2500 **Oral Abstract Session**

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

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Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds to the intermediate-affinity interleukin-2 (IL-2) receptor (IL-2R) to preferentially activate antitumor $CD8^+$ T cells and natural killer (NK) cells with minimal expansion of immunosuppressive regulatory T cells. It is sterically occluded from binding to the high-affinity IL-2R, leveraging antitumor effects of the IL-2 pathway but mitigating toxicity associated with preferential binding of IL-2 to the high-affinity IL-2R. **Methods:** ARTISTRY-1 (NCT02799095) is a 3-part, first-in-human, phase 1/2 study of IV nemvaleukin alone and in combination with pembrolizumab in pts with advanced solid tumors. Parts A (dose escalation to 10 μg/kg/day), B (monotherapy in pts with melanoma or renal cell carcinoma [RCC]), and C (combination) included nemvaleukin 3 or 6 μg/kg/day ´5 and pembrolizumab every 21 days. Investigator-assessed antitumor activity (confirmed responses as per RECIST v1.1) and safety are reported as of 29 October 2021. **Results:** In Part A (N = 46), nemvaleukin recommended phase 2 dose was 6 μg/kg/day IV; maximum tolerated dose not reached. One pt had dose-limiting toxicity (grade 4 acute kidney injury) at 10 μg/kg. Pts in Parts B and C were heavily pretreated (1–9 prior lines of therapy, including prior checkpoint inhibitor therapy). Durable antitumor activity was observed for nemvaleukin monotherapy, including in RCC (objective response rate [ORR], 18.2% [4/22]) and in melanoma (ORR, 8.7% [4/46]), with 2 partial responses (1 unconfirmed) in 30 pts with cutaneous melanoma (ORR, 6.7%) and 2 PRs (1 unconfirmed) in 6 pts with mucosal melanoma (ORR, 33.3%). Durable antitumor activity was also observed for combination therapy (ORR, 16.1% [22/137]; disease control rate [DCR], 59.9%), including in platinum-resistant ovarian cancer (PROC; ORR, 28.6% [4/14]; DCR, 71.4%), with 2 complete responses and 2 PRs (1 unconfirmed) in 14 pts. Forty-three pts remain on therapy. The most frequent grade 3/4 treatment-related adverse events in Parts B and C, respectively, were anemia (9%, 10%), neutropenia (34%, 9%), and decreased neutrophil count (12%, 9%). Safety was consistent with previous reports. In pharmacodynamic studies, nemvaleukin monotherapy induced robust expansion of CD8+ T and NK cells, with minimal effect on regulatory T cells. **Conclusions:** ARTISTRY-1 showed proof of principle for preferential expansion of $CD8^+$ T cells and NK cells by nemvaleukin. Nemvaleukin was generally well tolerated and demonstrated promising efficacy. Durable responses were observed with monotherapy and combination therapy in heavily pretreated pts across a range of tumors, warranting further investigation. The US FDA granted nemvaleukin Fast Track designation for treatment of mucosal melanoma and PROC, and Orphan Drug designation for mucosal melanoma. Clinical trial information: NCT02799095. Research Sponsor: Alkermes, Inc.

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2501 **Oral Abstract Session**

First-in-human study of SRF388, a first-in-class IL-27 targeting antibody, as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors.

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Background: The immunoregulatory cytokine IL-27 upregulates inhibitory immune checkpoint receptors (eg, PD-L1, TIGIT) and downregulates proinflammatory cytokines (eg, IFNγ, TNFα). SRF388 is a fully human IgG1 blocking antibody to IL-27 with potential to promote immune activation in the tumor microenvironment. A phase 1 study was conducted to establish the preliminary safety of SRF388 and to identify recommended phase 2 doses (RP2D) suitable for monotherapy and combination expansions (NCT04374877). **Methods:** The dose-escalation study (accelerated single patient followed by standard 3+3) enrolled patients (pts) with advanced treatment-refractory solid tumors. Upon RP2D selection, monotherapy and combination expansions opened for treatment-refractory clear cell renal cell cancer (ccRCC), hepatocellular cancer (HCC), and non-small cell lung cancer. SRF388 was administered IV every 4 weeks (wks) as monotherapy and every 3 wks with pembrolizumab. Tumor response was assessed by RECIST1.1. **Results:** The monotherapy dose-escalation enrolled 29 pts with doses ranging from 0.003 to 20 mg/kg. Median age was 64 years. Most pts were female (62%) with ECOG PS of 1 (72%). Approximately 80% had prior PD-(L)1 blockade, and 48% had ≥4 prior therapies. Treatment-related adverse events (TRAEs) occurred in 21%, and all were low grade. Fatigue was the only TRAE reported in ≥10% (n = 3). No dose-limiting toxicities (DLTs) or Grade ≥3 TRAEs were observed. Median time on study was 9 wks (range 0–59). One patient with highly treatment-refractory NSCLC experienced a confirmed partial response (PR) at 8 wks that was durable for 20 wks. Nine pts (31%) experienced disease stabilization at 8 wks, with 6 of 9 exhibiting durable disease control at 6 months. Of the 7 pts with ccRCC in the dose-escalation portion of the trial, 3 (43%) experienced durable disease control for ≥20 wks (range: 20-32). With doses up to 20 mg/kg, SRF388 PK remain linear with an estimated $T_{1/2}$ of 10-12 days. PK characteristics and safety profile support dosing every 3 or 4 wks. Based on safety, tolerability, PK, peripheral pSTAT1 inhibition, and preliminary efficacy, 10 mg/kg was selected as the RP2D. Both the pembrolizumab safety cohort (n = 10) and Stage 1 of the ccRCC monotherapy expansion (n = 17) have fully enrolled. Of the 10 evaluable pts with ccRCC, 1 confirmed monotherapy PR has been reported, enabling Stage 2 initiation. Changes in several serum cytokines and chemokines were observed after SRF388 administration, including expected increase in circulating IL-27 levels. **Conclusions:** Results of IL-27 pathway blockade with a first-in-class therapeutic demonstrates that SRF388 has good tolerability with encouraging preliminary antitumor activity as a monotherapy. Updated data, including safety and clinical outcomes as well as correlative biomarker analyses, will be presented. Clinical trial information: NCT04374877. Research Sponsor: Surface Oncology, Cambridge, MA, USA;.

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2502 **Oral Abstract Session**

Interim safety and efficacy results from AURELIO-03: A phase 1 dose escalation study of the IL-2/IL-15 receptor $\beta\gamma$ superagonist SOT101 as a single agent and in combination with pembrolizumab in patients with advanced solid tumors.

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Background: SOT101 (previously SO-C101) is a fusion protein of IL-15 and the IL-15 receptor α sushi+ domain. Synergistic effects of SOT101 and an anti-programmed cell death protein 1 antibody have been validated in various tumor mouse models inducing a protective memory response. **Methods:** In this phase 1 study, safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of increasing doses of SOT101 administered subcutaneously were investigated in patients (pts) with advanced solid tumors as monotherapy (Part A) and in combination with pembrolizumab every 3-week cycle (Part B). Dose escalation followed a standard 3+3 design. Data cut-off was 26 January 2022. **Results:** Overall, 51 pts were treated: 30 in Part A monotherapy at 0.25 to 15 μg/kg SOT101 and 21 in Part B combination therapy (Tx) at 1.5 to 12 μg/kg SOT101. The median (range) number of previous lines of Tx was 3 (1-9) in Part A and 2 (1-6) in Part B. In Part A, 19 (63.3%) pts had previous checkpoint inhibitor (CPI) Tx, of whom 9 (30 %) were refractory, 5 (16.7%) relapsed. In Part B, 11 pts (52.4%) had previous CPI Tx, and the outcome was 9 (42.9%) pts relapsed, 1 (4.8%) refractory. The most common treatment-emergent adverse events (TEAEs) were transient, and included pyrexia, chills, lymphopenia, anemia, transaminase elevation and vomiting. Most TEAEs were $\leq$ Grade 2. No treatment-related death was reported. For both monotherapy and combination Tx, the recommended phase 2 dose of SOT101 was determined to be 12 μg/kg. In Part A, in 13 pts at 6 to 12 μg/kg SOT101, the observed clinical benefit rate was 38%. A partial response (PR) was confirmed in 1 pt with skin squamous cell carcinoma, CPI refractory, PR duration 46 days (d), on treatment 154 d. Four pts (all CPI pretreated) had stable disease (SD), range 33-183 d. Final median duration on treatment was 84 d, range 43-183 d. The median duration of clinical benefit was 190 d. In Part B, the observed clinical benefit rate across all SOT101 doses was 63%. A complete response (CR) was confirmed in 1 pt with mesothelioma, CPI naïve, starting at the first tumor assessment, and the pt is ongoing in cycle 5. Three pts, 2 CPI pretreated, had a PR, range 51-232 d, 2 ongoing with PR, and 1 Tx discontinuation while still on PR. Five pts, 3 CPI pretreated, had SD, range 92-340 d, 2 ongoing with SD. The 3 CPI pretreated pts had SD range 41-340 d, 1 pt ongoing. The preliminary median duration on combination Tx was 113 d, range 7-429 d. The preliminary median duration of clinical benefit was 131 d. **Conclusions:** SOT101 as monotherapy and in combination with pembrolizumab showed a favorable safety profile. Highly promising efficacy signals with one ongoing CR and several long-lasting PRs were reported in CPI-naïve and CPI pretreated pts, including CPI-resistant tumors. Clinical trial information: NCT04234113. Research Sponsor: Sotio Biotech AG.

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2503 **Oral Abstract Session**

Dose escalation of a phase 1b/2 study of modakafusp alfa, an immune-targeting attenuated cytokine, in patients (pts) with metastatic solid tumors.

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Background: Modakafusp alfa (TAK-573) is a first-in-class immune-targeting attenuated cytokine designed to deliver attenuated interferon alpha-2b (IFNα2b) moieties to CD38-expressing cells. It consists of two attenuated IFNα2b molecules genetically fused to the Fc portion of a humanized, anti-CD38, IgG4 monoclonal antibody. Specificity for CD38 and reduced IFN receptor binding affinity of the attenuated IFNα2b molecules significantly reduces the potential for off-target binding and toxicity. Modakafusp alfa has demonstrated immune cell activation and antitumor activities in preclinical mouse models, including tumor models that do not express CD38, and has shown strong clinical responses and immune activation in pts with refractory/relapsed multiple myeloma. The dose-escalation phase of this phase 1b/2 study (NCT04157517) investigated safety, pharmacokinetics, immunogenicity, pharmacodynamics (PD), and preliminary efficacy of modakafusp alfa in metastatic solid tumors. **Methods:** Adult pts with advanced/metastatic solid tumors received modakafusp alfa IV on day 1 of a 21-day cycle (Q3W). Dose escalation started at 0.1 mg/kg and proceeded based on cycle 1 safety data via a Bayesian model with overdose control principles. **Results:** Twenty-one pts were dosed in the escalation phase at 0.1 (n = 3), 0.2 (n = 3), 0.4 (n = 3), 0.75 (n = 3), 1.0 (n = 3), and 1.5 mg/kg (n = 6) Q3W; median age 63 y (range 42–80); male 57.1%; GI malignancies 71.4%; median prior lines of therapy 3 (range 2–7). Two pts had dose-limiting toxicities in cycle 1 at 1.5 mg/kg; 1 pt with baseline bone infiltration had grade 4 thrombocytopenia and 1 pt had grade 3 confusion. As of Nov 2021, across all doses, pts received a median of 2 treatment cycles (range 1–11). Modakafusp alfa treatment-related adverse events (TRAEs) reported in 81% of pts included infusion-related reactions (52.4%), chills (47.6%), and nausea (33.3%). Grade $\geq$3 TRAEs reported in 42.9% of pts included neutropenia (14.3%) and hypertension (9.5%). There was a greater than dose proportional exposure increase in the dose range 0.1–1.5 mg/kg, with no exposure accumulation after Q3W dosing. Incidence rate of post-treatment anti-drug antibody (ADA) was 100%. PD data suggested saturation of peak IFN pathway modulation at $\geq$0.2 mg/kg in the peripheral blood with duration of modulation increasing with dose. Among the 14 response-evaluable pts, 7 had best response of stable disease, including 1 with cutaneous melanoma who had 21% target lesion reduction. **Conclusions:** Modakafusp alfa had a manageable safety profile in the dose range 0.1–1.5 mg/kg in pts with solid tumors. Proof of mechanism was validated. The recommended phase 2 dose was determined as 1.0 mg/kg Q3W based on assessment of holistic data and will be tested in combination with a checkpoint inhibitor in selected tumor types. Characterization of ADA and its impact is ongoing. Clinical trial information: NCT04157517. Research Sponsor: This study was funded by Takeda Pharmaceutical Company Limited.

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2504 **Oral Abstract Session**

Phase 1 trial of TIM-3 inhibitor cobolimab monotherapy and in combination with PD-1 inhibitors nivolumab or dostarlimab (AMBER).

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Background: TIM-3 expressed on tumor-infiltrating T cells is associated with T-cell suppression. AMBER (NCT02817633) is evaluating cobolimab (TSR-022/GSK4069889) monotherapy and with PD-1 inhibitors in advanced solid tumors. **Methods:** Multi-center, open-label study conducted with the following escalation arm (Parts 1A–C primary analysis reported here): (1A) cobolimab (IV Q2W) monotherapy at 7 doses (6 weight-based [0.03–10 mg/kg] and 1 flat [1200 mg] dose); (1B) cobolimab (1 mg/kg) + nivolumab (3 mg/kg IV Q2W); and (1C) cobolimab (100, 300, or 900 mg) + dostarlimab (500 mg IV Q3W). Primary endpoints were safety, tolerability, and recommended phase 2 dose (RP2D, monotherapy and combination). **Results:** 104 patients (pts) were included: 1A (n=46), 1B (n=7), or 1C (n=55); 4 pts from 1A crossed over to 1C (included in 1A and 1C safety and efficacy analyses). Most common cancers were non-small cell lung cancer (NSCLC) and melanoma (1A), NSCLC (1B), and NSCLC, skin, and peritoneal mesothelioma (1C). In 1A, 30.4% had ≥5 lines (L) of prior therapy; 42.9% had 3L in 1B; 33.3% had 2L in 1C. Treatment-related treatment-emergent adverse events (TR-TEAE) occurred in 67.4% (1A), 85.7% (1B), and 67.3% (1C); most commonly in 1A (n≥4) fatigue (13.0%) and nausea (8.7%); 1B (n≥3) diarrhea (57.1%) and nausea and vomiting (42.9% each); and 1C (n≥8) fatigue (20.0%) and rash (14.5%). Grade (Gr)≥3 TR-TEAEs occurred in 4.3% (1A), 28.6% (1B), and 14.5% (1C). There were no Gr5 TR-TEAEs or TR-TEAEs leading to dose delay. Serious TR-TEAEs occurred in 2.2% (1A), 0% (1B), and 12.7% (1C). TR-TEAEs led to discontinuation in 2.2% (1A), 28.6% (1B), and 9.0% (1C). Dose limiting toxicities (DLTs) occurred in 3.0% (1/33) in 1A (Gr3 lipase increased [10 mg/kg]); 40.0% (2/5) in 1B (Gr3 diarrhea and ALT and AST elevation); and 0% in 1C. Cobolimab serum exposure increased in a dose proportional manner at the therapeutic dose range. Preliminary mean terminal phase $t_{1/2}$ ranged from 2.5–5.8 days for 0.03–0.3 mg/kg and 6.9–10.2 days for 1–10 mg/kg doses (1A), 6.9 days for 1B, and 9.5–12.3 days for 1C. **Conclusions:** Cobolimab + dostarlimab was well tolerated and showed preliminary anti-tumor activity, warranting further investigation of the RP2D + docetaxel in a randomized, phase 2 study. Funding: GSK (213348). Clinical trial information: NCT02817633. Research Sponsor: GlaxoSmithKline.

Efficacy by cobolimab dose.

n (%)	1A* (cobolimab): 1 mg/kg N=9	1A*: 10 mg/kg N=13	1A*: 1200 mg N=7	1B (cobolimab + nivolumab): 1 mg/kg N=7	1C (cobolimab + dostarlimab): 100 mg N=13	1C: 300 mg N=20	1C: 900 mg N=22
ORR	0	0	0	3 (42.9)	1 (7.7)	5 (25.0)	3 (13.6)
DCR	1 (11.1)	4 (30.8)	1 (14.3)	3 (42.9)	2 (15.4)	14 (70.0)	9 (40.9)

4 pts in 1A crossed over to 1C (included in 1A and 1C analyses). *ORR and disease control rate (DCR) were 0% in 0.03, 0.1, 0.3 (n=3 each) and 3 mg/kg (n=8) groups.

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2505 **Oral Abstract Session**

Phase 1 first-in-human study of anti–ILT3 mAb MK-0482 as monotherapy and in combination with pembrolizumab in advanced solid tumors: Dose escalation results.

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Background: Immunoglobulin-like transcript 3 (ILT3) is an inhibitory receptor associated with immune tolerance and T-cell suppression within the tumor microenvironment. MK-0482, a novel humanized IgG4 mAb targeting ILT3, is undergoing phase 1 evaluation ± pembrolizumab (pembro) in advanced solid tumors (NCT03918278; MK-0482-001). Dose escalation data are presented. **Methods:** Eligible patients with advanced solid tumors were enrolled into sequentially escalating dose cohorts of MK-0482 monotherapy (0.2-2250 mg) or MK-0482 (7.5-2250 mg) + pembro 200 mg; both were administered IV Q3W for up to 35 cycles or until progressive disease (PD), unacceptable toxicity, death, or withdrawal. Patients receiving MK-0482 monotherapy could cross over to MK-0482 + pembro after PD. Primary objectives were safety, tolerability, and determination of the recommended phase 2 dose (RP2D). Secondary and exploratory objectives included assessing pharmacokinetics (PK), blood receptor occupancy (RO), anti–drug antibodies (ADA), and objective response rate (ORR) per RECIST v1.1 by investigator assessment. **Results:** Seventy-five patients were enrolled (n = 29, MK-0482 monotherapy; n = 46, MK-0482 + pembro); 8 patients crossed over to receive the combination. Median age was 63 years (range, 34-86); 73% had ECOG PS 1, 72% received ≥2 lines of prior anticancer therapy, and 32% received prior PD-1/PD-L1 inhibitors. Treatment-related AEs (TRAEs; any-grade/grade 3 or 4) were reported in 34%/7% of patients with MK-0482 monotherapy, 67%/4% with MK-0482 + pembro, and 50%/13% in those who crossed over. The most common TRAEs (≥10% of all patients) were pyrexia (10%) with MK-0482 monotherapy; fatigue (24%) and arthralgia, diarrhea, hyperthyroidism, hypothyroidism, and pruritus (11% each) with MK-0482 + pembro; and arthralgia (25%), hyperthyroidism and hypothyroidism (13% each) for patients who crossed over. Dose-limiting toxicities occurred in 2 patients who received MK-0482 + pembro: 1 grade 5 myositis (MK-0482 750 mg; the only TRAE leading to death) and 1 grade 2 myositis (MK-0482 2250 mg). Preliminary PK and blood RO data suggested that target-mediated drug disposition of MK-0482 was likely saturated in blood mononuclear cells at doses ≥75 mg. ADA to MK-0482 was observed in ~20% of patients, but no clear impact on MK-0482 PK was observed. A confirmed ORR of 15% (8 PR) was observed in patients who received MK-0482 + pembro, including patients who crossed over; no confirmed responses were observed in patients who received MK-0482 monotherapy. MK-0482 750 mg + pembro was selected as the RP2D based on the totality of data. **Conclusions:** MK-0482 ± pembro was generally well tolerated, and combination therapy provided modest antitumor activity in patients with heavily pretreated advanced solid tumors. The RP2D of MK-0482 + pembro is under further evaluation in tumor-specific cohorts. Clinical trial information: NCT03918278. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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2506 **Oral Abstract Session**

A phase 1b, multicenter, dose-escalation study of subasumstat (TAK-981) in combination with pembrolizumab in patients (pts) with advanced solid tumors.

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Background: SUMOylation is a post-translational modification with a role in limiting type 1 interferon (IFN-1)-dependent immune responses. Subasumstat is a small-molecule inhibitor of SUMOylation with the potential to increase antitumor immunity and overcome tumor resistance to checkpoint inhibitors (CPI) by inducing IFN-1 signaling. Preclinical data suggest that subasumstat enhances antigen cross-presentation, promoting T cell dependent antitumor responses; subasumstat plus an anti-PD-1 CPI has shown synergistic tumor growth inhibition and activation of CD8+ T cells and natural killer cells in syngeneic mouse models. We report data from the dose escalation part of a phase 1b study of subasumstat with pembrolizumab in pts with relapsed/refractory, CPI-exposed, non-squamous non-small-cell lung cancer (NSCLC) or microsatellite-stable colorectal cancer (MSS-CRC). **Methods:** Pts received escalating doses (40, 60, 90, and 120 mg) of subasumstat IV in 3 dosing schedules: days 1 and 8 (QW), days 1, 4, 8, and 11 (BIW), or days 1, 8, and 15 (90 mg only) of 21-day cycles, plus pembrolizumab 200 mg IV on day 1 of each cycle for 2 years or until disease progression or unacceptable toxicity. Dose escalation was guided by Bayesian optimal interval design. Phase 1b primary objectives were safety, tolerability, and the recommended phase 2 dose of subasumstat with pembrolizumab. **Results:** As of October 13, 2021, 43 (35 MSS-CRC; 8 NSCLC) pts had received ≥1 dose of subasumstat (22 BIW [40–120 mg]; 15 QW [90 –120 mg]; 6 on days 1, 8, 15 [90 mg)]. Median number of treatment cycles was 3; 28 (65%) pts had discontinued treatment, 21 (49%) due to progressive disease. Median age was 58 years (range 34–77); 56% of pts were male. One pt had a dose-limiting toxicity of grade 3 angioedema at 120 mg BIW. The maximum tolerated dose was not identified. Treatment-emergent adverse events (TEAEs) occurred in 38 (88%) pts; subasumstat-related TEAEs occurred in 34 (79%) pts, and included chills in 20 (47%), pyrexia in 16 (37%), fatigue in 9 (21%), anemia in 6 (14%), and stomatitis in 5 pts (12%; 3 [50%] in the 120 mg BIW cohort). Grade ≥3 TEAEs occurred in 24 (56%) pts; subasumstat-related grade ≥3 TEAEs reported in 10 (23%) pts included anemia, pyrexia, and increased aspartate aminotransferase (2 [5%] pts each). Pharmacokinetic activity of subasumstat was linear and decreased in a tri-phasic manner. Subasumstat exerted pharmacodynamic activity including target engagement, SUMOylation inhibition and increased IFN-1 signaling. Partial responses were observed at ≥40 mg dose levels in pts with NSCLC and MSS-CRC. **Conclusions:** Subasumstat plus pembrolizumab showed a favorable safety profile and promising anti-tumor activity in pre-treated NSCLC and MSS-CRC pts. Updated data will be presented at the meeting. Subasumstat plus pembrolizumab is currently in phase 2 clinical development (NCT04381650). Clinical trial information: NCT04381650. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

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2507 **Oral Abstract Session**

Single-cell profiling of human heart and blood in immune checkpoint inhibitor-associated myocarditis.

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Background: Myocarditis due to immune checkpoint inhibitors (ICIs) is uncommon; however, myocarditis due to ICIs leads to severe morbidity and even death in 20-40% of cases. The molecular underpinnings of ICI-associated myocarditis are poorly understood, and there is an unmet clinical need to identify therapeutic targets and biomarkers that can aid in disease management. **Methods:** Heart tissue was obtained through endomyocardial biopsy or autopsy of patients receiving ICIs and was profiled with paired single-cell RNA sequencing (scRNA-seq) and T cell receptor sequencing (TCR) using the 10x Genomics Chromium system. A control dataset was constructed using scRNAseq data of heart tissue from patients receiving ICIs but without myocarditis and a published dataset from healthy patients not receiving ICIs. Peripheral blood mononuclear cells (PBMCs) were collected at the time of myocarditis diagnosis in a larger cohort of patients and analyzed with ICI-treated controls. The CITE-Seq protocol was used to measure paired scRNA-seq, TCR, and surface proteomics in PBMCs, using serial timepoints where available. **Results:** Heart tissue from 13 patients with myocarditis, including three fatal cases, and seven controls yielded 77,712 single cells. Blood profiling from 27 patients with ICI myocarditis and ICI-treated controls across 54 samples yielded over 230,000 cells. ICI myocarditis tissue demonstrated an increased T cell infiltrate (OR 8.94, FDR = 0.0021). Expression of multiple inflammatory pathways, most notably interferon responses, was up-regulated across multiple immune and non-immune cell types in the setting of myocarditis, providing important pathophysiological insights. T cell clones were also found to be shared between blood and heart, enabling the identification of putative pathogenic T cell subsets. **Conclusions:** Increased intramyocardial T cells and the activation of interferon response gene networks were seen in the setting of ICI myocarditis. These preliminary findings highlight potential pathological pathways in ICI myocarditis that could serve as biomarkers or therapeutic targets. Research Sponsor: U.S. National Institutes of Health.

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2508 **Oral Abstract Session**

Major adverse cardiac events (MACE) with immune checkpoint inhibitor (ICI)-based therapies for cancer: A pooled analysis of investigational clinical trials sponsored by the National Cancer Institute Cancer Therapy Evaluation Program (NCI-CTEP) in the United States and Canada.

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Background: MACE due to ICIs are infrequent immune-related adverse events (irAEs) that comprise a spectrum of cardiac toxicities with variable manifestations. ICI-related MACE can lead to significant morbidity and mortality, hence the need to better define presentations of MACE and their association with non-cardiac irAEs in ICI-treated patients. **Methods:** We conducted a retrospective pooled analysis of MACE captured in the serious adverse events reporting database of the NCI-CTEP for NCI-sponsored investigational clinical trials between 6/2015-12/2019. Patients (pts) were eligible if they had been treated with anti-programmed cell death protein-1/programmed death-ligand 1 (anti-PD-[L]1) alone or in combination with additional anti-cancer therapies. **Results**: A total of 6,925 pts received anti-PD-(L)1-based therapies; 48% (n = 3354) were treated with single-agent anti-PD-(L)1 therapy. Of 6925 pts, 0.6% (n = 40) qualified as ICI-related MACE. Myocarditis accounted for 45% (n = 18/40) of total ICI-MACE. Approximately 77.5% (n = 31/40) of MACE were ≥ grade 3. Multi-system organ involvement with other non-cardiac irAEs was seen in 65% (n = 26/40). Most pts with myocarditis (83%, n = 15/18) had one or more non-cardiac irAEs associated; non-cardiac irAEs were observed in 50% (n = 11/22) of non-myocarditis MACE. Incidence of MACE was higher with anti-PD-(L)1 + targeted therapies vs. anti-PD-(L)1 + anti-CTLA-4 (2.1% vs. 0.09%,*p = 0.08*). Most of these were non-myocarditis MACE. There was a significantly higher incidence of myocarditis with anti-PD-(L)1-based combinations vs. single-agent anti-PD-(L)1 therapies (0.39%, n = 13/3341 vs. 0.14%, n = 5/3566, *p = 0.04*. Most pts with myocarditis had been treated with anti-PD-1-based combinations (72%, n = 13/18); the most common combination being anti-PD1+ anti-CTLA-4 (92%, n = 12/13). Pts with myocarditis presented after a median of 2 ICI doses and after a median of 35 days from the initial ICI administration. In pts with myocarditis, a concurrent or preceding history of myositis was present in 53% (n = 8/15). Deaths related to myocarditis were identified in 22.5% (n = 4/18). All four patients who died had concurrent myositis, with three having concurrent transaminitis. **Conclusions**: Our results represent the first report of a comprehensive pooled analysis of ICI-MACE obtained from NCI CTEP-sponsored investigational clinical trials. Based on our results, increasing patient and prescriber awareness in understanding patterns of ICI-MACE and associated non-cardiac irAEs should be emphasized. Furthermore, better characterization of the risk and patterns of non-myocarditis MACE with the use of anti-PD(L)-1 ICIs concurrently with non-ICI-based anti-cancer therapies is needed. Research Sponsor: U.S. National Institutes of Health.

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2509 **Clinical Science Symposium**

Efficacy of anti-PD1/PD-L1 immunotherapy in non–small cell lung cancer is dependent upon Immunoscore IC CD8 and PD-L1 status.

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Background: Anti-PD1 and PD-L1 antibodies (mAb) are immune checkpoint inhibitors (ICIs) to treat patients with metastatic non–small cell lung cancer (NSCLC). Unfortunately, only a handful of patients respond to ICIs. **Methods:** A cohort of patients with metastatic NSCLC (n=133) treated with anti-PD1 or anti-PD-L1 mAb in two independent care centers was evaluated. An independent cohort of 132 patients from another hospital was used as a validation. Immunoscore IC, an in vitro diagnostic test (CE-IVD), was used on a routine single FFPE slide, and duplex immunohistochemistry CD8 and PD-L1 staining was quantified using digital pathology. Quantitative and spatial parameters related to cell location, number, proximity, and clustering were analyzed. An Immunoscore IC–based model discriminated patients into 2 categories or 3 categories. **Results:** Anti–PD-L1 clone (HDX3) had similar characteristics as other anti–PD-L1 clones (22C3, SP263) with a mean overall agreement above 95%. Intra- and inter-laboratory concordances for classifying patients at 1% cut-off according to digital anti–PD-L1 (HDX3) were 100% and 94%, respectively. Routine laboratory evaluation of PD-L1 expression showed an agreement with digital anti–PD-L1 quantification of 92% and 97% at 1% and 50% cut-offs, respectively. Using univariate Cox model after FDR correction, 5 pathological dichotomized variables were significantly associated with PFS (all $p < 0.0001$). These variables included: CD8 free of PD-L1, CD8 clusters, CD8 cells in proximity of PD-L1 cells, CD8 number, PD-L1 cells in proximity of CD8 cells. Similar results were found using univariate Cox analysis on continuous variables (all $p < 0.003$) in two independent cohorts of patients. Using multivariate Cox model Immunoscore IC classification improved the discriminating power of prognostic model, which included clinical variables and pathologist PD-L1 assessment. In two categories, the Immunoscore IC risk score was significantly associated with both patients' PFS ($p < 0.0001$) and OS ($p < 0.0001$) in the training cohort and in the validation cohort (PFS: $p = 0.0047$, OS: $p < 0.0001$). Further increased hazard ratios were found when stratifying patients into 3 categories of Immunoscore IC. At 6 months, PFS rates were 10% versus 60% in the training cohort and 20% versus 62% in the validation cohort for high-risk and low-risk Immunoscore IC score, respectively. All patients (100%) with high-risk Immunoscore IC score relapsed in less than 18 months, in contrast to 34% and 33% of low-risk Immunoscore IC patients who did not relapse for more than 36 months in the training and validation cohorts, respectively. **Conclusions:** These data underline that Immunoscore IC is a potent tool to predict the efficacy of ICIs in patients with NSCLC. Immunoscore IC characterized patients who are resistant to ICIs. Research Sponsor: Veracyte, Other Foundation, Other Government Agency.

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2510 **Clinical Science Symposium**

External validation of the VIGex gene-expression signature (GES) as a novel predictive biomarker for immune checkpoint treatment (ICT).

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Background: VIGex is a 12- gene GES classifier initially developed on the Nanostring platform and validated for RNA-seq. VIGex classifies samples into Hot, intermediate-Cold (I-Cold) and Cold subgroups. The Hot subgroup as defined by VIGex has been associated with better (PFS) in patients (pts) treated on phase 1 ICT trials at Vall D'Hebron Hospital (VH) (ESMO2020). We investigated the performance of VIGex in pts treated with Pembrolizumab (P) in the INSPIRE clinical trial (NCT02644369) at Princess Margaret Cancer Centre (PM) and compared VIGex with other predictive ICT biomarkers. **Methods:** Pts with advanced solid tumors were treated with P 200 mg IV Q3wks. RNA-seq from baseline biopsies was performed using the Illumina NextSeq550 platform. Tumor RNA-seq data were transferred from PM to VH and classified by the VIGex algorithm blinded to clinical data. Bespoke circulating tumor DNA (ctDNA) was assayed at baseline (B) and start of cycle 3 (C3) using a pt-specific amplicon-based NGS assay (Signatera). Tumor mutational burden (TMB) was defined as the number of non-synonymous mutations per megabase and PD-L1 was assessed by immunohistochemistry (22C3). Hot subgroup (HOT) was compared to I-Cold + Cold (COLD). We defined 4 groups based on the combination of VIGex subgroups and the change in ctDNA at cycle 3 from baseline (ΔctDNA). Survival times were calculated with the Kaplan–Meier method and Cox proportional-hazard models were constructed. **Results:** Out of 76 pts, median age was 55y (range 21-81y), M:F 31:45, all ECOG 0-1, 16 High-grade serous ovarian, 12 triple negative breast, 12 head and neck, 10 melanoma and 26 other. Median no. of P cycles was 3 (range 1–35); follow up was 14m (range 1-67); Median PFS 10.9m and median overall survival (OS) 14m. Overall response rate (RECIST 1.1) was 24% in HOT and 10% in COLD (p = 0.22 two-sided Fisher's exact test). The HOT subgroup was significantly associated with higher OS and PFS when included in a multivariate model adjusted by tumor histology, TMB and PD-L1 (HR 0.43; 95%CI 0.23-0.81; p = 0.009) and (HR: 0.48; 95%CI 0.25-0.95; p = 0.036) respectively. A total of 57 pts had both VIGex and ΔctDNA data. The addition of ΔctDNA further improved the predictive performance of VIGex for OS (Table). **Conclusions:** VIGex maintained its predictive power for ICT outcomes when applied to an independent external dataset using RNA-seq. The predictive information provided by VIGex was independent of PD-L1 and TMB. Our data indicates that the addition of ΔctDNA to baseline VIGex may refine prediction for ICT outcomes. Research Sponsor: Drug only from MERCK and study is supported in part by Princess Margaret Cancer Foundation.

Subgroup	Median OS (months) [95CI%]	HR (95%CI)	P value
COLD + ↑ ΔctDNA	4.8 [3.02-NA]	Reference	NA
HOT + ↓ ΔctDNA	46 [27.5-NA]	0.16 (0.06 - 0.43)	**< 0.001**
COLD + ↓ ΔctDNA	22 [17.6-NA]	0.36 (0.12 – 1.04)	0.059
HOT + ↑ ΔctDNA	13 [6.6-NA]	0.34 (0.14 - 0.81)	**0.015**

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2511 **Clinical Science Symposium**

Identifying gut microbial signatures associated with B cells and tertiary lymphoid structures (TLS) in the tumor microenvironment (TME) in response to immune checkpoint blockade (ICB).

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Background: While ICB has significantly improved clinical outcomes across several cancer types, only 15-20% of patients develop a durable response. Thus, novel and targetable biomarkers are needed. There is increased appreciation of the role of the gut microbiome, and TLS and B-cells in the TME in response to ICB. Here, we investigate the association between these two determinants of response in patient specimens from three randomized phase 2 neoadjuvant ICB trials of nivolumab +/- ipilimumab (melanoma (MEL; NCT02519322; n=23), non-small-cell lung cancer (NSCLC; NCT03158129; n=31), sarcoma (SARC; NCT02301039; n=17). **Methods:** Patients were categorized as responders (R) or non-responders (NR) based on major pathologic response, as defined in each histotype (MEL and NSCLC viable tumor ≤10%; SARC hyalinization>30%). Baseline fecal samples were profiled via 16S rRNA gene sequencing from all three cohorts to assess the composition of patient gut microbiomes. Transcriptional profiles of biopsies collected pre-ICB for MEL and SARC, and post-ICB for MEL, SARC, and NSCLC were used to assess TLS (CXCL13, CCL18, CCL19, CCL21) and B-cell (PAX5, CD79B, CR2, MS4A1) signatures in the TME, by calculated mean values of normalized gene expressions. Comparison between samples were carried out using the Wilcoxon signed-rank test. **Results:** There were 21 R overall (NSCLC n=9; MEL n=9; SARC n=3). Despite significant differences in alpha and beta diversity across cohorts, relative abundance of *Ruminococcus* was significantly higher in R ($p=0.003$; NSCLC $p<0.001$; MEL $p=0.049$; SARC $p=0.7$). B-cell signature was significantly higher post-ICB in R (R vs NR, post, TLS $p=0.13$; B-cell $p=0.003$), with consistent trends in each cohort. Longitudinal evaluation of transcriptional profiles showed that expression of TLS and B-cell signatures increased with treatment in R (pre vs post, MEL and SARC; TLS $p=0.0098$; B-cell $p<0.001$) but not NR (pre vs post; TLS $p= 0.87$; B-cell $p= 0.15$), with consistent trends in sarcoma and melanoma subgroups. Combined correlative analysis with matched specimen showed that patients with higher pre-ICB relative abundance of *Ruminococcus* (above median) had significant increase in B-cell signatures (pre vs post, MEL and SARC; TLS $p=0.052$; B-cell $p=0.002$) which was not seen in patients with low abundance (below median) of *Ruminococcus* (pre vs post, MEL and SARC; TLS $p=0.56$; B-cell $p=0.69$). **Conclusions:** Unifying signatures in the gut microbiome are associated with response to ICB and increased B-cell infiltration and TLS formation in the TME. We expect these findings to energize mechanistic studies and new microbiome-based interventional approaches to improve clinical outcomes with ICB. Clinical trial information: NCT02519322, NCT03158129, NCT02301039. Research Sponsor: None.

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2512 **Poster Discussion Session**

Phase I/IIa study of PM8001, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with advanced tumors.

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Background: PM8001 is a bifunctional protein composed of the extracellular domain of the TGF-β RII receptor (a TGF-β "trap") fused to a humanized anti-PD-L1 IgG1 single-domain antibody. This is the first dose escalation and expansion phase I/IIa study to evaluate the safety and preliminary anti-tumor activity of PM8001 in advanced tumors. **Methods:** This study is comprised of a standard 3+3 dose escalation (Part A: 1, 3, 10, 20, 30, and 45 mg/kg Q2W) followed by dose expansion (Part B). Primary endpoints include safety for Part A, and ORR per RECIST 1.1 for Part B. Secondary endpoints include pharmacokinetics (PK), immunogenicity, DCR, PFS, and OS. **Results:** As of 16 December, 2021, a total of 108 subjects had received at least 1 dose of PM8001 with 25 subjects in Part A (0.3 mg/kg [n = 1], 1 mg/kg [n = 3], 3 mg/kg [n = 3], 10 mg/kg [n = 4], 20 mg/kg [n = 7], 30 mg/kg [n = 3], and 45 mg/kg [n = 4]) and 83 subjects in Part B (10 mg/kg Q2W [n = 1], 20 mg/kg Q2W [n = 63], 20 mg/kg Q3W [n = 11]), and 30 mg/kg Q3W [n = 8]). In Part A, only 1 DLT occurred in the 20 mg/kg dose group. MTD was not reached. Finally, 20 mg/kg Q2W was recommended as the RP2D for Part B. Of the 108 subjects, the median duration of PM8001 exposure was 6.9 weeks (range, 1.4-71.9). Any-grade TRAEs occurred in 84 subjects (77.9%), with 18 subjects (16.7%) reported with ≥ Grade 3. The most commonly reported ≥ Grade 3 TRAEs were anemia and rash (3 subjects each). Any-grade irAEs occurred in 66 subjects (61.1%), with 13 subjects (12.0%) reported with ≥ Grade 3. The most commonly reported ≥ Grade 3 irAEs were anemia (3 subjects). PK analysis showed a nearly linear dose-exposure relationship with PM8001 dosing from 1 to 45 mg/kg. Pharmacodynamic analysis demonstrated close to 100% PD-L1 target occupancy on PBMCs from the 20 to 45 mg/kg groups after multiple doses. An adequate inhibition to below the limit of quantitation of TGF-β1 was observed in the 1 mg/kg and higher dose groups. Of the 108 enrolled subjects, 67 subjects completed at least one efficacy evaluation. The ORR per RECIST 1.1 by investigator was 10.4% (7/67; 95% CI, 4.3%-20.4%), with 7 subjects achieving PR; the DCR was 53.7% (36/67; 95% CI, 41.1%-66.0%). Four additional PRs were observed after the data cut-off date. Of the total 11 PRs, 4 PRs occurred in patients who previously progressed after anti-PD-1 treatment. Most responses (10/11) occurred within 6 infusions, which indicates a rapid response towards PM8001 treatment. To date, 8 responders are still on treatment. **Conclusions:** PM8001 showed an acceptable safety profile and promising anti-tumor activity in advanced solid tumors, especially in patients previously treated with checkpoint inhibitors, which supports further studies to explore the safety and efficacy of PM8001 as a monotherapy and in combination with other anti-tumor agents. Global Phase II monotherapy and combination studies are currently ongoing. Clinical trial information: ChiCTR2000033828. Research Sponsor: Biotheus Inc.

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2513 **Poster Discussion Session**

A phase 1 trial of the bifunctional EGFR/TGFβ fusion protein BCA101 alone and in combination with pembrolizumab in patients with advanced solid tumors.

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Background: BCA101 is a first-in-class bifunctional fusion protein consisting of an anti-EGFR monoclonal antibody (mAb) and TGFβ receptor 2 extracellular domain (TGFβRII-ECD). Herein, we report the safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy data of BCA101 as monotherapy and in combination with pembrolizumab among patients (pts) with advanced solid tumors refractory to standard therapies. **Methods:** Pts received BCA101 as a single agent (SA) or in combination with pembrolizumab at escalating doses in a parallel 3+3 design starting at 64 mg intravenously (IV) weekly (qw); and at 240 mg IV qw with pembrolizumab 200 mg IV q3w. Primary endpoint: safety and tolerability (CTCAE v5.0); dose limiting toxicity (DLT) period: 21 days. Secondary endpoints: overall response rate (ORR), PK/PD profile, progression-free survival (PFS), and changes in plasma and intra-tumoral TGFβ signaling assessed by SMAD2 phosphorylation. **Results:** As of 08-Feb-2022, 60 pts have received BCA101 (part A). Forty-five pts (colorectal, n=14; pancreatic, n=7; head and neck squamous cell carcinoma [HNSCC], n=6) received SA BCA101 at doses up to 1500 mg IV weekly. Fifteen subjects (SCC of the anal canal [SCAC], n=8; HNSCC, n=7) received BCA101 doses ranging from 240 to 1500 mg IV qw in combination with pembrolizumab. Maximum tolerated dose has not been reached. Common adverse events (AEs) attributed to BCA101 include rash (70%), fatigue (23%), pruritis and epistaxis (17% each); all grade (G)2 or less. One DLT was observed at the 1250 mg SA dose (G3 anemia, hematuria). No drug-related G4 AEs or deaths were observed. At data cutoff, best response in the SA arm was stable disease (SD) in 15/39 (39%) evaluable pts. In combination, partial response (PR) was observed in 3/11 (27%) evaluable pts (2 in SCAC, 1 in HNSCC) and a disease control rate (DCR) of 9/11 (82%). Two of 3 responders have been on study >4 months; including 1 confirmed PR in a HNSCC pt refractory to anti-PD-1 therapy and cetuximab. Saturation of the EGFR target was observed at BCA101 doses $\geq$750 mg. Dose proportional increase in Cmax and AUC were observed with doses of BCA101 750-1500 mg. Prolonged neutralization of plasma TGFβ1 was achieved at all doses $\geq$500 mg. Among paired tumor biopsies (n=23), pSMAD2 reduction up to 62% was observed at doses $\geq$500 mg. **Conclusions:** BCA101 is well tolerated and clinically active as a SA and in combination with PD-1 blockade with a predictable PK/PD profile. A recommended dose of 1500 mg both as SA and in combination has advanced to the part B expansion phase for pts with HNSCC, SCAC, and cutaneous SCC. Clinical trial information: NCT04429542. Research Sponsor: Bicara Therapeutics.

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2514 **Poster Discussion Session**

Efficacy and safety of NT-I7, long-acting interleukin-7, plus pembrolizumab in patients with advanced solid tumors: Results from the phase 2a study.

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Background: Checkpoint inhibitors (CPIs) are usually ineffective in patients (pts) with immune-cold microsatellite stable colorectal cancer (MSS-CRC) or pancreatic cancer (PDAC) and in those who progressed on previously treated with antibodies against PD1 or PD-L1. Here, we report the combination of NT-I7 plus pembrolizumab (pembro) on CPI-naïve MSS-CRC and PDAC cohorts, and patients (pts) with CPI-treated triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC) cohorts of this ongoing phase 2a trial. **Methods:** Pts with CPI-naïve relapsed/refractory (R/R) MSS-CRC and PDAC, and CPI-treated R/R TNBC, NSCLC, and SCLC, were enrolled. NT-I7 (efineptakin alfa) 1200 μg/kg intramuscularly every 6 weeks and 200 mg pembro intravenously every 3 weeks were administered until disease progression/unacceptable toxicity. The primary endpoint of the Phase 2a is the objective response rate (ORR), assessed by RECIST v1.1 and iRECIST. The secondary endpoints are duration of response (DoR), disease control rate, progression-free survival, and overall survival. **Results:** As of 14 Jan 2022, 92 pts with metastatic or locally advanced cancer who had received a median of 3 prior treatments were enrolled in the study; 32 in PDAC, 28 in MSS-CRC, 22 in NSCLC, 6 in TNBC, and 4 in SCLC. The median age was 62 years [29-81], ECOG PS 0 in 23 (25%), 1 in 68 (74%) and 2 in 1 (1%). Among 71 evaluable pts, the median follow up (months) was 7.7, 5.3, 5.0, 3.7, and 2.4 in TNBC, MSS-CRC, NSCLC, PDAC and SCLC, respectively. The ORR was 50% (1/2) in SCLC, 12% (3/25) in MSS CRC, 8% (2/26) in PDAC 6% (1/16) in NSCLC and 0% (0/2) in TNBC per iRECIST; and 50% (1/2) in SCLC, 4% (1/25) in MSS CRC, and 4% (1/26) in PDAC per RECIST 1.1. All 7 responders are ongoing. The two PDAC pts had DoR over 1.35 months (mos) and 6.64 mos with the best tumor reduction 100% and 72% respectively. The one SCLC pt had DoR over 1.5 mos with the tumor reduction 67%. The one NSCLC pt had DoR over 2.73 mos with the tumor reduction 60%, and the three MSS-CRC pts had DoR 6.34, 2.96, and 0.03 mos with the tumor reduction 60%, 56%, and 43% respectively. A sustained and significant (approximate 3X from baseline) increase of peripheral lymphocytes in all arms was observed as shown in our previous report. Among 92 treated pts, NT-I7-related adverse events (AEs) occurred in 67 (72.8%) pts, including 52 (56.5%) Grade (G)1-2, 13 (14.1%) G3, and 2 (2.2%) G4. There were no NT-I7 related G5 AEs. Additional updated efficacy, safety and biomarker data will be presented. **Conclusions:** The combination of NT-I7 and pembro demonstrated antitumor activity and manageable toxicity profile in heavily pretreated pts with CPI-naïve MSS-CRC and PDAC and CPI-treated TNBC, NSCLC, and SCLC, suggesting that the addition of NT-I7 to CPI can overcome the primary resistance to CPI in the former group and acquired resistance in the latter. Clinical trial information: NCT04332653. Research Sponsor: Neoimmunetech, Inc.

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2515 **Poster Discussion Session**

First clinical and immunogenicity results including all subjects enrolled in a phase I study of Nous-209, an off-the-shelf immunotherapy, with pembrolizumab, for the treatment of tumors with a deficiency in mismatch repair/microsatellite instability (dMMR/MSI).

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Background: Defective DNA mismatch repair (dMMR) leads to high levels of microsatellite-instability (MSI-H) and insertions or deletions in coding regions, triggering the generation of tumor-specific frameshift peptides (FSPs). We selected 209 shared FSPs among subjects with dMMR/MSI-H cancers, to generate an off-the-shelf vaccine for the treatment of dMMR/MSI-H tumors. Those FSPs were cloned into four proprietary Great Apes Adenoviral (GAd) and four Modified Vaccinia Ankara (MVA) vectors to create a polyvalent viral vectored vaccine named Nous-209 *[Leoni, G. et al. Cancer Res, 2020. 80(18): p. 3972-3982.]*.. **Methods:** This phase 1 first in human (FIH) study (NCT04041310) evaluates safety and tolerability of two dose levels of the Nous-209 in combination with pembrolizumab, assesses immunogenicity and detects preliminary evidence of anti-tumor activity. Nous-209 is administered intramuscularly, concomitantly with pembrolizumab: one prime (GAd-209-FSP) at the 2nd pembrolizumab infusion and three boosters (MVA-209-FSP) at subsequent infusions each 3 weeks apart. The study is composed of two sequential cohorts i.e. dose escalation and dose expansion. **Results:** All evaluable subjects with 1st- or 2nd-line metastatic dMMR/MSI-H colorectal (CRC), gastric or gastroesophageal junction (GEJ) cancers enrolled in this phase I (n = 20) were evaluated as of February 03, 2022. Three subjects enrolled in dose level (DL) 1 (2 CRC and 1 GEJ cancer) showed durable confirmed partial responses (PRs). In DL 2 (12 CRC and 5 gastric cancers), 7 subjects had PRs, 6 had stable disease (SD) and 4 had progressive disease (PD) as best response. Most progressors progressed at the 1st CT and none of the responders have progressed. The median follow-up for subjects in DL1 is 24.7 months (22.3-26.7), and 7.6 months (0.9-19.4) in DL 2. The median progression free survival (PFS) and median duration of response (DoR) have not been reached. No dose limiting toxicities (DLTs) were observed. Vaccine immunogenicity was demonstrated in periphery by *ex-vivo* interferon-gamma ELISpot in 67% of subjects in DL 1, and 82% of subjects with evaluable samples in DL 2. The intratumoral TCR repertoire on pre/post tumor biopsies was analyzed in 3 evaluable subjects with PR and in 1 with PD: expansion and diversification of T cells post treatment with Nous-209 was noted only for the former. Vaccine-reactive TCR clones infiltrating the tumor biopsy post treatment were found in the only subject evaluated to date, with a long-term response. **Conclusions:** The combination of the Nous-209 and pembrolizumab is safe and well tolerated, and shows signs of clinical efficacy. Nous-209 elicits a neoantigen-specific T cell response expanding within the tumor, possibly contributing to the clinical outcome. Clinical trial information: NCT04041310. Research Sponsor: Nouscom Srl.

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2516 **Poster Discussion Session**

Phase I trial of adjuvant autogene cevumeran, an individualized mRNA neoantigen vaccine, for pancreatic ductal adenocarcinoma.

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Background: Pancreas ductal adenocarcinoma (PDAC) is a lethal cancer that claims ~90% of patients in <24 months of diagnosis. PDAC is also refractory to immunotherapy as most tumors exhibit an immune excluded/desert phenotype. However, although characterized by low mutation rates, most PDACs harbor mutations that can generate immunogenic neoantigens. Here, we report the results of a phase-I trial of autogene cevumeran, a systemic RNA-lipoplex individualized neoantigen-specific immunotherapy (iNeST) vaccine, to stimulate immunity against neoantigens in resected PDAC patients. **Methods:** We conducted an investigator-initiated, single-center, phase-I trial of adjuvant autogene cevumeran containing up to 20 neoantigens in each individualized vaccine, identified from resected PDACs using real-time next generation sequencing and bioinformatic neoantigen discovery. Following surgery, patients received atezolizumab (1 dose; week 6), autogene cevumeran (8 weekly doses starting week 9; doses 9,10 – weeks 17, 46), and modified (m) FOLFIRINOX (12 cycles; starting week 21). Primary endpoint: safety. Other endpoints: feasibility (actual vs. target treatment time), vaccine response (responder = positivity by two independent blood assays: IFNg ELISpot and T cell clonal expansion), and recurrence-free survival (RFS). Target accrual: n=20. **Results:** n=19 patients underwent surgery and received atezolizumab at 6.3 weeks (median; 95% CI 6.0–6.57) after surgery with no ≥ grade 3 (Gr3) adverse events. n=16/19 patients (84%) received autogene cevumeran at 9.4 weeks (median; 95% CI 9–10) after surgery. n=1/19 (5%) had insufficient neoantigens for vaccine manufacture. n=1/16 (6%) developed a vaccine-related Gr3 fever and hypertension. n=15/16 vaccinated patients (94%) received mFOLFIRINOX (median 12 cycles; 95% CI 7–12). Autogene cevumeran expanded polyclonal (median 7.5 clones, 95% CI 2–28), IFNg-producing neoantigen-specific $CD8^+$ T cells in 50% (n=8/16) of patients from undetectable levels to large fractions (median 2.9%, Table) of all blood T cells. At an early median follow-up of 15 months, vaccine responders (n=8) had a longer RFS vs. non-responders (n=8) (median not reached vs. 13.7 months, HR 0.08, 95% CI 0.01-0.5, $P = 0.007$). **Conclusions:** Autogene cevumeran is safe, feasibly manufactured in a clinically relevant timeframe, and immunogenic in PDAC. Vaccine induced neoantigen-specific immunity preliminarily correlates with improved PDAC outcome. Further clinical trials in PDAC are warranted. (This imCORE Network project was funded by Genentech Inc and BioNTech; additional funding from Stand Up To Cancer, Lustgarten Foundation). Clinical trial information: NCT04161755. Research Sponsor: Genentech Inc, BioNTech, Other Foundation.

Vaccine-induced T cells.

	Median % of all blood T cells (95% CI)		
	Pre-vaccine	*Post-vaccine*	*P* value
Non-responders (n=8)	0 (0-0)	0 (0-0.6)	0.001
Responders (n=8)	0 (0-0)	2.9 (0.2-10.4)	

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2517 **Poster Discussion Session**

Recommended phase 2 dose (RP2D) of HB-200 arenavirus-based cancer immunotherapies in patients with HPV16+ cancers.

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Background: Treatment options are limited for patients with recurrent or metastatic human papillomavirus 16 positive (HPV16+) cancers. Generation and maintenance of HPV16+ cancers requires stable expression of HPV16-specific E7 and E6 oncoproteins, which are also a source of tumor-specific immunogenic neoantigens. HB-201 and HB-202 are replicating live-attenuated vectors based on lymphocytic choriomeningitis virus and Pichinde virus, respectively, which express the same non-oncogenic HPV16 E7E6 fusion protein and infect antigen presenting cells to induce tumor-specific T cell responses. The Phase 1 part of this study of HB-200 therapy (HB-201 single-vector therapy and HB-202/HB-201 two-vector alternating therapy) was conducted to determine RP2D for further exploration alone or in combination with pembrolizumab. **Methods**: The Phase 1 part used a 3+3 dose escalation design with up to 3 dose levels (DLs) of HB-201 and 4 DLs of HB-202/HB-201 explored. Patients with HPV16+ head and neck squamous cell carcinoma (HNSCC) or with other HPV16+ cancers were evaluated. Safety, tolerability, immunogenicity, and preliminary antitumor activity by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or immune RECIST were assessed to determine RP2D. **Results**: As of January 2022, 65 patients with a median of 3 prior anticancer treatments have been enrolled in the Phase 1 part of the study. All had HPV16+ confirmed genotype; the most common primary site was oropharynx, followed by anal and cervix. Adverse events were generally mild or moderate. For HB-201, 3 DLs, 2 dosing schedules and 2 administration routes were assessed across 40 patients. At DL3 of HB-201 administered intravenously (IV), dose-limiting toxicity (DLT) occurred in 1/6 patients in the HNSCC group (Grade 4 encephalopathy, fully recovered) and 1/2 patients in the non-HNSCC group (Grade 3 rash, fully recovered). Preliminary safety, efficacy, and immunogenicity data support IV injection of DL3 (5×10^7 units) every 3 weeks (Q3W) as the RP2D for HB-201 single-vector therapy. For HB-202/HB-201, 4 DLs and 2 administration routes were assessed across 25 patients. At DL4 of HB-202/HB-201 IV, 1/5 subjects in the HNSCC group reported a DLT (Grade 4 hepatitis, recovering at time of discontinuation). RP2D for HB-202/HB-201 will be determined in the very near future. Tumor control, including partial response, have been observed in subjects treated with either HB-201 or HB-202/HB-201 as monotherapy. **Conclusions**: HB-201 and HB-202/HB-201 were generally well tolerated and showed preliminary antitumor activity in heavily pre-treated patients with HPV16+ solid tumors. DL3 was selected as RP2D for HB-201 monotherapy. In the Phase 2 part of the study a combination of HB-201 at 5×10^6 units IV Q3W with pembrolizumab is being tested in HPV16+ HNSCC patients. Clinical trial information: NCT04180215. Research Sponsor: Hookipa Biotech Gmbh.

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2518 **Poster Discussion Session**

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

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Background: More than 630,000 cases of HPV related cancer occur worldwide annually. About 15-20% of cases respond to PD-(L)1 inhibitors and about 30% respond to dual PD-L1/TGF-β blockade including 10% of checkpoint refractory pts, but for the majority of pts with checkpoint refractory disease there is no effective standard therapy. Preclinical studies show that the combination of PDS0101, a therapeutic vaccine targeting HPV 16 E6/E7, M9241, a tumor-targeting IL-12 immunocytokine, and bintrafusp alfa (BA), a bifunctional fusion protein targeting TGF-β and PD-L1, resulted in maximum T cell infiltration and tumor reduction compared to any 1 or 2 of these agents alone. Prior clinical data suggests that the combination is preferentially active in HPV 16+ disease. **Methods:** 30 pts with advanced HPV 16+ cancer were treated with PDS0101, M9241 and BA (NCT04287868). Pts received BA at 1200 mg IV q2wks, M9241 at 16.8 mcg/kg SC q4wks or 8 mcg/kg SC q2wks, and PDS0101 as two 0.5 ml SC injections q4wks. Dose reductions or skipped doses for toxicities of BA and M9241 were allowed. 5 pts had surgical resection of tumor for disease control and were censored for PD but not survival. **Results:** 30 pts (9 cervical, 2 vaginal/vulvar, 6 anal, 13 oropharyngeal) were treated. 13/30 had grade 3 treatment related AEs including grade 3 anemia in 9 pts associated with grade 3 hematuria in 3 pts and grade 3 GI bleeding in 3 pts. 2 pts had grade 3 AST/ALT elevation. Grade 3 flu like symptoms and grade 3 hemophagocytic lymphohistiocytosis were each seen in 1 pt. One pt had grade 3 lymphopenia/leukopenia plus grade 4 neutropenia and one pt had grade 4 AST/ALT elevation. There were no grade 5 treatment related AEs. 7/8 (88%) pts with checkpoint naïve disease had objective responses (OR) including 1 delayed response after initial PD with 4/7 (57%) responses ongoing (median 17 months follow up). 10/22 (45%) with checkpoint refractory disease have had disease reduction including 6/22 (27%) with OR and 4/6 (67%) responses ongoing (median 12 months follow up). 6/8 (75%) pts with checkpoint naïve disease and 17/22 (77%) pts with checkpoint refractory disease are alive after a median of 17 and 12 months follow up respectively. For checkpoint refractory pts, M9241 dosing appears to affect response rates. 5/8 (63%) pts receiving M9241 at 16.8 mcg/kg had an OR compared to 1/14 (7%) who received M9241 at 8 mcg/kg with an OR. However, despite differences in response rates with higher vs lower M9241 dose, survival outcomes were similar irrespective of M9241 dose ($p = 0.99$ by Kaplan Meier analysis). **Conclusions:** The combination of PDS0101, M9241 and BA appears to have a manageable safety profile along with early evidence of clinical activity for pts with checkpoint naïve and refractory advanced HPV 16+ cancer. Moreover, growing data suggest that all 3 drugs in the combination contribute to the encouraging outcomes being observed. Clinical trial information: NCT04287868. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

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2519 **Poster Discussion Session**

Identifying mechanisms of acquired immune escape from sequential, paired biopsies.

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Background: Resistance to immune checkpoint blockade (ICB) can manifest as disease progression either at the initiation of treatment (primary resistance) or after some initial response (acquired resistance). To better understand the mechanisms underlying acquired resistance, the imCORE Network is conducting a study (NCT03333655) to examine changes in tumor biology from pre-treatment to disease progression across cancer types. **Methods:** Eligible patients included those experiencing clinical benefit on ICB (defined as objective response or stable disease longer than 6 months) and had evaluable tissue samples from both pre-treatment and within 30 days of progression. Samples were subjected to whole exome sequencing (WES), RNA sequencing (RNA-Seq), and immunohistochemistry (IHC). Whole blood samples or adjacent normal tissue were used as a reference for tumor variant calling. **Results:** As of December 3rd, 2021, 24 enrolled patients have complete sample pairs. Of those, melanoma, bladder, and lung were most common (n = 7, 6 and 5 pairs, respectively), but our cohort also included patients with breast cancer, squamous head & neck, and renal cell carcinoma. IHC data unexpectedly showed a modest, but consistent increase in tumor infiltrating CD8+ T cells at progression. In addition, IHC evidence of a decrease in MHC-I proteins (HLA-A and B2M) suggest that in 5 out of 24 cases, key proteins needed for antigen presentation are lost. Global differential gene expression analysis showed that immune gene expression was significantly increased at progression, including numerous chemokines and significant enrichment in gene sets responsible for antigen presentation machinery. Protein-altering mutations at progression appeared in B2M in one patient, and CXCL9 in another. However, in most cases it is unclear what genetic alterations are responsible. We do not observe evidence of consistent IFNγ and Jak/stat signaling loss or antigen presentation loss. **Conclusions:** While ICB resistance is thought to be associated with a lack of immune response within the TME, we found that acquired resistance is usually associated with either maintenance or an increase in immune infiltration. Multiple alterations that are unique to individual patients also continue to emerge. Our data shows ICB resistance is multifactorial and associated with dynamic changes to markers amid immune activation and inhibition. Clinical trial information: NCT03333655. Research Sponsor: Roche/Genentech.

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2520 **Poster Discussion Session**

Effect of intratumoral INT230-6 on tumor necrosis and promotion of a systemic immune response: Results from a multicenter phase 1/2 study of solid tumors with and without pembrolizumab (PEM) [Intensity IT-01; Merck KEYNOTE-A10].

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Background: INT230-6 is a new product with a unique dual anti-cancer mechanism. The drug is comprised of cisplatin (CIS) and vinblastine (VIN) co-formulated with an amphiphilic molecule that enables drug dispersion throughout a tumor and passive diffusion into cancer cells following intratumoral (IT) delivery. A neoadjuvant study in breast cancer confirms that a single injection can kill 95% of an injected tumor and recruit TILs. **Methods:** INT230-6 treatments are Q2W for up to 5 treatments followed by maintenance dosing every 9 weeks. Dose is set by the tumor's longest diameter or volume. One arm received INT230-6 plus PEM 200mg IV Q3W. Biopsies from injected tumor are taken pretreatment and Day 28 for immunohistochemistry (IHC) analysis. **Results:** Sixty-two subjects received INT230-6 alone (median age 61, with 4 prior treatments), and 21 INT230-6 + PEM (median age 70, with 3 prior treatments). To these subjects over 575 image guided INT230-6 IT injections were given (320 to visceral tumors such as lung, liver, pancreas). Doses ranged from 0.14 to 175mL (87.5 mg of CIS, 17.5 mg VIN - higher than typical IV doses). Pharmacokinetic data shows > 95% of the INT230-6 active agents remain in the tumor. The most common (> 25%) adverse events (AEs) related to INT230-6 were localized pain (58%), nausea (40%), and fatigue (29%). The most common AEs attributed to the PEM combination were nausea (62%), localized pain (57%), vomiting (57%), decreased appetite (43%), fatigue (43%) and constipation (29%). The incidence of grade 3 AEs for the INT230-6 arm was 11% and for the PEM combination was 14%. There were no related grade 4 or 5 AEs in the INT230-6 arm; and one grade 4 neutrophil count decrease was seen on the PEM combination. There were no dose limiting adverse events. No patient discontinued therapy due to toxicities related to either drug or injection procedure. The monotherapy arm enrolled patients from 17 tumor types; while the PEM combo recruited primarily pancreatic, CRC, triple negative breast, or bile duct cancer. IHC results confirm a marked reduction in proliferating tumor cells with influx of CD4 and CD8 T-cells. Seven of the INT230-6 monotherapy patients had non injected tumor shrinkage in 9 visceral/deep lesions. Estimated median overall survival (mOS) was over 1 year for both arms. **Conclusions:** In this clinical trial, deep and superficial tumor injections into patients with widely metastatic disease was feasible and well tolerated. Biopsies confirm the dual anti-cancer mechanism, and study patients live longer than would be expected for these refractory populations. INT230-6's rapid tumor killing and immune activation properties may offer an alternative to control refractory patients (even those that are chemotherapy refractory) and the product is moving into randomized controlled registration trials. Clinical trial information: NCT03058289. Research Sponsor: Intensity Therapeutics, Inc.

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2521 **Poster Discussion Session**

First-in-human dose escalation and expansion study of MT-6402, a novel engineered toxin body (ETB) targeting PD-L1, in patients with PD-L1 expressing relapsed/ refractory advanced solid tumors: Interim data.

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Background: MT-6402 is a unique and potent PD-L1-targeted engineered toxin body (ETB) capable of directly killing PD-L1 expressing tumor and immune cells by internalization of a fused Shiga-like toxin A subunit (SLTA) resulting in permanent SLTA-mediated ribosomal inactivation. The targeting of PD-L1 expressing tumor cells may directly drive tumor regression whereas targeting of PD-L1 expressing immune cells may release immunosuppression and drive immune recognition of the tumor. MT-6402 also delivers an HLA-A*02 restricted cytomegalovirus (CMV) class I antigen into PD-L1 expressing cells (antigen seeding) that can be recognized by existing CMV-specific cytotoxic T cells. **Methods:** A first-in-human dose escalation and expansion study in patients with PD-L1-expressing advanced solid tumors was initiated in 2021. As of 1 Jan 2022, 6 patients received at least one dose of MT-6402, 4 of whom were eligible for Dose Limiting Toxicity (DLT) assessment in Cohort 1. **Results:** A significant reduction in CD14+ monocytes starting in cycle 2 was observed in patients on therapy after each MT-6402 administration, indicating an HLA-independent PD effect consistent with preclinical observations. 5 of 6 patients had a marked decrease in Monocytic Myeloid Derived Suppressor Cells (MDSC). The reduction in MDSC and monocytes in the periphery overlapped with increased CCL2 levels, a chemokine that directs movement of myeloid cells. One patient with osseous metastases from non-small cell lung cancer (NSCLC) who is HLA-A*02 and CMV+ showed complete CMV-specific T-cell extravasation at day 8 and serum cytokine signatures consistent with antigen dependent responses and T cell mobilization. This patient had reduced tracer uptake of metastatic bone lesions with 3/4 lesions resolving completely. A second HLA A*02 CMV+ patient followed a similar trend towards loss of peripheral CMV-specific T cells with a concurrent increase in total CD8 T cells. The CD8 T cells from these 2 patients had elevated T-bet expression from baseline, indicating antigen specific TCR stimulation and expansion. The activated immune response was also accompanied by increased IP-10 and IL-2 cytokine signatures in the serum. Consistent with these findings, one of these two patients had transient (1-12 h) grade 2 infusion related reaction and the other had transient (1-12 h) grade 2 cytokine release syndrome, both on Day 15. These results describe a novel approach to checkpoint modulation by MT-6402, that adds antigen seeding to PD-L1 directing mechanisms. MT-6402 was well tolerated and no DLT was observed in Cohort 1 (16 μg /kg, QW in 4-week cycles). **Conclusions:** Dose escalation is ongoing. The results hold promise for development of MT-6402 for solid tumors, including in the R/R setting. Data for additional patients will be presented at the meeting. Clinical trial information: NCT04795713. Research Sponsor: Molecular Templates, Inc.

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2522 **Poster Discussion Session**

The association of pre-existing autoimmune disease and immune-related adverse events secondary to immune checkpoint inhibition therapy in a UK multicenter cohort.

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Background: Pre-existing autoimmune disease (AID) potentially increases the propensity for the development of immune related adverse events (irAE) in response to oncological immune checkpoint inhibitors (ICIs) is biologically plausible and clinically observed. However, due to consistent clinical trial exclusion of those with pre-existing AID, the impact on the frequency and severity of irAEs is uncertain. Here we analyse this relationship in a large, real-world, UK multi-centre cohort. **Methods:** A retrospective analysis of 2049 patients treated with ICIs over a two year period was undertaken across 12 National Health Service centres by the UK National Oncology Trainees Collaborative for Healthcare Research (NOTCH). Patients received ICIs as standard of care for malignant melanoma, non-small cell lung cancer and renal cell carcinoma. The presence of pre-existing AIDs was assessed and classified as either autoantibody driven or autoinflammatory then correlated with clinically significant irAEs (i.e. ≥grade 2 or all-grade endocrinopathies). Statistical analyses included T-test, Mann-Whitney and Chi-squared. For overall survival (OS) Kaplan-Meier and log-rank tests were utilised. **Results:** Pre-existing AID were present in 13% (n = 257) of the overall cohort. Pre-existing endocrinopathies (30%; n = 76) were most common followed by rheumatological AIDs (18%; n = 46). In the pre-existing AID cohort there was a female predominance (48% vs 39%; p = 0.006) but no difference in smoking history (p = 0.074) or ethnicity (p = 0.12). There was no difference in ICI treatment between those with and without pre-existing AID (p = 0.2800). IrAEs occurred in 45% (n = 117) patients with pre-existing AID vs 33% (n = 583) without (p£0.001). The median time to onset of irAEs was similar. IrAEs with an increased incidence in the pre-existing AID cohort were colitis (p = < 0.001), arthralgia (p = 0.008) and dermatological irAEs (p = 0.014). There was no difference in the incidence of irAEs in patients with autoantibody driven vs autoinflammatory pre-existing AID (44.0 % vs 44.8%, p = 0.905). In the overall cohort, those with pre-existing AIDs had a median OS of 20.4 months (95% CI: 19.4-21.7) vs 14.1 months (95% CI: 12.8-16.3) in those without pre-existing AID (p = 0.004). **Conclusions:** This large multi-centre ICI-treated cohort demonstrates that pre-existing AID is a predisposing factor for the development of irAEs, however the incidence is lower than previously quoted. The pathological basis of pre-existing AID did not differentially affect irAE manifestation. Patients with pre-existing AID had improved OS compared to those without which has not been observed in previously reported studies. ICI treatment should be considered in those with pre-existing AID but further studies are needed to determine how best to optimise outcomes whilst mitigating the impact of irAEs. Research Sponsor: None.

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2523 **Poster Discussion Session**

Preexisting autoantibodies as predictor of immune-related adverse events for advanced solid tumors treated with immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICIs), used alone or as a combination are standard of care in many cancers. Generally well tolerated, they can generate immune-related adverse events (irAEs). No biomarkers are available to identify patients who are more likely to develop irAEs. The aim of this study was to assess the association between preexisting autoantibodies, occurrence of irAEs and survival outcomes. **Methods:** We performed a prospective study including 221 patients receiving ICIs for advanced solid tumors between May 2015 and July 2021. Autoantibodies testing (anti-neutrophil cytoplasmic, anti-nuclear, thyroid peroxidase and thyroglobulin) was performed before ICIs initiation. The associations among preexisting autoantibodies, the occurrence, the severity, the delay of irAEs and the survival outcomes, including progression-free survival (PFS) and overall survival (OS) were analyzed. Statistical analyses were performed with T-test, Cox regression models, univariate and multivariate analyses and Kaplan-Meier's method. **Results:** Of the 221 patients, 151 (68%) were men, the median age was 66,5 (range 21-90) years and 103 (81%) had an ECOG-PS of 0 or 1. Seventy-three percent (n=162) received an anti-PD-(L)1 in monotherapy, 27% (n=59) an anti-PD-(L)1 in combination, for a renal cell carcinoma in 45% (n=99) and a lung carcinoma in 41% (n=90). In total, 129 (58%) patients had preexisting antibodies. IrAEs were significantly more frequent in patients with preexisting autoantibodies: 64 patients (50%) in the positive group vs. 20 patients (22%) in the negative group, OR = 3.5 (95%CI=1.8 - 6.8), p=0.00002. Median time interval between ICI initiation and irAE was shorter in the positive group vs. the negative group, 13 weeks (IQR=43weeks) vs. 28.5 weeks (IQR=12weeks) respectively (p=0.01). Twelve patients (9.4%) experienced multi toxicities in the positive group vs. two (2%) in the negative group, OR=4.5 (95%CI0.98-36), p=0.04. ICIs exposure was identical in preexisting and non-preexisting autoantibodies groups. After a median follow-up of 25 months (95%CI=19-31), median PFS and OS were significantly longer among patients experiencing irAE: 12.6 months (95%CI=11-22.7) vs 5 months (95%CI=4.2-7.0), p= 0.0003 and 30 months (95%CI= 22.7-NR) vs 21 months (95%CI=15-34.6), p= 0.016. In multivariate analyses irAEs remain statistically associated with survival outcomes. Preexisting autoantibodies were not associated with survival outcomes. **Conclusions:** The presence of preexisting autoantibodies is significantly associated with the occurrence of irAE in patients treated with ICIs. Earlier and multiple irAEs were observed in the presence of preexisting autoantibodies. Thus, these biomarkers could help to identify patients at risk of irAEs and would prompt us to closely monitor them. Research Sponsor: None.

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2524 **Poster Session**

Safety and efficacy results from the expansion phase of the first-in-human study evaluating TGFβ inhibitor SAR439459 alone and combined with cemiplimab in adults with advanced solid tumors.

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Background: SAR439459 (SAR459) is a human anti-TGFβ monoclonal antibody that neutralizes all isoforms of TGFβ. In preclinical models, combining SAR459 with an anti-PD-1 showed improved anti-tumor activity compared to SAR459 single agent. In the dose escalation, acceptable tolerability was observed, the MTD was not reached and the preliminary RP2D was 22.5mg/kg Q3W when combined with cemiplimab (CEMI; S. Williamson et al. J Clin Oncol 39, 2021[suppl 15; #2510]). Reduction of plasma TGFβ was ≥90% at doses ≥0.25mg/kg Q2W, with a trend of a decrease in intra-tumoral TGFβ (D. Robbrecht et al. JITC 2021;9 [suppl 2; #250]). Here we report safety and efficacy results of the dose expansion. **Methods:** The expansion phase of this open-label, phase 1/1b study aimed to determine the optimal dose of SAR459 (7.5 mg/kg or 22.5 mg/kg Q3W) in patients (pts) with advanced melanoma (MEL) resistant to anti-PD(L)1 therapy (Part 2A); and the ORR (confirmed responses) in all treated pts with SAR459 22.5 mg/kg + CEMI 350 mg Q3W in pts with MEL, Non-small Cell Lung Cancer (NSCLC), or Hepatocellular Carcinoma (HCC), resistant to anti-PD(L)1; as well as in pts with mesenchymal Colorectal Cancer (CRC) or Urothelial Cancer (UC), anti-PD(L)1 naïve (Part 2B). **Results:** From October 2019 to September 2021, 109 pts with ECOG PS 0-1 enrolled in Part 2A (14) and Part 2B (95). Overall, the median age was 63 years and 83% of pts received up to 3 prior treatment lines for advanced disease (range 1-8). Based on preliminary data, the ORR in Part 2B was 8% (Table). No significant association between clinical response and plasma TGFb level at baseline or modulation upon treatment was observed. The correlation between tumor TGFb level and clinical benefit is inconclusive due to limited number of tumor biopsies. No response was observed in Part 2A. Overall, 100% of pts had at least one treatment emergent adverse event (AE), 67% were G≥3, 34% related G≥3, 17% G5, and 4% related G5. The limited number of patients treated with SAR459 alone at the RP2D did not allow to demonstrate added toxicity due to the combination. Overall, 51 pts (47%) reported hemorrhagic AE of any grade, 8 pts (7%) had G≥3 and 5 pts (5%) had fatal outcome. The rate of bleeding and severe hemorrhagic AE was higher in HCC pts compared to the other cohorts: 11/14 (79%) pts had a hemorrhagic AE, of which 3 (21%) G≥3 and fatal. An exploratory analysis showed a trend for higher frequency of any grade SAR459-related and fatal hemorrhagic AE in patients with higher exposure. **Conclusions:** The NCT03192345 study was discontinued due to a lack of efficacy, and a high bleeding risk particularly in pts with HCC. Clinical trial information: NCT03192345. Research Sponsor: Sanofi.

Part 2B objective response rate.

	MEL	NSCLC	HCC	CRC	UC	Part 2B all cohorts
N	25	17	14	24	15	95
ORR n(%)	2(8)	1(6)	1(7)	1(4)	3(20)	8(8)
PR	2	1	1	1	3	8
SD	6	7	4	5	3	25
PD	16	7	6	16	9	54
Not evaluable	1	2	3	2	0	8

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2525 **Poster Session**

The impact of COVID-19 infection on immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors.

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Background: Immune checkpoint inhibitors (ICIs) can cause a variety of inflammatory autoimmune tissue damage, referred to as immune-related adverse events (irAEs). COVID-19 is associated with increased amounts of proinflammatory cytokines, which may synergistically affect the outcome of irAEs. Data are limited regarding the impact of COVID-19 on irAEs in ICI-treated cancer patients. **Methods:** We retrospectively analyzed adult patients with malignant solid tumors treated with ICIs at AdventHealth Orlando between August 2020 and August 2021. All COVID-19 infections were confirmed by PCR. Patients who had the most recent ICI treatment over one month before or after the positive COVID-19 test were excluded from the study. For COVID-19 positive group, only the irAEs that developed after COVID-19 infection were considered as events. **Results:** A total of 579 patients were included in our study, with 46 (7.9%) in COVID-19 positive group, and 533 (92.1%) in COVID-19 negative group. The baseline characteristics of patients in the two groups were similar in terms of age, ethnicity, ECOG, cancer histology, and type of ICI. With a median follow-up of 10 months (1-73 months), no differences in the time from ICI initiation to irAE onset, corticosteroid use, or additional immunosuppressant use were seen. A trend in higher incidence of all-grade diarrhea/colitis (8.7% vs. 3.0%, p=0.07) and grade 3 and 4 hepatitis (4.3% vs. 0.8%, p=0.08) was noted in the COVID-19 positive group, however the difference was not statistically significant. No significant difference in the incidence of pneumonitis (2.2% vs. 1.1%, p=0.44), nephritis (2.2% vs. 0.8%, p=0.34) or dermatitis (6.5% vs. 6.4%, p=1.00) were noted between COVID-19 positive and negative groups. We noticed a higher incidence of all-grade irAEs in the COVID-19 positive group (30.4% vs. 19.9%, p=0.18), but the difference was not statistically significant. The incidence of grade 3 and 4 irAEs was significantly higher in the COVID-19 positive group (10.9% vs. 3.2%, p=0.02). Nine COVID-19 related death occurred while no irAE-related death was noted in the entire cohort. **Conclusions:** Our study suggested that COVID-19 may pose a risk of severe irAEs in cancer patients receiving ICIs. Close monitoring and possible delaying ICI administration could be considered when cancer patients were infected with COVID-19. Research Sponsor: None.

Clinical features of the irAE between COVID-19 positive and COVID-19 negative groups.

Variable	COVID-19 positive N=46	COVID-19 negative N=533	P-value
All grades irAE, n (%)	14 (30.4)	106 (19.9)	0.18
Grade 3-4 irAE, n (%)	5 (10.9)	17 (3.2)	0.02
Corticosteroid use for irAE, n (%)	8 (57.1)	60 (56.6)	0.78
Use of additional immunosuppressant for irAE	0 (0.0)	4 (3.8)	1.00
Time to irAE, median (range)			
Treatment cycle	6 (2-72)	6 (1-56)	0.54
Days	255.5 (48-1662)	153.5 (7-1415)	0.25
Death related to irAE, n (%)	0 (0.0)	0 (0.0)	1.00

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2526 **Poster Session**

A multicenter, randomized, double-blind, phase III trial comparing denosumab biosimilar QL1206 and denosumab in patients with bone metastases from solid tumors.

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Background: This phase III study compared clinical efficacy, safety of the first biosimilar QL1206 with denosumab in solid tumor patients with bone metastases. **Methods:** Patients aged 18-80 years, with bone metastatic solid tumors and ECOG performance status of 0-2 were randomly assigned 1:1 to receive subcutaneous QL1206 or denosumab (120 mg Q4W, both) based on stratification factors (tumor types, previous skeletal-related event [SRE], and current systemic anti-tumor therapy). The primary efficacy endpoint was the percentage changes from baseline to week 13 in urinary N-telopeptide/creatinine ratio (uNTX/uCr); Clinical equivalence would be confirmed if the two-sided 90% confidence intervals (CI) of the least-squares mean (LSM) difference of natural log-transformed ratio of week 13 uNTX/uCr to baseline calculated by analysis of covariance were within the margins of ±0.135. The secondary endpoints included the percentage changes from baseline to week 25 and 53 in uNTX/uCr, the percentage changes from baseline to week 13, 25 and 53 in serum bone-specific alkaline phosphatase (s-BALP) and the time to on-study SRE. Adverse events (AE), immunogenicity (IG) and pharmacokinetics (PK) were also assessed. Population PK was analyzed using nonlinear mixed effects model. **Results:** 717 patients were randomized to the QL1206 (n = 357) and denosumab (n = 360) groups, respectively. The median percentage changes at week 13 in uNTX/uCr were -75.2% for QL1206 and -75.8% for denosumab. LSM of natural log-transformed ratio of week 13 uNTX/uCr to baseline were -1.429 (standard error 0.130) and -1.441 (0.130) in the two groups. The LSM difference between the two groups was 0.012 (90% CI -0.078 to 0.103; P = 0.8208), within the equivalence margins. Analyses for subgroups of sex, age, and randomization strata showed almost no significant differences. The secondary endpoints were also similar between the two groups (median percentage changes in s-BALP from baseline to week 13: -38.0% vs -37.1%; hazard ratio of time to SRE: 1.264 [95% CI 0.670 to 2.383]; both P > 0.05). In the safety set, treatment-emergent AE occurred in 332 of 356 patients (93.3%) in the QL1206 group and 348 of 361 (96.4%) in the denosumab group. The proportions of positive anti-drug antibody (14/345 [4.1%] vs 16/352 [4.5%]), neutralizing antibody (three [0.9%], each), and PK characteristics were similar between the two groups. **Conclusions:** The results suggest that QL1206, the first biosimilar denosumab, is similar to denosumab with respect to clinical efficacy, acceptable safety, IG, and PK characteristics. The totality of evidence supports clinical equivalence of QL1206 and denosumab. Clinical trial information: NCT04550949. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

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2527 **Poster Session**

Safety, tolerability, and preliminary efficacy of nadunolimab, a first-in-class monoclonal antibody against IL1RAP, in combination with pembrolizumab in subjects with solid tumors.

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Background: Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed on cancer and stromal cells of many solid tumors. IL1RAP interacts with IL-1R1, modulating downstream factors (e.g. IL-6, IL-8) and CRP level. Nadunolimab (CAN04), a fully humanized ADCC-enhanced IgG1 antibody, targets IL1RAP and blocks IL-1α and IL-1β. IL-1 promotes an immune suppressive microenvironment, e.g. by recruitment of MDSC which may induce checkpoint inhibitor resistance. Here, initial data are reported from the phase Ib clinical trial CIRIFOUR, evaluating nadunolimab combined with pembrolizumab in solid tumor patients (pts) progressed on prior anti-PD-(L)1 therapy. **Methods:** Primary objective was evaluating safety and tolerability of nadunolimab combined with pembrolizumab in pts with metastatic NSCLC (n = 5), head and neck squamous cancer (n = 9) or malignant melanoma (n = 1), progressed on prior anti-PD-(L)1 therapy of $\geq$12 weeks (wks). Dosing started with a priming dose of 0.5 mg/kg nadunolimab on Day -7, followed by 5 mg/kg nadunolimab weekly combined with standard pembrolizumab dosing. A safety lead-in phase 3+3 design was employed. Secondary objectives included preliminary efficacy and responses based on RECIST/iRECIST. Serum biomarkers and tumor biopsies were also analyzed. **Results:** Fifteen pts received at least one dose of 5 mg/kg nadunolimab with pembrolizumab: median age 63 years (50-79), 27% female, 100% Stage IV, 93% and 7% received prior pembrolizumab or nivolumab respectively, 7% ECOG 0, 93% ECOG 1. The pts had received a mean of 2.3 (range 1-6) previous lines of treatment. SAE were reported in 47% with one considered treatment-related (febrile neutropenia). Two treatment-related grade 3 AE were reported: one febrile neutropenia (DLT), one pneumonitis. No pts discontinued treatment due to treatment-related AE. One patient (7%) had unconfirmed PR as best response, 8 (53%) showed SD, and 6 (40%) iUPD. At time of analysis, 5 pts (33%) received ongoing treatment. Of these, two pts had received therapy for over 31 wks, another two for over 49 wks. Decreased IL-6 was observed after four wks and persisted during treatment. Reduced neutrophil-lymphocyte ratio (NLR) was observed throughout the study, appeared after first treatment, and was driven by a moderate reduction in circulating neutrophils. Decreased IL-6 and NLR were most pronounced in pts with longest disease control duration. IL1RAP expression on cancer and stromal cells was confirmed in tumor biopsies. **Conclusions:** The nadunolimab and pembrolizumab combination was considered safe and tolerable with preliminary evidence of prolonged disease control. The favorable safety provides basis for evaluation of further therapy with this combination. Next, nadunolimab and pembrolizumab will be assessed with carboplatin/pemetrexed in non-squamous NSCLC. Clinical trial information: NCT04452214. Research Sponsor: Cantargia AB.

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2528 **Poster Session**

Customized autoantibodies (autoAbs) profiling to predict and monitor immune-related adverse events (irAEs) in patients receiving immune checkpoint inhibitors (ICI).

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Background: Using a customized microarray, we previously reported that patients (pts) who develop irAEs grade (G)≥2 and those who do not, have different median fluorescent intensity (MFI) levels of specific autoAbs at baseline (pre-ICI). Leveraging a larger dataset, we evaluated whether overall baseline autoAbs elevation and early increases in autoAbs after ICI can predict irAEs as well as if steroid treatment can reduce autoAbs. **Methods:** Plasma was obtained from pts receiving ICI in two clinical trials (MET4-IO, NCT03686202 and INSPIRE, NCT02644369) and from healthy controls (hc). Collection time points in MET4-IO and INSPIRE studies included: baseline, 3-4 weeks (w), 6-8 w, 24 w and at the end of treatment and baseline and 6 w respectively. Arrays with 162 autoAg customized for frequent irAEs were incubated with plasma and probed with Abs to detect IgG and IgM reactivity. AutoAbs with MFI >500 per individual were compared between hc and pts with and without irAEs G≥2 by the Student-t test. **Results:** Samples from 114 pts and 14 hc were analyzed (pts characteristics are summarized in the Table). G≥2 irAEs included: hypothyroidism (13), pneumonitis (10), colitis (7), hepatitis (4), skin toxicity (7), infusion reaction (2), pancreatitis (2), meningitis (1), hypophysitis (1), corneal ulcer (1), high creatinine (1), myocarditis (1), myositis (1), diabetes (1), mucositis (1), myasthenia (1) and adrenal failure (1). Hc had less autoAbs with MFI >500 as compared to pts at baseline (median 32 vs 62 $p<0.001$). IgG with MFI >500 were higher at baseline in pts who developed G≥2 irAEs vs those without G≥2 irAEs (median 39 vs 33, $p=0.03$). In 23 pts with plasma collected at the time of irAEs, we observed a significant increase of autoAbs with MFI>500 from baseline (median 84 vs 77 $p= 0.009$). Paired samples at the time of irAEs and after steroids were available for 9/23 pts, showing lower autoAbs after steroid treatment (54 vs 79 $p=0.006$). No differences in autoAbs with MFI>500 pre and post ICI were seen in pts without G≥2 irAEs (baseline vs first post ICI collection median 58 vs 60, $p=0.13$). **Conclusions:** We observed a higher number of IgG with MFI >500 at baseline and a greater increase after ICI administration in individuals with irAEs compared to those without irAEs. Steroid treatment resulted in a decrease in autoAbs. A prospective study is ongoing to validate the potential role of autoAbs for risk stratification and monitoring of irAEs. Research Sponsor: Dr. Spreafico's research founding.

Pts characteristics.

	MET4-IO	INSPIRE	TOTAL
N of pts	30	84	114
Median age	67(24-81)	59 (21-81)	61(21-81)
Gender			
M	19 (63%)	39 (46%)	58 (51%)
F	11 (37%)	45 (54%)	56 (49%)
irAES≥G2			
Yes	18 (60%)	19 (23%)	37 (32%)
No	12 (40%)	65 (77%)	77 (68%)
Tumor type			
Melanoma	14 (47%)	11 (13%)	25 (23%)
HNSCC	14 (47%)	19 (23%)	33 (29%)
Other tumor types	2 (7%)	52 (64%)	56 (49%)
Type of ICI			
Anti PD1	18 (60%)	84 (100%)	102 (89%)
Anti PD1 + anti-CTLA4	12 (40%)	0 (0%)	12 (11%)

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2529 **Poster Session**

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

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Background: ATOR-1017 is a human agonist Fcγ-receptor cross-linking dependent IgG4 antibody targeting the co-stimulatory receptor 4-1BB (CD137). ATOR-1017 activates T cells and natural killer cells in the tumor environment, leading to immune-mediated tumor cell killing. **Methods:** In this first-in-human, dose escalation, multicenter, phase 1 study (NCT04144842), adult patients with solid tumors refractory to standard therapy were enrolled in single patient cohorts for doses up to 40 mg, and thereafter in cohorts of 3-6 patients, to receive ATOR-1017 in a 21-day cycle. Intra-patient dose escalation of ATOR-1017 is allowed depending on the occurrence of Dose-Limiting Toxicities (DLTs) during cycle 1. ATOR-1017 is administered intravenously as monotherapy every three weeks until unacceptable toxicity, progressive disease, or withdrawal of consent. The primary objectives of the study are to determine the maximum tolerated dose, assess adverse events (AEs), evaluate DLTs, and to determine the recommended phase 2 dose. Secondary objectives include pharmacokinetics (PK), immunogenicity, and clinical efficacy, assessed with CT scans using Immune Response Evaluation Criteria in Solid Tumors (iRECIST). Exploratory objectives include assessment of pharmacodynamic (PD) biomarkers. **Results:** 22 patients (18 females), median age 55 years (34-76) with solid tumors, previously treated with median of 4 (0-6) lines of chemotherapy and/or 2 (0-3) lines of immunotherapy, were included and received at least one cycle ATOR-1017. Nine dose levels have been evaluated; 0.38 mg, 1.5 mg, 5 mg, 15 mg; 40 mg, 100 mg, 200 mg, 360 mg, and 600 mg and dose escalation is ongoing. Treatment-related (TRAEs) were reported in 12 out of 22 patients (54.5%); most common ($\geq$10%) were fatigue (13.6%) and neutropenia (13.6%). Five patients experienced a grade 3-4 TRAE; neutropenia (n = 2), febrile neutropenia (n = 1), chest pain (n = 1), increased liver enzymes (n = 1) and leukopenia/thrombocytopenia (n = 1). No patients discontinued due to TRAEs, no DLTs were observed, and the maximum tolerated dose has not been reached. The median time for patients in the study was 12 weeks (range 4-67). As per data cut-off, January 18, 2022, four patients remained on treatment and 18 patients had discontinued treatment. The reasons for discontinuation include confirmed disease progression (n = 10), clinical deterioration (n = 4), withdrawal of consent (n = 1), death due to disease progression (n = 3). Preliminary PK data showed dose-proportional kinetics. Dose-dependent increase in PD biomarkers demonstrated target-mediated biological activity and proof-of-mechanism. The best response was stable disease observed in a total of 10 patients (45%). **Conclusions:** ATOR-1017 is safe and well-tolerated at doses up to 600 mg and has shown biologic activity. No DLTs have been reported so far and dose escalation continues. Clinical trial information: NCT04144842. Research Sponsor: Alligator Bioscience.

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2530 **Poster Session**

Novel platform for identifying multiple cancer-specific antigens.

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Background: Virtually all cancer treatments that kill cancer cells also adversely affect normal cells and often have debilitating side effects. A key challenge has been to identify antigens that are suitable for antibody-based targeted therapeutics. We have developed a novel platform to detect and identify multiple cell surface antigens that are unique to human cancers. **Methods:** Breast Cancer cells (Hs578T) or Melanoma cells (Hs895.T) were injected into rabbits to generate polyclonal xeno-antibodies. The resulting serum against each cancer was then incubated with normal cells of the same tissue type derived from the same patients; Breast Epithelium (matched-pair Hs578Bst) or Skin Fibroblasts (matched-pair Hs895.Sk) in order to absorb antibodies that cross-react with antigens on normal tissue (U.S. Patent Application No. 16/243,161). Flow cytometry was used for measuring the binding capacity of the unfiltered serum and filtered serum (lacking cross-reacting antibodies) on both the cancer cells and normal cells. Cytotoxicity assays were performed using a secondary ADC (anti-rabbit IgG specific antibody conjugated to MMAF), to determine the cytotoxicity of the unfiltered antibodies and filtered antibodies on normal and cancer cells. **Results:** Flow cytometry revealed, for antibodies against breast cancer, there was 90.3% and 88.6% binding to breast cancer cells and normal breast epithelial cells, respectively, pre-filtration; and 78.9% and 23% binding, respectively, post-filtration. For antibodies against melanoma, there was 89.2% and 86.6% binding to melanoma cells and normal skin fibroblasts, respectively, pre-filtration; and 55.1% and 0% binding, respectively, post-filtration. The Table summarizes the cytotoxicity of unfiltered and filtered antibodies on cancer cells and normal cells. Remarkably, there was preferential killing of all the cancer cells tested by both unfiltered and filtered antibodies, while there was no cytotoxicity in the normal cells using filtered antibodies. Cytotoxicity was also observed when antibodies generated against one type of cancer were incubated with other cancer types. **Conclusions:** This data suggests that our xeno-antibody based method can detect cancer-specific sites, not found on normal cells, and diverse cancer types may share a common antigenic signature. These findings are significant for identifying unique antigens on cancer cells and designing targeted therapies against cancer. Research Sponsor: Cancer Antibodies Inc.

Antibodies against:	Incubated with:	% Cytotoxicity with Unfiltered Antibodies	% Cytotoxicity with Filtered Antibodies
Breast Ca (Hs578T)	Breast Cancer (Hs578T)	93.8 ± 4.2	61.27 ± 11.33
	Normal Breast Epithelium (Hs578Bst)	87.1 ± 8.9	1 ± 1.6
	Breast Cancer (MDA-MB-231)	80.15 ± 2.150	79.5 ± 0.5
Melanoma (Hs895.T)	Melanoma (Hs895.T)	66.96 ± 7.775	59.02 ± 7.530
	Normal Skin Fibroblasts (Hs895.Sk)	21.87 ± 11.96	0
	PBMCs	0	0
	Prostate Ca (PC3)	19.83 ± 10.81	38.03 ± 6.894
	Prostate Ca (LNCaP)	77.85 ± 9.850	73.95 ± 15.35
	Prostate Ca (DU145)	52.93 ± 1.870	41.6 ± 7.308

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2531 **Poster Session**

Phase I clinical trial of NEO-201, an anti-tumor-associated CEACAM-5/6 monoclonal antibody in solid tumors.

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Background: NEO201 is a humanized IgG1 monoclonal antibody generated against tumor-associated antigens from colorectal cancer which binds specifically to tumor-associated CEACAM-5 and CEACAM-6 variants without binding CECAM 5/6 on normal epithelial tissues. NEO-201 reactivity is positive in the majority of adenocarcinomas including colon (85%), pancreas (86%), lung (79%), and breast (53%). Preclinical data showed that NEO-201 exerts anti-tumor activity through antibody dependent cellular cytotoxicity and complement dependent cytotoxicity. Here we present outcomes from a phase I trial of NEO-201 in advanced solid tumors (NCT03476681). **Methods:** This was a classic 3+3 dose escalation trial, with cohort expansion at the RP2D. NEO-201 was administered intravenously every two weeks in a 28-day cycle. The primary objective was to assess the MTD/RP2D of NEO-201 in patients with advanced solid tumors. The secondary objective was to assess the preliminary antitumor activity and exploratory objectives assessed pharmacokinetics and the effect of NEO-201 administration on immunologic parameters and possible relationships with response. Of 17 patients enrolled, 11 had colorectal, 4 had pancreatic and 2 had breast cancer. 4 patients received NEO-201 at dose level (DL) 1 (1 mg/kg), 6 patients at DL 1.5 (1.5 mg/kg) and 7 patients at dose DL 2 (2 mg/kg). **Results:** At the time of data cutoff, all patients had discontinued therapy. 11 of 14 evaluable patients discontinued due to disease progression and 3 patients discontinued due to DLT (grade 4 febrile neutropenia and prolonged neutropenia, each in 1/6 patients at DL2, and grade 3 febrile neutropenia in 1/6 patients at DL 1.5). Most common grade 3/4 toxicities were neutropenia (94%), white blood cell decrease (59%), lymphocyte decrease (29%), and febrile neutropenia (24%). Protocol was modified to allow administration of G-CSF and based on safety and PK data the RP2D was established as 1.5mg/Kg. Median number of doses received was 4.7. 13 subjects were able to undergo disease assessment after two cycles. The best response observed was stable disease (SD) in 5/9 evaluable patients with colorectal cancer. Minor CA-19-9 reductions were observed in two pancreatic cancer patients at DL 1.5. Correlative endpoints revealed that all patients enrolled in the trial expressed NEO-201 target antigen on their tumor tissue. Analysis of soluble factors in serum revealed that a high level of soluble MICA at baseline was correlated with a downregulation of NK cell activation markers and progressive disease. Unexpectedly, flow cytometry showed that NEO-201 also binds to circulating T regulatory cells and depleted these cells especially in patients with SD. **Conclusions:** NEO-201 was safe and well tolerated at the MTD of 1.5 mg/kg. Depletion of T regulatory cells suggests that the combination of NEO-201 with immune checkpoint inhibitor should be tested in future clinical trials. Clinical trial information: NCT03476681. Research Sponsor: U.S. National Institutes of Health.

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2532 **Poster Session**

In-vivo reprogramming macrophages and dendritic cells with Allocetra-OTS: Successful mono- and combination-antitumor therapy.

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Background: Chimeric antigen receptor (CAR) T cells can activate an immune response to a cancer-specific antigen but is less effective in solid tumors. Immune check point inhibitors (ICI) revolutionized the treatment of solid tumors, however, in many tumors only partial response is achieved. Here we questioned the role of synergistic effect of Allocetra-OTS (cellular therapy for in-vivo reprogramming macrophages and dendritic cells, Enlivex Therap.) on solid tumor progression. **Methods:** To follow tumor growth *in vivo*, HeLa-CD19 cells were stably transduced with pLenti-PGK-V5-Luc-Neo. For CAR preparation, fresh mononuclear cells (MNC) were transfected with CD19-CAR plasmids. For the intraperitoneal solid tumor model, SCID-Bg mice were injected intraperitoneally (IP) with human HeLa-CD19 or HeLa-CD19-luciferase cells, 10×10^6 allocetra-OTS or vehicle, and 10×10^6 CD19-CAR T cells or mock T cells. In an immune-competent model, Balb/c mice were treated IP with AB12 (mesothelioma) with pLenti-PGK-V5-Luc-Neo and treated with anti-CTLA4 with or without Allocetra-OTS. Mice were monitored daily for clinical signs and peritoneal fluid accumulation and weekly for tumor growth. Kaplan-Meier log rank test was done for survival. Peritoneal cells were evaluated using single cell analysis and flow cytometry. Tumors were examined for bacterial presence by immunohistochemistry staining with antilipoteichoic acid (LTA) and antilipopolysaccharide (LPS). For allocetra-OTS preparation, enriched mononuclear fractions were collected by leukapheresis from healthy eligible human donors and induced to undergo early apoptosis. **Results:** SCID mice survived 30±5 days (range 27–37) and were sacrificed or died from solid tumor in the peritoneal cavity after accumulation of bloody peritoneal fluid and clinical deterioration. Results were verified using IVIS of intraperitoneal HeLaCD19-Luc cells. CAR T cell therapy significantly ameliorated survival to 55±11 days ($p < 0.05$ vs MOCK) but Alloctra-OTS further ameliorated survival to 75±10 ($p < 0.001$) with 20-40% complete remission. In AB12 model, anti CTLA4 therapy significantly ameliorated survival from 26±5 to 38 ±9 days ($p < 0.05$). However, Allocetra-OTS monotherapy ameliorated survival to 45 ±12 days ($p < 0.02$) and combinational therapy to 75±9 days ($p < 0.0001$) with complete remission in 60-75% of mice. Single cell analysis revealed that restoration of large peritoneal macrophages (LPM), were associated with antitumor activity. **Conclusions:** During intraperitoneal tumor progression, allocetra-OTS as monotherapy or combinational therapy with CAR or anti-CTLA4 significantly reduced tumor size and enable complete remission in up to 75% treated mice. Based on excellent safety profile in > 30 patients treated for sepsis and Covid19, human phase I/II of allocetra-OTS plus ICI, for peritoneal metastases, is planned for 2022. Research Sponsor: Enlivex Ltd.

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2533 **Poster Session**

A phase 1, first-in-human (FIH) study of the anti-HER2 CAR macrophage CT-0508 in subjects with HER2 overexpressing solid tumors.

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Background: Most solid tumors are resistant to immunotherapy. In pre-clinical studies, CAR-M infiltrate tumors, phagocytose tumor cells, activate the tumor micro environment (TME), recruit T cells, and present tumor antigens to T cells leading to robust anti-tumor immunity. CT-0508 is a first in class CAR-M, comprised of autologous monocyte derived macrophages expressing an anti-HER2 CAR. Here we present preliminary clinical results from the CT-0508 Phase 1 FIH study. **Methods:** This multi-center, open-label study is evaluating CT-0508's safety, tolerability, and manufacturing feasibility in 18 participants (pts) with advanced solid tumors overexpressing HER2 who have progressed on prior therapies. Monocytes are isolated from mobilized apheresis products, differentiated into macrophages and engineered with an anti-HER2 CAR. Group 1 pts (n = 9) receive a fractionated dose (D1, D3, D5) and Group 2 pts (n = 9) receive the full dose on D1. CT-0508 is administered without preparative chemotherapy (bridging is permitted). Serial blood samples, 1 pre and 2 post-treatment biopsies are collected to investigate safety, pharmacokinetics and mechanism of action. **Results:** Seven pts (4F/3M), median age 64 (49-73), have been treated [breast (2), esophageal (2), cholangiocarcinoma, ovarian and parotid gland cancers]. A median of 3 (2-10) prior lines of therapy have been administered, most pts (85.7%) received prior anti HER2 therapy. CT-0508 was successfully manufactured with high viability, purity and CAR expression, and was well tolerated with no dose limiting toxicities or AEs leading to discontinuation or dose modification. Two related SAEs were reported in the same pt (Grade 1 CRS, hospitalized for monitoring and Grade 2 infusion reaction, resolved within 1h). Three other pts had Grade 1-2 CRS; resolved within 4d with no use of tocilizumab needed. There were no major organ toxicities and no on-target off-tumor toxicities. Post-infusion cytokines were transiently elevated in most pts and were self-limiting. Among the 4 pts who reached week 8, the best overall response was stable disease (n = 3) and 1 pt progressed, with a median follow up of 8w. CT-0508 rapidly egressed from peripheral blood. CT-0508 CAR mRNA was detected in all tumor biopsies of the first 2 pts. CT-0508 activated the TME, with increased myeloid cell activation, T cell infiltration, activation and proliferation. TCR sequencing demonstrated peripherally expanding T cells enriched for tumor infiltrating lymphocyte clones, suggesting expansion of tumor reactive T cells. Correlative data from additional pts will be presented. **Conclusions:** In 7 pts, CT-0508 was safe and feasible to manufacture. Early correlative data demonstrate trafficking, TME modulation, and potential induction of anti-tumor T cell immunity. The study is actively enrolling. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

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2535 **Poster Session**

Antitumor activity of T cells expressing a novel anti-folate receptor alpha (FOLR1) costimulatory antigen receptor (CoStAR) in a human xenograft murine solid tumor model and implications for in-human studies.

Owen R. Moon, Yun Qu, Michael G. King, Michelle Mojadidi, Cynthia Chauvin-Fleurence, Clare Yarka, Alicia Evans, Xingliang Zhou, Tania (Theoni) Katopodi, Akshata Udyavar, John S. Bridgeman, Gray Kueberuwa, Rubén Alvarez-Rodríguez; Instil Bio, Inc., Dallas, TX

Background: ITIL-306 is an autologous tumor-infiltrating lymphocyte (TIL) therapy that integrates T-cell receptor (TCR)-specific antigen recognition (Signal 1) with robust costimulation via the novel CoStAR transgene upon engagement with FOLR1 (Signal 2; Sukumaran, et al. *JITC*. 2021;9:198). Here, we assessed IL-2 independent effector function by anti-FOLR1 CoStAR T cells in vitro and evaluated activity in a novel, more representative murine solid tumor model. **Methods:** For in vitro studies, healthy donor T cells were manufactured to express anti-FOLR1 CoStAR or left nontransduced (NTD). Product cells were stimulated with a single (Day [D]0; ±IL-2) or serial (D0, 7, 14, 21; no IL-2) addition of target cells expressing membrane-anchored OKT3 (Signal 1) and FOLR1 (Signal 2). T-cell activation and proliferation were measured. For in vivo studies, the carcinoembryonic antigen (CEA)-positive (Signal 1) H508 cell line was engineered to express FOLR1 (Signal 2) and injected into 6 mice/group (D–21). NTD or healthy donor T cells expressing HLA-A*02-restricted anti-CEA TCR only, anti-FOLR1 CoStAR only, or dual TCR+CoStAR were given intravenously (D0), and compared with PBS control. Tumor growth, survival, and T-cell expansion were assessed in 2 donors to D96. **Results:** After single and serial stimulation, only anti-FOLR1 CoStAR T cells showed sustained proliferation without exogenous IL-2. PD-1 positivity was low (< 10%) on anti-FOLR1 T cells up to D24. In vivo, T-cell persistence on D14 was increased in dual TCR+CoStAR vs anti-CEA TCR only mice ($P<.001$) and all other groups ($P<.01$-$.001$). Tumor growth up to D58 was significantly lower in dual TCR+CoStAR (<.5 cm^3) vs all other groups (each > 2 cm^3; $P<.0001$). Survival was significantly longer in dual TCR+CoStAR ($P<.01$) vs all other groups; only dual TCR+CoStAR mice were alive at D58, with 5/6 alive at D96. The second donor showed similar tumor control irrespective of exogenous IL-2 in responder mice, with > 50% alive at D96, and robust T-cell expansion in dual TCR+CoStAR mice. **Conclusions:** When combined with TCR-specific binding, CoStAR significantly enhanced T-cell proliferation, persistence, and antitumor activity in vivo vs TCR alone, resulting in tumor control and prolonged survival. Effects were not observed with CoStAR alone, underscoring that signaling through CoStAR alone does not induce T-cell effector function. The sustained proliferation of anti-FOLR1 CoStAR T cells without exogenous IL-2 support in vitro and in vivo supports a clinical TIL regimen free of high-dose IL-2. These results suggest that CoStAR may improve the clinical performance and benefit/risk profile of TILs, whereby fewer toxicities are expected with the removal of post-TIL IL-2 support. This will be explored in an upcoming first-in-human clinical study with ITIL-306. Research Sponsor: Instil Bio, Inc.

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2536 **Poster Session**

Efficacy and safety of autologous expanded tumor infiltrating lymphocytes (TILs) in multiple solid tumors.

Rodabe Navroze Amaria, David J. Vining, Scott Kopetz, Michael J. Overman, Milind M. Javle, Mara Antonoff, Ching-Wei D. Tzeng, Robert A. Wolff, Shubham Pant, Kathryn Lito, Kelly M. Rangel, Louis Wilson, Bryan M. Fellman, Cara L. Haymaker, Ying Yuan, Marie-Andree Forget, Patrick Hwu, Chantale Bernatchez, Amir A. Jazaeri; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Diagnostic Radiology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center and SWOG, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX; MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Virginia, Charlottesville, VA

Background: TIL therapy has been used extensively in metastatic melanoma patients for many years, now with ongoing efforts to commercialize treatment. The efficacy of TIL outside of melanoma is largely unknown thus we designed and implemented a trial using TIL manufactured at a single academic center for treatment refractory metastatic colorectal (CRC), pancreas (PDAC) and ovarian (OVA) cancers. **Methods:** Patients with CRC, PDAC and OVA refractory to standard therapies with ECOG PS 0-1 and normal organ function were eligible for TIL harvest. Ex vivo TIL expansion and manufacturing was conducted at the MD Anderson TIL lab under conditions that included IL2 and 41BB stimulation (using urelumab). All patients received a lymphodepletion regimen consisting of cyclophosphamide 60mg/kg days -7 and -6 and fludarabine 25mg/m2 days -5 through day -1, followed by infusion of pooled *ex-vivo* expanded TIL. Patients received up to 6 doses of high dose IL-2 (600,000 IU/kg) after TIL infusion. The primary endpoint was evaluation of the objective response rate (ORR) using RECIST 1.1 criteria with secondary endpoints including disease control rate, duration of response, PFS, OS and safety. **Results:** A total of 17 patients underwent TIL harvest and 16 were treated on protocol; including 8 CRC, 5 PDAC and 3 OVA. Median age was 57.5 (range 33-70) and 50% were females. Median number of lines of prior therapy was 2 (range 1-8). Median number of TIL infused was 76 X 10^9 (range 20.3 x 10^9-150 x 10^9). Median doses of cyclophosphamide and fludarabine administered were 2 (range, 2-2) and 3 (range, 1-5), respectively. Median doses of IL-2 administered was 6 (range, 1-6). There were no responders. Best response included prolonged SD in a patient with PDAC lasting until 18 months. Grade 3 or higher toxicities attributable to therapy was seen in 14 subjects (87.5%; 95% CI: 61.7 – 98.4) with the majority of toxicities representing expected pancytopenia from lymphodepletion. Infusion product analysis showed the presence of effector memory cells with high expression of CD39 irrespective of tumor type. Early on-treatment biopsy of PDAC patient with prolonged SD showed presence of proliferating (KI67+) CD4+ and CD8+ TIL. **Conclusions:** Generation of TIL at a single academic center for CRC, PDAC and OVA is feasible and treatment is associated with no new safety signals. For these tumor types, further research is required to identify host factors associated with resistance to TIL therapy and optimize manufacturing processes to create more effective TIL cell therapy. Clinical trial information: NCT03610490. Research Sponsor: Iovance.

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2537 **Poster Session**

Examination of mutation signature and mutation spectrum as predictors of response to immune checkpoint blockade therapy.

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Background: In recent years, there has been promising progress in the use of immune checkpoint blockade (ICB) as a treatment for various cancer types such as lung, kidney, bladder, skin, colon, and breast cancer. In order for this modality to have increased success, more precise selection tools are needed to predict which patients will benefit from treatment. Tumor Mutational burden (TMB) has been implicated as a biomarker for ICB response due to the increased tumor immunogenicity present in high TMB samples. However, we hypothesize that the quality of mutations may also have an impact in determining immune response, rather than just the quantity of mutations alone. **Methods:** A retrospective analysis of 2041 patients across multiple solid tumor types was conducted using an open-access, open-source cancer genomics database (Gao, Sci Signal, 2013), with the goal of assessing the influence of mutational signature on patient response to ICB (including CTLA-4, PD-1, and PDL-1). Patient demographics, treatment variables/outcomes, and tumor variables, including mutation spectrum, and mutation count, were evaluated. A paired two sample test for means was used to analyze data with $p < 0.05$ considered statistically significant. Response outcomes were determined per RECIST v 1.1. **Results:** Our data demonstrate that mutational spectrum profiles show distinct patterns when considering response to ICB, independent of TMB. Patients with breast invasive ductal carcinoma who responded to ICB had less C > A mutations ($p = 0.020$) and more C > T mutations ($p = 0.017$) compared to non-responders. Lung adenocarcinoma responders had less C > T mutations ($p = 0.003$) and more C > A mutations ($p = 0.0003$) compared to non-responders. Furthermore, both head and neck squamous cell carcinoma and glioblastoma multiforme responders had more T > A mutations ($p = 0.047$ and $p = 0.011$, respectively) than non-responders. However, in other cancer types studied (urothelial, colon, renal, lung squamous, and melanoma), there were no obvious trends to distinguish responders from non-responders. Preferentially mutated gene targets were also considered for all 10 cancer types (including CARD11, SMARCA4, GLI1, PIK3R1, PTPRT, among others), many of which were also tied to the unique mutational signatures observed and which may be separately identified as novel ICB therapy targets. **Conclusions:** We found that specific mutation type may impact response to ICB in at least 4 cancer types, including breast, lung adenocarcinoma, head and neck squamous cell carcinoma and glioblastoma multiforme. Of note, this trend was not found in other cancer types which are typically found to have higher TMB. Moving away from solely considering the magnitude of mutations in tumor samples and towards identifying specific mutational signatures may aid in providing necessary specificity for selecting patients for ICB cancer therapy. Research Sponsor: The program above is funded through the following: National Cancer Institute R25 grant CA225513, the Concern Foundation for Cancer Research, and Tri Delta.

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2538 **Poster Session**

Multicenter phase Ib trial in the U.S. of salvage CT041 CLDN18.2-specific chimeric antigen receptor T-cell therapy for patients with advanced gastric and pancreatic adenocarcinoma.

Gregory P. Botta, Carlos Roberto Becerra, Zhaohui Jin, Dae Won Kim, Dan Zhao, Heinz-Josef Lenz, Hong Ma, Audrey Ween, Petra Acha, Zonghai Li, Harry H. Yoon; UCSD Moores Cancer Center, La Jolla, CA; Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; Division of Medical Oncology, Mayo Clinic, Rochester, MN; H. Lee Moffitt Cancer Center, Tampa, FL; MD Anderson Cancer Center, Houston, TX; Division of Medical Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA; CARsgen Houston, Houston, TX; University of California San Diego, Moores Cancer Center, San Diego, CA; CARsgen Therapeutics, Inc., Houston, TX; CARsgen Therapeutics Ltd., Shanghai, China; Mayo Clinic, Rochester, MN

Background: Claudin 18.2 (CLDN18.2) is a highly selective cell lineage marker with limited expression in normal gastric tissues and significantly higher expression in primary gastric, pancreatic tumors and their metastases. Anti-CLDN18.2-targeted CAR T cells, termed CT041, were developed to evaluate tumor response and patient-reported outcomes in the gastric and pancreatic cancer. Preliminary results of the trial (NCT03874897) showed an objective response rate (ORR) of about 60% in gastric cancer from a non-Western population. Here we report the results of CT041 for metastatic gastric cancer after $\geq$ 2 prior lines of systemic therapy or pancreatic cancer $\geq$ 1 prior line from six centers in the United States. **Methods:** This single-arm, open-label, phase Ib study (NCT04404595) investigated autologous CT041 CAR T cells in patients with CLDN18.2 positive advanced gastric (including diffuse, signet-ring) or pancreatic adenocarcinoma. All patients completed a conditioning regimen consisting of fludarabine, cyclophosphamide, and nab-paclitaxel prior to CT041 CAR T cells. The primary objective was to assess the safety, efficacy and cytokinetic profile of CT041. Adverse Events (AEs) were graded according to CTCAE 5.0, and tumor response was assessed per RECIST 1.1. **Results:** As of February 15, 2022, 11 patients (5 gastric and 6 pancreatic) with a median of 2 prior lines of therapy (range 1-4) were treated with CT041 at a dose between 2.5 and 4 x 10^8 cells. There were no dose limiting toxicities, treatment-related deaths, severe cytokine release syndrome (CRS), immune effector cell-associated neurologic syndrome (ICANS), or severe gastrointestinal (GI) related AEs. All CRS were grade 1 or 2. Only one patient received tocilizumab. No grade 4 AEs were observed except for hematologic toxicities related to conditioning. The first eight patients were evaluable for response by the date of data cut-off: 1 patient achieved a complete response after two CT041 doses (gastric), 2 had partial response (gastric), 2 had stable disease with tumor shrinkage (pancreatic) and 3 (pancreatic) had progression of disease after an initial biochemical response. ORR was 37.5% (3/8) in all patients including 100% (3/3) in the gastric subgroup (all $\geq$ 3 prior lines). The last three patients had not reached the time for response assessment. CAR T cell expansion correlated with ctDNA reduction. The median duration of response and the progression-free survival had not been reached. **Conclusions:** These preliminary results indicate that CT041 therapy was safe and had therapeutic efficacy in patients with advanced GI cancers. In heavily pre-treated gastric cancer, CT041 may have significantly improved anti-tumor activity compared to historical treatment regimens. Clinical trial information: NCT04404595. Research Sponsor: CARsgen.

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2539 **Poster Session**

The addition of fludarabine to cyclophosphamide for lymphodepleting chemotherapy enhances the persistence of infused NY-ESO-1 TCR anticancer therapy TBI-1301.

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Background: Adoptive transfer of T cell receptor (TCR) gene-engineered T cells can induce durable anti-cancer responses. TBI-1301 is a novel gene therapy produced by engineering autologous lymphocytes to express an NY-ESO-1-specific TCR using a retrovirus vector that encodes siRNA to silence endogenous TCR. In this study, we examined a repeat infusion of TBI-1301 and the addition of fludarabine to cyclophosphamide for pre-infusion lymphodepletion. **Methods:** Eligibility included informed consent, HLA-A*02:01 or A*02:06 haplotype, and NY-ESO-1 expression by IHC. Eligible patients underwent harvest of PBMC which were processed at the treating site to generate engineered TBI-1301 cells. The study design infused $5x10^9$ cells on day 0 and day 14 to patients following lymphodepletion with cyclophosphamide (CY; 750 mg/m^2 on day -7 and -6) plus fludarabine (FLU; 30 mg/m^2 on day -7 and -6). Repeat infusions were performed in two cohorts: Cohort B - patients who had previously received NY-ESO-1 TCR-transduced cells and Cohort C - NY-ESO-1 TCR treatment naïve patients. Endpoints included safety, efficacy, and biological correlates for persistence of NY-ESO-1-specific T cells post infusion. **Results:** Ten patients were enrolled in cohorts B and C. Nine patients in total are evaluable for response and toxicity, and no DLTs have been observed. In cohort B, 5 patients (5 synovial sarcoma) were treated, and 5 have received the target dose. In cohort C, 5 patients (3 synovial sarcoma, 2 melanoma) were treated, and 4 have received the target dose. One patient received a single infusion due to bacteremia on week 2. One of 5 patients in cohort B was previously treated with TBI-1301 cells in cohort C. In each cohort, 4 patients experienced grade 1-2 cytokine release syndrome. Best overall response by RECIST v1.1 was 3 stable disease, and 2 progressive disease in cohort B; and 2 stable disease and 2 progressive disease in cohort C. When compared to the earlier cohort, biomarker analysis demonstrated substantially longer persistence of transferred TBI-1301 cells in infused patients who received fludarabine (up to 372+ and 460+ days), and the cells displayed a less differentiated phenotype. **Conclusions:** Repeat infusions of TBI-1301 following lymphodepletion appears to be safe and to possess anti-tumor activity. Addition of FLU to the lymphodepletion regimen may contribute to longer persistence of gene-engineered T cells. Clinical trial information: NCT02869217. Research Sponsor: Takara Bio, Other Foundation.

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2540 **Poster Session**

Predictors of severe CRS in longitudinal CAR T-cell clinical trial data.

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Background: Cytokine release syndrome (CRS) is a life-threatening toxicity of chimeric antigen receptor (CAR) T-cell therapy and there is a limited understanding of its risk factors. Known markers of severe CRS lack specificity or require central lab facilities, making them unsuitable for safety surveillance during trials. Using data from anti-CD19 CAR-T trials from the Medidata Enterprise Data Store (MEDS) we analyzed laboratory tests with repeated measurements to identify differences in trends that persist across a variety of study designs, sponsors and indications. Our aim was to capture the dynamic response to lymphodepletion (LD) and CAR-T infusion events in the time course values of laboratory markers and compare these in the severe CRS (grade 3 and higher) and non severe CRS groups. **Methods:** Subjects in the anti-CD19 CAR-T trials obtained from MEDS had relapsed or refractory disease in one of the following: B Acute Lymphoblastic Leukemia (B-ALL), Mantle Cell Lymphoma (MCL), Non-Hodgkin Lymphoma (NHL) and Diffuse Large B-cell Lymphoma (DLBCL). Laboratory markers with repeated measurements across all studies were included in the analysis. Response to LD, CAR-T infusion and the onset of hematologic recovery was modeled with piecewise linear splines with knots at the boundaries of the pre LD (-18d to LD), the LD - infusion and post infusion (1d to 6d and 6d to 18d) intervals using linear mixed effects regression. **Results:** The dataset consisted of 542 patients: 24.1% B-ALL, 44.4% NHL, 16.8% MCL, 14.6% DLBCL; mean age 54.8 (SE = 0.021) years, 67.7% males. 27.3% had CRS 3+ with a median time-to-event of 4.5 days. Average rates of change (units per day) for the severe CRS subjects in the pre LD, LD-infusion and post infusion intervals relative to the rest are shown (table). None of the markers had a significant relative rate of change prior to LD. The average change in Albumin, Platelets and Hematocrit was consistently lower in severe CRS patients. **Conclusions:** Longitudinal laboratory marker data may be used to derive predictors of severe CRS in patients undergoing anti-CD19 CAR-T therapy. While some of the laboratory markers discussed above corroborate earlier findings, modeling the pre and post infusion kinetics can yield novel markers with improved precision in severe CRS prediction and better patient safety. Research Sponsor: None.

PARAM	Pre LD (-18d - LD)	LD-Infusion (LD - 1d)	Post infusion (1d - 6d)	Post infusion (6d - 18d)
Albumin (g/L)	-14.15	-13.61 (p < 0.001)	-16.83 (p < 0.001)	-14.78 (p < 0.001)
Basophils/Leukocytes (%)	-1.28	-1.26	-1.36 (p = 0.04)	-1.29
Hematocrit (%)	-18.24	-18.97 (p = 0.01)	-18.79 (p = 0.02)	-19.28 (p = 0.005)
Hemoglobin (g/L)	-72.40	-73.71 (p = 0.02)	-73.09	-75.95 (p = 0.006)
Platelets (10^9/L)	-86.09	-83.15 (p = 0.02)	-94.86 (p < 0.001)	-88.07 (p = 0.002)
Leukocytes (10^9/L)	-0.73	-1.38 (p = 0.001)	-0.37	-1.09 (p = 0.03)

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2541 **Poster Session**

STRIvE-01: Phase I study of EGFR806 CAR T-cell immunotherapy for recurrent/refractory solid tumors in children and young adults.

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Background: The epidermal growth factor receptor (EGFR) is a cell surface tyrosine kinase receptor associated with cell proliferation and differentiation. EGFR expression and activating mutations are associated with aggressive neoplastic disease, chemotherapy resistance, and increased metastatic potential. Published data and EGFR immunohistochemistry (IHC) performed on tissue microarrays indicate that 15-40% of pediatric solid tumors (ST) express EGFR. The unique EGFR monoclonal antibody (mAb) 806 selectively binds to an epitope that is conformationally hidden when EGFR is tethered but revealed when tethering is perturbed as occurs with EGFR overexpression, truncation, or through extra-cellular domain missense mutations. **Methods:** Children and young adults (CYA) with EGFR-expressing recurrent/refractory (R/R) ST were enrolled on a Phase 1 trial to examine the safety and feasibility of administering autologous chimeric antigen receptor (CAR) T cells derived from autologous T cells genetically modified to express a second generation EGFR806-specific scFV-IgG4hinge-CD28tm/cyto-4-1-BB-zeta and EGFRt tracking/suicide contract. All subjects received lymphodepleting chemotherapy with fludarabine and cyclophosphamide prior to the administration of cryopreserved CAR T cells a the prescribed dose level. The biologically effective dose (BED) or maximum tolerated dose was determined based upon observed toxicity through day 28 from initial CAR-T infusion and using a 3+3 statistical design. **Results:** Eleven subjects (n=10 evaluable, age range 9-25, median 18) were enrolled and received either dose level (DL) 1 (0.5×10^6 CAR-T/kg, n=4) or DL2 (1×10^6 CAR-T cells/kg, n=7). CAR T were manufactured successfully in all subjects. Most common toxicities were fatigue, tumor-related pain and cytokine release syndrome (n=2, maximum CTCAE grade 1). Dose limiting toxicity of CTCAE grade 4 transaminase level and hyperbilirubinemia occurred at DL2 (n=1). Maximum circulating CAR-T expansion was 29.66 cells/uL (range 0.05-29.66 cells/uL) with median persistence of 28 days (range 0-90). Two subjects on DL1 and one subject on DL2 demonstrated mixed response on day 28 and tolerated additional CAR T infusion without dose limiting toxicity. **Conclusions:** EGFR806 directed CAR-T cells have an acceptable toxicity profile in CYA with R/RST and demonstrate anti-tumor activity in some patients. Additional analyses are ongoing to identify biomarkers of response and toxicity. Clinical trial information: NCT03618381. Research Sponsor: Seattle Children's Therapeutics.

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2542 **Poster Session**

Development of B-cell maturation antigen (BCMA)-specific CD8$^+$ cytotoxic T lymphocytes using induced pluripotent stem cell technology for multiple myeloma.

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Background: A strategy for reversal of T cell exhaustion is reprograming of antigen-specific CTL to early lineage memory T cells with selective anti-tumor activities. To accomplish this goal, we epigenetically reprogrammed BCMA-specific CD8$^+$ CTL to a pluripotent state through key defined transcription factors, established "induced Pluripotent Stem Cells (iPSC)" exhibiting transcriptional and epigenetic features, re-differentiated them back into antigen-specific CTL and evaluated their properties and functional activities against multiple myeloma (MM). **Methods:** Functionally activeIFN-g producing HLA-A2 heteroclitic BCMA$_{72\text{-}80}$ (YLMFLLRKI)-specific CD8$^+$ CTL were applied for iPSC via transduction of four reprogramming factors (OCT3/4, SOX2, KLF4, c-MYC). Upon characterization of the BCMA-specific iPSC with high pluripotency potential, embryoid body was formed from the iPSC and further polarized into mesoderm layer development as evidenced by upregulation of transcriptional regulators (ABCA4, BMP10, CDH5, FOXF1, HAND1, PLVAP, SNAI2, TBX3). Next, BCMA-specific embryoid body-derived hematopoietic progenitor cells (HPC; CD34$^+$ CD43$^+$/CD14$^-$ CD235a$^-$) were sorted and induced to undergo T cell differentiation in the presence of Fc-DLL4 signaling and rectonectin. **Results:** Our RNAseq analyses demonstrated unique transcriptional profiles of HPC from different iPSC clones committing to CD8$^+$ T cells or other cell lineages (monocytes/granulocytes, B lymphocytes/NK cells). Principal component analyses demonstrated a high similarity and low variability of transcription profiles within the replicates of HPC committed to the same cell lineage. In addition, distinct genome-wide shifts and differential gene expression profiles were detected in HPC committed to each specific cell differentiation pathway. Specifically, the HPC commit to CD8$^+$ T cells utilized a diverse repertoire of modulators promoting development of T cell maturation, specific immune response regulation, memory T cells, cytotoxicity and interferon induction, which were significantly higher than shown in HPC that differentiate to other cell lineages. In parallel, specific repression genes were identified in the HPC commit to CD8$^+$ T cells, which develop TGF-β receptor, rearrangement of Ig heavy chain genes and inhibitory receptors. The T cells differentiated were mainly CD45RO$^+$ memory CTL and fully rejuvenated without immune checkpoints expression and regulatory T cells and with high anti-MM activities. **Conclusions:** These findings identify genetic and epigenetic mechanisms and regulatory elements, which play key roles during lineage specific commitment of HPC developed in iPSC into CD8$^+$ CTL and help to further design a next generation of regenerative medicine that provide the appropriate signals for T cell lineage commitment from progenitor cells. Research Sponsor: Donation.

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2543 **Poster Session**

CD19/CD20 bispecific chimeric antigen receptor (CAR) in naïve/memory T cells for the treatment of relapsed or refractory non-Hodgkin lymphoma.

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Background: Although chimeric antigen receptor (CAR)-T cells produce impressive outcomes in B-cell malignancies, a substantial fraction of patients with relapsed/refractory B-cell leukemia and lymphoma treated with anti-CD19 CAR-T cell therapy (CART19) either do not respond to treatment or relapse, with poor CAR-T cell persistence or CD19 antigen escape being two key factors that limit durability of response. In order to address these factors, we initiated a clinical trial with naïve/memory T ($T_{N/MEM}$) cells engineered to express bispecific anti-CD19/CD20 CARs (CART19/20) (NCT04007029). **Methods:** This trial is a Phase 1, first-in-human, dose-escalation trial enrolling patients with relapsed or refractory follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle-cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Following lymphodepletion chemotherapy with fludarabine and cyclophosphamide, patients received CART19/20 cell doses ranging from 50 x 10^6 to 200 x 10^6 CAR-positive cells. The primary endpoint was to evaluate the safety of CART19/20 as measured by adverse events and dose limiting toxicities. Secondary endpoints were efficacy as assessed by disease response, progression-free survival (PFS), overall survival (OS), and CAR transgene persistence. **Results:** As of February 7, 2022, dose-escalation has been completed with 9 patients enrolled and 8 patients infused (3 FL, 4 DLBCL including 2 transformed follicular and 1 primary mediastinal B cell, and 1 MCL). with CART19/20 cells on this study. The median age at the time of CART19/20 infusion was 59 and median prior lines of therapy was 3.5. All patients had stage IV disease and 7 of 9 patients required bridging therapy. Grade-1 cytokine release syndrome (CRS) occurred in 6 of 8 patients, and no patient experienced immune effector cell-associated neurotoxicity syndrome (*ICANS*). Among all patients, only one dose of tocilizumab was administered to one subject, and no steroids were given. With a median follow-up of 12 months from time of CART19/20 infusion (range: 4+ to 24+ months), 7 of 8 of patients remain in a complete remission. Median PFS and OS were not reached, and all patients with a complete remission demonstrate ongoing B-cell aplasia. **Conclusions:** This study demonstrates that CART19/20 cells are safe and effective in patients with relapsed/refractory NHL and potentially obviates the challenges of the commonest causes of relapse after CAR-T cell therapy by means of modifying $T_{N/MEM}$ cells and dual-antigen targeting, respectively. Given the strong safety and response observed, dose escalation was completed with the second dosing level (DL2) of 200 x 10^6 CAR-positive cells, and DL1 of 50 x 10^6 CAR-positive cells was chosen as the therapeutic dose for future trial expansion. Clinical trial information: NCT04007029. Research Sponsor: Parker Institute for Cancer Immunotherapy, The Kaplan Family Foundation, UCLA.

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Changes in circulating tumor DNA (ctDNA) and outcomes in solid tumors treated with immune checkpoint inhibitors (ICIs).

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Background: Quantification of ctDNA levels can be a reliable prognostic tool in several malignancies. More recently, detection of genomic alterations in ctDNA have been validated as a predictive biomarker to guide treatment planning. Dynamic changes in ctDNA levels over time and in response to treatment may also provide prognostic information. However, less is known about the value of changes to ctDNA levels in response to immune checkpoint inhibitors (ICIs). **Methods:** We searched MEDLINE (host:PubMed) and reviewed trials exploring outcomes of patients with advanced solid tumors receiving ICIs in which outcomes were reported based on changes to ctDNA levels. ctDNA clearance was defined as reported in individual trials. Typically, this was defined as either >50% reduction or a reduction to undetectable levels. We extracted progression free survival (PFS) and/or overall survival (OS) values, related 95% Confidence intervals (CI) and/or p-values. Data were then included in a meta-analysis utilizing the generic inverse variance and random effects model. Variation in effect size was examined using random effects meta-regression analysis. **Results:** A total of 17 trials were included in the meta-analysis; ctDNA levels were detectable in all participants in all studies prior to initiation of ICIs. Method of detection included next generation sequencing and/or droplet digital polymerase chain reaction assays. Overall, low to undetectable ctDNA levels, measured 6-16 weeks after starting treatment was associated with significantly better PFS, (HR 0.20 95% CI, 0.14-0.28; p<0.001). Similarly, OS was superior in patients with substantially reduced or undetectable ctDNA levels after receiving ICIs, (HR 0.18, 95% CI, 0.12-0.26; p<0.001. The results were consistent across all disease sites, lines of treatment, level of change (undetectable vs. >50% reduction) and whether treatment exposure comprised single or multiple ICIs (see Table). **Conclusions:** In unselected advanced solid tumors, a substantial fall in ctDNA levels in response to ICIs is associated with substantial improvements in both PFS and OS. ctDNA change is an early response biomarker which may allow for de-escalation of cross-sectional imaging in patients receiving ICIs, or support treatment de-escalation strategies. Further research is needed to quantify variations in sensitivity between the available NGS assays, as well as differences discovery range between assay platforms. Research Sponsor: None.

Subgroups/outcome	Hazard Ratio	95% CI	Subgroup difference P
All patients (overall survival)	0.18	0.12-0.26	NA
Disease site			
Melanoma	0.20	0.12-0.33	0.27
Lung	0.16	0.08-0.31	
Others	0.05	0.01-0.26	
Treatment			
Single agent	0.14	0.07-0.31	0.45
Multiple/mixed	0.20	0.12-0.32	
Treatment line			
First line	0.22	0.13-0.36	0.31
Second or later line	0.14	0.07-0.28	
Level of ctDNA change			
>= 50% reduction	0.17	0.05-0.62	0.93
Undetectable levels	0.18	0.12-0.27	

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2545 **Poster Session**

Baseline peripheral T-cell composition in relation to radiographic phenotypes of immune-related pneumonitis.

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Background: Pneumonitis is one of the most morbid complications from immune checkpoint inhibitor (ICI) treatment, but pathogenic mechanisms are unclear and no biomarkers permit pre-treatment risk assessment. We sought to characterize peripheral T cell subsets of pneumonitis patients on the single cell level. **Methods:** Blood was collected before and during ICI treatment in 24 patients. Cells were processed for single cell RNA sequencing (scRNAseq) employing CITEseq methodology using multiplexed cell surface markers labelled with a cocktail of oligonucleotide-tagged Total-Seq anti-human antibodies against CD4, CD8, CD45RA and CD27 followed by Chromium 10X sequencing. Principal Component Analysis was performed with iCellR, K-nearest-neighbor-based Network graph drawing Layout, and PhenoGraph clustering to assign cell types. CT scans were performed per standard of care and were reviewed by an experienced thoracic radiologist. **Results:** Seven of 24 patients developed pneumonitis; 9 did not experience an immune-related adverse event, and the remainder experienced arthritis (4), thyroiditis (3), or neurotoxicity (1). Pneumonitis patients had expanded proportions of TH2 $TCF7^+$ T cells at baseline as compared to the other patients. Radiographically, two patients' pneumonitis manifested as Chronic Hypersensitivity Pneumonitis (CHP), and four had Organized Pneumonia (OP). At baseline, CHP patients had significantly lower levels of $CD8^+$ TCM cells (CXCR3+), double-positive T cells, gamma-delta T cells, and higher levels of naïve-like $CD4^+$ TN $TCF7^+LEF1^+$ and $CD4^+$ TH1/2 $CXCR3^+GATA3^+$ cells compared to OP. Gene expression levels also distinguished between these radiographic phenotypes. **Conclusions:** The peripheral T cell composition of patients who developed pneumonitis was distinct from those who did not in our cohort and unique by radiographic manifestation, suggesting potential pathogenic mechanisms and a prelude to circulating predictive markers of ICI toxicity. Research Sponsor: U.S. National Institutes of Health.

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2546 **Poster Session**

Early circulating tumor DNA (ctDNA) kinetics using a tumor-naïve assay as a predictive biomarker in early-phase immunotherapy (IO) clinical trials.

Enrique Sanz Garcia, Sofia Genta, Xiaoxi Chen, Qiuxiang Ou, Daniel Vilarim Araujo, Albiruni Ryan Abdul Razak, Aaron Richard Hansen, Anna Spreafico, Hua Bao, Xue Wu, Lillian L. Siu, Philippe L. Bedard; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Nanjing Geneseeq Technology Inc., Nanjing, China; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China; Princess Margaret Cancer Centre, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Geneseeq Technology Inc., Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada

Background: ctDNA kinetics with tumor-informed assays can predict treatment outcome in patients (pts) treated with anti-PD1 IO (*Bratman et al*, Nature Cancer 2020). We evaluated whether early ctDNA kinetics with a tumor-naïve assay were associated with clinical outcomes in advanced solid tumor patients treated on early phase IO trials. **Methods:** Advanced solid tumor pts treated with investigational IO agents at the Princess Margaret Phase I program were enrolled. Baseline (B) and pre-cycle 2 (C2) (3-4 weeks after first dose) plasma samples were prospectively collected via an institutional liquid biopsy program (LIBERATE, NCT03702309). ctDNA was assessed using the tumor-naïve 425-gene Geneseeq Prime panel in a clinical laboratory. Mutations in each gene detected in ctDNA were measured as Variant Allele Fraction (VAF). Mean VAF from all mutations was calculated. Radiological response was measured per RECIST criteria and correlated using ROC curves. Hyperprogression (HPD) was defined using VHIO criteria (*Matos et al*, CCR 2020). Survival outcomes were estimated using the Kaplan Meier method. **Results:** From 12/2017 to 3/2020, 162 plasma samples from 81 pts with 25 different tumor types were collected. Pts were treated within 25 different IO phase I/II trials, 72% of which involved a PD-1/PD-L1 inhibitor. Median age was 58y (range 21 – 79), 54% female, 76% ECOG1. Sarcoma and colorectal (11%, each) followed by breast (8%) and melanoma (7%) were the most frequent tumors. Median follow up was 10.3 months (m) (1.8-46.9). CR 4% (n = 3), PR 6% (n = 5), HPD 11% (n = 9). Clinical benefit (CB) rate (CR+PR+SD > 6 months) was 20% (n = 16). ctDNA was detected in 122/162 samples (75.3%) (60 at B, 62 at C2). The most frequent mutations were *TP53* (32%), *PI3KCA* (12%), *PKHD1* (11%), and *KRAS* (9%). Mean VAF at B below median was not associated with OS (HR = 0.68 95%CI 0.4-1.16; p = 0.16) or PFS (HR = 0.93 95%CI 0.56-1.54; p = 0.77). Mean VAF change (difference between mean VAF at B and at C2) was associated with response (AUC = 0.99) and CB (AUC = 0.86). A decrease in mean VAF from B to C2 was seen in 24 pts (37.5%) and was associated with longer PFS (median PFS 2.7 vs 1.8 m; HR: 0.43, 95%CI 0.24-0.77; p < 0.01) and OS (median OS 10.8 vs 9.1 m; HR: 0.54; 95%CI 0.3-0.96; p = 0.03) compared to an increase in mean VAF. These differences were more marked if there was > 50% decrease in mean VAF from B to C2 (n = 11, 17%) compared to decrease < 50% or increase: median PFS 3.6 vs 1.8 m (HR: 0.29, 95%CI 0.13-0.62; p < 0.01) and median OS not reached vs 9.6 m (HR: 0.23, 95%CI 0.09-0.6; p < 0.01). No differences in mean VAF change were seen between HPD and PD pts. **Conclusions:** In a pan-cancer solid tumor early phase trial IO cohort, a decrease in ctDNA within 4 weeks of treatment was associated with increased CB, OS and PFS. HPD pts did not show greater increases in ctDNA. Tumor-naïve ctDNA assays may be useful to identify early treatment benefit in phase I/II trials with IO. Research Sponsor: Princess Margaret Cancer Centre, Pharmaceutical/Biotech Company.

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2547 **Poster Session**

Pharmacogenomic prediction of immune-related adverse events from immune checkpoint inhibitors among Asian patients.

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Background: Immune checkpoint inhibitors (ICIs) have ushered in a unique entity known as immune-related adverse events (IrAEs) that can be debilitating and challenging for physicians. Given that genomic variation underlies both disease susceptibility and drug response, there is reasonable cause to believe that genomic markers are predictive of IrAEs. We perform a pioneering pharmacogenomic study to uncover genomic biomarkers associated with IrAEs from ICIs. **Methods:** Since March 2018, we recruited cancer patients treated with ICIs from the National University Cancer Institute Singapore and Tan Tock Seng Hospital. IrAEs were clinical characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5. DNA was extracted and genotyped by Infinium Global Screening Array (700K markers). Statistical analyses were performed using SVS/HelixTree. Genetic association was performed by logistic regression. Bonferroni corrected $P <$ 7.1E-08 was considered statistically significant. **Results:** We conducted a pilot pharmacogenomic genome-wide association study (GWAS) on 307 patients of Asian Ancestry. Median age was 62. Majority were male (68.1%), Chinese (75.9%), ECOG PS 0-1 (91.6%), stage IV cancer at diagnosis (64.6%). Non-small cell lung cancer (36.2%), renal cell carcinoma (12.4%) and hepatocellular carcinoma (7.2%) were the three most common cancers. Top four ICIs used were pembrolizumab, nivolumab, atezolizumab and durvalumab, respectively (44.6%, 26.1%, 10.1% and 10.1% respectively). Nine percent of patients received dual ICIs concurrently. Median duration of treatment was 152 days and median follow up was 212 days. IrAEs were seen in 50.5% of patients. Skin (21.8%), endocrine (6.8%) and hepatotoxicity (5.9%) were the most common IrAEs. Eight percent of patients had CTCAEv5 grade $\geq$3 toxicity, of which hepatotoxicity (2.6%), skin (1.6%) and pulmonary toxicities (1.3%) were the most common. A preliminary pharmacogenomic investigation revealed one potential novel genetic locus associated with IrAEs: *LOC105373202* rs5915369; Unadjusted P= 6.6E-08, OR (95%CI) = 27.8 (3.7-206.5), minor allele = A, 10.7% in cases vs 0.4% in controls. We also identified an additional 3 independent SNPs (rs167609, rs2341687, *DMD*rs5928214) with nominal significance (7.1E-0-8$\leq P <$ 5.0E-7). **Conclusions:** This pilot pharmacogenomics GWAS uncovered 4 potential novel genetic loci predictive of IrAEs from ICIs amongst Asian patients. Further pharmacogenomic discovery/replication and functional validation studies are currently on-ongoing to identify specific genomic biomarkers that predispose individual patients to IrAEs. Research Sponsor: National Research Foundation, Singapore and National Medical Research Council (NMRC), Singapore under its NMRC Centre Grant Programme (NMRC/CG/M005/2017_NCIS).

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2548 **Poster Session**

Circulating *KRAS* variant-specific shedding and association with survival in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving chemoimmunotherapy.

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Background: Circulating tumor DNA (ctDNA) is increasingly used as a prognostic marker with high ctDNA shedding associated with poor survival. Gene-, but not variant-specific, differences in ctDNA shedding have been reported. Tumor burden, mitotic rate, and cell death rate have been proposed as contributors to ctDNA shedding. Here we investigate associations of ctDNA shedding for the two most common mPDAC *KRAS* variants, G12D and G12V, with tumor burden, mitotic score, and overall survival (OS). **Methods:** Pretreatment (baseline) ctDNA was analyzed by droplet digital PCR for 86 (including 44 G12D, 30 G12V) patients with mPDAC receiving front-line chemoimmunotherapy in a randomized open-label Phase II study (NCT03214250). Baseline tumor burden in total, within the pancreas, and distally, was assessed by sum of RECIST target lesion diameters. Tumor tissue variant allele fraction (tVAF) and mitotic score (geometric mean expression of 65 mitosis-associated genes) were calculated from DNA and RNA sequencing. **Results:** ctKRAS shedding (dichotomized at median mutant copies/mL) was associated with OS for G12D bearing tumors ($p = 0.03$) but not G12V ($p = 0.17$, log-rank test). To identify variant-specific features of shedding, we examined the Spearman correlation for total tumor burden and ctKRAS shedding; G12D but not G12V shedding was correlated with tumor burden ($p = 0.01$ and $p = 0.22$ respectively). However, the higher tVAF in G12V compared to G12D tumors ($p = 0.048$, Mann-Whitney test) could result from differences in purity, ploidy, and *KRAS* copy number. Thus, we used tVAF as a scalar to calculate an adjusted tumor burden which was significantly correlated with both G12D and G12V ctDNA shedding ($p = 0.004$ and 0.02, respectively). When a patient's distal vs. pancreatic lesions were analyzed separately, pancreatic tumor burden was not correlated with G12D or G12V shedding ($p = 0.10$ and 0.33, respectively) but distal burden was correlated with both ($p = 0.001$ and 0.02, respectively). While there was no difference by *KRAS* variant for the correlation between adjusted tumor burden and shedding, these results do suggest that, in patients with mPDAC, distal rather than primary tumor burden may drive ctDNA shedding. Finally, tumor mitotic rate was combined with adjusted total tumor burden in a linear regression model; both were significant for predicting G12D shedding ($p = 0.007$ and $p < 0.0001$, respectively) but not for G12V ($p = 0.045$ and $p = 0.16$, respectively). **Conclusions:** These data suggest that ctDNA shedding and survival associations may be *KRAS* variant-specific in mPDAC. Tumor mitotic score and location of tumors may explain some variant-specific differences in shedding. As clinical ctDNA tests become more widely used, further investigation of variant-specific shedding in *KRAS* and other genes may be key for proper interpretation of ctDNA tests. Research Sponsor: Parker Institute for Cancer Immunotherapy, Other Foundation, Pharmaceutical/Biotech Company.

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2549 **Poster Session**

Circulating cytokines as predictors of response to immune checkpoint inhibitors (ICIs) in patients (pts) with melanoma (Mel) and non–small cell lung cancer (NSCLC).

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Background: ICIs lead to durable response and a significant survival improvement in a limited number of advanced stage Mel and NSCLC pts. The identification of predictive circulating biomarkers could be a promising tool to optimize pts' selection and outcome for ICIs treatment. **Methods:** This is a prospective real-world study enrolling advanced stage Mel and NSCLC pts referred to four Italian Centers and treated with ICIs. The primary endpoint is to verify the presence of an association between circulating cytokines (IL-1b, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNFα, GM-CSF) and disease control rate (DCR), progression free survival (PFS) and overall survival (OS). Pts undergo a blood collection, before every cycle for 6 cycles (T1-T6) and at tumor assessment till disease progression (PD) or for 2 years. Biomarker levels were assessed by Luminex xMAP based technology using R&D High Sensitivity kits. Each marker was categorized according to high and low levels by maximizing its discriminative ability, and the association with the outcome was tested in univariate and multiple analyses. **Results:** We report preliminary results on the T1-T2 blood samples from the first 78 enrolled pts (32 females/46 males; 43 Mel/35 NSCLC; median age 69 years). Serum IL-6, IL-8 and IL-10 were significantly higher at T1 and T2 in pts with PD (Kruskal-Wallis test). The median relative increase (RI) of IL-8 was 32% and 2% in pts with PD and disease control (DC), respectively (p = 0.0001). At multiple logistic analysis, IL-6 and IL-8 at T2 and the RI of IL-8 were independent factors predicting the probability of DC, with an overall accuracy of 83.8%. High levels of IL-6 and IL-8 at T2 were significantly associated with a low probability of DC (OR = 0.13, 95%CI: 0.03-0.52 and OR = 0.09, 95%CI: 0.02-0.37, respectively), and the RI showed a significantly lower probability of DC (OR = 0.14, 95%CI: 0.02-0.58). With a median follow-up of 10.6 months (m), mPFS and mOS were 5.8 m, 95%CI: 2.3-7.4 and 8.3 m, 95%CI: 4.0-13.8 for NSCLC; 6.9 m, 95%CI: 2.8-15.9 and 12.6 m, 95%CI: 4.7-NE for Mel pts, respectively. In the multiple Cox model, elevated IL-6 and IL-8 at T1 (HR = 3.03, 95%CI: 1.55-6.37, HR = 2.86, 95%CI: 1.46-5.63), elevated IL-10 at T2 (HR = 2.86, 95%CI: 1.39-5.94), and a RI of IL-8 (HR = 4.22, 95%CI: 1.85-11.21) remained significantly associated with a worse PFS. Higher levels of IL-6 (HR = 3.85, 95%CI: 1.13-20.0) and IL-8 (HR = 4.29, 95%CI: 1.98-9.83) at T2 and a RI of IL-8 (HR = 3.06, 95%CI: 1.43-6.72) remained significantly associated with a worse OS. **Conclusions:** High serum levels of IL-8 and IL-6 at T2 of ICI, combined with an increase of IL-8 from baseline, are strong predictors of PD, PFS, OS, in pts with advanced Mel and NSCLC. The role of the other cytokines tested, their time fluctuations and associations with clinical prognostic factors, gender, and immuno-related adverse events will be presented at the meeting. Research Sponsor: RF-2018-12367604 MoH; 2018 5x1000 Istituto Oncologico Veneto.

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2550 **Poster Session**

Methylated circulating tumor DNA (cfMeDIP) as a predictive biomarker of clinical outcome in pan-cancer patients (pts) treated with pembrolizumab (P).

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Background: Bespoke mutation-based circulating tumor DNA (ctDNA) predicts response to P but relies on availability of tumor tissue and presence of mutations. Cell-free methylated immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) may overcome these limitations and be applied to more pts. **Methods:** Pts with mixed solid tumors divided into 5 cohorts received P 200 mg Q3wks in the investigator-initiated INSPIRE trial (NCT02644369). cfMeDIP-seq was performed at baseline (B), pre cycle 3 (C3) and later cycles. Methylation probability was inferred from read depths in 300 bp bins. cfMeDIP score was the probability-weighted sum of 3270 pan-cancer differentially-methylated regions in the TCGA PanCanAtlas. ctDNA concentration was assayed using tissue-informed bespoke targeted NGS (Signatera). ΔctDNA and ΔcfMeDIP denote the change in ctDNA or cfMeDIP between B and C3, respectively. Association with OS or PFS was assessed using Cox proportional hazards model, adjusting for cohort (aHR). Multivariable analysis (MVA) also included tumor mutation burden and PD-L1 status. **Results:** 194 plasma samples from 87 pts were analysed with cfMeDIP-seq (84 at B, 55 at C3, 55 at later cycles). Demographics: male 33%; median age = 61 yrs (34–82); Cohorts: triple negative breast (26%), ovarian (25%), head & neck (21%), melanoma (12%), others (15%). Median follow-up = 10.6m (0.6–64.4); Median PFS = 1.9m; Median OS = 10.6m. cfMeDIP at B below median was associated with better OS (aHR = 0.51, 95%CI 0.29-0.91; p = 0.02) in MVA. ΔcfMeDIP was evaluable in 53 pts; any decrease in ΔcfMeDIP was predictive for OS (aHR = 0.36, 95%CI 0.18-0.72; p < 0.01) and PFS (aHR = 0.42, 95%CI 0.22-0.82; p = 0.01). Both ΔctDNA and ΔcfMeDIP were evaluable in 51 pts; decrease in ΔctDNA and ΔcfMeDIP predicted for longer OS (aHR = 0.45, 95%CI 0.23-0.86; p = 0.02 vs aHR = 0.39, 95%CI 0.19-0.80; p = 0.01); and PFS (aHR = 0.44, 95%CI 0.23-0.83; p = 0.01 vs aHR = 0.5, 95%CI 0.25-0.99; p = 0.04), respectively. When both ΔctDNA and ΔcfMeDIP are integrated in MVA, ΔcfMeDIP was predictive for OS (aHR = 0.48, 95%CI 0.23-1; p = 0.05). A decrease in ΔcfMeDIP and/or ΔctDNA was associated with longer OS (aHR = 0.2, 95%CI 0.09-0.45) and PFS (aHR = 0.27, 95%CI 0.13-0.58) compared to an increase in both assays (p < 0.01) (Table). **Conclusions:** We applied for the first time cfMeDIP-seq and mutation-based ctDNA analysis concurrently in pan-cancer pts treated with checkpoint blockade. ΔcfMeDIP correlated strongly with OS and PFS, representing a promising plasma-based predictive epigenetic biomarker in pts treated with P. ΔctDNA and ΔcfMeDIP can complement each other to predict outcomes, demonstrating that they may capture different biological changes. Clinical trial information: NCT02644369. Research Sponsor: BMO Chair in precision cancer genomics, Pharmaceutical/Biotech Company.

Group	OS-12m (%) (95%CI)
↓ΔctDNA ↓ΔcfMeDIP (n = 16)	87.5 (72.7-100)
↓ΔctDNA ↑ΔcfMeDIP (n = 10)	70 (46.6-100)
↑ΔctDNA ↓ΔcfMeDIP (n = 8)	62.5 (36.5-100)
↑ΔctDNA ↑ΔcfMeDIP (n = 17)	29.4 (14.1-61.4)

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2551 **Poster Session**

The FLARE score, circulating neutrophils, and association with COVID-19 outcomes in patients with solid tumors.

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Background: Inflammation and neutrophils play a central role in severe Covid-19 disease. In previous data, we showed that the FLARE score, combining both tumor and Covid-19-induced proinflammatory status (proinflam-status), predicts early mortality in cancer patients (pts) with Covid-19 infection. We aimed to assess the impact of this score in a larger cohort and characterize the immunophenotype (IF) of circulating neutrophils. **Methods:** Multicenter retrospective cohort (RC) of pts with cancer and Covid-19 infection across 14 international centers. Circulating inflammatory markers were collected at two timepoints: baseline (-15 to -45d before Covid-19 diagnosis) and Covid-19 diagnosis. Tumor-induced proinflam-status was defined by high dNLR (neutrophils/(leucocytes-neutrophils)>3) at baseline. Covid-19-induced proinflam-status was defined by +100% increase of dNLR between both timepoints. We built the FLARE score combining both Tumor and Infection-induced inflammation: T+/I+ (poor), if both proinflam-status; T+/I- (T-only), if inflammation only due to tumor; T-/I+ (I-only), if inflammation only due to Covid; T-/I- (favorable), if no proinflam-status. The IF of circulating neutrophils by flow cytometry was determined in a unicenter prospective cohort (PC) of pts with cancer during Covid-19 infection and in healthy volunteers (HV). Primary endpoint was 30-day mortality. **Results:** 524 pts were enrolled in the RC with a median follow-up of 84d (95%CI 78-90). Median age was 69 (range 35-98), 52% were male and 78% had baseline PS <1.Thoracic cancers were the most common (26%). 70% had active disease, 51% advanced stage and 57% were under systemic therapy. dNLR was high in 25% at baseline *vs* 55% at Covid-19 diagnosis. The median dNLR increase between both timepoints was +70% (IQR: 0-349%); 42% had +100% increase of dNLR. Pts distribution and mortality across FLARE groups is resumed in the Table. Overall mortality rate was 26%. In multivariate analysis, including gender, stage and PS, the FLARE poor group was independently associated with 30-day mortality [OR 5.27; 1.37-20.3]. 44 pts were enrolled in the PC. Median circulating neutrophils were higher in pts with cancer (n=10, 56.7% [IQR: 39-78.4%]) vs HV (n=6, 35.8% [IQR: 25.6-21%]), and particularly higher in pts with cancer and severe Covid-19 infection (n=7, 88.6% [IQR: 80.9-94%] (p=0.003). A more comprehensive characterization of the IF of circulating neutrophils, including Lox1/CD62/CD64, will be presented at ASCO. **Conclusions**: The FLARE score, combining tumor and Covid-19-induced proinflam-status, can identify the population at higher risk for mortality. A better characterization of circulating neutrophils may help improve the prediction of Covid-19 outcomes in pts with cancer. Research Sponsor: AMGEN.

	Distribution	30d mortality	
FLARE T+/I+	5% (n=19)	68%	p=0.001
FLARE T+/I-	20% (n=74)	39%	
FLARE T-/I+	37% (n=136)	33%	
FLARE T-/I-	38% (n=140)	3%	

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2552 **Poster Session**

NK cell activity and methylated HOXA9 circulating tumor DNA as prognostic biomarkers in patients with non-small cell lung cancer treated with PD-1/PD-L1 inhibitors.

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Background: PD-1/PD-L1 inhibitors have improved survival for patients with non-small cell lung cancer (NSCLC), but better prognostic biomarkers are needed. **Methods:** We prospectively collected plasma from 82 patients with NSCLC before initiating treatment with PD-1/PD-L1 inhibitors and before treatment cycles 2-4. We used the NK Vue assay to measure interferon gamma (IFNγ) as a surrogate for natural killer cell activity (NKA) with a cutoff of 250 pg/mL. Circulating tumor DNA (ctDNA) in the form of methylated HOXA9 was measured by droplet digital PCR. ctDNA status was classified as detectable or undetectable ctDNA. **Results:** Patients were classified into three groups according to IFNγ levels at the available time points. The NKA-low group had a persistently low level of IFNγ or dropped to and remained at a low level after baseline (<250 pg/mL, n=29), the NKA-mixed group experienced either an increase from low to normal levels or vice versa (n=34), while the NKA-high group maintained a normal level of IFNγ (≥250 pg/mL, n=13). The median PFS was 64 days (95% confidence interval (CI) 48-115 days), 228 days (95% CI 146-353 days), and 214 days (95% CI 101-693 days), respectively, for NKA-low, NKA-mixed, and NKA-high (p=0.003). The median OS was 170 days (95% CI 110-285 days), 487 days (95% CI 361-761 days), and 1,131 days (95% CI 235 days to not reached), respectively (p<0.001). Patients were divided according to detectable (ctDNA+, n=41) or undetectable (ctDNA-, n=32) ctDNA after one treatment cycle. Median PFS was 97 days (95% CI 58-192 days) and 228 days (95% CI 146-353 days), respectively, for ctDNA+ and ctDNA- (p=0.018). Median OS was 235 days (95% CI 170-525 days) and 544 days (95% CI 361-1158 days), respectively (p=0.007). A score combining NKA and ctDNA both measured after the first treatment cycle had a strong prognostic impact. Group 1 had a low level of IFNγ (<250 pg/mL) and detectable ctDNA (n=27), group 2 had either low levels of IFNγ and undetectable ctDNA or vice versa (n=29), and group 3 had normal levels of IFNγ (≥250 pg/mL) and undetectable ctDNA (n=15). Median PFS was 69 days (95% CI 48-213 days), 183 days (95% CI 102-235 days), and 307 days (95% CI 140-693 days), respectively, for group 1, 2, and 3 (p=0.022). Median OS was 221 days (95% CI 121-539 days), 419 days (95% CI 235-650 days), and 1,158 days (95% CI 250 days to not reached), respectively (p=0.002). Biomarker score 1 was a marker of poor prognosis for OS with a hazard ratio (HR) of 3.971 (95% CI 1.763-8.943, p=0.001) compared to biomarker score 3. It remained statistically significant with a HR of 5.560 (95% CI 2.359-13.101, n=71, p<0.001) when adjusting for PD-L1 status, histology, and performance status. **Conclusions:** A biomarker score combining the levels of NKA and ctDNA status after the first cycle of treatment may be used to stratify the prognosis in patients with NSCLC treated with PD-1/PD-L1 inhibitors. Research Sponsor: Dansk Kræftforskningsfond / Danish Cancer Research Fund, Other Foundation, Pharmaceutical/Biotech Company, Grants within the Department of Oncology, Vejle Hospital.

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2553 **Poster Session**

Network analysis to determine association between immuno-related toxicities and immune soluble profile in patients treated with anti–PD-1.

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Background: Immune checkpoint inhibitors (ICIs) have peculiar, immune-related adverse events (irAEs), as a consequence of interfering with self-tolerance mechanisms. The incidence of irAEs varies by ICI class, administered dose and treatment schedule. The aim of the study was to define a baseline (T0) immune profile (IP) predictive of irAE development. **Methods:** A prospective, multicenter study evaluating the IP of 79 patients with advanced cancer, treated with anti-PD-1drugs as a first- or second-line setting was performed. The results were then correlated with irAEs onset. The IP was studied by means of multiplex assay, evaluating circulating concentration of 12 cytokines, 5 chemokines, 13 soluble immune checkpoints and 3 adhesion molecules. IDO levels were evaluated through a modified liquid chromatography–tandem mass spectrometry. Data were first pre-processed by performing logarithmic transformation and Shapiro-Wilk-test. A connectivity heatmap was obtained by calculating Spearman correlation coefficients. Two different networks of connectivity were constructed, based on the toxicity profile. **Results:** Toxicity was predominantly of low/moderate grade. High-grade irAEs were relatively rare, while cumulative toxicity was high (23%). A positive and statistically significant correlation between the cumulative toxicity and IP10 and IL8, sLAG3, sPDL-2 sHEVM, sCD137, sCD27 and sICAM1 was found. Moreover, patients who experienced irAEs had a markedly different connectivity pattern characterized by disruption of most of the paired connections between cytokines (all the connections of the cytokine IL8, most of the connections between the pro-inflammatory chemokines, or all the connections of CD137, CD27, and CD28), while sPDL-2 pair-wise connectivity values seemed to be intensified. Network connectivity analysis identified a total of 187 statistically significant interactions in patients without toxicity and a total of 126 interactions in patients with toxicity. Ninety-eight interactions were common to both networks, while 29 were specifically observed in patients with toxicity. **Conclusions:** A peculiar pattern of immune dysregulation in patients who develop irAEs was defined. This immune serological profile could lead to the design of a personalized therapeutic strategy in order to prevent, monitor and treat irAEs at an early stage. Research Sponsor: None.

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2554 **Poster Session**

Auto-reactive antibodies as predictive markers for immune checkpoint–induced pneumonitis.

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Background: Certain immune-related adverse events (irAEs) that emerge with immune checkpoint blockade share clinical features of autoimmune conditions. Preexisting auto-reactive antibodies and their contribution to irAEs have not been well defined, and observations are limited. **Methods:** We longitudinally collected patient plasma samples from a clinical trial that combines immune checkpoint inhibitors, Ipilimumab, and Nivolumab (I+N) with subsequent radiation therapy (Lonestar, NCT03391869). Plasma samples were collected at baseline, after 12 weeks of I+N (induction), and at the time of Grade $\geq$ 2 pneumonitis (CTCAEv5.0). Auto reactive antibody profiles were analyzed using a fluorescence-based assay system that measures more than 130 antigens and is capable of assaying antibody reactivity for IgG and IgM fractions, including nuclear-cytosolic and tissue-specific antigens. Selected antibodies had a reportable result range, reference intervals, and reproducibility with quality controls. A paired t-test was used to compare the mean of longitudinally collected baseline and toxicity samples. An unpaired t-test was used to compare differences between groups. The False Discovery Rate was used to control the Type I error rate of multiple comparisons. **Results:** In the study cohort, G$\geq$2 pneumonitis was observed in 11 patients out of 194 (5.6%). Serum was collected at baseline for all 11 patients, and 9 of the 11 patients had a serum sample collected at the time of pneumonitis event. Longitudinal serum samples (baseline and post-induction) collected from 32 patients without any irAEs were used as control. At baseline AChR3 and calmodulin antibodies were elevated in patients who developed pneumonitis, compared with baseline samples from controls ($p \leq 0.05$). At the time of pneumonitis IgM antibodies against AChR3, CXCL10, NSE, BAFF, CA242, Cytokeratin 19 were noted to be elevated in serum for pneumonitis cases compared with post induction samples from control ($p \leq 0.005$). **Conclusions:** We identified auto reactive antibodies associated with a higher risk of immunotherapy associated pneumonitis in patients treated with ipilimumab and nivolumab. These included auto reactive antibodies against proteins associated with lung injury (AChR3), lung inflammation (BAFF, CXCL10) and against alveolar epithelium (Cytokeratin 19). Future studies are warranted to determine if auto-reactive antibodies can be used as pre-treatment risk markers or to diagnose pneumonitis and may offer insights into to mechanisms that predispose toward pneumonitis. Research Sponsor: LUNGevity foundation.

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2555 **Poster Session**

Comprehensive transcriptomic analysis of immune checkpoint markers in a pancancer cohort: Implications for response and resistance.

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Background: Although immune checkpoint blockade (ICB) has revolutionized cancer treatment, not all patients with cancer benefit from ICB. One possible explanation for poor responders/resistance is the variable expression level of the target molecules (e.g., PD-1 and PD-L1) in the tumor microenvironment. There are recent or ongoing trials targeting variable pathways for immune evasion (e.g., LAG3 or IDO1). It is therefore of interest to know the expression levels related to variable immune checkpoints so that clinical trials can focus on the patients who can benefit from the cognate treatment. **Methods:** Overall, 514 patients with various solid tumors seen at the University of San Diego, Moores Center for Personalized Cancer Therapy were analyzed. The expression levels of checkpoint markers (ADORA2A, BTLA, CD276, CTLA4, IDO1, IDO2, LAG3, NOS2, PD-1, PD-L1, PD-L2, PVR, TIGIT, TIM3, VISTA, and VTCN) in the tumor samples were measured through RNA sequencing and normalized to internal housekeeping gene profiles, and ranked from 0 to 100 percentile based on a reference population. The expressions of each checkpoint marker were correlated with cancer types, microsatellite instability (MSI), tumor mutational burden (TMB), and programmed death-ligand 1 (PD-L1) status on immunohistochemistry. **Results:** In this cohort, 60% were female, median age of 60, and included 30 different tumor types, with colorectal cancer being the most common (27%). The rank values of all checkpoint markers were distributed broadly from 0 to 99 or 100. CD276 and NOS2 had the highest (68^{th} percentile) and lowest (13.5 percentile) median rank values, respectively. When rank values were categorized to “Low” (0-24), “Intermediate” (25-74), and “High” (75-100), 41.6% of patients showed high expression of CD276 while only 13% showed high expression of PD-L1. Each patient had a distinctive protfolio of the categorical expression levels of 16 checkpoint markers. Several checkpoint markers, especially NOS2, showed a significant correlation with cancer type. (median rank values in colorectal, stomach, pancreatic, and breast cancer were 79, 76, 5 and 0 respectively, $p < 0.001$) Five markers (IDO1, LAG3, PD-1, PD-L1, and TIGIT) showed significant correlation with MSI, while seven markers (CTLA4, IDO1, LAG3, PD-1, PD-L1, PD-L2, and TIGIT) were significantly associated with positive PD-L1 status. However, no significant association was seen based on TMB or tissue-specific grouping of patients. **Conclusions:** The expression of immune checkpoint markers varies from patient to patient, though transcript expression of several markers correlates with cancer type, MSI, and PD-L1 status. Clinical trials with patient selection based on the expression level of checkpoint markers matched to the corresponding ICB drug are warranted. Research Sponsor: None.

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2556 **Poster Session**

The immune micro-environment of inflammatory breast cancer is characterized by an influx of CD163+ tumor-associated macrophages.

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Background: Inflammatory breast cancer (IBC) is a rare form of breast cancer characterized by rapid progression. A specific immune response seems to be an important driver for the aggressive biological behavior. We previously demonstrated that the spatial composition of the tumor immune micro-environment (TIME) is associated with survival in IBC. However, it remains an enigma how the TIME can contribute to the IBC phenotype. Since the number of tumor-infiltrating lymphocytes (TILs) between IBC and non-inflammatory breast cancer (nIBC) is similar and PD-L1 expression is higher, the functional state or composition of the immune infiltrate might determine the fulminant course of IBC. In this study, we assess the composition of the TIME in both IBC and a cohort of subtype-matched nIBC patients. **Methods:** We collected clinicopathological variables, evaluated PD-L1 positivity (SP142, Ventana) and scored TILs in a cohort of 161 IBC and 115 molecular subtype-matched nIBC patients. Affymetrix data (for CIBERSORT analysis) was available for 30 IBC and 20 nIBC patients. Immunostainings for CD8+ cytotoxic T cells, FOXP3+ Tregs, CD79a+ activated B cells and CD163+ TAMs (Hematoxylin-DAB) were done according to validated protocols. All slides were were evaluated in Visiopharm to quantify the number (density) and area (relative marker area, RMA) of DAB+ immune cells in both the invasive margin (IM) and the tumor stroma (TS). **Results:** Patients with IBC presented with higher stage disease (P< 0.001), but there were no other significant differences in clinicopathological parameters. In both cohorts, TAMs were the most abundant immune subset followed by B cells, CD8+ T cells and Tregs. For every subset the number of immune cells was higher in the IM than in the TS. Independent of molecular subtype or stage, IBC patients had more infiltration with TAMs in the TS. This was shown using both density (Median IBC: 424/mm2 vs nIBC: 290/mm2, OR: 0.82, 95% CI 0.76 – 1.00, P= 0.008) and RMA (Median IBC: 1.02% vs nIBC: 0.73%, OR: 0.87, 95% CI 0.77 – 1.00, P= 0.04). As previously described, PD-L1 positivity was significantly higher in the IBC cohort (P= 0.005), but no other significant differences in TIME composition between IBC and nIBC were found. Gene expression of CD163 correlated with the number of CD163+ TAMs (R= 0.38, P= 0.005) and CIBERSORT analysis confirmed a profile enriched for macrophages in IBC. Interestingly, the number of M1 macrophages was also higher in IBC (P= 0.03) and there was a strong correlation between the number of CD163+ TAMs in the TS and the M1 macrophage CIBERSORT subset (R=0.48, P< 0.001), possibly indicating that not only the number but also the functional state of TAMs is different in IBC. **Conclusions:** Using an extensive immune-phenotyping protocol we demonstrate, in a large cohort of IBC patients, that IBC is characterized by a specific tumor micro-environment in which TAMs play an important role. Research Sponsor: FWO.

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2557 **Poster Session**

Characterization of tumor antigen expression and myeloid immune profiles to inform the development of immune stimulating antibody conjugates (ISACs).

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Background: Immuno-oncology (IO) has historically focused on T cell-driven effects, but a growing class of myeloid therapies are under investigation. This class includes immune-stimulating antibody conjugates (ISACs), which comprise a tumor-targeting antibody conjugated to an immune-stimulating payload. ISACs may require both tumor-associated antigens and tumor-resident myeloid cells for activity. As new IO strategies such as TLR-activating ISACs are developed, understanding the myeloid landscape is relevant for cancer biology and drug development. **Methods:** Tumor microarrays with formalin-fixed paraffin embedded sections of breast (BC), colorectal (CRC), gastric (GC), head and neck squamous cell (HNSCC), and non-small cell lung (NSCLC) cancers were analyzed by immunohistochemistry for tumor antigens (HER2, CEA, PD-L1), myeloid cell markers (CD68/CD163/CD11c/BDCA2), and CD8+ T cells. **Results:** Tumor infiltrating myeloid cells and CD8+ T cells varied across indications (Table). Low densities of intra-tumoral CD8+ T cells (<100/mm^2) were observed in CRC, with higher CD8+ T cell counts observed in other cohorts. In contrast to T cells, substantial myeloid infiltrates were observed across tumor types. While MSI status was associated with higher CD8+ T cell infiltration in CRC, myeloid cells were abundant in both MSI and MSS samples. Monocyte-derived (mDC) and conventional DCs (cDC), which respond strongly to TLR activation, were present in all indications, with highest numbers observed in NSCLC. HER2+ BC samples had high infiltration of plasmacytoid DCs, a key TLR7-responsive population. PD-L1 expression on immune cells was associated with higher CD8+ T cell and myeloid cell numbers. In contrast to HER2 and PD-L1, CEA expression was independent of immune infiltration. **Conclusions:** Abundant myeloid infiltrates were observed across solid tumors, independent of T-cell infiltration. The presence of myeloid cells in multiple tumor types offers broadscale therapeutic targets for ISACs and other myeloid-directed therapies that can activate the innate immune system as a bridge to adaptive immunity. Research Sponsor: Bolt Biotherapeutics.

Median density (interquartile range) of cells/mm^2.

	N	CD8+ cells	Macrophages *(CD68+BDCA2- or CD163+CD11c-BDCA2-)*	cDC & mDCs *(CD11c+ CD68-BDCA2-)*	Plasmacytoid DCs *(BDCA2+ CD68-CD163-)*
CRC: Total	245	99 (23, 228)	217 (84, 493)	50 (19, 193)	12 (4, 33)
CRC: MSI-L/H	38	224 (92, 405)	283 (132, 492)	41 (16, 210)	9 (4, 21)
CRC: MSS	157	68 (22, 187)	217 (98, 429)	49 (17, 171)	12 (4, 35)
BC: Total	178	140 (41, 384)	398 (215, 723)	96 (41, 215)	11 (4, 70)
BC: HER2+	37	212 (116, 780)	241 (166, 403)	20 (5, 62)	1423 (665, 2392)
BC: Triple Negative	70	187 (31, 593)	699 (346, 1117)	93 (44, 234)	10 (3, 31)
NSCLC	74	207 (74, 510)	549 (324, 787)	445 (246, 861)	7 (4, 17)
HNSCC	74	223 (77, 626)	585 (311, 879)	166 (59, 353)	9 (3, 20)
GC	98	109 (31, 473)	434 (234, 659)	204 (80, 339)	8 (5, 17)

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Assessment of a 4-chemokine signature in prediction of T-cell inflammation and response to immune checkpoint inhibition across tumor types.

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Background: Immune checkpoint inhibitors (ICI) are highly effective in select cancers. Novel predictors of T cell-inflammation may identify a broader subset of tumors with ICI responsiveness. Our group has identified four chemokines (CCL4, CCL5, CXCL9, CXLC10) able to predict a T cell-inflamed phenotype in primary and metastatic pancreatic tumors. Here, we test whether this 4-chemokine signature can predict T cell-inflammation across additional tumor types and response to ICI. **Methods**: Using matched genomic and transcriptomic data from 6,455 patients spanning 25 tumor types from The Cancer Genome Atlas, we searched for associations between the 4-chemokine signature and metrics of antitumor immunity. Further, we tested the association of this signature with markers of DNA damage repair deficiency. We also investigated the ability of this signature to predict response to immunotherapy using real-world data from a pan-cancer cohort of 82 patients in the Personalized OncoGenomics Program who had received ICI. **Results**: The majority of tumor types displayed sub-populations with high expression of the 4-chemokines (4-chemokine^{hi}) and transcriptional hallmarks of the cancer-immunity cycle. Testicular germ cell tumors, cervical squamous cell carcinomas, and head and neck squamous cell carcinomas were the strongest expressors of the signature. Immunomodulatory genes, including *PD-L1*, *PD-1*, *TIM3*, *LAG3*, *TIGIT*, *CTLA-4*, and *FASLG*, were significantly overexpressed ($p<0.05$) in the 4-chemokine^{hi} cohorts. Genesets of processes involved in the cancer-immunity cycle, including MHC I expression and cytolytic activity, were upregulated in the 4-chemokine^{hi} cohorts ($p<0.05$). While a global relationship between tumor mutation burden (TMB) and 4-chemokine expression across tumor histological type was seen (rho=0.42, p=0.02), high TMB was associated with only a subset of 4-chemokine^{hi} tumors. Among patients treated with ICIs, those with 4-chemokine^{hi} tumors had a longer median time to progression (104 versus 71 days, p=0.013) and overall survival (391 versus 195 days, p=0.016). The 4-chemokine signature outperformed TMB for overall survival prediction. **Conclusions**: Sub-populations of T cell-inflamed patients exist across tumor types and may therefore respond favourably to ICI. The 4-chemokine signature has the potential to select a wider spectrum of patients that may benefit from ICIs. Research Sponsor: Terry Fox Research Institute, Other Foundation, Other Government Agency.

Multivariate cox proportional hazards model for TTP and OS.

	Metric	Group	N	HR	P value
TTP	TMB	<10	42	Reference	
		≥10	23	0.39 (0.18, 0.86)	0.020
	4-chemokine score	lo+med	39	Reference	
		hi	26	0.37 (0.19, 0.73)	0.004
OS	TMB	<10	42	Reference	
		≥10	23	0.59 (0.28, 1.26)	0.174
	4-chemokine score	lo+med	39	Reference	
		hi	26	0.37 (0.20, 0.72)	0.003

HR = Hazard Ratio. OS = Overall survival from ICI initiation. TTP = Time to progression from ICI initiation.

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2559 **Poster Session**

FORTITUDE: Results of a phase 1a study of the novel transgene-armed and tumor-selective vector NG-350A with and without pembrolizumab (pembro).

Lee S. Rosen, D. Ross Camidge, Danny Khalil, Thomas Lillie, Jo Carter, David Krige, Jessica Davies, David Miles, Minesh Patel, Vladimir Evilevitch, Isabel Prieto González-Albo, Brian Champion, Aung Naing; UCLA Division of Hematology-Oncology, Santa Monica, CA; University of Colorado Cancer Center, Aurora, CO; Memorial Sloan Kettering Cancer Center, New York, NY; PsiOxus Therapeutics Ltd, Abingdon, Middlesex, United Kingdom; PsiOxus Therapeutics Ltd, Abingdon, United Kingdom; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Stimulating CD40 may support anti-cancer immune responses; however, on-target toxicity limits systemic dosing. NG-350A is a tumor-selective and blood stable adenoviral T-SIGn vector expressing a potent fully human IgG agonistic anti-CD40 antibody (mAb). NG-350A was designed to selectively deliver anti-CD40 to multiple tumor sites via IV delivery, driving immunological tumor re-engineering while avoiding systemic toxicity. We report results from a first-in-human trial after completion of enrollment. **Methods:** FORTITUDE (NCT03852511) is a phase 1 study of NG-350A ± pembro in patients (pts) with metastatic/advanced epithelial tumors. NG-350A monotherapy (mTx) was dose-escalated in separate intratumoral (IT; increasing numbers of doses) or IV (one cycle; three increasing dose levels) cohorts. IV NG-350A + pembro (200 mg Q3W for ≤8 cycles) was then assessed. **Results:** As of Jan 2022, 28 heavily pre-treated pts had received NG-350A, either as IT mTx (n=9; two dose levels), IV mTx (n=16; IV dose levels 1, 3 & 4) or IV + pembro (n=3; IV dose level 2). The MTD of NG-350A ± pembro was not reached, with no DLTs at the highest IT and IV dose levels. The safety profile of NG-350A was consistent with acute reactions to viral particles and asymptomatic aPTT prolongations (Table). No systemic CD40 transgene protein was detected at any dose level and the only SAE to occur in >1 pt was pneumonia. No objective responses were observed; however, 3/6 patients treated with NG-350A mTx at IV dose level 4 achieved stable disease (dose not yet tested with pembro). Dose-dependent specific increases in serum IL-12, IFNγ and IL-17a were detected in pts treated with IV NG-350A mTx from ~Wk 2. Increases were sustained at ≥5x baseline levels 7 wks after dosing in the majority of evaluable pts treated at higher IV dose levels. These responses did not occur with IT dosing (or in prior studies with an unarmed vector); further follow-up is ongoing for NG-350A + pembro. IV NG-350A also led to the expansion of T cell clones in blood; most of these were newly detected. **Conclusions:** NG-350A ± pembro was well-tolerated, with no evidence of CD40-related toxicity. NG-350A IV mTx led to specific and sustained cytokine responses consistent with the MoA of the encoded anti-CD40 Ab. Peak cytokine elevations were typically higher than reported with systemic anti-CD40 Abs, suggesting NG-350A can drive local immunological tumor changes while avoiding systemic toxicity. A further trial (FORTIFY, NCT05165433) will continue dose-escalation of NG-350A + pembro to identify a dose level for efficacy assessments. Clinical trial information: NCT03852511. Research Sponsor: PsiOxus Therapeutics Ltd.

n (%)	IT NG-350A mTx (n=9)	IV NG-350A mTx (n=16)	IV NG-350 + pembro (n=3)
Most common TEAEs			
aPTT prolongation	6 (67)	5 (31)	2 (67)
Pyrexia	4 (44)	6 (38)	0
Nausea	3 (33)	6 (38)	0
Chills	2 (22)	7 (44)	0
Any Grade ≥3 TEAE	4 (44)	6 (38)	3 (100)
Any TE-SAEs	3 (33)	8 (50)	2 (67)
Any treatment-related SAE	1 (11)	3 (19)	1 (33)
DLTs	0	1 (dose level 1)	0

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2560 **Poster Session**

Dose escalation of davoceticept, a conditional CD28 costimulator and dual checkpoint inhibitor, in advanced malignancies (NEON-1).

Diwakar Davar, Justin C Moser, Michael Millward, Mark Voskoboynik, Nehal J. Lakhani, Rachel E. Sanborn, Jaspreet Singh Grewal, Ajita Narayan, Mario Sznol, Stacey R. Dillon, Keren Schieber, Hany Zayed, Christine Marie Dela Cruz, Graciela Noemi Perez, Stanford L. Peng; University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA; HonorHealth Research and Innovation Institute, Scottsdale, AZ; Linear Clinical Research & University of Western Australia, Nedlands, Australia; The Alfred Hospital and Monash University, Melbourne, Australia; START Midwest, Grand Rapids, MI; Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR; Norton Cancer Institute, Louisville, KY; Horizon Medcl Grp, Lafayette, IN; Yale Cancer Center, Smilow Cancer Hospital of the Yale–New Haven Hospital, Yale University School of Medicine, New Haven, CT; Alpine Immune Sciences, Seattle, WA; Alpine Immune Sciences, Inc., Seattle, WA; Bristol-Myers Squibb Co, Parkway Parade, NJ, Singapore; PRA Health Sciences, San Diego, CA

Background: Strong preclinical rationale supports combining checkpoint inhibition (CPI) with T cell costimulatory agonists, particularly of CD28, a critical T cell costimulatory molecule recognized as a key target of checkpoint inhibition. Davoceticept (ALPN-202) is a variant CD80 vIgD-Fc fusion that mediates PD-L1-dependent CD28 costimulation and inhibits the PD-L1 and CTLA-4 checkpoints. It has demonstrated superiority to CPI-only therapies in multiple tumor models *in vitro* and *in vivo*, while demonstrating favorable preclinical safety. **Methods:** This is an open-label dose escalation and expansion study of davoceticept in adults with advanced solid tumors or lymphoma (NCT04186637). Patients with cancers refractory to standard therapies including CPIs, or cancers without available standard or curative therapy are eligible. Dose escalation studied two dose schedules, Q1W and Q3W. Objectives include safety and tolerability, PK, PD and preliminary anticancer activity. Disease assessments are evaluated by RECIST v1.1 for solid tumors. A prior presentation discussed the first 5 cohorts of the Q1W schedule; this presentation updates progress in dose escalation, including the Q3W schedule. **Results:** As of January 2022, 57 adults with various advanced solid tumors, most commonly colorectal and pancreatic, received davoceticept monotherapy, which was well tolerated through 10 mg/kg Q3W. It demonstrated dose-dependent PK and target saturation. Immune-related AEs (irAEs), occurred in 20/57 (35%), mostly of the skin, endocrine and gastrointestinal systems. All but 4 of the irAE were grade 1-2. Only one DLT (chronic active gastritis grade 3) was observed at 3 mg/kg Q3W. Among 48 evaluable patients, unconfirmed partial responses were observed in 2 (colorectal and renal cell). Stable disease, at first scan at 6 weeks, was observed in 23 (48%); 11 (23%) demonstrated volume reduction (target lesion ΔSLD $< 0\%$); 2 had SD for > 6 months, and 1 had an ongoing SD at 8 months. At doses above 0.1 mg/kg, *ex vivo* analyses showed agonism of T cell CD28, and flow cytometry demonstrated increased circulating activated (ICOS+), proliferating (Ki-67+) and central memory T cells, and reduced regulatory T cells, consistent with CD28 engagement. **Conclusions:** Davoceticept was well tolerated at doses capable of engaging CD28 costimulation *in vivo*, with early signs of activity and peripheral immune activation in a largely treatment-refractory, non-immunogenic tumor population. These findings support an additive benefit of combining CD28 agonism with checkpoint inhibition and identify biologically active dose regimens of davoceticept for subsequent single agent development, and provide further rationale for combination study. Expansion cohorts, including cutaneous melanoma and PD-L1-positive cancers, are planned, and a combination study with pembrolizumab has initiated (NCT04920383). Clinical trial information: NCT04186637. Research Sponsor: Alpine Immune Sciences.

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2561 **Poster Session**

LAG3 transcriptomic expression correlates with high levels of PD-1, PD-L1, PD-L2, and CTLA-4 checkpoints and with high tumor mutational burden across cancers.

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Background: Lymphocyte Activation Gene 3 (LAG3) or CD223 is an immune checkpoint that can be found on various T cells: CD4+, CD8+, regulatory T cells (Tregs), natural killer T cells, natural killer cells, and plasmacytoid dendritic cells. The expression of LAG3 molecule acts to increase T-cell exhaustion, leading to decreased tumor killing as well as an increase in immune suppressive cytokine release. Many clinical trials of LAG3 inhibitors have had modest effects, but recent data suggests that the LAG3 antibody relatlimab together with nivolumab (anti-PD1) provided greater benefit than nivolumab alone in patients with melanoma. **Methods:** The RNA expression levels of 397 genes in various types of solid tumors from 514 patients seen at the UCSD Moores Cancer Center were analyzed at a CLIA-licensed laboratory, OmniSeq (https://www.omniseq.com/). Following removal of germline variants, synonymous variants, indels and SNVs with < 5% VAF, TMB is reported as mutations/megabase. Transcript abundance was normalized to internal housekeeping gene profiles and ranked (0-100 percentile) in a standardized manner to a reference population of 735 tumors spanning 35 histologies. Odds ratio for high LAG3 expression was calculated and Bonferroni corrected for multiple genes and cancer histologies with > 40 samples. **Results:** A total of 116 (22.6%) tumors had high LAG3 (≥75) across 32 different histologies. Cancers with the highest proportion of LAG3 were neuroendocrine (47%), uterine (43%), sarcoma (33%), breast (31%), ovarian (30%), pancreatic (24%), lung (20%), stomach (16%), and colorectal (15%). There was significant association for high LAG3 with high PD-L1 (adj $P < 0.001$), high PD-1 (adj $P < 0.0014$), high PD-L2 (adj $P < 0.0014$), high CTLA-4 (adj $P < 0.0014$), TMB ≥10 mt/mb (adj $P = 0.0504$). There was no significant association between histologies colorectal (adj $P = 0.1834$), breast (adj P = NS), ovarian (adj P = NS), pancreatic (adj P = NS), or gender (adj $P = 0.272$). **Conclusions:** High LAG3 was found in almost a quarter of tumor samples and significantly associated with other immune checkpoints with FDA-approved drugs. Ongoing studies combining LAG3 inhibitors and specific immune checkpoint inhibitors may yield more clinical benefit if individualized immunomic transcript interrogation is undertaken, rather than population-based approaches without employment of rationally combined agents matched to each patient's cancer. Research Sponsor: None.

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2562 **Poster Session**

LB101, a conditionally tetravalent PD-L1xCD47 bispecific monoclonal antibody (mAb), combines tumor microenvironment (TME) targeted delivery (PD-L1) and a single biological high potency effector (CD47).

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Background: Anti-PD-L1 antibodies are well-established as potent immune effectors in solid tumors expressing PD-L1 and demonstrate binding to these tumor cells within the TME. By contrast, due to the ubiquitous expression of CD47 on normal cells and tissues, anti-CD47 therapeutic agents with an active antibody Fc can lead to serious dose-limiting toxicities and profound biodistribution problems. To overcome these issues, we have generated LB101, a next-generation conditionally activated PD-L1xCD47 bispecific mAb with two anti-CD47 domains blocked by two further anti-PD-L1 domains, linked by two proprietary IgG-derived hinges, which inhibit CD47 interactions in the periphery, but are degraded in the PD-L1+ TME, thereby activating CD47 blockade to induce antibody-dependent cellular phagocytosis (ADCP). **Methods:** An IgG1-based, conditionally activated bispecific molecule was examined in binding, phagocytosis, PD-L1 blocking and flow cytometry assays. Efficacy analyses were performed in an hPD-L1+ syngeneic model in hPD-L1+/hPD1+ C57BL/6 mice, and preliminary safety and exposure analyses were completed in monkey. **Results:** In its intact locked form, LB101 exhibited anti-PD-L1 assay potency similar to atezolizumab. CD47 binding was only observed for LB101 after unlocking by hinge linker cleavage, leading to strongly enhanced ADCP by human CD14+ cells. In monkey, plasma stability of the locked construct was established with a PK profile mimicking that of a typical PD-L1 mAb. In the MC38 mouse model, systemically administered LB101 monotherapy delivered at equimolar dose to atezolizumab, led to no anemia, weight-loss, or overt toxicity. Monotherapy LB101 exhibited greatly improved efficacy and durability of response (14/16 tumors eradicated) over isotype control IgG (0/16) and atezolizumab (1/16). The CD47 naked parent IgG1 mAb was not tolerated in mouse, with 100% lethality above 2mg/kg. In rechallenge experiments, all naïve mice established tumors rapidly while none of the mice from groups with prior LB101-induced regressions exhibited tumor growth. **Conclusions:** Single agent LB101 immunotherapy delivered systemically in a difficult to treat syngeneic mouse model resulted in PD-L1 directed, local tumor-specific CD47 effector engagement leading to significant tumor regressions as compared to atezolizumab without overt toxicity. Future developments will focus on developing LB101 as a single agent therapeutic and exploring the potential of LockBody technology in improving the therapeutic index of other anti-cancer biological effectors through conditional activation within the TME. Research Sponsor: Centessa Pharmaceuticals.

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2563 **Poster Session**

TransCon IL-2 β/γ, a novel long-acting prodrug with sustained release of an IL-2Rβ/γ-selective IL-2 analog, demonstrates improved pharmacokinetics and profound expansion of cytotoxic immune cells in non-human primates.

David Rosen, Anne Månsson Kvarnhammar, Janne Damm Olling, Burkhardt Laufer, Thomas Knappe, Jens Jakob Karlsson, Thomas Kurpiers, Joachim Zettler, Josefine Runz, Frank Faltinger, Laura Viet, Mathias Krusch, Meike Schnabel, Diana Reich, Philipp Glock, Stina Mui Singel, Kennett Sprogøe, Kristin Laura Abel, Vibeke Miller Breinholt, Juha Punnonen; AscendisPharma, Redwood City, CA; Ascendis Pharma A/S, Copenhagen, Denmark; Ascendis Pharma, Copenhagen, Denmark; Ascendis Pharma, Heidelberg, Germany; Ascendis Pharma, Palo Alto, CA; Ascendis Pharma, Redwood City, CA

Background: Recombinant interleukin-2 (IL-2, aldesleukin) is an approved cancer immunotherapy but causes severe side effects including cytokine release syndrome (CRS) and vascular leak syndrome (VLS). This is believed to be due to activation of IL-2Rα^+ endothelial cells and inflammatory eosinophils as well as high C_{max} due to the short half-life requiring frequent high dose administrations. Also, potent activation of immunosuppressive IL-2Rα^+ regulatory T cells (Tregs) may limit IL-2's efficacy. TransCon IL-2 β/γ is a novel long-acting prodrug with sustained release of an IL-2Rβ/γ-selective IL-2 analog designed to optimally address these shortcomings. **Methods:** Naïve male and female cynomolgus monkeys received 2-3 doses of TransCon IL-2 β/γ intravenously Q2W. Blood samples were taken to assess plasma concentrations of IL-2 β/γ (active drug), serum cytokines, hematology and immunophenotyping. Histopathology was also performed. **Results:** Administration of TransCon IL-2 β/γ induced robust increases in absolute lymphocyte counts (ALC), with no/minor increases in eosinophil counts. The increase in ALC was primarily driven by potent activation and expansion of $CD8^+$ T cells, NK cells and γδ T cells, relative to $CD4^+$ T cells and Tregs. At doses with maximum pharmacodynamic (PD) responses, TransCon IL-2 β/γ induced on average > 20-fold ALC increases, > 19-fold $CD8^+$ T cell increases, > 50-fold Effector Memory $CD8^+$ T cell increases, > 18-fold NK cell increases and > 400-fold γδ T cell increases compared to pre-dose levels. These changes corresponded with a low C_{max} and a long effective half-life (> 30 hours) for IL-2 β/γ. A clear induction of soluble CD25 and chemokine MCP-1 was seen after dosing, while levels of IL-5, IL-6, IFN-γ and TNF-α remained low. Further, histopathology showed no signs of vascular damage, tissue necrosis, pulmonary edema or eosinophilia. **Conclusions:** In cynomolgus monkeys, TransCon IL-2 β/γ demonstrated remarkable PD responses in $CD8^+$ T cells, NK cells and γδ T cells over Tregs and eosinophils. No signs of VLS or CRS were observed. These results are likely due to the selective IL-2Rβ/γ bias along with the slow and sustained release of IL-2 β/γ resulting in low C_{max} and long circulatory half-life enabled by the TransCon prodrug technology. The massive expansion of γδ T cells, which are known to possess considerable anti-tumor activity, is to our knowledge a unique finding for TransCon IL-2 β/γ among IL-2 variants in clinical development. Altogether, the responses seen in monkeys are suggestive of a potentially substantial improvement in the therapeutic index beyond what has been achieved by aldesleukin or new IL-2 variants to date. TransCon IL-2 β/γ is currently being evaluated in a clinical Phase 1/2 trial as monotherapy and in combination with pembrolizumab (NCT05081609). Research Sponsor: Ascendis Pharma.

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2564 **Poster Session**

A novel polymeric peptide delivery platform and association with targeted co-delivery of antigens and STING agonists with antitumor immune response.

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Background: Use of tumor antigens for the development of patient-specific cancer vaccines has been a promising therapeutic strategy. However, challenges remain in delivering subunit vaccine components in a coordinated fashion to elicit antitumor immune responses. To overcome these, we developed rationally designed vaccines using a novel nanoplatform called the Protein-Like Polymer (PLP), in reference to its globular structure reminiscent of native proteins, with unique characteristics that allow for sustained/targeted delivery of tumor antigens in conjunction with STING agonists. **Methods:** PLPs containing a model melanoma antigen were synthesized via ring-opening metathesis polymerization (ROMP) and characterized. A library of compounds were generated with different sidechain linkage chemistries (amide, ester, or disulfide), degrees of polymerization, and inclusion/exclusion of Oligo(ethylene glycol) (OEG) side chains. *In vitro* uptake and functional assays using gp100-specific T Cells were conducted with fluorescently-labeled and non-labeled polymers respectively. *In vivo* experiments were done using a B16F10 murine melanoma tumor model over-expressing gp100. Ability of PLPs to co-deliver immunomodulatory compounds was tested by electrostatically coupling a small molecule STING agonist 2'3' cGAMP which formed stable nanostructures. The optimized construct was also tested in an OVA system to prove generalizability. **Results:** Conjugating peptide antigens using a cleavable disulfide linkage, which reduces intracellularly in antigen presenting cells (APCs), resulted in increased endosomal localization and efficacy. Incorporating a diluent amount of OEG side chains increased resistance to enzymatic degradation while improving bioactivity and uptake by APCs. *In vivo* studies using PLPs conjugated with gp100 resulted in significant increases in survival time and reduced tumor burden in B16 melanoma. Increasing the DP, and therefore the density of antigen side chains, improved vaccine efficacy and resistance to proteolysis. Mice treated with STING-PLP complexes showed significantly smaller tumors vs control at day 14 (0.038g vs 0.76g; $p < 0.0001$) and allowed for subcutaneous administration of 2'3' cGAMP, which otherwise diffuses rapidly away from the injection site. OVA-PLPs behaved similarly in their cognate system but showed no activity when tested on gp100-specific cells and vice versa demonstrating antigen-specificity. **Conclusions:** This work validates the potential of PLPs to overcome major limitations in cancer vaccine development. The modularity of the platform allows for complex nano-architectures including systems capable of delivering challenging compounds, ie small molecule STING agonists, subcutaneously through electrostatic coupling. This technology has the potential to revolutionize cancer vaccinology. Research Sponsor: U.S. National Institutes of Health.

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2565 **Poster Session**

Exploiting GLAAD molecules to drive an antitumor immune response in a colorectal cancer mouse model.

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Background: Only a minority of colorectal cancer (CRC) patients benefit from immune checkpoint inhibitors (ICI), with less than half of eligible patients responding to the treatment. Abnormal glycosylation of tumor cells is a signature of cancer development. Here, we described novel immunomodulatory molecules, named GLAAD (glycopeptides with adjuvant and tumor-associated antigen delivery). We hypothesized that GLAAD, by sharing similarities with aberrant glycans expressed in many cancers, may be a safe and effective treatment strategy to promote response and overcome resistance to ICI, thus addressing an urgent clinical need. Using a CRC mouse model, we tested whether two GLAAD candidates reduce tumor burden when orally administered alone or in combination with ICI. **Methods:** C57/BL6J mice were supplemented with 3% GNU-201 or 3% GNU-101 in the drinking water starting 14 days prior to tumor cell injection (d-14), while control mice received normal drinking water. On day 0, all mice were injected subcutaneously with MC38 CRC cells in each flank. On days 6, 9, 12, and 15, mice in each group received anti-PD1 antibody (aPD1) or an isotype control. Tumor size was measured every 3rd day. On day 18, the mice were sacrificed. **Results:** The aPD1 therapy alone showed a limited anti-tumor efficacy overall. Groups treated with GNU-201, GNU-101, GNU-201+aPD1 or GNU-101+aPD1 exhibited reduced growth, resulting in a significantly reduced tumor volume vs control on day 18. In contrast, GLAAD candidates alone significantly reduced tumor volume compared with control and led to a numerically larger decrease than aPD1 treatment alone, suggesting a higher efficacy. When analyzing tumor infiltrating myeloid cells on day 18, no differences were seen for neutrophils or dendritic cells but the proportion of macrophages was decreased in mice receiving GNU-201 or GNU-101. GNU-101 resulted in reduced serum levels of IL-10, a molecule participating in the suppression of antitumor immune responses. The tested GLAAD candidates stimulated robust anti-tumor T cell responses. GNU-201 and GNU-101 supplementation alone or in combination with aPD1 increased the proportion of T cells and among those CD8+ T cells, IFNγ producing CD4+ T cells, IFNγ+ and perforin+ CD8+ T cells. GNU-101 and GNU-201 elicited memory T cell responses after priming of the mice, measured as the *ex vivo* recall response (CD69 expression) of CD8+ T cells isolated from the tumor. **Conclusions:** GNU-201 and GNU-101 as standalone treatment induce a strong anti-tumor response that is as good as or even better than aPD1 alone. The therapeutic efficacy is associated with increased tumor infiltration and activation of T cells, in particular CD8+ T cells, highlighting the role of these GLAAD candidates as potent adjuvants in supporting specific tumor-associated antigen recognition by the immune system. Research Sponsor: Gnubiotics Sciences SA.

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2566 **Poster Session**

Phase 1b study of GS-3583, a novel FLT3 agonist Fc fusion protein, in patients with advanced solid tumors.

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Background: We have previously shown that systemic administration of GS-3583, a Fms-like tyrosine kinase 3 (FLT3) agonist Fc fusion protein leads to expansion of conventional dendritic cells (cDC), both subtype 1 (cDC1) and subtype 2 (cDC2), in the periphery of healthy volunteers (Rajakumaraswamy N, et al. *J Clin Oncol*. 2021;39[suppl_15]:2559.). This mechanism may increase cDC in the tumor microenvironment and promote T cell mediated antitumor activity in patients with solid tumors. **Methods:** This ongoing, Phase 1b, open label study is investigating the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of escalating multiple doses of GS-3583 monotherapy in adult patients with advanced solid tumors using a standard 3 + 3 design. GS-3583 was administered intravenously on Days 1 and 15 of Cycle 1 and on Day 1 of each subsequent 28-day cycle for up to 52 weeks or until progressive disease or unacceptable toxicity. Dose-limiting toxicity (DLT) was evaluated during the first 28 days of GS-3583 therapy at each dose level. **Results:** At the time of the Dec 3, 2021 data cut-off, 9 patients have enrolled in 3 dose escalation cohorts. Median (range) age was 71 (44-79); 4 (44%) patients were male. Tumor types were pancreatic (n=3), ovarian (n=4), and rectal (n=2). To date, no DLTs or discontinuation due to adverse events (AE) have been observed. Three patients had Grade ≥3 AEs which were also recorded as serious AEs, none of which were considered related to GS-3583. Dose dependent increase in GS-3583 exposure was observed in the evaluated dose range 2 to 12 mg with target-mediated drug disposition appearing to be saturated at doses above Dose Level 2. GS-3583 accumulation was observed at higher dose levels. GS-3583 treatment resulted in expansions of cDC1 and cDC2 at all 3 doses (Table); a dose-dependent trend in the magnitude and the durability of cDC expansion was observed. At the highest dose evaluated, GS-3583 produced ≥100-fold expansion of both cDC1 and cDC2 at multiple time points. Dose escalation on the study is still ongoing. **Conclusions:** GS-3583 was safe and well tolerated and induced dose-dependent expansion of cDCs in the periphery in patients with advanced solid tumors up to doses of 12 mg. These findings support further dose escalation and clinical development of GS-3583 in combination with agents that would stimulate the expanded cDCs to produce anti-tumor responses. Clinical trial information: NCT04747470. Research Sponsor: Gilead Sciences, Inc.

Dose Level (mg GS-3583)	1 (2 mg)	2 (6 mg)	3 (12 mg)
Median peak cDC1 fold expansion (range)	124 (188 – 15)	83 (0)	191 (283 – 99)
Observation of peak cDC1 expansion	C1D24	C2D15	C2D1
Median peak cDC2 fold expansion (range)	147 (154 – 34)	201 (0)	217 (273 – 162
Observation of peak cDC2 expansion	C1D15	C2D15	C2D1

C = cycle; D = day.

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2567 **Poster Session**

A phase II study to evaluate the safety and efficacy of radiotherapy combined with irinotecan liposome followed by camrelizumab and apatinib for advanced solid tumors that failed standard treatments.

Jie Shen, Rutian Li, Jing Yan, Juan Du, Jia Wei, Sihui Zhu, Ying Liu, Huajun Li, Baorui Liu; The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China; The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China; Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University, Clinical Cancer Institute of Nanjing University, Nanjing, China; The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China; Department of Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: Liposomes deliver the drug to tumors based on enhanced permeability and retention (EPR) effects. Radiotherapy further prompts the distribution of liposomal drugs to tumor sites receiving radiotherapy by altering the tumor microenvironment. In addition, radiotherapy might enhance systemic antitumoral responses to immunotherapy. Herein, we aimed to explore safety and efficacy of radiotherapy in combination with irinotecan liposome, immunotherapy, and antiangiogenic therapy in advanced solid tumors patients (pts) that failed standard treatments. **Methods:** Anopen single-arm, multi-center, phase II study was conducted to enroll solid tumors pts who have failed standard treatments. Eligible pts would receive radiotherapy combined with irinotecan liposome followed by camrelizumab and apatinib. Radiotherapy of 24 Gy/3 fractions/3-10 days was given to the targeted lesions. Irinotecan liposome (80mg/m^2 i.v.) was administered once within 48 hours after radiotherapy and followed by camrelizumab (200mg i.v. q3w) and apatinib (250mg po qd) until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR) of the irradiated lesions evaluated by the investigators as per RECIST V1.1. The secondary endpoints were disease control rate (DCR) and treatment-related adverse event (TRAE). **Results:** As of Dec 2021, 55 pts were enrolled includin 9 with biliary tract cancer, 8 with pancreatic cancer, 8 with sarcoma, 5 with lung cancer, 2 with liver cancer, 2 with cervical cancer, 2 with gastric cancer, and 22 with other cancer types. 26 (47.3%) pts failed at least 3 lines of therapy before enrollment. The median follow-up was 41 weeks and 42 pts can be evaluated. 15 partial response, 26 stable disease, and 1 progressive disease were achieved. The ORR and DCR of irradiated target lesions were 35.7% and 97.6%, respectively. The ORR and DCR of every cancer type are listed in table. TRAEs (all grades) occurred in 87.3% (48/55) pts. The most common grade 3-4 related TRAEs were lymphocyte count decreased (29.1%), white blood cell count decreased (10.9%), and anaemia (10.9%). **Conclusions:** The combination of radiotherapy, irinotecan liposome, camrelizumab, and apatinib demonstrated promising anti-tumor activity and well tolerance in various advanced solid tumors that failed standard treatments. Clinical trial information: NCT04569916. Research Sponsor: None.

Cancer types	Evaluable(N≥2)	ORR of theirradiated lesions	PR	SD
Biliary tract cancer	8	12.5%	1	7
Sarcoma	7	28.6%	2	5
Pancreatic cancer	4	0	0	3
Lung cancer	3	33.3%	1	2
Liver cancer	2	0	0	2
Cervical cancer	2	50.0%	1	1
Gastric cancer	2	100%	2	0
Other cancer types	14	57.1%	8	6

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2568 **Poster Session**

Safety results of Q-1802, a Claudin18.2/PD-L1 bsABs, in patients with relapsed or refractory solid tumors in a phase 1 study.

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Background: Q-1802 is a humanized bispecific antibody that targets both the tumor -specific antigen CLDN18.2 and the immune checkpoint PD-L1. **Methods:** This is a first-in-human, phase 1a/1b, multicenter, dose escalation and dose expansion study of Q-1802 administered intravenously to adult pts with resistant/refractory advanced or metastatic solid tumors who had failed standard therapies. Monotherapy of Q-1802 was conducted in 20-30 enrolled subjects. In the dose escalation phase (phase 1a), an accelerated titration followed by a 3+3 design was used to assess the safety and tolerability of Q-1802 monotherapy (dose range 0.1 mg/kg to 20 mg/kg); and determine the maximum tolerated dose (MTD). Q-1802 was administered Q3w on a 21-day treatment cycle and dose limiting toxicity (DLT) observation period. Tumor assessments per RECIST v1.1 were performed once every 6 weeks (2 cycles). Q-1802 PK and PD analyses were performed. **Results:** As of Jan 20, 2022, a total of 9 patients (median age 57y; most patients received ≥3 prior regimens) were enrolled in phase 1a with DLT evaluation of the 20 mg/kg cohort currently in progress. The most common tumor types were GI cancers. There were no DLTs up to 10 mg/kg of Q-1802, inclusive. Phase 1a with DLT evaluation of the 20 mg/kg cohort currently in progress. The most common treatment related adverse events (TRAEs) were Gastrointestinal AE (66.7%, 6/9), including nausea 6/9 (66.7%), vomiting 5/9 (55.6%), abdominal pain 2/9 (22.2%) and diarrhea 2/9 (22.2%). The second common TRAEs were IRR (infusion related reaction) (33.3%, 3/9), including Fatigue 3/9 (33.3%), Fever 2/9 (22.2%), Chill 2/9 (22.2%), face pain 1/9 (11.1%). There was G1/2 except for one patient experienced a G3 skin rash, and one patient reported with a G3 Gastrointestinal AE. Two SAEs (G2 fever and G3 Gastrointestinal AE) were reported, both were considered as possibly related to study drug, but recovered shortly. No death reported due to study related treatment. Safety evaluation of the 20 mg/kg dose level is in progress. One Gastric cancer patient (moderate CLDN18.2 expression at baseline) with prior heavily treatment observed clinical benefit and response with Non-CR/Non-PD at first tumor assessment at dose of 10mg/kg and continues the therapy. Q-1802 drug exposure increased with increasing dose. The elimination of Q-1802 appears to follow first-order elimination kinetics. **Conclusions:** Q-1802 bsABs has presented safe and well-tolerated profile up to doses of 10 mg/kg. The dose escalation is still in progress. Clinical trial information: NCT04856150. Research Sponsor: QureBio Ltd.

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2569 **Poster Session**

Breath biopsy early detection of lung cancer using an EVOC probe targeting tumor-specific extracellular β-glucuronidase.

Christiaan Frederick Labuschagne, Rob Smith, Neelam Kumar, Max Allsworth, Billy Boyle, Sam Janes, Phil Crosbie, Robert Rintoul; Owlstone Medical, Cambridge, United Kingdom; The Lungs for Living Research Centre, Division of Medicine, London, United Kingdom; Lungs for Living Research Centre, UCL Respiratory, University College London, London, United Kingdom; North West Lung Centre, University Hospital of South Manchester, Wythenshawe, United Kingdom; Papworth Hospital, Cambridge, United Kingdom

Background: Lung cancer is a leading cause of mortality with 5-year survival less than 20%, largely a result of many cases being diagnosed late. Early detection can increase cancer survival up to 13-fold underscoring the need for effective screening. Targeted Low dose computed tomography (LDCT) has been shown to be effective but its impact to date has been limited due to slow adoption and variable uptake in high-risk populations. Breath analysis represents a non-invasive screening approach either alone or alongside LDCT. Numerous studies have investigated potential endogenous breath biomarkers of lung cancer. Many have produced promising results but to date, no validated biomarkers with clear connections to cancer metabolism have been revealed. We have explored an alternative, probe-based approach based around Exogenous Volatile Organic Compound Probes (EVOC Probes). The probes target tumour associated extracellular b-glucuronidase, a glycosidase enzyme that normally resides within lysosomes. **Methods:** We use a hydrophilic non cell permeable substrate probe D5-ethyl-βD-glucuronide (D5-EtGlu) that upon hydrolysis by the target enzyme releases D5-ethanol, a unique volatile reporter molecule detectable on breath. This provides a readout of tumour associated enzyme activity using breath analysis. **Results:** Administering D5-EtGlu to mice resulted in tumour specific release of D5-ethanol, enabling discrimination between healthy and tumour bearing animals. Increased expression of b-glucuronidase in lung cancer tissue and the tumour microenvironment was confirmed with immunohistochemistry (IHC) in clinical samples. A phase 1a clinical trial administered D5-EtGlu to healthy individuals in a single ascending dose study to establish safety and background D5-ethanol levels in healthy individuals. This resulted in no adverse events and low/no D5-ethanol signal verifying the inaccessibility of D5-EtGlu to intracellular b-glucuronidase. The next stage, currently ongoing, is a proof of mechanism in humans. D5-EtGlu is administered intravenously to confirmed lung cancer patients followed by breath analysis. D5-ethanol breath levels will be compared to cancer free individuals receiving the same dose of D5-EtGlu. **Conclusions:** Non-invasive breath testing has great potential to contribute to diagnosis for lung cancer including a potential role in screening. Our current work is evaluating the use of an administered probe to stimulate tumour-specific enzyme activity and produce a marker detectable on breath. Continued success could result in a sensitive and highly specific method for lung cancer early detection. Research Sponsor: Owlstone Medical.

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2570 **Poster Session**

Artificial intelligence-powered pathology image analysis merged with spatial transcriptomics reveals distinct TIGIT expression in the immune-excluded tumor-infiltrating lymphocytes.

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Background: TIGIT is a promising emerging immunotherapeutic target. However, the specific sources of TIGIT expression within the tumor microenvironment are largely unknown. Here, we present an AI-powered spatial tumor-infiltrating lymphocyte (TIL) analyzer, Lunit SCOPE IO, to integrate image analysis from whole slide images with single-cell molecular profiling. **Methods:** We used The Cancer Genome Atlas (TCGA) RNA expression data across 23 cancer types (n=6,930). Lunit SCOPE IO was developed, trained, and validated based on >17k H&E whole-slide images, to segment cancer area (CA) and cancer-associated stroma (CS) and to detect tumor cells and TILs. The intra-tumoral TIL, stromal TIL, and tumor cell purity (TCP) in the CA+CS area were calculated. The public spatial transcriptomics (ST) dataset for breast cancer was downloaded from the 10X Visium web page. Lunit SCOPE IO was applied to the associated H&E WSIs to match distinct TIGIT expression to single cells identified in the WSIs. **Results:** TIGIT was highly expressed in TGCT (3.45±0.11; median±SEM), LUAD (3.07±0.05), and HNSC (2.89±0.06), and was highly enriched in samples with microsatellite instability-high or tumor mutational burden-high (≥ 10/Mb) compared to those without them (fold change = 1.30, $p < 0.001$). At a macroscopic, bulk-level in the TCGA dataset, TIGIT expression was positively correlated with intra-tumoral TIL density ($R=0.37$, $p<0.001$) and stromal TIL density ($R=0.42$, $p<0.001$), but it was negatively correlated with TCP ($R=-0.27$, $p<0.001$). Lunit SCOPE IO analyzed the images from ST analysis and calculated intra-tumoral TIL, stromal TIL, and TCP of each region of interest, containing 2 (IQR 0-7) cells. Interestingly, at a microscopic, cell-level, TIGIT expression was still higher in areas of enriched stromal TIL ($P < 0.001$) and lower in tumor cell-dense areas, but it was not significantly correlated with enriched intra-tumoral TIL areas, meaning that TIGIT expression is likely derived from the excluded TILs in the CS area. **Conclusions:** Interactive analysis of spatial transcriptomics with AI-powered pathology image analysis revealed that TIGIT expression in the tumor microenvironment is exclusive to confined areas with stromal TIL enrichment, reflecting the exclusion of TIL from the tumor nest. Research Sponsor: None.

	Fold change of TIGIT expression	P value
TCGA: iTIL < mean versus iTIL ≥ mean	1.58	< 0.001
TCGA: sTIL < mean versus sTIL ≥ mean	1.55	< 0.001
TCGA: TCP < mean versus TCP ≥ mean	0.75	< 0.001
ST: iTIL < mean versus iTIL ≥ mean	0.47	< 0.001
ST: sTIL < mean versus sTIL ≥ mean	2.39	< 0.001
ST: TCP < mean versus TCP ≥ mean	0.28	< 0.001

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2571 **Poster Session**

Evaluation of pharmacodynamic and patient enrichment biomarkers for SAR444881, a first-in-class anti-ILT2 monoclonal antibody for cancer immunotherapy.

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Background: Leukocyte Ig-like receptor B1 [LILRB1; ILT2] is an inhibitory receptor expressed on various immune cells. ILT2 binds to classical and nonclassical MHC class I molecules, with highest affinity to HLA-G. ILT2-mediated inhibition leads to impairment of immune cell proliferation, differentiation, phagocytosis, cytotoxicity and cytokine secretion. Antagonism of ILT2 signaling may serve as a novel target for anti-cancer immunotherapy. SAR444881 (BND-22) is a novel humanized IgG4 monoclonal antagonist antibody which selectively binds to ILT2 and blocks its interaction with MHC I molecules. SAR444881 induces robust macrophage and lymphocyte-driven anti-tumor activity in *in vitro* and *in vivo* models. To overcome the limitation that LILRB proteins are not expressed in rodents, we conducted a series of *in vivo* studies using humanized mouse models, cancer patient biopsies and *ex vivo* co-culture systems to interrogate the pharmacodynamic (PD) response of ILT2 antagonism as well as inform the combinatorial and patient enrichment strategies for SAR444881. **Methods:** SAR444881-induced modulation of PD biomarkers was evaluated in humanized xenograft models. Ex vivo co-culture system has been established using patient tumor tissues and isolated PBMC or other immune cells. Biomarker expression on immune cells and secreted soluble proteins were monitored by flow cytometry and ELISA, respectively. Procured tumor samples of patients with various advanced solid tumors, including Head and neck squamous cell carcinoma (HNSCC), Gastric Cancer (GC), Non-Small Cell Lung Cancer (NSCLC) and Colorectal Cancer (CRC) were utilized to evaluate protein or gene expression levels of potential predictive biomarkers (ILT2, HLA = G, PD-L1) using immunohistochemistry (IHC) and whole transcriptomic analysis (RNAseq). **Results:** 1) PD biomarkers: in murine models, SAR444881 modulates intra-tumoral sub-populations of CD8+ T cells, NK cells and Macrophage polarization; 2) Combination strategy: functional study in an *ex vivo* system showed that addition of an anti-PD-1 antibody induced an increased production of pro-inflammatory cytokines, including IFNγ and TNFα, compared to SAR444881 or anti-PD-1 alone. Concomitantly, combining SAR444881 with cetuximab resulted in increased phagocytosis compared to isotype control. 3) Predictive biomarkers: protein and gene profiling results suggest enriched expression of ILT2 in majority of biopsies from several tumor types including NSCLC, HNSCC and CRC. **Conclusions:** These data inform the PD response biomarkers, combination, and patient enrichment strategies for the clinical development of SAR444881 to maximize its benefits for cancer patients. An ongoing phase 1/2 trial of SAR444881 mono- and combination therapy in patients with advanced solid tumors is testing these concepts in the clinic (NCT04717375). Research Sponsor: Sanofi, Biond Biologics.

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2572 **Poster Session**

Safety and tolerability of T-SIGn vectors when administered using "flat" versus "low-high-high" (LHH) dosing regimens.

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Background: Tumor-selective viruses, particularly those dosed systemically to deliver transgenes, are potentially powerful cancer therapies. However, acute cytokine reactions to viral particle (vp) infusion may affect vector tolerability [Small 2006], thereby limiting the maximum tolerated dose (MTD) and subsequent transgene delivery. T-SIGn vectors (e.g. NG-641 and NG-350A) are transgene-armed variants of the epithelial tumor-selective adenovirus enadenotucirev (EnAd). Acute serum cytokine increases post-dosing have been seen at the MTD of EnAd ("flat" dosing of 3 x 10^{12} vp on Days [D] 1, 3 and 5) [Machiels 2019]. Following supportive preclinical data [McElwaine-Johnn 2019], we explored if a LHH dosing regimen, in which a lower dose is given on D1 prior to two higher doses on D3 and 5, may improve vector safety/tolerability thereby allowing higher cumulative doses to be given. **Methods:** Data were pooled from three Phase 1 dose-escalation studies in advanced/metastatic epithelial cancer: SPICE (EnAd + pembrolizumab/nivolumab; NCT02636036), FORTITUDE (NG-350A ± pembrolizumab; NCT03852511) and STAR (NG-641; NCT04053283). Serum cytokines were measured using a 17-analyte Luminex assay. IL-6/MCP-1 data for D1, 3 and 5 (pre- and 6-10 hrs post-dose) were analyzed to examine acute cytokine changes. TNFα/IFNγ were examined due to their association with cytokine release syndrome (CRS). Samples analyzed from SPICE/FORTITUDE were taken before PD-1 inhibitor administration. **Results:** 84 patients (SPICE n=51; FORTITUDE n=18; STAR n=15) were included in these analyses; 79 had cytokine data. AEs and Gr≥3 AEs within 1 wk of first dose, and DLTs at any time, were less frequent with a LHH vs flat dosing regimen (Tbl). Importantly, a LHH dose of 1-6-6 (1 x 10^{12} vp on D1; 6 x 10^{12} vp on D3 and 5; greater than the previous flat MTD) was tolerated. Acute increases in TNFα/IFNγ were limited and no severe CRS was seen. Increases in IL-6/MCP-1 with 1 x 10^{11} or 1 x 10^{12} vp flat dosing were negligible, whereas acute increases in IL-6/MCP-1 were seen after the first dose of 3 x 10^{12} vp when given as a flat dose (negligible increases on D3/5). Notably, cytokine responses with 1-3-3 dosing (1 x 10^{12} vp on D1; 3 x 10^{12} vp on D3 and 5), including after the first 3 x 10^{12} vp dose on D3, were negligible. Cytokine responses after the first dose of 6 x 10^{12} vp in the 1-6-6 regimen were similar to those seen with the first dose of the flat 3 x 10^{12} vp regimen. **Conclusions:** LHH dosing appears to induce a desensitization mechanism allowing higher cumulative doses of T-SIGn vectors to be given without the associated acute reactions to viral infusions. This finding may have implications for optimizing safety-efficacy profiles of viral vectors in cancer. Clinical trial information: NCT02636036, NCT03852511 and NCT04053283. Research Sponsor: PsiOxus Therapeutics Ltd.

Safety summary (% of patients).

	Flat 1 x 10^{11} (n=10)	Flat 1 x 10^{12} (n=26)	Flat 3 x 10^{12} (n=22)	1-3-3 and 1-6-6 (n=26)
Days 1-7				
AE	100	100	100	92
Gr≥3 AE	0	19	41	15
SAE	30	8	5	15
Related SAE	30	8	0	4
DLTs any time	10	15	14	4

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2573 **Poster Session**

Micro-organospheres retain patient tumor microenvironment for precision immuno-oncology.

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Background: Current patient-derived organoid (PDO) models are largely devoid of immune components. We developed a precision microfluidic and membrane platform to generate patient-derived micro-organospheres (MOS) that retain tumor-resident immune and stromal components for personalized immuno-oncology (IO) assays. **Methods:** MOS were generated from lung, kidney, and colorectal cancer patients. The composition and function of patient tumor-resident immune cells in MOS were characterized by flow cytometry, single-cell RNA-seq, antibody staining, and TCR-seq. High-content and longitudinal imaging with AI analyses were used to quantify tumor cell death and immune cell dynamics inside MOS in response to IO therapies including checkpoint inhibitors, T cell bispecific antibodies, and adoptive tumor infiltrating lymphocyte (TIL) therapies, followed by single-cell analyses. **Results:** Tumor and stromal cells quickly form tissue niches inside MOS to sustain the viability and function of encapsulated immune cells. MOS derived from lung and kidney cancer patients respond to Nivolumab, indicated by the Annexin V apoptosis marker. ESK1* (TCB antibody targeting HLA-A2/WT1) induces killing in eight lung tumor patients derived MOS. We further developed a MOS T-cell potency assay as autologous TILs or PBMC efficiently infiltrate MOS from lung, kidney and CRC patients and induce tumor cell apoptosis. Adjunctive therapies combining TCB with TILs enhanced the potency of adoptive cell therapy against lung tumor. Based on the data, three ongoing and upcoming personalize IO clinical trials will further validate the ability of the MOS assay to predict patient response to TCB, checkpoint combinations, and adoptive cell therapy. **Conclusions:** MOS provide a rapid and scalable personalized platform for developing and testing IO therapies such as checkpoint inhibitors, bispecific antibodies, and T cell therapies on patient tumor models that still retain the original tumor microenvironments. Research Sponsor: None.

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2574 **Poster Session**

Phase 1b study of the novel first-in-class G protein-coupled estrogen receptor (GPER) agonist, LNS8801, in combination with pembrolizumab in patients with immune checkpoint inhibitor (ICI)-relapsed and refractory solid malignancies and dose escalation update.

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Background: LNS8801 is an oral, highly selective, small molecule agonist of the G protein-coupled estrogen receptor (GPER). LNS8801 normalizes c-Myc levels in cancer cells, inhibits proliferation, suppresses invasion, and enhances immune recognition. In preclinical models, LNS8801 has demonstrated increased activity with ICIs. In the first-in-human dose escalation study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with metastatic solid tumors (NCT04130516). **Methods:** Patients who are relapsed and refractory (r/r) to PD-1/L1 ICIs and have measurable disease are enrolling in a Phase 1b cohort and receive LNS8801 (125 mg, QD, PO) and pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective is safety and tolerability assessed according to NCI CTCAE v5.0. Secondary endpoints include pharmacokinetic, pharmacodynamics (eg., increase in serum prolactin over the initial 10 hours of dosing to assess GPER engagement), objective response rate and clinical benefit rate per RECIST v1.1. **Results**: Updates from the dose escalation portion of the study include long term benefit in a monotherapy patient with cutaneous melanoma on treatment for 2 years with RECIST stable, metabolically inactive disease by PET; a metastatic uveal melanoma patient on therapy for a year, and growing confidence in LNS8801's favorable safety profile and predictive systemic biomarkers. As of 2/1/22, 13 ICI r/r patients were treated with LNS8801 and pembrolizumab, including those who entered the study directly after confirmed progression on ICIs. Cancer types include lung (3), colorectal, vaginal, nasopharyngeal, neuroendocrine, uterine, and pancreatic cancer, mesothelioma (2), and cutaneous and uveal melanoma. 46% of patients had AEs possibly related to study drugs (31% grades 1-2 and 31% grade 3), with colitis (15%) and fatigue (23%) appearing in more than 10% of patients. Of the 10 evaluable patients, 7 had stable disease (SD), with 4 patients demonstrating tumor regression. At the data cut-off, duration of treatment ranged from 0.7–7.5 months with 4 patients treated between 4.8 and 7.5 months and 4 patients continuing on treatment. All evaluated patients with SD had a prolactin response indicative of systemic target engagement. **Conclusions**: The combination of LNS8801 and pembrolizumab is tolerable without unanticipated toxicities and demonstrates encouraging anti-tumor activity in patients that are r/r to ICIs, including patients who enrolled immediately after confirmed progression on pembrolizumab alone. These data, as well as continued follow-up on patients with long-term benefit from dose escalation, support further development of LNS8801 as a cancer therapeutic. Clinical trial information: NCT04130516. Research Sponsor: Linnaeus Therapeutics.

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2575 **Poster Session**

Phase I study of epacadostat in combination with sirolimus in advanced malignancy.

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Background: Epacadostat (E) is an inhibitor of Indoleamine 2,3 dioxygenase-1 (IDO1) which is a rate-limiting enzyme in the catabolism of tryptophan to kynurenine. The inhibition of IDO1 leads to increase tryptophan and reversal of immunosuppression by increasing the proliferation of T cells, suppression of regulatory T cells (Tregs) and activation of mTOR which suppresses autophagy. Sirolimus (S) can reverse the mTOR activation induced by E, suppress the expression of PD-L1 and function of Tregs. We initiated a phase I trial to test the safety and tolerability of SE combination in patients with advanced solid tumors, with plans for an expansion phase II study in patients with advanced recurrent lung cancer once maximum tolerated dose (MTD) was defined. **Methods:** The phase I trial portion of the study used a modified 3+3 design in which the dose transition rule was similar to standard 3+3 design with the modification based on sirolimus PK data. S had a lead-in of 3mg/day(d) at day -7 followed by 1mg/d with E added on day 1 of Cycle 1 starting at 300mg bid in a 28d cycle at dose level 1; then S is escalated to 6mg/d followed by 2mg/d maintenance with E at 300mg bid at level 2. An additional level 3 was added with S at 6mg/d followed by 2mg/day with E at 400 bid based on results of E at 400-600 mg bid in combination with a checkpoint inhibitor with improved control of peripheral kynurenine and intra-tumoral kynurenine reductions. Enrollment continued until Dose limiting toxicity (DLT) which was defined as grade 3 hematologic toxicities or grade 3 or 4 non-hematologic toxicities up to Cycle 2 day 1. MTD was defined as DLT not exceeding 33% of subjects. **Results:** The phase I study enrolled 15 patients, with 9 patients evaluable. The types of cancers were non-small cell lung ca (1), colorectal (5), esophagus (1), gallbladder (1) and sarcoma (1). DLT was not observed up to level 3. Adverse events attributed to SE were Grade 1 Diarrhea (2), stomach pain (1); elevated liver enzymes (ELE) (1), decreased white blood cell (1), anorexia (1), hypokalemia (1), dizziness (1), skin rash (1); Grade 2 ELE (1), Anemia (1), Vertigo (1), Constipation (1), Nausea (2); Grade 3: Diarrhea (1), serotonin syndrome (1), dyspnea (1). The best response observed was stable disease in 3 patients, 5 patients had disease progression and 1 patient was not assessable for response due treatment discontinuation related to side effect of serotonin syndrome. The Expansion Cohort (Part 2) did not proceed since the sponsor decided to discontinue further development of E. **Conclusions:** The combination of SE is feasible, tolerable with mostly grade 1 and 2 toxicities. There were few grades 3 toxicities. SE produced stable disease as best response in 33% of patients. Research using the combination of SE as an immunomodulatory therapy in patients with lung cancer resistant to checkpoint inhibitor is worth additional exploration. Clinical trial information: NCT03217669. Research Sponsor: Epacadostat.

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2576 **Poster Session**

Systemic TLR7/8 micelles trigger a novel and potent anti-tumor response by strong recruitment of neutrophils leading to massive tumor cell killing.

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Background: Clinical use of TLR7/8 agonists is currently restricted to topical application of Imiquimod for treatment of superficial basal cell carcinoma since systemic administration is prevented due to dose-limiting toxicity. Here, we present a novel micelle-based drug delivery technology containing a lipid-anchored TLR7/8 agonist for intravenous administration. The MBS8 formulation shows good efficacy in mouse cancer models, is well tolerated in rodents and non-human primates and is currently being tested in clinical studies (NCT04855435). **Methods:** MBS8 was tested in 12 syngeneic mouse cancer models as monotherapy or in combination anti-PD-1 and anti-PD-L1 antibodies. MBS8 was administered IV as slow bolus. Tumors and spleens were analysed using histology, immunohistochemistry, ELISPOT and flow cytometry. Phenotyping of tumor microenvironment was done using flow cytometry and Nanostring analyses. Safety and tolerability were tested in mice, rats and monkeys. Safety-related and PD biomarkers were identified in monkeys using a multiplex MSD technology and validated in whole human blood stimulated with MBS8 *ex-vivo*. **Results:** In several syngeneic mouse tumor models, MBS8 led to complete eradication of established tumors. The complete responders showed tumor rejection upon re-challenge. In these mice, a $CD8^+$-dependent tumor-specific immune memory response was evident. Tumors demonstrated a massive tissue necrosis (> 80%) within 24-48h after the first drug administration and showed massive neutrophil infiltration 6h after dosing. Antigen specific $CD8^+$ T-cells were detected in tumors 24 hours after treatment with increased $CD8^+$:T_{reg} cell ratio and enhanced antigen presentation in tdLN. MBS8 showed both additive and synergistic effect when combined with anti-PD-1 or anti-PD-L1 antibody treatment. Moreover, in tumors being resistant to anti-PD-1 treatment, co-administration of MBS8 reverted sensitivity to anti-PD-1 treatment in a synergistic manner. A panel of cytokines induced by MBS8 upon repeat dose administration in monkeys was identified in plasma as potential biomarkers. Ten of them were further evaluated in whole human blood treated with MBS8 *ex vivo*. Currently, these cytokines are being used in Phase I clinical studies. **Conclusions:** MBS8 showed significant anti-cancer activity in multiple *in vivo* solid tumor models when administered either as monotherapy or in combination with ICIs. MBS8 demonstrated a novel mode of action with neutrophils playing a central role as primary effector cells causing a rapid killing of tumors. Further, adaptive immune response was initiated including generation of tumor specific $CD8^+$ cells and establishment of the immune memory. MBS8 was well tolerated in rodents and cynomolgus monkeys at the dose levels above therapeutic effective doses identified in mice, thus providing a good therapeutic window. Research Sponsor: MonTa Biosciences.

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2577 **Poster Session**

Phase I dose escalation of LAVA-051, a novel bispecific gamma-delta T-cell engager (Gammabody), in relapsed/refractory hematological malignancies.

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Background: LAVA-051 is a 27kD humanized bispecific single domain antibody (VHH) that directly engages CD1d and the Vδ2-TCR chain of Vγ9Vδ2-T cells and additionally stabilizes the interaction between CD1d and type 1 NKT cells (Nature Cancer 2020;1:1054-1065) to mediate potent killing of CD1d-expressing tumor cells. By engaging innate-like T cell subsets with inherent antitumor activity, namely Vγ9Vδ2-T and type 1 NKT cells, LAVA-051 has the potential to combine high therapeutic efficacy with limited off-tumor toxicity. CD1d is expressed by tumor cells in the majority of patients with CLL (chronic lymphocytic leukemia) and MM (multiple myeloma), while expression in AML (acute myeloid leukemia) is most pronounced on (myelo)monocytic subtypes. Tolerability studies in non-human primates with cross-reactive surrogate bispecific $\gamma\delta$-T cell engagers showed a good safety profile without signs of CRS (cytokine release syndrome). **Methods:** This is an open label, accelerated titration design, phase 1/2a study in patients with relapsed/ refractory CLL, MM, and AML (NCT04887259). The phase 1 study starts with single-patient cohorts for the first 3 dose levels followed by a 3+3 design. The primary objectives of the study are to investigate the safety and tolerability of LAVA-051 and to determine its recommended Phase 2a dose (RP2D). Secondary objectives of the study include evaluation of PK, PD, immunogenicity, and preliminary antitumor activity. The (flat) starting dose was determined to be 0.45 μg. LAVA-051 is administered by IV infusion over 2 hours twice a week. **Results:** As of Feb 14, 2022, a dose level of 45 μg has been reached with no reports of CRS (ASTCT grading) or dose limiting toxicities (DLTs). Six patients in total have been treated with LAVA-051; 4 patients (2 MM, 2 CLL) were evaluable for DLTs during cycle 1 at dose levels 0.45 μg, 3 μg, 15 μg and 45 μg. Treatment emergent AEs (TEAEs) (CTCAEv5.0) were predominantly of grade 1 and 2 severity (e.g. fever, chills, and headache). One patient (45 μg) reported a grade 2 infusion related reaction (IRR) that lasted less than 12 hours following the first administration only. Frequency and severity of TEAEs did not increase with escalating doses and all TEAEs were reversible. One patient with CLL developed symptoms consistent with a tumor flare reaction during cycle 1, and continues on cycle 5 of treatment with stable disease at 15 μg. PK data indicate increasing drug exposure in correlation with increasing doses of LAVA-051, and PD data indicate a dose-dependent increase in LAVA-051 receptor occupancy of the Vγ9Vδ2-T cell receptor. Importantly, no consistent or significant changes in measured cytokines have been observed. Updated results will be presented at the congress. **Conclusions:** LAVA-051 has been well tolerated early in dose escalation with on-mechanism pharmacodynamics consistent with Vγ9Vδ2-T cell engagement. Clinical trial information: NCT04887259. Research Sponsor: LAVA Therapeutics N.V.

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2578 **Poster Session**

Assessing PD-L1 without a biopsy and through PD-L1 PET imaging with 18F-BMS-986229.

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Background: Programmed death ligand-1 (PD-L1) is usually determined by immunohistochemistry (IHC). Determining PD-L1 status by whole body, non-invasive PD-L1 PET imaging with 18F-BMS-986229 tracer infusion may be a way to circumvent limitations to PD-L1 IHC such as poor tissue availability; discrepant PD-L1 IHC results among different tumors within the same patient; and inability to measure PD-L1 longitudinally given challenges with repeated biopsies. **Methods:** Within the prospective ADAPT-IT trial (NCT03122522) testing an abbreviated course of nivolumab (nivo) + ipilimumab (ipi) in patients with unresectable stage III or IV melanoma, we investigated PD-L1 PET imaging in a 10-patient expansion cohort at baseline and after 6 weeks of treatment. Maximum standard uptake value (SUV max) and mean of all SUV max for lesions for PD-L1 PET were calculated on a whole patient level for each target/ non target lesion. Standard treatment response was determined by RECIST v1.1 at weeks 6 and 12. PD-L1 IHC was scored using the E1L3N antibody by tumor proportion score (TPS), Immune Cell Score (ICS), and a Combined Positive Score (CPS). Comparisons between PD-L1 PET parameters and response were determined by complete or partial response (CR/PR); stable disease (SD), and progressive disease (PD) at respective imaging timepoints. Absolute changes in PD-L1 SUV mean and max were calculated between scans. The correlation between PD-L1 PET and IHC was estimated using Spearman's coefficient correlation. **Results:** Five patients (50%) had a PR to treatment at week 6; one of these PR became a CR at week 12 and one PR was not assessable at week 12. All RECIST responders at week 6 (n = 5) had baseline PD-L1 SUV mean $\geq$3.00, and all progressors at week 6 (n = 3) had baseline PD-L1 SUV mean $\leq$2.60 (Table). A similar trend was observed when assessing response at week 12 and when considering baseline PD-L1 SUV max. Patients had changes in their PD-L1 SUV levels between baseline and week 6. Baseline PD-L1 SUV mean (inclusive of all lesions within a patient) correlated with PD-L1 IHC by TPS, ICS, and CPS (r = 0.64, 0.5, 0.47, respectively). No patients had side effects from 18F-BMS-986229 tracer infusion. **Conclusions:** The signal of PD-L1 positivity by PET imaging with 18F-BMS-986229 at baseline appears associated with early efficacy from nivo + ipi in this small cohort and may offer additional information than PD-L1 IHC. The ability to assess PD-L1 on a whole patient level at multiple timepoints on treatment may have future implications in how best to sequence and combine immunotherapies but further study in larger patient cohorts is needed. Clinical trial information: NCT03122522. Research Sponsor: Bristol Myers-Squibb.

	PR[1], N = 5	SD[1], N = 2	PD[1], N = 3
Mean of Baseline PD-L1 SUV[2] (PD-L1 positive lesions only)	5.40 [3.00 – 8.60]	3.58 [3.15 – 4.00]	2.40 [2.20 – 2.60]
Max of Baseline PD-L1 SUV[2]	7.30 [3.20 – 8.60]	4.90 [4.60 – 5.20]	2.20 [0.00 – 2.60]

[1]Assessed at Week 6
[2]Median [Range]

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2579 **Poster Session**

The effects of AVM0703 mobilization of endogenous gamma delta/invariant TCR+ bispecific natural killer T-like cells against solid tumors and blood cancers.

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Background: Glucocorticoids (GC) are a common component of blood cancer regimens, typically at doses 40 mg or lower due to concerns of pancreatitis and hepatotoxicity (Walasik-Szemplińska et al. Thyroid Research. 2019;12:13; Ataallah et al. Cureus. 2020;12[7]) and neuropsychiatric effects. AVM Biotechnology has developed a high concentration, high volume, preservative-free, patent pending formulation of dexamethasone (AVM0703), that allows administration of up to 21 mg/kg (1470 mg for 70 kg) over a one-hour IV infusion. Prophylactic use of circadian physiologic hydrocortisone reduces the risk of GC neuropsychiatric side-effects (Warris LT, et al. J. Clin. Oncol. 2016;34:2287; Meijer & de Kloet Endocrinology. 2017;158:448). Acute supra-pharmacologic doses (>6 mg/kg) AVM0703 mobilizes endogenous bispecific gamma delta invariant TCR+ bi-specific Natural Killer T-like cells (AVM-NKT) (PCT/US21/19773), via a non-GC receptor, that rapidly home to diseased organs in preclinical models and are directly related to tumor killing, including Non-Hodgkin's Lymphoma, Melanoma, and Multiple Myeloma. **Methods:** Cancer cell lines and (mouse host) were i) immune-resistant mouse A20 B lymphoma (Balb/c), ii) xenografted human T-ALL CCRF-CEM (NCRnu), iii) mouse B16F10 melanoma (B62DF1), and iv) mouse MOPC315 (Balb/c). Cancer cell lines were inoculated into the flank either as single cell suspensions or encased in Matrigel. When tumor volume reached between 100-500mm^3 well-established tumors, mice were orally gavaged with a human equivalent dose (HED) of 15-18 mg/kg AVM0703 as monotherapy, or as a preconditioning prior to adoptive cell transfer (ACT), or in combination with chemotherapy. Responses were determined by tumor volume measurements, tumor immunohistochemistry or flow cytometry detection of residual cancer cells. **Results:** Immunohistochemistry analysis of tumors from AVM0703 treated mice demonstrated pseudoprogression similar to checkpoint inhibitors: *i.e.* tumors were measurable however in some cases all cancer cells had been eradicated. Therefore, subsequent tumor monitoring at end point was done by flow cytometry to quantify the total number of live cancer cells more accurately than tumor measurements by calipers or immunohistochemistry, due to pseudoprogression and limitations of examining only a few sections from each tumor. **Conclusions:** AVM0703 led to: i) complete response (CR) in 27% of immune-resistant mouse A20 tumors as monotherapy and CR in 60% when combined with 2 doses of cyclophosphamide/fludarabine (CyFlu); ii) tumor eradication and long-term memory against xenografted human T-ALL; iii) enhancement of ACT equivalent to CyFlu preconditioning in mouse melanoma; and iv) preliminary 95% CR against mouse multiple myeloma. Research Sponsor: AVM Biotechnology, U.S. National Institutes of Health.

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2580 **Poster Session**

Radiotherapy-immunotherapy related pneumonitis prediction from pre-treatment CT using a deep graph-based integrative model.

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Background: Early prediction of symptomatic pneumonitis (grade ≥ 2) could potentially assist the comprehensive management for non-small cell lung cancer (NSCLC) patients who received radiotherapy combined with immunotherapy. A more accurate integrative model for symptomatic pneumonia prediction using CT images is needed. **Methods:** This retrospective study contains 243 NSCLC patients (62 symptomatic pneumonitis) who underwent radiotherapy combined with immunotherapy between January 2015 and June 2021. Five-fold cross-validation was performed for training and testing. There were 195 cases in the training set (50 symptomatic pneumonitis) and 48 cases in the validation set (12 symptomatic pneumonitis) in each fold. The deep graph integrative model (DG) was composed of two pre-trained 3D UNet encoders to extract deep features from tumor and lung volumes of pre-treatment CT images, respectively, and a graph attention layer (GAT) for integration and classification. The encoders were fine-tuned using manually segmented tumor and lung CT volumetric patches from the training set. Evaluation measures include area under ROC curve (auc), sensitivity (sen), and specificity (spe). **Results:** Our new DG achieved auc, sen, and spe of 0.823, 0.767, and 0.810, which outperformed conventional CT radiomics model (auc 0.743, sen 0.620, spe 0.752), 3D UNet based deep radiomics model (auc 0.761, sen 0.746, spe 0.737), and our model without GAT (auc 0.796, sen 0.762, spe 0.782). The improvement was statistically significant ($p < 0.001$). **Conclusions:** Our DG model improved symptomatic pneumonia prediction using CT images, which can be used as a tool to effectively improve the safety and personalized treatment of combined radiotherapy with immunotherapy for NSCLC patients. Research Sponsor: National Natural Science Foundation of China.

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2581 **Poster Session**

Outcomes of patients (pts) treated with novel immunotherapy (IT) agents in phase 1 clinical trials (Ph1-CT) at early lines for advanced disease.

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Background: The overall survival (OS) benefit observed with immune checkpoint inhibitors led to their approval in many tumor types. Given the large number of IT compounds in early clinical development, many pts are offered IT within Ph1-CT even before having exhausted standard of care (SOC) therapies. We assessed outcomes of pts receiving novel IT treatments within Ph1-CT at the Phase 1 Unit of Catalan Institute of Oncology (ICO), Barcelona, Spain. **Methods:** We retrospectively reviewed a correlative series of pts with advanced/metastatic solid tumors treated with IT within Ph1-CT at ICO from January 2018 to June 2021. Primary endpoint was to assess clinical outcomes measured by median progression-free survival (mPFS) and median OS (mOS) according to number of prior lines (PL) for recurrent/metastatic disease, grade 3-4 toxicity (G3-4 Tox) and age. Data on prior IT (yes vs no) and availability of alternative SOC were evaluated. Overall response rate (ORR) was assessed according to RECIST 1.1. Clinical benefit rate (CBR) was defined as complete/partial response + stable disease for ≥6 months (m). PFS/OS were calculated by Kaplan-Meier method. Log-rank test was used for comparisons. Median PFS of alternative SOC according to historical data was recorded by tumor type and line of treatment. **Results:** A total of 104 pts received IT within Ph1-CT: IT monotherapy = 39 (37.5%), IT combinations = 65 (62.5%) (IT+IT = 59 [90.8%], IT+targeted therapy = 6 [9.2%]). Median age was 54 y (42-77), 62.5% were men and all had ECOG 0-1. Four most frequent cancers were urothelial (19.2%), colorectal (15.3%), head & neck (12.5%) and glioblastoma (11.5%). Number of PL: 0 = 20 (19.2%) pts, 1 = 37 (35.6%) pts, ≥2 = 47 (45.2%) pts. Nine (8.6%) pts had received prior IT. G3-4 Tox rate for the overall population was 19.2% and for pts who had received prior IT was 33%. ORR was 11.5%; CBR was 24%. Overall mPFS and mOS were 2.7m and 8.6m, respectively. Pts with less PL had greater mPFS and mOS ($p < 0.05$) (Table). Pts with available alternative SOC had lower mPFS but similar mOS compared to historical SOC (2.6m vs 4.8m, 11.4m vs 11.8m, respectively). G3-4 Tox (yes vs no) and age (< 70 vs ≥70) did not significantly impact on mOS or mPFS ($p = 0.18$ and $p = 0.83$, respectively). At end of Ph1-CT treatment, 47 (45.2%) pts worsened their ECOG status, 15 (14.4%) pts were enrolled in a subsequent trial and 22 (21.1%) pts received SOC. **Conclusions:** In our cohort of pts treated with novel IT within Ph1-CT, overall clinical outcomes were modest in terms of mPFS, mOS, and CBR. However, pts with less pre-treated tumors seem to achieve higher survival benefit from early treatment with IT within Ph1-CT, although this benefit remains unclear in pts with alternative SOC. Research Sponsor: None.

Pts	PFS(m)	OS(m)
≤1 PL vs ≥2 PL	3.8 vs 2.5, **p 0.003**	14.1 vs 8.7, **p 0.002**
≤2 PL vs > 2 PL	3.6 vs 1.3, **p 0.002**	11.5 vs 1.7, **p 0.004**
Pts in IT Ph1-CT (with vs without available SOC)	2.6 vs 2.1, **p 0.048**	11.4 vs 4, **p 0.0083**

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2582 **Poster Session**

A phase 1 first-in-human dose finding/randomized phase 2 study of IMM60 and pembrolizumab (PEM) in advanced melanoma and non–small cell lung cancer (NSCLC; IMP-MEL).

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Background: Invariant natural killer T-cells (iNKTs) share features of innate cells (NK-like) and T-cells (can prime and boost an adaptive immune response). The importance of this relatively rare lymphocyte subset has generated increased interest due to its dual ability to have a direct cytotoxic effect on CD1d expressing tumors and also its ability to induce long-lasting antitumor CD8 T cell responses mediated by cross priming and licensing of dendritic cells. Various clinical approaches involving the use of allogenic iNKT cells (both untransduced and CARs) are in development and here we describe initial clinical studies with IMM60, a synthetically derived agonist of iNKT cells which is formulated in a liposome(PORT-2). In preclinical studies, IMM-60 treatment results in maturation of DCs and B cells and a potent stimulation of iNKT cell-derived IFN-g. In efficacy studies, IMM60 demonstrated monotherapy activity in PD-1 resistant models, (eg., B16-F10), up-regulation of PD-L1 expression on cancer cells as a consequence of its priming effect, and was able to overcome resistance to PD-1 antibody therapy. **Methods:** IMP-MEL is an open-label first-in-man phase 1/2 study, currently enrolling adult subjects with advanced NSCLC and melanoma. IMM60 containing liposomes were administered IV Q3W at 3 escalating dose levels for 6 doses alone or with PEM 200mg Q3W. The study seeks to assess the safety and efficacy of IMM-60 alone and in combination with PEM. **Results:** 5 subjects have been enrolled in the monotherapy cohort having a median of 3 prior therapies (min 2, max 5). Median age was 64.5 years. No treatment related adverse events have been reported nor any objective disease responses in the evaluable monotherapy subjects (n=3) to date. **Conclusions:** IMM-60 is well tolerated when administered IV as monotherapy at the doses tested. The liposomal formulation leads to a favorable preliminary safety profile. Full results of the phase 1 will be reported at the meeting with analysis of circulating cytokines and flow cytometric analysis. The trial plans to transition to phase 2 testing IMM60-alone vs PEM monotherapy vs the combination of IMM60 with PEM. Clinical trial information: 80472712. Research Sponsor: iOX Therapeutics, University of Oxford.

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2583 **Poster Session**

A phase 1 study of the novel immunotoxin MT-5111 in patients with HER2+ tumors: Interim results.

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Background: MT-5111 is a 55kD engineered toxin body (ETB) targeting HER2 in solid tumors that binds to an epitope distinct from trastuzumab and pertuzumab, offering potential combination strategies with other HER2-targeting agents. MT-5111 may demonstrate efficacy in patients (pts) resistant to other HER2-targeting agents, as its mechanism of action induces direct cell kill via enzymatic and permanent ribosome destruction. **Methods:** This is a phase 1 study in adults with advanced HER2+ solid tumors. The dose-escalation portion (Part A) enrolls pts into sequential dose cohorts, followed by Part B expansion cohorts for HER2+ breast cancer (BC), gastroesophageal adenocarcinoma (GEA), and any other HER2+ cancer (CA). MT-5111 is dosed weekly IV over 30 min in each 21-day treatment (tx) cycle until disease progression, unacceptable toxicity, death or withdrawn consent. **Results:** As of Jan 2022, 27 pts had enrolled in Part A cohorts (0.5 to 10 μg/kg/dose) with completed DLT assessments: 9 (33%) pts were male and 18 (67%) female, median age 67 and a median of 4 prior systemic and 2 prior HER2-targeting tx. Common tissue types were BC (9/30%), biliary CA (6/22%), GEA (4/15%). The following safety data reflect 33 treated pts to date including ongoing 13 μg/kg/dose Part A and 10 μg/kg/dose BC expansion cohorts. No Grade (G) 4/5 tx-emergent adverse events (AEs) or DLTs occurred. Tx-related AEs occurred in 17 (52%) pts, most commonly G1/2 fatigue (8/24%). 3 pts had G1 troponin elevations without clinical signs or symptoms of cardiac distress: 1 at 6.75 μg/kg/dose, 2 at 10 μg/kg/dose. 2 pts (3 and 4.5 μg/kg/dose) had reversible G2 and G1, respectively, infusion-related reactions (IRR)s. A comparison of cytokines from baseline to on-treatment timepoints reveals no evidence of significant changes, even in pts with IRR. Best response per RECIST thus far was stable disease (SD) in 7 pts or non-CR/non-PD in 2 pts: 1 pt had SD for 12 weeks (wks) (4.5 μg/kg, pancreatic CA); 1 pt (1 μg/kg/dose, BC) had non-CR/non-PD for 30 wks; 1 pt (10 μg/kg/dose, GEA) has ongoing SD for 18 wks. AUC_{last} data match PK simulations in non-human primate studies. C_{max} at 10 μg/kg/dose is ≥5 times the IC_{50} values of high HER2 expressing gastric CA and BC cell lines while approaching the IC_{50} of a moderately HER2 expressing liver CA cell line. **Conclusions:** MT-5111 is well tolerated to-date with no clinically significant immuno/cardiotoxicity. Dose escalation is ongoing at a dose of 13μg/kg, expected to be required for efficacious exposure. Clinical trial information: NCT04029922. Research Sponsor: Molecular Templates, Inc.

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2584 **Poster Session**

Factors associated with acute kidney injury among patients with cancer treated with immune checkpoint inhibitor therapy: A population-based study.

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Background: Cancer immune checkpoint inhibitor (ICI) therapy may be associated with kidney immune-related adverse events (IRAEs) and other causes of acute kidney injury (AKI). In clinical trials, the frequency of AKI events was uncommon, however, further real-world study is warranted. **Methods:** We evaluated the proportion of AKI events among patients with advanced cancer (bladder, head and neck, lung, kidney and malignant melanoma) treated with ICI therapy in Ontario, Canada from 2012 - 2018. AKI was defined by a rise in the concentration of serum creatinine as per Kidney Disease: Improving Global Outcomes (KDIGO) criteria. A multivariable regression model was used to identify predictors of AKI while accounting for the competing risk of death. **Results:** A total of 4,380 patients received ICI therapy. In follow-up, 1,283 (29%) had recorded AKI event (any stage AKI) and 289 (7%) had a severe AKI event (≥ stage 2). Median time to AKI was 6 months (Interquartile Range 2-16 months) and ≤ 1 % of patients received dialysis therapy. Within 30 days of any observed AKI event, 853 (58%) discontinued ICI therapy, 372 (29%) were hospitalized and 266 (21%) died. Mortality was significantly higher among patients who experiencing a severe AKI event (≥ stage 2) as compared to patients with a less severe AKI event (stage 1) or no observed AKI event. Among patients alive at 30 days following an AKI event, 14% received an outpatient corticosteroid or immunosuppressive therapy prescription, 7% had a visit with a nephrologist. Characteristics associated with a higher risk of AKI included female sex, bladder or kidney cancer (reference malignant melanoma), history of hypertension or diabetes, higher Charlson comorbidity score, a baseline estimated glomerular filtration rate less than 30 mL/min/1.73 m^2, or outpatient prescription for either a proton pump inhibitor or non-steroidal anti-inflammatory drug. Among patients with an AKI event and treatment discontinuation, re-challenge of ICI therapy was infrequent (16%) with a significant risk of a recurrent AKI event (57%). **Conclusions:** In a population-based study among patients with cancer receiving ICI therapy, the rate of AKI was common (29%) but severe AKI was less frequent (7%). Rates of ICI discontinuation, hospitalization and death are substantial following an AKI event. Kidney function should be monitored carefully among patients undergoing ICI therapy who have common risk factors for developing renal disease. Nephrology consultation may be optimized among patients who develop a severe AKI event, especially among individuals who are considered for ICI therapy re-challenge. Research Sponsor: Medical Oncology Research Fund (MORF) London Regional Cancer Program.

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2585 **Poster Session**

Systematic review and meta-analysis evaluating the impact of antibiotic use on the clinical outcomes of patients with cancer treated with immune checkpoint inhibitors.

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Background: In recent years, the gut microbiome has increasingly emerged as influencing the response to immune checkpoint inhibitors (ICIs) and antibiotic (ABX) exposure has repeatedly been shown to impair clinical outcomes of patients suffering from different cancer types and treated with ICIs. We published in 2020 a meta-analysis confirming that ABX use hampered survival of non-small cell lung cancer (NSCLC) patients treated with ICIs. The present study aims to determine whether ABX use also reduces survival of patients receiving ICIs for other cancers. **Methods:** PubMed and major oncology conferences' proceedings were systematically searched to identify studies assessing the impact of ABX on the clinical outcomes of cancer patients treated with ICIs. Studies were included when reporting data on Overall Survival (OS), Progression-Free Survival (PFS), Overall Response Rate (ORR) and Progressive Disease Rate (PD), according to ABX exposure. Pooled Hazard Ratios (HRs) for OS and PFS and Odds Ratios (ORs) for ORR and PD were calculated, as well as HRs for OS and PFS according to different cancer types and different ABX exposure time windows (TWs). **Results:** Overall, 94 independent cohorts were included, representing 26,174 patients suffering from various types of cancer. The pooled HRs for PFS (61 cohorts, 13,224 patients) and OS (88 cohorts, 25,480 patients) were 1.47 [95% Confidence Interval (CI) 1.31-1.66] and 1.66 [95% CI 1.50-1.83], respectively, confirming a significant harmful impact of ABX on patient' survival, observed across all cancer types (Table). The analyses of OS and PFS based on ABX exposure TWs suggested a stronger deleterious effect of ABX when taken around ICI treatment initiation. The response to treatment among ABX users was also impaired: the pooled ORs for ORR (30 cohorts, 4,590 patients) and PD (33 cohorts, 4,972 patients) were 0.55 [95% CI 0.39-0.77] and 1.97 [95% CI 1.48-2.64], respectively. **Conclusions:** ABX were shown to impair the clinical outcomes of cancer patients treated with ICIs, regardless of cancer type. Research Sponsor: Da Volterra.

Impact of ABX use on the survival of cancer patients treated with ICIs.

Cancer Type	Number of Patients for OS (ABX Users)	Pooled HR OS [95% CI]	Number of Patients for PFS (ABX Users)	Pooled HR PFS [95% CI]
All Cancer Types	25,480 (6,994)	1.66 [1.50-1.83]	13,224 (4,142)	1.47 [1.31-1.66]
NSCLC	12,674 (2,834)	1.62 [1.38-1.90]	5,463 (1,368)	1.49 [1.26-1.76]
Urothelial Carcinoma	3,371 (1,545)	1.60 [1.09-2.34]	3,232 (1,499)	1.26 [0.84-1.90]
Melanoma	2,812 (339)	1.81 [1.27-2.59]	708 (111)	1.72 [0.95-3.10]
Renal Cell Carcinoma	1,029 (212)	1.84 [1.30-2.62]	529 (127)	2.04 [1.40-2.98]
Other Cancers*	2,285 (766)	1.74 [1.26-2.39]	1,983 (684)	1.55 [0.87-2.75]

*Head and neck cancer, esophagogastric cancer, Hodgkin's lymphoma, gynecologic cancers, and sarcoma.

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2586 **Poster Session**

Outcomes of responders to PD-1/PD-L1 inhibitors who discontinue therapy after sustained disease control.

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Background: PD-1/PD-L1 immune checkpoint inhibitors (ICIs) are widely used in the treatment of metastatic malignancies. Judiciously balancing disease control (DC) against development of immune-related adverse events (irAE) remains a crucial aspect of treatment. The effect of treatment discontinuation after sustained disease control (SDC) is unknown. The purpose of this analysis was to evaluate outcomes of responders to ICI who discontinue treatment after a minimum of 12 months (SDC). **Methods:** We retrospectively reviewed the database of the University of New Mexico Comprehensive Cancer Center between 2014 and 2021 and identified patients who had received ICI. Patients with metastatic solid tumors who had stopped ICI therapy after achieving SDC [stable disease, partial response, complete response (SD,PR,CR)] were selected and outcomes reviewed from their electronic health records. **Results:** We identified 204 patients who were treated with ICI for various solid cancers. Forty-four patients (21.6%) met the criteria, of whom 35 with follow-up data were included in the final analysis; including 11 melanoma, 5 non-small cell lung, 4 head & neck, 8 renal, 4 urothelial, 1 anal, 1 Merkel cell carcinoma, and 1 liposarcoma. Patients were divided into two groups: those who stopped ICI due to an irAE [irAE group, n=14, median treatment time (MTT), 16.6 mo] and those who stopped due to other reasons (eg completion of 2 years of therapy, n=20, non-cancer related surgery, n=1) (non-irAE group, n=21, MTT, 23.7 mo). Among the irAE group, the most common irAE included pneumonitis, rash, transaminitis, and fatigue. As of data cutoff date, 10 of 14 (71%) patients continued to show SDC. Only 4 of 14 (28.6%) patients in this group experienced progression of disease (PD), one of whom was re-challenged with nivolumab and achieved DC (median follow-up of 19.2 mo after last dose of treatment, range 3-50.2 mo). Among the non-irAE group, 13 of 21 (62%) continued to have SDC. Eight of 21 (38%) experienced PD after stopping treatment, 7 of whom received ICI rechallenge, with 2 of 7 achieving DC (median follow-up of 22.2 mo, range 3.6-54.8 mo). At a median follow-up of 21.3 mo from stopping ICI therapy (range, 3-54.8 mo), 10 patients (71%) from the irAE group and 13 (61.9%) from the non-irAE group are in DC and have not experienced PD. **Conclusions:** We demonstrate that 23 (66%) patients experienced SDC, regardless of cancer type or development of irAE. After including patients who were re-challenged with ICI due to PD, 26 (74%) remain in DC. Future prospective malignancy-specific trials such as NCT04637594 are warranted to evaluate optimal treatment duration. Research Sponsor: None.

Outcomes of ICI responders who discontinued therapy after ≥ 12 months.

Response to therapy	Non-irAE Group, n=21 (60%)	irAE Group, n=14 (40%)	Total, N=35 (100%)
Disease control	13 (61.9%)	10 (71.4%)	23 (65.7%)
PD	8	4	12
Rechallenge after PD	7	1	8
Disease control after rechallenge	2	1	3

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2587 **Poster Session**

Efficacy and safety of dostarlimab in patients (pts) with mismatch repair deficient (dMMR) solid tumors: Analysis of 2 cohorts in the GARNET study.

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Background: Dostarlimab is a programmed death 1 (PD-1) inhibitor approved in the US as a monotherapy in pts with dMMR solid tumors that have progressed on or after prior treatment, with no satisfactory alternative treatment options; or dMMR advanced/recurrent (AR) endometrial cancer (EC) that has progressed on or after treatment with a platinum-based chemo; and in the EU as a monotherapy in pts with dMMR/microsatellite instabilityhigh (MSI-H) AR EC that has progressed on or after treatment with a platinum-based chemo. Here we report on efficacy and safety in 2 expansion cohorts that enrolled pts with dMMR solid tumors. **Methods**: GARNET is a multicenter, open-label, single-arm phase 1 study. Cohort A1 enrolled pts with dMMR/MSI-H AR EC; cohort F enrolled pts with dMMR/MSI-H/POLε-mut non-EC solid tumors. Pts received 500 mg of IV dostarlimab Q3W for 4 cycles, then 1000 mg Q6W until PD, discontinuation, or withdrawal. Primary endpoints were ORR and DOR by BICR per RECIST v1.1. Biomarker status was based on local assessment. **Results**: For this third interim analysis, 153 pts with dMMR/MSI-H EC and 210 pts with dMMR/MSI-H/POLε-mut non-EC solid tumors (56% colorectal cancer, 11% gastric) were enrolled and treated. Efficacy analysis was performed for 143 dMMR/MSI-H EC and 204 dMMR/MSI-H/POLε-mut non-EC pts who had measurable disease at baseline and $\geq$6 mo of follow-up. ORRs were 45.5% (dMMR/MSI-H EC) and 43.1% (dMMR/POLε-mut non-EC solid tumors; Table). Probability of PFS at 6, 9, and 12 mo was 49.5%, 48.0%, and 46.4% in dMMR/MSI-H EC and 51.8%, 48.1%, and 46.4% in dMMR/MSI-H/POLε-mut non-EC. Median (m) DOR and mOS were not reached for either cohort. A total of 13 pts (8.5%) with dMMR/MSI-H EC and 12 pts (5.7%) with dMMR/MSI-H/POLε-mut non-EC solid tumors discontinued owing to a treatment-related adverse event (TRAE). TRAEs occurring in $\geq$12% of pts were diarrhea, asthenia, fatigue, nausea, and pruritis (dMMR/MSI-H EC) and diarrhea, asthenia, and pruritus (dMMR/MSI-H/POLε-mut non-EC solid tumors). 2 deaths (1 hepatic ischemia, 1 suicide) were attributed by investigators to dostarlimab in pts with non-EC solid tumors. **Conclusions**: Dostarlimab demonstrated durable antitumor activity across 16 tumor types in pts with dMMR solid tumors, confirming efficacy in a larger sample size with extended follow-up. The safety profile was acceptable, with manageable toxicities. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

	dMMR/MSI-H EC N = 143	dMMR/MSI-H/POLε-mut non-EC N = 204
Median follow-up time, mo	27.6	27.7
ORR, n (%, 95% CI)	65 (45.5; 37.154.0)	88 (43.1; 36.250.2)
Response ongoing, n (%)	54 (83.1)	77 (87.5)
mDOR (range), mo	NR (1.18+ to 47.21+)	NR (2.76 to 41.49+)
mPFS (95% CI), mo	6.0 (4.118.0)	7.1 (3.619.5)

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2588 **Poster Session**

Extended duration of anti-PD-1 therapy, using reduced frequency dosing, in patients with advanced melanoma and Merkel cell carcinoma.

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Background: Optimal duration of treatment (DoT) with immune checkpoint inhibitors (ICI) in patients with metastatic melanoma (Mel) and Merkel cell carcinoma (MCC) is unclear. ICI discontinuation in Mel patients, especially those without CR, may be associated with a higher rate of progression over time, as compared to ICI continuation. Thus, extending DoT could improve outcomes. However, indefinite continuation at standard frequency doses (SFD) is not logistically or financially viable. Based on data from phase I studies suggesting sustained PD-1 receptor occupancy beyond 3 months after a single dose of nivolumab, we employed reduced frequency dosing (RFD) of anti-PD-1 antibodies every 2-3 months, to extend ICI duration beyond 2 years. **Methods:** This retrospective study analyzes patients in our skin cancer clinic with metastatic Mel and MCC who experienced initial clinical benefit with anti-PD-1 administered at SFD and then transitioned to RFD. We analyzed safety and efficacy endpoints including progression free survival (PFS) and rates of immune-related adverse events (irAE) with RFD. We also compared the pharmaceutical costs and patient-centered costs between 2 years of treatment at SFD versus extended DoT at RFD. **Results:** From 2014 – 2021, 23 patients with either metastatic Mel (N = 18) or MCC (N = 5) received anti-PD-1 therapy at RFD. Median DoT at SFD in this cohort was 1.1 years (range 0.2 – 2.2) with best objective tumor responses of CR (N =6), PR (N = 11), SD (N = 6). Median DoT at RFD was 1.2 years (range 0.2 – 3.5). The median follow-up for the entire cohort is 3.7 years (range 0.7 – 6.3) after ICI initiation. The 3-year PFS in Mel patients was 100% in those with CR (3/3), 89% with PR (8/9), and 50% with SD (3/6). The 3-year PFS in MCC was 100% in all 5 patients, including patients with CR (3/3) and with PR (2/2). Any-grade irAEs occurred in 43% of patients by 3 years on RFD, and grade 3/4 irAEs presented in 15%. Among the subset of 15 patients with DoT >2 years (median 3.4 yr, range 2.0 – 5.0), total savings amounted to $1.1 million in drugs costs and 384 hours of clinic and travel time despite the increased DoT, as compared to the calculated values for 2-year DoT at SFD. **Conclusions:** RFD may provide an alternative approach to extending DoT in patients receiving ICI without additional logistical and financial burden, while preserving outcomes. Efficacy and safety data suggest sustained biologic activity of ICI with RFD administration. PK/PD analyses on patient samples are ongoing to further characterize the RFD approach. The RFD approach could be utilized to expand ICI access to communities with limited healthcare resources, thereby impacting cancer outcomes at a global scale. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

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2589 **Poster Session**

The effect of circadian rhythm on clinical outcome in patients receiving pembrolizumab in the INSPIRE pan-cancer trial.

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Background: The molecular networks comprising circadian rhythm are expressed in immune cells where they affect immune-related processes. Within the emerging field of chrono-immunotherapy, it has been proposed that immunotherapies should be applied at certain times of day to optimize efficacy. Two recent reports have suggested that earlier administration of immune checkpoint inhibitors (ICIs) in non-small cell lung cancer and melanoma may offer improved survival outcomes (Karaboué et al. ASCO 2021, PMID 34780711). Whether this observation applies to other tumour types, or occurs in geographic regions with differing seasonality, is not known. **Methods:** We retrospectively analyzed the time of administration data from the INSPIRE single-centre, phase II, multi-cohort study of pembrolizumab (200 mg IV over 1 hour, q3w to maximum 35 cycles) in patients with advanced solid tumours (NCT02644369). Kaplan-Meier methods were used to estimate PFS and OS. Cox proportional hazards models were fitted to assess the association between time of administration and PFS or OS, adjusting for cohort. Fisher's exact test was used to test for association with immune-related adverse events (irAEs). **Results:** A total of 106 patients (19 head and neck squamous cell, 22 triple negative breast, 21 epithelial ovarian, 12 melanoma, 32 other solid tumours) were accrued between March 21, 2016, and May 9, 2018. Median time of follow-up was 11.5 months. Start of infusion times were obtained for 806 total doses. The median time of administration was 15h06 for the first dose and 15h11 for all doses (range 09h19 – 18h34). No differences in PFS or OS were observed between patients who received their first dose before or after noon, or before or after 15h06. Furthermore, no differences in PFS or OS were observed between patients who received ≥ 50% of their doses before or after noon, or before or after 15h11. There was also no difference in PFS or OS between patients who did or did not have a significant proportion of doses (≥ 20%) after 16h30 ("evening" in previous reports). There were no differences in the frequency of grade ≥ 2 irAEs amongst the various groups. No differences in efficacy were found when individual cohorts were evaluated separately. Finally, no differences in PFS or OS were observed when participants were grouped by season of first dose. **Conclusions:** Despite previous reports of improved survival with earlier ICI dosing, we did not identify any association of time of pembrolizumab administration with clinical outcomes. Our analysis is limited by small sample size and patient heterogeneity which may hinder identification of smaller associations. It is also unclear whether lower response rates in a pan-cancer population (relative to prior reports in lung cancer and melanoma) might impact correlation analysis. Further studies will be necessary to interrogate this phenomenon and ensure that ICI are optimally applied. Research Sponsor: Princess Margaret Cancer Foundation, Pharmaceutical/Biotech Company.

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2590 **Poster Session**

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

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Background: Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus (HPV) types 6 & 11. RRP proliferates in the squamous epithelium lining the respiratory tract impacting breathing, swallowing, and voice and carries a 3-5% risk of malignant transformation. Given the multifocality of the disease and tolerized host immune response against HPV, in part through upregulation of the PD1:PDL1 axis, the safety and efficacy of systemic pembrolizumab (pembro) as a novel treatment for this benign tumor patient (pt) population was evaluated in a phase II clinical trial. **Methods:** RRP pts > 12 years of age were treated with pembro 200mg every 3 weeks. Primary endpoints were best overall response (ORR) (measured by endoscopic lesional burden) and safety. Greater than 5 pts with disease response out of 21 (assuming > 1 of first n = 11 with disease in response) provided 86% power to distinguish between a 15% and a 38% ORR (one-sided 8% binomial test). HPV-specific CD8+ T cell frequency and functional states and biomarkers of response and immune resistance are being evaluated in serial tissue and liquid biopsies (up to 8 biopsies/patient over the 24 months of treatment). **Results:** The Simon two-stage, stage 1 criteria was met. A total of 21 patients were enrolled and all are now off treatment. Median age (range) was 45 (19-68), 57% (12/21) were male and 67% (14/21) were white. 48% (10/21) had Juvenile-onset (Jo)-RRP, 57% (12/21) had pulmonary RRP involvement, and 19% (4/21) had SCC derived from their RRP. 62% (13/21) completed 24 months of treatment. Reasons for discontinuation included disease progression (14%, 3/21), treatment related adverse event (TRAEs) (14%, 3/21), and study withdrawal (10%, 2/21). A partial response (≥25% reduction in endoscopic tumor burden score) was observed in 57% (12/21) (95% CI: 34%-78.2%) of pts (7 of 10 with Jo-RRP and 5 of 11 with Adult-onset (Ao)-RRP disease responded). Stable disease was observed in 33% (7/21). No complete responses were observed. Fatigue was the most frequent TRAEs; Grade 3 TRAEs included uveitis and hypophysitis, both of which were reversible upon pembro discontinuation and steroid use. At a median follow-up: 25.6 (6.2-38.1 months), the mean number of surgical interventions was reduced by 7 surgeries/year (p = 0.004) in pts treated on the trial for > 12 months, and, upon treatment completion, durable clinical benefit was observed with no additional treatment needed for the duration of the clinical trial follow-up for some pts. **Conclusions:** Pembro reduces the need for routine surgical interventions based on the durable response rates being achieved. Further study of pembro +/- other agents is warranted to achieve and sustain complete responses in this population. Clinical trial information: NCT02632344. Research Sponsor: Merck, Other Government Agency.

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2591 **Poster Session**

Efficacy of immune checkpoint inhibitors in patients with non–small cell lung cancer harboring *ERBB2* exon 20 insertions and non-*ERBB2* exon 20 insertions.

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Background: Immune checkpoint inhibitors (ICIs) have suboptimal efficacy in non-small cell lung cancer (NSCLC) patients with *ERBB2* mutations, including *ERBB2* exon 20 insertions. This study aims to investigate the efficacy of ICIs and immune characteristics in NSCLC patients harboring *ERBB2* ex20ins and non-ex20ins mutations. **Methods:** Advanced NSCLC patients harboring *ERBB2* mutations were recruited from January 2016 to December 2020. Pre-ICI tumor tissue samples were collected and performed with targeted next-generation sequencing. Patients received ICIs were followed up every 3 months until November 2021. Genomic features were compared between patients with *ERBB2* ex20ins and non-ex20ins mutations. Progression-free survival (PFS), overall survival (OS), and tumor immune microenvironment (TIME) features characterized by multiplex immunohistochemistry (IHC) were further analyzed in patients receiving ICIs. Two-sample T-tests were performed to compare means; Cox models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Two external datasets of *ERBB2*-mutant NSCLC patients, including TCGA (n = 23) and META (n = 33), were used for validation. **Results:** A total of 117 eligible patients were enrolled (median age: 59 [range: 24-82], males 57.3%, stage IV 68.4%, adenocarcinoma 93.2%), of whom 37 received subsequent ICI treatment. similar PD-L1 tumor proportion score (mean: 8.1% *vs.* 13.2%, $p = 0.25$) and significantly lower mutation number (mean: 3.0 *vs.* 6.2 muts/person, $p < 0.01$) were detected in patients with *ERBB2* ex20ins, compared to patients with *ERBB2* mutations other than ex20ins. Similarly, in the TCGA cohort, tumor mutation burden was significantly lower in *ERBB2* ex20ins patients (mean: 2.2 *vs.* 10.3 muts/Mb, $p = 0.02$). Of 37 patients receiving ICIs, *ERBB2* non-ex20ins patients displayed superior PFS (mPFS: 13.5 *vs.* 4.4 months, HR: 0.31, 95% CI: 0.14-0.71), relatively long OS (mOS: 27.5 *vs.* 8.1 months, HR: 0.47, 95% CI: 0.20-1.14), and a relatively high rate of durable clinical benefit (64.3% *vs.* 34.8%, $p = 0.10$) than ex20ins patients, consistent with what was observed in the META cohort (PFS, mPFS: 13.2 *vs.* 2.5 months, HR: 0.20, 95% CI: 0.06-0.68; OS, mOS: 23.3 *vs.* 8.0 months, HR: 0.32, 95% CI: 0.11-0.90). Moreover, the CD4+ T cell density appeared to be lower in the tumor stroma of *ERBB2* ex20ins patients than that of non-ex20ins patients (300.5 *vs.* 1288.0 /mm^2, $p = 0.08$), even though the general TIME features of ex20ins patients were similar to those of non-ex20ins patients. **Conclusions:** NSCLC patients carrying *ERBB2* ex20ins demonstrated worse clinical outcome under ICI treatment, similar PD-L1 expression and lower mutation number when compared to those with non-ex20ins mutations. Genomic and TIME characteristics should be further investigated to elucidate the efficacy of ICIs in lung cancer patients carrying *ERBB2* mutations. Research Sponsor: Guangdong Provincial People's Hospital Young Talent Project (Grant No. KY012021191 to Yang-Si Li).

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2592 **Poster Session**

Updated efficacy and safety results from the phase 2 study of serplulimab, a novel anti-PD-1 antibody, in patients with previously treated unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors.

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Background: Serplulimab is a novel humanized monoclonal antibody against PD-1. At ASCO 2021, we have presented the results from the phase 2 serplulimab study (NCT03941574) in patients with unresectable/metastatic microsatellite instability-high or mismatch repair-deficient (MSI-H/dMMR) solid tumors who have progressed on or been intolerant to standard therapies with a median follow-up of 7.7 months. Here, we report the updated efficacy and safety results together with the results from sensitivity analysis after another 6-month follow-up. **Methods:** In this single-arm, open-label, multicenter, phase 2 study, patients aged 18–75 years with histologically or cytologically confirmed unresectable or metastatic MSI-H/dMMR solid tumors were enrolled to receive 3 mg/kg of intravenous serplulimab every two weeks for up to two years. The primary endpoint was objective response rate (ORR) assessed by an independent radiological review committee (IRRC) per RECIST v1.1. Secondary endpoints included ORR assessed by the investigators, duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of July 10, 2021, 108 patients had received at least one dose of study treatment and were included in the safety set (SS). Among them, 68 patients with confirmed MSI-H (by local sites or central lab) were included in the main efficacy analysis population (MEAP); 58 patients with confirmed MSI-H (by central lab) and had no major protocol deviations were included in the sensitivity analysis population (SAP). The median follow-up duration was 13.5 months in the MEAP and 14.0 months in the SAP. IRRC-assessed ORR per RECIST v1.1 was 39.7% (95% CI 28.0–52.3; 3 complete response [CR]) in the MEAP and 43.1% (95% CI 30.2–56.8; 2 CR) in the SAP. Investigator-assessed ORRs were 38.2% (95% CI 26.7–50.8; 1 CR) and 41.4% (95% CI 28.6–55.1; 1 CR) in the MEAP and the SAP, respectively. Median DoR, PFS, and OS were not reached; 12-month OS rate was 74.5% (95% CI 62.2–83.3) in the MEAP and 82.4% (95% CI 69.7–90.1) in the SAP. In the SS, 57 (52.8%) patients had grade ≥3 treatment-emergent adverse events, most commonly anemia (9.3%). Thirteen (12.0%) patients had grade ≥3 immune-related adverse events. Three (2.8%) deaths (2 progressive disease and 1 intestinal obstruction) that might be related to serplulimab were reported. **Conclusions:** The encouraging antitumor activity and the manageable safety profile sustained after a longer duration of follow-up, supporting the further development of serplulimab as a potential tissue-agnostic antitumor treatment. Clinical trial information: NCT03941574. Research Sponsor: Shanghai Henlius Biotech, Inc.

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2593 **Poster Session**

Preliminary data from an ongoing phase 1 dose-escalation study of CCX559, an orally administered small molecule PD-L1 inhibitor, in patients with advanced solid tumors.

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Background: The novel small molecule CCX559 is a highly potent and selective PD-L1 inhibitor that induces the dimerization and internalization of cell-surface PD-L1. CCX559, when orally administered in animal models, demonstrated anti-tumor efficacy, including the ability to induce complete responses (Li C, et al. Cancer Res 2021;81(13_Suppl): Abstract nr 1274). Safety pharmacology and toxicology studies in animals demonstrated an acceptable safety profile for CCX559. Taken together, the preclinical data supports the initiation of human trials in patients with advanced solid tumors. PD-(L)1 therapies have been shown to increase peripheral T cell activation and cytokines such as IFNγ and CXCL9 in patients (Herbst RS, et al. Nature.2014; 515(7528):563–567). **Methods:** This phase 1, first-in-patient, multicenter, open-label, dose-escalation study evaluates safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity of CCX559 in patients with refractory, locally advanced or metastatic solid tumors. CCX559 is dosed orally once daily with a starting dose level of 30 mg. Dose escalation/de-escalation is based on the Bayesian Optimal Interval (BOIN) design. PBMC and plasma samples were collected from patients over the first 2 cycles (6 weeks) of treatment, and PD assays were performed, including measurement of cytokines and T cell proliferation. **Results:** As of February 1, 2022, one patient per cohort was enrolled at the 30 mg and 60 mg levels, and 9 patients were enrolled in the 120 mg dose cohort. Of the 11 patients enrolled, 5 patients (all 120 mg cohort) remain on treatment. No DLTs, treatment-related SAEs, or severe (Grade 3 or higher) treatment-related AEs have been reported. PD assays have been performed with samples from the 30 mg (n=1), 60 mg (n=1), and 120 mg (n=3) cohorts. Patients in all three cohorts showed increased peripheral CD4 and CD8 T cell proliferation starting in the first cycle (21 days) of treatment, as measured by Ki67 positivity. Increases in plasma IFNγ, CXCL9, CXCL10, and CXCL11 levels were observed, in particular in one patient (120 mg cohort) starting 15 days after treatment initiation. **Conclusions:** Initial results from the phase 1 dose-escalation study of CCX559 indicate on-target PD effects consistent with PD-L1 inhibition. Updated PD data, together with the safety and PK profile, will be presented. Clinical trial information: ACTRN12621001342808. Research Sponsor: ChemoCentryx, Inc.

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2594 **Poster Session**

Cancer PD1/PD-L1 inhibitor efficacy as stratified by smoking status: A population large database study.

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Background: Delineating clinical factors that predict immune checkpoint inhibitor (ICI) cancer therapy response is a pressing need and smoking is a known factor. In this study we leveraged a large international (heavily US) database to perform the largest study to date for all cancers and major cancer subsites/types. **Methods:** Utilizing the TriNetX electronic health records database with 84.3M patients we tested the hypotheses that ICI response stratifies based on smoking, and continued smoking after ICI. Queries were constructed using billing codes for all cancer types treated with an ICI with and without smoking. The smoking cohort was subsequently sub-stratified for continuing vs cessation of smoking after ICI. Next, using ICI therapy as the index event, odds ratios (OR) with 95% confidence intervals for death, and treatment related secondary outcomes were calculated between 0.5-5 years after ICI treatment. Statistics were calculated using TriNetX's integrated statistical platform before and after 1:1 propensity score matching (PSM) for smoking related co-morbidities. **Results:** The OR for death after ICI therapy for smokers (*n* 13336) vs non-smokers (*n* 38973) for any cancer type was 1.27(1.21-1.34) and decreased to 1.11(1.04-1.19) after PSM. Further sub-stratifying the smoking cohort for continued vs cessation of smoking yielded ORs of 1.13(1.03-1.24) and 1.12(1.01-1.24) before and after PSM respectively. Secondary outcomes included ablative surgery, chemotherapy, radiation, and secondary neoplasm. ORs for receiving chemotherapy, and developing secondary neoplasm were most consistently statistically significant across comparisons. **Conclusions:** Smoking adversely potentiates cancer outcomes after ICI therapy. PSM for smoking related comorbid conditions decreased the magnitude of this association although the findings remained clinically and statistically significant. This highlights the key role in smoking related co-morbid conditions as prognostic clinical characteristics. Furthermore, this suggests that smoking affects ICI on a mechanistic/biological level beyond increasing burden of medical comorbidities. Lastly, as smoking cessation also improved outcomes after PSM this further suggests that washout of smoke toxins has a mechanistic/biological effect on ICI activity. Research Sponsor: None.

Propensity score matching corrected	Alive	Deceased (between 0.5-5yrs after ICI)
Smoker	9,379	2,754
Non-Smoker	9,337	2,540

Odds ratio = 1.11(1.04-1.19)

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2595 **Poster Session**

Extended interval dosing in patients with cancer receiving immune checkpoint inhibitors: Safety analysis from the EDICI study.

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Background: Healthcare costs and need of frequent patients' (pts) access to oncology departments led to an increasing interest in alternative immune check-point inhibitors (ICIs) administration schedules able to offer longer dose intervals. The extended interval dosing (ED) of nivolumab and pembrolizumab was approved based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. We aimed to investigate real-life immune-related adverse events (irAEs) incidence in pts treated with ED-ICIs. **Methods:** Clinicopathological and treatment characteristics of all consecutive solid cancer pts treated with ICIs (pembrolizumab, nivolumab) monotherapy who received at least one cycle of the ED (pembrolizumab 400 every 6 weeks or nivolumab 480 mg every 4 weeks) were identified from patient electronic records of 37 oncology departments across Europe and entered into a prospectively maintained database. **Results:** Among 756 pts enrolled in the EDICI study, 733 pts (229 treated with pembrolizumab, and 504 with nivolumab) were included in the final safety analysis (median follow up time: 24.7 months). 476 pts were males, with melanoma (441, 60%) and non-small cell lung cancer (151, 20%) being the prevalent tumor types. Median age was 67 years old, and 589 (80%) pts received ICIs in the advanced setting. 501 (68%) of the enrolled pts started ICIs with canonical interval dosing (CD, median number of cycles administered: 13) and subsequently switched to ED after a median time interval of 210 days. During CD-ICI, 197 pts (39%) developed irAEs of any grade and 14 patients (3%) G3/G4 events; after switching to ED-ICI treatment, which was administered for a median of 7 cycles and 336 days, irAEs of any grade and G3/G4 events were experienced by 155 (36%) and 20 (5%) pts, respectively; 73 (47%) cases of any grade-toxicity and 12 (60%) of G3/G4-toxicity were *de novo*. 33 (7%) pts switched back to CD, in 45% of the cases due to toxicity. Pts who started *upfront* with ED (n = 232, 32%) were exposed to the drug for a median of 7 cycles; 56 of them (25%) developed irAEs of any grade and 9 (6%) G3/G4 irAEs. Skin (12% of patients), endocrine (11%), rheumatic (10%) and gastrointestinal (9%) were the most common irAEs during ED; 42% were "multiple-site" irAEs, showing no difference with CD (p = 0.21). Lower creatinine values before switch to ED (adjusted odds ratio [aOR], 1.24; 95%CI, 1.03-1.48; P = 0.02) and previous toxicity during CD (aOR, 1.20; 95%CI, 1.08-1.33; P < 0.01) were independent risk factors for development of irAEs during ED. **Conclusions:** Despite similar exposure time, the safety profile of ED treatment did not differ from CD, confirming that ED-ICI administration is a safe and feasible option also in cancer pts outside of clinical trials. Future investigations are needed to explore efficacy data and economic impact of this strategy. Research Sponsor: None.

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2596 **Poster Session**

Identification of super-exhausted T cells: A novel population predictive of response to immunotherapy.

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Background: Given that most of cancer patients treated with anti-PD1/PD-L1 immune checkpoint blockers (ICB) do not derive benefit, there is a crucial need to identify reliable predictive biomarker of response. Besides PD-1, several key immune checkpoints, such as CTLA4, LAG3, TIM3 and TIGIT, are associated with a T cell exhausted phenotype and play a crucial role in leading to cancer immune evasion. The impact of simultaneous expression by T cells of distinct inhibitory receptors on outcome of patients treated with ICB is still unknown. **Methods**: We analyzed the tissue samples, collected before ICB initiation, from patients with solid tumors and included in an institutional molecular profiling program (NCT02534649). We used multiplexed-immunohistofluorescence with the following panel CD3/PD1/TIM3/LAG3/TIGIT/CTLA4, and performed immune cell characterization using multispectral images analysis. We then investigated the correlation between coexpression of T cell-associated exhaustion markers, clinical response rate, progression-free survival (PFS) and overall survival (OS) by Cox proportional hazards models. **Results**: Four hundred thirty five patients were included in the analysis (NSCLC: n=207, 47.6%; sarcoma: n=42, 9.7%; urothelial: n=30, 6.9%; others: n=156, 35.9%). Digital pathology analysis allowed us to identify a population of "super-exhausted" T cells characterized by the co-expression of PD1, LAG3, TIGIT and TIM3 which was enriched in 125 cases (28.7%), and was significantly associated with better PFS (HR 1.60, CI95 1.26-2.04, p<0.001) and OS (HR 1.42, CI95 1.07-1.89, p=0.016) in the whole cohort. Patients with super-exhausted high tumors had higher objective response rate (38.4%) compared to super-exhausted low tumors (19.7%, p<0.001). The presence of super-exhausted T cells was significantly higher in responders (10%) versus non responders (4%, p<0.001). Correlation with better outcome was observed whatever the subgroup considered (NSCLC vs other tumors, CD8 T cells density and presence of tertiary lymphoid structure [TLS]). In multivariate analysis (n=372, 85.5%), increased tumor infiltration by super-exhausted T cells (>1 %) was significantly associated with better PFS (HR 0.61, CI95 0.46-0.81, p<0.001, Table) and OS (HR 0.68, CI95 0.48-0.97, p=0.033, Table). **Conclusions**: The presence of super-exhausted T cells may represent a new predictive biomarker of response to ICB and pave the way for the development of effective ICB combinations. Data from an independent validation cohort will be presented at the meeting. Research Sponsor: None.

Patients	Endpoint	PFS			OS		
372	Subgroup	HR	CI	p-value	HR	CI	p-value
	Super Exhausted T cells (>1.09%)	0.61	(0.46-0.81)	<0.001	0.68	(0.48-0.97)	0.033
	TLS positive	0.72	(0.56-0.94)	0.014	0.66	(0.48-0.90)	0.010
	CD8 density (<152 cells/mm^2)	1.11	(0.88-1.42)	0.74	1.06	(0.80-1.41)	0.69
	Performance Status (>1)	1.60	(1.15-2.24)	0.006	2.19	(1.51-3.19)	<0.001

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2597 **Poster Session**

Novel, small molecule inhibitors of PD-1/PD-L1 pathway.

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Background: Programmed Cell Death 1 (PD-1) protein plays a key role in inhibiting immune responses and enhancing self-tolerance via modulation of T-cell activity, inducing T-cell apoptosis and inhibiting apoptosis of regulatory T cells. PD-L1 also plays an important role in various malignancies where it can attenuate the host immune response to tumor cells thereby favouring tumor progression and metastasis. High expression of PD-L1 in glioblastoma tumor tissues is associated with poor survival of patients, and PD-L1 may act as a prognostic predictor and an effective therapeutic target for glioblastoma. A number of monoclonal antibodies targeting PD-1/PD-L1 have approved for various malignancies. Still, efficacy of these antibodies in glioblastoma and brain metastasis continues to be moderate potentially owing to lack of or poor brain penetrance of these agents. Therefore, there is still a need for potent, selective small molecule PD-1/PD-L1 inhibitors with enhanced brain penetration in the treatment of such cancers. **Methods:** Rational design approaches were used to design novel small molecule PD-1/PD-L1 pathway inhibitors; potency of these inhibitors was assessed in an *in-vitro* TR-FRET assay. Checkpoints signalling reporter assays as well cell based PD-L1 dimerization assays were used to assess the mechanistic and functional effects. *In vivo* efficacy was assessed in orthotopic GBM as well as in syngeneic and humanized subcutaneous tumor models in mice. **Results:** Our lead PD-L1 inhibitor JBI-2174 showed strong *in vitro* IC50 of ~1 nM in TR-FRET assay that measures interaction between hPD-1 and hPD-L1 and a picomolar IC50 against monkey PD-L1. In selectivity assays for immunooncology targets, JBI-2174 was highly selective for PD-L1. JBI-2174 also inhibited PD-L1/PD-1 mediated signalling essential for T-cell modulation. JBI-2174 induced dimerization of PD-L1 as observed by size exclusion chromatography, which was confirmed by co-crystal structure and recapitulated in cell based dimerization assay. Elucidation of the co-crystal structure, clearly demonstrated that JBI-2174 clearly interacts with multiple amino acids on PD-L1 that are critical for PD-1 binding. JBI-2174 showed excellent oral bioavailability across pre-clinical species and sustained brain exposure. In the in vivo efficacy studies, JBI-2174 showed comparable efficacy to the anti-PD-L1 antibody or Atezolizumab in syngeneic (4T1, CT-26) and in partially humanized models (MC-38/hPD-L1). Further, oral administration of JBI-2174 resulted in statistically significant increase in survival (Day 27 in control vs day 38 in treated, $p < 0.05$) in a mouse glioma orthotopic model. **Conclusions:** The oral bioavailability and brain exposure of this molecule will make it attractive for cancers with unmet medical needs such as GBM and brain metastasis. IND enabling studies are being initiated for this compound. Research Sponsor: Jubilant Therapeutics.

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2598 **Poster Session**

Association between body mass index and treatment efficacy with immune checkpoint inhibitor therapy: A retrospective study.

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Background: Increased body mass index (BMI) has been associated with improved efficacy of immune checkpoint inhibitor therapy (ICI) in cancer patients. We aimed to retrospectively assess the relationship between patient BMI and response to ICI at two unique health care systems in our institution. **Methods:** We identified patients treated with ICI from 2015-2021 at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) Cancer Center and Baylor St. Luke's Medical Center (BSLMC), a private hospital-based cancer center, both academic affiliates of Baylor College of Medicine. Clinical details, including BMI, and treatment efficacy were collected. We defined BMI categories as follows: underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (≥30). Progression free survival (PFS), overall survival (OS), and overall response rate (ORR) were the primary end points calculated for treatment efficacy. Survival curves were generated using the Kaplan-Meier method, and intergroup comparisons were performed with log-rank test. Cox regression analysis was used to determine whether BMI at ICI initiation was associated with survival. Chi-square testing was used to determine any association between BMI and ORR. **Results:** We identified 430 patients treated with ICI, 257 (60%) from BSLMC and 173 (40%) from MEDVAMC. 341 patients (79%) were male and 89 (21%) female. Cancer types included 127 (30%) lung, 49 (11%) kidney, 40 (9.3%) bladder, 38 (8.8%) melanoma, and 38 (8.8%) mesothelioma, 34 (7.9%) head and neck, and 104 (24%) other. 160 (37%) patients had a normal BMI at ICI initiation, 37 (8.6%) underweight, 132 (31%) overweight, and 101 (23%) obese. Mean BMIs of different cancer types were as follows: lung (24.7), kidney (29.2), bladder (26.0), melanoma (29.9), mesothelioma (25.25), head and neck (23.7). 292 (68%) patients were treated with ICI monotherapy. The ORR for patients with normal vs. obese BMIs treated with ICI were 28% and 42%, respectively ($p = 0.03$). In a subset of patients evaluable for survival ($n = 322$), patients with an obese BMI had a significantly improved median PFS compared to those with normal BMI (36.4 vs. 23.5 months, respectively, $p < 0.0001$). Multivariable analysis demonstrated that patients with an obese BMI had significantly improved overall survival compared to patients with a normal BMI (HR 0.64, 95% CI 0.44-0.91, $p = 0.014$). This relationship was also seen in the subset of patients treated with ICI monotherapy (HR 0.66, 95% CI 0.45-0.95, $p = 0.029$). This association was noted regardless of health care systems. **Conclusions:** Increased BMI in cancer patients treated with ICI may predict better treatment efficacy and survival outcomes. More research is needed to define this relationship more clearly. Research Sponsor: None.

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2599 **Poster Session**

Cisplatin (Cis) combined with sintilimab (Sint) and niraparib (Nir) in advanced solid tumors: Updated results.

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Background: PARP inhibitors or chemotherapy combined with PD1/PDL1 inhibitors resulting in enhanced antitumor activity. We previously reported the part 1 result of a phase Ib study exploring the safety and efficacy of Cis plus Sint and Nir. Here we presented the updated survival and safety data. **Methods:** Eligible pts will receive Sint and Cis on D1, plus Nir on D1-21, every 21-day for up to 4 cycles, following Sint and Nir until disease progression or intolerable toxicity. Part 1 was dose escalation phase followed 3+3 model, and part 2 was dose expansion phase enrolled more patients based on part 1. The primary objective was to determine maximum tolerated dose (MTD)/ recommended part 2 dose (RP2D). Secondary endpoints include objective response rate (ORR) per RECIST v1.1, and safety based on CTCAE v5.0. **Results:** PR2D of Cis and Nir were 60 mg/m^2 and 100 mg, respectively when combined with sint 200mg. From 7/2019 to 9/2021, 22 pts (13 pts in part2) were enrolled, including 12 small cell lung cancer (SCLC), 7 lung squamous cell carcinoma (LUSC), 2 ovarian cancer (OC) and 1 cervical squamous cell carcinoma (CSCC). Most were male (77.3%, n=17), ECOG=1 (63.6%, n=14), current smoker(68.2%, n=15) and PDL1 < 1(50%, n=11). 36.4% (8/22) and 27.3% (6/22) had brain and liver metastasis at baseline, separately. Median follow-up was 6.2 months (range 2.5-10.8). ORR was 27.3% (6/22), DCR was 59.1% (13/22). Median progression-free survival (PFS) was 3.3 months (95%CI 1.9-3.9), and PFS rates at 6 months and 12 months were 28.8% and 10.8%. Median overall survival (OS) was 8.0 months (95%CI 4.9-14.1), 12 months OS rates was 28.5%. Median treatment duration was 4.7 months (range 1.9-15.1). The most common treatment-related adverse events included anemia (90.9%, 20/22, [5 Grade 3/4]), fatigue (77.3%, 17/22, [1 Grade 3/4), γ-glutamyl transpeptidase increased (72.7%, 16/22, [0 Grade 3/4]), leukopenia (68.2%, n=15, [4 Grade 3/4]) and neutropenia (59.1%, n=13, [5 Grade 3/4]). **Conclusions:** In this updated analysis, Cis combined with Sint and Nir showed clinically meaningful efficacy and an adequate safety profile in previously treated advanced solid tumors. Data need longer follow-up. Clinical trial information: ChiCTR1900024488. Research Sponsor: None.

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2600 **Poster Session**

Study to evaluate intraperitoneal (IP) ONCOS-102 with systemic durvalumab in patients with peritoneal disease who have epithelial ovarian (OC) or metastatic colorectal cancer (CRC): Phase 2 results.

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Background: Locoregional treatment with oncolytic viruses may be used to improve the efficacy of immune checkpoint inhibitors at both treated and distant tumor sites. This study evaluated the combination of IP-administered ONCOS-102, an oncolytic adenovirus encoding for granulocyte macrophage colony stimulating factor (GM-CSF), with systemic durvalumab (durva) in patients (pts) with advanced OC or CRC who have failed prior chemotherapy. **Methods:** This open-label study (NCT02963831) evaluated ONCOS-102 (IP 3 x 10^{11} VP in 500ml saline [recommended phase 2 dose] weekly x 6) + durva (IV 1500 mg every 4 weeks x 12). One dose of cyclophosphamide was given prior to first ONCOS-102 dose. Phase 2 evaluated the activity of the combination using Simon's 2-stage MINIMAX design. In MINIMAX stage 1, if $\geq$ 5 of 18 OC pts or $\geq$ 1 of 13 CRC pts met the efficacy criteria (progression free at end of week 24), 15 additional OC pts or 14 additional CRC pts were to be enrolled in stage 2. The efficacy endpoint would be met if $\geq$ 11 OC pts or $\geq$ 4 CRC pts remained progression free at 24 weeks. Safety, response rate and progression-free survival (PFS) by RECIST 1.1, overall survival (OS), and immunologic effects in tumors were evaluated. ITT population = all pts who received at least one dose of durva or ONCOS-102; per protocol (PP) population = all pts who received at least 60% of ONCOS-102 doses and at least 1 durva dose in the first 2 cycles. **Results:** In MINIMAX stage 1, the OC cohort did not meet the efficacy criteria and was closed. For CRC, stage 1 efficacy criteria were achieved and the cohort was opened for stage 2. As of the 14 Dec 2021 cutoff, CRC enrollment was complete, and all pts were followed for 24 weeks or until progression or off study. Two pts were progression free at 24 weeks (see table). Treatment-related adverse events (TRAEs) occurring in > 30% pts were vomiting, nausea, fatigue, chills, and pyrexia. There were no grade 4 or 5 TRAEs. Grade 3 TRAEs were reported in 8 pts, 2 in the OC cohort and 6 in CRC. All grade 3 TRAEs occurred in no more than 1 pt for each AE except abdominal pain, which occurred in 2 pts. **Conclusions:** The combination of IP ONCOS-102 and durva was well tolerated. The study did not meet its efficacy endpoint. Evaluation of pre- and on-therapy translational parameters is ongoing. Clinical trial information: NCT02963831. Research Sponsor: Ludwig Institute for Cancer Research, Other Foundation, Pharmaceutical/Biotech Company.

	CRC Completed Stage 2		OC Closed after Stage 1	
Population	**ITT (36)**	**PP (28)**	**ITT (19)**	**PP (15)**
Sex, n (%)	F 21 (58.3) M 15 (41.7)	F 18 (64.3) M 10 (35.7)	F 19 (100.0)	F 15 (100.0)
Median age (range) years	58.5 (39 - 74)	58.5 (44 - 74)	67.0 (49 - 77)	68.0 (49 – 77)
Progression free at week 24	2 (5.6%)	2 (7.1%)	0	0
Best response	0 CR, 0 PR, 9 SD, 22 PD, 5 missing	0 CR, 0 PR, 7 SD, 19 PD, 2 missing	0 CR, 0 PR, 4 SD, 15 PD, 0 missing	0 CR, 0 PR, 4 SD, 11 PD, 0 missing
Median PFS (95% CI) months	1.8 (1.6, 1.9)	1.8 (1.6, 1.9)	1.8 (1.2, 1.9)	1.9 (1.6, 1.9)
Median OS (95% CI) months	7.1 (5.4, 11.5)	7.1 (5.4, 11.5)	6.6 (3.6, 19.7)	7.5 (4.4, 19.8)

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2601 **Poster Session**

PRaG regimens (PD-1 inhibitor combined with radiotherapy and GM-CSF with or not IL-2) rechallenge for patients with acquiring resistance to PD-1/PD-L1 inhibitors in refractory advanced solid tumors.

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Background: Immune checkpoint inhibitors, especially PD-1/PD-L1 inhibitors can promote tumor regression and long-term survival in patients with advanced solid tumors. Despite the characteristic durability of response to ICI, unfortunately some patients may develop acquired resistance after an initial response. The underlying mechanism and effective measure are remarkably limited, perhaps restraining development of immunotherapies. The PRaG trial as a salvage therapy in patients with refractory metastatic solid tumors has obtained satisfactory results(Yuehong Kong et al. ASTRO 2021). With great surprise we found that patients with PD-1/PD-L1 inhibitors acquired resistance are more likely to benefit from the PRaG regimens. This is the PRaG regimen rechallenge that could represent an attractive option in advanced solid tumors. We retrospectively analyzed the clinical efficacy and safety of PRaG regimen (PD-1 inhibitors combined with radiotherapy and GM-CSF with or not IL-2) rechallenge to treat immunotherapy-refractory patients with advanced solid tumors. **Methods:** This is a retrospective analysis of patients who showed initial resistance to PD-1/PD-L1 inhibitors were retrospectively collected from PRaG serial trails (ChiCTR1900020175 and NCT04892498). Patients received SBRT or HFRT (2-3 doses of 5-8Gy) to a target metastatic site, PD-1 inhibitor was dosing intravenously within one week after completion of SBRT or HFRT, and GM-CSF subcutaneous (SC) injection once daily for 14 days after radiotherapy(the PRaG 2.0 regimen, GM-CSF 200μg SC d1-7, sequentially IL-2 2million IU d8-14.). The specific PRaG regimens had been reported at the meeting of 2020 ASCO. Pooled analysis of response rate (ORR), median progression-free survival (mPFS), and treatment-related adverse events were calculated. **Results:** A total of 15 multi-metastatic patients were enrolled between October 2020 and February 2022. Thirteen patients showed acquired resistance and underwent at least one assessment, 5 patients were lung cancer, 3 patients were renal cancer, 2 patients were liver cancer, 2 patient was colon cancer, 1 patient was sarcoma. The ORR was 18.2%, and the disease control rate (DCR) was 90.9%. The median PFS was 8.87 months (95%CI, 1.41 to 16.33 months). One lung cancer achieved complete remission, with PFS over 17 months. Treatment-related adverse events of any grade occurred in 11 of 15(73.3%) patients, while there was no grade 3 or higher adverse events. **Conclusions:** Our preliminary results suggested that PRaG regimens rechallenge maybe an active and feasible strategy in PD-1/PD-L1 inhibitors acquired resistance. The therapy was well tolerated and had acceptable toxicity. A phase III prospective study is being planned to clarify the role of rechallenge after acquired resistance. Clinical trial information: ChiCTR1900020175 and NCT04892498.
Research Sponsor: None.

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2602 **Poster Session**

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

Vinod Ganju, Adam Cooper, Bo Gao, Kate Wilkinson; PSEHOG, Frankston, VIC, Australia; St. George Private Hospital, Kogarah, NSW, Australia; Blacktown and Westmead Hospital, Blacktown, NSW, Australia

Background: YH001 is a humanized anti-hCTLA-4 IgG1 mAb that relieves CTLA-4-mediated immunosuppression, and thereby enhances the T-cell-mediated antitumor immune response. Pre-clinical data have shown potent anti-cancer activity when combined with anti-PD-1 mAb. **Methods:** This is an ongoing phase 1 dose-escalation study conducted in Australia. Patients (pts) with advanced solid tumors received YH001 by IV administration at 0.05 to 6.0 mg/kg for 1 cycle (21 days) then in combination with Toripalimab (anti-PD-1 mAb) at 240 mg Q3W for 4 cycles. An accelerated titration method followed by the standard "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. **Results:** As of 31-Dec-2021 data cut-off, 24 pts with advanced solid tumors were enrolled and dosed at 0.05 mg/kg (n=2), 0.1 mg/kg (n=3), 0.3 mg/kg (n=3),1mg/kg (n=5), 2mg/kg (n=5), 4mg/kg (n=3) and 6mg/kg (n=3). Baseline ECOG scores were 0 (n=14), 1 (n=10) with all pts progressed after a median of 2 prior lines of available standard therapy (range 1-5) including 5 pts progressed after prior immunotherapy of anti-PD-1 antibody. Overall, 6 cases of Grade(G) 3 or above treatment-related AEs (TRAEs) have been reported in 5 pts at 0.3 mg/kg, 4 mg/kg and 6 mg/kg dose level respectively, including 1 G3 colitis, 1 G4 thrombocytopenia, 1 G3 Enterocolitis, 1 G3 Rash, 1 G3 Pruritus and 1 G3 hepatitis. There were no death events due to TRAEs. 18 pts (75%) had 63 TRAEs of any level, including 28 G1 TRAEs, 29 G2 TRAEs. 2 of the first 3 pts at MAD (6mg/kg) met protocol defined DLT in Combo phase. Among the 23 pts having imaging tumor assessment by RECIST v1.1, 4 achieved PR and 9 achieved SD in Best of Response. 1 subject with gastroesophageal junction carcinoma at 0.3 mg/kg has achieved PR since the 2nd tumor assessment, target lesion decreased by up to 84.5% from baseline. 1 subject with urothelial carcinoma at 2 mg/kg progressed after prior anti-PD-1 antibody has achieved PR since the 2nd tumor assessment, target lesion decreased by up to 74% from baseline. 1 subject with uterine carcinosarcoma at 2 mg/kg has achieved PR since the 1st tumor assessment, target lesion decreased by up to 52.3% from baseline. 1 subject with vulva adenocarcinoma at 6 mg/kg has achieved PR since the 1st tumor assessment, target lesion decreased by up to 71.4% from baseline. ORR (CR+PR) and DCR (CR+PR +SD) were 17.4%, 56.5% respectively. **Conclusions:** YH001 was well tolerated up to 4 mg/kg dose levels when combined with toripalimab and has shown encouraging antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04357756. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

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2603 **Poster Session**

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

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Background: YH003, a recombinant, humanized agonistic anti-CD40 IgG2 monoclonal antibody (mAb) specifically recognizes and agonizes CD40 on the antigen-presenting cells to enhance immune responses. Preclinical data have shown potent anti-cancer activity when combined with anti-PD-1 antibodies. **Methods:** This is an ongoing phase 1 dose-escalation study conducted in Australia using an accelerated "3+3" design. Patients (pts) with advanced solid tumors receive YH003 by IV administration Q3W as monotherapy at 0.03 to 3.0 mg/kg for the first cycle (21 days) then in combination with Toripalimab at 240 mg Q3W for the 4 subsequent cycles. Treatment continuation beyond cycle 4 is possible if subject is deriving an ongoing clinic benefit. The safety, tolerability and preliminary efficacy data will be analyzed. **Results:** Between 29 Jul 2020 and 30 Dec 2021, a total of 20 patients with various advanced solid tumors were enrolled including 0.03 mg/kg (n = 3), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3), 1.0 mg/kg (n = 8) and 3.0 mg/kg (n = 3). The median age was 60 years (range 33-75). Baseline ECOG scores were 0 (13 pts) and 1 (7 pts). 8 pts had received prior immunotherapy (anti-PD-1/PD-L1 or anti-PD-1+CTLA-4mAb). Dose escalation has been completed and only one dose-limiting toxicity relating to YH003 was observed at 1.0 mg/kg (grade 3 transaminitis). The maximum tolerated dose (MTD) was not reached. 13 (65%) pts experienced any grade treatment related adverse events (TRAEs). The most common (≥ 10%) TRAEs were infusion reaction, pyrexia, fatigue, nausea, diarrhea, transaminitis. Most TRAEs were grade 1 or 2. Only 3 (15.0%) pts experienced Grade 3 TRAEs including one each of neutropenia (YH003 0.3 mg/kg), transaminitis (YH003 1.0 mg/kg) and elevated lipase (Toripalimab 0.1 mg/kg). Only 2 pts have permanently discontinued treatment due to TRAEs including grade 3 transaminases increased and grade 2 hepatitis. There were no ≥grade 4 TRAEs and drug related serious adverse events (SAEs) were not observed. Among 14 pts assessable for response, the overall response rate (ORR) was 14.3% (2/14) and disease control rate (DCR) was 35.7% (5/14). One partial response (PR) occurred in a pt with anti-PD1/anti-CTLA4 refractory ocular melanoma with liver metastases (YH003 0.1 mg/kg) who continued on treatment for > 1 year. The other PR occurred in a pt with Non-Small Cell Lung Carcinoma (YH003 1.0 mg/kg) who continued on treatment for almost 9 months. **Conclusions:** YH003 was well tolerated up to 3.0 mg/kg dose levels when combined with Toripalimab and has shown encouraging antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04481009. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

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2604 **Poster Session**

A phase 1 multiple-ascending dose study to evaluate the safety and tolerability of XmAb23104 (PD-1 x ICOS) in subjects with selected advanced solid tumors (DUET-3).

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Background: XmAb23104 is a bispecific antibody targeting T cells that simultaneously express PD-1, an immune checkpoint, and ICOS, a costimulatory molecule expressed after T cell activation. DUET-3 is a Phase 1, first-in-human, dose-escalation and expansion study in subjects with advanced solid tumors, designed to assess safety, tolerability and to identify the maximum tolerated dose (MTD) of XmAb23104. Secondary objectives are to assess pharmacokinetics (PK), immunogenicity, and preliminary anti-tumor activity. We report preliminary data from the completed dose-escalation phase. **Methods:** A 3+3 monotherapy dose escalation with 9 dose levels from 0.002 to 15 mg/kg has been completed. Subjects with measurable disease who progressed on prior standard therapy were eligible. A minimum 6-week washout from prior pembrolizumab was required. XmAb23104 was administered biweekly and RECIST 1.1 assessment was performed every 8 weeks. **Results:** Sixty-two subjects were treated in escalation at doses up to 15 mg/kg; no dose-limiting toxicities were observed and an MTD was not reached. These subjects had advanced disease, 92% were Stage IV at screening, the median number of prior therapies was 3, and 37% had previous checkpoint therapy. Thirty-seven subjects (59.7%) experienced a treatment-related adverse event (TRAE); the most common were diarrhea (9.7%), decreased appetite (9.7%), and fatigue (9.7%). The majority of TRAEs were Grades 1 or 2, with 6 subjects (9.7%) having a Grade 3 or higher TRAE. Thirteen immunotherapy-related adverse events (irAEs) occurred in 8 subjects; no individual irAE occurred in more than 1 subject. Most irAEs were mild (Grades 1 and 2) with 1 Grade 3 pruritus and 1 asymptomatic Grade 4 lipase elevation. Partial responses were observed in 3 subjects (sarcoma; prior PD-1 head and neck squamous cell carcinoma [HNSCC] and renal cell carcinoma [RCC]), and stable disease > 12 months was observed in 2 subjects with colorectal cancer (CRC; 1 MSS and 1 MSI-H). A dose of 10 mg/kg was selected after consideration of PK, safety, and clinical activity data in consultation with the investigators and continues to be evaluated in the expansion part of the study. **Conclusions:** The dose escalation part of this study indicates XmAb23104 was generally well tolerated at doses up to 15 mg/kg and has shown clinical activity in subjects with advanced solid tumors. CTLA4 blockade has been found to increase the frequency of ICOS-expressing T cells in prostate cancer, bladder cancer, melanoma, and hepatocellular cancer (Chen, 2009; Liakou, 2008; Wei, 2017) and may be applicable to other immunogenic tumor types. XmAb23104 is currently being studied alone or in combination with ipilimumab in expansion in non-squamous non-small cell lung carcinoma, melanoma, CRC, undifferentiated pleomorphic sarcoma, HNSCC, and RCC. Clinical trial information: NCT03752398. Research Sponsor: Xencor.

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2605 **Poster Session**

Retrospective analysis of the effect of angiotensin receptor blockers and angiotensin converting enzyme inhibitors on the efficacy of anti-PD-1/PD-L1 immunotherapy in patients with advanced cancer.

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Background: Components of the renin angiotensin system (RAS) are expressed in tumors with activation leading to tumor and stromal cell release of immunomodulatory cytokines promoting an immunosuppressive microenvironment and increased infiltration of tumor associated macrophages. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are anti-hypertensives that inhibit the RAS. It is unknown if ACEi and ARB treatment modulates the efficacy of anti-PD-1/PD-L1 immunotherapy. **Methods:** A retrospective chart review was conducted to identify patients with unresectable malignancies initiating treatment with a PD-1 or PD-L1 inhibitor based regimen between 1/1/13 and 6/1/19 at Valley Hospital in New Jersey. IRB approval was obtained. Efficacy of treatment was measured by medical oncologist documentation of clinical benefit (CB = stable disease / treatment response) versus disease progression. Chi-square tests were performed to assess relationship between ACEi or ARB exposure and immunotherapy benefit. To assess for a broader anti-hypertensive effect, the relationship in patients on a beta-blocker but not ACEi/ARB was assessed. **Results:** 197 patients were identified of which 190 had documentation of clinical outcome. The mean age was 72.8 years with 54% female and 46% male. 56 patients were exposed to ACEi (N = 28) or ARB (N = 28) and 141 patients to neither. 37 patients were exposed to beta blocker but not ACEi or ARB. 60 patients had nonsquamous NSCLC (16 on ACEi or ARB), 26 squamous NSCLC (7 on ACEi or ARB) and 24 melanoma (10 on ACEi or ARB). 71% of ACEi/ARB exposed patients had CB by clinician assessment as opposed to 47% in those not on ACEi or ARB ($p = 0.003$). In ACEi exposed patients, 71% had CB versus 51% in unexposed patients ($p = 0.048$). In ARB exposed patients, 70% had CB versus 51% in unexposed patients ($p = 0.069$). By contrast, 51% of beta-blocker treated patients had CB versus 55% in untreated patients ($p = 0.72$). 36% of ACEi/ARB exposed patients remained on treatment at 12 months versus 22% of ACEi/ARB unexposed patients. Subset analyses were performed on the 3 largest patient populations: squamous NSCLC, nonsquamous NSCLC and melanoma. ACEi/ARB exposed melanoma patients had CB rate of 70% versus 43% in those unexposed. ACEi/ARB exposed squamous NSCLC patients had CB rate of 86% versus 47% in unexposed patients. By contrast, ACEi/ARB exposed nonsquamous NSCLC patients had a 56% CB rate versus 48% in unexposed patients. **Conclusions:** Based on retrospective analysis, advanced cancer patients treated with anti-PD-1/PD-L1 regimens had a statistically significant increase in clinical benefit if administered in the context of renin angiotensin system blockade. Prospective disease specific trials can further validate these findings and define the degree of clinical benefit. Research Sponsor: None.

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2606 **Poster Session**

First-line PD-1 inhibitors immunotherapy and chemotherapy combined with or without radiotherapy for patients with advanced non-small cell lung cancer.

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Background: Immunochemotherapy has become a standard first-line regimen for advanced non-small-cell lung cancer (NSCLC). Several studies showed the synergistic effects of immunotherapy and radiotherapy on local and abscopal tumour control. But the data of first-line immunochemotherapy combined with radiotherapy for the advanced NSCLC is still scarce. **Methods:** Patients with advanced NSCLC receiving first-line PD-1 inhibitors immunotherapy plus chemotherapy in a single center were retrospectively analyzed in this study. They were divided into two groups according to whether they had received radiotherapy. The efficacy and safety of first-line immunochemotherapy combined with radiotherapy (ICRT group) and immunochemotherapy alone (ICT group) were investigated. **Results:** A total of 135 patients were included; 65 patients received PD-1 inhibitors plus chemotherapy and radiotherapy, while other 70 patients were treated with immunochemotherapy alone. The median interval time between radiotherapy and PD-1 inhibitors immunotherapy was 5 days (range, 0-96 days). The overall response rate (ORR) was 50.8% in the ICRT group and 40.0% in the ICT group, respectively. Patients in the ICRT group achieved significant longer progression-free survival (PFS, median 16.5 vs 10.4 months, P= 0.043) and overall survival (OS, median not reached vs 21.0 months, P= 0.030) compared with those in the ICT group. The addition of radiotherapy was the only prognostic factor for PFS (HR = 0.617, 95%CI: 0.385-0.989, P= 0.045) and OS (HR = 0.512, 95%CI: 0.277-0.947, P= 0.033) by univariate Cox regression analysis. Patients were well tolerated and the overall incidence of adverse events was similar between the ICRT group and ICT group. One patient in ICRT group stopped immunotherapy because of severe immune-associated pneumonia. 3.1% of grade 3-4 radiation-related adverse events were observed. **Conclusions:** Adding radiotherapy to first-line PD-1 inhibitors immunotherapy and chemotherapy improved outcomes of patients with advanced NSCLC and showed acceptable toxicity. Additional prospective studies exploring the first-line combination of immunochemotherapy and radiotherapy are warranted. Research Sponsor: National Natural Science Foundation of China (grant number 82103004).

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2607 **Poster Session**

Resistance to anti-PD-1/anti-PD-L1: GB1211 reverses galectin-3 induced blockade of pembrolizumab and atezolizumab binding to PD-1/PD-L1.

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Background: Galectin-3 (Gal-3) is a β-galactoside binding lectin highly expressed across many cancers (Li et al. Biomedicines, 2021) with high expression associated with poor response to the PD-1 inhibitor pembrolizumab (Capalbo et al., Int J Mol Sci, 2019). In addition, it has also been shown preclinically in in vivo mouse non-small cell lung carcinoma (NSCLC) models that inhibition of Gal-3 enhances the performance of checkpoint inhibitors targeting the PD-1/PD-L1 axis (Vuong et al., Cancer Res, 2019; Zhang et al., FEBS Open Bio, 2020). The mechanism by which Gal-3 negatively impacts the effect of PD-1/PD-L1 based checkpoint inhibitors is not fully understood. We investigated the hypothesis that anti-PD1/anti-PDL1 is induced by direct binding and blockade of Gal-3 to the PD-1/PD-L1 complex itself. **Methods:** SPR was used to investigate the effect of recombinant hGal-3 in combination with a Gal-3 inhibitor (GB1211) on the binding of recombinant hPD-L1 to hPD-1 in the absence and presence of either pembrolizumab or atezolizumab. SPR analysis was performed with a BIAcore (Cytiva, USA). hPD-1 was immobilized onto a CM5 Series S sensorchip via amine coupling and proteins, antibodies or small molecules flowed over in various combinations. Observations made at the protein level were further confirmed in cell binding assays using flow cytometry measuring pembrolizumab and atezolizumab binding to cells lines over expressing high levels of either PD-1 (Jurkat cells) or PD-L1 (RAJI-hPD-L1 cells), respectively. **Results:** Gal-3 potentiated the binding of PD-L1 to PD-1 with a 3-fold increase in its K_D observed and the efficiency of pembrolizumab and atezolizumab binding to and blocking the PD-1/PD-L1 axis was reduced. A 6-fold reduction in K_D of pembrolizumab for the PD-1/PD-L1 complex was observed in the presence of Gal-3. In addition, atezolizumab PD-L1 blockade was reversed in the presence of Gal-3 and dramatically improved by GB1211. Similarly, in cell systems expressing high levels of PD-1 or PD-L1, Gal-3 reduced the binding of pembrolizumab and atezolizumab to their respective targets on cell surfaces that was also reversed by GB1211. **Conclusions:** Gal-3 was shown to vastly reduce the binding of the checkpoint inhibitors pembrolizumab and atezolizumab, by potentiating the interaction between PD-1 and PD-L1. GB1211 restored the binding of the anti-PD1/anti-PDL1 therapeutics and may thus reduce tumor resistance to these agents. These findings harmonize excellently with *in vivo* and clinical data showing an association between Gal-3 expression and lack of efficacy of PD-1/PD-L1 targeted checkpoint inhibitors. Galecto is now investigating the safety and efficacy of GB1211 in combination with atezolizumab in NSCLC. Research Sponsor: Galecto, Inc.

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2608 **Poster Session**

Actual immune checkpoint inhibitor drug use in U.S. patients with cancer.

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Background: By 2018, seven Immune Checkpoint Inhibitor (ICI) drugs had gained FDA approval in nine cancers and the number of indications has continued to increase. Haslam et al. estimated that between 36.1 and 38.5% of US patients with cancer were eligible for ICI therapy in 2019. We report the use of ICI dugs in the first-line of therapy (LOT1) and second-line (LOT2) among enrollees treated for 9 cancers with an FDA indication approval in or before 2017. **Methods:** A cohort of patients treated for one of the nine most common cancers with an FDA indication for ICI drugs in 2017 was identified using de-identified data from the OptumLabs Data Warehouse, and clinical information from the Optum Cancer Guidance Program's electronic prior authorization (ePA) platform. De-identified administrative claims data were then linked to ePA information (cancer type & diagnosis date) at the patient level to identify details of treatment received. Eligible patients were enrolled in a commercial or Medicare Advantage (MA) plan and initiated treatment within six months of diagnosis, enrolled at least six months prior to diagnosis date (ensuring this was the LOT1) and at least thirty days after start of first identified treatment regimen (to identify the full treatment regimen). LOT1 treatment initiation ranged from 1/1/2017 to 12/31/2020 for those who were diagnosed before 6/30/2020. ICI regimens are defined as those with an ICI drug received within first thirty days of the LOT start date. **Results:** In this population, we identified 17,283 eligible patients treated for non-small cell lung cancer (4654), melanoma (705), renal cell carcinoma (554), bladder cancer (1974), colorectal (4502), hepatocellular carcinoma (673), gastric cancer (1786), head and neck cancer (1923), or Hodgkin lymphoma (512) in 2018, 2019, and 2020. Overall, 3,291 (19%) of these patients received an ICI in LOT1 with rates increasing over time. The highest rates of ICI use in LOT1 are for the treatment of melanoma, remaining consistent over time, while ICI use in LOT2 is highest for the treatment of non-small cell lung cancer although evidence from 2020 suggests this may be waning. Among patients being treated for renal cell carcinoma, ICI use in LOT2 decreased from 43% (2018) to 15% (2020) while LOT1 ICI use increased to 81% in 2020. **Conclusions:** Overall, ICI use has changed over time in both the first- and second-line setting. In particular, we observe a shift in ICI use from LOT2 to LOT1, consistent with the more recent FDA approvals in earlier lines of therapy. Research Sponsor: None.

Regimens containing immune checkpoint inhibitors.

	1st line			2nd line		
	2018	2019	2020	2018	2019	2020
Overall	14%	20%	22%	19%	18%	12%
Non-small cell lung cancer	35%	41%	42%	44%	42%	29%
Bladder cancer	2%	5%	10%	13%	14%	9%
Renal cell carcinoma	51%	77%	81%	43%	23%	15%
Melanoma	92%	95%	95%	38%	22%	11%
Hepatocellular carcinoma	5%	10%	14%	11%	12%	8%
Head and neck cancer	1%	4%	8%	13%	12%	6%
Other Cancers	1%	1%	2%	3%	5%	1%

*2020 data for those diagnosed through 6/30/2020.

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2609 **Poster Session**

A prospective, multicenter, single-arm clinical trial of PD-1 inhibitors in combination with radiotherapy and GM-CSF, sequentially followed by IL-2 (PRaG 2.0) therapy in advanced refractory solid tumors.

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Background: It's been widely recognized that T cells play an essential role in immunotherapy of malignant tumors. Notably, in our previous PRaG trial, we observed that T cell decreasing occurred in some patients with advanced refractory solid tumors during PD-1 inhibitor combined with stereotactic body radiation therapy (SBRT) / hypo-fractionated radiotherapy (HFRT) and granulocyte macrophage-colony stimulating factor (GM-CSF) treatment which might be one of the reasons for their poor efficacy. To further improve the efficacy of immunotherapy combined with radiotherapy, we optimized the PRaG regimen and added interleukin-2 (IL-2), which amplifies and activates T cells. We conducted PRaG 2.0 trial to further explore the effect of T cells on efficacy. **Methods:** Patients with advanced refractory solid tumors who lacked or were intolerant to the available standard of care were enrolled to receive PRaG 2.0 regimen. A treatment cycle consisted of SBRT or HFRT (5 or 8Gy$\times$2-3f) delivered for one metastatic lesion, PD-1 inhibitor dosing within one week after completion of radiotherapy, GM-CSF 200μg subcutaneous (SC) injection once daily for 7 days (d1-7), and then sequentially followed by IL-2 2million IU SC once daily for 7 days(d8-14). PRaG 2.0 regimen was repeated every 21 days for at least 2 cycles until no appropriate lesions for irradiation or reached the tolerance dose of normal tissues. Patients who could not continue radiotherapy and had not yet developed progression disease (PD) allowed PD-1 inhibitors to be continued as maintenance therapy until PD or unacceptable toxicity but no more than one year. The primary endpoint was Progression-Free Survival (PFS). This trial was registered at www.clinicaltrials.gov with identifier number NCT04892498. **Results:** With the cutoff date of 31 December 2021, a total of 34 patients were enrolled, in which 28 patients (82%) completed at least 1 tumor assessment with a median follow-up time of 5.5 months (95%CI: 4.4, 6.6). Median PFS and overall survival (OS) were currently not reached. The objective response rate (ORR) was 21.4%, and the disease control rate (DCR) was 71.4% by RECIST1.1. Compared to baseline, no significant decrease of T cells, including $CD3^+$, $CD4^+$, and $CD8^+$ T cells, have been observed in 19 patients who completed $\geq$ 4 treatment cycles. Treatment-related adverse events (TRAE) occurred in 28 of 34 (82.4%) patients, Grade $\geq$ 3 TRAEs occurred in three patients (8.8%). TRAEs leading to treatment interruption occurred in three patients (8.8%). **Conclusions:** These preliminary results of PRaG 2.0 trial demonstrate that PD-1 inhibitors in combination with radiotherapy, GM-CSF, and IL-2 could potentially maintain the T cells and improve clinical outcomes in patients with advanced refractory solid tumors with acceptable toxicity. Clinical trial information: NCT04892498. Research Sponsor: None.

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2610 **Poster Session**

A phase 1/2 study of onatasertib, a dual TORC1/2 inhibitor, combined with the PD-1 antibody toripalimab in patients with advanced solid tumors (TORCH-2).

Pei Shu, Xiaoyu Li, Li Yuan, Hui Xie, Qi Zhou, Yongsheng Wang, Qiu Li, Li Zheng; Clinical Trial Center, National Medical Products Administration Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, West China Hospital, Sichuan University, Chengdu, China; Gynecological Oncology Center, Chongqing University Cancer Hospital, Chongqing, China; Antengene Corporation, Shanghai, China; Department of Gynecological Oncology, Chongqing University Cancer Hospital, Chongqing, China; Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Pre-clinical studies suggest synergistic activity of the combination of inhibitors of mTOR with a PD-1 antibody in solid tumors. Here we report initial results of a phase 1/2 open-label, dose escalation and expansion trial of the oral TORC1/2 inhibitor, onatasertib (ATG-008) in combination with toripalimab (tori), a PD-1 monoclonal antibody, in patients (pts) with advanced solid tumors (NCT04337463). **Methods:** This study consists of two phases: dose escalation and dose expansion. The primary objective in the dose escalation phase was to evaluate safety and tolerability of onatasertib combined with tori, followed by a dose expansion phase to assess antitumor efficacy and verify the safety and tolerability profile of the combination therapy. Primary endpoints included maximum tolerated dose (MTD), recommended phase II dose (RP2D) and efficacy of the combination. Other endpoints included pharmacokinetics, and exploratory biomarkers of drug activity. Prior check point (anti-PD-1, anti-PD-L1, CTLA-4), mTOR and/or PI3K/AKT/mTOR inhibitor therapy was excluded, regardless of PD-L1 expression. Onatasertib was administered orally once a day (QD) at three dose levels (15, 20 and 30mg) in combination with tori at the approved dose of 240 mg, once every 21 days (Q3W). Efficacy assessments are reported based on RECIST1.1 criteria. **Results:** As of Dec 20, 2021 cut-off, 28 advanced solid tumor pts were enrolled in the study with 10 pts in the dose escalation phase and 18 pts in the dose expansion phase. Median age was 52 years. Baseline ECOG scores were 0 (4 pts) and 1 (24 pts) with a median of 2 prior lines therapy (0-7), 21 pts had stage IV disease. No dose-limiting toxicities were reported in dose escalation phase. The study did not reach MTD. All pts had $\geq$ 1 TEAEs; 19 (67.9%) pts had grade $\geq$ 3 TEAEs. The most common grade $\geq$ 3 TEAEs included lymphocyte count decreased (21.4%), rash (14.3%) and hyperglycemia (10.7%). AEs lead to discontinuation in 2 pts (7.1%). The RP2D for onatasertib was determined to be 15-20 mg in combination with the recommended dose of tori. Among the 21 efficacy evaluable (EE) pts, the ORR was 28.6% (6 pts, 5 confirmed) and DCR was 71.4% (15 pts). In 5 EE pts with cervical cancer, 1 complete response (CR) and 3 partial responses (PR) were observed (all confirmed). One cervical cancer pt with negative PD-L1 expression achieved CR and remains on treatment after 580 days. Two other PRs were seen (one nasopharyngeal carcinoma, one ovarian carcinoma). Median progression free survival (PFS) in the whole cohort was 3.52 months and 18-month PFS rate was 31.2%. **Conclusions:** Onatasertib in combination with tori is tolerable with encouraging response rates and disease stabilisation in subjects with advanced solid tumors, especially in cervical cancer. Expansion enrolment for cervical cancer is ongoing and updated information will be presented. Clinical trial information: NCT04337463. Research Sponsor: Antengene Corporation.

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2611 **Poster Session**

Safety of dual checkpoint-blockade with PSB205, an anti-PD-1/CTLA4 monoclonal antibody combination, manufactured and dispensed as a single product: A phase 1 study.

Rashmi Chugh, Judy S. Wang, Anthony J. Olszanski, Breelyn A. Wilky, Paul Algate, Leah Plato, Alexander I. Spira, Borys Korchin, Jelle W. Kylstra; University of Michigan, Ann Arbor, MI; Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; Fox Chase Cancer Center, Philadelphia, PA; University of Colorado, Aurora, CO; Sound Biologics, Bothell, WA; Mary Crowley Cancer Center, Dallas, TX; Virginia Health Specialists, Fairfax, VA; ICON plc, Edison, NJ

Background: PSB205 is a new biological agent consisting of two engineered monoclonal antibodies (anti-PD-1 IgG4 and anti-CTLA-4 IgG1) expressed in a fixed ratio (2:1) from a single cell-line, manufactured as one product and dispensed from a single vial. PSB205 was designed to optimally balance efficacy and safety through differential target coverage of PD-1 and CTLA-4: the anti-CTLA-4 antibody was engineered to have a shorter half-life to modulate exposure and lower risk of immune-related adverse events (irAEs). **Methods:** We report safety data from a first-in-human study, conducted in standard 3+3 Phase 1 dose escalation format, enrolling subjects with refractory solid tumors with mixed histologies, who had exhausted available standard treatments. Primary objectives were safety (including Dose Limiting Toxicities), tolerability and selection of a Phase 2 dose. Secondary objectives were PK and preliminary evaluation of effectiveness. Treatment was Q3 wks. Inclusive the 1st week following the 2nd infusion, the DLT-period was 28 days. **Results:** Nine US-centers enrolled 27 subjects, representing 19 tumor histologies, in 5 ascending dose cohorts ranging from 0.1 mg/kg to 5 mg/kg; an additional N = 49 pts were dosed in expansion cohorts at 5 mg/kg and 400 mg (fixed dose). Median number of prior systemic treatments for metastatic disease was 4. No DLT was observed at any of dose level evaluated. The most frequent Treatment-Related Adverse Events (TRAE) reported were diarrhea (9%), Infusion-Related Reaction (IRR) (5%) and fatigue (4%). Among the subset (N = 33) who completed at least 4 cycles of treatment, the most common TRAE were diarrhea (21%), IRR (12%), Fatigue (9%), and irAEs, specifically colitis, rash and arthralgia (6% each symptom). Most TRAEs were Grade 1 /2, with just 1 case each of diarrhea and colitis Graded as G 3/4. Tumor responses (all PRs) were observed at dose levels of 3 mg/kg and 5 mg/kg in 4 pts - 1 each with with RCC, SCLC, HNSCC and gastric cancer. **Conclusions:** PSB205 provides dual checkpoint blockade with a very tolerable side effect profile, with less AEs than typically noted in published studies of anti-PD1 and anti-CTLA-4 combination therapy. Further studies are ongoing to confirm this observation. Dose levels of 5 mg/kg and 400 mg fixed were selected for Phase 2, which has commenced enrollment. Clinical trial information: NCT03986606. Research Sponsor: Sound Biologics.

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2612 **Poster Session**

Predictors of response to immune checkpoint inhibitors (ICI) rechallenge post-disease progression in solid tumors: A systematic review and meta-analyses.

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Background: Rechallenge with the same or different ICI has been proposed as a second line option in patients who progress on an initial ICI course. Considering rechallenge risks of limited benefit and further toxicity, identifying predictors for patients benefiting from rechallenge would provide much needed guidance for practice. We present a systematic review and meta-analyses of response predictors to ICI rechallenge after disease progression in solid tumors. **Methods:** A systematic search of PubMed, Cochrane database and ASCO meeting library was done for studies published up to Jan 2022 evaluating the efficacy of ICI rechallenge in patients with advanced solid tumors after disease progression on initial ICI. Predictors of interest included duration of the initial ICI course using a cutoff point of 6 months, and best overall response (BOR) to initial ICI: stratified into responders (complete or partial response or stable disease) and non-responders (progressive disease). Odds ratios (OR) for ICI rechallenge response were calculated & pooled in reference to initial ICI duration and its BOR using the fixed effects model. ORs with a 95% confidence interval [CI] not overlapping the null value (1) were considered statistically significant. **Results:** A total of 56 studies reporting on ICI rechallenge upon progression, comprising 3579 patients, of which 31 studies have switched their second ICI regimen. Initial ICI was anti-PD-1 in 37 studies, anti-CTLA-4 in 14 studies, and anti-PD-L1 in 10 studies. Involved solid cancers included melanoma (n = 30), NSCLC (n = 15), RCC (n = 6), and others (n = 5). Pooled objective response rate for rechallenge was 18.4% ([15.4-21.4], I^2 = 84.6%), with the highest being among melanoma patients (21.2% [17.2-25.2], I^2= 83.4%). For BOR, no significant difference was found for the entire cohort (OR = 1.34 [0.86 - 2.09], I^2 = 27.1%). In melanoma studies, response to ICI rechallenge was significantly higher in patients responding to the initial ICI prior to progression (OR = 1.87 [1.03-3.39], I^2 = 24.5%). For treatment duration, there was no difference in the entire cohort concerning ICI rechallenge (OR = 1.54 [0.86-2.75], I^2 = 14.2%), yet melanoma patients showed a significant difference favoring those who had longer response durations on initial ICI (OR = 2.05 [1.01-4.16], I^2 = 0.0%). **Conclusions:** Response to rechallenge in advanced melanoma patients was more common in initial ICI responders with a longer course duration (> 6 months). More homogeneous studies are needed to validate our findings and investigate other potential markers for rechallenge such as PD-L1 status & mutational burden. Research Sponsor: None.

	Total	Melanoma	NSCLC	RCC
# of studies/pts	15/439	7/230	5/83	3/126
BOR OR (95% CI)	1.34 (0.86-2.09)	1.34 (0.86-2.09)	0.65 (0.24-1.7)	1.17 (0.44-3.1)
# of studies/pts	10/236	6/168	4/68	
Duration OR (95% CI)	1.54 (0.86-2.75)	2.05 (1.01-4.16)	0.79 (0.27-2.31)	

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2613 **Poster Session**

Association of proton pump inhibitor use with survival outcomes in patients with cancer treated with immune checkpoint inhibitors: A systematic review and meta-analysis.

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Background: Proton pump inhibitors (PPIs) were revealed to regulate gut microbiome alterations and further impact the response to immune checkpoint inhibitors (ICIs). Contradictory impacts on survival were observed in ICI-treated patients when concomitantly use PPI or not. We performed this systematic review and meta-analysis to analyze the association of PPI use with survival outcomes in ICI-treated cancer patients. **Methods:** EMBASE, MEDLINE/PubMed, Cochrane Library databases and major oncology conferences proceedings were comprehensively searched. Studies comparing overall survival (OS) and progression-free survival (PFS) between PPI use and PPI non-use in ICI-treated cancer patients were included. Data regarding the characteristics, ICI and PPI treatments and survival outcomes for patients were extracted. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using random-effect models. Subgroup meta-analyses and meta-regressions were performed to explore possible factors of heterogeneity among study results. **Results:** A total of 20 studies were included, comprising 2812 ICI- and PPI-treated patients and 3990 ICI-treated and PPI-free patients. The pooled HR is 1.30 (95% CI, 1.17-1.45; $P<.001$) for OS and 1.20 (95% CI, 1.08-1.34; $P<.001$) for PFS, indicating a significant negative association between PPI use and survival of ICI-treated patients. Subgroup meta-analyses by factors including cancer types, ICI types and time window of PPI use, revealed such associations were in patients with non-small cell lung cancer (OS: HR = 1.40, 95% CI = 1.23 to 1.59, $P<.001$; PFS: HR = 1.27, 95% CI = 1.16 to 1.40, $P<.001$) or urothelial cancer (OS: HR = 1.50, 95% CI = 1.26 to 1.80, $P<.001$; PFS: HR = 1.37, 95% CI = 1.17 to 1.60, $P<.001$), patients treated with anti-PD-1/PD-L1 (OS: HR = 1.41, 95% CI = 1.30 to 1.53, $P<.001$; PFS: HR = 1.29, 95% CI = 1.20 to 1.38, $P<.001$), patients receiving PPI as baseline treatment (OS: HR = 1.43, 95% CI = 1.21 to 1.69, $P<.001$; PFS: HR = 1.29, 95% CI = 1.16 to 1.44, $P<.001$) or 60 days before ICI treatment initiation (OS: HR = 1.28, 95% CI = 1.11 to 1.48, $P<.001$; PFS: HR = 1.27, 95% CI = 1.16 to 1.40, $P<.001$), rather than concomitantly with ICI initiation. **Conclusions:** PPIs use in patients treated with ICIs is associated with a shorter OS and PFS, especially in several specific subgroups of cancer patients. PPIs should be strictly controlled, and appear to not impact survival if given temporarily after ICIs initiation. These detailed observations could provide basis for clinical guidelines when concomitantly use PPIs and ICIs. Research Sponsor: National Natural Science Foundation of China (No.81902462), U.S. National Institutes of Health, U.S. Department of Defense (W81XWH2110030), and Berlin Institute of Health.

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2614 **Poster Session**

A pan-cancer analysis of P21 activated kinase (PAK) family genes as potential biomarkers for immune checkpoint therapy.

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Background: PAK (P21 activated kinase) is a family of serine threonine kinases, that consist of 6 members, PAKs 1-6, which are positioned at an intersection of multiple signaling pathways implicated in oncogenesis. Recent studies have found relationship between mutations of some PAK family genes and antitumor immunity. Here, we explored the associations of PAK family gene mutations with ICI response based on multidimensional data from multiple solid tumors. **Methods:** An immunotherapy cohort (Broad/Dana-Farber, Nat Genet 2018, N = 249) within 7 types of tumors as discovery stage, was used to explore the association of PAK family genes mutations with tumor mutation burden (TMB) and efficacy of immunotherapy. To further validate the predictive value of PAK family genes, we employed another ICI-treated cohort, MSKCC cohort (Samstein, Nat Genet 2019, n = 1661), as a validation cohort. TMB was calculated as the total count of nonsynonymous mutations in coding sequence. **Results:** In discovery cohort, compared to that in the PAK-Wt group, longer OS was observed in the PAK-Mut group (mOS: 31.3 vs 15.4 months, HR = 0.59, 95% CI: 0.36 to 0.96, P= 0.03). In addition, PAK-Mut group had higher TMB (P< 0.001). Median TMB in PAK-Mut group and PAK-Wt group is 17.79 (IQR, 7.45-36.55) Mut/Mb and 5.47 (IQR, 2.46-9.09) Mut/Mb, separately. In validation cohort, PAK-Mut patients also achieved significant improved OS compared with PAK-Wt patients (mOS: 44.0 vs 17.0 months, HR = 0.51, 95% CI: 0.37 to 0.69, P< 0.001). Moreover, multivariable analysis of validation cohort demonstrated that PAK-Mut was associated with better OS (HR = 0.71; 95%CI, 0.52-0.98; P = 0.036), after adjusting for Age, Gender, Metastasis, Treatment, TMB, Cancer type. Compared with PAK-Wt group (median [IQR]: 5.90 [2.95-10.04]), PAK-Mut group (median [IQR]: 21.19 [11.81-43.29]) also had higher TMB (P< 0.001). **Conclusions:** The results indicated that PAK family genes mutation was associated with a higher TMB both discovery and validation cohort. Analysis of discover and validation immunotherapy cohort data showed PAK family was associated with better OS. These findings indicate that these genes mutation may serve as a potential predictive biomarker for ICI in solid tumor patients. Research Sponsor: None.

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2615 **Poster Session**

WDR49 mutation as a novel predictive biomarker in patients with non–small cell lung cancer with immune checkpoint inhibitors.

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Background: Application of Immune Checkpoint Inhibitors (ICIs) has become the first-line therapy for advanced or metastatic non-small cell lung cancer (NSCLC). *WDR49* gene belongs to the WDR (WD40-repeat) protein family which participates in a wide range of biological processes, including DNA damage repair and immune regulation, etc. However, the correlation between *WDR49* mutation and immune efficacy is unclear. **Methods:** A total of three independent cohorts of NSCLC patients treated with immunotherapy were analyzed in this study: the Miao cohort (n = 56), the Rizvi cohort (n = 34), the Hellmann cohort (n = 75). Survival was estimated by Kaplan-Meier curves, with the p value determined by a log-rank test. HR was determined through the univariable and multivariable Cox regression. The CIBERSORT analysis relied on RNA-seq data in The Cancer Genome Atlas (TCGA) database. Two-sided P value < 0.05 was considered statistically significant. All the statistical analyses were conducted with R version 4.0.3. **Results:** In this merged cohort, the frequency of *WDR49* mutation (*WDR49*-mut) was 10.30% (17 in 165), and most patients with *WDR49* mutation were lung adenocarcinoma (LUAD) (11.85%, 16 in 135). Meanwhile, the frequency of *WDR49*-mut in TCGA database was 7.05 % and 3.84% in LUAD and lung squamous cell carcinoma (LUSC), respectively. The Kaplan-Meier curves survival analysis indicated that *WDR49*-mut was associated with longer progression free survival (PFS) (median PFS 23 months vs 5.2 months, hazard ratio [HR] = 0.17 [95% CI, 0.06–0.47], P < 0.001) and higher objective response rate (ORR) (76% vs 27%, P < 0.001). Furtherly, *WDR49*-mut was significantly related to higher tumor mutational burden (TMB) (median TMB 495 vs 149, P < 0.001), but it had nothing to do with the expression of PD-L1 (Proportion of PD-L1 positive 72.7% vs 68.5%, P = 1). The CIBERSORT analysis revealed that CD8+ T cell infiltration was significantly higher in *WDR49*-mut group than *WDR49* wildtype group (p < 0.05). **Conclusions:** Better treatment response and survival benefit in the mutant group suggest that the *WDR49* mutation may serve as a novel predictive biomarker in NSCLC patients with ICIs. The significantly higher TMB and CD8+ T cell infiltration in *WDR49*-mut group may be the potential mechanism. Research Sponsor: None.

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2616 **Poster Session**

Molecular predictors of response among patients with MMRd tumors treated on NCI-MATCH Arm Z1D.

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Background: On arm Z1D of the NCI-MATCH trial, the PD-1 inhibitor nivolumab was found to have activity among patients with mismatch repair-deficient (MMRd) tumors as defined by complete loss of MLH1 or MSH2 nuclear expression determined by immunohistochemistry, with 6-month progression free survival of 51%. We aimed to identify molecular predictors of response in this population. **Methods:** Among patients treated on NCI-MATCH Z1D, we evaluated genomic and tissue predictors of clinical benefit (CB), defined as patients with RECIST v1.1 complete or partial response or stable disease for $\geq$ 6months. WES files were processed and filtered using GATK best practices preceding TMB and MSI calculations according to MSI sensor score, a WES-based MSI rating system. Cutoffs were set to define TMB (TMB-Low: $\leq$10 mutation/Mb; TMB-High: >10) and MSI (MSS: $\leq$10% unstable loci; MSI-Low: $10 > x \leq 20$; MSI-High: >20). Multiplex immunofluorescence (mIF) used formalin-fixed paraffin-embedded slides stained using a BOND RX automated stainer. Expression analyses followed normalization in DEseq2's median of ratios method. Gene set enrichment analysis was conducted by "empirical phenotype-based permutation test." Additional RNA, WES, and mIF comparisons used the Wilcoxon rank-sum test. **Results:** Among 36 patients accrued to NCI-MATCH Z1D with pretreatment correlative samples available, 7 were unevaluable for response, and 1 was misclassified as having an MMRd tumor. Of the remaining 28, 15 had CB (2 CR, 10 PR, 3 SD $\leq$ 6 months) and correlative data were available for 26 (WES), 27 (RNAseq), and between 10-20 for mIF based on the marker assessed. According to MSI-sensor score, 11 were MSI-high, 8 were MSI-low, and 7 were MSS. MSI-sensor status, but not TMB was associated with CB (p=0.037 and p=0.185, respectively). Similar results were seen when using CR+PR vs SD+PD evaluation. Using RNAseq gene set enrichment analyses, CB patients had increased expression of interferon alpha (p=0.01), interferon gamma (p=0.03), PI3K-AKT-mTOR (p=0.02), cytotoxicity (p=0.05) and antigen processing (p=0.01) gene sets, while hedgehog signaling genes were increased in non-CB patients (p=0.04). The ESTIMATE immune index and infiltration of CD4+/PD1+/Ki67+ cell populations as determined by mIF were nominally higher in patients with CB (p=0.051 and p=0.075). **Conclusions:** Among patients with MMRd tumors treated with PD-1 checkpoint blockade, correlative analyses demonstrate associations between CB and MSI-sensor score as well as biomarkers indicative of immune infiltration and antigen presentation. This suggests that these measures may help differentiate patient response in MSI tumors. Clinical trial information: NCT02465060. Research Sponsor: U.S. National Institutes of Health.

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2617 **Poster Session**

PAPPA2 mutation as an indicator stratified patients benefit from immune checkpoint inhibitors in NSCLC and SKCM.

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Background: Pappalysin 2 (*PAPPA2*) mutation, most occurring in skin cutaneous melanoma (SKCM) and non-small cell lung cancer (NSCLC), is found to be related to anti-tumor immune response. However, the association between *PAPPA2* and efficacy of immune checkpoint inhibitors (ICIs) therapy remains unknown. **Methods:** Forty-one NSCLC patients receiving anti-PD-(L)1 (China cohort, n = 41) and seven public cohorts with whole-exome sequencing (WES) data were included to analyze the performance of *PAPPA2* mutation as an indicator stratifying patients benefit from ICIs, consolidating a discovery set (n = 34) and two validation sets (NSCLC validation set, n = 172 ; SKCM validation set, n = 210). The mechanism was analyzed in the Cancer Genome Atlas (TCGA) database (n = 1467). **Results:** In the discovery set, patients with *PAPPA2* mutation exhibited a significantly predominant PFS (HR, 0.11 [95% CI, 0.01-0.83]; P = 0.01), ORR (100.0% vs 21.4%; P < 0.001) and durable clinical benefit (DCB, 83.3% vs 32.1%; P = 0.012) compared to those with wide-type *PAPPA2*, consistent in NSCLC validation set (PFS, HR, 0.3 [95% CI: 0.16-0.56], P < 0.001; ORR, 70.8% vs. 20.9%, P < 0.001; DCB, 83.3% vs. 36.5%, P < 0.001) and SKCM validation set (OS, HR, 0.49 [95% CI: 0.31-0.78]; P = 0.002; ORR, 34.1% vs. 16.9%, P = 0.039; DCB, 50.0% vs. 30.7%; P = 0.036). Similar results were observed in multivariable models. In contrast, no association between *PAPPA2* mutation and OS or PFS was observed in TCGA datasets, suggesting that *PAPPA2* mutation may be a predictive but not a prognostic factor in ICI treatment for NSCLC patients. Based on CIBERSORT-inferred tumor infiltrating lymphocytes from TCGA, we found that *PAPPA2* mutation was significantly associated with higher activated CD4 memory T cells and lower Treg cells in tumor immune microenvironment, related with higher TMB ($P < 0.001$) and neoantigen load ($P < 0.001$). In addition, gene set enrichment analysis (GSEA) analysis revealed that *PAPPA2* mutation was correlated with upregulated DNA damage repair (DDR) signaling pathway. **Conclusions:** Our findings indicated that *PAPPA2* mutation could serve as a novel indicator to stratify beneficiaries from ICIs therapy in NSCLC and SKCM, warranting further prospective studies. Research Sponsor: CAMS Innovation Fund for Medical Sciences.

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2618 **Poster Session**

Predictors of immunotherapeutic benefits in patients with advanced melanoma and other malignancies treated with immune checkpoint inhibitors utilizing ORIEN "real-world" data.

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Background: Despite the significant improvements in treating cancer with immune checkpoint inhibitors (ICIs), many patients (pts) do not achieve disease control. Using Oncology Research Information Exchange Network (ORIEN) Avatar real-world data conducted under the Total Cancer Care protocol we investigate predictive biomarkers of ICI benefits in pts with advanced malignancies. **Methods:** Clinical data were normalized as part of ORIEN Avatar. RNA-seq was performed on tumor samples following the RSEM pipeline and gene expressions were quantified as Transcript Per Million (TPM). Gene expressions (GE) were log2(TPM+1) transformed. Mann-Whitney U-test was used to compute differences between groups, and Kaplan-Meier survival analysis was performed. **Results:** Pts (n=1214) with 27 cancer types treated with ICIs were retrieved from the database, where 1143 and 875 patients were profiled by WES and RNA-seq, respectively. 804 pts had both WES and RNA-seq data. The top six cancer types were renal cell carcinoma (n=206), non-small cell lung cancer (n=173), head and neck cancer (n=157), melanoma (n=154), sarcomas (n=99) and bladder cancer (n=87). The ICI regimens included therapy with atezolizumab (n=87), avelumab (n=12), cemiplimab (n=6), ipilimumab (n=47), nivolumab (n=424), pembrolizumab (n=525) and ipilimumab+nivolumab (n=113). Median overall survival (OS) for the entire cohort was 21.9 months. Patients had significant improvement in OS if ICI was given in the first line (P<0.0001). Previously published GE signatures were tested in the melanoma cohort. Signatures related to IFNg, effector T cells, chemokines, MHC II and Tertiary Lymphoid Structures were significantly prognostic and predictive of ICI benefits in advanced melanoma (Table). Analyses in the other cancer types are ongoing. **Conclusions:** GE data analyses validate the predictive value of immune related gene signatures following ICI immunotherapy in melanoma. Ongoing analyses are investigating these signatures in other malignancies and integrating the GE data with data related to TMB, somatic mutations and germline genetic variations. Research Sponsor: ORIEN Foundation and Community Foundation of Tampa Bay.

GE signatures and correlation with survival (>24 versus <24 months and overall survival) in cutaneous melanoma (n=123 pts).

Gene Signature Name	Description	Reference	Survival >24 vs <24 months; *P*-value	OS (log-rank test) *P*-value
IFNg-6	6-gene IFNg associated	Ayers 2017	0.0017	0.019
IFNg expanded immune 18	18-gene IFNg associated	Ayers 2017	0.0035	0.0031
Effector T cell	Effector T cell gene set	Bolen 2011	0.0013	0.0435
IFNg/Effector T cell	IFNg and effector T cell gene set	Fehrenbacher 2016	0.0009	0.0096
Chemokine	Chemokine gene set	Coppola 2011,Messina 2012	0.0073	0.0257
MHC II	13 MHC-II genes	Liu 2021	0.0185	0.0076
TLS	Tertiary lymphoid structures gene signature	Cabrita 2020	0.25	0.0031

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2619 **Poster Session**

A deep learning approach utilizing clinical and molecular data for identifying prognostic biomarkers in patients treated with immune checkpoint inhibitors: An ORIEN pan-cancer study.

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Background: Immune checkpoint inhibitors (ICIs) have made significant improvements in the treatment of cancer patients (pts), but many continue to experience primary or secondary resistance. Here, we leveraged clinical and genomic data to identify prognostic biomarkers in pts treated with ICIs utilizing a pan-cancer approach. **Methods:** Pts were enrolled to the Total Cancer Care protocol across 18 cancer centers within the Oncology Research Information Exchange Network (ORIEN). RNA-seq was performed on tumors following the RSEM pipeline and gene expressions were quantified as Transcript Per Million (TPM) and were logarithmically normalized. An Auto-Encoder Survival Deep Network (AE-SDN) architecture was developed that combined the reconstruction loss of AE with Cox regression for modeling time to event. For comparison, immunoscore for each pt was calculated based on the estimated densities of tumor CD3+ and CD8+ T cells (Galon, 2020) utilizing CIBERSORTx. The quality of overall survival (OS) predictions was assessed using Harrell's concordance index (C-index). Log-rank test was used to assess stratified group differences (by ICI or cancer histology) along with Kaplan-Meier (KM) survival analysis of AE-SDN and immunoscore. **Results:** Pts (n=522) with 4 cancer types including melanoma (n=125), renal cell carcinoma (n=149), non-small cell lung cancer (n=128) and head and neck cancer (n=120) treated with 6 ICI regimens were included in this analysis. ICI regimens were nivolumab (n=219), pembrolizumab (n=202), ipilimumab+nivolumab (n=69), ipilimumab (n=30), avelumab (n=1) and cemiplimab (n=1). The Table summarizes the overall C-index and associated 95% CIs and log-rank *P* values for the entire cohort (regardless of histology) resulting from our proposed AE-SDN model and the separate estimated immunoscore categorization. AE-SDN top selected genes were mostly related to immunity, carcinogenesis and tumor suppression. The corresponding KM plots showed significantly wider separations of the survival curves in favor of our proposed AE-SDN model relative to the immunoscore with more than 20% improvement in prediction power. **Conclusions:** Deep network machine learning analysis is a promising approach to identifying relevant prognostic biomarkers in cancer pts treated with ICI. This may lead to novel therapeutic predictive signatures and identification of mechanisms of ICI resistance. Our AE-SDN gene expression signature was significantly prognostic and outperformed the estimated CD3+, CD8+ T Cell immunoscore. Further refinements to our prediction power are ongoing along with more advanced neural network architectures to elucidate related functional pathways. Research Sponsor: ORIEN Foundation and Community Foundation of Tampa Bay.

	Avg. C-index	95% CI	Log-rank test p-value
AE Deep	0.6556	(0.6484, 0.6629)	2.80E-14
Immuno-score	0.5402	(0.5345, 0.5459)	8.20E-04

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2620 **Poster Session**

Analysis of the contribution of macrophages to the overall tumor PD-L1 microenvironment using a screening multi-tumor tissue microarray and rapid multiplex fluorescence digital phenotyping approach.

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Background: Programmed death ligand-1 (PD-L1) contributes to immune suppression in the tumor microenvironment (TME) by interacting with programmed cell death-1 (PD-1) on infiltrating T lymphocytes leading to tumor immune escape. Application of omics technologies has shed light on the relevance of the TME for response to immunotherapies and development of novel treatment options. Here we have applied a multi-plex immunofluorescence/multi-tumor tissue microarray (TMA) approach to examine the immunobiology of different TMEs with respect to the contribution by tumor cells and macrophages to overall PD-L1 expression. **Methods:** A TMA comprising 11 tumor types and a total of 144 different donors, each represented by two cores [1mm; 1 from invasive margin (IM) and 1 from tumor center (TC)], was stained using Ultivue's Immuno8 FixVUE panel (CD3, CD4, CD8, FOXP3, CD68, PD-1, PD-L1, pan-CK/SOX10). Whole slide images from two rounds of imaging (x20 magnification; four markers in each round) were aligned using Ultivue's UltiStacker software based on the nuclear counterstains from the two imaging rounds, to provide precise marker colocalization data. Cell phenotype data for each core was generated using Visiopharm software. **Results:** Overall PD-L1 positivity was greatest for NSCLC, SCLC, TNBC and gastric cancer ranging from approximately 600-1000 PD-L1+ cells/mm^2/core, compared with CRC, breast, pancreatic, liver, and gastric esophageal junction (GOJ) cancers (approx. 50-300 PD-L1+ cells/mm^2/core). Contribution by macrophages to overall PD-L1 expression (dual CD68+/PD-L1+) varied by tumor type representing 25-35% for NSCLC (SCC and ADC) and gastric cancer, whereas a converse pattern was apparent for SCLC, TNBC, breast (ER+ and Her2+) and pancreatic cancers where PD-L1+ macrophages accounted for a large proportion (approx. 60-85%) of overall tumor PD-L1 expression. Interestingly, as a proportion of total macrophage infiltration, approximately 65% of CD68+ macrophages were PD-L1+ for SCLC and TNBC, compared with less than 10% for pancreatic and liver cancer. Spatial analysis revealed PD-L1+ macrophage infiltration to be generally higher for IM versus TC, and the distribution between tumor (CK+) and stroma (CK-) remained similar despite exclusion of CD3+/CD8+ cytotoxic T cells from CK+ tumor regions for pancreatic and liver cancer. **Conclusions:** Taken together, these data illustrate the benefits of combining multiplexed immunofluorescence staining, with digital analysis of cell phenotypes within well characterized tumor samples to better understand the relative immunobiology of different TMEs. Here we demonstrate that the relative contribution of macrophages to the overall PD-L1 microenvironment varies between tumor types, which may help guide options for successful immunotherapy strategies. Research Sponsor: None.

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2621 **Poster Session**

The inflamed immune phenotype (IIP): A clinically actionable artificial intelligence (AI)-based biomarker predictive of immune checkpoint inhibitor (ICI) outcomes across >16 primary tumor types.

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Background: The IIP, defined by enriched intratumoral tumor-infiltrating lymphocytes (TIL), is a potential tumor-agnostic biomarker of responsiveness to ICI therapy. Here, we validate the IIP, as assessed by Lunit SCOPE IO, an AI-powered spatial TIL analyzer that runs on routine H&E-stained whole-slide images (WSI), for clinical outcome prediction in a large, multi-center international cohort of ICI-treated patients, demonstrating its utility as a practical biomarker to guide ICI treatment planning. **Methods:** Lunit SCOPE IO was developed using 17,849 H&E WSI of multiple cancer types, annotated by 104 board-certified pathologists (13.5×10^9 μm^2 area and 6.2×10^6 TIL). IIP+ tumors were defined as those with ≥ 20% of all 1 mm^2 tumor tiles in a WSI classified as having a high intratumoral TIL density. We evaluated the correlation between IIP and ICI treatment outcomes (overall response rate (ORR) and progression-free survival (PFS), assessed by RECIST v1.1) in a real-world dataset of 1,806 patients (> 16 primary tumor types) retrospectively collected from Stanford University Medical Center, Samsung Medical Center, Chonnam National University Hospital, Seoul National University Bundang Hospital, and Northwestern University. IIP status was sub-analyzed by PD-L1 22C3 tumor proportion score (TPS, n = 798), microsatellite status, and tumor mutational burden (TMB, n = 130). **Results:** The IIP+ phenotype (35.2%, 636 of 1,806) was highly enriched in nasopharyngeal carcinoma (68.0%), melanoma (56.3%), renal cell carcinoma (52.9%), and non-small cell lung cancer (NSCLC, 33.7%). The IIP+ proportion by PD-L1 TPS (< 1% / ≥ 1%) was 21.6% and 40.7%, respectively. While 33.3% of microsatellite unstable (MSI-H) or TMB-high (≥ 10/Mb) tumors were IIP+, a substantial proportion (26.1%) of microsatellite stable (MSS), TMB-low tumors were IIP+. The ORR in IIP+ patients was significantly higher (26.0% vs. 15.8% in IIP-, $p < 0.001$). Median PFS for IIP+ was 5.3 months (95% CI 4.6-6.9 m), significantly longer than that for IIP- (3.1 m, 95% CI 2.8-3.6 m), with a hazard ratio (HR) of 0.68 (95% CI 0.61-0.76, $p < 0.001$). The association held after excluding NSCLC patients (n = 909) (HR 0.69, 95% CI 0.59-0.81, $p < 0.001$). On subgroup analysis, IIP+ correlated significantly with prolonged PFS, regardless of ICI regimen (mono / combo therapy) or PD-L1 TPS (< 1% / ≥ 1%). Of note, IIP+ was predictive of favorable PFS only in the MSS, TMB-low group (n = 88, HR 0.56, 95% CI 0.33-0.96), but not in the MSI-H or TMB-high groups. **Conclusions:** The IIP, as evaluated by Lunit SCOPE IO, may represent a practical, clinically-actionable biomarker predictive of favorable ICI treatment outcomes across diverse cancer patient populations, including those with PD-L1 negative, MSS/TMB-low tumors, in whom predictive biomarkers are urgently needed. Research Sponsor: Lunit Inc.

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2622 **Poster Session**

Dual *CDKN2A/MTAP* loss compared to *CDKN2A* loss alone and response to immune-checkpoint inhibitors (ICI) in advanced solid tumors.

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Background: We previously showed that *CDKN2A* genomic alterations (GAs) are associated with resistance to ICI (Adib E, Clinical Cancer Research, 2021). The majority of such GAs are homozygous deletions, which commonly (~50-80%) include *MTAP*, located 100kb telomeric of *CDKN2A.* MTAP loss leads to 5′-deoxy-5′-methylthioadenosine (MTA) accumulation and immunosuppressive effects in tumors. We examined combined *CDKN2A/MTAP* deletion vs. *CDKN2A* deletion/mutation alone as predictors of poor ICI response. **Methods:** We curated clinical data for cancer patients (pts) treated with ICI at Dana-Farber Cancer Institute through 6/2021, who had targeted panel sequencing. Inclusion criteria were: ICI in metastatic setting, ≥2 cycles, no concurrent systemic therapy, cancer type with > 50 pts treated. *CDKN2A*/*MTAP* GAs were defined as a deep deletion affecting both genes; *CDKN2A* only GAs included both homozygous deletions and truncating mutations. Hazard ratios (HR) for overall survival (OS) and time-to-treatment failure (TTF) were derived using multivariable Cox regression, adjusted for prior lines of therapy, treatment type (single vs. combination ICI), tumor mutational burden and ECOG PS. We also used a machine learning approach to quantify the density of tumor-infiltrating lymphocytes (TILs) in digital whole-slide H&E images of 144 melanoma pts with available genomic data. **Results:** 921 pts with 6 cancer types were studied: non-small cell lung cancer (NSCLC, n = 366), melanoma (mel, n = 228), urothelial carcinoma (UC, n = 120), esophagogastric carcinoma (EGC,n = 90), head and neck squamous cell carcinoma (HNSCC, n = 58), and renal cell carcinoma (RCC, n = 59). UC pts with *MTAP*/*CDKN2A* GAs had shorter OS and TTF than pts without GA in either gene (OS HR = 1.9[1.1-3.4], p = 0.005; TTF HR = 1.8[1.0-3.1], p = 0.0016) after adjusting for covariates. Similar results were seen for melanoma (OS HR = 2.5[1.4-2.6],p = 0.00065; TTF HR = 1.9[1.1-3.2],p = 0.018). There was no significant difference between pts with *CDKN2A* GA only and those without GA in either gene for OS or TTF in either UC or melanoma. *CDKN2A/MTAP* status was not associated with significantly shorter survival for NSCLC and EGC; while the analysis was confounded by HPV events for HNSCC, and underpowered for RCC. ML-based analysis of digital slides for melanoma, showed that tumors with *CDKN2A* GAs only (n = 42) had similar median density of TILs compared to tumors without GAs in either gene (n = 84; 920 vs. 943 TILs/mm2; p = 0.42). In contrast, tumors with co-occurring *CDKN2A*/*MTAP* GAs had lower TIL density (529 TIL/mm2, n = 17 vs. 925 TIL/mm2, n = 126 (pooled); p = 0.018, Wilcoxon rank sum). **Conclusions:** In this study, we showed that co-occurrence of *MTAP/CDKN2A* GAs, but not CDKN2A GA only, was associated with worse outcomes in pts with UC and melanoma treated with ICI. Lower TIL density was also seen in melanoma tissue samples with combined *MTAP/CDKN2A* GA. Research Sponsor: None.

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2623 **Poster Session**

Comprehensive genomic and immune profiling defines immunotherapy treatment in patients with NSCLC with low PD-L1 IHC.

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Background: Immune checkpoint inhibitors (ICIs) have emerged as effective treatments in non-small cell lung cancer (NSCLC). While the clinical utility of single agent ICI or in combination with chemotherapy has been well established, there remains an unmet need for the development of biomarkers that can better predict response. To address this need, we developed and applied a combination genomic and immune biomarker strategy to ICI-treated NSCLC patients which identified distinct patient subgroups with differential benefit among single agent or combination ICI treatment strategies. **Methods:** A discovery cohort (DC) of 5450 tumors across 37 histologies were evaluated by comprehensive genomic and immune profiling of the tumor immune microenvironment. Individual and combination biomarker assessment included PD-L1 IHC, TMB, tumor inflammation (TIGS), cell proliferation (CP) and cancer testis antigen burden (CTAB). From this cohort, combinations of molecular and immune biomarkers were identified and applied to a retrospective cohort (RC) of 225 metastatic NSCLC patients treated with pembrolizumab + chemo or pembrolizumab alone to correlate with response. Comparison of objective response rates (ORR) was performed using Chi-square test. Kaplan-Meir analysis was performed to test for differences in overall survival (OS) and 1-year OS. **Results:** Unsupervised analysis of the DC revealed four distinct biomarker combination groups that describe underlying tumor immunobiology: tumor dominant (CTAB, TMB, CP High), proliferative (CP High), inflamed (TIGS High), and checkpoint (PDL1, TIGS and TMB High). Application of these biomarker groups to the RC demonstrated significant differences in response to ICI regimens between groups ($p = 0.04$). Patients in the proliferative group (35.1%, 79/225; median PD-L1 = 20% TPS) treated with single agent pembrolizumab showed a significantly higher ORR (59%; 16/27) compared to pembrolizumab + chemo (27%; 14/52; $p = 0.005$), significantly improved 1-yr OS ($p = 0.03$), and trend towards better OS ($p = 0.14$). Importantly, patients in the inflamed group (16%, 36/225; median PD-L1 = 1% TPS), suggested that pembrolizumab + chemo (ORR 26.1%; 6/23) was not associated with ORR compared to pembrolizumab (ORR 31%; 4/13, $p = 0.76$), or OS ($p = 0.37$) and 1-yr OS ($p = 0.57$). **Conclusions:** Comprehensive genomic and immune profiling may identify PD-L1 low NSCLC patients who benefit from single agent pembrolizumab. PD-L1 low NSCLC patients with a proliferative phenotype may benefit from single agent pembrolizumab, whereas PD-L1 low cases with an inflamed phenotype may benefit from both single agent and combination pembrolizumab. Although further clinical validation of these predictive biomarker combinations is required, this data-driven approach demonstrates the potential to provide treatment decision support when selecting an ICI therapeutic strategy in lung cancer. Research Sponsor: Omniseq, Inc.

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2624 **Poster Session**

Correlation between MSI, TMB, and RAS gene mutation in solid tumors.

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Background: RAS gene family encodes a protein that is a member of the small GTPase super family and plays an important role in the regulation of cell proliferation and promoting oncogenic events. Studies have reported that RAS gene shows a high mutation frequency in lung cancer, colorectal cancer and pancreatic cancer. However, the relation between RAS-mutant and RAS-wild type tumors in tumor mutation burden (TMB) and microsatellite instability (MSI) remain unclear in pan-cancer. **Methods:** We retrospectively analyzed 15188 Chinese patients with pan-cancer from laboratory of Simcere Diagnosis (Nanjing, China) during 2019-2021. Somatic mutations in tumor samples were assessed by next-generation sequencing (NGS). We evaluated RAS (KRAS, NRAS and HRAS) mutation frequency, TMB and MSI in RAS-mutant and RAS wild-type tumors. **Results:** RAS mutations were detected in 2663 (17.5%) samples, including 88.7% of KRAS mutations, 9.1% of NRAS mutations and 3.5% of HRAS mutations. The top 6 frequently cancers were colorectal cancer (829, 31.1%), lung cancer (747, 28.1%), pancreatic cancer (358, 13.4%), biliary tract cancer (210, 7.9%), liver cancer (78, 2.9%), and gastric cancer (73, 2.7%). We found that the incidence of MSI-H in patients with RAS-mutant solid tumors was 3.3% and the frequency of MSI-H was significantly higher in RAS-mutant gastric cancer than that in RAS wild-type (RAS-MUT vs RAS-WT, 20.5% vs 3.5%, $p < 0.001$). Contrary to our assumption, it was not observed in colorectal cancer (RAS-MUT vs RAS-WT, 5.8% vs 6.9%). In the analysis of TMB, RAS gene mutation was associated with higher TMB ($P < 0.01$). 27.4% of RAS-mutant gastric cancer and 10.8% RAS wild-type gastric cancer were classified as TMB-H (TMB $\geq$10 muts/Mb) ($P < 0.01$), while 13.4% of RAS-mutant colorectal cancer was TMB-H, with no significant difference between RAS wild-type. However, we did not observe a close association between MSI, TMB and RAS gene mutations in lung cancer, pancreatic cancer, biliary tract cancer, and liver cancer. **Conclusions:** We analyzed RAS gene mutations in Chinese patients with solid tumor. Our data showed that RAS mutations were associated with TMB-H and MSI-H in solid tumors, especially gastric cancer. In colorectal cancer, RAS mutations were associated with higher TMB, but not TMB-H. It was showed that RAS mutations in specific cancer types, such as gastric cancer and colorectal cancer, may be related to the efficacy of immunotherapy. Research Sponsor: None.

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2625 **Poster Session**

Prevalence of high tumor mutational burden (TMB-H) and microsatellite instability-high (MSI-H) status in neuroendocrine neoplasms.

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Background: Neuroendocrine neoplasms (NENs) encompass a rare group of tumors arising in nearly any organ site. Patients with advanced-stage NENs have limited treatment options, and molecular profiling is not routinely performed in NENs. However, given tissue-agnostic FDA approvals for immunotherapy in biomarker-selected solid tumors, we sought to assess the frequency of TMB-H and MSI-H in NENs by organ site and in comparison to non-NEN counterparts. **Methods**: We retrospectively analyzed de-identified records from the Tempus database of NENs sequenced with the Tempus xT assay (DNA-seq of 595-648 genes at 500x coverage). Patients were included if their primary cancer arose in the lungs, GI tract (esophagus, stomach, small bowel, colon, rectum), pancreas, or prostate. Histologic diagnoses were grouped as NENs (including high grade or low/intermediate grade), and non-NENs (e.g. adenocarcinoma, squamous cell carcinoma) based on data abstracted from pathology reports. TMB-H was defined as ≥ 10 mutations/megabase. MSI-H was calculated as previously published (PMID: 31570899). Statistical comparisons were limited to groups of 10 or larger. **Results**: We characterized a total of 1,477 NENs from the following anatomic sites: lung (64%, N=951), pancreas (15%, N= 220), GI (15%, N= 224) and prostate (6%, N=82). TMB-H was most common in NENs arising in the lungs (17%, N=155), followed by the pancreas (5.4%, N=11), GI tract (4.8%, N=10), and prostate (3.8%, N=3) ($p< 0.001$). Overall, TMB-H was more common in high-grade NENs compared to low/int-grade NENs [17% (N=147) vs. 6.2% (N=31), $P<0.001$]. This was also observed in lung NENs [high-grade 19% (N=135) v low/int grade 10% (N=19), $P=0.006$], with other organ site analyses limited by sample size (although a similar trend was noted for GI NENs). The majority of patients with TMB-H lung NENs had a current or prior smoking history (94%, N=119). Overall, TMB-H was similar in NENs compared to non-NENs [13% (N=179) vs. 12% (N=3018), $P=0.4$]. However, in the pancreas, TMB-H was more common in NENs vs. non-NENs [(5.4% (N=11) v 1.6% (N=59), $P<0.001$] while the reverse was true in lung NENs [17% (N=155) v 22% (N=2006), $P=0.001$]. MSI-H was observed in only 0.9% (N=12) of NENs overall, including in 0.4% (N=4) of lung, 1.4% (N=3) of pancreas, 1.9% (N=4) of GI, and 1.2% (N=1) of prostate NENs. MSI-H status was less common in NENs compared to non-NENs [0.9% (N=12) vs. 2.5% (N=614), $P<0.001$]. **Conclusions**: In this real-world NEN cohort, the actionable molecular alterations of TMB-H (13%) and MSI-H (0.9%) were observed. Taken together, the data suggest that molecular profiling (regardless of grade) may help identify a small but meaningful subset of patients with NENs who may benefit from immunotherapeutic treatment approaches. Furthermore, the identification of MSI-H NENs has important implications related to germline testing. Research Sponsor: None.

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2626 **Poster Session**

Automated tumor immunophenotyping and response to immunotherapy in non-small cell lung cancer using a spatial statistics approach.

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Background: Based on the clinical success of immuno-oncology therapeutics, tissue-based, biomarker analyses have shifted from a focus on tumor cell phenotypes to spatial and functional analyses of the tumor immune environment. Distribution and composition of immune infiltrates have shown prognostic or predictive value in various studies; however, standardized approaches to categorize tumors into "Desert", "Excluded" or "Inflamed" immunophenotypes based on the density and pattern of immune infiltrates are missing. This categorization is typically based on visual inspection of a stained tissue section; it is labor-intensive and associated with poor inter-observer concordance. To eliminate these barriers we developed an automated approach that relies on a set of derived spatial features and named this analysis pipeline LATIS (metric Learning based Automated Tumor Immunophenotyping with Spatial statistics). **Methods:** We used two clinical trials, POPLAR (phase II; n=258) and OAK (phase III; n=623) that compared anti-PD-L1 treatment vs chemotherapy in patients with advanced non-small cell lung cancer to develop and validate this approach. LATIS utilizes scans of slides stained immunohistochemically for CD8 and cytokeratin (CK); images were tiled and classified according to CK status (positive/negative). First, CD8 positive and CK density was calculated for each tile. Twenty six spatial features were then extracted for each tiled image scan. We used a labeled (manual immunophenotype calls) POPLAR dataset to learn a metric that separates classes of labeled data best with respect of spatial features provided for each data point. Then, to co-embed OAK dataset with POPLAR dataset into the same space, we used that learned metric as a measure of distance between new unlabeled points (OAK data set). K-means clustering in the embedded space was used to identify clusters of data points followed by QFMatch to assign class labels ("Inflamed", "Excluded", "Desert") to each data point. **Results:** LATIS successfully relates spatial features to both, manual reads and patient response to therapy. In OAK, anti-PD-L1 treated patients experienced longer median overall survival (OS) when tumors showed intra-epithelial CD8+ cells (Inflamed) compared to tumors with a stromal pattern of CD8+ cells (Excluded) or a low density of CD8+ cells (Desert): 17.6 months vs 10.3 (Excluded) vs 12.1 (Desert) [p=0.0061]. Median progression-free survival (PFS) was 3.2 months (Inflamed) vs 2.6 (Excluded) vs 1.4 (Desert) [p=0.00058]. OS and PFS were not significantly different for the three categories in chemotherapy only arm. **Conclusions:** We suggest that tumor immunophenotype categories generated in an automated fashion by LATIS can serve as predictive biomarker for cancer immunotherapy. Research Sponsor: Roche/Genentech.

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2627 **Poster Session**

Immuno-multiple reaction monitoring (iMRM) for quantitation of PD-L1 and PD-1-signaling proteins in non-small cell lung carcinoma (NSCLC).

Vincent Lacasse, Vincent Richard, Hangjun Wang, Georgia Mitsa, Olivier Poetz, Andreas I Papadakis, Mounib Elchebly, Victor Cohen, Jason S. Agulnik, Gerald Batist, Rene P. Zahedi, Christoph H. Borchers, Alan Spatz; Lady Davis Institute & McGill University, Montreal, QC, Canada; Lady Davis Institute, Montreal, QC, Canada; Jewish General Hospital, Lady Davis Institute, McGill University Health Center, McGill University, Montréal, QC, Canada; SIGNATOPE GmbH, Reutlingen, Germany; McGill University & Jewish General Hospital, Montreal, QC, Canada; Jewish General Hospital, McGill University, Montréal, QC, Canada; Segal Cancer Centre-Jewish General Hospital, McGill University, Montreal, QC, Canada; Lady Davis Institute & Skolkovo Institute of Science and Technology, Montreal, QC, Canada; Jewish General Hospital, Lady Davis Institute, McGill University, Montréal, QC, Canada

Background: More accurate predictive biomarkers of response to checkpoint inhibitors (CPIs) still is a major unmet need in oncology. PD-L1 immunohistochemistry (IHC) limitations include its analytical variability and the post-translational modifications of PD-1 signaling-associated proteins like glycosylation. Moreover, PD-L1 IHC is an imperfect surrogate of the tumor immune microenvironment, and immunoscoring is important but difficult to assess in a clinical setting. Proteomic based technologies can overcome these challenges, but the low concentration of these proteins and the presence of high background noise in formalin-fixed paraffin embedded (FFPE) tumors were limiting obstacles. In this study, we evaluate the benefit of a new approach we used with anti-peptide antibodies to purify surrogate peptides, while liquid chromatography (LC) was coupled to multiple reaction monitoring mass spectrometry (iMRM) to improve specificity and precision of protein quantitation. **Methods:** To determine the concentration of PD-L1, PD-1, PD-L2, NT5E, LCK and ZAP70, we used unique and well detectable proteolytic peptides as surrogates. In a refined protocol, we optimized protein extraction and digestion, peptide immuno-enrichment, LC and MRM parameters to maximize recovery, increase target-specific signal and reduce noise. Plus, we assessed the glycosylation status of PD-L1, PD-L2, and PD-1. The entire workflow was fully validated using 31 NSCLC FFPE tumors. PD-L1 quantitation by iMRM was compared to PD-L1 IHC clone 22C3. **Results:** On average, 71±29 μg (n = 52) of protein could be extracted from each 1–3 mm^3 NSCLC tumor FFPE core. The optimized iMRM method allowed the quantitation of PD-L1 and PD-1 down to 21 amol on-column. Inter- and intra-day repeatability were well below FDA guidelines (coefficients of variation [CV] < 20%) with average CVs of 5.2±4.0% (intra-day) and 4.5±2.6% (inter-day). Sample storage had no significant effect on peptide quantitation. The final multiplexed iMRM assay enables quantitation all targets and glycosylation states for > 40 samples in only 3 days (including external calibration and quality controls) and was used to quantify the PD-1/PD-L1 axis proteins successfully in all 31 NSCLC FFPE tumors. PD-L1 expression ranged from 2 amol/μg to 61 amol/μg of total protein. As expected, iMRM results correlated moderately ($R = 0.56$, $\rho < 0.001$) with PD-L1 IHC. PD-L1 glycosylation status ranged from 99.9±0.2%, and therefore did not explain the discrepancies between IHC and iMRM for these samples. **Conclusions:** Herein a robust iMRM workflow was developed for the quantitation of the PD-1/PD-L1 axis in FFPE. This proof-of-concept supports that MS-based assay can provide otherwise unavailable data (e.g., PD-L1 concentration, glycosylation status). CPI treated patient tumors are being currently processed to validate the predictive value of the assay. Research Sponsor: Genome Canada, Other Government Agency.

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2628 **Poster Session**

The expression of aryl hydrocarbon receptor predicts responses to anti-PD-1 antibodies in non-small cell lung cancer.

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Background: Blockade of programmed cell death receptor 1 (PD-1) by antibodies such as pembrolizumab has revolutionized treatment for patients with non-small cell lung cancer (NSCLC). However, a significant number of patients achieve only marginal benefit. The predictive abilities of the frequently used biomarkers, including programmed cell death 1 ligand (PD-L1) and tumor mutation burden (TMB), are yet limited, highlighting the urgent need for more reliable biomarkers. Aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that controls the transcription of its targets including PD-L1. Whether AhR could be used as a predictive biomarker for response to PD-1 blockade immunotherapy in NSCLC warrants further investigation. **Methods:** We collected formalin-fixed, paraffin-embedded (FFPE) slides from 104 NSCLC patients before PD-1 blockade immunotherapy treatment, who had sufficient follow-up data for progression-free survival (PFS), and detected the expression of nuclear localized AhR (AhR^N) and membrane localized PD-L1 ($PD\text{-}L1^M$) with multiplex immunohistochemistry (mIHC). H-score was applied to characterize the specific value with the following formula [1 × (% cells intensity =1) + 2 × (% cells intensity = 2) + 3 × (% cells intensity = 3)]. Survival curve for each group was estimated by the Kaplan–Meier method and log-rank test. The diagnostic performance was assessed with the area under the receiver operating characteristic (ROC) curve (AUC), which was calculated based on the Wilcoxon rank-sum test. All statistical tests were two-sided and *P* values less than 0.05 were considered statistically significant. **Results:** Both AhR^N and $PD\text{-}L1^M$ could distinguish responders from non-responders, and patients with higher H-score had longer PFS than those with lower H score. The AUC of AhR^N was 0.804 (95 % CI: 0.721-0.881), higher than that of $PD\text{-}L1^M$ (0.714; 95 % CI: 0.618-0.811) and AhR^N+$PD\text{-}L1^M$ (0.743; 95 % CI: 0.649-0.837), indicating AhR^N might show better predictive capacity to the efficacy of PD-1 blockade immunotherapy than $PD\text{-}L1^M$. Besides, AhR^N exhibited the most significant accuracy in prognosis prediction, since the hazard ratio (HR) of AhR^N was 0.1529 (95 % CI: 0.07704-0.3033, $P<0.0001$), significantly higher than that of $PD\text{-}L1^M$ [HR:0.283 (95 % CI: 0.1525-0.525, $P<0.0001$)] and AhR^N+$PD\text{-}L1^M$ [HR: 0.2456 (95 % CI: 0.1309-0.4607, $P<0.0001$)]. Yet, among the 54 smokers, AhR^N+$PD\text{-}L1^M$ was the best classifier for the efficacy of immunotherapy, of which the AUC was 0.8937 (95 % CI: 0.816-0.971) and HR was infinitely approaching 0 ($P<0.0001$). **Conclusions**: AhR might be a reliable predictive biomarker for PD-1 blockade immunotherapy in NSCLCs. Research Sponsor: National Natural Science Foundation of China.

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2629 **Poster Session**

Pan-cancer analysis of YAP1 expression as a predictive biomarker for cancer immunotherapy.

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Background: High YAP1 expression correlates with the 'T-cell inflamed' expression phenotype in small cell lung cancer (SCLC), but its association with other biomarkers of immune checkpoint vulnerability and in tumor types beyond SCLC is not known. We examined whether YAP1 expression correlates with other established markers of immune checkpoint blockade (ICB) efficacy (PDL1 expression and TMB) in a tumor agnostic manner to determine clinical relevance. **Methods:** Next-generation sequencing of DNA (592 gene panel or whole exome) and RNA (whole transcriptome) was performed for patient samples (n = 57,134), representing 13 cancer types, submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). The 'T-cell inflamed' signature (TIS) score was calculated as an 18-gene weighted coefficient composite value (Cristescu, 2018). PDL1 expression was assessed by immunohistochemistry (IHC) with cancer type-specific antibodies and thresholds, and high tumor mutational burden was defined as ≥10 mut/Mb. Patients were stratified into subgroups based on median YAP1 expression (YAP1-High/YAP-Low) within each cancer type. Significance was tested by Chi-square, Fisher's exact test, or Mann-Whitney U test. **Results:** YAP1-High tumors were associated with significantly increased TIS scores compared to YAP1-Low across all 13 cancer types examined, with the largest fold increase observed in SCLC (1.33-fold, $p < 0.0001$), followed by pancreatic cancer (1.28-fold, $p < 0.0001$), while the smallest occurred in melanoma (1.13-fold, $p < 0.0001$). Spearman correlation strength (range 0.23-0.57) between YAP expression and TIS scores was consistent with increased TIS scores in YAP1-High samples. TMB-High rates were similar in YAP-High and YAP1-Low subgroups for most cancer types, with slightly lower rates in YAP1-High tumors observed for endometrial (23.0 vs 26.6%, $p < 0.001$) and esophageal (7.0 vs 9.5%, $p < 0.05$) cancers. YAP1 expression was not significantly increased in PDL1+ (IHC) tumors for most cancer types. However, significantly decreased YAP1 expression was associated with PDL1+ samples in RCC (Renal Cell Carcinoma) (0.91-fold change, $P < 0.05$), MM (0.90-fold change, $P < 0.001$), and ENCA (0.80-fold change, $P < 0.0001$). **Conclusions:** Our analyses provide confirmation that YAP1 expression positively correlates with the 'T-cell inflamed' phenotype across many cancer types, including those with approvals for (ICB) therapy. YAP1 expression was independent of established markers of ICB response, including TMB and PDL1. Further analysis of YAP1 expression as an additional tumor agnostic predictive biomarker is warranted. Research Sponsor: None.

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2630 **Poster Session**

A pancancer analysis of impact of *MDM2*/*MDM4* on immune checkpoint blockade (ICB).

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Background: *MDM2/MDM4* are implicated in hyperprogression after immune checkpoint blockade (ICB). Our preclinical studies showed reduced T-cell killing of *MDM2*-amplified tumor cells that was overcome by an MDM2 antagonist or gene knockdown, and we observed additional tumor killing by T-cells with MDM2 inhibition plus anti-PD1. We hypothesized that *MDM2/4* gene amplification/overexpression correlates with resistance to ICB and investigated the association of MDM2/4 alterations to overall survival (OS) following ICB across multiple solid tumors. **Methods:** Solid tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (NGS) were analyzed. *MDM2/4* amplification (amp) was tested by NGS and determined as either amp4 (cutoff of >=4.0 copies) or amp6 (>=6.0) or amp8 (>=8.0). Real-world OS was obtained from insurance claims data and calculated from treatment start or tissue collection to last contact. Kaplan-Meier estimates were calculated for molecularly defined groups. X^2/Fisher-Exact were used and significance determined as P-value adjusted for multiple comparisons ($q<0.05$). **Results:** In a large cohort of TP53-wild type solid tumors, 2785 had *MDM2* amp4 (262 were ICB-treated), 2108 had *MDM2* amp6 (ICB: 192), 1721 had *MDM2* amp8 (ICB: 149); 1040 tumors had *MDM4* amp4 (ICB: 59), 293 had *MDM4* amp6 (ICB: 8) and 217 had amp8 (ICB: 4). NSCLC, GBM, breast, bladder cancer and liposarcoma had the highest *MDM2* amp and breast cancer, GBM, uterine, NSCLC and ovarian cancers had the highest *MDM4* amp. When all tumors were considered, *MDM2* amp4, 6 and 8 significantly associated with shortened OS (amp4: HR 1.31; amp6: HR 1.31; amp8: 1.29, all $p<0.0001$); similar results were seen with *MDM4* (amp4: HR 1.14, $p=0.004$; amp6: HR 1.51, $p<0.00001$ and amp8: HR 1.6, $p<0.00001$). Of note, *MDM4* amp4 but not *MDM2* amp4 was associated with significantly worse post-ICB survival (HR: 1.55, $p=0.009$)**.**When comparing molecular differences between *MDM2* amp4 and *MDM4* amp4, significantly higher PDL1 expression was associated with *MDM2* amp (Ab clone 28.8: 58% vs. 28%; clone 22c3: 48% vs.25%, $q<0.05$); while higher mutation rates of *ARID1A*, *PIK3CA*, *PTEN*, *KRAS* and *CTNNB1* were associated with *MDM4* amp (all $q<0.05$). When investigating NSCLC, *MDM4* amp4 was associated with decreased post-ICB survival in NSCLC (HR: 2.59, $p=0.001$) but not *MDM2*; when comparing the molecular alterations, *MDM2* amp was associated with significantly higher PDL1 (22c3) (54% vs. 27%), *EGFR* mutation (36% vs. 14%) but less prevalent *KRAS* (15% vs. 50%), *STK11* (11% vs. 41%), *KEAP1* (2.5% vs. 27%) and *BRAF* (2% vs. 16%) mutations. The association with poor prognosis of *MDM2* amp4/6 (HR: 1.2 and 1.3, $p<0.05$) and *MDM4* amp4/6 (HR: 1.3 and 1.6, $p<0.05$) was seen in breast cancer, but not in NSCLC, GBM, bladder or uterine cancers. **Conclusions:** *MDM2* and *MDM4* amplification are negative prognostic factors in TP53-WT breast cancer while *MDM4* amp is associated with reduced survival in ICB-treated NSCLC. Research Sponsor: None.

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2631 **Poster Session**

Systematic assessment of tumor mutational burden calculation across different sequencing platforms and cancer types and its implication in clinical decision-making.

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Background: Tumor mutation burden (TMB) has been validated as a biomarker to predict the response of immune checkpoint inhibitors (ICIs) treatment in various cancers. However, the effects of different sequencing platforms, cancer types and calculation methods on TMB as well as its cut-off value for predicting immunotherapy efficacy are still need to be further investigated. **Methods:** 4140 tumor samples were performed with targeted panel sequencing or whole exome sequencing (WES) in different platforms such as illumina and MGI. Public sequencing data from 3680 samples which contained targeted panel sequencing, WES and whole genome sequencing were obtained. The impact of different sequencing platforms, sequencing methods and calculation methods on the calculation of TMB were assessed. Further, targeted panel sequencing data from 71 sample of lung cancer patients treated with ICIs were used to determine the best cut-off value of TMB for predicting immunotherapy response. **Results:** TMB values calculated by different platforms and different sequencing methods were similar and there was no significant difference. The distribution of TMB at different sequencing depths and tumor purity were analyzed. We found that there was no significant difference in the distribution of TMB when the sequencing depth was greater than 500′, the HE purity was greater than 0.1 or NGS purity was greater than 0.3. In addition, the correlation of TMB calculated from single-sample and paired-sample is 0.95. Further, the optimal cut-off value of TMB in lung cancer treated with ICIs was determined to be 8 through ROC curve analysis, and patients with TMB $\geq$ 8 had better outcomes than patients with TMB $<$ 8. **Conclusions:** This study systematically analyzed the factors which influenced the TMB calculation, and verifies the feasibility of TMB calculation from single-sample. More importantly, the cut-off value of TMB for predicting immunotherapy efficacy in lung cancer was defined as 8 in East Asian populations, which can help in clinical decision-making. Research Sponsor: None.

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2632 **Poster Session**

Association between tumor mutational burden (TMB) and mutational profile and its effect on overall survival: A post hoc analysis of patients with TMB-high and TMB-low metastatic cancer treated with immune checkpoint inhibitors (ICI).

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Background: High-TMB was recently approved as an agnostic biomarker for pembrolizumab in advanced cancers. Still, several patients with high-TMB do not respond to ICI, while some patients with low-TMB benefit from immunotherapy. **Methods:** We collected genomic (MSK-IMPACTassay) and survival data from 1,661 patients and assessed OS (Kaplan-Meier method) according to the mutational status. To better qualify patients with TMB ≥ 10 mut/Mb (TMB-H) (N = 488, 29%) and TMB < 10 mut/Mb (TMB-L) (N = 1,173, 71%) for ICI treatment, we analyzed single gene alterations impacting OS ($P < 0.05$). For all genes exhibiting a correlation with OS, we conducted a Cox multivariate analysis stratified by median TMB, sex, median age, microsatellite instability (MSI) status, and histology. **Results:** Survival to ICI increased with higher TMB. Median OS was 42 and 15 months for TMB-H and TMB-L ($P < 0.05$), respectively. For TMB-H tumors, 5 genes (*STK11, KEAP1, CIC, E2F3, TP53*) exhibited reduced OS on ICI, and 22 genes (*NTRK3, TERT, NOTCH3, RNF43, TET1, PTPRD, NCOA3, TENT5C, ZFHX3, RIT1, CCNE1, PPM1D, GATA2, ALK, DNMT1, PTPRT, MET, EPHA7, BCL6, SMO, CDK6, MED12*) were associated with better OS, $P < 0.05$. Cox multivariate analysis confirmed a correlation between mutations in *STK11* and *E2F3* with worse OS, while mutations in *NTRK, PTPRD, RNF43, TENT5C, TET1,* and *ZFHX3* were associated with better OS ($P < 0.05$). Histology did not play a relevant role in ICI response except for melanoma (better OS; $P < 0.05$). MSI status did not significantly affect OS. For TMB-L tumors, 20 genes were related with reduced OS (*TP53, H3C2, DAXX, SMARC4, STK11, SOX17, RB1, PIK3CA, CTNNB1, KMT2D, HLA-A, FBXW7, CDH1, RBM10, KEAP1, IGF1R, H3C11, EGFR, RUNX1, B2M*), while 8 genes were associated with better OS (*VHL, SETD2, PBRM1, BRAF, KDM5C, MAP2K1, CSF1R, RET),* $P < 0.05$. Cox multivariate analysis confirmed 15 genes associated with superior (*KDM5C, PBRM1,* and *VHL*) and inferior (*CTNNB1, DAXX, FBXW7, H3C2, H3C1, IGF1R, KMT2D, PIK3CA, RB1, SMARC4, SOX17, TP53*) OS ($P < 0.05$). In the TMB-L context, melanoma histology and MSI status (except among VHL-mutated tumors) were independently associated with better OS. **Conclusions:** This pan-cancer analysis demonstrates that genomic alterations in single cancer genes can help define outcomes of TMB-H and TMB-L patients treated with ICI. Research Sponsor: None.

	BETTER OS	WORSE OS
TMB-H	*NTRK3*, TERT, NOTCH3, RNF43*, TET1*, PTPRD*, NCOA3, TENT5C*, ZFHX3*, RIT1, CCNE1, PPM1D, GATA2, ALK, DNMT1, PTPRT, MET, EPHA7, BCL6, SMO, CDK6, MED12*	*STK11*, KEAP1, CIC, E2F3*, TP53*
TMB-L	*VHL*, SETD2, PBRM1*, BRAF, KDM5C*, MAP2K1, CSF1R, RET*	*TP53*, H3C2*, DAXX*, SMARCA4*, STK11, SOX17*, RB1*, PIK3CA*, CTNNB1*, KMT2D*, HLA-A, FBXW7*, CDH1, RBM10, KEAP1, IGF1R*, H3C11*, EGFR, RUNX1, B2M*

*Genes that exhibited correlation with OS in both uni- and multivariate analysis.

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2633 **Poster Session**

Age-associated differences in transcriptional expression and tumor immune microenvironment composition among older patients with cancer.

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Background: Older patients (pts) with cancer are underrepresented in registrational clinical trials for immune checkpoint inhibitor (ICI) therapies. There may be relevant differences in the makeup of the tumor microenvironment (TME) and in genomic signatures of cancer in older pts. This analysis explores differences in the genomic makeup of common cancers and their TME in pts ≥ 80 years (yr) of age, compared to younger pts. **Methods:** Next-generation sequencing of DNA (592 gene panel, NextSeq or whole-exome sequencing, NovaSeq) and RNA (whole transcriptome sequencing, NovaSeq) was performed for non-small cell lung carcinoma (NSCLC; n = 19,891), melanoma (MEL n = 2,899), and renal cell carcinoma (RCC; n = 1,333) pt samples submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ). PD-L1 expression was assessed by immunohistochemistry (IHC), and high tumor mutational burden (TMB-H) was defined as ≥10 mut/Mb. Pts were stratified into age subgroups of ≥80 and < 80 yr for comparison of DNA damage response (DDR) gene alterations, gene expression profiling, and TME analysis (MCP-counter; Becht, 2016). *P-values* were adjusted for multiple hypotheses testing (Benjamini-Hochberg) unless noted as exploratory. **Results:** Pts ≥80 yr accounted for 16.0%, 19.9% and 5.3% of NSCLC, MEL and RCC pts, respectively. Compared to pts < 80 yr, NSCLC and MEL pts ≥80 yr had similar DDR gene mutation rates, while *BRCA1* mutations were more common in MEL pts ≥80 yr (2.1 *vs* 0.8%; exploratory-$p < 0.05$). NSCLC ≥80 yr TMEs had increased abundance of fibroblasts (1.09-fold, $p < 0.01$), dendritic cells (1.07-fold, $p < 0.01$) and macrophages (1.04-fold, $p < 0.01$), and MEL≥80 yr TMEs had fewer infiltrating T-lymphocytes (0.87-fold, $p = 0.02$). Increased expression of immune checkpoint (IC) genes *PDCDL1G2* (PD-L2; 1.11-fold), *HAVCR2 (*TIM-3; 1.11-fold*)*, and *CD80/86* (1.07/1.08-fold, $p < 0.05$) was seen in NSCLC pts ≥80 yr, while *IL-6* expression was decreased (0.88-fold; $p < 0.05$). The largest change in IC gene expression was for *IL-6* (1.24-fold, $p = 0.78$) in MEL, and *GZMB* (0.56-fold*;* $p = 0.17$) in RCC ≥80 yr. TMB-H was less common in NSCLC (29.7 vs 36.5%, $p < 0.001$) and more common in MEL pts ≥80 yr (65.7 vs 49.0%, $p < 0.01$), and PD-L1 (IHC-SP142, ≥2+l5%) expression was less frequent in RCC pts ≥80 yr (9.1 vs 19.4%, exploratory $p < 0.05$). Profiling of glutamine and glucose metabolism-related genes revealed increased *SLC38A5* (1.17-fold; $p < 0.0001$) and decreased *G6PC* (0.65-fold, $p < 0.01$) expression in NSCLC ≥80 yr. While not statistically significant, MEL and RCC pts ≥80 yr had opposite trends for *SLC38A5* and *G6PC* expression. **Conclusions:** Our analysis provides new insights to immune landscape of NSCLC, MEL, and RCC pts ≥80 yr. Differential gene expression and TME composition changes in this population suggest unique, cancer-specific therapeutic opportunities, and a potential to explore biomarkers of response to ICIs. Research Sponsor: None.

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2634 **Poster Session**

Microsatellite-stable tumors with high tumor mutational burden in association with tumor response to immune checkpoint inhibitor therapy across solid tumors and correlation with specific oncogenic alterations.

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Background: High tumor mutational burden (TMB-H) has shown promise as a predictive biomarker in certain tumors, but broad applicability across tumors is unclear. In 2020, pembrolizumab was approved for treatment refractory metastatic or unresectable solid tumors with TMB ≥10 mutations/megabase based on exploratory analysis of the KEYNOTE-158 study. Growing evidence suggest limitations of TMB-H across tumors. Our aim is to evaluate outcomes of patients (pts) with advanced microsatellite-stable (MSS) solid tumors with TMB ≥10 mutations/megabase treated with immune checkpoint inhibitors (ICIs) and identify genetic alterations that predict poor response to therapy. **Methods:** Pts treated between 01/2015 to 12/2020 at Robert H Lurie Cancer Center, Northwestern University, with ICIs and TMB ≥10 mutations/megabase on next generation sequencing by FoundationOne CDx, Tempus xT or Guardant360 CDx platforms were identified. Tumors other than carcinomas and microsatellite instability were excluded. Radiologic response was assessed using iRECIST criteria. Responders (CR/PR) were compared with non-responders (SD/PD). Subgroup analyses were conducted based on tumor type, genetic alterations within signaling pathways. Survival curves were calculated using Kaplan-Meier method. Multivariate analyses were performed to determine impact of clinical variables on response. **Results:** Of 119 pts, median age was 68 yrs, and 61% of pts were male. 15 tumor types were represented, most commonly melanoma (33%), NSCLC (28%), small cell lung carcinoma (5.9%), colorectal carcinoma (5%), and pancreatobiliary carcinoma (5%). When evaluating for efficacy (n = 106), ORR was 36% with CR 14%. Median PFS and OS overall were 10.9 mo and 29.9 mo. Lack of exposure to previous therapy was associated with response (p = 0.039). PD-L1 status, specific ICI regimen, age, and sex did not have prognostic significance. When comparing melanoma/NSCLC (n = 66) and other tumor types (n = 40) there was no significant difference in response (p = 0.3). When comparing response by specific gene mutations, *TP53* (p = 0.026) and *PIK3CA* (p = 0.025) were associated with worse response. Similarly, *ROS1* alteration trended to poorer response (p = 0.057). When evaluating genetic pathways, mutations within TP53 pathway were associated inferior response (p = 0.018). There was no significant difference in RTK/RAS, NRF2, PI3K, TGFβ, WNT, MYC, Cell Cycle, and Notch pathways. **Conclusions:** Growing evidence shows limitations of TMB-H as a predictive biomarker for ICI therapy in MSS tumors. Our data suggests alterations within *TP53* and its signaling pathway, *PIK3CA* mutations, and likely *ROS1* alterations are associated with non-responders in MSS TMB-H solid tumors. Further analysis of tumor-specific cohorts and genetic alterations will be presented. Research Sponsor: None.

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2635 **Poster Session**

PD-L1 expression and microsatellite instability in tumors of unknown primary site.

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Background: Cancer of unknown primary site is a heterogeneous group of tumors for which the origin remains unknown, despite detailed investigation. Its clinical presentation occurs due to symptoms resulting from metastasis, which can be influenced not only by biological processes of the tumor, but also due to regulatory processes in the tumor microenvironment such as PD-L1. Microsatellite instability (MSI) is a predictive biomarker for cancer immunotherapy and its status as well as co-occurrence with PD-L1 expression is poorly evaluated. The aim of this study was to evaluate the expression of PD-L1 and the status of MSI in tumors of unknown primary site and their possible associations with clinical-pathological characteristics and clinical outcomes in patients with this type of tumor. **Methods:** The PD-L1 expression was evaluated using the immunohistochemistry technique and measured by CPS and TPS scores. MSI status was assessed using a hexa-plex marker panel by polymerase chain reaction followed by fragment analysis. Overall survival was analyzed using the Kaplan Meier method and comparisons of the curves using the log rank test. **Results:** Of the 121 conclusive cases for MSI status, only two cases (1,6%) were MSI-High. PD-L1 expression, assessed by both TPS and CPS, was positive in approximately 18% of 108 conclusive cases. PD-L1 expression is significantly less frequent in patients with a predominance of hepatic or bone metastasis and more frequent in patients with a predominance of nodal metastasis. The median overall survival was about 4 months, and the predominance of liver metastases was associated with a worse prognosis, while the use of chemotherapy and low ECOG-PS were associated with better survival. PD-L1 expression was associated with better overall survival. **Conclusions:** PD-L1 is expressed in a subset of patients with cancer of unknown primary site, while MSI is a rare event. It is necessary to better explore the microenvironment of this type of tumor as well as the role of immunotherapy to change such a dismal clinical outcome. Research Sponsor: Barretos Cancer Hospital - Research Institute.

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2636 **Poster Session**

14-gene immunoglobulin (IGG) and proliferation signatures and association with overall survival across cancer-types.

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Background: The HER2DX prognostic assay in early-stage HER2-positive breast cancer integrates clinical variables and 4 gene expression signatures (GES) tracking IGG, tumor proliferation, luminal cell differentiation, and the expression of the HER2 amplicon. Here, we assessed the prognostic value across cancer-types of each of these four individual GES and a research-based version of the HER2DX risk-score. **Methods:** RSEM batch normalized RNA-sequencing gene expression data from The Cancer Genome Atlas (TCGA) project were downloaded from cBioPortal. The association between a research-based version of the HER2DX risk-score, and each GES, with overall survival (OS) was assessed as continuous variables using univariate Cox regression model. The research-based version of the HER2DX risk-score tested did not include clinical variables. The Cox model was applied to estimate hazard ratios (HR) with 95% confidence intervals. The threshold for statistical significance was set at $p< 0.05$. **Results:** Gene expression data from 9,852 patients representing 30 different cancer-types were evaluated. The proliferation, IGG, luminal and HER2 amplicon GES were significantly associated with OS in 40.0%, 33.3%, 23.0% and 6.7% of the cancer-types tested, respectively. The IGG GES was found significantly associated with a favorable OS in breast cancer (HR: 0.73, $p < 0.001$), cervical and head & neck squamous cell carcinomas (HR: 0.75, $p = 0.021$ and HR: 0.78, $p < 0.001$), lung adenocarcinoma (HR: 0.84, $p = 0.020$), skin melanoma (HR: 0.73, $p < 0.001$) and sarcomas (HR: 0.78, $p = 0.029$). Conversely, association of IGG GES with unfavorable OS was observed in uveal melanoma (HR: 1.74, $p = 0.008$), kidney clear cell and papillary cell carcinomas (HR: 1.29, $p < 0.001$ and HR: 1.44, $p = 0.017$, respectively), as well as brain low-grade gliomas (LGG) (HR: 1.56, $p < 0.001$). Finally, the research-based HER2DX risk-score was found significantly associated with OS in 11 of 30 (36.7%) cancer-types, including breast (HR: 1.42, $p < 0.001$) cervical and head & neck squamous cells cancers (HR: 1.36, $p = 0.018$ and HR: 1.30, $p < 0.001$), lung adenocarcinoma (HR: 1.34, $p < 0.001$), skin melanoma (HR: 1.34, $p < 0.001$), sarcomas (HR: 1.41, $p = 0.003$), adrenocortical carcinoma (HR: 2.31, $p < 0.001$), endometrial carcinoma (HR: 1.36, $p = 0.005$), hepatocarcinoma (HR: 1.26, $p = 0.012$), LGG (HR: 1.37, $p = 0.001$) and mesothelioma (HR: 1.48, $p = 0.005$). **Conclusions:** The 14-gene IGG and proliferation signatures are strong prognostic biomarkers across cancer-types. The opposite association of IGG with OS depending on the cancer-type warrants further investigation. Research Sponsor: None.

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2637 **Poster Session**

Phase 1 studies of personalized neoantigen vaccine TG4050 in ovarian carcinoma (OC) and head and neck squamous cell carcinoma (HNSCC).

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Background: Mutation-associated neoantigens (MANAs) constitute attractive antigens for the design of cancer vaccines. However, clinical implementation remains challenging because of the patient specific nature of MANAs, hereby requiring that a bespoke vaccine is designed for each subject. We developed a pipeline for the genomic characterization and the design of tailored vaccine using a modified vaccinia Ankara viral vector. **Methods:** Immunogenicity, safety and early clinical activity of personalized cancer vaccines are being assessed in two phase I trials, respectively in high grade serous OC and HPV-negative HNSCC. Patients (Pts) at high risk of relapse are enrolled in the study being in remission following surgical primary treatment. High risk is defined as stage IIIC or IVA for OC and stage III or IVA for HNSCC. A vaccine is manufactured for each patient. OC pts are treated at asymptomatic relapse based on radiological finding or elevation of CA-125 with the vaccine alone; HNSCC pts in complete remission after surgery and adjuvant therapy are randomized to receive the vaccine either at the end of locoregional treatment or in combination with standard of care at relapse. The vaccine was administered weekly for 6 weeks and a booster dose every three weeks over a year or until progression, whichever occurred first. **Results:** At the time of the data cut-off, a total of 8 pts were treated: 4 relapsing OC pts, 3 HNSCC pts in complete remission and 1 relapsing HNSCC pt. AE attributable to the vaccine were mainly grade 1 injection site reactions and fatigue. One OC pt displayed an objective response 6 weeks after initiation of vaccine and for 9 months with a normalization of CA-125 until death from an unrelated cause; 1 other OC pt remains on treatment with a stable radiological disease for 11 months. The 2 other OC progressed at the first evaluation on day 43. HNSCC pts treated in complete remission received respectively 20, 15 and 4 doses, and remain on treatment and disease free. One HNSCC patient received 9 doses of vaccine after relapse in conjunction with chemotherapy and anti-PD-1 therapy and remains on treatment with stable disease after 5 months. Immune monitoring demonstrates priming of a polyepitopic T cell response against class I and II antigens. Responses were observed regardless of HLA and without cross-reactivity to the germline protein. Adaptive response was associated with a shift of CD4 and CD8 T cells toward an effector phenotype and innate cellular immunity was activated with a strong maturation and activation of NK cells. Immune changes were stronger in pts with controlled disease versus progressors. **Conclusions:** Data demonstrate that TG4050 is safe, well tolerated and able to induce T cell responses whatever the HLA haplotype. Early signs of clinical activity were observed in OC pt. These data pave the way for further development and synergistic immunotherapeutic combinations. Clinical trial information: NCT04183166. Research Sponsor: TRANSGENE.

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2638 **Poster Session**

Personalized neoantigen DNA vaccines expand tumor-specific T cells in the periphery which infiltrate the tumor in hepatocellular carcinoma.

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Background: Tumor neoantigens are epitopes derived from tumor-specific mutations that can be incorporated in personalized vaccines to prime T cell responses. DNA vaccines delivered with electroporation have recently shown strong CD8 and CD4 T cell responses in clinical trials. In preclinical studies, DNA-encoded neoantigen vaccines have shown induction of CD8 T cells against 50% of predicted high affinity epitopes with the ability to impact tumor growth. **Methods:** Paired blood and tumor biopsy samples were collected from a patient with hepatocellular carcinoma before and after treatment with GNOS-PV02 (DNA neoantigen targeted vaccine) + plasmid IL-12 + pembrolizumab. Treatment resulted in a partial response with a decrease in tumor size of 44% by RECIST (168 mm to 94 mm). TCRbeta sequencing was performed on all 4 samples and single cell TCR and transcriptome sequencing was performed from T cells isolated from the post-treatment blood sample. Newly identified TCRs in blood and tumor after vaccination were inserted into an expression vector and used to generate engineered TCR T cells. Engineered TCR T cells were tested against the neoantigens included in the vaccine and their responses characterized by flow cytometry. **Results:** We identified 67,893 new clones in PBMC after vaccination, 3 of which comprised between 0.1 to 1% of the total T cell clones. Moreover, we identified 5126 new clones in the tumor post vaccination, out of these, 3878 (75.68%) were not found within the patient's pre vaccination PBMCs and 556 (10.86%) were identified within the pre vaccination PBMC pool. Importantly, of the newly identified T cells infiltrating the tumor post vaccination, we observed high frequency TCR clones of which 44 and 7 clones were above 0.1% and 1%, respectively. The majority of the newly identified T cell clones were CD8 T cells (68.75%) with an activated phenotype. Importantly, the 6 most expanded clones in blood were identified to be activated CD8+CD69+ T cells (81.82%). Engineered TCR T cells generated encoding the TCRs of these newly identified CD8 T cells showed activation when exposed to the tumor neoantigens encoded in the neoantigen DNA vaccine GNOS-PV02. **Conclusions:** GNOS-PV02, a neoantigen DNA vaccine, in combination with plasmid IL-12 and pembrolizumab resulted in expansion of newly identified T cells, primarily activated CD8, which trafficked to the tumor. These new tumor infiltrating T cells showed TCR specificity against tumor neoantigens encoded in GNOS-PV02 and may account for the observed objective decrease in tumor size. Research Sponsor: Geneos Therapeutics.

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2639 **Poster Session**

Preliminary results from an early phase trial of in situ immunization of lymphoma with a virus likeparticle containing a TLR9 agonist combined with anti-PD1 therapy (NCT03983668).

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Background: *In situ* immunization involves intratumoral (IT) injection of immunostimulatory agents to modify the tumor microenvironment with the goal of inducing an anti-tumor T cell response. Here, we report preliminary results of a clinical trial exploring *in situ* immunization with a virus like particle (VLP) combined with systemic pembrolizumab (Pembro) in lymphoma. The VLP, known as CMP-001 or vidutolimod (Vidu), is composed of the bacteriophage Qb capsid encapsulating the TLR9 agonist G10. Preclinical studies demonstrated generation of antibodies against the Qb capsid (anti-Qb) is necessary for Vidu to induce an anti-tumor response. In other cancers, early phase clinical trials of *in situ* immunization with Vidu, with and without systemic anti-PD1 therapy, have revealed early promising results. **Methods:** This trial included patients with relapsed lymphoma that have failed at least 1 line of therapy. The first dose of Vidu is given subcutaneously to stimulate anti-Qb that opsonizes the VLP. This is followed by IT Vidu administered weekly for seven doses, then at 3-week intervals. Pembro (200 mg fixed dose) is given intravenously every 3 weeks. Subjects continue treatment if they do not experience unacceptable toxicities and in the investigator's opinion continued treatment is in the subject's best interest. Fine needle aspirates for flow cytometric analysis are obtained prior to therapy and 4-6 weeks following initiation of therapy. **Results:** Six patients have enrolled to date (1 CR, 2 PR, 1 SD, 2 PD). The first 3 patients received 5mg Vidu per dose and the second cohort 7.5 mg per dose. Common side effects included chills, rigors, mild headache, and fatigue. These typically resolved within 4 hours after receiving the injection. **Conclusions:** *In situ* immunization with Vidu plus systemic anti-PD1 is a promising therapy in lymphoma. The ability to generate anti-Qb that opsonizes the VLP appears to be necessary for Vidu to induce an immune and therapeutic response. Accrual and correlative studies are continuing with the modification that generation of functional-Qb after the first dose of Vidu is required before patients receive IT therapy. Clinical trial information: NCT03983668. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Pt.	Diagnosis and key prior Rx	Clinical and correlative findings	Preliminary interpretation
1	DLBCL Post CAR-T	No benign B cells, toxicity, or anti-Qb generated - Progression	Anti-Qb is required for therapeutic response
2	FL < 1 yr post rituximab		
3	FL > 2 yrs post rituximab	Flare reaction on PET but achieved CR	Vidu can cause PET pseudo-progression
4	ALK + ALCL	- PR	T cell lymphomas can respond
5	FL ~ 1.5 yrs post obinutuzumab	Generated very low, but functional levels of anti-Qb, Low grade toxicity - SD	Low levels of anti-Qb are adequate for opsonization of VLP
6	FL > 2 yrs post rituximab	Regression of injected and contralateral (un-injected) nodes - PR	Anti-tumor effect is systemic

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2640 **Poster Session**

First-in-human/phase I trial of PE0116 (4-1bb Ig G4 McAb) as single agent in patients with solid tumors progressed after lines of therapies in China.

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Background: The 4-1BB co-stimulatory protein is an important modulator of the adaptive T Cell immune responses, and potentially a vital target for immunotherapies in oncology. HE0116 is a humanized agonist antibody to 4-1BB that promotes proliferation and activation of T cells. The FIH/phase Ia/Ib study was conducted to establish a maximum tolerated dose, identify dose-limiting toxicities (DLTs) and to assess safety, tolerability, and pharmacokinetics of HE0116 as single agent in patients with solid tumors who have progressed on standard of care (SoC) and experimental therapies. **Methods:** Patients (pts) with histologically confirmed solid tumors who progressed after prior SoC and experimental therapies were enrolled. A Fibonacci 3+3 design was employed for the phase 1a dose escalation of 9 dose levels. HE0116 was administered intravenously once in first 28-day cycle for PK analysis and DLT assessment. Pts continued HE0116 treatment every 3 weeks until experiencing an intolerable toxicity, disease progression or withdrawing consent. **Results:** As of January 25, 2022, 19 pts were enrolled in the dose-escalation phase). All pts had progressed on multiple lines of therapies, including but not limited to, chemotherapy, hormonal therapy, or/and immunotherapy. As defined in study protocol, pts received HE0116 intravenously at least once at six dose levels: 0.03 mg/kg (n = 1), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3), 1 mg/kg (n = 4), 2 mg/kg (n = 3), and 3 mg/kg (n = 5). One DLT of Grade (g) 4 platelets decrease was reported at 3 mg/kg, thus 3 new pts were added at this dose. The grade1 and grade2 HE0116 related adverse events (AEs) per CTCAE v5 that occurred (< 10% frequency) were ALT and AST increase, platelet decrease, WBC decrease, anemia, hypokalemia, hyponatremia, hypoalbuminemia, hypothyroidism, or bone pain. Three SAE were reported: 1 g2 ascites, 1 g4 dyspnea, 1 g2 fever. To date there was one iPR at 1 mg/kg for a pt with advanced ovarian cancer with liver met after 6 cycles of treatment, and 4 iSD (1 in 2 mg/kg, 3 in 3 mg/kg) were recorded. **Conclusions:** HE0116 administrated intravenously every 3 weeks is well tolerated with minimal toxicities. Preliminary data are very encouraging as single agent HE0116 showed durable responses with 1 iPR, 4 iSD in several difficult to treat late-stage cancer pts. Dose escalation is ongoing as per study protocol. Phase II in select patient populations, and clinical investigation of the combination of HE0116 with CTLA-4 or PD-1 are warranted. Clinical trial information: CTR20201794. Research Sponsor: HyaMab Biotech.

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2641 **Poster Session**

A phase I dose-escalation and expansion study of HBM4003, an anti-CTLA-4 heavy chain only monoclonal antibody, in patients with advanced solid tumors.

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Background: HBM4003 is a fully human heavy chain only monoclonal antibody (HCAb) to CTLA-4, which has been engineered to deplete Treg cells by enhanced antibody-dependent cellular cytotoxicity (ADCC) activity. In the Phase 1 dose escalation part, HBM4003 showed favorable safety and efficacy profile in patients (pts) with advanced solid tumors. Here, we present the updated data from the dose escalation part and most recent safety and clinical activity data from three expansion cohorts of pts with advanced hepatocellular carcinoma (HCC), melanoma, and renal cell carcinoma (RCC). **Methods:** In the dose-escalation part, pts were enrolled into 3 dose levels (DL): 0.3mg/kg QW (28-day cycle), 0.45mg/kg Q3W (21-day cycle), and 0.6mg/kg Q3W (21-day cycle). In the dose-expansion part, pts with advanced HCC, melanoma, and RCC received 0.45 mg/kg Q3W (21-day cycle). Tumor measurements were performed every 6 weeks for up to 12 months and subsequently every 12 weeks per RECIST v1.1. **Results:** In total 60 pts were included for this analysis, including 24 pts with advanced solid tumors in the dose escalation part and 36 pts in the dose expansion part: 18 pts with HCC, 4 pts with melanoma, and 14 pts with RCC, from 12 sites in mainland China, 5 sites in Australia, and 1 site in Hong Kong. 46 pts (77%) received $\geq$ 2 lines of previous systemic therapies and 37 pts (62%) received previous PD-1/PD-L1 treatment. For the HCC cohort, 19 pts were treated in dose-escalation (1 pt, 0.45 mg/kg Q3W) and dose-expansion parts. All 19 pts received previous PD-1/PD-L1 therapy. 12 pts were evaluable for efficacy. Two had stable disease (SD), 2 pts had partial response (PR) as best response. For 12 evaluable pts, ORR was 16.7% and disease control rate (DCR) was 33.3%. For the RCC cohort, 19 pts were treated in dose-escalation and dose-expansion parts; 18 pts were evaluable for efficacy. Eight had SD as best response; the DCR was 44.4%. Overall, the most common treatment-related adverse event (TRAE) (incidence $\geq$ 10%) of all grades was rash (16 [26.7%] pts). At the 0.45 mg/kg Q3W DL, the most common TRAE of all grades was hepatic function abnormalities (12 [27.9%] pts) and rash (12 [27.9%] pts). 30 (69.8%) pts reported Gr 1 or 2 TRAEs. Gr $\geq$3 TRAEs occurred in 4 (9.3%) pts. 1 pt reported Gr 4 TRAE: blood creatine phosphokinase increased. No Gr 5 TRAE was reported. TRAE leading to discontinuation occurred in 4 pts. In mouse model, only tumor infiltrating lymphocytes Treg was depleted upon HBM4003 treatment while no Treg change in blood and spleen. In pts, Treg depletion was observed only in tumor tissue on day 21 post dosing. Overall, HBM4003 demonstrated dose proportional pharmacokinetics and low immunogenicity. **Conclusions:** HBM4003 showed a favorable safety profile, promising antitumor activity and intratumoral Treg depletion in pts with advanced solid tumors at the 0.45 mg/kg Q3W DL. Clinical trial information: NCT04135261. Research Sponsor: Harbour BioMed US, Inc.

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2643 **Poster Session**

Phase Ia dose-escalation study of the anti-BTLA antibody icatolimab as a monotherapy in patients with advanced solid tumor.

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Background: The B- and T-lymphocyte attenuator (BTLA) is an inhibitory receptor expressed on B, T and NK cells. Icatolimab (TAB004 or JS004) is a humanized IgG4 monoclonal antibody (mAb) with a hinge mutation (S228P) that binds BTLA and blocks its interaction with its ligand HVEM. In preclinical studies, icatolimab monotherapy suppressed tumor growth in murine tumor models using human BTLA knock-in mice. In this first-in-human dose-escalation study, we report the preliminary safety and efficacy of icatolimab as a single agent in patients with advanced solid tumors. **Methods:** Eligible patients with advance solid tumors refractory to standard therapies were enrolled in this study. Icatolimab was administered at escalating doses of 0.3, 1, 3 and 10 mg/kg intravenously Q3W and followed by dose expansion in 3 and 10 mg/kg cohorts until disease progression or intolerable toxicity. Dose-limiting toxicity (DLT) was evaluated by a safety monitoring committee. Study objectives included safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity. **Results:** A total of 25 patients with solid tumor were enrolled in the Part A of this phase I study (NCT04137900). The median age was 62 (range 32-85) years with 16 (64%) male patients. Patients were heavily pretreated with a median of 4 prior lines of therapy. Fifteen (60%) patients received and progressed upon prior anti-PD-1/L1 therapy. By the data cutoff date of December 31, 2021, the median follow-up was 32 weeks. No DLT was observed. 24 (96%) patients experienced treatment emergent adverse event (TEAEs), with 7 (28%) experienced grade 3 TEAEs. No grade 4 or 5 TEAE occurred. The incidence or severity of AE was not associated with the dose. The most common TEAEs were fatigue (32%), abdominal pain (20%), diarrhea (16%), arthralgia (16%), aspartate aminotransferase increased (16%), constipation (16%), and contusion (16%). One (4%) TEAE led to discontinuation of study drug. Four (16%) patients experienced immune related AE. Among 19 evaluable patients by the cutoff date, 1 confirmed PR (melanoma) and 6 SD were observed as assessed by the investigator per RECIST v1.1. The response was still ongoing over 12 months in the melanoma patient who had progressed upon prior nivolumab and BRAF/MEK inhibitors treatments. BTLA receptor was fully occupied in the 3 and 10 mg/kg cohorts. The mean elimination half-life of icatolimab was 7.5 to 19.2 days in four dose cohorts. Biomarker analysis indicated co-expression of HVEM and CD8 was associated with favorable response. **Conclusions:** Icatolimab monotherapy were well tolerated in all doses evaluated and showed preliminary clinical efficacy as a monotherapy. Icatolimab in combination with toripalimab (anti-PD-1) for the treatment of patients with advanced solid tumors is currently ongoing. Clinical trial information: NCT04137900. Research Sponsor: Shanghai Junshi Biosciences and TopAlliance Biosciences.

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2644 **Poster Session**

Preliminary analysis of a phase I study of SNK01 (Autologous Non-genetically Modified Natural Killer Cells With Enhanced Cytotoxicity) monotherapy in patients with advanced solid tumors.

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Background: Natural killer (NK) cells play a key role as the main effector cells toward cancer in innate immunity. Thus, a leading approach is to boost NK-cell mediated anti-tumor activity using adoptive transfer of ex vivo activated NK cells. NK cells have always been challenging to grow ex vivo especially when derived from heavily pretreated donors, thus most have focused on universal allogenic donor derived products. SNK01 is a first-in-kind, autologous non-genetically modified NK cell product with significant anti-tumor cytotoxicity and over 90% expression of CD16, NKG2D, NKp46, and DNAM-1, that can be consistently produced even from heavily pre-treated cancer patients (pts). While most if not all NK cell therapy has focused on liquid malignancies, SNK01 has been found to have strong activity against both liquid and solid tumors preclinically. We hypothesized that SNK01 would be safe without need for lymphodepletion and may demonstrate activity against heavily pre-treated solid tumors. **Methods:** In this Phase 1 dose escalation study (NCT03941262), SNK01 was administered intravenously (IV) weekly for 5 consecutive weeks using a 3+3 design in pts with advanced solid tumors. The starting dose was 1 x 10^9SNK01 cells and the highest dose was 4 x 10^9 SNK01 cells. Primary endpoint was safety based on AEs, vitals, laboratory tests, and PEs. Individual NK cell expansion was characterized for increases in cytotoxicity and changes in activating receptor expression. **Results:** As of Feb 1, 2022, 10 pts with advanced refractory solid tumors have been enrolled. Median age is 50 (range 32 – 75) and 6 were male. Pts had a median 5.5 lines of prior therapy (range 2-10). The subtypes were 4 leiomyosarcoma, 1 chondrosarcoma, 1 NSCLC, 1 small round cell tumor, 1 colorectal, 1 synovial cell sarcoma, 1 angiosarcoma. NK cells were successfully activated and expanded, even from heavily pre-treated pts. Average cytotoxicity was increased over 400% and average activating receptor expression was greater than 90%. There were only two Grade 1 adverse events reported in the 50 total doses given. Best objective response of SD was demonstrated in 7 pts. Of patients who progressed in the dose escalation cohorts, several reported an overall improvement in their QOL. Based on this improvement, patients then became eligible to be treated with additional salvage chemotherapy to which some then showed additional response. **Conclusions:** SNK01 with high cytotoxicity and activating receptor expression can be consistently produced from heavily pretreated patients. SNK01 was very safe and appears to have some clinical activity against heavily pretreated solid tumors and may even sensitize tumors to additional chemotherapy. SNK01 will be studied further as monotherapy and in various combination regimens. Clinical trial information: NCT03941262. Research Sponsor: NKGen Biotech.

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2645 **Poster Session**

Promising clinical benefit rates in advanced cancers alongside potential biomarker correlation in a phase I/II trial investigating bexmarilimab, a novel macrophage-guided immunotherapy.

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Background: Clever-1 is an immunosuppressive scavenger receptor expressed on tumor associated macrophages. High levels of Clever-1 are associated with poor survival and immunotherapy resistance. Bexmarilimab (FP-1305) is a novel humanized anti-CLEVER-1 IgG4-antibody capable of inducing a phenotypic M2 to M1 immune switch of tumor-associated macrophages. **Methods:** MATINS (Macrophage Antibody To INhibit immune Suppression) trial is a first-in-human phase I/II study (NCT03733990) to assess safety and preliminary efficacy of Bexmarilimab in patients with refractory advanced solid tumours. Part I has been completed with initial good safety profile of the IMP, preliminary signs of efficiency, and recommended dose of 1mg/kg Q3W for part II (ESMO 2020). In Part II (ESMO 2021), 10 distinct solid tumour types were enrolled to assess preliminary efficacy (overall survival (OS), progression free survival (PFS), and clinical benefit rate (CBR). Clever-1 IHC in pre-treatment biopsies with Ventana platform using a primary antibody 4G9 (Santa Cruz) was scored by % of positive cells compared to the viable tumor cells. **Results:** At the Jan 2022, a total of 193 patients have been enrolled to the study. In the completed cohorts, 138 patients have received 1-21 doses (median 3) of Bexmarilimab Q3W. Bexmarilimab was well tolerated, and no new safety signals were detected. Part I and Part II fully enrolled 11 cancer cohorts, the median PFS was 2.0 months (95% CI 1.9 – 2.0) and the median OS was 5.2 months (95% CI 4.3 – 6.4). CBR for Part II was 17.3% (19/110) at cycle 4 of treatment (by RECIST v.1.1). Notably, 30-40% CBR at cycle 4 was seen in cutaneous melanoma (30%), gastric cancer (30%), cholangiocarcinoma (30%), hepatocellular cancer (40%), and ER+ breast cancer (40%). Six-month survival rates (landmark analysis) were 70.1% for CBR compared to 34.7% for non-CBR patients, with a similar duration of prior therapy in both groups. Preliminary biomarker analysis (n = 77) demonstrated positive trend (p = 0.038) between CBR and higher intratumoral Clever-1 positivity (median of 15% positivity (range 0-25) in CBR and 3% (range 0-85) in non-CBR patients). **Conclusions:** Bexmarilimab continues to demonstrate promising anti-tumour activity as a monotherapy in several refractory solid tumours. Furthermore, preliminary biomarker analysis suggests a possibility for patient selection based on tumour Clever-1 expression. Further expansion of the study will investigate optimal dosing and biomarkers of efficacy. Clinical trial information: NCT03733990. Research Sponsor: Faron Pharmaceuticals.

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2646 **Poster Session**

Phase I study of the efficacy and safety of IBI319 in patients with advanced malignant tumors.

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Background: IBI319 is a recombinant fully human anti-CD137/PD-1 bispecific antibody. In preclinical studies, IBI319 demonstrated a better anti-tumor efficacy and safety. Here we report the initial results from the first-in-human study of IBI319 in patients with advanced malignancies. **Methods:** Enrolled patients (pts), ECOG PS $\leq$ 1, had advanced solid tumors or hematological malignancies and failed standard treatment. This phase 1 monotherapy dose-escalation includes accelerated titration (0.03 and 0.1mg/kg) and conventional 3+3 dose escalation (0.3, 1.0, 3.0, 6.0 and 10.0 mg/kg). IBI319 is administered intravenously every 14 days after dose-limiting toxicity (DLT) evaluation. Objectives include evaluation of safety, DLT, pharmacokinetic (PK) and antitumor activity. Adverse events (AEs) were reported per CTCAE v5.0 and DLTs evaluated within a 28-day window. **Results:** At cutoff date of February 10, 2022, 21 pts were enrolled (median age 55 years; 81.0% male; 19.1% ECOG PS 1; 52.4% advanced solid tumors). The following dose levels have been evaluated; 0.03 mg; 0.1 mg; 0.3 mg; 1 mg; 3 mg and 6 mg. Dose escalation is ongoing. The maximum tolerated dose has not been reached. Treatment-emergent adverse events (TEAEs) was reported in 15 out of 21 (71.4%) pts, among which 1 pts had back pain and nausea of grade 3. The most common TEAEs (> 10%) were interleukin level increased (6 pts, 28.6%) and C-reactive protein increased (3 pts, 14.3%). Eleven pts (52.4%) experienced treatment-related AEs; none were grade 3 or higher. The most common TRAEs (> 10%) were interleukin level increased (6 pts, 28.6%) and C-reactive protein increased (3 pts, 14.3%). Importantly, no drug-related elevations in transaminases (ALT, AST) or bilirubin have been seen. No DLT was observed. PK analysis of IBI319 demonstrated consistent exposure with linear PK. For 14 evaluable pts, 1 classical Hodgkin lymphoma patient achieved PR as best response. **Conclusions:** IBI319 demonstrates good tolerability in patients with advanced solid tumors or hematological malignancies, with a safety profile characterized by a lack of hepatotoxicity frequently observed with CD137-targeting antibodies. Clinical trial information: NCT04708210. Research Sponsor: Innovent Biologics Inc.

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2647 **Poster Session**

Phase 1 dose escalation study of DSP107, a first-in-class CD47 and 4-1BB targeting multifunctional immune-recruitment protein, in patients with advanced solid tumors.

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Background: DSP107 is a bi-functional, trimeric, fusion protein composed of sequences from the extracellular domain of SIRPα and 4-1BBL. The SIRPα arm targets CD47 overexpressed on tumor cells, blocking the "don't eat me" checkpoint and triggering tumor cell phagocytosis. The trimeric 4-1BBL arm, once cross-presented and immobilized by SIRPα binding to CD47, interacts with 4-1BB expressed on activated immune cells, mainly T- and NK cells in the tumor microenvironment, and stimulates their proliferation and activation. Thereby, DSP107 triggers both an innate and an adaptive immune response. Here we describe data from the completed DSP107 monotherapy dose escalation portion of study NCT04440735. **Methods:** Adult patients with advanced solid tumors were treated with weekly intravenous DSP107 infusions (0.01 - 10 mg/kg) during 3-week treatment cycles. An accelerated dose escalation in single patient cohorts (dose levels 1-3) was followed by a standard 3 + 3 design. The primary objective was to determine safety, tolerability and pharmacokinetic (PK) parameters. Paired biopsies were obtained from 8 patients (screening, after cycle 2). Restaging imaging was performed every two months and evaluated by RECIST criteria. **Results:** In 23 patients, DSP107 demonstrated no treatment related hematologic or hepatic adverse events (AEs) and no dose limiting toxicities. Grade 1-2 treatment related AEs were observed in 70% of patients (16/23). The most frequent AEs included infusion related reaction (IRR; 26%), diarrhea (17%), fatigue (17%), nausea (13%) and constipation (9%). IRRs were managed during subsequent infusions by reducing the infusion rate and administering IV fluids. No significant systemic cytokine release was measured at any dose level using a 10-plex, pro-inflammatory panel. PK analysis revealed 100% CD47 receptor engagement on peripheral T and NK cells at doses of 3 mg/kg and above. DSP107 did not bind CD47 on red blood cells at any dose. Preliminary histologic assessment of paired biopsies by an independent, blinded pathologist demonstrated increased tumor necrosis compared to screening in 3 out of 4 patients associated with immune cell infiltration. Immuno-profiling of tumor by immunofluorescence is on-going. Stable disease as best response was observed in 11/22 patients with treatment duration up to 26 weeks. **Conclusions:** DSP107 is a novel, CD47 and 4-1BB targeting fusion protein with a differentiated safety, binding and pharmacodynamic profile compared to other CD47 and 4-1BB targeting agents. Clinical trial information: NCT04440735. Research Sponsor: KAHR Medical Ltd.

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2648 **Poster Session**

A phase 1a dose-escalation study of PY314, a TREM2 (Triggering Receptor Expressed on Macrophages 2) targeting monoclonal antibody.

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Background: To characterize the safety and tolerability of PY314, an immunosuppressive macrophage depleting antibody, as a single agent and in combination with pembrolizumab in subjects with advanced refractory solid tumors including subject's refractory to checkpoint inhibitors if approved for that indication. **Methods:** Two were evaluated in subjects with advanced solid tumors, single agent PY314 and PY314 in combination with 200 mg of pembrolizumab using a 3+3 dose escalation study design. Dosing was intravenous and administered once every 3-weeks, a defined cycle. Disease assessment by RECIST 1.1 was performed every 6 weeks. Each stratum included 4 dose levels of PY314 (1, 3, 10, and 20 mg/kg). Pharmacokinetics were evaluated at specified time points. Archival tumor tissue was analyzed for TREM2 expression by immunohistochemistry. Based on preclinical evaluation of TREM2 expression, HR+ HER2- and triple negative breast cancer, colorectal cancer, renal cell cancer, non-small cell lung cancer and gynecologic cancers were studied. **Results:** 28 subjects (median age 60 years [range 26-76], 22 females and 6) with an ECOG PS <2 were enrolled and all, but one was (1 subject withdrew consent after dosing). 15 subjects were treated with single agent PY314 and 13 were treated with the combination. No infusion-related reactions, dose limiting toxicities, suspected unexpected serious adverse reactions or high-grade treatment related adverse events (TRAEs) that resulted in treatment discontinuance was seen. 12 subjects experienced at least one TRAE, and in all but one subject, these were low grade. One subject experienced a treatment-related immune system disorder. serious adverse events, all unrelated to treatment. TREM2 expression in archival tumor ranged from 0.0-20%. PY314 pharmacokinetics were linear, dose proportional, unaffected by concomitant pembrolizumab and with a half-life of 8-9 days. Best radiographic response was stable disease seen in 11 subjects (39.3%) ranging in duration from 9-42 weeks. 6 subjects with stable disease have progressed and 5 remain on treatment. **Conclusions:** PY314 was well tolerated and has an excellent safety profile both as a single agent and in combination with pembrolizumab. A recommended dose for expansion was derived and enrollment in five prespecified cancers is ongoing. Clinical trial information: 04691375. Research Sponsor: Pionyr Immunotherapeutics.

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2649 **Poster Session**

Pan-cancer (ca) analysis of the safety and efficacy of immune checkpoint inhibitors (ICI) in patients (pts) living with HIV (PLWH): Results from the international CATCH-IT consortium.

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Background: PLWH and ca are inadequately represented in clinical trials evaluating ICI especially in the setting of low CD4 counts (ct) and elevated HIV viral loads (VL). We assembled an international cohort of PLWH and ca treated with ICI to evaluate toxicity profiles and clinical outcomes. **Methods:** We retrospectively collected data on 204 PLWH and ca receiving ≥ 1 cycle of ICI between 2015-2021 at 14 academic medical centers in the US and Europe. Immune-related adverse events (irAEs) were graded per the Common Terminology Criteria for Adverse Events (CTCAE) V5.0. Baseline CD4 ct, CD8 ct and HIV VL were collected within 3 months (mo) of ICI initiation when available. Fisher's exact test was performed to compare categorical variables. Median (med) Overall Survival (OS) and Objective Response Rate (ORR) were calculated for 186 pts treated in the metastatic (met) setting. **Results:** Among 204 PLWH treated with ICI, 174 (85%) were cis-gender males. 61 (31%) were Black and 34 (18%) were Hispanic/Latinx. Pts were treated with pembrolizumab (n=93), nivolumab (n=71), atezolizumab (n= 20), nivolumab and ipilimumab (n=13), durvalumab (n=6), or avelumab (n=1). Med number of prior lines of systemic therapy was 1 (range: 0-5). Among pts with available baseline data, 36/133 (27%) had CD4 ct <200 cells/μL while 12/136 (9%) had VL ≥400 copies/mL. irAEs of any grade occurred in 43 (21%) pts and 13 (7%) were grade ≥3 while 19 (9%) required steroids. Pts with CD4 ct <200 cells/μL experienced fewer irAEs than pts with CD4 ct ≥200 cells/μL (2/36 vs 26/97; p<0.01). The incidence of any grade irAEs was similar between pts with CD4/CD8 ratio <0.4 vs ≥0.4 (8/54 vs 18/72; p=0.16) and between pts with HIV VL ≥400 vs <400 copies/mL (1/12 vs 28/124; p=0.46). Clinical outcomes are shown in the table below. Among 29 pts with met non-small cell lung ca (NSCLC) with available CD4 ct, the ORR of pts with CD4 ct <200 cells/μL was 13% (95% CI:0-53) vs 38% (95% CI:18-62) in pts with CD4 ct ≥ 200 cells/μL (1/8 vs 8/21; p=0.38). **Conclusions:** In the largest dataset to our knowledge, we demonstrate tolerability and activity of ICI among PLWH regardless of CD4 ct and HIV VL levels. CD4 ct <200 cells/μL may be associated with a lower incidence of irAEs. An analysis of a larger cohort is underway. Research Sponsor: None.

Ca Type	N total (%) (N=204)	Grade 3+ irAEs N (%)	Med baseline CD4 ct, cells/μL (range)	N met (%) (N=186)	Med OS (95% CI), mo	ORR (95% CI), %
NSCLC	50 (25)	2 (4)	314 (6-1721)	46 (25)	10.6 (7.4-NR)	23 (11-38)
Hepatocellular ca	19 (9)	1 (5)	375 (234-1034)	17 (9)	14.9 (4.2-NR)	0 (0-22)
Anal ca	17 (8)	2 (12)	190 (110-494)	16 (9)	7.5 (1.3-11.6)	19 (4-46)
Kaposi sarcoma	17 (8)	1 (5)	251 (10-1210)	16 (9)	6.5 (2.1-30.3)	67 (38-88)
SCLC	16 (8)	2 (13)	662 (236-844)	15 (8)	9.6 (4.3-14.5)	8 (0-38)
Head and neck ca	15 (7)	2 (13)	270 (115-385)	15 (8)	5.8 (0.9-NR)	7 (3-34)
Others	70 (34)	3 (4)	281 (20-1154)	61 (33)	NA	NA

NR: Not Reached; NA: Not Applicable

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2650 **Poster Session**

IBI110 (anti-LAG-3 mAb) as a single agent or in combination with sintilimab (anti-PD-1 mAb) in patients with advanced solid tumors: Updated results from the phase Ia/Ib dose-escalation study.

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Background: Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor protein that functions to control T cell response, activation and growth. Dual inhibition of PD-1 and LAG-3 may improve anti-tumor effect synergistically. A phase Ia/Ib dose-escalation study evaluated IBI110 ± sintilimab in patient with advanced solid tumors; initial efficacy and safety data were previously presented (C Zhou et al. ASCO 2021; NCT04085185). Here, we reported the updated results. **Methods:** Eligible patients were ECOG PS 0-1 and had locally advanced, recurrent or metastatic solid tumors for whom standard therapy had failed. Patients received escalating doses of IBI110 (0.01/0.1/0.3/1/3/10/20mg/kg) IV Q3W in phase Ia and escalating doses of IBI110 (0.3/0.7/1.5/3/5/8/10 mg/kg) in combination with sintilimab 200 mg IV Q3W in phase Ib. Crossover from monotherapy to combination therapy was allowed at progression. The primary objectives were safety, tolerability, and anti-tumor activity of IBI110 alone or IBI110+sintilimab (per RECIST v1.1). **Results:** Phase Ia: 28 patients (median age of 60.5 years [range 35-72], ECOG PS of 0 [n = 14] and 1 [n = 14]) were enrolled. Dose escalation was completed and no dose-limiting toxicity (DLT) was observed in all dose cohorts. The safety profile was generally consistent with the initial. By investigator-assessment, best response was 1 confirmed partial response (PR) and 6 stable diseases (SD) with monotherapy. After crossing to combination therapy at progression, 8 patients who failed prior anti-PD-(L)1 mAb therapy achieved SD. Phase Ib: Overall, 45 patients (median age: 60.0 yr [range 33-74]; ECOG PS: 0 [n = 14], 1 [n = 31]) were enrolled in all dose levels. Dose escalation was completed and no DLT was observed. The most common treatment-related adverse events (TRAEs) were aspartate aminotransferase increased (28.9%), anaemia (24.4%), and alanine aminotransferase increased (22.2%). TRAEs ≥ grade 3 occurred in 10 (22.2%) patients. Immune-related AE (irAE) incidence was 31.1%, and the most common irAE was hypothyroidism (15.6%). In 43 patients who had undergone at least 1 post-baseline tumor assessment, the investigator-assessed best response included 6 PRs (1 endometrial cancer, 4 NSCLC, and 1 SCLC patients) and 23 SDs. Three patients showed a progression-free survival > 1 year and continued treatment. **Conclusions:** IBI110 alone or plus sintilimab demonstrated acceptable safety profile and promising antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04085185. Research Sponsor: Innovent Biologics, Inc., China.

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2651 **Poster Session**

Safety and efficacy of etigilimab in combination with nivolumab in select recurrent/ advanced solid tumors.

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Background: Etigilimab (etig), a humanized IgG1 monoclonal antibody, blocks TIGIT interaction with PVR (poliovirus receptor) and inhibits downstream signalling with target cell killing. Etig +/- nivolumab (nivo) showed acceptable safety and preliminary activity in a FIH Phase 1a/b study in solid tumors. ACTIVATE, an open-label Phase 1b/2 basket study is evaluating further efficacy, safety, tolerability and PK/PD of etig+nivo. This is a preliminary efficacy and safety analysis from ACTIVATE. **Methods:** Subjects with advanced/metastatic solid tumors without curative/standard of care therapies are given IV etig+nivo Q2W until disease progression or intolerable toxicity. Six open cohorts are enrolling in parallel: endometrial cancer (post-front-line platinum), endometrial cancer (2-3 prior lines), PD-L1+ checkpoint-inhibitor-naïve (CPI-n) cervical cancer, rare cancers (germ cell tumor (GCT), sarcoma, uveal melanoma), ovarian cancer (post-front-line platinum) and TMB-h/MSS, (TMB >10mut/mb) tumors. Tumor assessments are done every 8 weeks following baseline scan. Primary endpoint is investigator-assessed ORR by RECIST 1.1. Secondary endpoints include duration of response and safety. **Results:** Of 27 efficacy-evaluable subjects enrolled in the 6 open cohorts with minimum 1 staging scan or radiological/clinical progression at data cut-off of 02/10/22, 12 had clinical benefit with 1 complete response (CR), 2 partial responses (PRs) and 9 stable diseases (SDs) and 15 had radiological/clinical progressive disease (PD), with an overall response rate (ORR) of 11% and disease control rate (DCR) of 44%. **Conclusions:** Etig+nivo is safe and well tolerated with no new safety signals. Early efficacy was noted in cervical cancer (1CR, 1PR and 1SD) and uveal melanoma (3 SDs >20 weeks). Encouraging activity was also noted in ovarian cancer and post-CPI treated TMB-H/MSS NSCLC. These early data support continued evaluation of the combination of etig+nivo. Clinical activity was notable as below. Clinical trial information: NCT04761198. Research Sponsor: Mereo BioPharma 5 Inc.

	Best Observed Response (BOR)[1] (n), CR/PR/SD Duration on study			
COHORTS	**CR**	**PR**	**SD**	**PD**
CPI-n CPS>1% Cervical Cancer (n=3)	1[2] 63 days^	1 72 days*	1[3] 174 days^	**0**
CPI-n Uveal Melanoma(n=6)	-	-	3 175 days^; 178 days*; 143 days*)	3
Ovarian cancer (n=8)	-	1 112 days^	3 80 days^; 58 days*; 51 days*	4
TMB-H/MSS (n=4)	-	-	1[4] 100 days*	3
Rare: Sarcoma (n=3)	**-**	**-**	1 63 days*	2
Rare: GCT (n=3)	-	-	-	3
Total (n=27)	1	2	9	15

[1]BOR at data cut-off,*On-study, ^Off-study. [2]Off study, withdrew consent with ongoing CR. [3]Unrelated death with ongoing SD. [4]NSCLC, CPS <1%. Treatment-related adverse event (TRAE) rate was 25% (safety analysis set n=41, ≥ 1 dose of etig+/-nivo). Two G3 TRAEs (immune-related diabetes mellitus and maculopapular rash), and 3 G2 infusion-related AEs occurred. There were no >G3 TRAEs and no treatment-related SAEs/discontinuations. Most common TRAEs were G1-2 skin rashes (36% of TRAEs); 1 G3 rash AE required systemic steroids for resolution.

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2652 **Poster Session**

Enhanced tumor control with a combination of APG-157 and immune checkpoint inhibitors for head and neck cancer.

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Background: Natural botanical drugs containing flavonoids are under clinical investigation for the treatment of malignancies. A phase I clinical study for patients with locally advanced head and neck cancer with a new class of botanical drug APG-157 showed excellent tolerability, systemic absorption via sublingual administration, and enhanced immune cell infiltration into the tumor microenvironment and suppression of T cell inhibitory inflammatory cytokine production. We sought to evaluate the efficacy of tumor control for the combination of APG-157 and checkpoint blockade immunotherapy using a head and neck cancer mouse model. **Methods:** SCCVII (HPV-) and MEER (HPV+) head and neck cancer murine cell line models were utilized in *in vivo* tumor growth study. After optimization for route and cell number, we measured tumor growth after treating mice with following groups: i) control, ii) APG-157, iii) anti-PD-1, iv) anti-CTLA-4, v) APG-157 + anti-PD-1, vi) APG-157 + anti-CTLA-4, vii) anti-PD-1 and anti-CTLA-4, viii) APG-157 + anti-PD-1 + anti-CTLA-4. Tumors were collected after 2 injections of immune checkpoint inhibitors and characterized for immunophenotype by multi-color flow cytometry, immunohistochemistry, and RNA-sequence analysis. Fecal microbiome was analyzed by 16S rRNA sequence for SCCVII model to assess the impact of APG-157 on the microbiome as we observed the shift of oral microbiome species in the human trial. **Results:** We confirmed by serum concentration of APG-157 metabolites that the best route of administration is via oral route by mixing with APG-157 with mouse chow. Tumor growth optimization experiments determined that 100,000 cells of SCCVII is the ideal number of cells to inject and day 5-6 is the time to initiate treatment. Among 8 treatment groups, APG-157 + anti-CTLA-4 demonstrated best tumor control ($p = 0.0065$ compared to control), followed by anti-PD-1 + anti-CTLA-4 treatment group ($p = 0.48$ compared to control). The immunophenotype assessment by flow cytometry showed over 30% of CD8+ T cell in APG-157 + anti-CTLA-4 group compared to 4-5% of CD8+ T cell for the control group. GSEA analysis from the SCCVII tumors revealed that APG-157 + anti-CTLA-4 group showed an enriched set of genes for inflammatory response, apoptotic signaling pathways. The fecal microbiome analysis showed a substantial difference of lactobacillus genus among groups, highest in the group of APG-157 + anti-CTLA-4 treatment group. The MEER model (HPV positive) tested with same immunotherapy as single or in combination with APG-157 did not grow the tumor, thus we were unable to collect the tumor for immunophenotyping and other studies. **Conclusions:** These study results indicate that APG-157 is able to modulate the immune system and fecal microbial species that could potentially lead to improved anti-tumor immunity and warrants further studies to define mechanism and the potential for human clinical trial. Research Sponsor: Institutional Start Up fund and pharmaceutical company (AvetaBiomics).

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2653 **Poster Session**

Immune checkpoint inhibitor-related endocrinopathies: A nationwide population-based study.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. However, unleashing the body's immune system against cancer is not without consequences and may trigger immune-related adverse events (irAEs), such as endocrinopathies. Real-world data of these endocrinopathies is lacking. This study aims to obtain the prevalence of endocrine irAEs and identify possible underlying demographic risk factors or disparities. **Methods:** A cross-sectional study was performed using a US-based population database (Explorys) that aggregates records from 26 healthcare systems and includes over 79 million patients. Our sample included all patients on an ICI, and we further identified patients who developed endocrinopathies while on different ICI regimens. The demographic data extracted was categorical, hence presented as counts and percentages. The odds ratio (OR), standard error, and 95% confidence interval were calculated with the use of SPSS software version 28.0 (IBM). **Results:** There were 20,950 patients on an ICI; 58% males, 83% Caucasians, 10% African-Americans (AA), 38% aged between 18-65, and 63% were over 65 years. The prevalence of the studied endocrinopathies is listed in the table. The most prevalent ICI-induced endocrinopathy was hypothyroidism (7.9-13%). Combination therapy with ipilimumab and nivolumab showed the highest prevalence of ICI-induced endocrinopathies, followed by durvalumab. The odds of developing ICI-induced endocrinopathy were significantly higher with combination therapy than nivolumab monotherapy (OR 1.6; 95% CI 1.4-1.9). There was no statistically significant difference in endocrinopathy prevalence when comparing Caucasians to AA and adults18-65 years to seniors over 65 years. **Conclusions:** This is the largest epidemiological study of ICI-related endocrinopathies. We find an intriguing divergence from endocrinopathy prevalence reported in the literature and real-world data we are presenting here. Over diagnosis of overt hypothyroidism, as opposed to subclinical hypothyroidism, is concerning as the former necessitates levothyroxine therapy. More alarming is the under diagnosis of hypopituitarism and PAI, in which delay in treatment can be fatal. The diagnosis of these conditions can be challenging. Raising awareness, setting protocols for testing, and involving endocrinologists are crucial. Further studies are needed to clarify our findings. Research Sponsor: None.

Prevalence of immune checkpoint related endocrinopathies.

ICI (Total patients on ICI)	ICI-induced endocrinopathy	Acquired hypothyroidism	Subclinical hypothyroidism	Hyperthyroidism	Hypopituitarism	PAI	Type 1 DM
Nivolumab (6700)	10.4%	8.2%	1%	2.2%	0.3%	0.07%	1.19%
Pembrolizumab (9580)	11%	8.9%	2%	2.5%	0.4%	0.3%	1.04%
Atezolizumab (2020)	10.4%	7.9%	0.2%	2.97%	0.24%	0.24%	1.48%
Durvalumab (940)	17%	13.8%	0.5%	6.38%	0.5%	0.5%	0 %
Ipilimumab & nivolumab (1760)	17.6%	13%	0.3%	3.4%	1.13%	1.7%	1.7%

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2654 **Poster Session**

Immune-related adverse events and immunotherapy efficacy in patients with cancer: A retrospective study.

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Background: Immune checkpoint inhibitors are revolutionizing cancer care and providing new treatment options with promising outcomes for many cancers. However, immune-related adverse events (irAEs) are not infrequent and can be severe. An intriguing relationship between the presence of irAEs and treatment efficacy has been described but lacks thorough characterization. We aimed to further elucidate a relationship between immune checkpoint inhibitor (ICI) irAEs and efficacy. **Methods:** We identified cancer patients treated with ICI from 2015-2021 across two institutions: Michael E DeBakey Veterans Affairs Medical Center (MEDVAMC) and Baylor St. Luke's Medical Center (BSLMC). Clinical data including cancer type, irAEs type and grade, ICI response, progression free survival (PFS) and overall survival (OS) was collected. Using the Kaplan Meier method, survival curves were generated and comparisons were made amongst groups using the log-rank test. Fisher's exact test was used to compare progression of disease between groups. To determine if variables were associated with survival, multivariable Cox regression analysis was used. **Results:** Of the 456 patients treated with ICI, irAEs were seen in 165 (36%) patients. Of these, 81 (49%) patients had grade 1 toxicities, most commonly arthritis, diarrhea, and dermatitis. 47 (28%) patients had grade 2 toxicities (colitis, hypothyroidism, adrenal insufficiency). 34 (21%) patients had grade 3 toxicities (pneumonitis, pancreatitis, hepatitis). 3 patients had grade 4 toxicities (pneumonitis, DRESS syndrome, and hepatorenal syndrome). 1 patient expired and 24 (15%) patients discontinued ICI due to irAEs. 55 (33%) of patients with irAEs were treated with steroids. For patients assessed for efficacy, objective response rate (ORR) to ICI was higher in patients with irAEs [47% (12% CR) vs 33% (11% CR)]. In fact, the presence of any irAEs was significantly likely to predict response to ICI (OR 1.90, 95% CI 1.25 - 2.86, p = 0.0026). In a subset of patients evaluable for survival (n = 375), patients with any irAEs had a significantly improved median PFS compared to those without irAEs (9.0 vs. 4.8 months, p = 0.0018). Multivariable analysis demonstrated that the development of any irAEs was related to a significantly improved OS (HR 0.63, 95% CI 0.43-0.89, p = 0.01). **Conclusions:** The development of irAEs in cancer patients treated with immunotherapy may predict better treatment efficacy and overall survival. Further prospective studies are needed to confirm these associations and mechanism of action. Research Sponsor: None.

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2655 **Poster Session**

Comparison of the checkpoint inhibitor pneumonitis incidence between immunotherapy alone or in combination with chemotherapy for lung cancer: An observational, retrospective pharmacovigilance study.

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Background: Clinical trials lack direct cross-comparison in safety between immune checkpoint inhibitor (ICI) as monotherapy and in combination with chemotherapy. The adverse event of checkpoint inhibitor pneumonitis (CIP) is an important factor influencing the treatment decision making. We performed a real-world pharmacovigilance study in the US Food and Drug Administration Adverse Event Reporting System (FAERS) to determine if ICI combination therapy is superior to monotherapy for lung cancer patients in terms of CIP incidence. **Methods:** The database of lung cancer patients receiving ICI between 2015 and 2020 was extracted for this study. The strategy-specific durations of the pneumonitis event were compared using the Kaplan-Meier method. Reporting odds ratio (ROR), a surrogate measure in disproportionality analysis, was used to assess the signal of CIP between ICI treatment strategies. **Results:** A total of 27,882 lung cancer patients with reported adverse events were involved. Among them, 1763 (6.3%) CIP after ICIs therapy were identified. In general, ICI usage was associated with over-reporting frequencies of CIP, but this association was no longer significant after adjustment (ROR: 1.14, 95%CI 0.86-1.49). The median times to CIP occurred early after therapy onset, either in ICI monotherapy or in combination with chemotherapy (41 days and 37 days, log-rank $p>0.05$). Different reporting frequencies emerged when we further compared different ICI strategies. Combination therapy with anti-PD-1 and chemotherapy was associated with a higher CIP incidence compared with anti-PD-1 monotherapy (ROR: 1.86, 95%CI 1.37-2.51), whereas anti-PD-L1/ CTLA-4 medications had lower risks in combination with chemotherapy (ROR: 0.31, 95%CI 0.16-0.56 and ROR: 0.41, 95%CI 0.09-1.22). Subgroup analyses on those with recorded therapy duration also indicated that reports of CIP were significantly lower with combination therapy of PD-L1 and CTLA-4 (ROR: 0.52, 95%CI 0.36-0.74 and ROR: 0.22, 95%CI 0.09-0.51 respectively). **Conclusions:** Compared with ICI monotherapy, the combination with chemotherapy might have an acceptable risk of CIP. Anti-PD-1 medications with additional chemotherapy could increase the risk of pneumonitis, whereas the risk was lower in the combination strategy with anti-PD-L1/CTLA-4. The combination might be a better therapeutic strategy than ICI monotherapy in treating lung cancer, regarding the CIP incidence. Research Sponsor: Guangzhou Science and Technology Planning Program (202002030023).

Disproportionality of checkpoint inhibitor pneumonitis in those treated with ICI combination therapy versus monotherapy.

	Crude ROR (95%CI)		Adjusted ROR (95%CI)	
All ICIs	0.91	(0.78-1.05)	1.14	(0.86-1.49)
Anti-PD-1	1.21	(1.02-1.44)	1.86	(1.37-2.51)
Anti-PD-L1	0.41	(0.31-0.54)	0.31	(0.16-0.56)
Anti-CTLA-4	0.28	(0.13-0.54)	0.41	(0.09-1.22)

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2656 **Poster Session**

Comparing rate of immunotherapy treatment change due to toxicity by gender.

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Background: Immunotherapy (IO) is associated with a variety of treatment related toxicities. However, the impact of toxicity on the treatment discontinuation rate between males and females is unknown. We hypothesized that immune related adverse events would lead to more frequent treatment changes in females since autoimmune diseases occur more frequently in females. **Methods:** The Oncology Research Information Exchange Network (ORIEN) Avatar Database collects clinical data from ten different United States cancer centers, where patients receive IO. Of 1,035 patients receiving IO, 447 patients were analyzed, excluding those (N = 573) who did not have documentation noting if a patient changed treatment. 15 additional patients with an unknown or gender-specific cancer were excluded. All cancer types and stages were included. Primary endpoint was documented treatment change due to toxicity. Significance was calculated with logistic regression, linear regression, chi-squared test for categorical variables and Mann-Whitney U test for continuous nonparametric variables. **Results:** 447 patients (281 males and 166 females) received IO treatment for cancer. The most common cancers treated were kidney, skin, and lung for 99, 84, and 54 patients, respectively. Females had a shorter IO course compared to males on Mann-Whitney U test (median 3.7 vs 5.1 months, respectively, p=0.02) and multivariable linear regression (Beta -3.87, 95% CI -6.591, -1.149, p=0.005). 54 patients changed IO treatment due to toxicity. There was no significant difference in the rate of treatment change due to toxicity between females and males on chi-square test (11.4% vs. 12.5%, respectively, p = 0.75) and logistic regression (Table). Pembrolizumab, Nivolumab, Ipilimumab/Nivolumab, Ipilimumab, Durvalumab, Avelumab, and Atezolizumab were given to 16, 14, 9, 9, 3, 2 and 1 patients who changed treatment due to toxicity, respectively. The median length of time for IO treatment prior to change for toxicity was 3 months (IQR 1.4 – 5.9 months). Significantly more patients with COPD changed treatment due to toxicity (Table). **Conclusions:** Females received a shorter course of IO than males. However, there was no significant difference in the treatment discontinuation rate due to toxicity between males and females receiving IO. Toxicity related treatment change was associated with COPD. Studies with larger sample sizes with more granular data (i.e., type of adverse effects) are needed to truly characterize if a difference between genders and IO toxicity exists. Research Sponsor: U.S. National Institutes of Health.

Analysis of risk factors associated with changing IO due to toxicity.

	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Female	0.908	0.501-1.647	0.752	0.924	0.453-1.885	0.827
Age ≥ 60	1.241	0.688-2.240	0.473	1.409	0.699-2.842	0.338
BMI ≥ 25	0.838	0.426-1.648	0.608	0.760	0.374-1.544	0.448
COPD	2.335	1.045-5.220	0.039	2.491	1.025-6.054	0.044
Combo IO	1.719	0.853-3.466	0.130	2.122	0.951-4.738	0.066

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2657 **Poster Session**

Inpatient complications of immunotherapy-associated colitis in solid malignancies: Real-world data analysis.

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Background: Immune checkpoint inhibitors (ICPis) and their containing regimens have been proven beneficial for the treatment of multiple malignancies, while immune-related adverse events (IrAEs) have become constant safety challenges in their clinical management through all ICPi therapies. Diarrhea resulted from immune-mediated colitis has been one of the most common IrAEs. The Aim of this study is to evaluate the real-world incidence and factors that contributed to colitis among patients hospitalized for anti-neoplastic immunotherapy using a large nation-wide database. **Methods:** We performed a retrospective analysis with the National Inpatient Sample (NIS) using ICD10-CM and PCS codes to identify patients with solid tumors hospitalized for immunotherapy between October 2015 and 2018. A comparison analysis was made between patients who developed diarrhea (or colitis) or not during their hospitalizations. Patient characteristics included past medical history, location, charges, length of stay (LOS) and inpatient complications variables, data were compared between the two groups. **Results:** The data from 5,795 admissions for immunotherapy were included, of which 615 (10.61%) inpatient events were complicated by diarrhea (colitis). Patients with diarrhea tended to be males (60%), slightly older at age 57 years, higher percentage of white patients (78%) though not statistically significant from those who did not have colitis. On the other hand, the length of inpatient stay was statistically longer (7 vs 5 days, $p < 0.05$), and associated with higher expenses ($214,612 vs $ 134,195, $p < 0.05$). In addition, inpatient admissions with colitis were more towards larger academic hospitals (80% vs 67%, $p = 0.01$). ICPi-treated patients with genitourinary (GU) cancers were observed more with colitis among these admissions (27% vs 15%, $p < 0.05$). Though no difference from mortalities observed, serious complications, such as acute kidney injury (AKI) (44% vs 20%, $p < 0.05$) and non-septic shock rates were higher (7% vs 2%, $p = 0.01$) among colitis admissions. **Conclusions:** This real-world data analysis of inpatient admissions from ICPi-treated cancer patients demonstrated colitis with diarrhea as a common safety concern over ICPi-therapies, a higher risk among patients of GU primaries, higher risk with serious medical complications: acute renal dysfunction and non-septic shock, led to increased length of stays (LOS) and financial burden. Special attention and further study may be placed among ICPi-treated GU cancer patients. Research Sponsor: Henry Ford Cancer Institute.

	No Diarrhea	Diarrhea	p value
Male	62%	60%	0.71
Age	56	57	0.28
LOS	5.14	7.24	**0**
Total Charges	$134,195	$214,612	**0**
Race (White)	66%	78%	0.08
Large Academic Hospital	67%	80%	**0.01**
Cancer type			**0**
Other	66%	41%	
Lung Ca	15%	20%	
GU ca	15%	27%	
Melanoma	4%	13%	
Inpatient complications			
AKI	20%	44%	**0**
Non-Septic Shock	2%	7%	**0.01**
Death	0.48%	0.00%	0.45

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2658 **Poster Session**

Association between germ-line HLA and immune-related adverse events.

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Background: In recent years, great progress has been made in immune checkpoint inhibitors (ICIs), opening a new chapter for cancer treatment. However, accompanied by remarkable efficacy, immune-related adverse events (irAEs) also arose. Though some pilot studies have explored the possible factors that may influence the development of irAEs, the mechanism of irAEs remains unclear. Previous studies indicated a positive association between certain HLA types and irAEs. To uncover the relationship between irAEs and divergent HLA types, we initiated a large cohort study. **Methods:** We screened 626 patients who have been treated in the clinical research ward, Cancer Hospital of Chinese Academy of Medical Sciences. All participants included should be diagnosed with malignant tumors and have received at least 2 cycles of ICIs with complete security follow-up data in the original electronic medical records. The blood samples were collected before the first cycle of treatment. Sequencing libraries were generated using a customized panel. Six digit formatted HLA alleles were extracted from HLA-HD (v1.4.0) results for further analysis. Fisher-exact test was used to perform association analysis between HLA and different irAEs. To control the type I error, we introduce two external reference groups as well as the non-irAE control group. In addition, false discovery rate (FDR) correction was performed with the resulting p-values when comparing the HLA allele frequency between patients with irAEs and the MHC-han Chinese reference cohort. We also explored the relationship between zygosity of HLA genes, evolutionary divergence of HLA class I genotype (HED) and irAEs. **Results:** Of the 626 participants, 530 received at least 2 doses of ICIs. The median follow-up time was 10.3 months. 97% patients received anti-PD-1/PD-L1 treatment. Of all participants, 78% reported irAEs of any grade, with 10.2% reporting grade 3 and above irAEs. The occurrence of overall irAEs showed no significant difference between homozygous group and heterozygous group. We did not find any significant association between irAEs and HED. We found that some HLA types are associated with irAEs of different organs, including the significant association between HLA-DRB3*01:01 and thrombocytopenia (OR 3.48 (1.19,9.42), p = 0.011), HLA-DPB1*04:02 and hypokalemia/ hyponatremia (OR 3.44 (1.24,9.1), p = 0.009), leukopenia (OR 2.1 (0.92,4.8), p = 0.037) as well as anemia (OR 2.33 (1.0,5.41), p = 0.026), HLA-A*26:01 and bilirubin elevation (OR 2.67 (0.92,8.31), p = 0.037). **Conclusions:** IrAEs in specific organs and tissues may be associated with certain HLA types, while HLA heterogeneity have no significant influence on the happening of irAEs. More research is needed to explore the role of germline genetic changes in the risk assessment of irAEs, and potential therapies targeting irAE-inducing HLA types without influencing the anticancer effect may be considered to benefit the patients. Research Sponsor: None.

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2659 **Poster Session**

Dysthyroidism during immune checkpoint inhibitors is associated with improved overall survival in solid tumors: Data-mining of 1,382 electronic patient records.

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Background: Medical treatment of solid tumors cancer has irreversibly changed since the development of immune checkpoint inhibitors (ICI). However, immune-related adverse events (irAE) are challenging in routine practice. Dysthyroidism is the most common endocrine irAE and small series suggest that dysthyroidism might be associated with ICI efficacy. This led us to explore the association between ICI-induced dysthyroidism and overall survival (OS) in a large cohort of solid tumor patients (pts) using data mining of electronic patient records (EPR). **Methods:** ConSoRe is a new generation data analytics solution using natural language processing to search aggregated data and perform advanced data mining. It was used for data extraction from EPR of pts treated with ICI for solid tumors in Institut Paoli-Calmettes (Marseille Cancer Center, France), with validation using manual screening of 28.8% EPR. All dysthyroidism were verified and only dysthyroidism ICI-induced were retained. Survival analyses were performed by Kaplan-Meier method and compared using the log-rank test (survminer R package). In the uni/multivariate analysis, the Cox proportional-hazards model was used to estimate the variables associated with OS, using hazard ratio (HR) and its associated 95% confidence interval. **Results:** Data extraction identified 1,385 pts treated with ICI in 2011-2021. Dysthyroidism was observed in 90 pts (6.5%), including 22 hyperthyroidism (24%), 36 hypothyroidism (40%) and 32 hyperthyroidism and hypothyroidism (36%). In this cohort, 81 % of the dysthyroidism were related to PD(L)-1 inhibitors and 19 % to CTLA-4/PD(L)-1 inhibitors combination. No statistical difference was observed in term of tumor location between patients with or without dysthyroidism. Dysthyroidism was associated with improved OS (HR=0.46, 95%CI 0.29-0.70, p=0.0005) with a median OS of 65 months (mo) *vs.* 30 mo in patients without dysthyroidism. Survival impact of dysthyroidism was consistent using a 2-mo landmark analysis, fixed on median time to dysthyroidism. In multivariate analysis including sex, age, tumor localization, line numbers and type of ICI, dysthyroidism was independently associated with an improved OS (HR=0.49, 95%CI 0.32-0.75, p=0.001), as presented in the Table. **Conclusions:** Data mining identified a large number ICI-induced dysthyroidism, associated with an improved OS. The onset of dysthyroidism might help oncologist detecting patients more likely to benefit from ICI. Research Sponsor: None.

Characteristic	HR	95% CI	p
Age: >65 vs <65	1.18	0.99, 1.41	0.071
Sex: Female vs Male	0.83	0.68, 1.00	0.051
Dysthyroidism (yes vs no)	**0.49**	**0.32, 0.75**	**0.001**
Tumor localization (ref : lung):			
melanoma	0.87	0.51, 1.50	0.6
bladder	1.21	0.86, 1.70	0.3
kidney	1.00	0.78, 1.29	>0.9
ICI group (ref : anti-PD(L)1)			
anti-CTLA4	1.00	0.58, 1.73	>0.9
ipilimumab/nivolumab	0.65	0.41, 1.04	0.071

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2660 **Poster Session**

The impact of pembrolizumab on patients with pre-existing autoimmune diseases.

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Background: Immune checkpoint inhibitors (ICI) have changed the therapeutic landscape across a range of solid and hematologic malignancies. With the mechanistic activation of the adaptive immune response and known unique development of immune-related adverse effects (irAE), there is a theoretical risk of causing detrimental effects on patients with pre-existing autoimmune diseases (AID). However, this patient population was excluded from many clinical trials, and there is limited and conflicting retrospective data speculating upon the impacts of using ICI therapy in patients with AID. This study aims to report the impact of pembrolizumab in patients with AID. **Methods:** Patients who received pembrolizumab for treatment of any type of cancer between 1/1/2017-8/1/2021 were retrospectively reviewed, and patients with AID (rheumatologic or non-rheumatologic) were identified. Data including age, gender, race, ECOG, and primary cancer diagnosis were collected. AID was characterized by type, activity (symptomatic vs. asymptomatic at ICI initiation), and immunosuppressive treatment (IST) use. Outcomes included flare of AID, irAE, and ICI discontinuation. **Results:** Out of 810 patients, 12 with pre-existing AID were found and being treated for non-small cell lung cancer (NSCLC) (58% N=7), renal cell carcinoma (RCC) (16.6% N=2), colorectal cancer (CRC) (8% N=1), head and neck cancer (8% N=1), and cervical cancer (8% N=1). Around 67% of these patients were females with a median age of 65 years (50-77). Median ECOG was 1 (0-2). 9 patients (75%) had rheumatologic disease (5 rheumatoid arthritis (RA), 1 systemic lupus erythematosus (SLE), 2 psoriatic arthritis, and 1 systemic sclerosis (SS)). 3 patients (25%) had non-rheumatologic AID (1 multiple sclerosis (MS), 1 autoimmune hepatitis, and 1 Evan's syndrome). All patients were asymptomatic prior to initiation of therapy. At the time of ICI initiation, 11 patients (92%) were on therapy, including steroids, methotrexate, and other IST. Due to concern for severe flare, pembrolizumab was discontinued in 3 (25%) MS, RA, and SS patients treated for RCC, CRC, and NSCLC, respectively. 3 patients (25%) developed irAE unrelated to their AID (pneumonitis, dermatitis, arthritis, gastritis) and received steroids. 4 patients (33.3%) had documented flares while on pembrolizumab requiring escalation of their ongoing therapy, and 1 NSCLC patient had a severe exacerbation of SS requiring cyclophosphamide and rituximab infusions. **Conclusions:** This analysis adds to the limited available literature that patients with an AID and on IST appear to have minimal AID-associated flares requiring intervention and tolerate pembrolizumab with a similar rate of irAE compared to patients without AID. Additional larger studies are needed to assess the efficacy of treatment in this population. Research Sponsor: None.

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2661 **Poster Session**

Immune-related adverse effects of long-term PD-1/PD-L1 inhibtor treatment.

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Background: Immune-related adverse effects (irAE) are autoimmune-like toxicities caused by immune checkpoint inhibitor (ICI) treatment and often necessitate interventions such as corticosteroids, treatment interruptions/discontinuation, or hospital admission. Although ICI related irAEs are well described in literature, data on the toxicity profile associated with long-term ICI use remains limited. Since the optimal duration of therapy with ICI agents is currently unknown, it is crucial to assess the risks of long-term ICI use. **Methods:** This was a retrospective, observational, single-center study of adult oncology patients who received at least 1 year of programed death 1 (PD-1) inhibitor or programmed death ligand-1 (PD-L1) inhibitor treatment. The objective of this study was to characterize late-onset irAEs defined as greater than 1 year with long-term ICI treatment. Clinically significant irAEs were defined as those requiring corticosteroid treatment, hospital admission, treatment interruption or treatment discontinuation. This study included patients who received at least 1 year of nivolumab, pembrolizumab, atezolizumab or durvalumab between January 2016 and September 2021. Disease states included head and neck cancer, renal cell carcinoma, non-small cell lung cancer, and melanoma. Patients with concurrent exposure to other treatment such as chemotherapy, radiation, surgery, tyrosine kinase inhibitors and monoclonal antibodies while on ICI treatment were included in the study. Exclusion criteria included patients with treatment breaks of greater than 6 months, two malignancies undergoing active treatment, and treatment administration outside of the study center. **Results:** Of 282 patients assessed, 143 met study inclusion criteria. The median ICI treatment duration was 19 months (IQR 14-27). There was a 30% incidence of late-onset irAEs, of which 22% were clinically significant. Most late-onset irAEs were low in severity, as 45 (90%) were grade 1-2 and 5 (10%) were grade 3. The most common late-onset irAEs were pulmonary (8%) and gastrointestinal (7%). Univariate analysis suggests risk factors potentially associated with late-onset irAEs include concurrent exposure to additional therapies during ICI treatment and past medical history of rheumatologic disease. **Conclusions:** Although the optimal duration of ICI therapy is unknown, this study suggests that long-term ICI use was associated with a low but notable incidence of toxicities, of which most were low in severity. Research Sponsor: None.

Characterization of late-onset irAEs.

irAE	Incidence N=143 (%)	Median time to onset (months)
Dermatologic	7 (5)	15
Endocrine	7 (5)	17
Gastrointestinal	10 (7)	15
Hematologic	1 (1)	17
Hepatic	6 (4)	22
Ocular	2 (1)	19
Pulmonary	12 (8)	18
Rheumatologic	5 (4)	19

There were no incidences of late-onset cardiovascular, renal, neurologic, or pancreatic irAEs. Seven patients experienced multiple irAEs.

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2662 **Poster Session**

Density patterns of tumor-infiltrating lymphocytes and association with objective response to nivolumab in patients with lung adenocarcinoma from CheckMate 057.

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Background: Immune checkpoint inhibitors (ICIs) are currently approved for use as therapy in advanced stage lung adenocarcinoma (LUAD). ICIs can decrease risk of progression by up to 60% when compared to chemotherapy, but only about 20% of patients (pts) show response. Given that high levels of tumor-infiltrating lymphocytes (TILs) have been shown to be associated with better prognosis, here, we assess whether computationally derived TIL density measures on digitized H&E images can predict RECIST derived response to nivolumab in LUAD in Checkmate 057 (CM057). CM057 is a clinical trial designed to compare the overall survival of metastatic non-squamous non-small cell lung cancer subjects treated with either nivolumab or docetaxel after failing platinum-based chemotherapy. **Methods:** H&E-stained samples of 683 LUAD pts were collected from TCGA (n = 421), University of Bern (UBern) (n = 100), and CM057 (n = 162). Tumor response was assessed using RECIST v1.1. Samples were digitized as whole slide images. 294 pts randomly selected from TCGA formed the training set. The remaining 389 pts were used for validation in response to nivolumab in CM057 and prognosticating overall survival (OS) in UBern and TCGA. Computerized algorithms automatically identified TILs and extracted features related to quantity and compactness of TILs with respect to other surrounding nuclei. The top 6 features, determined by least absolute shrinkage and selection operator, were used to train Cox regression models that assign a death risk score to each patient. Pts with risk scores higher than the training median score were considered "high risk" or "non-responders" while pts with lower scores were considered "low risk" or "responders". **Results:** The classifier predicted objective response in CM057 with an AUC = 0.61. Additionally, survival analysis showed that the model was prognostic for OS with hazard ratios of 2.38 (confidence interval (CI): 1.32-4.29, p = 0.01, n = 127) in TCGA and 2.37 (CI: 1.32-4.25, p < 0.01, n = 100) in UBern. **Conclusions:** A computerized image analysis model based on measurements of TIL density showed association with response to treatment in LUAD pts who received nivolumab and was prognostic of OS. Although the AUC was not high, the results suggest analysis of TILs has potential to identify pts who will respond to treatment. Future work will include training a classifier using response to treatment as endpoint and combining the TIL measures with other biomarkers like TMB or PD-L1. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency.

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2663 **Poster Session**

Tumor-infiltrating lymphocyte enrichment predicted by CT radiomic analysis is associated with clinical outcomes of immune checkpoint inhibitor in non–small cell lung cancer.

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Background: Enrichment of tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment (TME) is a reliable biomarker of immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC). Phenotyping through CT radiomics has the overcome the limitations of tissue-based assessment, including for TIL analysis. Here, we objectively assess TIL enrichment using an artificial intelligence-powered H&E analyzer, Lunit SCOPE IO, and analyze its association with advanced quantitative imaging features extracted via radiomic analysis. Clinical significance of the selected radiomic features (RFs) is then validated in independent NSCLC patients who received ICI. **Methods:** In the training cohort, which included 235 NSCLC patients with both tumor tissue and corresponding CT images obtained within 1 month, we extracted 86 RFs from the CT images. From tissue, a patient's TIL enrichment score (TILes) was defined as the fraction of tissue area with high intra-tumoral or stromal TIL density, divided by the whole TME area, as measured on an H&E slide. From the corresponding CT images, the least absolute shrinkage and selection operator model was then developed using features that were significantly associated with TIL enrichment. The CT model was then applied to CT images from the validation cohort, which included 242 NSCLC patients who received ICI as ≥ second line. **Results:** Among the extracted RFs, 22 features were significantly associated with TILes ($p < 0.005$). After excluding features of multicollinearity and/or zero-coefficient, two features, gray level variance (coefficient 1.71×10^{-3}) and low gray level emphasis (coefficient -2.48×10^{-5}), were finally included in the model. The two features were both computed from the size-zone matrix (SZM), the idea of which is to break down a given tumor volume into smaller spatially contiguous compartments of different sizes. In the validation cohort, the patients with high predicted TILes (≥ median) had significantly prolonged progression-free survival compared with those with low predicted TILes (median 3.81 months [95% CI 2.14 – 5.69] versus 1.94 months [95% CI 1.58 – 2.93], hazard ratio 0.69 [95% CI 0.53 – 0.90], $p = 0.007$). **Conclusions:** This CT radiomics model is able to assess TIL enrichment in TME, which is significantly associated with favorable ICI outcomes in NSCLC. Analyzing the TME through radiomics may overcome limitations of tissue-based analysis and inform clinical decisions, particularly related to use of ICI. Research Sponsor: None.

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2664 **Poster Session**

Increased incidence of immune-mediated myocarditis in advanced skin malignancies treated with immune checkpoint inhibitors in the COVID-19 era.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced stage skin malignancies. Immunotherapy related adverse events (irAE) are toxicities associated with ICI therapy. Myocarditis is a rare life-threatening irAE. We attempt to characterize cases of myocarditis related to ICI therapy that have occurred since the start of the COVID-19 pandemic. **Methods:** We performed a single-center, retrospective cohort analysis of patients with advanced stage skin cancers who were treated with ICIs and identified cases of ICI-mediated myocarditis. ICI-mediated myocarditis was defined as evidence of myocardial injury in the setting of irAEs and exclusion of cardiovascular causes. Clinicopathologic variables and clinical outcomes were assessed in these patients. **Results:** A review of 361 patients that received ICI from 9/2014 – 10/2019 found 0 cases of ICI-mediated myocarditis. From 11/2019 – 12/2021, an additional 425 patients were identified of whom 11 (2.6%) developed ICI-mediated myocarditis. 10 patients had melanoma and 1 patient had Merkel cell carcinoma. 10/11 patients were male. 9/11 were treated with anti-PD-1 monotherapy and 2/11 were treated with ipilimumab with nivolumab. All patients had elevated high sensitivity troponin (median 361 pg/mL on presentation, reference range 0-19 pg/mL). 11/11 patients presented with elevated CPK (median 1734 IU/L, reference range 38-240 IU/L) and 8/11 presented with elevated AST:ALT ratio (median 1.58:1) on routine screening which prompted further investigation. 1 patient tested positive for COVID-19 13 days after initial biochemical concern for myocarditis, and 5 patients had received COVID-19 vaccines between 2.5-11 months prior to myocarditis onset. All patients were treated with high dose steroids, and 4 were treated with abatacept. 2 patients died within 30 days after diagnosis of myocarditis and 2 patients later died from malignancy progression. 2 patients developed progressive disease and 1 was successfully rechallenged with ICI with no myocarditis recurrence. 2 patients remain on active surveillance, 2 continue on a steroid taper, and 1 was lost to follow up. All patients with at least 5 months of follow up from myocarditis onset (n = 5) had persistently elevated HS-troponin despite normalization of CPK levels. **Conclusions:** In this single center study, we noted an increase in the frequency of ICI-mediated myocarditis in patients with advanced skin cancers during the pandemic era (2.6% vs 0% pre-pandemic) which is higher than reported in the literature (0.04-1.14%). The impact of COVID-19 during this time is suspicious and warrants further investigation. Therefore, we suggest heightened awareness in the COVID-19 era that elevated CPK levels and AST:ALT ratios merits further diagnostic investigation of ICI-mediated myocarditis. Research Sponsor: None.

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2665 **Poster Session**

Management of infliximab-refractory immune checkpoint inhibitor gastrointestinal toxicity: A multicenter case series.

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Background: Immune checkpoint inhibitor (ICI) GI tox (gastritis, enteritis, colitis) is a major cause of morbidity and treatment-related death. Guidelines agree steroid-refractory cases warrant infliximab (IFx); however not all pts respond and best management of IFx-Refractory ICI GI toxicity (IRIGItox) is not clear. **Methods:** We conducted an international multi-centre retrospective case series. IRIGItox was defined as failure of symptom resolution $\leq$ Gr 1 (CTCAE v5.0) following $\geq$ 2 IFx doses *or* failure of symptom resolution $\leq$ Gr 2 after 1 dose. Data were extracted regarding demographics, steroid use, response and survival. Tox was graded at symptom onset and time of IFx failure. Efficacy of IFx refractory therapy was assessed by symptom resolution, time to resolution and steroid wean. **Results:** 78 pts were identified; med age 60 yrs (95% CI 56-65), 56% male. 70 (90%) had melanoma, 55 (71%) had advanced-stage, 60 (77%) received anti-CTLA-4 (with anti-PD1 50, single agent 10). Most had colitis (N=75, 96%) and $\geq$ Gr 3 tox (N=74, 95%) at symptom onset. Pre-IFx investigation varied: imaging 37%; faecal calprotectin 29%; endoscopy 59%. All pts received Med time to steroid initiation was 3 days (95% CI 2-4). 46 (59%) had primary steroid refractory disease,. Med time from symptom onset to IFx was 18 days (95% CI 12-23), a med 2 (range 1-6) doses of IFx were given, 69 (88%) pts received > 1 IFx dose. Across 78 pts, 105 post IFx treatments were given: calcineurin inhibitors (ciclosporin, tacrolimus, 32); antimetabolites (mycophenolate, azathioprine, 26); non-TNF-α MABs (vedolizumab, ustekinumab, 20); non-targeted anti-inflammatory (mesalazine, 16); non-pharmacological (colectomy 5, faecal transplant 1, photophoresis 1). 4 pts did not receive therapy for IRIGItox. Of these, 2 died of melanoma prior to resolution of tox; 1 had resolution after 4 doses IFx, 1 had recurrent melanoma and flare of tox on PD1 re-challenge. IRIGItox outcomes by post IFx treatment are shown in Table. **Conclusions:** This retrospective case series confirms heterogeneous management of IRIGItox. Non-pharmacological interventions and calcineurin inhibitors appear most likely to result in tox resolution. Calcineurin inhibitors have the shortest time to resolution in responders. Further details on post-IFx management and oncological outcomes will be examined. Research Sponsor: None.

Post IFx treatment (n)	Tox resolution n (%)	If resolved, time to resolution (med (95% CI), days)	If resolved, time to physiological steroid (med (95% CI), days)
All (105)	55 (52)	28 (16-44)	54 (49-67)
Calcineurin inhibitor (32)	22 (67)	14 (8-30)	51 (38-74)
Antimetabolite (26)	12 (46)	18 (10-68)	54 (43-225)
Non TNF-α MAB (20)	8 (40)	66 (50-217)	126 (72-293)
non-targeted anti-inflammatory (16)	7 (44)	41 (10-64)	7 (0-64)
non-pharmacological (7)	5 (71)	28 (22-369)	53 (42-61)
Nil (4)	1 (25)	55*	55*

*Calculated from last dose IFx

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2666 **Poster Session**

Evaluating survival following severe immune-related adverse events requiring hospitalization.

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Background: As immune checkpoint inhibitors (CPI) are increasingly approved for the treatment of multiple cancer types, hospitalizations related to severe immune-related adverse events (irAE) will increase in tandem. Here, we identify patients hospitalized due to irAEs and describe survival outcomes across irAE, CPI, and cancer type. **Methods:** We identified patients exposed to CPIs who were hospitalized from 1/2012 to 12/2020 at our tertiary care hospital by computationally extracting data from the electronic health record. We then performed manual chart review to include only confirmed irAE-related hospitalizations. Survival outcomes were analyzed using Kaplan-Meyer survival curves with log-rank tests. **Results:** Of 3137 patients treated with CPIs, 117 were hospitalized for irAEs (cumulative incidence 4%). Of these, 36% had melanoma, 15% had lung cancer, 9% had renal cell carcinoma (RCC), and the rest were distributed across other cancers. The average number of irAE-related hospitalizations per patient was 1.25 (ranging from 1-3). Among 153 irAEs requiring hospitalization, 39% were gastrointestinal (GI) (including hepatitis), 12% endocrine, 12% pulmonary, 12% neurologic, 12% musculoskeletal, 7% cardiovascular, 6% dermatologic, and the rest affected other organs. Across all patients hospitalized for irAEs, median survival following hospitalization was 980 days. Patients with GI and endocrine irAEs had longer median survival (1474 days and median not reached [NR], respectively), while patients with pulmonary irAEs had shorter median survival (64 days) [p=0.002]. Patients with melanoma and RCC had longer median survival (2796 days and NR, respectively), while patients with lung cancer had shorter median survival (165 days) [p=<0.001]. Survival was not significantly different across CPI type [p=0.20]. **Conclusions:** Although hospitalization for severe irAE was rare, these findings suggest that among these patients, survival differs by irAE and cancer type. This real world data can contribute to clinical models that predict the risk of hospitalization and the risk of death due to severe irAEs, which may inform patient counseling and treatment decision-making. Research Sponsor: U.S. National Institutes of Health.

Frequency, survival, and follow up across irAE, cancer, and CPI type for sample sizes greater than ten.

irAE, Cancer & CPI type	Frequency (n)	%	Median Survival (days)	Time at Risk (days)	Survival IQR (days)	Median follow up (days)	Median follow up range (days)
GI irAE	46	39	1,474	38,213	172 - NR	469	3 - 3,304
Endocrine irAE	15	13	NR	10,876	552 - NR	861	60 - 1,699
Pulmonary irAE	14	12	64	3,789	21 - 604	83	10 - 859
Multiple irAEs	24	21	1,958	14,718	85 - NR	420	7 - 2,309
Melanoma	42	36	2,796	47,128	604 - NR	778	2 - 3,304
Lung Cancer	17	13	165	3,432	105 - NR	160	15 - 787
RCC	11	9	NR	7,535	552 - NR	513	85 - 1,787
PD-1 Inhibitor	65	56	789	36,746	113 - NR	430	2 - 2,192
Combination PD-1/ CTLA-4 Inhibitors	40	34	1,476	29,341	181 - NR	558	30 - 2,309

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2667 **Poster Session**

Landscape of tumor mutation burden and correlation to clinical outcomes in 1,744 solid cancers.

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Background: Tumor mutation burden (TMB) has proven clinical utility and efficacy related to immune checkpoint inhibitor (ICI) treatment in different tumor types. However, limited data were available to understand the landscape and matched clinical outcomes to a pan-cancer extent. **Methods:** Target sequencing results, using TruSight Oncology 500, from 1,744 solid cancer between 2019 and 2021 as a part of real-world clinical practice were collected. Matched clinical and histological outcomes, including PD-L1 expression (n= 798) and immunotherapy treatment (n= 400), were analyzed. **Results:** Among the 33 different cancer types, high TMB was observed in 257 patients (14.7%) with a significantly higher incidence observed in carcinoma of unknown origin (33.3%), bladder cancer (32.3%), and small bowel cancer (30.0%). TMB was positively correlated with the degree of mutation in homologous recombination genes (HRD, 0.76) and microsatellite instability (MSI, 0.51). The predictive value of high TMB to ICI treatment seemed to be enhanced when it was combined with PD-L1 expression, showing higher response rates in the PD-L1 high group (63.3%) than in the low group (22.2%). In the patients with high TMB, both longer overall survival (p = 0.015) and progression-free survival (p = 0.020) were observed compared to the patients with low TMB. **Conclusions:** We examined the landscape of TMB in a different type of cancer using clinical-level target sequencing outcomes. High TMB seems to be a promising predictive biomarker of ICI, showing a positive correlation with alteration in other DNA damage response and repair-related genes and additive value to PD-L1, which needs to be validated through further prospective trials. Research Sponsor: None.

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2668 **Poster Session**

Immune checkpoint inhibitor–induced diabetes mellitus across NCI trials.

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Background: Immune checkpoint inhibitors (CPI) are known to rarely cause new onset diabetes (CPI DM). While rare, this adverse event is quite challenging for patients and clinicians to manage. Therefore, it is important to identify risk factors and clinical characteristics. This is the first comprehensive, multi-institutional study of CPI-DM across multiple agents and cancer types. **Methods:** The NCI Cancer Therapy Program (CTEP) database of adverse events (AEs) was queried for AEs related to diabetes (Grade 3 or 4 hyperglycemia, Acidosis including Diabetic Ketoacidosis (DKA), glucose intolerance and diabetes mellitus) among 6,925 patients who had been treated with a PD-(L)1 inhibitor alone or in combination from 6/2015 to 12/2019. Each AE report was reviewed and classified as due to CPI DM, new onset type 2 diabetes mellitus (T2DM), T2DM exacerbation without medication non-compliance, existing DM with medication non-compliance, or association with steroids (SDM). CPI DM was diagnosed based on: evidence of insulin deficiency either through presentation in DKA or low c-peptide with need for long term basal bolus insulin to maintain euglycemia and/or positive islet autoantibodies. **Results:** In total, there were 82 cases with at least one of these AEs; 41 had CPI-DM, 22 had SDM, 1 had new T2DM, 4 had T2DM exacerbation, 3 had medication noncompliance and 11 had acidosis not attributable to diabetes or had insufficient data. After excluding non-hyperglycemic acidosis, 57.8% had CPI-DM. Furthermore, if not on steroids and in good compliance with diabetes medications, 89.1% had CPI-DM. The incidence of CPI-DM was 0.59%; it was most common on combination PD-1/CTLA-4 inhibitor therapy (0.85%, 15/1767), followed by PD-(L)1 inhibitor monotherapy (0.54%, 18/3354), followed by CPIs combined with additional agents including chemotherapy and targeted agents (0.44%, 8/1804)(p = 0.25). Hospitalization was required for 87.5% of CPI-DM cases with 74.3% of those requiring an inpatient endocrine consult. All but one CPI-DM case had an endocrine consult at as either an inpatient or outpatient. **Conclusions:** While rare, this cohort shows the large health care burden of CPI-DM and that any hyperglycemia, and especially marked hyperglycemia, should be treated as CPI-DM until proven otherwise. Research Sponsor: American Diabetes Association.

	Total (n 41)		PD-(L)1 inhibitor (n 18)		Combination PD-1/ CTLA-4 Inhibitor (n 15)		CPI & non-CPI Agent (n 8)	
	n or Median	% or range	n or Mean	% or range	n or Mean	% or range	n or Mean	% or range
Melanoma	14	34.1	6	33.3	8	53.3	0	0
Lung Cancer (NSCLC & SCLC)	5	12.2	1	5.6	1	6.7	3	37.5
GU Cancer (Renal/ Urothelial/ Bladder)	6	14.6	4	22.2	1	6.7	1	12.5
Other Cancer	16	39.0	7	38.9	5	33.3	4	50.0
Any Islet Autoantibody Positive	12	29.3	7 (9 tested)	77.8	5 (9 tested)	55.6	4 (8 tested)	50.0
Prior Thyroid irAE or Pre-CPI hypothyroidism	17	41.5	8	44.4	4	26.7	5	62.5
ICU and/ or insulin drip	29	70.7	12	66.7	11	73.3	6	75.0
Glucose at CPI-DM diagnosis (mg/ dL)	650	279-1193	615	279-1037	652	367-1044	733	359-1193

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2669 **Poster Session**

A systematic review and meta-analysis of early death (ED) upon immune checkpoint inhibitors (ICI) alone or combined with other non-ICIs treatments as first-line treatment of advanced solid tumors.

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Background: An early crossing of the Kaplan-Meier overall survival curves in randomized clinical trials (RCTs) comparing ICI alone to standard treatments has been observed across different cancer types, suggesting the existence of an excess of mortality upon ICI. Whether ED reflects the natural history of the disease or it is a treatment specific phenomenon remains unclear. Therefore, we conducted a meta-analysis of RCTs to analyze the association of ICI treatment with ED. **Methods:** PubMed, Embase and Cochrane were searched (until 12/2021) for RCTs comparing 1st-line PD-1/PD-L1 inhibitors +/- CTLA-4 inhibitors (ICI-only group) or the same drugs in combination with other non-ICI therapies (ICI+OT group) (experimental arms) vs non-ICI treatments (control arm) in patients (pts) with advanced solid cancers. ED was defined as death within the first 3 months of treatment. RCTs providing the number of pts in the intention-to-treat (ITT) population who were alive within 0-3 months from randomization were considered eligible. Primary outcome was ED rate both in the ICI-only and in the ICI+OT groups vs control arm. Secondary outcome was to compare ED risk between ICI-only group and ICI+OT group. Further analysis according to PD-L1 level were performed. The ED rates were estimated by risk-ratio (RR) with 95% confidence intervals (CI) and pooled by random effect model. Heterogeneity was assessed by I^2 statistics. **Results:** 56 RCTs (n = 38697 pts) were eligible, 48.2% included pts with thoracic malignancies. In the ICI-only group (18 RCTs, n = 6638 pts) 50.5% of pts received anti-PD-1/PD-L1 monotherapy and 43.4% anti-PD-1/PD-L1 + anti-CTLA-4 agents. In the ICI+OT group (43 RCTs, n = 15421 pts) 80.1% of pts received ICI + chemotherapy. Compared to control arm, risk of ED was significantly higher for pts who received ICI-only therapies (RR 1.27, 95% CI 1.04-155, p = 0.02, I^2: 73%), but significantly lower in ICI+OT group (RR 0.80, 95% CI 0.71-0.89, p < 0.00001, I^2: 36%). Risk of ED was also significantly higher with ICI-only compared to ICI-OT (RR 1.59, 95% CI 1.26-2.00). ED risk was higher upon ICI-only also in pts with high PD-L1 expression (TPS ≥50%, TC or IC 3, CPS ≥10) and, after excluding Keynote-024, this result became statistically significant (7 RCTs, RR 1.54, 95% CI 1.13-2.10, p = 0.007) with I^2 reducing from 63 to 46%. **Conclusions:** Across cancer types ED is a treatment specific phenomenon, increasing with first-line anti-PD-1/PD-L1 +/- CTLA-4 inhibitors and occurring also in pts with high PD-L1 expression, whereas it can be prevented by combining ICI with other non-ICI treatments. Research Sponsor: None.

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TPS2670 **Poster Session**

Phase I study of HFB200301, a first-in-class TNFR2 agonist monoclonal antibody in patients with solid tumors selected via Drug Intelligent Science (DIS).

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Background: Tumor necrosis factor receptor-2 (TNFR2) is expressed on effector CD8+ T cells, CD4+ T cells, T regulatory cells, natural killer cells, and myeloid cells. Targeting TNFR2 is anticipated to yield effective anti-tumor immunity by stimulating T-cell and NK-cell activation and proliferation in the tumor microenvironment. HFB200301 is a first-in-class anti-TNFR2 agonistic monoclonal antibody that triggers both innate and adaptive immune stimulation by binding to a specific epitope on TNFR2. HFB200301 has demonstrated dose-dependent anti-tumor activity in human TNFR2 knock-in mice bearing MC38 and Hepa1-6 syngeneic tumors. **Methods:** HFB200301 is being evaluated in a first-in-human, open-label, multi-center, dose escalation and expansion study in adult patients with advanced solid tumors. A single-cell immune profiling platform, DIS, was deployed to identify unique tumor-infiltrating T cell signatures that could help optimize patient selection for HFB200301 treatment. It is hypothesized that the presence of an effector T cell subpopulation that express both TNFR2 and CD8A in solid tumors may represent a tumor microenvironment favorable to TNFR2 agonism. The following cancer indications have been identified based on the prevalence of a TNFR2 high/CD8 high signature: Epstein-Barr Virus positive (EBV+) gastric cancer, clear cell renal cell carcinoma (ccRCC), cutaneous melanoma, testicular germ cell tumor (TGCT), soft tissue sarcoma (STS), and PD-L1+ cancers: cervical cancer, pleural mesothelioma, lung adenocarcinoma, and head and neck squamous cell carcinoma (HNSCC). The escalation portion of the study explores increasing doses in cohorts of up to six patients, utilizing mTPI-2 design to determine recommended dose(s) for expansion (RDE(s)). Based on pharmacokinetic modeling to maximize HFB200301 activity, 60-minute intravenous infusions of HFB200301 are administered every 4 weeks. Once RDE(s) is determined, expansion into three indication-specific cohorts is planned to determine the recommended phase 2 dose (RP2D). Key eligibility criteria include histologically documented advanced or metastatic solid tumors in the above listed indications. Patient enrollment opened in February 2022 in the USA, with plans for additional clinical sites in Spain and China. The primary objective is to identify the RDE, characterize safety and tolerability of HFB200301, and determine RP2D. Secondary objectives include pharmacokinetic parameters, preliminary evidence of anti-tumor efficacy (e.g., ORR, DCR, DOR) and pharmacodynamic evaluation (e.g., T cell subsets) in the blood and in the tumor. Furthermore, a potential predictive biomarker signature derived based on the DIS single-cell immune profiling approach will be investigated retrospectively. Clinical trial information: NCT05238883. Research Sponsor: HiFiBiO Inc.

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TPS2671 **Poster Session**

Trial in progress: A phase 1-2, first-in-human, open label, dose escalation and expansion study of AU-007, a monoclonal antibody that binds to IL-2 and inhibits IL-2Rα binding, in patients with advanced solid tumors.

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Background: AU-007 is a computationally designed, monoclonal antibody that binds to IL-2 on its CD25 binding epitope. AU-007 bound IL-2 (A/IL-2) cannot bind to high affinity trimeric IL-2 receptors (IL-2R) consisting of CD25, CD122, and CD132 expressed on Tregs and vascular endothelium, but its binding to low affinity dimeric IL-2Rs (CD122 and CD132) expressed on T effector and NK cells is unhindered. Thus, AU-007 redirects endogenously produced or exogenous IL-2 (aldesleukin) towards activation of immune stimulating T effector and NK cells, while diminishing Treg activation and expansion. AU-007 will also bind and redirect newly secreted endogenous IL-2 resulting from A/IL-2 driven T cell expansion in the tumor, converting a Treg mediated autoinhibitory loop into an immune stimulating loop. AU-007 is unique in the IL-2 therapeutic field as engineered exogenous, recombinant "non-CD25" IL-2s in development cannot address the autoinhibitory effect of endogenous IL-2. Preclinically, AU-007 has been demonstrated to capture endogenous human IL-2 *in vivo*. AU-007 with a single low dose of IL-2 has demonstrated efficacy in multiple cancer models and has an excellent safety profile in non-human primates. **Methods:** This first-in-human, multicenter, open label Phase 1- 2 study evaluates the safety, tolerability, and initial efficacy of AU-007 +/- aldesleukin in patients with advanced solid tumors (CT-2021-CTN-03938-1). Phase 1 consists of 3 escalation arms each starting with a single 1+2 escalation cohort followed by 3+3 escalation cohorts to define the recommended Phase 2 dose (RP2D) or maximum tolerated dose (MTD). Patients with melanoma, renal cell carcinoma (RCC) and 17 selected solid tumors are eligible. Prior treatment with check point inhibitors is allowed. In Arm A, escalating doses of Q2w AU-007 are evaluated in sequential escalation cohorts. In Arm B, a single dose of aldesleukin is given with the initial AU-007 dose. AU-007 is given at a fixed dose Q2w with an escalating single aldesleukin dose in sequential escalation cohorts. In Arm C, AU-007 is evaluated in combination with aldesleukin, both given Q2w. AU-007 is administered at a fixed dose with an escalating dose of aldesleukin in sequential cohorts. The Phase 2 cohort expansion portion of the study evaluates the initial efficacy at the RP2D defined in escalation cohorts A, B, and C in 3 matching expansion cohorts of up to 20 patients each. Patients with advanced melanoma, RCC and other tumors including, but not limited to, Merkel Cell Carcinoma, NSCLC, and urothelial cancer are eligible. Enrolment to the study commences in Australia, with US sites planned to open later in 2022. Clinical trial information: CT-2021-CTN-03938-1. Research Sponsor: Aulos Bioscience.

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TPS2672 **Poster Session**

A phase 1/2a open label, multicenter study to assess the safety, tolerability, pharmacokinetics, and efficacy of AFM24 in patients with advanced solid cancers: Study design and rationale.

Omar Saavedra Santa Gadea, Elena Garralda, Juanita Suzanne Lopez, Mark M. Awad, Jacob Stephen Thomas, Crescens Diane Tiu, Daniela Morales-Espinosa, Christa Raab, Bettina Rehbein, Gabriele Hintzen, Kerstin Pietzko, Paulien Ravenstijn, Michael Emig, Anthony B. El-Khoueiry; Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; Hospital Vall d'Hebron, Barcelona, Spain; The Royal Marsden and The Institute of Cancer Research, London, United Kingdom; Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA; Division of Oncology, USC Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA; Peter MacCallum Cancer Centre, Sutton, United Kingdom; Quirón Salud-Dexeus University Institute, IOR, Medical Oncology Department, Barcelona, Spain; Affimed GmbH, Heidelberg, Germany; University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA

Background: AFM24 is a first-in-class, tetravalent, bispecific, fragment crystallizable-silenced antibody that targets epidermal growth factor receptor-expressing (EGFR+) solid tumors. Of its 4 binding sites, 2 are specific for EGFR, and 2 are specific for CD16A, the Fcγ receptor expressed by natural killer (NK) cells and macrophages. The primary mode of action of AFM24 is not to inhibit EGFR signaling, but to redirect NK cells and macrophages to EGFR+ tumor cells to induce antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), respectively. Preclinical studies showed AFM24 induced killing of EGFR+ tumor cell lines, and the activity was independent of EGFR cell surface expression level. A favorable safety profile was also demonstrated in cynomolgus monkeys. Therefore, AFM24 may utilize the patients' innate immunity to redirect and activate immune cells, overcoming resistance to current therapies and offering a favorable safety profile. An ongoing Phase 1/2a, first-in-human study (NCT04259450) is evaluating AFM24 in patients with locally advanced or metastatic, treatment refractory solid tumors that are known to express EGFR. The Phase 1 dose escalation study was designed to establish the maximum tolerated dose and/or the recommended Phase 2 dose (RP2D) of AFM24 and evaluated the safety, efficacy, immunogenicity, pharmacokinetic (PK) and pharmacodynamic (PD) responses. AFM24 was administered intravenously once weekly until disease progression, intolerable toxicity, patient withdrawal, or termination at the investigator's discretion. AFM24 had a well-managed safety profile and the RP2D was established. **Methods:** In parallel to the continuing dose escalation phase, the Phase 2a dose expansion study was initiated, and the first patient was enrolled in January 2022. This study will assess AFM24 at the RP2D of 480 mg in patients with different EGFR-expressing tumors and will follow a Simon's two-stage design; the trial will progress to the second stage unless the null hypothesis, that the true tumor response rate is below a specified value, is confirmed at the end of stage one. Eligible patients must have positive histological or cytological staining of EGFR in > 1% of tumor cells. The primary endpoint is to establish the overall response rate (assessed by the investigator per RECIST v1.1) in three disease-specific cohorts. These comprise patients with clear cell renal cell carcinoma (ccRCC), KRAS wild-type colorectal cancer (KRASwt CRC), and EGFR-mutant non-small cell lung cancer (EGFRmut NSCLC). Secondary endpoints include treatment-emergent adverse events, serious adverse events, PK, PD, and immunogenicity. Clinical trial information: NCT04259450. Research Sponsor: Affimed GmbH.

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TPS2673 **Poster Session**

AFM24 in combination with atezolizumab in patients with advanced EGFR-expressing solid tumors: Phase 1/2a study design and rationale.

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Background: Innate Cell Engagers (ICE) are bispecific molecules that bind both a tumor cell-surface antigen and to CD16A expressed on natural killer (NK) cells and macrophages, inducing antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), respectively. As epidermal growth factor receptor (EGFR) is often overexpressed in several types of solid tumors, this provides an ideal tumor-cell surface antigen which may be targeted using ICE molecules. AFM24 is a first in class, tetravalent, bispecific, novel ICE targeting EGFR. By binding to EGFR on tumor cells and CD16A on innate immune cells, AFM24 may utilize a patient's innate immunity to induce ADCC/ ADCP towards tumor cells. Anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors, which enhance the anti-tumor activity of a patient's adaptive immunity, have also demonstrated efficacy as monotherapy and are playing an increasingly prominent role in treatments. The combination of AFM24 and the PD-L1 inhibitor, atezolizumab, may therefore represent a rational new treatment modality, enhancing both the innate and adaptive immune responses to target EGFR+ tumor cells. **Methods:** An ongoing Phase 1/2a open-label, non-randomized, multicenter, dose escalation (Phase 1) and dose expansion (Phase 2a) study was initiated in November 2021 (NCT05109442) to evaluate the safety, tolerability and efficacy of AFM24 in combination with atezolizumab. The primary aim of the Phase 1 study is to determine the maximum tolerated dose and the recommended Phase 2 dose (RP2D) of AFM24. Eligible patients must have advanced histologically confirmed EGFR+ disease and confirmed disease progression after treatment with $\geq$1 prior therapy. Patients undergo a safety lead-in phase with AFM24 as a single agent 7 days before receiving the combination therapy. A standard 3+3 design will be used to determine the RP2D. Escalating doses of AFM24 will be given to each cohort as weekly intravenous (IV) infusions; the starting dose and at least two planned dose escalations are based on results from the ongoing AFM24 monotherapy trial (NCT04259450). Atezolizumab will be given at a fixed dose of 840 mg as a biweekly IV infusion. Patients will receive AFM24 and atezolizumab treatment until disease progression, intolerable toxicity, patient withdrawal, or termination at the investigator's discretion. The Phase 2a study will then establish the overall response rate (as per RECIST v1.1) and safety of combination therapy in patients with advanced/ metastatic, or treatment refractory gastric, esophagogastric, hepatocellular, hepatobiliary, pancreatic, or non-small cell lung cancer. For both phases, secondary endpoints include treatment-emergent adverse events, serious adverse events, pharmacokinetics, pharmacodynamics, and immunogenicity. Clinical trial information: NCT05109442. Research Sponsor: Affimed GmbH.

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TPS2674 **Poster Session**

A non-inferiority randomized phase III trial of standard immunotherapy versus reduced dose intensity in responding patients with metastatic cancer: MOIO study.

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Background: Immunotherapy (IO) is increasingly used for treating various metastatic cancers. With respect to the pharmacologically-active levels of IO drugs and their pharmacokinetics features, standard scheduling lead to plasma exposures largely exceeding the thresholds associated with target engagement. Indeed, phase I studies have shown that saturation of the target can persist far beyond the serum IO drugs half-life. *In silico* modeling has suggested that alternate scheduling (i.e. 3-monthly dosing) could be performed without compromising efficacy. Indeed, prolonged IO half-lives, time-varying clearance plus plasma concentrations far above the threshold associated with maximal target-engagement, suggest that the rhythm of IO administration could be slowed down. A phase II showed that extending IO dosing intervals did not compromise efficacy, while reducing toxicity in metastatic renal cell cancer. **Methods:** This non-inferiority, randomized, French national multicenter (36 centers involved) phase III study (NCT05078047) aims to compare the standard scheduling of a variety of IO drugs VS. 3-monthly scheduling in adult patients with metastatic cancer in partial (PR) or complete response (CR) after 6 months of standard IO dosing (except melanoma in CR). The main objective is to demonstrate the non-inferiority in Progression-Free Survival (PFS) of the reduced intensity group compared to the standard regimen. Secondary objectives are cost-effectiveness, quality of life, anxiety and fear of relapse, response rate, overall survival, and toxicity. A 1:1 randomization by minimization will be conducted on the following stratification factors: therapy line (first line vs others), tumor type, IO type (anti-PD-1 vs anti-PD-L1) and response status (PR, CR). A total of 646 pts will be randomized to get the 498 events necessary to prove non-inferiority between groups. The main analysis will conclude that reduced dose intensity is non-inferior to standard scheduling if the hazard ratio for PFS, estimated by a Cox model after adjustment for stratification factors, is significantly lower than the predefined 1.30 non-inferiority margin. In order to minimize the number of patients exposed to suboptimal treatment, an independent data monitoring committee will specifically review the efficacy data and recommend the early termination of the trial if lack of efficacy is evidenced. Ancillary studies of pharmacokinetics and immune-monitoring will be conducted to provide mechanistic insights supporting the clinical outcomes observed in both groups. **Conclusion:** Should the hypothesis of non-inferiority with an IO reduced dose intensity be validated, alternate scheduling could preserve efficacy while being cost-effective and allowing a reduction of the toxicity, with an increase in patient's quality of life. Clinical trial information: NCT05078047. Research Sponsor: Institut National du Cancer France.

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TPS2675 **Poster Session**

The combination of CD16A/EGFR innate cell engager, AFM24, with SNK01 autologous natural killer cells in patients with advanced solid tumors.

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Background: Natural killer (NK) cells are a critical component of the innate immune system involved in the eradication of transformed cells via antibody-dependent cellular cytotoxicity (ADCC). For treatment of solid tumors autologous NK cell transfer represents a promising treatment strategy, with *ex vivo* expansion and activation enhancing the specificity and anti-tumor activity of NK cells. The efficacy of this approach may be enhanced through the addition of tumor-targeting antibodies, augmenting NK cell-mediated ADCC. Innate Cell Engagers (ICE) are bispecific antibodies that target a tumor cell-surface antigen and bind to CD16A expressed on NK cells. AFM24 is a novel ICE that targets epidermal growth factor receptor (EGFR), which is often overexpressed in solid tumors. The Phase 1 study of AFM24 monotherapy showed patients had a manageable safety profile, and SNK01 monotherapy has also shown to be well-tolerated in patients with rapidly progressive solid tumors. This study seeks to investigate AFM24 in combination with SNK01 autologous NK cells in patients with advanced EGFR+ solid tumors. **Methods:** An ongoing Phase 1/2a open-label, non-randomized, multicenter, dose escalation (Phase 1) and dose expansion (Phase 2a) study was initiated in November 2021 (NCT05099549) to evaluate the safety, tolerability and efficacy of AFM24 in combination with SNK01 NK cells in EGFR+ solid tumors. The primary aim of the Phase 1 study is to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D) of AFM24 in combination with SNK01 at a fixed dose NK cells using a standard 3+3 design. Eligible patients must have advanced or metastatic disease with positive immunohistochemical staining for EGFR in >1% of tumor cells and be refractory to standard-of-care treatment. Treatment begins with a safety lead-in phase with a single dose of AFM24 7 days prior to combination therapy. AFM24 will be administered at an escalating dose as weekly intravenous (IV) infusions; the starting dose (160 mg) and dose escalations for each cohort are based on results from the ongoing AFM24 monotherapy trial (NCT04259450). SNK01 NK cells will be given at a fixed dose (4.0×10^9 cells) as a weekly IV infusion concomitantly with AFM24. Patients will receive combination therapy until disease progression, intolerable toxicity, patient withdrawal or termination at the investigator's discretion. Phase 2 will then establish the overall response rate (as per RECIST v1.1) of combination therapy in patients with treatment refractory, advanced or metastatic squamous cell carcinoma of the head and neck, non-small cell lung cancer, or colorectal cancer as the primary endpoint. Efficacy will also be assessed by assessing progression-free and overall survival. Secondary endpoints for both phases include treatment-emergent adverse events, serious adverse events, pharmacokinetics and immunogenicity. Clinical trial information: NCT05099549. Research Sponsor: Affimed GmbH and NKGen Biotech, Inc.

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TPS2676 **Poster Session**

BASECAMP-1: Leveraging human leukocyte antigen (HLA) loss of heterozygosity (LOH) in solid tumors by next-generation sequencing (NGS) to identify patients with relapsed solid tumor for future logic-gated Tmod CAR T-cell therapy.

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Background: Solid tumors comprise > 90% of cancers. Metastatic colorectal cancer, non-small cell lung cancer, and pancreatic cancer are among the leading causes of cancer-related mortality (5-year overall survival: 14%, 6%, and 3%, respectively) (ACS. 2021). Chimeric antigen receptor (CAR) T-cell therapy has demonstrated clinical efficacy in hematologic malignancies (Neelapu S. et al. *N Engl J Med*. 2017). Translating engineered T-cell therapies to solid tumors has proven to be challenging due to a lack of tumor-specific targets that can discriminate cancer cells from normal cells. Previous studies using carcinoembryonic antigen (CEA) T-cell receptors and mesothelin (MSLN) CARs resulted in dose-limiting on-target, off-tumor toxicities (Parkhurst M, et al. *Mol Ther*. 2011; Tanyi J. Cellicon Valley '21). To create a therapeutic safety window, Tmod CAR T-cell therapy utilizes dual-signaling receptors to create a robust NOT logic gate capable of killing tumor cells, while leaving healthy cells intact (Hamburger A, et al. *Mol Immunol*. 2020). The 2 receptors in Tmod CAR T-cell therapy comprise an activator that recognizes an antigen on the surface of tumor cells that may also be present on normal cells, such as CEA and MSLN, and a blocker that recognizes a second surface antigen from an allele lost only in tumor cells. The frequency of HLA LOH among advanced GI solid tumor cancers in the Tempus real-world dataset is 16.3% with a range of 15.6%-20.8% between colorectal, pancreatic, and gastroesophageal tumors (Hecht R. et al. ASCO-GI 2022. Abstract #190). As such, HLA LOH offers a definitive tumor versus normal discriminator target for CAR T-cell therapy. Different activator/blocker combinations can be engineered with the Tmod platform technology and may be applied to T cells and natural killer cells in autologous and allogeneic settings. BASECAMP-1 is a currently enrolling observational study with key objectives of 1) To identify patients with somatic HLA LOH eligible for Tmod CAR T-cell therapy, and 2) To obtain leukapheresis and feasibility for the future EVEREST Tmod CAR T-cell trial. **Methods**: BASECAMP-1 (NCT04981119) patient eligibility has 2 parts: 1) Patients will be initially screened to identify germline HLA-A*02 heterozygosity by central NGS. If HLA-A*02 heterozygosity is confirmed, primary archival tumor tissue will be analyzed for somatic mutations by xT-Onco NGS testing. 2) If the tumor demonstrates HLA-A*02 LOH and the patient is eligible after screening, the patient will undergo leukapheresis. Banked T cells will be available for the autologous EVEREST Tmod CAR T-cell therapy interventional study to reduce waiting time at relapse. Clinical trial information: NCT04981119. Research Sponsor: A2 Biotherapeutics.

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TPS2677 **Poster Session**

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

Kim Anna Reiss, Yuan Yuan, Naoto T. Ueno, Melissa Lynne Johnson, Saar Gill, Elizabeth Claire Dees, Joseph Chao, Mathew Angelos, Olga Shestova, Jonathan Stuart Serody, Saul Priceman, Debora Barton, Ramona F. Swaby, Amy Ronczka, Thomas Condamine, Daniel Cushing, Rehman Qureshi, Madison Kremp, Michael Klichinsky, Yara Abdou; University of Pennsylvania Abramson Cancer Center, Philadelphia, PA; City of Hope National Medical Center, Duarte, CA; Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX; Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN; University of Pennsylvania, Philadelphia, PA; UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC; City of Hope Comprehensive Cancer Center, Duarte, CA; University of Pennsylvanya, Philadelphia, PA; University of North Carolina, Chapel Hill, NC; City of Hope, Duarte, CA; Carisma Therapeutics, Springfield, NJ; Merck & Co., Inc., Kenilworth, PA; Carisma Therapeutics, Philadelphia, PA; Incyte Corporation, Philadelphia, PA; Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Adoptive T cell therapies have led to remarkable advances among patients with hematologic malignancies, but have had less success in those with solid tumors. Macrophages are actively recruited and abundantly present in the solid tumor microenvironment (sTME). Tumor associated macrophages are predominantly immunosuppressive and support tumor growth (M2), while a subset of proinflammatory macrophages enhance anti-tumor immunogenicity (M1). M1 macrophage function can be augmented by CAR expression to selectively recognize and phagocytose antigen overexpressing cancer cells. Moreover, CAR macrophages can reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and anti-tumor immune memory. Human Epidermal Growth Factor Receptor 2 (HER2) overexpression promotes tumorigenesis in many solid tumors (Table). CT-0508 is a cell product comprised of autologous monocyte-derived proinflammatory macrophages expressing an anti-HER2 CAR. Pre-clinical studies have shown that CT-0508 induced targeted cancer cell phagocytosis while sparing normal cells, decreased tumor burden, prolonged survival, and were safe and effective in a semi-immunocompetent mouse model of human HER2 overexpressing ovarian cancer. **Methods:** This Phase 1, FIH study is evaluating safety, tolerability, cell manufacturing feasibility, trafficking, and preliminary evidence of efficacy of investigational product CT-0508 in 18 participants (pt) with locally advanced (unresectable) or metastatic solid tumors overexpressing HER2. Pt previously treated with available therapies, including anti-HER2 therapies, as indicated, and subsequent progression are permitted. Filgrastim is used to mobilize autologous hematopoietic progenitor cells for monocyte collection by apheresis. CT-0508 is manufactured, prepared, and cryopreserved from mobilized peripheral blood monocytes. Group 1 pt (n=9) receive CT-0508 infusion split over D1, 3, and 5. A Safety Review Committee will review dose limiting toxicities. Group 2 pt (n=9) will receive the full CT-0508 infusion on D1. Pre- and post-treatment biopsies and blood samples will be collected to investigate correlates of safety (immunogenicity), trafficking (RNA scope), CT-0508 persistence in blood and in the tumor, target antigen engagement, TME modulation (single cell RNA sequencing), immune response (TCR sequencing) and others. Radiographic imaging is also being conducted to assess preliminary tumor activity. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

HER2 overexpression across tumor types.

Tumor	HER2 Overexpression (%)
Bladder	8 - 70
Salivary duct / mucoepidermoid	30 – 40 / 17.6
Gastric	7 - 34
Ovarian / Cervical / Uterine	26 / 2.8 – 3.9 / 3
Breast	11 - 25
Esophageal	12 - 14
Gallbladder / Cholangiocarcinoma	9.8 – 12.8 / 6.3 - 9
Colorectal	1.6 - 5
Testicular	2.4

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TPS2678 **Poster Session**

A phase I trial of T-cell receptor gene therapy targeting KK-LC-1 for gastric, breast, cervical, lung and other KK-LC-1 positive epithelial cancers.

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Background: T cell receptor (TCR)-T cell therapy is an emerging cancer treatment strategy. Thus far, demonstration of clinical activity has been limited to a subset of solid tumors including melanoma, synovial cell sarcoma and HPV-associated cancer. It is estimated that metastatic epithelial cancers are responsible for approximately 90% of cancer deaths in the United States. The estimated 600,000 cancer deaths each year is driven largely by lung adeno- and squamous cell carcinoma and invasive breast cancer, which account for approximately 30% of all cancer-related deaths. Kita-Kyushu Lung Cancer Antigen 1 (KK-LC-1) is a cancer germline antigen with expression restricted to germ cells in adults and certain epithelial cancers including lung, breast, gastric and cervical. We identified a KK-LC-1 TCR from the tumor-infiltrating lymphocytes (TIL) of a patient with cervical cancer who had a complete tumor response to TIL therapy. The KK-LC-1 TCR was the most dominate clonotype in the infused TIL product and persisted in the peripheral blood following infusion, suggesting that it may have contributed to cancer regression in this patient. **Methods:** We are conducting a phase I cell dose escalation trial to test the safety and efficacy of KK-LC-1 TCR-T cell therapy in patients with metastatic KK-LC-1 positive epithelial cancer. Patients receive a lymphocyte depleting conditioning regimen followed by a one-time infusion of genetically engineered T cells expressing the KK-LC-1 TCR (KK-LC-1 TCR-T cells) and high-dose systemic aldesleukin. KK-LC-1 positivity is determined by RNAscope assay measuring the percentage of cancer cells expressing CT83 (gene encoding KK-LC-1) with a percentage of 25 or greater considered positive. Main inclusion criteria include HLA-A*01:01 allele, prior first-line therapy, ECOG of 0 or 1 and adequate organ and hematologic function. Main exclusion criteria include active major medical illness of the cardiovascular, respiratory or immune system, primary or secondary immunodeficiency and autoimmune disease. Participants will be entered in sequential dose levels and receive escalating doses of cells beginning at $1x10^8$ and ending with $6x10^{10}$. Dose-limiting toxicities will be assessed during the first 30 days of cell infusion. The primary objective is to determine the maximally tolerated dose of KK-LC-1 TCR-T cells. Exploratory objectives include assessing the safety and efficacy of KK-LC-1 TCR-T cells and to conduct immunologic studies to understand and improve the administered treatment. Clinical trial information: NCT05035407. Research Sponsor: U.S. National Institutes of Health.

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TPS2679 **Poster Session**

First-in-human phase 1/2 study of autologous T cells engineered using the Sleeping Beauty System transposon/transposase to express T-cell receptors (TCRs) reactive against cancer-specific mutations in patients with advanced solid tumors.

Marcelo Vailati Negrao, Maria Pia Morelli, Amir A. Jazaeri, Benny Johnson, Partow Kebriaei, Drew Deninger, Eleanor De Groot, Matthew R. Collinson-Pautz, Nathan A. Demars, Jaymes S. Holland, John Heymach, Raffaele Baffa, Scott Kopetz; Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation & Cellular Therapy, Houston, TX; Alaunos Therapeutics, Houston, TX; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In 2022 approximately 1.7 million Americans will die from solid cancers. Recently there have been significant advances in the genetic engineering of T lymphocytes to recognize neoantigens on tumors in vivo, resulting in remarkable cases of tumor regression and remission. Cancer cells frequently harbor *KRAS, TP53,* and *EGFR* somatic hotspot mutations that can be processed and presented by tumor HLA as neoantigens to T cells through their T-cell receptor (TCR). These neoantigens are not present in the normal tissues; thus, they are attractive targets for adoptive T cell therapy. Given the number and complexity of different neoantigen/HLA combinations on solid tumors, a TCR library approach is warranted. Therefore, we have developed a library of TCR-T cell therapies including those targeting shared *KRAS*, *TP53* and *EGFR* mutations. **Methods:** Patients for whom a TCR matching the subject's somatic mutation(s) and HLA type is available in our TCR library, and have progressive or recurrent disease following standard therapy are eligible for enrollment on this protocol. Patients with the following tumor types will be enrolled: ovarian, endometrial, colorectal, pancreatic, cholangiocarcinoma, and non-small cell lung cancer. This first-in-human study includes Screening, Pre-Treatment, Treatment and Follow-up Periods. During the Pre-Treatment Period, subjects will undergo apheresis for PBMCs isolation. The PBMCs will be transposed using the *Sleeping Beauty* system to express the subject's mutation specific TCR. Bridging therapy after apheresis is allowed once the apheresis product has been accepted. During the Treatment Period, patients will undergo lymphodepletion with cyclophosphamide and fludarabine. After which, the TCR-T cell drug product will be administered to the subject by infusion at the assigned dose level. The starting dose level of Arm A (monotherapy) will be DL1 (5×10^{9} TCR+ Cells) administered on Day 0. Dose escalation will continue utilizing the accelerated BOIN design (planned escalation dose levels: 5×10^{9}, 4×10^{10} and 1×10^{11} TCR+ Cells). In Arm B, if initiated by protocol, subjects will also receive aldesleukin (interleukin-2) infusion starting on Day 0 (within 24 hours of TCR-T cell product infusion) at 720K IU/kg, every eight hours for up to 4 days. The Follow-up Period will begin after the subject completes their Day 28 visit. Clinical and radiologic response will be assessed at 6 and 12 weeks after TCR-T cell drug product infusion and every 12 weeks thereafter until up to 2 years or study discontinuation (e.g., disease progression, initiation of new anti-cancer therapy, consent withdrawn), whichever occurs first. All subjects will continue to be followed in the Long-Term Follow-up Protocol for up to 15 years post-TCR-T cell drug product infusion. Clinical trial information: NCT05194735. Research Sponsor: Alaunos Therapeutics.

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TPS2680 **Poster Session**

A phase 1/2 study of RTX-224, an engineered red blood cell expressing 4-1BB ligand and membrane-bound IL-12, for the treatment of patients with select advanced solid tumors.

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Background: RTX-224 is a genetically engineered off-the-shelf, allogeneic red blood cell that expresses the costimulatory molecule 4-1BB ligand (4-1BBL) and cytokine interleukin-12 (IL-12) on the cell surface. The use of 4-1BB and IL-12 agonists for cancer immunotherapy has been limited due to systemic toxicities. Unlike agonist antibodies and recombinant cytokines, which are distributed systemically, Red Cell Therapeutics, such as RTX-224, are restricted to the vasculature and spleen, which may limit toxicities previously observed with agonist 4-1BB monoclonal antibodies and recombinant IL-12. RTX-224 is designed to be a broad immune agonist of both adaptive and innate responses that activates and expands effector and memory CD8+ and CD4+ T cells, cytotoxic natural killer (NK) cells and produces inflammatory cytokines and chemokines, leading to enhanced antigen presentation. In preclinical studies, the combined activation of both adaptive and innate immune responses by the murine surrogate of RTX-224 led to antitumor activity while the restricted biodistribution improved the safety profile. **Methods:** The RTX-224-01 study is a Phase 1/2, first-in-human, multi-center, dose-escalation and expansion study of RTX-224 in patients with relapsed or refractory urothelial cancer, squamous cell carcinoma of the head and neck, non-small cell lung cancer, triple negative breast cancer and cutaneous melanoma. Safety, tolerability, pharmacokinetics and pharmacodynamics and anti-tumor activity of RTX-224 will be assessed. Approximately 28 patients will be enrolled across dose level cohorts to identify the recommended Phase 2 dose (RP2D). The starting dose is 100 million ($1x10^8$) cells administered intravenously every 3 weeks (Q3W) and the dose will be escalated by half-log increments following a Bayesian logarithmic regression model (BLRM) with overdose control. Following RP2D selection, each of the 5 expansion cohorts will enroll approximately 20 patients. Pharmacodynamic and exploratory biomarker studies correlative to clinical response will be evaluated on peripheral blood and paired tumor biopsies. Multiple technologies will be employed to profile the innate and adaptive responses following RTX-224 treatment. The study is open and enrolling patients in Phase 1. Clinical trial information: NCT05219578. Research Sponsor: Rubius Therapeutics, Inc.

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TPS2681 **Poster Session**

ZENYTH-ESO: Master protocol to assess the safety and recommended phase II dose of next generation NY-ESO-1-specific TCR T-cells in HLA-A*02 patients with synovial sarcoma and myxoid/round cell liposarcoma [Substudy 3, GSK4427296].

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Background: Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy expressing an affinity-enhanced T-cell receptor (TCR) to improve recognition of cancer cells expressing NY-ESO-1 and/or LAGE-1a. Next generation NY-ESO-1 TCR T-cell therapy, GSK4427296, utilizes the same TCR as lete-cel, as well as an epigenetic reprogramming process (Epi-R) developed by Lyell Immunopharma to alter the phenotypic T-cell profile of the manufactured product, and is intended to increase the proportion of cells with properties of durable stemness. T cells with properties of durable stemness are able to proliferate, persist, and self-renew with anti-tumor functionality. A first-time-in-human master protocol (NCT04526509) is underway to evaluate the safety, tolerability, and recommended phase II dose (RP2D) of next generation NY-ESO-1 TCR T-cell therapies. Substudy 3 is added to this master protocol to assess GSK4427296 in patients with advanced synovial sarcoma (SS) or myxoid/round cell liposarcoma (MRCLS). **Methods:** This substudy includes a dose confirmation stage to assess RP2D and a dose expansion stage, aiming to dose 10 participants at the RP2D. Key inclusion criteria: age ≥18 years; measurable disease per RECIST v1.1; HLA-A*02:01, A*02:05, or A*02:06 positivity; NY-ESO-1/LAGE-1a tumor expression; advanced (metastatic/unresectable) SS with t(X;18) translocation or MRCLS with a translocation involving *DDIT3* and/or *FUS* and/or *EWSR1* genes; and anthracycline-based therapy receipt/completion/intolerance. Key exclusion criteria: prior malignancy that is not in complete remission or clinically significant systemic illness; prior receipt of gene or allogenic stem cell/solid organ transplant; and central nervous system metastases. Primary endpoints: safety (adverse events) and tolerability (dose-limiting toxicities). Secondary endpoints: investigator-assessed overall response rate, duration of response, maximum transgene expansion (C_{max}), T_{max}, and $AUC_{(0\text{-}t)}$. Analyses will be descriptive. The master protocol is open for recruitment. Clinical trial information: NCT04526509. Research Sponsor: GlaxoSmithKline; GSK4427296 produced by and used in collaboration with Lyell Immunopharma.

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TPS2682 **Poster Session**

NEBULA: A multicenter phase 1a/b study of a tumor-selective transgene-expressing adenoviral vector, NG-641, and nivolumab in patients with metastatic or advanced epithelial tumors.

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Background: Tumor-Specific Immuno Gene Therapy (T-SIGn) vectors are next-generation transgene-armed variants of the adenoviral vector enadenotucirev that selectively replicate in epithelial tumor cells. T-SIGn vectors are blood-stable, allowing IV delivery to be coupled with local transgene expression in the tumor microenvironment (TME), thereby targeting all lesions while limiting systemic exposure. The T-SIGn vector NG-641 encodes four immunostimulatory transgenes: fibroblast activation protein-directed bi-specific T-cell activator antibody to target cancer-associated fibroblasts (CAFs), IFNα2 to promote innate and adaptive immune responses, and CXCL9/10 to induce T-cell infiltration. Through this novel multimodal combination of immunostimulatory effects NG-641 is designed to reprogram the TME to allow functional anti-cancer immune responses. In the ongoing STAR study (NCT04053283), NG-641 has been successfully dose-escalated to 1×10^{12} viral particles (vp) on Day 1 and 3×10^{12} vp on Days 3 and 5, with promising preliminary safety/tolerability and pharmacodynamic results. Based on these encouraging preliminary data with NG-641 monotherapy, we designed a new study to assess NG-641 + nivolumab. **Methods:** NEBULA (NCT05043714) is an open-label, dose-escalating, phase 1a/b study of NG-641 + nivolumab in patients (pts) with advanced/metastatic epithelial tumors that have progressed after $\geq$1 line of systemic therapy and are incurable by local therapy. Pts are eligible for phase 1a if they have received prior PD-1/PD-L1 inhibition as part of any line of therapy. During phase 1a, up to 30 pts will receive escalating doses of IV NG-641 to a maximum dose of 1×10^{12} viral particles (vp) on Day 1 and 1×10^{13} vp on Days 3 and 5 (1 cycle; Bayesian Optimal Interval design). Pts will receive a fixed-dose of nivolumab (480 mg IV) on Day 15 and then every 4 weeks thereafter for up to 8 cycles. In phase 1b, the recommended dose regimen will be further studied in patients with primary resistance to PD-1/PD-L1 inhibition; patients will be enrolled in up to 3 tumor-specific cohorts (Cohorts A-C; Simon 2-stage design). Co-primary objectives are to characterize the safety and tolerability of NG-641 + nivolumab and to identify a recommended dose. Preliminary efficacy and immunogenicity are secondary endpoints. Pharmacodynamic outcomes will also be assessed. Viral replication, transgene expression, immune/inflammatory responses and effects on CAFs by IHC and gene expression analysis will be analyzed using tumor tissue from serial biopsies (taken at baseline and Day 15 of cycles 1-3 [cycles 1-2 only in Phase 1b]). Serial blood samples will be analyzed to study cytokine production and changes in peripheral immune cell subsets. Enrollment to the first dose-escalation cohort is ongoing. Clinical trial information: NCT05043714. Research Sponsor: Funded by PsiOxus Therapeutics Ltd, in collaboration with Bristol Myers Squibb.

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TPS2683 **Poster Session**

Davoceticept (ALPN-202), a PD-L1-dependent CD28 costimulator and dual checkpoint inhibitor, in combination with pembrolizumab in patients with advanced malignancies (NEON-2).

Amita Patnaik, Nehal J. Lakhani, Meredith McKean, Justin F. Gainor, Cathy Vo Buu, Stacey R. Dillon, Hany Zayed, Michael Jon Chisamore, James Michael Pluda, Stanford L. Peng; START, San Antonio, TX; START Midwest, Grand Rapids, MI; Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; Department of Medicine, Massachusetts General Hospital, Boston, MA; Alpine Immune Sciences, Inc., Seattle, WA; Alpine Immune Sciences, Seattle, WA; Merck & Co., Inc., Kenilworth, NJ; ICON Clinical Research, Blue Bell, PA

Background: Despite successes with checkpoint inhibition (CPI) in a wide range of tumors, most demonstrate primary or acquired resistance, warranting better therapeutic strategies. PD-1 is now recognized to effect much of its benefit by disinhibiting CD28 signaling – a mechanism expected to require intra-tumoral engagement of CD28 by its ligands CD80/CD86. Davoceticept (ALPN-202), a variant CD80 vIgD-Fc fusion protein, was engineered to provide tumor localizing PD-L1-dependent CD28 agonism, while inhibiting PD-L1 and CTLA-4. Davoceticept has demonstrated superiority to CPI-only therapies in both in vitro and in vivo tumor models, while also demonstrating additional benefit in combination with targeted PD-1 axis blockade (Lewis et al. (2019) J Immunother Cancer 7(S1): P467). The benefit appeared at least additive in models of poorly immunogenic tumors, suggesting the possibility of meaningful clinical benefit where CPI therapeutic efficacy is limited, such as noninflamed tumors. Single agent safety and tolerability of davoceticept has been demonstrated along with pharmacodynamic evidence of CD28 engagement with immune checkpoint inhibition (Moser et al. (2021) J Clin Oncol 39(s15): 2547). **Methods:** NEON-2 is an open-label dose escalation and expansion study of davoceticept combined with pembrolizumab in adults with advanced solid tumors or lymphoma that was initiated in June 2021 (NCT04920383). Eligibility includes tumors where single agent PD-(L)1 antagonists are SOC, are refractory or resistant to standard therapies (including approved CPIs), or have no standard or curative therapy. The study employs a standard 3+3 dose escalation design with two schedules, Q1W and Q3W of davoceticept. Pembrolizumab is given per label at 400 mg IV Q6W. Objectives include evaluation of safety and tolerability, identification of the recommended phase 2 dose(s) (RP2D), PK, PD, exploratory predictive biomarker analysis (i.e., PD-L1, CD28, CD80 and CD86 expression, as well as immunophenotyping of immune cell populations on treatment) and preliminary anticancer activity of davoceticept in combination with pembrolizumab. Disease assessments are evaluated by RECIST v1.1 for solid tumors or by Lugano Classification for lymphoma. Efficacy endpoints include ORR, duration of response and disease control rate. Once the RP2D combination is identified, tumor-specific expansion cohorts of ~ 30- 35 patients will be performed, including histologies that have not been demonstrated to be CPI responsive, as well as those where CPIs are approved SOC. The 0.1 mg/kg cohorts have been completed without DLT. Enrollment to the 0.3 mg/kg cohorts began in September 2021. Clinical trial information: NCT04920383. Research Sponsor: Alpine Immune Sciences.

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TPS2684 **Poster Session**

ARTISTRY-3: Effect of nemvaleukin alfa with a less frequent IV dosing schedule as monotherapy and in combination with pembrolizumab and impact on the tumor microenvironment (TME) in patients (pts) with advanced solid tumors.

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Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine that selectively binds the intermediate-affinity interleukin-2 (IL-2) receptor, preferentially activating and expanding antitumor $CD8^+$ T cells and NK effector cells, with minimal effect on regulatory T cells. Nemvaleukin was designed to leverage antitumor effects of the IL-2 pathway while limiting typical IL-2–associated toxicity. In ARTISTRY-1, the recommended phase 2 dose (RP2D) for nemvaleukin monotherapy of 6 μg/kg IV on days 1 to 5 of a 21-day cycle elicited durable and deep responses in pts with advanced melanoma and renal cell carcinoma (Boni et al. ASCO 2021:abstr 2513). Responses with nemvaleukin plus pembrolizumab were also observed in platinum-resistant ovarian, breast, cervical, gastrointestinal, and genitourinary cancers. ARTISTRY-3 will investigate the effects of nemvaleukin as monotherapy and in combination with pembrolizumab on the TME in pts with advanced solid tumors, and in an additional cohort (Cohort 2), to further assess a less frequent IV dosing schedule for nemvaleukin. **Methods:** The phase 1/2, open-label ARTISTRY-3 (NCT04592653) study will enroll adults (≥18 years) with select advanced solid tumors, ≥1 accessible lesion for biopsy, ≥1 target lesion (per RECIST v1.1), ECOG PS of 0 or 1, estimated life expectancy of ≥3 months, adequate hematologic reserve, and adequate hepatic and renal function. Primary objectives: to evaluate effects of nemvaleukin monotherapy on the TME (Cohort 1) and to determine RP2D for less frequent dosing schedule (Cohort 2). Additional objectives are to evaluate: efficacy, safety, immunogenicity, and pharmacokinetics of nemvaleukin monotherapy; effects of nemvaleukin plus pembrolizumab on the TME; and correlative biomarkers of nemvaleukin as monotherapy and combination. Following the protocol amendment, additional pts enrolled in Cohort 1 will receive lead-in monotherapy at a dose selected based on results from Cohort 2, and pre- and on-treatment biopsies will be collected for TME assessments. Subsequent cycles will be administered in combination with pembrolizumab, and a biopsy may be collected at cycle 4 or 5. Tumor types eligible for Cohort 2 are selected based on activity observed in the ARTISTRY-1 study. A quantitative system pharmacology model was applied to identify a less frequent schedule for nemvaleukin monotherapy and combination. Cohort 2 will initially assess safety and tolerability of nemvaleukin at 1 dose per 21-day cycle. Two doses per 21-day cycle may be implemented to achieve optimal PK/PD parameters. Bayesian optimal interval design methodology with open enrollment will be applied to facilitate dose escalation decisions. Clinical trial information: NCT04592653. Research Sponsor: Alkermes, Inc.

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TPS2685 **Poster Session**

BMC128: A rationally designed live bacterial consortium for the potentiation of immune checkpoint therapy in solid tumors.

Corinne Maurice-Dror, Osnat Tirosh, Sheerli Kruger Ben-Shabat, Shiri Eshar, Omri Plolonsky, Noa Davis, Elran Haber, Shiri Meshner, Ruth Perets; BC Cancer, Vancouver, BC, Canada; Biomica, Rehovot, Israel; Biomica Ltd., Rehovot, Israel; Rambam Medical Center and Technion-Israel Institute of Technology, Haifa, Israel

Background: Immune-Checkpoint inhibitors (ICI) have transformed the treatment of solid tumors, specifically in cutaneous melanoma, clear cell renal cell carcinoma (ccRCC) and non-small cell lung cancer (NSCLC). Despite these advances, a significant proportion of patients do not respond to ICI and only a fraction of responding patients will experience durable responses. Recent reports have found that patients showing poor response to ICI are characterized by a reduced gut microbiome diversity, suggesting that the gut microbiome might affect immune activation by ICI. BMC128 is a live bacterial consortium of 4 bacterial strains predicted to induce anti-tumor immune function when given in conjunction with ICI. These strains were identified by analyzing data obtained from NSCLC and ccRCC patients presenting varied responses to ICI, using a proprietary computational discovery platform enabling high-resolution functional microbiome analysis. In pre-clinical studies, treatment with BMC128 potentiated the efficacy of ICI in breast cancer and melanoma mouse models, reducing tumor volume, increasing the number of responders, and demonstrating an increase in infiltrating immunocytes: CD4, CD8 and NK cells. **Methods:** In this phase I, first-in-human trial, patients with ccRCC, cutaneous melanoma and NSCLC-adenocarcinoma (EGFR/ALK wild-type), who previously progressed on PD1/PDL-1 inhibitors will be treated with BMC128 $8*10^8$ CFU BID in combination with Nivolumab at a fixed-dose of 480mg q4weeks in a 3+3 design, followed by a 9 patient expansion phase. No dose escalation is planned. The primary objective is to investigate the safety and tolerability of BMC128 in combination with Nivolumab. Enrollment is intended to start in Feb, 2022. Clinical trial information: 202122207. Research Sponsor: Biomica Ltd.

Overall study design.

	Period		Duration (days)
1	Screening	Screening	
2	DLT period	Native microbiota depletion	1
3		Induction (BMC128 monotherapy)	14
4		Combination treatment, cycle 1: BMC128+Nivolumab	28
5	Cycles 2-4	Combination treatment, BMC128+Nivolumab	84
6	Cycles 5-26	Nivolumab monotherapy	~590
7	Follow up	Follow up	30

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TPS2688 **Poster Session**

A phase 1 dose-escalation study to investigate the safety, efficacy, pharmacokinetics, and pharmacodynamic activity of CLN-619 (anti-MICA/MICB antibody) alone and in combination with pembrolizumab in patients with advanced solid tumors.

John D. Powderly, Martin Gutierrez, Judy S. Wang, Erika P. Hamilton, Manish Sharma, Alexander I. Spira, Michael Millward, Mark J. Shackleton, Sophia Frentzas, Marianna Koczywas, Naveen Mehta, Ann Marie Christensen, Irina Shapiro, Kerry Whalen, Jennifer Michaelson, Patrick Baeuerle, John Edward Janik, Drew W. Rasco; Carolina BioOncology Institute, Huntersville, NC; John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; Florida Cancer Specialists, Sarasota, FL; Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; START Midwest, Grand Rapids, MI; Virginia Health Specialists, Fairfax, VA; School of Medicine and Pharmacology, The University of Western Australia, Western Australia, Australia; Department of Oncology, Alfred Health and Monash University, Melbourne, Australia; Monash Hospital, Victoria, Australia; City of Hope, Duarte, CA; Cullinan Oncology, LLC, Cambridge, MA; START, San Antonio, TX

Background: The major histocompatibility complex (MHC) class I-related proteins MICA and MICB are stress-inducible, surface glycoproteins that are up-regulated on human tumors. MICA/MICB are ligands for the activating receptor, Natural Killer Group 2 member D (NKG2D) expressed on Natural Killer (NK) cells, CD8+ T cells, $\gamma\delta$ T cells and iNKT cells. Proteases in the tumor microenvironment cleave MICA/MICB from the cell surface which enables tumor cells to evade immune cell recognition and destruction by NKG2D-expressing cells. Increased concentrations of shed MICA have been observed in serum from patients across multiple tumor types and correlate with poor survival. CLN-619 is a humanized, clinical-stage, MICA/MICB-specific IgG1 monoclonal antibody that prevents the proteolytic release of MICA/MICB thereby exposing tumor cells for immune destruction through both NKG2D-mediated and antibody-dependent cell-mediated cytotoxicity (ADCC). The antibody has been shown to restore the MICA/MICB-NKG2D axis to promote NK-mediated tumor cell lysis (AACR Annual Meeting abstract 3506, April 2022). In mice bearing MICA/MICB-expressing human tumor xenografts, CLN-619 treatment yielded robust anti-tumor activity at low doses. MICA/MICB is expressed in a wide range of solid tumors. Therefore, CLN-619 is expected to have broad anti-tumor activity. **Methods:** CLN-619 is being evaluated in an open-label, non-randomized, dose-escalation (phase 1) study as monotherapy, and in combination with pembrolizumab, in patients with advanced solid tumors. Cohort expansion in patients with specific indications as monotherapy and in combination with pembrolizumab will be conducted. The phase 1 study explores ascending intravenous doses of CLN-619 as monotherapy (0.1, 0.3, 1.0, 3.0, 6.0 and 10.0 mg/kg) and in combination with pembrolizumab (200 mg) in 21-day cycles to identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Key eligibility criteria include 1) histological or cytological diagnosis of cancer and 2) refractory metastatic disease, or locally advanced disease not amenable to local therapy. At the RP2D, CLN-619 monotherapy will be evaluated in non-small cell lung and cervical cancer. In parallel, a cohort of patients will be administered CLN-619 in combination with pembrolizumab. Serum levels of soluble MICA/MICB, identity of MICA/MICB alleles, phenotypes of peripheral blood mononuclear cells, cytokines and tumor biopsies will be investigated for correlative pharmacodynamic and predictive biomarkers. This clinical trial is in progress (NCT05117476) and has completed accrual of three participants at the first dose level. Clinical trial information: NCT05117476. Research Sponsor: Cullinan Oncology, LLC.

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TPS2689 **Poster Session**

A combined phase I/II study of a novel bicycle tumor-targeted immune cell agonist BT7480 in patients with nectin-4 associated advanced malignancies.

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Background: BT7480 is a novel, first-in-class, Nectin-4/CD137 *Bicycle* tumor-targeted immune cell agonist (*Bicycle* TICA) that co-ligates cluster of differentiation (CD)137 (on immune cells) and Nectin-4 (on tumor cells). BT7480 comprises 3 bicyclic peptides (*Bicycles)*, 1 that binds to Nectin-4 and 2 that bind to CD137. The *Bicycles* are conjugated via a branched trimeric polyethylene glycol linker. Co-ligation of Nectin-4 and CD137 by BT7480 is hypothesized to induce oligomerization and activation of CD137 resulting in a tumor-localized costimulatory signal that leads to an antitumor response in preclinical studies. Nectin-4 is reported to be highly expressed in numerous tumors with unmet medical need including bladder, pancreas, breast, ovary, esophagus, head and neck, stomach, and lung cancers. Many of these tumor types also contain CD137 expressing cells. BT7480 exhibited a favorable preclinical profile supporting initiation of a first-in-human study to investigate safety and efficacy in indications with evidence of Nectin-4 expression. **Methods:** BT7480-100 (NCT05163041) is a PhI/II study to evaluate safety and tolerability of BT7480 administered as an intravenous infusion QW in a 28-day cycle, and to determine a recommended Phase 2 dose to further explore efficacy and safety. Patients will be recruited with advanced solid tumors associated with Nectin-4 expression including urothelial; head and neck squamous cell; non-small cell lung; ovarian, breast, gastric or esophageal carcinoma after exhausting standard of care options. Patients must have available tumor tissue, acceptable hematologic and other critical organ function. Exclusion criteria include uncontrolled brain metastases, uncontrolled hypertension, significant history of autoimmune disease and prior CD137 targeted therapy. Pharmacokinetic and pharmacodynamic analyses will be performed to support dose escalation decisions and increase the understanding of safety and clinical activity signals observed during the study. Tumor response will be assessed per RECIST every 8 weeks. Cohorts 1 and 2 have been completed without DLT. Enrollment in cohort 3 began in January 2022. Clinical trial information: NCT05163041. Research Sponsor: BicycleTx Limited.

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TPS2690 **Poster Session**

Phase 1a/1b study design of the novel STING agonist, immune-stimulating antibody-conjugate (ISAC) TAK-500, with or without pembrolizumab in patients with advanced solid tumors.

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Background: Tumor resistance to immune checkpoint inhibitors (CPIs), including pembrolizumab, is common. Suggested mechanisms of resistance include reduced interferon (IFN) signaling, immune escape, and immunosuppressive tumor phenotypes. Innate immune cell stimulation in the tumor microenvironment may be a potential pathway to overcome this resistance. Stimulator of interferon genes (STING) is a cytosolic protein critical for initiation of type-1 IFN-dependent innate immunity. TAK-500 is a novel ISAC comprising a STING agonist (based on TAK-676, which is currently in phase 1 clinical trials [NCT04420884, NCT04879849]), an IgG1 anti-cysteine-cysteine chemokine receptor 2 (CCR2) antibody, and a self-immolating maleimide-containing protease-cleavable peptide linker. CCR2-expressing myeloid cells, including tumor associated macrophages (TAMs), promote immune evasion in part by reducing infiltration of CD8+ T cells into the tumor microenvironment. As such, TAK-500 has the potential to mitigate CPI resistance in solid tumors via targeted STING activation of tumor-infiltrating CCR2-expressing myeloid cells, thus leading to stimulation of innate and adaptive immunity within the tumor microenvironment through three potential mechanisms of action: activation of IFN signaling, reprogramming of CCR2-expressing myeloid cells to an inflammatory phenotype, and blockade of suppressive TAM recruitment. **Methods:** Adult patients with a diagnosis of locally advanced or metastatic gastroesophageal adenocarcinoma, pancreatic adenocarcinoma, hepatocellular carcinoma, non-squamous non-small cell lung cancer, squamous cell carcinoma of the head and neck, mesothelioma or triple-negative breast cancer are eligible. All patients must have progressive disease while on, or be intolerant to, all current standard therapies. Approximately 106 patients in total will be enrolled to the dose escalation and expansion cohorts. In the dose escalation phase, intravenous (IV) TAK-500 will be administered over the range 8–480 μg/kg on day 1 of every 21-day cycle (Q3W) to establish the pharmacologically active dose (PAD) range. An additional escalation cohort of patients will receive TAK-500 + IV pembrolizumab 200 mg Q3W, starting at a dose of TAK-500 that is 1–2 dose levels below the lowest PAD range established in the single agent cohort. Dose escalation in both cohorts will be guided by Bayesian Optimal Interval design. In the dose expansion phase, only the combination of TAK-500 + pembrolizumab will be evaluated. Primary objectives of this study are safety and tolerability; secondary objectives include determination of the PAD range, the recommended phase 2 dose, pharmacokinetics, pharmacodynamics, and antitumor activity of TAK-500 as a single agent and in combination with pembrolizumab. Clinical trial information: NCT05070247. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

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TPS2691 **Poster Session**

A first-in-human phase 1 trial of nx-1607, a first-in-class oral CBL-B inhibitor, in patients with advanced solid tumor malignancies.

Adam Sharp, Anja Williams, Sarah Patricia Blagden, Elizabeth Ruth Plummer, Daniel Hochhauser, Matthew Krebs, Simon Pacey, T.R. Jeffry Evans, Sarah Whelan, Srinand Nandakumar, Seema Rogers, Katherine L. Jameson, Frank G. Basile, Johann S. De Bono, Hendrik-Tobias Arkenau; The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Sarah Cannon Research Institute UK, London, United Kingdom; University of Oxford, Oxford, United Kingdom; Newcastle University Centre for Cancer, Newcastle University, Newcastle upon Tyne, United Kingdom; University College London Cancer Institute, London, United Kingdom; Christie NHS Foundation Trust, Manchester, United Kingdom; Cambridge Cancer Trials Centre, Cambridge, United Kingdom; University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Nurix, San Francisco, CA; Nurix Therapeutics, Inc., San Francisco, CA; The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom

Background: Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is an E3 ubiquitin ligase expressed in multiple immune cell lineages, which in contrast to cell surface immune checkpoints, acts as a regulator of both T and NK cell activation. Inhibition of CBL-B enhances T-cell response, increases response to suboptimal priming, and restores response in exhausted T cells. Thus CBL-B is a promising immune-oncology target and may overcome challenges seen with other T-cell directed therapies. NX-1607 is an oral small molecule inhibitor of CBL-B that has demonstrated anti-tumor activity and long-term survival in murine models as both a single agent and in combination with programmed cell death protein-1 (PD-1) antibodies. Further, NX-1607 elicits dose-dependent increases in cytokine secretion and proliferation in T-cell receptor-stimulated primary human T cells with enhanced tumor antigen-specific T-cell and NK cell anti-tumor responses. Thus, NX-1607 may be effective as a single agent or it may significantly enhance efficacy of other anti-tumor agents. **Methods:** NX-1607-101 is a first-in-human, multicenter, open-label, Phase 1 dose escalation and expansion trial evaluating NX-1607 in a variety of indications including platinum-resistant epithelial ovarian cancer (EOC), gastric cancer, squamous cell carcinoma of the head and neck (HNSCC), metastatic melanoma, non-small cell lung cancer (NSCLC), metastatic castration-resistant prostate cancer (mCRPC), malignant pleural mesothelioma (MPM), triple-negative breast cancer (TNBC), locally advanced or metastatic urothelial cancer, cervical cancer, microsatellite stable colorectal cancer (MSS CRC), and diffuse large B-cell lymphoma with Richter transformation (DLBCL-RT). The main objective is to establish the safety and tolerability of NX-1607, characterize PK/PD, and determine the recommended Phase 1b dose. NX-1607 will be given orally once daily at doses ranging from 5 to 100 mg in up to 6 dose levels. Dose escalation will proceed using an accelerated modified Fibonacci dose escalation design that transitions to a standard 3 + 3 design based on protocol-specific criteria. Up to 8 expansion cohorts in Phase 1b will be composed of patients with subsets of advanced cancers. Key eligibility criteria include patients with metastatic or unresectable disease that have progressed after prior therapy and for whom standard therapy with proven clinical benefit does not exist, is no longer effective, or is not appropriate. Prior treatment with immune checkpoint inhibitors or CAR-T cells with washout is allowed, but a history of active autoimmune disease is not. Up to 336 patients (60 in Phase 1a, 276 in Phase 1b using a Simon 2-stage design) will be enrolled at approximately 20 sites in the UK and US and treated until disease progression or unacceptable toxicity. Dose escalation is ongoing. Clinical trial information: NCT05107674. Research Sponsor: Nurix Therapeutics, Inc.

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TPS2693 **Poster Session**

A phase 1/2 dose escalation/expansion study of OR2805 alone or in combination in subjects with advanced solid tumors.

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Background: M2-like macrophages are thought to promote an immunoinhibitory environment and prevent activation and proliferation of T cells, leading to resistance to checkpoint inhibitor (CPI) therapy. OR2805 is a fully human monoclonal antibody identified in a patient who had an exceptional response to CPI. OR2805 recognizes CD163, an immunosuppressive scavenger receptor highly expressed on M2 tumor-associated macrophages (TAMs). OR2805 treatment reprograms M2 macrophages to take on an immunostimulatory, M1-like phenotype. In macrophage/T cell coculture assays, OR2805 treatment relieved the suppressive effect of M2c macrophages as demonstrated by increased T-cell proliferation and stimulation of IFN-γ and perforin release. OR2805 restored the IFN-γ production of exhausted T cells and showed a synergistic effect on cocultures treated in combination with CPI. OR2805 monotherapy demonstrated significant anti-tumor activity in lung cancer xenograft models in NSG-SGM3 mice. Relieving the immune suppression of CD163-expressing TAMs by OR2805 to improve anti-tumor T-cell responses will be evaluated alone and in combination with CPI therapy. **Methods:** This phase 1/2, open-label, multicenter, dose-escalation/expansion study is assessing the safety, tolerability and preliminary activity of OR2805 alone and in combination with anti-PD-1 or chemotherapy in up to 325 adults (≥18 years) with histologically or cytologically confirmed metastatic or locally advanced solid tumors. The study is divided into 3 parts. Part A will enroll subjects with advanced solid tumors of any histology to describe the preliminary safety profile of OR2805 and determine the recommended phase 2 dose (RP2D) of OR2805 alone and in combination with an anti-PD-1 monoclonal antibody. Part B will further characterize the safety and preliminary antitumor activity of OR2805 either alone or in combination with an anti-PD-1 or chemotherapy in previously treated non-small cell lung cancer (NSCLC), melanoma and liposarcoma, as well as in previously untreated NSCLC in combination with an anti-PD-1 antibody. Part C will evaluate OR2805 monotherapy in relapsed squamous cell carcinoma of the head and neck and other tumor types with an emphasis on correlative biomarker analysis. OR2805 will be infused on Day 1 of 21-day cycles. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities, and dose-level safety and activity. Secondary endpoints are objective response rates, duration of response, complete response, progression-free survival, overall survival, PK, and antidrug antibodies. Exploratory biomarkers of OR2805-mediated pharmacodynamic effects and immune stimulation will be explored. The study was opened September 2021 and is enrolling at sites in the United States with planned expansion within the US and to Europe. Clinical trial information: Clinical trial information: NCT05094804. Research Sponsor: Oncoresponse, Inc.

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TPS2694 **Poster Session**

An open-label, non-randomized, multi-center phase I study evaluating the safety, tolerability, pharmacokinetics and preliminary efficacy of bi-ligand-drug conjugate CBP-1018 in patients with advanced solid tumors.

Kaiwen Li, Yehui Shi, Junyan Wu, Liyan Zhou, Suiwen Ye, Xiuping Lai, Robert Huang, Yan Teng, Jiangang Yu, Xiaoyan Chai, Hai Huang; Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; Coherent Biopharma, Suzhou, China; Coherent Biopharma (Suzhou) Co. Ltd., Suzhou, China

Background: Folate-receptor 1 (FOLR1) and prostate specific membrane antigen (PSMA) are overexpressed on tumor and angiogenic endothelial cells in solid tumors, including prostate cancer, renal cell cancer and lung cancer. CBP-1018 is a first-in-class bi-ligand drug conjugate targeting to both FOLR1 and PSMA, with a tubulin inhibitor payload, monomethyl auristatin E (MMAE). We herein introduce its first-in-human study which is designed based on the significant anti-tumor potency and acceptable safety profile in nonclinical studies. **Methods:** This study is a phase Ia/Ib, multicenter, open-label study enrolling patients with advanced solid tumor relapsed after previous standard therapies. The primary objective is to assess CBP-1018 safety, tolerability, dose limiting toxicity and maximum tolerated dose. Preliminary efficacy including objective response rate, duration of response and progression-free survival will be observed. Pharmacokinetics, immunogenicity and biomarkers will be also evaluated. This study includes 2 parts: Ia (Dose Escalation) and Ib (Dose Expansion). CBP-1018 is administrated iv Q2W (4 weeks/cycle) in Ia, with accelerated titration at lower doses (0.03 mg/kg and 0.06 mg/kg) and an i3+3 design at following doses (0.08 mg/kg, 0.10 mg/kg, 0.12 mg/kg and 0.14mg/kg, etc.). Subjects will be enrolled in 4 cohorts in Ib: metastatic castration resistant prostate cancer, advanced renal cell cancer, advanced lung squamous cell cancer, and other advanced solid tumors. Efficacy will be assessed every 8 weeks (±7days) according to RECIST 1.1, PCWG3 and PSA assessment (only for prostate cancer). Treatment will be continued untill disease progression or intolerable toxicity. Enrollment has been started in Nov. 2021 and is ongoing. Clinical trial information: NCT04928612. Research Sponsor: Coherent Biopharma (Suzhou) Co., Ltd.

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TPS2695 **Poster Session**

IL believe: A phase 1/2, open-label, dose escalation and dose expansion study of TransCon IL-2 β/γ alone or in combination with pembrolizumab or standard-of-care chemotherapy in patients with locally advanced or metastatic solid tumors.

Alexander Starodub, Nashat Y. Gabrail, Ying Zhang, Davis Y Torrejon Castro, Sibel Slavsky, Stina Mui Singel, John D. Powderly; The Christ Hospital, Cincinnati, OH; Gabrail Cancer Center Research LLC, Canton, OH; Ascendis Pharma, Palo Alto, CA; Carolina BioOncology Institute, Huntersville, NC

Background: Advances in immunotherapy have led to significantly improved survival and quality of life in some cancer patients, but many with less immunogenic tumor types derive suboptimal clinical benefit. Recombinant human interleukin-2 (IL-2, aldesleukin) can induce a response rate of ~15% in metastatic renal cell carcinoma and metastatic melanoma, yet toxicities (vascular leak syndrome, cytokine storm) have limited its use. TransCon IL-2 β/γ, a novel prodrug with sustained release of a receptor-selective IL-2 (IL-2 β/γ), was designed to optimally address drawbacks of aldesleukin: potent activation of undesired IL-2Rα^+ cell types and high C_{max} with rapid clearance. TransCon IL-2 β/γ comprises 3 main components: IL-2 β/γ, a methoxy polyethylene glycol (mPEG) carrier molecule, and a linker connecting the two. Under physiological conditions, TransCon IL-2 β/γ releases active IL-2 β/γ from the mPEG carrier through cleavage of the TransCon Linker. This results in a lower C_{max} and much longer effective $t_{1/2}$ of free IL-2 β/γ compared to aldesleukin. PD-1 expression at the cell surface of activated cytotoxic T cells and natural killer cells provides a clear rationale to study TransCon IL-2 β/γ alone or in combination with pembrolizumab. **Methods:** IL Believe is a multicenter, first-in-human, Phase 1/2 study in 3 parts in adult patients with locally advanced or metastatic solid tumors. All patients need $\geq$1 measurable lesion per RECIST 1.1 and an ECOG score of $\leq$ 2. The primary objectives are to evaluate safety and tolerability, and to define the maximum tolerated dose and recommended Phase 2 dose (RP2D) of TransCon IL-2 β/γ alone or in combination with pembrolizumab. Parts 1 and 2 Dose Escalation (Phase 1) use a standard 3+3 design with increasing doses of intravenous (IV) TransCon IL-2 b/g alone (Part 1) or with 200 mg IV pembrolizumab in solid tumors where pembrolizumab monotherapy may have clinical activity (Part 2). Each part will enroll ~15 patients. Part 3, Combination Dose Expansion (Phase 2) will evaluate preliminary clinical efficacy of TransCon IL-2 β/γ at the RP2D determined in Part 2, combined with chemotherapy. Platinum Resistant Ovarian Cancer is currently planned for dose expansion with other indication specific cohorts to be included in a subsequent amendment. Each cohort will be analyzed using a Simon 2-stage design and will enroll ~56 patients. Other key objectives include the evaluation of pharmacokinetics, pharmacodynamic biomarkers, and antitumor activity according to RECIST 1.1. Recruitment started in January 2022 and is ongoing (NCT05081609). Clinical trial information: NCT05081609. Research Sponsor: Ascendis Pharma.

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TPS2696 **Poster Session**

A phase 1 study of TPST-1495 as a single agent and in combination with pembrolizumab in subjects with solid tumors.

Diwakar Davar, John D. Powderly, Susanna Varkey Ulahannan, Melissa Lynne Johnson, Manish Sharma, John C. Krauss, Robert Stagg, Brian Francica, Anne Moon, Yonchu Jenkins, Peppi Prasit, Thomas Walter Dubensky, Sam H. Whiting, Kyriakos P. Papadopoulos; University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA; Carolina BioOncology Institute, Huntersville, NC; Stephenson Cancer Center, OUHSC and Sarah Cannon Research Institute, Nashville, TN; Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN; START Midwest, Grand Rapids, MI; University of Michigan, Ann Arbor, MI; Tempest Therapeutics, South San Francisco, CA; START San Antonio, San Antonio, TX

Background: Prostaglandin E2 (PGE2) is a bioactive lipid that promotes cancer through diverse mechanisms including stimulating tumor proliferation, enhancing angiogenesis and suppressing immune function in the tumor microenvironment. PGE2 produced by tumor cells through upregulation of cyclooxygenase-2 (COX-2) is also a key mediator of adaptive resistance to immune checkpoint inhibitor therapy. While PGE2 signaling is important in cancer, how best to inhibit PGE2 for cancer treatment is under investigation. Inhibition of COX enzymes (e.g., with NSAIDS) has shown promise in large observational studies, but inconsistent results in prospective studies. Importantly, COX inhibition alters multiple prostanoids beyond PGE2, resulting in toxicity that limits therapeutic dosing for cancer. PGE2 signals through four receptors, EP1-4, that are variably expressed and have distinct activities. The tumor promoting and immunosuppressive activities of PGE2 predominantly arise from signaling through the EP2 and EP4 receptors, while signaling through the EP1 and EP3 receptors generally is pro-inflammatory. TPST-1495 is designed to be an oral, highly specific, antagonist of the EP2 and EP4 receptors, sparing the EP1 and EP3 receptors and the COX enzymes. Preclinical studies suggest that blocking EP2 and EP4 with TPST-1495 inhibits tumor proliferation and stimulates anti-cancer immunity better than inhibiting all 4 receptors together, the EP2 or EP4 receptors singly, or the upstream COX-2 enzyme. **Methods:** TPST-1495-001 is a first-in-human Phase 1 study (NCT04344795). In the Dose and Schedule Optimization Stage, the primary objectives are to characterize the safety and tolerability (including dose limiting toxicities) and determine the recommended phase 2 dose (RP2D) of TPST-1495 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors. Additional objectives include characterization of PK, PD, and evaluation of potential biomarkers, including through paired (pre- and on-treatment) tumor biopsies. Monotherapy dose-finding employs a modified 3+3 design evaluating BID and QD TPST-1495 schedules along with continuous or intermittent (Days 1-5 every 7 days) dosing. For the pembrolizumab combination, the starting dose and schedule of TPST-1495 are determined by safety, PK and PD of monotherapy. Indication-specific Expansion Stage cohorts will evaluate TPST-1495 at the selected RP2D and schedule for both monotherapy and combination in endometrial cancer, squamous cell carcinoma of the head and neck, and microsatellite stable colorectal cancer (combination only), as well as in a biomarker-specific cohort enrolling patients with pathogenic tumor PIK3CA gene mutation. Dose and Schedule Optimization enrollment (monotherapy and combination) is ongoing at abstract submission while Expansion Stages are planned after identification of the RP2Ds. Clinical trial information: NCT04344795. Research Sponsor: Tempest Therapeutics.

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TPS2697 **Poster Session**

A first-in-human, multicenter, phase 1/2, open-label study of XTX202, a masked and tumor-selective recombinant human interleukin-2 (IL-2) protein, in patients with advanced solid tumors.

Meredith McKean, John D. Powderly, Meghan Duncan, Teleen Norman, Ekta Patel, Jennifer O'Neil, George Lee, Katarina Luptakova, Howard E. Kaufman; Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; Carolina BioOncology Institute, Huntersville, NC; Xilio Therapeutics, Inc., Waltham, MA; Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: High-dose interleukin-2 (IL-2) has been approved in metastatic renal cell carcinoma (RCC) and metastatic melanoma, and can result in durable complete responses, including cures. Its use has been limited by life-threatening treatment-related multisystem toxicities, consisting mainly of vascular leak syndrome. XTX202 is a masked, tumor-selective IL-2 that is designed to be pharmacologically inactive in non-tumor tissue when circulating systemically and unmasked by matrix metalloproteases (MMPs) found preferentially in the tumor microenvironment (TME). XTX202 is expected, therefore, to achieve a wider therapeutic index resulting in increased efficacy and lower toxicity compared to existing non-tumor selective IL-2 based-therapies. The IL-2 domain of the XTX202 molecule is modified to reduce binding to the high-affinity IL-2 receptor while maintaining binding to the intermediate-affinity IL-2 receptor, thereby decreasing activation of regulatory T-cells relative to wild-type IL-2, while still activating effector T cells. A masking domain is designed to pharmacologically inactivate IL-2 until it is activated by MMPs that are enriched in the TME. Cleavage at a protease cleavage site in the XTX202 linker by MMPs results in an active IL-2 moiety when the masking domain is released. XTX202 is designed with the goal of producing a localized anti-tumor immune response and limiting exposure of the active form of XTX202 in non-tumor tissue. Preclinically, XTX202 exhibited tumor-selective activity in mice without peripheral toxicities in non-human primates [O'Neil et al. ASCO 2021]. **Methods:** XTX202-01 trial (NCT05052268) is a first-in-human Phase 1/2 study to determine a recommended Phase 2 dose of XTX202 (Phase 1) and to evaluate the efficacy of XTX202 monotherapy in patients with metastatic RCC and unresectable or metastatic melanoma (Phase 2). Patients with advanced solid tumors are eligible for Phase 1 and will receive XTX202 monotherapy administered every 21 days in an accelerated and standard 3+3 dose escalation design. Phase 2 will consist of 2 parts: Part 2a will enroll patients with metastatic RCC who have received a prior tyrosine kinase inhibitor therapy and have been treated and progressed on an anti-PD-1 therapy. Part 2b will enroll patients with unresectable or metastatic melanoma who have received immune-checkpoint therapy with an anti-PD-1 therapy and an anti-CTLA-4 therapy to determine the efficacy of XTX202 monotherapy in this population. Enrollment to the study began in January 2022. Clinical trial information: NCT05052268. Research Sponsor: Xilio Therapeutics.

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TPS2698 **Poster Session**

TAK-676 in combination with pembrolizumab after radiation therapy in patients (pts) with advanced non–small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), or squamous-cell carcinoma of the head and neck (SCCHN): Phase 1 study design.

Benjamin T. Cooper, Steven J. Chmura, Jason J. Luke, Stephen Lawrence Shiao, Reva K Basho, Wade Thomas Iams, David B. Page, Cong Li, Richard C. Gregory, Michael Shaw, Kristin Horn, John Gibbs, Vicky A. Appleman, Allison J. Berger, Adnan Abu-Yousif, Neil Lineberry, Kate Stumpo, Aymen Elfiky, Naamit Kurshan Gerber; Perlmutter Cancer Center, New York University School of Medicine, New York, NY; University of Chicago, Chicago, IL; University of Pittsburgh Medical Center, Pittsburgh, PA; Cedars-Sinai Medical Center, Los Angeles, CA; Vanderbilt University Medical Center, Nashville, TN; Providence Cancer Institute, Portland, OR; Takeda Development Center Americas, Inc. (TDCA), Lexington, MA

Background: The cyclic GMP-AMP Synthase (cGAS)–STimulator of INterferon Genes (STING) pathway is an important modulator of the innate immune system via induction of type I interferon (IFN-I). Cytosolic DNA generated as a result of tumor cell death following radiation therapy has been demonstrated to activate the cGAS-STING signaling axis resulting in antitumor immunogenicity. TAK-676 is a novel, synthetic STING agonist and it has been shown in preclinical studies to potently modulate the innate immune system and subsequently activate the adaptive immune system to produce antitumor responses. TAK-676 is designed for prolonged half-life in serum and enhanced tissue permeability compared with other STING agonists designed for intratumoral injection, allowing for systemic IV delivery with access to tumor sites and lymphatic tissue. IFN signaling impairment has been linked to checkpoint inhibitor (CPI) resistance in tumors. Treatment with TAK-676 after radiation therapy has the potential to stimulate T cell-mediated antitumor immunity via STING-mediated IFN-I release, particularly when used with anti-PD-1/PD-L1 therapies. Preclinical data support the addition of STING agonists to reverse resistance in tumors with prior exposure to CPIs. TAK-676 is being investigated (+/- pembrolizumab) in an ongoing first-in-human phase 1 study (NCT04420884). Here, we describe another phase 1 trial to investigate the safety and preliminary antitumor activity of TAK-676 plus pembrolizumab following radiation therapy in pts with advanced or metastatic NSCLC, TNBC, or SCCHN (NCT04879849). **Methods:** Adult pts with progressive disease (PD) following CPI treatment and who have ≥2 lesions, 1 of which can be targeted with radiation, are being enrolled. Pts receive 8 Gy x 3 fractions of image-guided radiation followed (after ≥40 hours) by IV pembrolizumab 200 mg on day 1 plus escalating doses of IV TAK-676 on days 1, 8, and 15 of a 21-day cycle. TAK-676 dose escalation is guided by the Bayesian optimal interval design. Pts receive TAK-676 plus pembrolizumab until PD, intolerance to treatment, or withdrawal. Pts enrolled at TAK-676 dose levels shown to have pharmacodynamic activity, and who have a safely accessible lesion outside the radiation field, will have paired biopsies collected at screening and between days 15 and 21 of cycle 1. The primary objective is to determine the safety and tolerability of TAK-676 plus pembrolizumab following radiation therapy; secondary objectives are to establish the recommended phase 2 dose of TAK-676 plus pembrolizumab following radiation therapy, and to assess preliminary antitumor activity both locally (within the radiation field) and systemically (non-radiated lesions). As of February 2022, we have enrolled ~10% of the planned pts. Clinical trial information: NCT04879849. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA).

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TPS2699 **Poster Session**

Phase 2 study of the IDO/PD-L1-targeted immune-modulatory vaccine, IO102-IO103, plus pembrolizumab as first-line treatment for metastatic non–small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), or urothelial bladder cancer (UBC).

Jonathan W. Riess, Paul Shaw, Devraj Srinivasan, Pilar Garrido, Jacqueline Vuky, Marya F. Chaney, Shane O'Neill, Alireza Alavi, Diane Opatt McDowell, Eva Ehrnrooth, Ezra Cohen; University of California Davis Comprehensive Cancer Center, Sacramento, CA; Velindre Cancer Centre, Cardiff, United Kingdom; Edinburgh Cancer Centre, Edinburgh, United Kingdom; Hospital Universitario Ramon y Cajal, Madrid, Spain; Oregon Health & Science University, Portland, OR; Merck & Co., Inc., Kenilworth, NJ; IO Biotech, Copenhagen, Denmark; University of California, San Diego, CA

Background: Immunotherapy has transformed the treatment of NSCLC and other solid tumors, such as SCCHN and UBC. However, even with standard-of-care anti-PD-1/PD-L1 therapies, few patients achieve durable benefit even when PD-L1 is overexpressed. IO102-IO103 is a potentially first-in-class, dual-antigen, immune-modulatory therapy that stimulates T cells to target tumoral immune escape via key checkpoint molecules IDO and PD-L1. It is thought that activating IDO/PD-L1-specific T cells in cancer patients through vaccination may support anticancer immunity by restricting immunosuppressive signaling and restoring the tumor immune microenvironment to render the tumor more susceptible to anti-PD-1 blockade. Thus there is a rationale for combining IO102-IO103 with anti-PD-1 therapy in the first-line treatment of metastatic tumors, such as NSCLC, SCCHN, or UBC. Combined IO102-IO103 and anti-PD-1 therapy (nivolumab) has already shown a robust signal of clinical activity (overall response rate [ORR], 80%; complete response rate [CRR], 43%; median progression-free survival [PFS], 26 months) and was well tolerated with minimal added toxicity to nivolumab in a Phase 1/2 study of anti-PD1-naïve patients with metastatic melanoma (Kjeldsen, et al. Nat Med 2021). **Methods:** This is a Phase 2, international, multicenter (US and Europe), non-comparative, open-label, multi-arm (basket) trial (EudraCT No. 2021-003026-69; ClinicalTrials.gov No. NCT05077709). Patients with recurrent, unresectable or metastatic solid tumors in 3 indications and no prior treatments for metastatic disease are being enrolled: NSCLC with a PD-L1 Tumor Proportion Score (TPS) ≥50% (Arm A); SCCHN with PD-L1 Combined Positive Scores (CPS) ≥20 (Arm B); or UBC with PD-L1 CPS ≥10 and not eligible for platinum-containing chemotherapy (Arm C). All patients, ~30 in each arm, will receive 3-week cycles of IO102-IO103 (85-85 μg on Day [D] 1 and 8 of Cycle 1 and 2, and D1 thereafter) subcutaneously plus pembrolizumab (200 mg on D1) intravenously, for up to 2 years. Primary endpoints are ORR by RECIST v1.1 or 6-month PFS rate by investigator assessment (to be analyzed either 6 months after last patient started treatment or after target ORR is achieved, whichever is earliest). Secondary endpoints include PFS, duration of response, complete response rate, disease control rate, time to response, overall survival, and safety. Exploratory endpoints include biomarker and immune marker correlative studies, and PFS by iRECIST. The trial will assess the opportunity for a positive risk–benefit based on 2 efficacy boundaries for the ORR and 6-month PFS rate in each arm, with cohort expansion permitted if a clinically relevant efficacy signal is observed. Clinical trial information: EudraCT No. 2021-003026-69; ClinicalTrials.gov No. NCT05077709. Research Sponsor: IO Biotech ApS & Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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TPS2700 **Poster Session**

A first-in-human, phase I, open-label study of a novel cancer vaccine labvax 3(22)-23 and adjuvant GM-CSF in patients with advanced stage adenocarcinomas.

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Background: Adenocarcinoma is the most common histologic type of solid tumors and can arise from almost anywhere in the body. Labyrinthin is a novel tumor-specific protein expressed on the cell surface of the majority of adenocarcinomas of various cancer types. Several therapeutic strategies targeting labyrinthin are under development. We hypothesize that vaccination against labyrinthin can elicit strong immune responses against the labyrinthin-positive adenocarcinomas in cancer patients. LabVax 3(22)-23 is a novel anti-tumor vaccine that contains 4 synthetic labyrinthin-based peptides designed to elicit both B-cell and T-cell responses. Sargramostim, a recombinant granulocyte macrophage colony-stimulating factor (GM-CSF), is given as an immunostimulator with LabVax 3(22)-23 to boost the antitumor immune response. Preclinical studies showed that LabVax 3(22)-23 significantly inhibited tumor growth that was augmented by GM-CSF without any significant toxicity in C57/BL6 transgenic mice expressing human PD-1/PD-L1 implanted with the murine colon adenocarcinoma cell line MC-38-huPD-L1. This single institution, first-in-human, phase I trial (UCDCC#296) evaluates LabVax 3(22)-23 and adjuvant sargramostim in patients with labyrinthin-positive metastatic or recurrent adenocarcinoma of any primary tumor site after all standard-of-care therapies. **Methods:** The primary objective is to assess the toxicity of LabVax 3(22)-23 and adjuvant sargramostim according to NCI CTCAE V5.0. The primary endpoint is dose limiting toxicity (DLT), which is defined as grade $\geq$ 2 allergic and autoimmune reaction, grade $\geq$ 3 injection site reaction, any grade 3 toxicities lasting >1 week, or any grade $\geq$ 4 toxicities. With a sample size of 10 patients, there is 89-97% of chance to observe $\geq$1 DLT if the true event rate is 20-30%. A secondary endpoint is the preliminary assessment of tumor response rate by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Exploratory objectives measure the effect of LabVax 3(22)-23 on various immune responses (cytokines, anti-labyrinthin antibody production) and the correlation between the level of labyrinthin expression and the efficacy of LabVax 3(22)-23. Eligible patients are required to have labyrinthin expression on their tumor cells by immunohistochemistry and adequate organ function. Patients receive sargramostim subcutaneously and LabVax 3(22)-23 intradermally on weeks 1, 2, 4, 8, and 12 in the absence of disease progression or unacceptable toxicity. After completion of study treatment, patients are followed every 3 months for 1 year. Two patients are enrolled at the time of submission. Clinical trial information: NCT05101356. Research Sponsor: UC Davis Comprehensive Cancer Center, Pharmaceutical/Biotech Company.

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TPS2701 **Poster Session**

First-in-human phase 1 trial of ELI-002 immunotherapy as treatment for subjects with Kirsten rat sarcoma (KRAS)-mutated pancreatic ductal adenocarcinoma and other solid tumors.

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Background: Mutations in KRAS and NRAS occur in one quarter of human solid tumors. The G12D allele is the most commonly occurring variant in pancreatic, colorectal, non-small cell lung, ovarian, biliary and gallbladder cancers. ELI-002 2P is an immunotherapeutic comprised of a lymph-node targeted amphiphile (AMP)-modified G12D and G12R mutant KRAS peptides together with an AMP-modified CpG oligonucleotide adjuvant. In preclinical models, ELI-002 demonstrated increased cytotoxic KRAS-specific T cells compared to non-lymph node targeted controls using the same peptide and adjuvant. Clinical evaluation of adoptively transferred KRAS-specific T cells demonstrated objective antitumor activity (Tran 2016). Circulating tumor (ctDNA) methodology permits identification of patients with minimal residual disease (MRD) following locoregional treatment. In MRD setting, immunotherapy is anticipated to succeed as the ratio of effector T cells to target tumor cells is maximized prior to bulk visible disease. The AMPLIFY-201 study (NCT04853017) is evaluating ELI-002 in patients with KRAS mutated solid tumors with MRD. **Methods:** AMPLIFY-201 is an open-label, dose-escalation and expansion phase I, first in human, trial evaluating ELI-002 2P in patients with KRAS mutated tumors with MRD following standard of care therapy. The initial phase I cohort enrolls patients with colorectal and pancreatic cancer to receive multiple doses of AMP-peptides 70mcg each (1.4 mg total) admixed with AMP-CpG 0.1 mg, administered once every two weeks. Subsequent phase I cohorts will enroll patients with RAS-mutated pancreatic, colorectal, non-small cell lung, ovarian, bile duct or gallbladder cancer, who will receive a fixed dose of AMP-peptides 70 mcg each, together with escalating doses of AMP-CpG. Safety and efficacy will be summarized with descriptive statistics. The maximum tolerated dose (if any) and the recommended phase II dose (RP2D) will be determined with the dose-response activity of ELI-002 2P in eliciting functional KRAS-specific T cells. Preliminary antitumor activity will be characterized using changes from baseline in ctDNA, serum biomarkers appropriate for tumor type, and progression free survival time. Eligibility includes patients who have received standard of care locoregional treatment according to NCCN guidelines and whom have MRD persistence or relapse (ctDNA positive). Patients with colon and pancreas cancer with Stage IV oligometastatic disease (< 3 lesions in one organ) rendered surgically free of disease and with MRD, are also eligible. The dose escalation portion of the study is currently enrolling. Clinical trial information: NCT04853017. Research Sponsor: Elicio Therapeutics.

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TPS2702 **Poster Session**

A phase 1 dose-finding and dose-expansion study evaluating the safety, tolerability, pharmacokinetics, and efficacy of a highly selective WEE1 inhibitor (Debio 0123) in adult patients with advanced solid tumors.

Kyriakos P. Papadopoulos, Manish Sharma, Reinhard Dummer, Esteban Rodrigo Imedio, Marie-Laurence Yge, Sandrine Micallef, Anne Bellon, Anastasios Stathis; START San Antonio, San Antonio, TX; START Midwest, Grand Rapids, MI; Universitätsspital Zurich, Dermatologische Klinik, Zurich, Switzerland; Debiopharm International SA, Lausanne, Switzerland; IOSI-Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Background: Debio 0123 is an oral, highly selective inhibitor of the tyrosine kinase WEE1. WEE1 is a key regulator of cell cycle progression that modulates the activity of CDK1 (CDC2), influencing entry into mitosis. WEE1 inhibition results in G2 checkpoint abrogation, triggering mitosis with unrepaired DNA leading to cell death. *In vitro* and *in vivo* tumor models have shown Debio 0123 antitumor activity. Continuous exposure seems to be needed to maximize monotherapy efficacy in preclinical models. Preliminary data from an ongoing phase 1 study of intermittent Debio 0123 combined with carboplatin, showed a manageable safety profile, and signals of antitumor activity in patients (pts) with advanced solid tumors. We present the design of a phase 1 study (NCT05109975) of continuous Debio 0123 administered as a single agent in pts with advanced solid tumors. **Methods:** The study comprises a dose escalation part and a dose expansion part. The primary objective of the dose escalation part of the study is to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of continuous Debio 0123 monotherapy in adults with previously treated advanced solid tumors. Key secondary objectives include characterization of safety and tolerability, pharmacokinetics (PK), and preliminary antitumor activity (overall response rate [ORR]). Key inclusion criteria are histologically or cytologically confirmed locally advanced or metastatic solid tumors, and ECOG-PS 0 or 1. Key exclusion criteria are asymptomatic or unstable brain metastases, history of cardiac disorders, inability to swallow oral medication or abnormalities affecting drug absorption. Approximately 30 dose-limiting toxicity (DLT)-evaluable pts are anticipated to be enrolled based on an escalation with overdose control (EWOC) approach for 21-day treatment cycles. When the pts of each cohort become evaluable, a safety monitoring committee will review safety and tolerability and based on EWOC recommendations will decide the next dose level or will declare the MTD and/or RP2D. Pharmacodynamic biomarkers will be correlated with tumor response and/or PK. The dose-expansion part may start after MTD and/or RP2D determination. The primary objective of this part will be to characterize the safety and tolerability (e.g. percentage of pts with DLTs, serious adverse events or discontinuations) of Debio 0123 monotherapy at the MTD/RP2D, and to evaluate the anti-tumor activity (ORR) in pts with selected recurrent/progressive solid tumors. Key inclusion criteria are measurable disease per RECIST 1.1 and specific tumor types. Based on a Simon 2-stage design, up to 34 pts per tumor type cohort may be enrolled. Currently accrual to the dose escalation is ongoing in the United States and Switzerland. Clinical trial information: NCT05109975. Research Sponsor: Debiopharma International SA.

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TPS2703 **Poster Session**

CAIRE: A basket multicenter open-label phase 2 study evaluating the EZH2 inhibitor tazemetostat in combination with durvalumab in patients with advanced solid tumors.

Antoine Italiano, Nicolas Isambert, Jean-Philippe Metges, Maud Toulmonde, Sophie Cousin, Simon Pernot, Mariella Spalato, Thomas Grellety, Celine Auzanneau, Barbara Lortal, Michèle Kind, François Le Loarer, Sabrina Sellan-Albert, Carine A. Bellera; Institut Bergonié, Bordeaux, France; Service d'Oncologie Médicale, CLCC Georges-François Leclerc, Dijon Cedex, France; CHU Brest–Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; Institut Bergonié, Department of Medical Oncology, Bordeaux, France; Department of Medical Oncology, Institute Bergonié Cancer Center, Bordeaux, France; Institut Bergonié, Department of Imaging, Bordeaux, France; Institut Bergonie, Bordeaux, France; Institut Bergonié, Clinical and Epidemiological Research Unit, Bordeaux, France

Background: Recent studies have shown shown that genetic depletion of EZH2 in Tregs (using FoxP3-creEZH2fl/fl mice) and pharmacological inhibition of EZH2 elicits phenotypic and functional alterations of Tregs, leading to an effector-like T cell profile. Further, EZH2 inhibition enhances the cytotoxicity of human Teffs in vitro and the proportion of tumor-infiltrating cytotoxic T cells in vivo in murine models. It has been shown that immune checkpoint inhibition (ICI) increases EZH2 expression in human T cells across various tumor types and that increased EZH2 expression in T cells inversely correlate with clinical outcome. Upregulation of EZH2 mediated by immune checkpoint inhibition in T cells modulates T cell responses and diminishes the effectiveness of immunotherapy. Consistent with this mechanism, pharmacologic inhibition of EZH2 has been shown to increase effector-like T cell responses and enhances effectiveness of immune checkpoint therapy in tumor-bearing mice [16-17]. Our group also reported first clinical data from a participant with sarcoma showing strong T cell infiltration after treatment with tazemetostat (Italiano et al Lancet Oncol 2018). Altogether, these findings pave the way for clinical trials combining ICI with the specific EZH2 inhibitor, tazemetostat in solid tumors. **Methods:** CAIRE (NCT04705818) is a multi-cohort, four single-arm phase 2, multicenter, open-label study investigating tazemetostat combined with durvalumab in patients with advanced cancers: pancreatic adenocarcinoma (cohort A), microsatellite stable colorectal cancer (cohort B), solid tumors with presence of tertiary lymphoid structures (assessed centrally) (cohort C), soft-tissue sarcomas (cohort D). Cohort A will enroll ~32 patients and cohorts B, C and D ~47 patients respectively. Eligible patients must have no standard treatment options available or a contraindication to standard treatment options, and ECOG PS 0–1. Patients with prior exposure to EZH2 inhibitor and/or PD1/PDL1 monoclonal antibodies are excluded. Tazemetostat will be administered per-os, twice daily (800 mg x 2), continuously. Treatment by Tazemetostat will start on Day 1 (of cycle 1). Durvalumab will be administered by intravenous infusion (1120 mg) on day 1, every 3 weeks. Treatment by Durvalumab will start on Day 1 of cycle 2. The primary endpoints are disease control rate within 24 weeks of treatment as per RECIST 1.1 in cohort A and B; objective response rate within 24 weeks of treatment as per RECIST 1.1 in cohort C, and 6-months non progression rate for cohort D. Secondary endpoints include adverse events (AEs)/serious AEs, duration of response, and progression-free survival. Pharmacodynamic and other biomarkers will be explored. The first patient received study drug on July, 30, 2022 and 1 site across France are currently enrolling patients. Clinical trial information: NCT04705818. Research Sponsor: Astra Zeneca, Other Government Agency.

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TPS2704 **Poster Session**

A phase 1 trial of RP2, a first-in-class, enhanced potency oncolytic HSV expressing an anti-CTLA-4 antibody as a single agent and combined with nivolumab in patients with advanced solid tumors.

Kevin Joseph Harrington, Joseph J. Sacco, Anna Claire Olsson-Brown, Tze Y Chan, Pablo Nenclares, Isla Leslie, Imran Saleem, Praveen Bommareddy, Christoph Matthias Ahlers, Robert S. Coffin, Mark R. Middleton; The Royal Marsden//The Institute of Cancer Research NIHR Biomedical Research Centre, London, United Kingdom; University of Liverpool, Liverpool, United Kingdom; Clatterbridge Cancer Centre, Liverpool, United Kingdom; Royal Liverpool University Hospital, Liverpool, United Kingdom; The Institute of Cancer Research, London, United Kingdom; Royal Marsden NHS Foundation Trust, London, United Kingdom; Replimune, Woburn, MA; Replimune Inc, Woburn, MA; Replimune Group Inc, Woburn, MA; Biovex LTD, Abingdon Oxon, United Kingdom; Churchill Hospital, Oxford, United Kingdom

Background: RP2 is a selective replication-competent herpes simplex virus 1 (HSV-1) that contains a codon-optimized sequence for human granulocyte-macrophage colony-stimulating factor (GM-CSF), the gibbon ape leukemia virus surface glycoprotein (GALV-GP) with the R- sequence deleted (R-), GM-CSF, and an anti–cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody-like molecule. These modifications are intended to increase oncolytic potency, cell-to-cell spread, tumor antigen release, and systemic anti-tumor immune activation. RP2 has demonstrated antitumor activity in preclinical models using viruses similar to RP2 expressing murine versions of anti-CTLA-4 and GM-CSF, both alone and in combination with PD1-1 blockade. **Methods:** This is a Phase 1 multicenter, open-label, study evaluating RP2 ± nivolumab (NCT04336241). Part 1 evaluated escalating doses of monotherapy RP2 with a modified 3 + 3 design. Patients (pts) received intratumoral (IT) injections of up to 10 mL of RP2 into superficial or visceral tumors Q2W x5 across two dose levels (DL1: 10^5 plaque-forming units (PFU)/mL once, then followed by 10^6 PFU/mL x4; DL 2: 10^6 PFU/mL once, then followed by 10^7 PFU/mL x4). The recommended Phase 2 dose of RP2 was identified as 10^6 PFU/mL once, followed by subsequent doses of 1×10^7 PFU/mL. In Part 2, up to 60 evaluable pts will be enrolled, including 30 pts in Cohort 2a and 30 in Cohort 2b. Cohort 2a was designed to evaluate the safety and antitumor activity of the combination in pts with solid tumors, and is fully enrolled. Cohort 2b is open for enrollment of pts with advanced or metastatic uveal melanoma, NSCLC, breast cancer, head and neck cancer or GI cancers (NSCLC, breast or GI cancers must have at least one liver tumor suitable for injection). Pts in Part 2 receive intra-tumoral RP2 at the RP2D Q2W for up to 8 doses in combination with 240 mg nivolumab IV Q2W or 480 mg nivolumab IV Q4W for up to two years from the first RP2 dose. In Part 3 (not yet open for enrollment), up to 15 evaluable pts are able to be enrolled to evaluate RP2 monotherapy including at least 10 pts with NSCLC, breast or GI cancers with at least one liver tumor suitable for injection. Re-initiation of up to 8 additional RP2 doses is permitted if prespecified criteria are met. Pts are dosed with RP2 by direct visualization or ultrasound-guided injection into superficial, subcutaneous, or nodal tumors and by image-guided injection into deeper lesions, including visceral lesions. Key inclusion criteria include histologically confirmed advanced or metastatic non-neurological solid tumors, at least one measurable and injectable tumor of diameter $\geq$1 cm, ECOG $\leq$1, and adequate hematologic, hepatic, and renal function. Exclusion criteria include prior treatment with oncolytic viruses, acute or chronic hepatitis B or C infection, and HIV infections. Clinical trial information: NCT04336241. Research Sponsor: Replimune Group Inc.

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TPS2705 **Poster Session**

An open-label, multicenter, phase 1 study of RP3 as a single agent and in combination with nivolumab in patients (pts) with solid tumors.

Kevin Joseph Harrington, Antonio Rullan, Louise Deighton, Joao Barata, Henry Castro, Christoph Matthias Ahlers, John McRae, Praveen Bommareddy, Robert S. Coffin, Mark R. Middleton; The Royal Marsden//The Institute of Cancer Research NIHR Biomedical Research Centre, London, United Kingdom; The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, United Kingdom; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Replimune Group Inc, Woburn, MA; Replimune Group Inc, Replimune Group Inc, MA; Replimune Inc, Woburn, MA; Biovex LTD, Abingdon Oxon, United Kingdom; Churchill Hospital, Oxford, United Kingdom

Background: RP3 is a genetically modified herpes simplex virus 1 (HSV-1) that contains insertions for the gibbon ape leukemia virus surface glycoprotein (GALV-GP) with the R- sequence deleted (R-), an anti–cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody-like molecule, CD40 ligand, and 4-1BB ligand. Together, these insertions are expected to increase oncolytic potency, cell-to-cell spread, immunogenic cell death, and systemic immune activation. RP3 has demonstrated antitumor activity in preclinical models using viruses similar to RP3 expressing murine versions of anti-CTLA-4, CD40L, and 4-1BBL both alone and in combination with PD1-1 blockade. **Methods:** This is an open-label, multicenter, Phase 1 study evaluating RP3 as monotherapy or in combination with nivolumab (nivo) in patients (pts) with solid tumors (NCT04735978). Part 1 evaluated escalating doses of RP3. Pts in Part 1 received IT injections of up to 10 mL RP3 into superficial, nodal, or visceral lesions Q2W x 5 across two dose levels (DL1: 10^5 plaque-forming units (PFU)/mL once, then 10^6 PFU/mL x 4; DL2: 10^6 PFU/mL once, then 10^7 PFU/mL x4). The RP2D is 10^6 PFU/mL once, followed by 10^7 PFU/mL IT Q2W. In Part 2, pts are being enrolled into expansion cohorts of 45 patients with GI (including HCC), lung, breast, and squamous cell carcinoma of the head and neck treated with RP1 combined with nivo. Additional cohorts will enroll patients treated with RP3 followed by nivo, RP3 monotherapy to further explore biomarkers in injected and uninjected tumors, and with the potential to also open a cohort in melanoma. Pts in both Part 1 and Part 2 may receive up to 8 additional doses of RP3 if protocol-specified criteria are met. Key inclusion criteria: confirmed advanced or metastatic non-neurological solid tumors, at least one measurable tumor $\geq$ 1 cm and injectable tumors $\geq$ 1 cm in aggregate, ECOG $\leq$1, and adequate hematologic, hepatic, and renal function. In Cohorts 1, 2, and 4, approximately 50% of the pts with lung, breast, and GI cancer must have liver lesions intended for injection. Exclusion criteria include prior oncolytic virus treatment, need for immunosuppressive therapy, an autoimmune disease requiring systemic therapy, active significant herpetic infections or prior complications of HSV-1 infection, active or chronic HBV or HCV infection, known HIV infection, or prior active malignancy within 3 years. Clinical trial information: NCT04735978. Research Sponsor: Replimune.

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