAE v5. The primary endpoint is ORR (RECIST v1.1 or PCWG-modified RECIST v1.1 by BICR). Secondary endpoints include DOR, PFS (RECIST v1.1 or PCWG-modified RECIST v1.1 by BICR), OS, and safety. ORR will be analyzed by the Clopper-Pearson method; and DOR, PFS, and OS by the Kaplan-Meier method. Clinical trial information: NCT04123366. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS3157 **Poster Session (Board #221), Fri, 8:00 AM-11:00 AM**

AGEN1181, a clinical stage Fc-engineered anti-CTLA-4 antibody with improved therapeutic potential for the treatment of patients with advanced malignancies. *First Author: Steven O'Day, John Wayne Cancer Institute, Santa Monica, CA*

Background: AGEN1181 is a novel Fc-optimized anti-CTLA4 antibody, currently being evaluated in an ongoing multi-center, open-label, phase 1 study in all advanced solid tumors as mono-therapy and combination with anti-PD-1 antibody, AGEN2034 (NCT03860272). AGEN1181 is Fc-engineered to harness a novel mechanism for enhanced FcγR-dependent functionality relative to first-generation CTLA-4 antibodies. In pre-clinical models, AGEN1181 enhances T cell priming, depletion of intratumoral regulatory T cells (Treg) and improved memory formation compared to first-generation anti-CTLA-4 antibodies. Most notably, AGEN1181 demonstrates improved binding to FcγRIIIA and superior T cell responsiveness in populations that only express the low affinity FcγRIIIA receptor relative to first-generation IgG1 CTLA-4 antibodies. The combination of AGEN1181 and AGEN2034 further enhances T cell activation and effector function. **Methods:** This phase 1 study is an open-label, multi-center dose-escalation designed to evaluate the safety, tolerability, dose limiting toxicity (DLT) PK, and pharmacodynamic profiles of patients with refractory advanced solid tumors who did not receive an anti-CTLA4 previously. The study is being conducted in 3 arms; with patients assigned using a standard 3+3 dose escalation design in the mono-therapy arms with AGEN1181 and an accelerated design in the combination with AGEN2034 arm. AGEN1181 is administered as IV infusion as mono-therapy on Day 1 of every 3 weeks (0.1,0.3,1,2,4 mg/kg), every 6-weeks (1,2,4 mg/kg) in parallel cohorts and every 6-weeks (0.1,0.3,1,2,4 mg/kg) in combination with AGEN2034 (3mg/kg Q2Weeks) until disease progression or unacceptable toxicity (maximum 2 years). All 3 Arms are open and enrolling patients. The study is expected to enroll approximately 80 evaluable patients with solid tumors. Dose reductions are not allowed in the event of AGEN1181-related toxicities. Currently 3 cohorts have been completed, first cohort in the combination arm and the fourth cohort in the monotherapy arm are enrolling. Preclinical and clinical assessment of AGEN1181 supports continued development as a potential therapy for refractory or relapsed advanced solid tumors. Clinical trial information: NCT03860272. Research Sponsor: Agenusbio.

TPS3158 **Poster Session (Board #222), Fri, 8:00 AM-11:00 AM**

A phase Ib study of nivolumab in patients with autoimmune disorders and advanced malignancies (AIM-NIVO). *First Author: Ecaterina Elena Ileana Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint inhibitors (ICI) such as anti-PD-1/PD-L1 antibodies have become a pivotal approach to cancer therapy. Nivolumab is an anti-PD1 antibody approved for 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 ICI. Consequently, the risks of flares and worsening of pre-existing autoimmune disorders in pts with 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, Sjögren's Syndrome 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. Key overall inclusion criteria include age ≥18 years, histologically confirmed advanced 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. 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, 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). Clinical trial information: NCT03816345. Research Sponsor: U.S. National Institutes of Health.

TPS3159 **Poster Session (Board #223), Fri, 8:00 AM-11:00 AM**

First-in-human phase I/II clinical trial of ONC-392: Preserving CTLA-4 immune tolerance checkpoint for safer and more effective cancer immunotherapy. *First Author: Christian Diego Rolfo, University of Maryland Marlene & Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD*

Background: A major paradigm in cancer immunotherapy is to use checkpoint inhibitors to break regulatory mechanisms that guard the host against autoimmune diseases. CTLA-4-targeting immunotherapy was the first example to establish this paradigm. However, the clinically tested anti-CTLA-4 antibodies exhibit suboptimal efficacy but high toxicity. Our recent studies have demonstrated that immunotherapy-related adverse events (irAE) and the cancer immunotherapeutic effect (CITE) represent distinct and therapeutically separable activities of anti-CTLA-4 antibodies. The irAEs are attributable to inactivation of the CTLA-4 checkpoint, while the CITE is effective through selective depletion of regulatory T cells (Treg) in the tumor microenvironment. We hypothesize that a safer and more effective CTLA-4-targeting immunotherapy should preserve the CTLA-4 checkpoint while enhancing the efficacy and selectivity of Treg-depletion in tumor microenvironment. In preparation to test this ground-breaking hypothesis clinically, we have generated a next generation of anti-CTLA-4 antibody that preserves the CTLA-4 immune checkpoint by avoiding lysosomal degradation of CTLA-4. The new antibody, ONC-392, has dramatically lower irAEs in a humanized mouse model and significantly more potent activity in depleting tumor-infiltrating Tregs, resulting in more effective CITE. **Methods:** This is an open label Phase IA/IB clinical study to test the safety, pharmacokinetics (PK), and efficacy of ONC-392 as a single agent and in combination with Pembrolizumab in advanced solid tumors and non-small cell lung cancer patients. The study consists of two linked parts: Part A is a dose-finding rapid titration study, with ONC-392 as a single agent in patients with advanced disease of various histology. The aim of this trial is to define the recommended Phase II dose for ONC-392 monotherapy (RP2D-M), Part B is a Phase IA/IB trial of ONC-392 in combination with a standard dose of 200 mg Pembrolizumab in patients with NSCLC. The trial consists of a dose-finding, dose escalation or de-escalation, Phase IA component aimed at defining the recommended phase II dose for ONC-392 in combination with a standard dose of Pembrolizumab (RP2D-C), then progressing into two parallel, single arm, Phase IB expansion cohorts to test for safety and initial efficacy in two groups of patients with NSCLC: Stage IV NSCLC anti-PD(L)1 immunotherapy naïve with PD-L1-positive (PD-L1 TPS ≥ 1%); Stage IV NSCLC refractory/resistant to anti-PD(L)1 immunotherapy. Clinical trial information: NCT04140526. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS3160 Poster Session (Board #224), Fri, 8:00 AM-11:00 AM

A phase Ib, open-label, dose-escalation trial of naptumomab estafenatox (Nap) in combination with durvalumab (MEDI4736) in subjects with selected advanced or metastatic solid tumors. *First Author: Ravit Geva, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Background: Immunotherapy with the anti-PD-(L)1 checkpoint inhibitors (CPIs) has been largely ineffective in so-called non-immunogenic "cold tumors". Facilitating T cell infiltration is necessary to invoke an immune response which may be augmented or complemented by the activity of CPIs like durvalumab. Selective T cell Redirection Proteins (STRs) are fusion proteins that consist of genetically engineered Superantigen (Sag) linked to Fragment antigen binding (Fab) moieties directed to tumor-associated antigens. Nap is a first in class STR compound, recognizing the tumor-associated oncofetal antigen 5T4, whereas the SAg moiety selectively engages the T cell receptor β variable (TRBV) 7-9. Nap has been shown to induce specific T cells expansion, activation and infiltration into the tumor in pre-clinical and clinical studies. Pre-clinical data demonstrated that the combination of STR with CPI may lead to long term durable responses not possible in most patients receiving single agent CPI therapy and suggests that combining CPIs with STR may be a promising therapeutic strategy for patients with solid tumors. **Methods:** Patients will be treated with the combination of Nap and durvalumab using a flat dose of durvalumab (1120 mg) and the 3+3 design for Nap dose escalation (2, 5, 10, 15 and 20 mcg/kg). The MTD of Nap for the combination treatment will be established based on DLTs occurring during the first treatment cycle. The dose escalation part will be followed by MTD expansion cohort in which 10–15 patients will be treated with MTD of Nap and 1120 mg durvalumab (Clinical trial registry number NCT03983954). Major eligibility criteria include patients with pretreated advanced or metastatic, 5T4 expressing solid tumors, including patients previously progressed on CPI therapy. As of January 2020, enrollment to dose levels 2, 5 and 10 mcg/kg has been completed without DLT, enrollment to dose level 15 mcg/kg will start on February 2020. Clinical trial information: NCT03983954. Research Sponsor: NeoTX Therapeutics Ltd., Pharmaceutical/Biotech Company

TPS3161 Poster Session (Board #225), Fri, 8:00 AM-11:00 AM

Phase II trial of Voyager-V1 (vesicular stomatitis virus expressing human IFNβ and NIS, VV1), in combination with cemiplimab (C) in patients with NSCLC, melanoma, HCC or endometrial carcinoma. *First Author: Mario Sznol, Yale School of Medicine and Smilow Cancer Center, Yale-New Haven Hospital, New Haven, CT*

Background: VV1 is an oncolytic vesicular stomatitis virus engineered to express human IFNβ to enhance cellular anti-tumor immune responses and tumor selectivity, and the human sodium iodide symporter (NIS) for virus tracking by SPECT imaging. Cancer cells are often hyporesponsive to IFNβ, enabling the efficient spread of VV1 and resulting in increased oncolysis. Differently from other oncolytic viruses, VV1 is suitable for both intra-tumoral (IT) and/or intra-venous (IV) administration. Despite considerable anti-tumor activity with checkpoint inhibitors (CPI) among some malignancies, long term survival and overall cures remain elusive. Prior Ph 1 studies have shown significant anti-tumor activity among several malignancies when VV1 was administered either as monotherapy or in combination with a CPI, despite progression on prior CPI monotherapy. Furthermore, pre- and post-treatment biopsy evaluations after VV1 treatment have demonstrated T cell infiltration and inflammation in both IT injected and non-injected lesions. Among IV treated patients (pts), IFNβ was detectable in the serum correlating with viral replication, making it an effective biomarker. C is a high-affinity potent human IgG4 anti-PD-1 monoclonal antibody. Though approved for use in cutaneous squamous cell carcinoma, C has shown anti-tumor activity, similar to other CPI, in several other indications. Therefore, VV1 and C could be an attractive combination for the immunotherapy for several solid tumors. This study represents the first clinical evaluation of VV1 in combination with C in pts with advanced solid tumors. **Methods:** The Ph 2 Simon 2 stage five-arm study of IV administration VV1 in combination with IV C will enroll pts with advanced NSCLC, HCC, melanoma & endometrial cancer. Enrolled pts with NSCLC & melanoma will be recent CPI-progressors, whereas enrolled HCC & endometrial cancer will be CPI-naïve. The study's objectives include assessment of preliminary anti-tumor activity, safety, & immuno-regulatory activity of the combination. Pts will receive IV VV1 once on D1 and IV C once every 3 weeks until confirmed disease progression or intolerable toxicity. Pts enrolled in one melanoma cohort will also receive IT VV1 administered to palpable lesions. Response will be assessed every 9 weeks per RECIST v1.1. The null hypothesis of each cohort's ORR will be tested versus a one-sided alternative yielding a Type I error rate of 5% and power of 80%. Cohorts will be expanded based on signal of activity. Clinical trial information: NCT. Research Sponsor: Vyriad Inc.

TPS3162 Poster Session (Board #226), Fri, 8:00 AM-11:00 AM

A phase Ia/Ib dose-escalation study of intravenously administered SB 11285 alone and in combination with nivolumab in patients with advanced solid tumors. *First Author: Filip Janku, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX*

Background: Activation of the Stimulator of Interferon Genes (STING) pathway in immune cells in the tumor microenvironment (TME) and tumor cells results in the induction of innate and adaptive immunity and subsequent activation of cytotoxic T cells and NK cells for durable anti-tumor responses. SB 11285 is a novel agonist of the STING pathway leading to the activation of tumor-resident APCs and priming of tumor antigen specific CD8+ T cells. In our preclinical studies using multiple tumor-derived cell lines, SB 11285 has been observed to cause the induction of cytokines, such as INF-b, INF- a, TNFa and others consistent with engagement of the STING target, as well as tumor cell death by STING-mediated apoptosis. SB 11285 reduced tumor volumes in multiple rodent tumor models when administered intravenously, intraperitoneally or intratumorally as monotherapy or in combination with checkpoint inhibitors such as anti-CTLA-4 or anti-PD-1 antibody. Systemic administration could additionally facilitate trafficking of newly activated CD8+T cells from periphery into the tumor site. **Methods:** This open-label, multicenter phase 1a/1b clinical trial (NCT04096638) aims to enroll approximately 110 patients in the dose escalation (Part 1) and expansion cohorts (Part 2). Part 1 of the trial is a dose escalation study with IV SB 11285 monotherapy followed by combination with the checkpoint inhibitor nivolumab. Part 1 Dose Escalation of the study will evaluate ascending doses of intravenously administered SB 11285 with respect to dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended phase 2 dose (RP2D) and the pharmacokinetic (PK)/pharmacodynamic profile as monotherapy and in combination with nivolumab. SB 11285, with a starting dose of 0.3μg/kg, will be administered as monotherapy weekly on Days 1, 8, 15, and 22 of repeated 28-day cycles in escalating doses and in combination with nivolumab administered on Q4W schedule. Part 2 Expansion Cohorts of the study will explore initial signs of efficacy in pre-specified tumor types (such as Melanoma, Head and Neck squamous cell carcinoma) using the recommended phase 2 dose (RP2D) of SB 11285 in combination with nivolumab. In addition, the biological effects of SB 11285 will be evaluated by changes in immune cell types and activation state, serum cytokines, and gene expression patterns indicative of activation of the immune compartment. The trial is being conducted at multiple sites in the U.S . Clinical trial information: NCT04096638. Research Sponsor: Spring Bank Pharmaceuticals, Inc.

TPS3163 Poster Session (Board #227), Fri, 8:00 AM-11:00 AM

Phase I/II dose-escalation and expansion study of FLX475 alone and in combination with pembrolizumab in advanced cancer. *First Author: John D. Powderly, Carolina BioOncology Institute, Huntersville, NC*

Background: Regulatory T cells (T_{reg}) can dampen anti-tumor immune responses in the tumor microenvironment (TME). The predominant chemokine receptor on human T_{reg} is CCR4, the receptor for the chemokines CCL17 and CCL22, which are produced by tumor cells, tumor-associated macrophages and dendritic cells, as well as by effector T cells (T_{eff}) in the setting of an inflammatory anti-tumor response. Preclinical studies with orally-available CCR4 antagonists have demonstrated potent inhibition of T_{reg} migration into tumors, an increase in the intratumoral T_{eff}/T_{reg} ratio, and anti-tumor efficacy as a single agent and in combination with checkpoint inhibitors. In a first-in-human trial conducted in healthy volunteers, the oral CCR4 antagonist FLX475 was demonstrated to be well tolerated with outstanding PK properties. A robust PD assay measuring receptor occupancy on circulating T_{reg} demonstrated the ability to safely achieve exposure levels predicted to maximally inhibit T_{reg} recruitment into tumors via CCR4 signaling. These human PK, PD, and safety data have enabled a streamlined design of a Phase 1/2 study of FLX475 in cancer patients both as monotherapy and in combination with checkpoint inhibitor. **Methods:** This clinical trial is a Phase 1/2, open-label, dose-escalation and cohort expansion study to determine the safety and preliminary anti-tumor activity of FLX475 as monotherapy and in combination with pembrolizumab. The study is being conducted in 2 parts, a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2). In Part 1 (Phase 1) of the study, at least 3 to 6 eligible subjects are being enrolled in sequential cohorts treated with successively higher doses of FLX475 as monotherapy (Part 1a) or in combination with pembrolizumab (Part 1b). In Part 2 (Phase 2) of the study, expansion cohorts of both checkpoint-naïve and checkpoint-experienced patients with tumor types predicted to be enriched for T_{reg} and/or CCR4 ligand expression (i.e. "charged tumors") -- including both EBV^+ and HPV^+ tumors and NSCLC, HNSCC, and TNBC -- will be enrolled using a Simon 2-stage design. As of February 4, 2020, Phase 1 dose escalation has been completed and a recommended Phase 2 dose chosen for both FLX475 monotherapy and combination therapy with pembrolizumab. Enrollment into Phase 2 expansion cohorts has been initiated. Clinical trial information: NCT03674567. Research Sponsor: RAPT Therapeutics.

TPS3164 Poster Session (Board #228), Fri, 8:00 AM-11:00 AM

AST-008: A novel approach to TLR9 agonism with PD-1 blockade for anti-PD-1 refractory Merkel cell carcinoma (MCC) and cutaneous squamous cell carcinoma (CSCC). *First Author: Mohammed M. Milhem, Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA*

Background: AST-008 is a potent spherical nucleic acid configuration of a toll-like receptor (TLR) 9 agonist oligonucleotide being developed for the treatment of MCC and CSCC in patients (pts) progressing on immune checkpoint inhibitor (CPI) monotherapy. Previously presented data suggests AST-008 elicits a Th1-type cytokine response and immune cell activation. This parallel-arm phase II design will permit assessment of efficacy in two advanced skin cancers with high unmet medical need. **Methods:** The study has an open label, multicenter phase Ib/II dose escalation/expansion design. The phase 1b dose escalation used a 3+3 design with increasing doses of intratumoral (IT) AST-008 plus standard flat dose pembrolizumab. The phase II dose expansion is using the recommended regimen (RP2D) of IT AST-008 plus flat dose pembrolizumab or cemiplimab to treat two cohorts of pts with advanced/metastatic MCC or CSCC, respectively. The key objective of the phase II expansion is to provide an estimate of preliminary efficacy of IT AST-008 with pembrolizumab or cemiplimab in pts whose disease progressed on a single-agent CPI therapy. Endpoints also include safety, pharmacokinetic and pharmacodynamic assessments. Pts must have at least two evaluable lesions by RECIST v1.1. One or more lesions may be injected with AST-008, but one lesion (the "witness" lesion) must remain un-injected throughout the study to differentially assess effects of AST-008 on the injected and witness lesions. The RP2D of AST-008 was derived from the dose escalation phase together with pembrolizumab. That RP2D is being used not only in the MCC cohort where AST-008 is combined with pembrolizumab, but also in the CSCC cohort where AST-008 is combined with cemiplimab. To ensure safety of the AST-008/cemiplimab combination, the first 6 pts in the CSCC cohort will be monitored for dose limiting toxicities through the first 5 weeks of dosing, and then the data review committee will assess safety before approving additional patient enrollment to that cohort. Each expansion cohort will enroll up to 29 pts with a Simon two-stage optimal design. In the first stage, 10 pts will be accrued. If there are 0 responses in these 10 pts, enrollment in that arm will be stopped. Otherwise, 19 additional pts will be accrued for a total of 29. The null hypothesis will be rejected if 4 or more responses are observed in 29 pts. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 20%. The planned phase II enrollment is 58 pts across about 15 US-based sites. Clinical trial information: NCT03684785. Research Sponsor: Exicure Inc.

TPS3165 Poster Session (Board #229), Fri, 8:00 AM-11:00 AM

A phase I/II first-in-human study of a novel anti-MAGE-A4 TCR/anti-CD3 bispecific (IMC-C103C) as monotherapy and in combination with atezolizumab in HLA-A*02:01-positive patients with MAGE-A4-positive advanced solid tumors (IMC-C103C-101). *First Author: George R. Blumenschein, Jr., Department of Thoracic and Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ImmTAC bispecifics are unique T cell receptor (TCR)/anti-CD3 bispecific molecules that are designed to redirect polyclonal T cells against intracellular antigens, in contrast to antibody-based therapies, which are limited to extracellular antigens. ImmTAC molecules recognize a specific peptide presented on defined Class I HLA molecules via an affinity enhanced, engineered, soluble TCR. Through the addition of an anti-CD3 scFv effector domain fused to the TCR targeting domain, ImmTAC molecules redirect T cell activity against cancer cells, regardless of the specificity of the T cell. IMC-C103C is an ImmTAC being investigated against MAGE-A4, which is among the most commonly expressed cancer testis antigens in solid malignancies, but with minimal to absent expression on normal tissues and/or hematopoietic cells. The most advanced ImmTAC in development, tebentafusp (IMCgp100), directed against melanocyte-associated lineage antigen gp100, has shown monotherapy activity in uveal melanoma and PD-1 refractory advanced cutaneous and uveal melanoma. Tebentafusp is being further evaluated in combination with durvalumab and tremelimumab. **Methods:** IMC-C103C-101 is a multi-center, open-label, Phase 1/2 first-in-human study of IMC-C103C as monotherapy and combination with atezolizumab in HLA-A*02:01-positive patients with MAGE-A4-positive advanced cancers. The study includes IMC-C103C monotherapy (Q1W) dose escalation, followed by expansion into indication specific arms to test for efficacy in defined patient cohorts. Concurrently, combinations with atezolizumab are planned. Primary objectives of dose escalation are to identify the MTD/RP2D, and characterize safety/tolerability. Secondary objectives include an assessment of efficacy (best overall response by RECIST v1.1), PK, PD, and ADA. IMC-C103C monotherapy dose escalation is in progress. Clinical trial information: NCT03973333. Research Sponsor: Immunocore Ltd, Pharmaceutical/Biotech Company.

TPS3166 Poster Session (Board #230), Fri, 8:00 AM-11:00 AM

Trial in progress: A phase I/II, open-label, dose-escalation, safety and tolerability study of NC318 in subjects with advanced or metastatic solid tumors. *First Author: Martin Gutierrez, Hackensack University Medical Center, Hackensack, NJ*

Background: Siglec-15 (S15) is a member of the Siglec family (Sialic acid-binding Immunoglobulin Lectins), a distinct subgroup of immunoglobulin (Ig) superfamily proteins involved in discriminating self from non-self-immune regulation (Macauley MS et al. 2014). Nonclinical models demonstrate S15 mediates suppression of T cell proliferation and negatively regulates T cell function. NC318 is a first-in-class monoclonal antibody that blocks S15-mediated immune suppression and prevents tumor growth by normalizing T cell function and restoring anti-tumor immunity in the tumor microenvironment (Wang J et al. 2019). The clinical hypothesis of this study is that NC318 targeting of S15 can improve anti-tumor immune response and provide benefit in multiple oncology indications. **Methods:** This is a multi-center, first in human, phase 1/2, open-label, non-randomized study to determine the safety and tolerability, define maximum tolerated dose and/or pharmacologically active dose, assess preliminary efficacy, and explore predictive and pharmacodynamic biomarkers of NC318 in subjects with advanced or metastatic solid tumors. Key eligibility criteria included measurable disease based on RECIST v1.1 and consent for collection of biopsies at screening and on treatment (optional for phase 1). Phase 1 used a 3+3 dose escalation design to determine the recommended phase 2 dose (RP2D) and schedule of NC318 while identifying drug related toxicities (DLTs). Phase 2 enrollment is limited to non-small cell lung, ovarian, head and neck, and triple negative breast cancer subjects with PD-L1 tumor proportion scores $<$50% (additional tumor types are being evaluated for inclusion). Ongoing exploratory analyses include the assessment of predictive biomarkers associated with treatment benefit, and pharmacodynamic markers associated with study drug activity (e.g. evaluation of tumor biopsies and peripheral markers of inflammation). Phase 1 enrollment began October 2018 and completed in August 2019. The RP2D was defined and the phase 2 opened to enrollment October 2019. Clinical trial information: NCT03665285. Research Sponsor: NextCure, Inc.

TPS3167 Poster Session (Board #231), Fri, 8:00 AM-11:00 AM

Phase II basket trial of olaparib and durvalumab in patients (pts) with isocitrate dehydrogenase (IDH) mutated solid tumors. *First Author: Eric Xueyu Chen, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Somatic IDH mutations are common in low grade gliomas, and rare in other solid tumors with the exception of intrahepatic cholangiocarcinoma (ICA) and certain subtypes of chondrosarcoma. IDH mutations confer a gain-of-function neomorphic activity, such that mutant IDH enzymes preferentially convert αKG to 2-hydroxyglutarate (2HG), resulting in abnormal accumulation of 2HG. 2HG competitively inhibits αKG-dependent dioxygenases, many of which are involved in DNA repair. Preclinical studies show that IDH mutated cancer cells have defective homologous recombination repair and are exquisitely sensitive to poly (adenosine 5'-diphophate-ribose) polymerase (PARP) inhibition. **Methods:** This is a single arm phase II basket study (NCT03991832). Pts with IDH mutated solid tumors are divided into three cohorts; A: low-grade glioma; B: cholangiocarinoma; C: all other solid tumors. Pts are treated with olaparib 300 mg twice daily continuously and durvalumab 1500 mg every 4 weeks until progression, intolerable toxicity or consent withdrawal. Radiological assessment is performed after every 2 cycles of study treatments. Major eligibility criteria include IDH mutation by immunohistochemistry or sequencing, up to 2 lines of systemic therapy for advanced disease, performance status 0 – 2 and adequate organ function. Pts are excluded if they received prior PARP inhibitors and anti-PD-1/PD-L1 antibody. The Simon's optimal 2-stage design is applied for Cohorts A and B. 10 pts will be enrolled in each of Cohort A and B initially. If 2 or more partial responses (PR) are seen in these 10 pts, additional 19 pts will be enrolled for a total of 29 pts in that cohort. The combination is considered to be of clinical interest for further development if $\geq$ 6 PRs are seen in each cohort. Cohort C will enroll 20 pts. Archival tumor tissues and serial blood samples will be collected on study. 2HG levels will be measured and correlated with responses. The study was activated in December 2019. 3 pts have been enrolled into Cohort B. Clinical trial information: NCT03991832. Research Sponsor: None.

TPS3168 Poster Session (Board #232), Fri, 8:00 AM-11:00 AM

First-in-human phase Ib study of ATRC-101, an engineered version of a patient-derived antibody targeting a tumor-restricted ribonucleoprotein complex. *First Author: Jonathan Eliot Benjamin, Atreca, Inc., South San Francisco, CA*

Background: ATRC-101 is a fully human, engineered IgG1 version of an antibody discovered through a a target-agnostic screen to identify patient-derived antibodies that bind selectively to public tumor antigens. The parental antibody was identified from B cells in the active immune response of a patient receiving checkpoint therapy for Stage IV non-small cell lung cancer (NSCLC). A fluorescently conjugated version of ATRC-101 binds selectively to human tumor specimens including a majority of NSCLC, acral melanoma, breast, colorectal, and ovarian cancer samples. No reactivity of toxicological significance is found across a wide range of normal human tissues. ATRC-101 displays dose-dependent, single-agent activity in syngeneic mouse tumor models, including the EMT6 breast cancer model, which displays a T cell-excluded microenvironment often observed in human tumors, and in which checkpoint inhibitors targeting the PD-1 axis exhibit limited activity. Dosing with ATRC-101 in the EMT6 model causes marked changes in the tumor microenvironment, including a shift from the M2 to the M1 macrophage phenotype and infiltration of T cells. ATRC-101 does not appear to act via NK cell-driven ADCC; instead, activity *in vivo* is dependent both on Fc region interactions with Fc receptors, likely on myeloid rather than lymphoid cells, and on the presence of CD8+ T cells. ATRC-101 binds to a target that is a ribonucleoprotein (RNP) complex containing polyadenylate-binding protein 1 (PABP-1) bound to poly(A)RNA. Whereas both PABP-1 and poly(A)RNA are ubiquitously expressed at high levels in normal tissues and have been localized intracellularly, the ATRC-101 target is detected extracellularly on tumor cells grown *in vivo*. The basis for the tumor-selectivity of ATRC-101 as well as the extracellular localization of the target is under investigation. Ascending doses of ATRC-101 were well tolerated in multiple non-clinical safety studies. **Methods:** ATRC-101-A01 is an open-label, 3+3, Phase 1b safety study in patients with acral melanoma, NSCLC, breast, ovarian, and colorectal cancers. Participants are accruing in the first dose cohort. ATRC-101 is administered every 21 days up to 24 months or until disease progression. The primary objective of the trial is to determine the safety and tolerability of ATRC-101. Secondary objectives are to characterize the pharmacokinetic profiles of ATRC-101 and to assess antitumor activity as determined by RECIST 1.1 and lymphocytic infiltration in the tumor microenvironment. Clinical trial information: NCT04244552. Research Sponsor: Atreca, Inc.

TPS3170 Poster Session (Board #234), Fri, 8:00 AM-11:00 AM

Phase I/II open label nonrandomized safety and efficacy study of the viral vectored ChAdOx1-MVA 5T4 immunotherapy in combination with PD-1 checkpoint blockade in intermediate-risk localized or locally advanced prostate cancer and advanced metastatic prostate cancer. *First Author: Mark Tuthill, The Jenner Institute, University of Oxford, Oxford, United Kingdom*

Background: Antigen-specific immunotherapy (Sipuleucel-T) is licenced for the treatment for castrate resistant prostate cancer, but has modest clinical efficacy and is complex to administer to patients. New therapeutic antigen-specific approaches are required to generate and sustain therapeutic immune responses against tumour specific antigens in men with early and advanced prostate cancer. We have previously reported immunogenicity and efficacy data of a novel viral vectored vaccines-based immunotherapy based on two replication-deficient viruses, chimpanzee adenovirus (ChAdOx1) and MVA, targeting an oncofetal self-antigen 5T4, administered as a single agent and in combination with anti-PD-1 in mouse tumour models. We tested this immunotherapy alone in a first-in-human trial, VANCE (NCT02390063), in intermediate risk prostate cancer patients. Based on encouraging safety and exceptional T cell immunogenicity of the VANCE study, the phase I/II trial, ADVANCE (NCT03815942) is being undertaken to test the immunotherapy safety and efficacy in combination with PD-1 blockade in intermediate risk disease and metastatic prostate cancer. **Methods:** Study design: ADVANCE, an open label non-randomised phase I/II study, will recruit 12 patients with intermediate-risk prostate cancer patients (Gleason score $\leq$ 7, local tumour stage $\leq$T3c, PSA$\leq$ 20 ng/ml) scheduled to undergo radical prostatectomy (Cohort 1) and 24 mCRPC patients with disease progression on anti-androgen therapy with either enzalutamide or abiraterone (Cohort 2). Cohort 1 will receive one cycle of ChAdOx1-MVA 5T4 immunotherapy and a single nivolumab infusion. Cohort 2 will receive 2 cycles of ChAdOx1-MVA 5T4 vaccination and three nivolumab infusions. Primary endpoint: Cohort 1 - PSA change from baseline to surgery, Cohort 2 – composite response rate measured as either $\geq$50% reduction of circulating tumour DNA or $\geq$50% serum PSA decrease from baseline at 24-week assessment and the maximal response rate. Secondary and exploratory endpoints include 5T4-specific immune response in the periphery, progression-free and overall survival and reduction of circulating tumour cells. 23 of planned 24 patients have been enrolled in Cohort 2. Enrolment to the Cohort 1 is ongoing. The data analysis is expected to be completed by Q4 2020 for Cohort 2. Clinical trial information: NCT03815942. Research Sponsor: Grant agreement No. 602705.

TPS3171 Poster Session (Board #235), Fri, 8:00 AM-11:00 AM

A phase I/II study of HB-201, an arenavirus-based cancer immunotherapy, alone, or in combination with anti-PD-1 in patients with HPV16+ cancers. *First Author: Bharat Burman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human Papillomavirus 16 (HPV16) is linked to several cancer types; treatment options are limited for patients with HPV16+ recurrent or metastatic cancers. The generation and maintenance of the HPV16+ malignant state requires the stable expression of HPV16-specific E7 and E6 oncogenes, which can also serve as immunogenic tumor-associated antigens. HB-201 is a replication-competent live-attenuated vector based on the arenavirus LCMV encoding a non-oncogenic E7 and E6 fusion protein. In preclinical models, both intravenously (IV) and intratumorally (IT) administered HB-201 demonstrate potent immunogenicity by induction of HPV16-specific cytotoxic T cells and associated efficacy. **Methods:** This is a first in human, Phase I/II study of HB-201 monotherapy or in combination with PD-1 immune checkpoint inhibitor (anti-PD-1) in HPV16+ confirmed recurrent/metastatic cancers. Phase I consists of 2 treatment groups, each conducted with a 3+3 dose escalation design. Group 1 is enrolling patients with HPV16+ head and neck squamous cell carcinoma who will receive HB-201 IV only. Group 2 is enrolling HPV16+ cancer patients with a safely accessible tumor site who will receive HB-201 IT for the first dose, followed by HB-201 IV for subsequent doses (IT-IV). HB-201 will be administered every 21 days. The Phase II component will be conducted with the recommended Phase II doses (RP2Ds) defined in Phase I and will consist of 3 groups: Group A (HB-201 IV only), Group B (HB-201 IV plus anti-PD-1), and Group C (HB-201 IT-IV). Key eligibility criteria include age $>$ 18, ECOG performance status 0-1, confirmed HPV16+ recurrent or metastatic cancer, disease progression from at least 1 systemic standard of care therapy, and measurable disease per RECIST v1.1. The Phase I primary objective is to determine RP2Ds for IV and IT HB-201. The Phase II primary objective is to assess antitumor activity. Secondary endpoints for both phases include safety, tolerability, overall survival, progression-free survival, and duration of response. Exploratory objectives include characterization of immunogenicity of HB-201 and biomarkers associated with immune or antitumor response. Enrollment to Groups 1 and 2 began in December 2019. Clinical trial information: NCT04180215. Research Sponsor: Hookipa Pharma.

TPS3172 Poster Session (Board #236), Fri, 8:00 AM-11:00 AM

Safety and efficacy of neoadjuvant intravesical oncolytic MV-NIS in patients undergoing radical cystectomy (RC) for urothelial carcinoma but ineligible for neoadjuvant cisplatin-based chemotherapy. *First Author: Bradley C. Leibovich, Mayo Clinic, Rochester, MN*

Background: Bladder cancer is a leading cause of cancer death in the United States. Over 90% of bladder cancer cases are urothelial carcinomas (UC) that may present as a non-muscle-invasive (NMIBC) or muscle-invasive disease (MIBC). Standard of care for NMIBC includes transurethral resection of bladder tumor (TURBT), intravesical chemotherapy and immunotherapy with Bacillus Calmette-Guerin (BCG). Patients (pts) with high-grade BCG-refractory NMIBC or MIBC undergo RC, which involves complete bladder removal and pelvic lymphadenectomy. RC severely impacts quality of life with significant morbidity. Oncolytic viruses are showing promise in UC, and MV-NIS has proven efficacy in other tumor types. MV-NIS is an investigational oncolytic measles virus with an excellent safety profile, irrespective of route of administration ($n > 100$). MV-NIS-related adverse events are limited to infusion reactions and transient CBC changes, and little local toxicity is anticipated with intravesical therapy. Clinical efficacy of this oncolytic may be related to absence of measles immunity. Based on this, the clinical strategy for MV-NIS is focused on targeting immune-privileged sites via intra-tumoral or intravesical routes, alone or in combination with checkpoint inhibitors. We hypothesize that intravesical therapy with oncolytic MV-NIS can improve clinical outcomes for (a) BCG refractory NMIBC pts to avoid or delay the need for RC; and (b) MIBC pts undergoing RC. **Methods:** This study is enrolling pts undergoing RC who are ineligible to receive neoadjuvant chemotherapy. The trial has 2 stages to (a) determine the safety and tolerability of intravesical MV-NIS, and (b) assess preliminary efficacy. Part (a) includes 4-24 pts in a timing cohort with doses administered at increasing durations (1-4 weeks) prior to RC to establish safety of a single MV-NIS dose. Part (b) includes an expansion cohort ($n = 12$) to evaluate the safety and efficacy of 2 intravesical doses of MV-NIS at 2-week intervals prior to RC. Safety is assessed using NCI-CTCAE V5 and Clavien-Dindo grading of operative complications. The efficacy endpoint is pathologic stage at time of RC (pT0 rate), which can be compared to pre-study TURBT stage. Additional exploratory studies include PK and PD analyses in urine, blood and tumor. Enrollment is ongoing at 2 Mayo Clinic sites (Rochester, MN and Jacksonville, FL) and the study has now progressed from the timing cohort into the expansion cohort. Clinical trial information: NCT03171493. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS3173 Poster Session (Board #237), Fri, 8:00 AM-11:00 AM

Phase I study of NBTXR3 activated by radiotherapy in patients with advanced cancers treated with an anti-PD-1 therapy. *First Author: Colette Shen, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Despite the past decade of transformative advances in immuno-oncology, the response rate to checkpoint inhibitors (ICIs) remains low (~15%). There is significant interest in developing strategies to overcome resistance to these treatments, thus increasing response rate. Emerging evidence suggests that radiation therapy (RT) could potentially augment the antitumor response to ICIs through synergic effect. However, RT dose and ultimate efficacy are limited by toxicity related to exposure of healthy tissues. NBTXR3 is a first-in-class radioenhancer administered by direct intratumoral injection, designed at the nanoscale to increase RT dose deposition within tumor cells and RT-dependent tumor cell killing, without increasing surrounding normal tissue toxicity. Preclinical and early clinical data suggest NBTXR3 activated by RT can trigger an anti-tumor immune response, producing both local and systemic (abscopal) effects. We hypothesize that NBTXR3 activated by RT, in combination with anti-PD-1 therapy (R3/RT/PD-1), will act synergistically to maximize the local RT effect and produce a systemic response sufficient to increase the proportion of ICI responders or convert ICI non-responders to responders. **Methods:** This trial [NCT03589339] is a multicenter, open-label, phase I study to evaluate safety and tolerability of R3/RT/PD-1 in three cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) amenable to re-irradiation of the HN field, (2) Lung metastases, or (3) Liver metastases, both from any primary cancer eligible for anti-PD-1 treatment. Approximately two-thirds of patients in each cohort will be anti-PD-1 non-responders. NBTXR3 injected volume is based on a percentage of gross tumor volume (GTV). The primary objective is to determine the R3/RT/PD-1 recommended phase 2 dose in each cohort. Secondary objectives are to evaluate anti-tumor response (objective response rate; ORR), safety and feasibility of NBTXR3 injection, and NBTXR3 body kinetic profile. Exploratory objectives will assess biomarkers of R3/RT/PD-1 response, including PD-L1 status by IHC, as well as mRNA and cytokine immune marker profiling. To date, three patients have been treated, one in cohort 1, two in cohort 2. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix, SA.