EMITT-1: Clinical and pharmacodynamic activity with the oral ERAP1 inhibitor GRWD5769 and cemiplimab in 6 completed phase 1b expansion cohorts in solid tumors with anti–PD-1 resistance or MSS-CRC.

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Background: Resistance to anti-PD-1 therapy remains a major unmet need. GRWD5769 is a first-in-class oral Endoplasmic Reticulum Amino Peptidase 1 inhibitor (ERAP1i) that modulates tumor antigen presentation on MHC-I. Dosing GRWD5769 Q3W on/off generates 2 alternating antigen repertoires (AgR) that could both broaden T cell responses and avoid T cell exhaustion from chronic tumor antigen exposure. We report clinical and translational results from 6 completed stage 1 expansion cohorts of combination GRWD5769 with cemiplimab in patients (pts) with secondary resistance to anti-PD1 and in MSS-CRC (NCT06923761). **Methods:** Pts with NSCLC, Urothelial (UC), HCC, Cervical & SCCHN with secondary resistance to ≥3 month 1st line aPD-1 or MSS-CRC without liver mets received 400 mg BD GRWD5769 and cemiplimab. ORR, Durable Clinical Benefit (DCB; defined as CR, PR or SD lasting ≥6 months) and PFS were assessed. T cell repertoire and immune phenotype changes were evaluated longitudinally. **Results:** All 6 cohorts are fully recruited (n= 81) with median follow up of 6.0 months at this interim analysis. Durable responses were observed in all cohorts (Table 1) with ORR 10-33%; DCB 26-57%. Median PFS ranged from 1.9-7.5 months across evaluable cohorts. Therapy was well tolerated with no observed safety signals. imARs were reported in 12 pts, with only 1 ≥Gr3 event (immune hepatitis) which required drug discontinuation. ≥Gr3 TRAEs occurred in 3% of pts. TCR repertoire diversity increased substantially in pts who achieved clinical benefit, driven by expansion of low-frequency, putative *de novo* TCR clonotypes. Responders exhibited cyclical Vß gene-usage dynamics indicative of broad T cell clonal expansion and contraction, consistent with AgR shifts resulting from ERAP1i. Dynamic activation of T cell associated genes further supported antigen-driven T-cell remodelling. **Conclusions:** GRWD5769 with cemiplimab demonstrated broad, durable activity across all 6 phase 1b expansion cohorts in pts with ≥2 prior lines of therapy and secondary anti-PD-1 resistance, or MSS-CRC. Translational analyses suggest that GRWD5769 exerts a dual mechanism of action, both reprogramming antigen-experienced T cells and inducing *de novo* T cell responses, in keeping with its potential to address both primary and secondary resistance to anti-PD-1 therapy. Based on the efficacy and tolerability of the combination, stage 2 cohort expansions are now ongoing, to inform a randomized Phase 2 study. Clinical trial information: NCT06923761. Research Sponsor: Greywolf Therapeutics.

Summary of expansion cohort efficacy by iRECIST.

	Dosed n	Evaluable* n	ORR % confirmed	ORR % unconfirmed	DCB %	PFS m
NSCLC	14	14	14	21	54	7.5
UC	14	12	25	33	44	2.1
HCC	15	14	14	14	32	3.9
MSS-CRC	12	7	29	29	57	2.1
SCCHN	11	7	14	14	26	3.7
Cervix	15	10	10	10	-	1.9

Data snapshot Jan 26, update for presentation.
*≥1 scan or PD or death before 1st scan.

Re-sensitizing PD-1/PD-L1 relapsed/refractory solid tumors: Phase 1a results of IOS-1002, a LILRB1/2 and KIR3DL1 checkpoint inhibitor, in combination with pembrolizumab.

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Background: Despite anti-PD-1/PD-L1 therapy success, 60-70% of patients develop progression with limited options (ORR 6-8% to retreatment). Upregulation of inhibitory receptors LILRB1/2 and KIR3DL1 mediates immune escape in anti-PD-1/PD-L1-resistant tumors. IOS-1002, a novel LILRB1/2 and KIR3DL1 antagonist, restores anti-tumor immunity when combined with pembrolizumab. **Methods:** Open-label, multicenter, dose-escalation Phase 1a study (NCT05235308) evaluated IOS-1002 (300-1800mg, Q2W IV) plus pembrolizumab 400mg (Q6W IV) in advanced solid tumors progressing on prior anti-PD-1/PD-L1 therapy. Primary endpoints: safety, tolerability; secondary: ORR, DCR, duration of response (DOR). Comprehensive biomarker analysis included serial cytokine profiling, target receptor expression (LILRB1/2, KIR3DL1), and tumor immune score (TIS) by gene expression analysis. Responses were assessed by RECIST v1.1. **Results:** As of January 1st, 2026, 28 patients received combination treatment with 16 anti-PD-1/PD-L1-relapsed/refractory patients (median age 65, ECOG 0-1). 3 confirmed PRs (tumor reduction -35% to -58% from baseline) leading to an ORR of 20% (3/15 evaluable) were noted with a DCR of 54% at week 12 (7/13) and 40% at week 24 (4/10), respectively. Durable responses included: 1 metabolic CR (urothelial cancer), 1 pathological CR confirmed by repeat biopsy showing absence of viable tumor cells (cutaneous SqCC), and 1 cervical cancer patient achieving -29% tumor reduction with concomitant $>$ 90% decline in CA-125 tumor marker. Median treatment DOR was 30+ weeks (range 12-46+); 8 patients remain on treatment. Biomarker analysis demonstrated strong predictive value for TIS and target receptor expression achieving 75% ORR (3/4) versus 0% in dual-low patients (0/5). Combined biomarker score significantly correlated with depth of response (R^2 = 0.72, p = 0.008) and progression-free survival (HR 0.31, 95% CI 0.11-0.88, p = 0.04). Safety profile was favorable with no increase in grade≥3 immune-related adverse events beyond pembrolizumab monotherapy. **Conclusions:** IOS-1002 plus pembrolizumab demonstrated clinically meaningful efficacy in pretreated anti-PD-1/PD-L1-relapsed/refractory patients. Biomarker-driven patient selection using dual-high TIS and target receptor expression enhanced ORR to 75% and strongly predicted response depth, durability, and survival benefit. The favorable safety profile with no incremental immune-related toxicity, coupled with durable responses and high disease control rates, provides compelling rationale for Phase 1b expansion in biomarker-selected PD-1/PD-L1-refractory solid tumors. Clinical trial information: NCT05235308. Research Sponsor: None.

Endpoint	Result
ORR (evaluable)	20% (3/15)
DCR Week 12	54% (7/13)
DCR Week 24	40% (4/10)
Biomarker-selected ORR	75% (3/4)
Ongoing treatment	8/16 (50%)

DART (NCI/SWOG S1609): Comprehensive results from dual checkpoint inhibition with CTLA-4 and PD-1 blockade in rare cancers.

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Background: Rare tumors are underrepresented in clinical trials, though they collectively comprise an estimated 22% of all cancer cases. The NCI/SWOG S1609 trial evaluated efficacy signals across 53 rare cancer cohorts treated with dual CTLA-4 and PD-1 inhibition. **Methods:** A prospective, open-label, multicenter phase 2 trial of ipilimumab (1mg/kg intravenously every 6 weeks) plus nivolumab (240mg intravenously every 2 weeks) was conducted from 1/13/2017 to 3/15/2023. A statistical framework was established to evaluate each cohort in a two-stage design. The primary end point was objective response rate (ORR); progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR, ORR + stable disease >6 months), i-outcomes, and toxicity were secondary and exploratory endpoints. **Results:** 798 patients were enrolled and 727 eligible patients received treatment. 1,083 national (USA) sites opened the trial. Median (range) patient age was 60 (18-88) years; 344 (47%) patients were male. 24 of 53 cohorts (45%) demonstrated clinical activity, defined as ≥2 patients with confirmed response. Median (range) ORR was 12% (0-75%); CBR, 27% (0-75%). Median (range) 2-year PFS was 10% (0-75%); 3-year OS was 23% (0-100%). 6-month PFS was moderately correlated with 1- and 3-year OS (R^2 =0.61 and 0.54, respectively). Patients who attained an iOR versus OR had similar OS. 82 patients (11%) had iPFS ≥2 years. Treatment-related adverse events (AEs) of any cause and immune-mediated occurred in 603 (82.9%) and 465 (64.0%) patients. AEs led to treatment discontinuation in 102 patients (14.0%). Most common AEs were fever (38.1%), diarrhea (21.2%), and rash/pruritis (19.3%). 13 patients (1.8%) experienced treatment-related grade 5 AEs. Patients alive at 6 months who discontinued treatment due to immune-related AE had longer OS than those who discontinued for other reasons (p = 0.021). **Conclusions:** Patients with multiple rare cancer types derived meaningful response to ipilimumab plus nivolumab. Characterization of biologically defined subsets is underway to optimize therapeutic selection. Clinical trial information: NCT02834013. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180819; Bristol-Myers-Squibb.

Response among all cohorts and cohorts with iRECIST iClinical benefit rate (iORR+iSD>6 mos) ≥50%.

Cohort	*N*	iConfirmed response	iClinical benefit	iCR	iPR	6-month iPFS	2-year iPFS	1-year OS	3-year OS	Median iPFS (months)
All	**727**	**13%**	**29%**	**3%**	**10%**	**30%**	**12%**	**48%**	**24%**	**2.2**
Gestational trophoblastic disease	4	75%	75%	25%	50%	75%	75%	100%	100%	Not Reached
Basal cell carcinoma	17	35%	71%	0	35%	76%	24%	76%	53%	12.1
Chordoma	10	0	70%	0	0	80%	30%	80%	30%	13.1
Bronchoalveolar carcinoma lung	8	25%	62%	0	25%	62%	33%	88%	44%	8.3
Desmoid tumors	16	19%	62%	0	19%	73%	40%	100%	80%	19.3
Carcinomas of pituitary, thyroid, para-thyroid, adrenal cortex	19	21%	53%	0	21%	58%	26%	74%	42%	9.4
Fibromyxoma, low grade mucinous adenocarcinoma	10	0	50%	0	0	50%	0	60%	30%	5.7
Malignant giant cell tumors	6	0	50%	0	0	50%	33%	83%	50%	3.4

Desmocolin-3–directed immunotherapy in recurrent/metastatic head and neck squamous cell carcinoma.

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Background: Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) are aggressive tumors. In pre-treated R/M HNSCC observed response rates were 13.0% (nivolumab; CheckMate 141) and 14.6% (pembrolizumab; KEYNOTE- 040), with median PFS 2.0 months and 2.1 months, respectively. Desmocollin3 (DSC3) is a surface protein expressed by HNSCC. DSC3 directed immunotherapy (CADI-05) is useful in DSC3 expressing cancer like Squamous NSCLC, bladder cancer, and melanoma. This study evaluated its efficacy (ORR, PFS, OS) in DSC3 expressing R/MHNSCC. **Methods:** In this investigator initiated single-arm, study patients with RMHNSCC expressing DSC3 were recruited. Tumor infiltrating lymphocytes (TIL), PD-L1, and P16 were also evaluated. All patients received 0.1ml CADI-05 intradermally + intralesional (for fungating/discharging solid lesions were present) every 4 weeks. Additional treatment was administered as per PI discretion. All patients were followed up until disease progression, or death. **Results:** Between May 2024 and July 2025, 20 patients were enrolled (males 17, females 3). The mean age was 55 yrs (range 34-87 yrs). Primary sites included tongue 9, buccal mucosa 9. All had undergone two lines of therapy with a mean of 2.55. Of 20 patients, 15 had progressed on prior therapy (6 stage IVC). Baseline mean parameters were mean DSC3 TPS - 41%, (95% CI, 32.67 - 49.33), mean PD-L1 CPS 27 (95% CI,10.61 - 33.39), mean TIL 17% (95% CI ,10.43 - 23.57). All were HPV negative. Additional therapy received included EGFR TKI (15), EGFR mAb (2), oral metronomic therapy (1) and none (2). Disease control rate was 45% (9/20) with overall response rate (ORR) 35% [7/20; 2 CR and 5 PR]. At a median follow-up of 155 days, mean (median) PFS and overall survival were 165 (115) and 197 (155) days, respectively. Mean (median) duration of response was 280 (332) days with 8 patients alive at the last follow up. This is significantly better than achieved with current therapies. Responders had higher DSC3 expression compared to non-responders (mean DSC3 50% vs 29%; p= 0 .002537). ORR was higher in patients with Stage IVA (57%) compared to IVC (20%) DSC3 TPS was higher than PD-L1 CPS in all patients with disease control. TIL and PD-L1 levels were not correlated with response. Injection site ulcer was the only side effect seen in 8 (40%), which include 6 (75%) of the responders. No systemic adverse events were observed. **Conclusions:** DSC3 targeted immunotherapy was safe and improved outcomes in pre-treated R/M HNSCC expressing DSC3, with disease control rate 45%, response rate 35%. Median duration of response was 332 days with median PFS and OS of 115 and 155 days, respectively. Research Sponsor: None.

RP2 oncolytic immunotherapy alone and in combination with nivolumab (nivo) in patients with advanced solid tumors: Final safety, efficacy, and biomarker results from the phase 1 first-in-human (FIH) study.

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Background: RP2 is an HSV-1-based oncolytic immunotherapy expressing a fusogenic glycoprotein (GALV-GP-R$^-$), human GM-CSF, and a human anti–CTLA-4 antibody. We present final safety, efficacy, and biomarker data from the FIH study of RP2 in patients (pts) with advanced solid tumors (NCT04336241). **Methods:** Enrolled pts had advanced/metastatic solid tumors with ≥1 measurable, injectable lesion (≥1 cm) and had progressed following, or could not tolerate, available standard therapy. Pts received RP2 monotherapy via intratumoral injection in dose escalation (Part 1; 5 doses Q2W). Pts in Parts 2 (RP2 + nivo) and 3 (RP2 monotherapy) received up to 8 doses of RP2 (Q2W × 8 or Q2W × 4 followed by Q4W × 4 doses) at the RP2D. In Part 2, nivo was administered starting at Cycle 2 or 4 for ~20 to 22 months. Pts could receive an additional course of RP2 per protocol. **Results:** As of 01DEC2025, 85 pts (median age 59 y) were enrolled and treated in RP2 (n = 25) or RP2 + nivo (n = 60) cohorts. Tumor types included uveal or cutaneous melanoma (UM, n = 17; CM, n = 11); colorectal (n = 14), head and neck (n = 13), and pancreatic (n = 12) cancers; and sarcoma (n = 7); 42% of pts received prior immune checkpoint inhibitor treatment. All pts have completed treatment. Treatment-related adverse events (TRAEs) in > 10% of pts included pyrexia, chills, fatigue, influenza-like illness, hypotension, pruritus, and nausea. Grade ≥3 TRAEs occurred in 20% of pts (no single event occurred in > 2 pts). A majority of pts (58/85) received injections into deep/visceral lesions, mainly in liver and lung, which were well tolerated. Among pts with ≥1 post-baseline scan (75/85), the ORR was 17.3% (13/75; 1 unconfirmed) with a median DOR of 22.1 months and DCR (CR+PR+SD) of 44.0% (33/75). Responses occurred in 5/15 (33.3%) pts with UM. RP2 monotherapy resulted in confirmed responses in 4/21 (19%) pts (1 esophagogastric adenocarcinoma, 1 UM, 1 chordoma, 1 mucoepidermoid), with best overall response of CR and median DOR not reached. Tumor regression occurred in both injected and non-injected lesions, including all 3 pts with monotherapy responses with non-injected lesions. A robust intratumoral immune response with increased CD8+ T-cell infiltrates, PD-L1 upregulation, and inflammatory immune pathway activation were observed, as well as epitope spreading with novel virus- and cancer-associated T-cell clones. **Conclusions:** RP2 ± nivo treatment was well tolerated in pts with both superficial and deep visceral metastases. Durable responses were observed with RP2 monotherapy and RP2 + nivo in heavily pretreated pts with diverse tumors with evidence of systemic anti-tumor immune activity, including tumor reduction in distant non-injected lesions. This study supports the ongoing evaluation of RP2 in pts with UM (NCT06581406) and the planned evaluation in other solid tumors. Clinical trial information: NCT04336241. Research Sponsor: Replimune, Inc.

Phase 2 basket trial of precision TIL therapy for immunotherapy-resistant advanced cancers.

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Background: Adoptive cell therapy (ACT) using unselected autologous tumor-infiltrating lymphocytes (TIL) has demonstrated clinical activity in metastatic cutaneous melanoma, an immunotherapy-sensitive cancer with high tumor mutational burden (TMB). However, we recently demonstrated in metastatic uveal melanoma, a prototypic low-TMB, immunotherapy-resistant cancer, that efficacy of TIL ACT requires infusion of TIL with measurable anti-tumor reactivity. Thus, to extend TIL ACT to additional immunotherapy-resistant cancers, we developed *TILScore*, a pan-cancer in situ transcriptomic biomarker designed to preoperatively identify metastases enriched with clinically active TIL. Here we report initial results from a pilot phase 2 TIL therapy trial prospectively evaluating *TILScore* as a precision biomarker for immunotherapy-resistant cancers. **Methods:** This single-center phase 2 trial (NCT03935893) enrolled patients with treatment-refractory, locally advanced, recurrent, or metastatic cancers into ten histology-defined cohorts. After a feasibility run-in, metastases with core biopsy *TILScore* $>$ 0.248 were selected for TIL harvest and manufacturing. Patients received non-myeloablative lymphodepletion (NMA-LD) with cyclophosphamide and fludarabine, followed by infusion of TIL and high-dose interleukin-2. The primary endpoint was cohort-specific objective response rate (ORR) by RECIST v1.1 using a Bayesian basket design targeting ORR $>$ 20% as evidence of promising activity. **Results:** As of 1/17/2026, 19 patients received TIL therapy. Tumor types included pancreatic adenocarcinoma (PDAC, n = 7), leiomyosarcoma (n = 3), peritoneal mesothelioma (PeM, n = 2), and single cases each of non–small cell lung cancer, cervical squamous cell carcinoma (SCC), nasopharyngeal SCC, and melanoma subtypes (cutaneous, acral, mucosal, unknown origin). All had progression after frontline therapy, with a median of 5 prior metastatic treatments; 58% had received checkpoint blockade. Liver metastases were the most common TIL source (37%), followed by lung and soft tissue (32% each). Infusion products contained a median of 5.36E10 TIL with an even mix of CD4 and CD8 cells. Adverse events were consistent with NMA-LD and interleukin-2; no grade 5 events occurred. Among 18 evaluable patients, ORR was 33% (6/18) with cohort specific responses in PDAC (50%, 3/6: 1 CR, 2 PR), PeM (100%, 2/2: 1 CR, 1 PR), and melanoma of unknown origin (100%, 1/1: 1 CR). *TILScore* predicted clinical response with an area under the receiving operating characteristic curve of 0.806 (P = 0.041). **Conclusions:** *TILScore*-guided selection of metastases for TIL manufacturing is feasible and enables consistent generation of clinically active TIL in patients with immunotherapy-resistant cancers. Promising clinical activity in PDAC and PeM supports evaluation of this biomarker-driven TIL ACT approach in larger, histology-specific cohorts. Clinical trial information: NCT03935893. Research Sponsor: UPMC Enterprises Translational Sciences.

Initial phase 1 study results of NT-175 engineered T-cell therapy in *TP53* R175H–mutated unresectable advanced solid tumors.

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Background: *TP53* is the most frequently mutated tumor suppressor gene across various tumor types, but no approved targeted therapies exist. NT-175 is an autologous engineered T-cell receptor (eTCR) T-cell therapy expressing an HLA-A*02:01-restricted TCR that targets the TP53 R175H tumor neoantigen. **Methods:** This open-label Phase 1 study (NCT05877599) enrolled HLA-A*02:01-positive adults with advanced/metastatic, TP53 R175H-mutated solid tumors. NT-175 was manufactured from autologous T cells modified by CRISPR/Cas9 gene-editing to delete endogenous TGFβR2 and replace the TCRα locus with the A*02:01-restricted R175H specific TCR. Patients (pts) received lymphodepletion with fludarabine and cyclophosphamide followed by a single NT-175 infusion along with subcutaneous recombinant IL-2. NT-175 was administered at 3 escalating dose levels (DLs) of eTCR+ T-cells. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT consensus definitions. Response was determined by investigator assessment per RECIST v1.1. The primary objective was safety; secondary and exploratory objectives included preliminary antitumor activity and pharmacokinetics (PK), respectively. **Results:** As of Oct 31, 2025, 26 pts were enrolled and 21 were infused with NT-175 (median age 58 years, [range 43–77] across all DLs (DL1, n = 3; DL2, n = 4; DL3, n = 13; other, n = 1). Pts had a median of 3 prior lines of systemic therapy. Median time from apheresis to NT-175 infusion was 36 days and median follow-up was 6.0 (range: 0.9–9.5) months. Pts had colorectal adenocarcinoma (CRC, n = 10), pancreatic adenocarcinoma (PDAC, n = 6), breast cancer (BC, n = 2), and other solid tumors (n =3). There were no DLTs or Grade 5 events. CRS occurred in 11 (52.4%) pts (Grade ≥3 in 2 [9.5%]); ICANS occurred in 1 pt (Grade 3, 4.8%). Across all dose levels, objective response rate (ORR, including 7 confirmed and 3 unconfirmed responses) was 47.6% (95% CI, 25.7–70.2); in DL3, ORR was 53.8% (95% CI, 25.1–80.8). Partial responses (PR) were observed in 10 pts including 5/6 pts (83%) with PDAC and 5 pts across various tumor histologies (2/10 CRC, 2/2 BC, 1 other), and stable disease in 4 pts. Of 7 evaluable PR pts with ≥6 months of follow up, 5 remain in PR (2 PDAC, 1 leiomyosarcoma, and 2 CRC). Overall, disease control rate was 66.7% (95% CI, 43.0–85.4). Peripheral blood PK analyses (n =21) showed dose-dependent NT-175 expansion, peaking at Week 1 post-infusion, and persistence > 300 days. **Conclusions:** Manufacturing and treatment with autologous NT-175 eTCR T cells was safe and feasible in pts with heavily pre-treated metastatic TP53-mutated malignancies. Further, NT-175 demonstrated encouraging preliminary antitumor activity across multiple histologies, with most notable early signals in PDAC and may offer a prolonged treatment-free interval in pts with refractory solid tumors. Clinical trial information: NCT05877599. Research Sponsor: AstraZeneca.

First-in-human results with IMA401, a MAGEA4/8-targeted T-cell receptor–based bispecific T-cell engager (TCER) in recurrent or refractory solid tumors.

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Background: IMA401 is a next-gen bispecific TCR-based T-cell engager designed to redirect T cells to antigen-positive cancer cells. It combines a high-affinity, highly specific TCR domain against an HLA-A*02:01-presented target peptide common to cancer-specific antigens MAGEA4 and MAGEA8 with a low-affinity T-cell–recruiting domain for improved tolerability and biodistribution, and an Fc part for half-life extension. IMA401-101 (NCT05359445) is a first-in-human phase 1a/b basket study evaluating IMA401 in pts with advanced solid tumors. **Methods:** Pts were ≥18 y, HLA-A*02:01+, MAGEA4+ and/or MAGEA8+, have R/R solid tumors, measurable disease (RECIST 1.1), ECOG performance status 0-2, and have exhausted SOC options. Dose escalation involved cohorts of 1-6 pts using adaptive design (BLRM). Doses ranged from 0.0066 mg - 2.5 mg IMA401 q2w (± pembrolizumab [pembro] q6w with 1.0 mg or 1.5 mg IMA401). Weekly step dosing of IMA401 was implemented for the first 2-3 doses at ≥1 mg . Primary endpoint was MTD assessed by BLRM and/or RP2D as monotherapy and in combination with pembro. Secondary endpoints included safety and initial antitumor activity (confirmed objective response rate [cORR] and disease control rate [DCR]). **Results:** As of Sep 26, 2025, 55 heavily pretreated pts across > 15 different tumor types with a median of 4 prior lines of therapy (range 1-9) received IMA401 ± pembro. Most frequent TRAEs were low-grade CRS (G1: 24%; G2: 11%; no ≥G3 events), expected and transient lymphopenia (any grade: 29%; ≥G3: 24% which typically improved within 1-3 days), and reversible neutropenia (any grade: 29%; ≥G3: 18%). No ICANS was observed. Tolerability of IMA401 + pembro (n = 9) was consistent with the IMA401 monotherapy safety profile. MTD was not reached (3 DLTs at 2.5 mg IMA401). RP2D range was determined to be 1-2 mg IMA401. Efficacy was evaluable in 38 pts receiving a target dose of ≥1 mg IMA401. Promising clinical activity was noted in pts with head and neck (HN) cancer (cORR: 25% [2/8]; DCR: 63% [5/8]) and melanoma (cORR: 29% [2/7]; DCR: 57% [4/7]) with duration of all confirmed responses beyond 6 months postinfusion. In squamous non-small cell lung cancer (sqNSCLC [n = 3]), 1 PR with reduction in all target lesions, 1 SD with OS of ~16 months and 1 PD with reduction in all liver target lesions were observed. After data cutoff, 2 more cPRs were observed in HN cancer resulting in a cORR of 33% (4/12). An updated full dataset will be presented. **Conclusions:** IMA401 demonstrated overall favorable tolerability without reaching formal MTD and encouraging antitumor activity in pts with HN cancer, melanoma, and sqNSCLC at RP2D range. Based on the promising results and preclinical proof of concept data, further development steps are being evaluated including a potentially synergistic combination with the PRAME-directed bispecific IMA402 in sqNSCLC and other solid tumor indications. Clinical trial information: NCT05359445. Research Sponsor: None.

Objective response rates with Ori-C101, an armored GPC3-directed CAR-T, in heavily pretreated advanced HCC: Updated results from the phase Ib BEACON study.

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Background: Advanced hepatocellular carcinoma (HCC) remains a high unmet-medical-need malignancy with limited therapeutic options. Ori-C101 is a novel, armored, autologous GPC3-directed CAR-T cell therapy. Following promising results from early-phase trials (ChiCTR190028121; NCT05652920, BEACON study), we shall herein update outcomes from the BEACON study with focusing on long-term safety, durability of response, and survival after more than 2 years of follow-up. **Methods:** This is an open-label, multi-center, phase Ib dose-escalation and expansion study enrolled patients (pts) with GPC3$^+$ advanced HCC who had progressed on ≥2 prior lines of systemic therapy (including ICIs and TKIs). A single dose of Ori-C101 was administered via hepatic arterial infusion to enhance regional cell delivery. Integrated analyses assessed safety, tolerability, PK, and efficacy (per RECIST v1.1) , aiming to determine the RP2D. **Results:** As of Dec 24, 2025, 19 pts received Ori-C101 infusion across 4 dose levels (DLs). All pts had BCLC stage B/C disease and 31.6% (6/19) had extrahepatic metastases. Pts were previously treated with a median of 3 lines (range 2–8) therapies. Safety: Safety remained manageable; no late-onset nor cumulative toxicities were observed through the extended follow-up period. The most common ≥G3 TEAEs (≥10.0%) were transient hematologic toxicities and hepatic laboratory abnormalities. CRS occurred in 100.0% (19/19) of pts; while ≥G3 CRS observed in 42.1% (8/19). No ICANS occurred. One pt at DL4 experienced a DLT of G4 CRS complicated by secondary DIC. Efficacy: In 18 efficacy-evaluable pts, Ori-C101 demonstrated a robust dose-dependent response. Confirmed ORR was 50.0% (9/18); DCR was 77.8% (14/18). At RP2D (DL3), the confirmed ORR and DCR were 66.7% (6/9) and 88.9% (8/9), respectively. Critically, responses were not only rapid but also remarkably durable. 88.9% (8/9) of responders achieved objective response within 1.1 months; at M3, 83.3% (5/6) of responders at the RP2D remained PR. Notably, 1 pt at DL4 achieved CR with a duration exceeding 20 months. Preliminary overall survival data indicate a substantial long-term survival benefit with a median OS of 14.4 months (range 2.6–22.0). In addition, Dose-Exposure-Responses analysis showed dose-dependent CAR-T cells expansion, pharmacodynamic effects and improved tumor response. **Conclusions:** Ori-C101 demonstrates a manageable safety profile and compelling, durable anti-tumor activity in GPC3$^+$ advanced HCC. The combination of high ORR and prolonged survival benefit distinguishes Ori-C101 as a potential paradigm-shifting therapy for patients who have failed standard-of-care treatments. A phase II/III study is currently underway to further confirm the efficacy and asses the safety of Ori-C101. Clinical trial information: NCT05652920. Research Sponsor: None.

An investigator-initiated phase I study evaluating the safety, tolerability, and preliminary efficacy of a personalized neoantigen mRNA vaccine (XP-004) combined with PD-1 inhibitor as adjuvant therapy in resected pancreatic cancer patients intolerant to chemotherapy.

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Background: Pancreatic cancer has a high postoperative recurrence rate. Although adjuvant chemotherapy is standard of care, many patients are unable to tolerate it, highlighting an unmet need for alternative adjuvant strategies. Personalized neoantigen mRNA vaccines can induce tumor-specific T-cell responses and may synergize with PD-1 blockade. This study evaluated the safety, tolerability, and preliminary clinical activity of XP-004 combined with a PD-1 inhibitor as adjuvant therapy in resected pancreatic cancer patients intolerant to chemotherapy. **Methods:** This open-label, single-arm, investigator-initiated phase I trial (2024PCV004; NCT06496373) initiated in May 2024 plans to enroll 16-20 patients with resected pancreatic cancer intolerant to chemotherapy. Patients received XP-004 intramuscularly (1.0 mg Q3W for 13 cycles), including a KRAS-targeted single-neoantigen vaccine for 4 cycles followed by a personalized multi-neoantigen vaccine for 9 cycles, combined with toripalimab (PD-1 inhibitor). Each personalized vaccine encoded 10–20 personalized neoantigens selected using next-generation sequencing and bioinformatic prediction. The primary endpoint was safety and tolerability; secondary endpoints included neoantigen-specific $CD4^+$ and $CD8^+$ T-cell responses, recurrence-free survival (RFS), and overall survival (OS). **Results:** As of December 15, 2025, 16 patients were enrolled. XP-004 mRNA vaccine was well tolerated. Treatment-related AEs included fever (100%), injection-site pain (87.5%), nausea (43.8%), vomiting (37.5%), pruritus (50.0%), rash (25.0%), and fatigue (37.5%). Grade $\geq$3 AEs were observed in 12.5% patients, including fever (12.5%) and pruritus (6.3%), the latter attributed to toripalimab. No other immune-related AEs were observed. Transient cytokine increases (IFN-γ, IL-5, IL-6, IL-8, IL-10) were observed without organ dysfunction. At a median postoperative follow-up of 43.9 weeks (range of 6.1–72.0 weeks), and a median follow-up of 37.6 weeks (range of 0.9–63.7 weeks) after first vaccination, all patients remained recurrence-free, with no clinical or molecular evidence of recurrence, including no tumor-informed MRD relapse. Among the 13 patients evaluable for immunogenicity, 13 (100.0%) developed neoantigen-specific T-cell responses; 53 of 165 neoantigens (32.1%) were immunogenic. **Conclusions:** XP-004 combined with PD-1 inhibitor demonstrated favorable safety and tolerability and induced robust neoantigen-specific T-cell responses in resected pancreatic cancer patients intolerant to chemotherapy. Early follow-up suggests potential RFS benefit, supporting further investigation of this adjuvant immunotherapy strategy. Clinical trial information: NCT06496373. Research Sponsor: None.

Synthetic lethality–informed neoantigen prioritisation to support mechanism-specific therapeutic strategies across human cancers.

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Background: Personalised neoantigen vaccines can elicit strong tumour-specific T cell responses, yet tumours may evade immune pressure by deleting or silencing the targeted gene. Current selection pipelines treat gene-based escape as an unpredictable failure. For tumour suppressor genes, however, loss of the target can create predictable synthetic lethal (SL) dependencies. We present a framework that classifies tumour suppressor mutations by their therapeutic implications. We hypothesised that hypomorphic mutations, which generate immunogenic neoantigens while retaining partial function, may be suited to sequential therapy, where vaccination selects for complete loss and exposes druggable vulnerabilities. In contrast, null mutations with pre-existing SL dependencies may benefit from upfront vaccine–drug combinations. **Methods:** We analysed 9,953 tumours across 32 cancer types from TCGA. Tumour suppressor mutations were assessed for neoantigen potential using NetMHCpan-4.2, MHCflurry 2.0, and PRIME 2.0 (%rank $< 2\%$), with filtering for clonality, expression (TPM > 1), and multi-allele HLA presentation. Functional status was assigned using gene-specific annotations, including TP53 transactivation scores. SL relationships were curated from DepMap, SynLethDB 2.0, and published clinical evidence, restricted to partners with approved or Phase II+ inhibitors. **Results:** 7.4% of patients (n = 741) harboured tumour suppressor neoantigens with matched SL vulnerabilities, which segregated into two distinct groups. The first group (4.6%, n = 458) carried hypomorphic mutations that generated immunogenic neoantigens while retaining partial gene activity, consistent with candidacy for sequential vaccination followed by SL inhibition upon escape. TP53 missense mutations predominated (58%), with progression to null status predicted to confer WEE1 or CHK1 vulnerability. Additional recurrent pairings included PTEN–AKT (14%), ATM–ATR or PARP (11%), KMT2D–EZH2 (9%), and BRCA2–PARP (8%). The second group (2.8%, n = 283) carried functionally null mutations with SL dependencies present at diagnosis, nominating these patients for upfront vaccine–drug combinations. Endometrial (12.1%) and colorectal (9.8%) cancers were enriched for both patterns, whereas high-grade serous ovarian cancer was dominated by hypomorphic mutations. **Conclusions:** This framework reframes immune escape from neoantigen vaccination, conventionally viewed as treatment failure, as a predictable and potentially exploitable therapeutic event. Functional classification of tumour suppressor neoantigens provides a rationale for distinguishing sequential from upfront vaccine–SL inhibitor strategies. Prospective trials with longitudinal monitoring will be required to determine whether vaccination-induced gene loss consistently exposes the predicted vulnerabilities. Research Sponsor: None.

2511 Clinical Science Symposium

Personalized neoantigen vaccine as adjuvant therapy in high-risk postoperative esophageal carcinoma.

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Background: Effective adjuvant strategies for patients with esophageal carcinoma (EC) with residual pathological disease (non-pCR) following neoadjuvant chemoimmunotherapy and radical surgery are urgently needed to reduce the high risk of recurrence. This investigator-initiated, single-arm clinical trial (NCT05307835) evaluated the safety, efficacy, and immunogenicity of iNeo-Vac-P01, a personalized neoantigen peptide vaccine, administered as adjuvant therapy in this high-risk setting. To our knowledge, this study represents the first and largest global cohort of a personalized neoantigen vaccine for postoperative EC, with the longest follow-up duration to date. **Methods:** Eligible stage IIA-IIIB EC patients with non-pCR were enrolled. For each patient, somatic mutations were identified, and up to 20 individualized long peptides (15-30 amino acids), encompassing predicted HLA-I and II neoantigens, were designed and synthesized using a proprietary bioinformatics platform. The vaccine (300μg per peptide) was administered subcutaneously in conjunction with GM-CSF (40μg) on a multi-dose schedule (Days 1, 4, 8, 15$\pm$3, 22$\pm$3, 52$\pm$7, and 82$\pm$7). The primary endpoints were safety and 1-year recurrence-free survival (RFS). Secondary endpoints included RFS, overall survival (OS), and antigen-specific T-cell responses assessed by ELISpot and TCR sequencing. **Results:** As of November 15, 2025, 26 patients were enrolled, with 23 patients constituting the efficacy-evaluable population. Treatment-related adverse events were primarily Grade 1-2 (fatigue: 39.1%; fever: 30.4%; injection site reactions: 21.7%), with one Grade III acute hypersensitivity event. All 23 patients completed the initial 7-vaccination course. With a median follow-up of 25.3 months from surgery, the 1-year, 2-year, and 3-year RFS rates were 91.3%, 85.6%, and 78.5%, respectively. The corresponding 1-year, 2-year, and 3-year OS rates were 100%, 95%, and 83.1%. These survival outcomes compare favorably with historical controls, notably exceeding the 3-year RFS of 43% reported in the landmark CheckMate 577 trial (adjuvant nivolumab). Immunological analyses confirmed robust vaccine-induced immunogenicity. ELISpot assays detected neoantigen-specific T-cell responses in 100% (23/23) of evaluated patients, with 79.5% (233/296) of the administered vaccine peptides eliciting de novo T-cell activation. TCR sequencing further demonstrated the durable expansion of neoantigen-reactive T-cell clones, which were detectable during treatment and persisted for at least six months following the final vaccination. **Conclusions:** These results demonstrates that adjuvant therapy with a personalized neoantigen peptide vaccine confers a substantial and durable survival benefit in high-risk EC patients following surgery, coupled with a favorable safety profile. Clinical trial information: NCT05307835. Research Sponsor: Hangzhou Neoantigen Therapeutics Co., Ltd.

Phase 2 trial of TIL therapy for metastatic uveal melanoma: Evaluation of T cell potency and an in situ precision biomarker.

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Background: Uveal melanoma (UM) is a rare eye cancer that frequently metastasizes to the liver and responds poorly to systemic therapies. We previously reported that adoptive transfer of autologous tumor-infiltrating lymphocytes (TIL) produced a 35% objective response rate (ORR) in metastatic UM, with infusion product tumor reactivity being the strongest predictor of response. To guide surgical harvest of metastases enriched for tumor-reactive TIL, we developed Uveal Melanoma Immunogenomic Score (UMIS), an in situ tumor transcriptomic biomarker. Here we present results of a phase 2 trial designed to validate the efficacy of TIL therapy in metastatic UM and prospectively evaluate predictors of response. **Methods:** In this single-center phase 2 trial (NCT03467516) metastatic UM patients underwent metastatectomy to generate early TIL cultures. Cultures demonstrating growth potential and autologous anti-tumor reactivity were expanded for infusion. Patients received non-myeloablative lymphodepletion with cyclophosphamide and fludarabine, followed by infusion of TIL and high-dose interleukin-2. The primary endpoint was ORR per RECIST v1.1. Exploratory analyses to identify response predictors were performed in the current cohort and a pooled dataset including the NCT01814046 cohort. **Results:** Thirty-three UM patients received TIL therapy. Most had high disease burden (82% M1b/M1c; 76% elevated LDH; 70% hepatic and extrahepatic metastases; 24% CNS), received a median of 2 prior metastatic treatments (64% checkpoint blockade, 33% tebentafusp), and had liver metastases as their TIL source (52%). Infusion products had a median of 5.24E10 TIL, were CD8-enriched (median 68%), and demonstrated autologous tumor reactivity in 61% (19/31). Among 32 evaluable patients, the ORR was 22% (7/32) with a median response duration of 10.8 months (maximum ongoing at 58 months). Tumor-reactive TIL conferred higher response rates (37%, 7/19) than nonreactive products (0%, 0/12; P = 0.026). Responders demonstrated higher persistence of infused TIL clones in peripheral blood (R/NR ratio = 10.69, P = 0.020). In the pooled cohort (n = 54, 52 evaluable), ORR was higher with reactive products (43%, 12/28) versus nonreactive products (0%, 0/20; P = 5.06E-4). UMIS of the source metastases predicted growth of tumor-reactive TIL cultures (Rho = 0.55, P = 2.72E-5), final infusion product reactivity (P = 0.040), and clinical response (P = 0.004). **Conclusions:** TIL therapy demonstrates clinically meaningful activity in advanced, pretreated metastatic UM. Infusion product tumor reactivity was the strongest predictor of response. UMIS identified metastases enriched with tumor-reactive TIL and predicted final product potency and clinical outcome. These findings support implementation of UMIS as a minimally invasive precision biomarker to guide patient and tumor selection for optimal therapeutic benefit. Clinical trial information: NCT03467516. Research Sponsor: None.

Perioperative tislelizumab plus chemotherapy versus chemotherapy in MHC-II positive/MHC-II negative locally advanced GC/GEJC: A prospective, randomized, open-label, biomarker-driven, phase 2 trial.

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Background: Neoadjuvant immunotherapy achieves major pathologic response (mPR) in 40% of locally advanced gastric cancer (LAGC) patients. Tumor-specific MHC-II expression(tsMHC-II) has been linked to a better enhanced response to immune checkpoint inhibitor therapy. Herein, we conducted a prospective, randomized study to evaluate the effectiveness of chemotherapy combined with anti-PD-1 therapy versus chemotherapy alone as neoadjuvant treatment for tsMHC-II-positive LAGC patients. **Methods:** Patients with locally advanced GC/GEJC (cT3-4N+M0, CY0, P0) were enrolled according to tsMHC-II expression. Within each stratum, patients were subsequently randomized 1:1 to receive either tislelizumab combined with chemotherapy or chemotherapy alone, including Arm A (tsMHC-II-positive, chemotherapy + tislelizumab), Arm B (tsMHC-II-positive, chemotherapy), Arm C (tsMHC-II-negative, chemotherapy + tislelizumab), Arm D (tsMHC-II- negative, chemotherapy). For experimental group, patients received either 3 preoperative and 3 postoperative cycles of tislelizumab plus SOX/XELOX, followed by 11 cycles of tislelizumab. For control group, patients received either 3 preoperative and 3 postoperative cycles of SOX/XELOX. The primary endpoint was mPR rate (Arm A vs. Arm B). The key secondary endpoint was pCR rate (Arm A vs. Arm B). This clinical trial was registered at Clinicaltrial.gov (NCT06374901). **Results:** 136 patients (34 per arm) were enrolled from July 2024 to March 2025, with a median age of 65 years (range, 30-75), and 105 (76.64%) were male. The study achieved its primary endpoint. The results revealed that tsMHC-II-positive patients in the tislelizumab plus chemotherapy group achieved a greater proportion of mPR (61.8% versus 26.5%; P = 0.003) and pCR (32.4% versus 8.8%; P = 0.016) than did those in the chemotherapy group, which met a prespecified endpoint. In contrast, this benefit was absent in tsMHC-II-negative patients (mPR: 23.5% vs 26.5%, P = 0.886; pCR: 5.9% vs 8.8%, P = 0.642). There were no significant differences in treatment-related adverse reactions among each group. **Conclusions:** In conclusion, compared with perioperative chemotherapy alone, the addition of tislelizumab to a given chemotherapy regimen significantly increased the proportion of mPR and pCR in tsMHC-II-positive patients with GAC/GEJAC only, which revealed that tsMHC-II could be a biomarker to guide the selection of appropriate GAC/GEJAC patients for perioperative immunotherapy. Clinical trial information: NCT06374901. Research Sponsor: None.

A randomized prospective trial evaluating duration of PD-1 and PD-L1 inhibitor therapy in advanced solid tumors.

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Background: Immune checkpoint inhibitors (IO) have revolutionized the treatment of advanced solid tumors. Despite their widespread adoption, the optimal duration of IO has not been clearly established, and this remains an unmet clinical need. **Methods:** In our prospective trial, patients (pts) with advanced solid tumors who achieved at least stable disease (SD) after 1 year of standard-of-care PD-1/PD-L1 inhibitors were randomized 1:1 to either stop or continue IO beyond one year. Pts who stopped IO and then progressed could be retreated with IO at physician discretion. Primary endpoint was cure rate, defined as the proportion of pts without progressive disease, death, or initiation of new treatment (including re-treatment with IO) at five years. Cure rate was calculated using Kaplan-Meier (KM) estimates with 95% confidence intervals (CI) and compared between arms using a multivariable logistic regression model to adjust for pre-specified stratification factors of tumor type and expected efficacy by IO indication, and reported as an odds ratio (OR) with CI and p-value. Secondary endpoints included PFS, OS, and incidence of iRAEs. Median PFS and OS were estimated from KM curves, with hazard ratios (HR) and p-values obtained from stratified Cox proportional hazards models. All analyses were conducted using R version 4.4.2. **Results:** From 2019 to 2025, leveraging our central hub and community network, a total of 161 pts (Stop = 81, Continue = 80) were enrolled. The trial was closed early due to slow accrual (goal 578 pts). Median age was 71 and the most common tumor types were: NSCLC(39.8%), mismatch repair-deficient tumors(18.6), RCC(11.8%), HNSCC(8.1%), and melanoma (7.5%). There was no difference in baseline characteristics between arms. With a median follow up of 43.2 months (mo), cure rate was 45% (32%-63%)in the stop arm vs 38% (27-54%) in the continue IO arm (OR 2.26, 95% CI [0.62-8.22], p = 0.22). Median PFS was 55.4(27.5-NR) vs. 31.2 mo(20-NR) HR 0.77, 95% CI (0.48-1.24), p = 0.28 and median OS was NR (55.4 vs. NR) vs. 53.5 mo(40.8-NR) HR 0.54, 95%CI (0.3-0.99), p = 0.04 for the stop vs continue IO arms, respectively. In the continue IO arm, the median number of IO doses was 11 (range 0-36) and 52 of these pts discontinued IO with the most common reason being disease progression (42.3%), and 7.7% discontinued for toxicity. In the stop IO arm, 17 pts who progressed were retreated with IO; 20% achieved subsequent partial response and the median PFS was 10.5 mo(6.5-NR) and median OS was 26.7 mo(10.5-NR) after retreatment. **Conclusions:** Our trial is unique as a prospective randomized evaluation of length of IO treatment in advanced solid tumors. Cure rates and PFS were similar across arms and OS was improved in pts that discontinued IO at 1 year. These findings suggest that stopping IO at 1 year may be as effective as indefinite IO therapy, though validation in a larger, adequately powered trial is needed. Clinical trial information: NCT04157985. Research Sponsor: Hillman Cancer Center; Pennsylvania Department of Health; SAP # 410095621.

2515 Rapid Oral Abstract Session

Clinical and translational study of p38 inhibitor pexmetinib plus nivolumab following anti–PD-1/L1 failure in advanced solid tumors.

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Background: Cancers resistant to immune checkpoint blockade typically harbor a non-T cell-inflamed phenotype, characterized by low type I/II interferon activity and limited $CD8^+$ T-cell infiltration within the tumor microenvironment. We previously identified p38 MAPK activation as a tumor-intrinsic immune exclusion mechanism associated with resistance to immunotherapy across solid tumors. Based on these preclinical observations, we conducted a Phase II clinical trial (NCT04074967) combining pexmetinib, a p38 inhibitor, with nivolumab in advanced solid tumors. Here, we report safety, clinical activity, and translational results in patients with PD-1 refractory head and neck (HN) cancer and lung cancers. **Methods:** Patients received pexmetinib 200 mg orally once daily plus nivolumab 480 mg intravenously every 4 weeks. The primary endpoint was overall response rate (ORR) assessed by RECIST v1.1. Translational analyses included pharmacodynamic assessment, plasma proteomics, single-cell RNA sequencing (scRNAseq), and computed tomography-based radiomic analyses. **Results:** Thirty-five patients were enrolled (HN cohort = 11 [31%; 100% squamous cell carcinoma]), lung cohort = 24 [69%; 63% adenocarcinoma]). Median age was 62 years; 60% were male and 89% had ECOG performance status 1. Twenty-nine patients were radiographically evaluable. Partial responses were observed in four patients (ORR 14%), and 13 patients (45%) experienced stable disease. Median duration of response was 11.1 months. Median progression-free survival (PFS) was 7.2 months and overall survival (OS) was 9.3 months. Treatment-related adverse events (TRAEs) of any grade occurred in 89% of patients; 47% experienced grade ≥ 3 TRAEs. No fatal TRAEs were reported. Plasma proteomic profiling identified on-treatment immune modulation relative to baseline, with increased T cell-associated cytokines/chemokines in patients with durable clinical benefit (PFS $>$ 6 months). Among three patients with paired pre- and on-treatment tumor scRNAseq, an increase in intratumoral T-cell abundance was observed in one patient with tumor shrinkage but not in two patients with progressive disease. On-treatment increases in T-cell radiomic score relative to baseline were significantly greater in responders vs. non-responders, and were associated with improved PFS and OS ($P < 0.05$). **Conclusions:** In patients with PD1-refractory HN cancer and lung cancers, pexmetinib plus nivolumab demonstrated an acceptable safety profile and durable clinical benefit. Multimodal translational profiling revealed increased inflammatory cytokine signaling and radiomic and molecular features consistent with enhanced $CD8^+$ T-cell engagement in responders. These findings suggest that targeting tumor-intrinsic p38 MAPK may represent a mechanistically informed strategy to overcome immunotherapy resistance. Clinical trial information: NCT04074967. Research Sponsor: U.S. National Institutes of Health; University of Pittsburgh Cancer Cell Biology Program; National Cancer Institute; The University of Pittsburgh Center for Research Computing and Data; Pfizer.

2516 Rapid Oral Abstract Session

PRaG 5.0: Personalized thymosin alpha-1 and radioimmunotherapy for advanced refractory solid tumors—Data from an expanded cohort.

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Background: Treatment-related lymphopenia and inadequate anti-tumor immune activation remains major barriers to improving outcomes of combination immunoradiotherapy, especially for advanced refractory solid tumors. PRaG 5.0 innovatively integrates personalized thymosin alpha-1 (Tα-1) into the PRaG regimen (PD-1 inhibitor + radiotherapy + GM-CSF) to preserve lymphocytes and enhance anti-tumor immunity. We report updated efficacy and safety data of PRaG 5.0 in advanced refractory solid tumors. **Methods:** This is a prospective, single-armed, phase II study enrolled 43 heavily pretreated patients. Eligible patients were stratified by baseline T-lymphocyte counts to receive personalized Tα-1 dosing: 7-day loading dose for low baseline T-lymphocyte counts, and maintenance Ta-1 (1.6 mg, thrice weekly) for those with normal counts. Tα-1 was combined with the PRaG regimen for at least 2 cycles. After PRaG cycles, patients continued PD-1 inhibitor plus Tα-1 until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included median progression-free survival (mPFS), disease control rate (DCR), safety, and immune cell dynamics (assessed by flow cytometry, single-cell sequencing, and TCR sequencing). **Results:** Among the 43 screened subjects, 39 received treatment, of whom 30 required loading dose thymosin α1 (Tα1) therapy, 36 were treated with PRaG regimen and 17 entered the maintenance phase with PD-1 inhibitor combined with Tα1. The objective response rate (ORR) of the 39 patients was 30.8% (95%CI 17.0%, 47.6%), including 4 cases of complete response (CR) and 8 cases of partial response (PR); the median progression-free survival (PFS) was 4.2 months (95%CI 2.3, 6.9). No Grade 3 or above TRAE was reported. Immune analysis revealed significant increases in CD8+ T cells, NK cells, and CD4+TEM cells post-Tα-1 loading, with a notable decrease in Tregs ($p = 0.001$). Single-cell sequencing demonstrated higher clonality in GZMK-CD8+T in responders, while TRDV2-CD8+T cells expanded in non-responders. **Conclusions:** Integrating of Tα-1 into the PRaG regimen is a promising therapeutic strategy, offering enhanced efficacy and a favorable safety profile. Detailed immune profiling identified distinct T-cell dynamics associated with treatment response, highlighting potential biomarkers for clinical application. Further validation in larger cohorts is warranted. Clinical trial information: NCT05790447. Research Sponsor: None.

2517 Rapid Oral Abstract Session

Evaluation of the combination of regorafenib + avelumab in patients with HPV-associated cancer: The phase II REGOMUNE study.

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Background: HPV-associated malignancies—including cervical, anal, head and neck, and penile cancers—form a biologically distinct group with limited responsiveness to immune checkpoint inhibitors (ICP) in monotherapy. Combining anti-angiogenic agents with immunotherapy may enhance efficacy by reshaping the tumor microenvironment. REGOMUNE explores this rationale by evaluating regorafenib plus avelumab association. **Methods:** REGOMUNE is a French multicenter, open-label, phase II trial assessing the combination of regorafenib (160 mg daily for 3 weeks of a 4-week cycle) and avelumab (10 mg/kg biweekly) in patients with advanced/metastatic HPV-driven solid tumors. The primary endpoint is the 6-month disease control rate (DCR) per RECIST 1.1 after central review. Secondary endpoints include overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Correlative studies will analyze baseline tumor samples to identify biomarkers of response. An exact single stage design was used testing 10% vs 25% DCR (5% type 1 error rate and 80% power), requiring ≥ 8 patients with disease control at 6 months among 40 patients to demonstrate efficacy. **Results:** From March 2023 and to February 2024, 44 patients were enrolled across 6 centers. Median age was 62 (range :33-80). Median follow-up was 18.3 months (95% CI : 14.9-21.1). Median number of prior treatment lines was 2 (range :0-7). Anal (41%) and cervical (32%) cancers were the predominant primary sites, with squamous cell carcinoma representing 70.5% of cases. Among 33 evaluable patients for efficacy, the 6-month DCR was 45.5% (N = 15) [90% CI : 30.5-61.1], with 12 (36.4%) partial response, 11 (33.3%) stable disease, and 10 (30.3%) progressions. Median PFS was 5.3 months (95% CI: [3.0 – 7.3]). Median OS was 15.0 months (95% CI [7.2 – 21.6]). Treatment modifications due to adverse events occurred in 33/42 (78.6%) patients. Common grade 3/4 adverse events included palmar-plantar eryhtrodysesthesia syndrome (11.9%), diarrhea (9.5%) and fatigue (7.1%). One treatment-related death was reported. **Conclusions:** REGOMUNE is the first phase II trial to demonstrate a clinically meaningful efficacy signal surpassing historical CPI outcomes as monotherapy with an anti-angiogenic plus immune CPI combination in patients with HPV-positive tumors. Biomarker analyses are ongoing to identify predictive signatures associated with the durable responses observed in this cohort. Clinical trial information: NCT03475953. Research Sponsor: None.

2518 Rapid Oral Abstract Session

Phase 1 study of NTX1088, a first-in-class anti-PVR monoclonal antibody, as monotherapy and combined with pembrolizumab, in patients with advanced solid malignancies.

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Background: Poliovirus Receptor (PVR; CD155), a transmembrane protein upregulated across multiple solid tumors and associated with poor clinical outcomes and resistance to immune checkpoint inhibitors (CPIs), plays a central role in tumor-mediated immune suppression. PVR suppresses anti-tumor immunity by interacting with the co-stimulatory receptor DNAM1 (CD226) on T and NK cells, leading to its internalization and degradation. PVR also engages the inhibitory immune receptors, TIGIT, CD96, and KIR2DL5A. NTX1088 is a first-in-class monoclonal antibody targeting PVR. **Methods:** NTX-1088-01 (NCT05378425) is a Phase 1a/1b, open-label, multicenter dose-escalation and expansion study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, recommended dose for expansion (RDE), and preliminary efficacy of NTX1088 alone and in combination with pembrolizumab in patients (pts) with advanced solid tumors known to express PVR (prescreening not required). NTX1088 was administered intravenously (IV) every 3 weeks (Q3W) in dose levels (DLs) from 12-1750 mg as monotherapy or from 160-1750 mg in combination with pembrolizumab 200 mg IV Q3W. Phase 1a employed a standard 3+3 dose-escalation design. Phase 1b comprises dose-expansion monotherapy and combination cohorts in gastric, bladder, lung, and other PVR-expressing solid tumors at the RDE. **Results:** As of January 2026, 81 pts were treated with NTX1088 (24 monotherapy; 57 combination). Median age was 61 years; median lines of prior therapy was 4 and prior CPI exposure was 70%. NTX1088 was well tolerated with no dose-limiting toxicity and 1750 mg was selected as the RDE in monotherapy and in combination with pembrolizumab, based on PK and target occupancy. Preliminary efficacy analysis was focused on active DLs of NTX1088 (1200 and 1750 mg) in combination with pembrolizumab. Forty-eight pts were treated at these DLs and 35 pts were evaluable for response. Of these 35 pts, median age was 57, median lines of prior therapy was 4 and 89% received prior CPI. Six (17%) pts achieved confirmed partial responses (PR) including gastric (2), bladder (1), non-small cell lung (1), squamous cell carcinoma of the head and neck (1), and melanoma (1). All PRs were seen in pts with prior CPI exposure. Sixteen (46%) pts achieved stable disease. At data cutoff, all but one PR pt remain on treatment, with a maximum treatment duration of 20 months. Exploratory analyses of tumor biopsies identified potential predictive biomarkers. **Conclusions:** NTX1088 demonstrated favorable tolerability and encouraging clinical activity in heavily pre-treated pts who had progressed on prior PD-1/PD-L1 inhibitors. These findings support further evaluation of NTX1088 in Phase 2 studies, incorporating less heavily pre-treated pts and biomarker selection. Clinical trial information: NCT05378425. Research Sponsor: Nectin Therapeutics; Cancer Focus Fund; European Innovation Council.

2519 Rapid Oral Abstract Session

KEYNOTE-B59: An open-label, multicenter, phase 1/2 study of efdelikofusp alfa (GI-101A; CD80-IgG4 Fc-IL2v2) in advanced solid tumors (part E & F of GII-101-P101).

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Background: Efdelikofusp alfa is a novel immunocytokine consisting of CD80 fused to an engineered IL-2 variant (IL-2v2) optimized to reduce IL-2Rα affinity. It blocks CTLA-4–mediated immune suppression while preferentially activating and expanding immune effector cells over regulatory T cells. Here, we report results from the dose-escalation phases of Part E (monotherapy) and Part F (combination with pembrolizumab) of the ongoing KEYNOTE-B59 study. **Methods:** KEYNOTE-B59 is an open-label, phase 1/2 study evaluating efdelikofusp alfa alone or in combination with pembrolizumab in patients (pts) with advanced solid tumors. In Part E, escalating doses of efdelikofusp alfa (0.05–0.3 mg/kg) were administered intravenously every 3 weeks (Q3W). In Part F, pts received efdelikofusp alfa (0.05–0.3 mg/kg) plus pembrolizumab (200 mg) Q3W. Primary objectives were to assess safety, tolerability, and to determine maximum tolerated dose (MTD) and/or recommended phase 2 dose. **Results:** As of 29 December 2025, a total of 84 pts who had progressed on available therapies were enrolled, including 36 pts in Part E and 48 pts in Part F. In Part E, one dose-limiting toxicity (DLT) occurred at 0.1 mg/kg (grade 3 hypertension). However, MTD was not reached up to 0.3 mg/kg, and efdelikofusp alfa was generally well tolerated. At the biologically effective dose range (0.2–0.3 mg/kg), monotherapy demonstrated clinical activity in immunotherapy (IO)-experienced bladder cancer (confirmed CR; DoR 5.8 months; PFS 13.9 months) and mesothelioma (confirmed PR; DoR 5.6 months; PFS 6.7 months). In Part F, 48 pts were treated with efdelikofusp alfa in combination with pembrolizumab. Median age was 63 years and 45.8% of pts had received prior IO. The overall safety profile of the combination was comparable to monotherapy, with common treatment-related adverse events including pyrexia (89.6%), liver enzyme elevation (47.9%), chills (37.5%), and decreased platelet count (33.3%). Objective responses were observed across multiple tumor types, including ccRCC, urothelial cancer, squamous NSCLC, cutaneous squamous cell carcinoma, pancreatic adenocarcinoma, and cervical cancer, irrespective of prior IO exposure. In pts with ccRCC (n = 10), the most frequently enrolled indication (70.0% prior IO-treated), the objective response rate was 40.0% and the disease control rate was 70.0%, with durable responses observed from 5.5+ to 16.7+ months; median DoR was not reached. Efdelikofusp alfa induced robust peripheral lymphocyte expansion, mainly $CD8^+$ T and NK cells, which correlated with longer median PFS. **Conclusions:** Efdelikofusp alfa was well tolerated as a monotherapy and in combination with pembrolizumab. Antitumor activity was observed with a favorable benefit–risk profile, supporting continued development in selected tumors, including ccRCC. Clinical trial information: NCT04977453. Research Sponsor: GI Innovation, Inc.; Korea Drug Development Fund; HN22C0451.

CS2009, a novel PD-1/VEGF/CTLA-4 trispecific antibody, in patients with advanced solid tumors: Updated results from an open-label, multicenter, phase 1 first-in-human study.

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Background: CS2009 is a first-in-class trispecific antibody targeting PD-1, VEGF and CTLA-4. Initial data from this phase 1 study showed a favorable safety profile and encouraging antitumor activity. Here, we report updated safety and efficacy results in 98 patients. **Methods:** This ongoing, open-label, multicenter, phase 1 dose-escalation trial enrolled patients with advanced solid tumors who progressed on standard therapy or had no available standard therapy. CS2009 was administered intravenously every 3 weeks at 6 dose levels ranging from 1 to 45 mg/kg. Dose escalation followed an accelerated titration design at the first dose level and a 3+3 design thereafter. In parallel, additional patients were backfilled to selected dose levels deemed safe to further evaluate safety and efficacy. Primary objectives include safety, tolerability and determination of the maximum tolerated dose (MTD)/tentative recommended phase 2 dose (RP2D). Secondary and exploratory objectives include pharmacokinetic/pharmacodynamic profile and preliminary efficacy per RECIST v1.1, etc. **Results:** As of January 4, 2026, 98 patients (55.1% male; median age 61 [range 19-80] years; 54.1% Asian, 43.9% White) had received CS2009 across 6 dose levels, with half (49/98) remaining on study treatment. Tumor types included non-small cell lung cancer (NSCLC, n = 49), ovarian cancer (n = 12), soft tissue sarcoma (n = 9), renal cell carcinoma (RCC, n = 6), triple-negative breast cancer (TNBC, n = 6), colorectal cancer (n = 4), and others. Most (98.0%) patients received at least one prior line of systemic anti-cancer therapy. No dose-limiting toxicities (DLTs) occurred; MTD was not reached. The incidences of any-grade and grade ≥3 treatment-related adverse events (TRAEs) were 69.4% and 20.4%, respectively. The most common (≥10%) TRAEs were pruritus (n = 14, 14.3%), alanine aminotransferase increased (n = 11, 11.2%) and aspartate aminotransferase increased (n = 10, 10.2%). Five (5.1%) patients discontinued treatment due to TRAEs. There were no treatment-related deaths. Encouraging antitumor activity was observed across multiple tumor types that have received heavy prior treatment including PD-1/PD-L1 inhibitors or antiangiogenesis therapies where appropriate, including NSCLC without known actionable oncogenic alterations (n = 27), soft tissue sarcoma (n = 9), non-clear cell RCC (n = 5), and TNBC (n = 6) with ORR of 18.5%, 33.3%, 20.0%, 16.7%, respectively, and DCR of 74.1%, 66.7%, 100.0%, 50.0%, respectively (detailed and updated data to be presented at the conference). **Conclusions:** CS2009 demonstrated a manageable safety profile and promising antitumor activity in heavily pretreated patients with advanced solid tumors, which warrants further clinical development in an ongoing phase 2 study in nine tumor types. Clinical trial information: NCT06741644. Research Sponsor: CStone Pharmaceuticals.

Pemivibart for prevention of COVID-19: Subset analysis of CANOPY participants with solid tumor or hematologic malignancies.

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Background: Due to the chronic immunosuppression associated with both their condition and treatments, patients with solid tumors or hematologic malignancies experience reduced vaccine protection and are at high risk of infections, including COVID-19. This post hoc analysis of the phase 3 CANOPY study assesses the safety and outcomes of pemivibart in the oncology subset from the open-label, single-arm, immunocompromised Cohort A. **Methods:** Cohort A dosing: 4500 mg of pemivibart (intravenous) on day 1; 2nd dose at month 3. Primary objectives: 1) Evaluation of pemivibart safety and tolerability via study drug-related treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and treatment interruption/discontinuation, 2) Evaluation of protection against symptomatic COVID-19 based on sVNA titers against SARS-CoV-2 after receiving pemivibart. Exploratory endpoint: composite incidence of RT-PCR-confirmed symptomatic COVID-19, including COVID-19-related hospitalization and all-cause mortality. Data were analyzed through Month 6. **Results:** Enrollment began in Sep 2023. The oncology subset included 55 (18.0%) Cohort A participants; median age [range] 65 [35-83] years; 25 (45.5%) female. Eight participants (14.5%) were receiving immunosuppressants, including 6 (10.9%) receiving corticosteroids. Prior to enrollment, 89.1% received ≥1 COVID-19 vaccine; seropositivity: N antigens (43.6%), S antigens (98.2%). Month 6 TEAEs were reported in 32 (58.2%) participants; 5 (9.1%) were considered study drug-related with 1 (1.8%) requiring treatment interruption due to infusion site extravasation and tachycardia (Table). SAEs occurred in 5 (9.1%) participants; none were considered drug-related. Following pemivibart dosing, sVNA titers in the oncology subset were elevated to levels associated with protection against COVID-19 and comparable with Cohort A. No anaphylaxis was reported in the oncology subset; 4 cases among 306 participants in Cohort A. Through Month 6, there was no RT-PCR-confirmed symptomatic COVID-19 in the oncology subset; with 9/298 (3.0%) in Cohort A. **Conclusions:** Pemivibart was well tolerated in the CANOPY Cohort A oncology subset. These data showed limited events overall and no development of symptomatic COVID-19 in the oncology subset through Month 6. Clinical trial information: NCT06039449. Research Sponsor: Invivyd, Inc.

Select outcomes through month 6.

Parameter	Immunocompromised Cohort A	Cohort A Oncology Subset[a]
Study drug-related TEAE, n (%)	34/306 (11.1)	5/55 (9.1)
- Leading to death	0/306 (0)	0/55 (0)
- Leading to interruption	14/306 (4.6)	1/55 (1.8)
- Leading to discontinuation	7/306 (2.3)	0/55 (0)
COVID-19 composite event, n (%)	11/298 (3.7)	1/55 (1.8)
PCR-confirmed COVID-19, n (%)	9/298 (3.0)	0/55(0)
All-cause mortality, n (%)	2/298 (0.7)	1/55 (1.8)[b]

[a]20 (36%) were being actively treated for solid tumor or hematologic malignancy; 40 (73%) had a hematologic malignancy.
[b]Unrelated to study drug.

A phase 1 study of BGB-A3055 (anti-CCR8) with or without tislelizumab (anti–PD-1) in patients with solid tumors.

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Background: BGB-A3055 is a humanized monoclonal antibody targeting C-C motif chemokine receptor 8 (CCR8), a receptor highly expressed on intratumoral regulatory T cells (Tregs). CCR8 overexpression correlates with poor prognosis in certain tumor types. Preclinical studies have shown potent antitumor activity of BGB-A3055. Here, we present results from a phase 1a dose-escalation trial of BGB-A3055 alone (Part A [A]) or combined with tislelizumab (TIS; Part B [B]) in patients (pts) with advanced or metastatic solid tumors (NCT05935098). **Methods:** Eligible pts had histologically confirmed advanced or metastatic solid tumors with high prevalence of CCR8 expression. In A, pts received BGB-A3055 (six dose levels) intravenously (IV) every 3 weeks (Q3W). In B, pts received BGB-A3055 (six dose levels) and TIS 200 mg IV Q3W. Primary endpoint was safety; secondary endpoints included preliminary antitumor activity (RECIST v1.1). **Results:** As of Nov 19, 2025, 98 pts were treated with BGB-A3055 ± TIS (A: n=42; B: n=56). Median (range) study follow-up was 3.94 (0.9-19.0) months in A and 4.67 (0.5-16.8) months in B. Treatment-emergent adverse events (TEAEs) are provided in the Table. The most common BGB-A3055-related TEAEs were neutrophil count decreased (23.8%) in A and pyrexia (23.2%) in B. The most common serious TEAE was immune-mediated enterocolitis (A: 4.8%; B: 7.1%). The most common immune-mediated adverse events (imAEs) were rash, rash maculo-papular, and hypothyroidism in A (7.1% each) and rash maculo-papular in B (17.9%). Dose-limiting toxicities occurred in 1 pt in A (immune-mediated hepatitis) and 3 pts in B (colitis, nephrotic syndrome, and rash maculo-papular in a single pt each). No treatment-related TEAEs leading to death were reported. Maximum tolerated dose was not reached. Unconfirmed objective response rate was 7.5% (95% confidence interval [CI]: 1.6-20.4; 3 partial responses [PRs]) in A and 18.2% (95% CI: 9.1-30.9; 1 complete response and 9 PRs) in B. Disease control rate was 35.0% (95% CI: 20.6-51.7) in A and 56.4% (95% CI: 42.3-69.7) in B. Among the 13 responders, 6 received prior immunotherapies. Robust Treg reduction was observed in peripheral blood and tumor tissue post-treatment, indicating potent on-target pharmacodynamic activity of BGB-A3055. **Conclusions:** BGB-A3055 ± TIS demonstrated a safety profile consistent with selective CCR8 on-target effects in pts with advanced solid tumors and had preliminary antitumor activity. Clinical trial information: NCT05935098. Research Sponsor: BeOne Medicines Ltd.

	Part A BGB-A3055 monotherapy (n=42)	Part B BGB-A3055 + TIS (n=56)
Any TEAE, n (%)	41 (97.6)	55 (98.2)
Grade ≥3	26 (61.9)	47 (83.9)
Serious	17 (40.5)	37 (66.1)
Leading to death	1 (2.4)	3 (5.4)
Leading to treatment discontinuation	9 (21.4)	23 (41.1)
Any BGB-A3055-related TEAE, n (%)	35 (83.3)	53 (94.6)
Grade ≥3	18 (42.9)	31 (55.4)
Serious	5 (11.9)	20 (35.7)
Any imAE, n (%)	15 (35.7)	33 (58.9)

Phase 1b dose-expansion study of IMC-002, a anti-CD47 monoclonal antibody, in patients with advanced triple negative breast cancer (TNBC).

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Background: IMC-002 is a novel therapeutic agent with a distinct mechanism of action. In a phase 1a dose-escalation study, IMC-002 demonstrated favorable safety and tolerability, and clinical activity was observed in patients with hepatocellular carcinoma (HCC) in a subsequent phase 1b trial. Here, we present results from the phase 1b expansion cohort in patients with triple-negative breast cancer (TNBC), focusing on safety, efficacy, and analyses of soluble biomarkers. **Methods:** Eligible pts had advanced TNBC with progression after ≥1 prior systemic therapy and ECOG PS ≤1. IMC-002 (20 mg/kg Q3W) was administered in combination with gemcitabine plus carboplatin or paclitaxel and continued until disease progression. Tumor response was assessed every 6 weeks per RECIST 1.1 and iRECIST. Baseline ctDNA was analyzed using the AlphaLiquid 1000 platform (1,023 -gene panel). To exclude germline and clonal hematopoiesis of indeterminate potential (CHIP) variants, paired PBMC sequencing was performed. The assay detected single nucleotide variants (SNVs), small insertions and deletions (INDELs), fusions, copy number alterations (CNAs), microsatellite instability (MSI), and blood-based tumor mutational burden (bTMB). **Results:** A total of 12 pts with advanced TNBC received IMC-002 in combination with gemcitabine plus carboplatin (n=9) or paclitaxel (n=3). Most pts had received ≥2 prior systemic therapy (n=11), and ECOG PS 1 was observed in 10 pts. TRAEs reported in > 1 pt included grade 3 hematologic events, namely anemia (n=6) and hemolytic anemia (n=5). Non-hematologic TRAEs were limited to grade 1–2 and included skin rash (n=9), vitreous floaters (n=4), photopsia (n=3), and IRR (n=2). Among 12 efficacy-evaluable pts, the ORR was 25%, the DCR was 75%, and the CBR (disease control ≥ 6 months) was 42%. Exploratory ctDNA analyses identified no MSI-H tumors. One patient with a partial response was BRCA-positive. Patients achieving clinical benefit showed a higher median maximum somatic allele frequency (MSAF) than those without clinical benefit (32.65 vs 1.00; p=0.19). No clear association between bTMB and clinical activity was observed. **Conclusions:** IMC-002 in combination with gemcitabine plus carboplatin or paclitaxel demonstrated encouraging antitumor activity with a manageable safety profile in heavily pretreated patients with advanced TNBC. Exploratory baseline ctDNA analyses did not identify molecular features clearly associated with clinical benefit. Clinical trial information: NCT05276310. Research Sponsor: ImmuneOncia Therapeutics Inc.

Phase I trial of the anti-CAPRIN1 antibody TRK-950 alone or with nivolumab in Japanese patients with advanced solid tumors.

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Background: CAPRIN-1 is expressed on the tumor-cell membrane across many solid cancers but not on normal cells. TRK-950 is a first-in-class humanized IgG1 that mediates antibody-dependent cellular phagocytosis and cytotoxicity. A series of pre-clinical studies demonstrates its potency and safety. In the phase I study of TRK-950 monotherapy (NCT02990481) in US and France, it appears safe and well tolerated. No DLT was observed and MTD was not reached at doses of 3-30mg/kg IV weekly. Here, we evaluated safety/tolerability, pharmacokinetics (PK), and preliminary antitumor activity in Japanese patients with advanced solid tumors. **Methods:** Open-label, single-center, dose-escalation study in Japan (NCT05423262). Part 1 evaluated TRK-950 at 5 or 10 mg/kg IV weekly in patients with locally advanced or metastatic solid tumors. Part 2 evaluated TRK-950 at 10 mg/kg weekly or 20 mg/kg every 2 weeks in combination with nivolumab 240 mg every 2 weeks in patients with locally advanced or metastatic solid tumors who were eligible for standard nivolumab monotherapy. Primary endpoints were safety/tolerability (DLT; Treatment-related AEs per CTCAE v5.0). Secondary endpoints included PK, immunogenicity, and antitumor activity by RECIST v1.1. **Results:** Thirteen patients were treated (Part 1 n=7; Part 2 n=6). No DLTs occurred and the MTD was not reached; both monotherapy and combination regimens were well tolerated. TRK-950 PK was consistent with IgG1; exposures were comparable between 10 mg/kg weekly and 20 mg/kg every 2 weeks, with no meaningful PK interaction with nivolumab. In Part 1, a partial response was achieved in a patient with melanoma achieved a partial response, and the response was sustained for an extended period. In Part 2, no response were observed. **Conclusions:** TRK-950, as monotherapy and with nivolumab, was safe and tolerable in Japanese patients with advanced solid tumors. Durable antitumor activity with monotherapy supports continued development. Both the 10 mg/kg weekly and the more convenient 20 mg/kg biweekly dosing regimens of TRK-950 in combination with nivolumab were safely administered, supporting the potential for further development of this combination. Clinical trial information: NCT0542326. Research Sponsor: Toray Industries, Inc.

Safety, pharmacokinetics, and immunogenicity of HLX6018, a monoclonal antibody targeting the GARP/TGF-β1 complex, in healthy subjects: A randomized, double-blind, placebo-controlled, phase I clinical study.

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Background: HLX6018 is a novel anti-GARP/TGF-β1 monoclonal antibody that inhibits TGF-β1 release and suppresses the activation, proliferation, and extracellular matrix secretion of fibroblasts. Preclinical studies have shown its efficacy in improving pulmonary fibrosis with a manageable safety profile. A phase 1 first-in-human study was conducted to evaluate the safety and tolerability of single-dose HLX6018 in healthy Chinese subjects. **Methods:** In this dose escalation phase 1 study, healthy subjects of age 18 to 55 were randomized to receive intravenous, single dose of either HLX6018 or placebo at 0.25 mg/kg, 1.0 mg/kg, 4.0 mg/kg, 12 mg/kg, 25 mg/kg, 50 mg/kg, and 70 mg/kg. A sentinel dosing approach was adopted: each dose group initially enrolled 2 subjects, with 1 receiving HLX6018 and the other receiving placebo in a blinded manner. These 2 subjects then entered a safety observation period after the infusion before the enrolment of remaining subjects for that dose group. The primary endpoint was safety. Secondary endpoints included pharmacokinetics (PK) and immunogenicity. **Results:** A total of 180 subjects were screened and 66 were randomized. 52 subjects received HLX6018 (0.25 mg/kg, 6; 1.0 mg/kg, 6; 4.0 mg/kg, 8; 12 mg/kg, 8; 25 mg/kg, 8; 50 mg/kg, 8; 70 mg/kg, 8) while 14 received placebo (2 subjects in each dose group). The median age was 42.0; 93.9% of the subjects were of Han ethnicity, 50.0% were male. Overall, 46 subjects (69.7%) experienced treatment-emergent adverse events (TEAEs), with 1 subject (1.5%) receiving HLX6018 at 25 mg/kg reporting a serious TEAE of osteonecrosis that was unrelated to HLX6018. 39 subjects (59.1%) experienced treatment-related adverse events (TRAEs). Most common TRAEs (≥ 10% in any dose group) included neutrophil count decreased (HLX6018 vs placebo group: 11.5% vs. 21.4%), injection site pain (11.5% vs. 21.4%), blood corticotrophin decreased (9.6% vs. 14.3%), blood triglycerides increased (9.6% vs. 14.3%) and blood follicle stimulating hormone increased (5.8% vs. 14.3%). There were no TEAEs leading to death, TRAEs leading to drug discontinuation, TRAEs of grade 3 or more in severity, or serious TRAEs. The incidence of TEAEs and TRAEs across the HLX6018 dose groups showed no clear dose-related pattern and was comparable to the placebo group. HLX6018 exhibited approximately linear PK characteristics after single intravenous infusion with the dose range of 0.25–70 mg/kg. Anti-drug antibody was detected in 3 subjects (5.8%) who received HLX6018; no neutralizing antibody was detected. **Conclusions:** HLX6018 is safe and well tolerated across the investigated doses. Further clinical investigation of its efficacy is warranted. Clinical trial information: NCT06310746. Research Sponsor: Shanghai Henlius Biotech, Inc.

Safety and efficacy of a novel PD-L1/4-1BB bispecific antibody QLF31907 in previously-treated patients with advanced melanoma: Results from a phase 2 study.

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Background: QLF31907, a bispecific antibody that simultaneously block PD-1/L1 immunosuppressive pathway on cancer cells and conditionally activate 4-1BB co-stimulatory pathway on tumor-specific T cells, was designed to restrict 4-1BB agonism to the tumor microenvironment, which might overcome resistance to PD-(L)1 inhibitor and reduce hepatoxicity as traditional 4-1BB monoclonal antibodies reported. Although immunotherapy (IO) has revolutionized the treatment of melanoma, a significant proportion of patients (pts), particularly those with mucosal and acral subtypes, either fail to respond initially or experience disease relapse after treatment. Here, we present results of QLF31907 in previously-treated pts with advanced melanoma, including IO-exposed. **Methods:** This phase 2 trial was comprised of safety observation stage and efficacy expansion stage. Pts with unresectable locally advanced or metastatic melanoma who failed, were intolerable to, or refused standard treatment were recruited and administered QLF31907 via intravenous infusion from 5 mg/kg to 20 mg/kg every 2 weeks (Q2W) or 3 weeks (Q3W). The primary endpoints were dose-limiting toxicity (DLT) and safety in safety observation stage, and was objective response rate (ORR) per RECIST v1.1 assessed by investigator in efficacy expansion stage. **Results:** As of Dec 31, 2025, 59 pts were enrolled (median age: 57.0 years; male: 47.5%; ECOG PS of 1: 42.4%; stage IV: 93.2%). The mucosal subtype accounted for the most (40.7%), followed by acral (33.9%), cutaneous (non-acral; 18.6%) and primary unknown (6.8%). Median prior lines of therapies were 2.0 (range, 1–5). Fifty-five (93.2%) pts received prior immunotherapy, including 50 (87.7%) pts received prior anti-PD-1/PD-L1 agents. No DLT occurred. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 34 (57.6%) pts. The most common grade ≥3 TEAEs (≥10%) were liver injury (18.6%), neutrophil count decreased (15.3%), anemia (13.6%), white blood cell count decreased (11.9%). In 57 efficacy-evaluable pts, seven had partial response. The ORR and disease control rate (DCR) was 12.3% (95% confidence interval [CI], 5.1%-23.7%) and 56.1% (95% CI, 42.4%-69.3%), respectively. The median progression-free survival, duration of response, and overall survival was 2.6 months (95% CI, 1.6-3.7), 5.8 months (95% CI, 2.3-not evaluable [NE]), and 15.3 months (95% CI, 11.6-NE), respectively. **Conclusions:** QLF31907 showed potential anti-tumor activity and acceptable safety profile in heavily-treated pts with advanced melanoma, including IO-exposed pts. These results warrant validation in further clinical trials. Clinical trial information: NCT05823246. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

Preliminary results of safety and antitumor activity from a first-in-human phase 1 study of AWT020, a bifunctional anti–PD-1/IL-2 fusion protein, in patients with advanced tumors.

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Background: Immune checkpoint inhibitors have transformed treatment landscape across multiple cancer types, however, resistance to anti-PD-(L)1 therapies remains a significant unmet medical need. AWT020 is a bifunctional fusion protein comprised of an anti-PD-1 antibody and a potency optimized IL-2. In preclinical studies, the mouse surrogate of AWT020 demonstrated superior antitumor activity compared to anti-mPD-1 alone or in combination with IL-2. These findings suggest that AWT020 monotherapy may benefit patients resistant to anti-PD-1 therapies. **Methods:** This first-in-human Phase 1 dose escalation study evaluates AWT020 monotherapy in adults with advanced or metastatic cancers who failed or were intolerant to standard therapies. The dose-escalation utilizes a Bayesian Optimal Interval design. Key endpoints include safety, maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics, immunogenicity, and antitumor responses. Initial dose escalation results are presented herein. Clinical trial information: NCT06092580. **Results:** As of January 14, 2026, 41 patients received AWT020 at doses of 0.3, 0.6, and 1 mg/kg, including single-step (0.1 or 0.3 mg/kg) and two-step (0.1→0.3 mg/kg) priming regimens. Preliminary PK analysis showed approximately dose-proportional exposure. The majority of treatment-related adverse events (TRAEs) were low grade. The most frequently reported TRAEs were arthralgia (59%), rash (34%), fatigue (32%), and nausea (32%). Grade ≥3 TRAEs occurring in more than one subject included arthralgia (n=4), colitis (n=2), and thrombocytopenia (n=2). No patient experienced vascular leak syndrome. Among the 27 RECIST-evaluable patients, the overall response rate was 30%, and the disease control rate was 67%. Of the eight responders, five partial responders (thymic carcinoma, thymoma, clear cell renal cell carcinoma, neuroendocrine non-small cell lung cancer, and cholangiocarcinoma) had developed secondary resistance to anti-PD-(L)1 therapies. The remaining three responders were anti-PD-(L)1-naïve, including a cervical cancer patient who experienced confirmed complete response, and two partial responders with proficient mismatch repair (pMMR) tumors (adrenocortical carcinoma and uterine sarcoma). Ten additional patients with diverse cancer types achieved stable diseases, with tumor shrinkage observed in half of the patients, further supporting preliminary antitumor activity across broad tumor types. **Conclusions:** AWT020 demonstrates a manageable safety profile and promising early antitumor activity, including in patients with acquired resistance to anti-PD-(L)1 therapies and in patients with pMMR tumors which typically are unresponsive to immune monotherapy. Dose escalation is ongoing to establish MTD/RP2D. Clinical trial information: NCT06092580. Research Sponsor: Anwita Biosciences Inc.

A phase II study of perioperative cadonilimab (AK104) in patients with recurrent resectable head and neck squamous cell carcinoma.

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Background: Salvage surgery is standard of care for patients with recurrent, resectable head and neck squamous cell carcinoma (HNSCC); However, the efficacy of salvage surgery remains limited. Therefore, there is an urgent need to explore new therapeutic strategies to further improve the survival of this patient subset. Cadonilimab, a PD-1/CTLA-4 bispecific antibody, uses an IgG-ScFv structure with Fc domain point mutations, allowing for high retention in tumor tissue, and providing enhanced stability and improved safety. In this study, we aim to explore the efficacy and safety of neoadjuvant and adjuvant Cadonilimab combined with salvage surgery in patients with recurrent, resectable HNSCC. **Methods:** This was an open-label, single-institutional phase II clinical trial (ChiCTR2400079741). Patients aged 18-75 years, pathologically confirmed recurrent HNSCC (oral, laryngeal, hypopharyngeal, and oropharyngeal carcinoma), and with resectable diseases assessed by surgeons were included. Eligible patients received two cycles of Cadonilimab (6mg/kg, ivgtt, q2w) 2-4 weeks before surgery, then treated by salvage surgery, followed by 12 cycles of adjuvant Cadonilimab. Primary endpoint was 1-year disease free survival (DFS), and secondary endpoints were objective response rate (ORR), major pathological response (MPR), OS and safety. **Results:** From November 2023 to December 2024, a total of 32 patients were enrolled. One patient refused surgery, and 31 patients were included in the final analysis. According to radiological assessment, the ORR was 28.1% (9/32), with 2 cases of complete response (CR) and 7 cases of partial response (PR). Among the patients receiving surgical resection, the MPR rate was 32.3% (10/31), with 9.7% (3/31) of patients achieving pathological CR. With a median follow-up of 18.8 months (range, 13.0-25.7 months), the 1-year DFS rate was 77.4%, and the 1-year OS rate was 87.1%. Treatment-related adverse events (TRAEs) occurred in 74.2% (23/31) of patients. The majority of TRAEs were grade 1 or 2. Grade ≥3 TRAEs occurred in 6.5% (2/31) of patients, including one case of grade 3 neutropenia and one case of grade 4 immune-related hepatitis. The most common TRAEs were hypothyroidism (25.8%, n=8), anemia (25.8%, n=8), lymphocytopenia (19.4%, n=6), fatigue (16.1%, n=5), myocarditis (12.9%, n=4), constipation (12.9%, n=4), rash (12.9%, n=4), elevated ALT/AST levels (12.9%, n=4), and neutropenia (6.5%, n=2). **Conclusions:** Cadonilimab demonstrated encouraging anti-tumor activity and acceptable safety profile in patients with recurrent, resectable HNSCC. Cadonilimab may change the therapeutic approach for recurrent, resectable HNSCC. Clinical trial information: ChiCTR2400079741. Research Sponsor: None.

Anti-tumor activity of Man 9 x PS targeting immunotherapies in diffuse intrinsic pontine glioma (DIPG) and pancreatic cancers.

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Background: Aberrant cell-surface glycans and lipids are attractive immunotherapy targets due to their stable tumor expression. High-mannose glycan mannose-9 (Man9), and phosphatidylserine (PS) are co-expressed across multiple malignancies and contribute to immune suppression. We developed Man9×PS-targeting effector immunotherapy platforms for the treatment of solid tumors, with a focus on pancreatic cancer and diffuse intrinsic pontine glioma (DIPG). **Methods:** The Man9×PS×CD3 trispecific T cell engager (TCE), VTRU200, was expressed and purified from CHO cells. The Man9×PS CAR T cell, VCAR300, was generated from murine splenic T cells transduced with a Man9×PS CAR-encoding viral vector. In vitro tumor cytotoxicity of VTRU200 was assessed using human T cells co-cultured with cell lines (PANC-1, AsPC-1) or patient-derived primary cultures (DIPG-008, DIPG-011) and compared with bispecific Man9×CD3 or PS×CD3 controls. Tumor selectivity and potential off-target binding were evaluated by immunohistochemistry (IHC) on pancreatic and breast tumors with matched normal tissues, and by immunofluorescence (IF) across a panel of 33 normal human tissues. *In vivo* dose escalation of VCAR300 was evaluated by bioluminescence imaging in a Panc02 murine orthotopic pancreatic tumor model. Cancer stem cell binding was verified by co-staining with anti-CD133 antibody. Previously, VTRU200 was evaluated in syngeneic, xenograft, and patient-derived xenograft (PDX) acute myeloid leukemia (AML) models, and VCAR300 persistence was tested in a pilot orthotopic pancreatic cancer model. **Results:** VTRU200 demonstrated potent, target-dependent cytotoxicity with 0.1-5 nM EC50 values across multiple solid tumor cell lines in the presence of human T cells. Cytotoxicity required engagement of both Man9 and PS, with additive effects relative to bispecific controls. IHC demonstrated strong staining in pancreatic and breast tumors with absence of staining in corresponding paired normal tissues, while there was no detectable reactivity across normal human tissue panels by IF. Consistent with prior AML studies showing robust anti-leukemic activity, VCAR300 exhibited high anti-tumor activity in vitro with an effector:target ratio at 50% maximum killing (ET50) of less than 1, and in a murine orthotopic pancreatic cancer model (25-fold reduction in tumor size after 2 weeks of treatment with $2x10^6$ CAR T/mouse) with an excellent safety profile. Anti-tumor activity was associated with tumor stem cell targeting and release of inflammatory cytokines. **Conclusions:** Man9 x PS dual targeting is a promising strategy for treating solid tumors. VTRU200 and VCAR300 are potential therapeutic candidates with potent anti-tumor activity across multiple tumor types and impressive safety. Following a successful pre-IND interaction with the FDA, first-in-human studies are planned to initiate in 2027. Research Sponsor: None.

Multiomic machine learning integration of DNA and RNA features to predict immunotherapy benefit in MSS-CRC and other rare cancers.

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized the oncology landscape, yet remain constrained by imprecise predictive biomarkers (i.e., PD-L1, TMB, MSI), which fail to capture the complexity of the tumor microenvironment. The Immune Profile Score (IPS), an AI/machine learning (ML) driven DNA-/RNA-based molecular signature addresses this gap in translational molecular biomarkers of ICI response. IPS integrates TMB, single-gene RNA features and RNA signatures, and was independently validated for prognostic utility in $>1,500$ advanced solid tumor patients (pts) treated with FDA-approved ICI. Here we evaluated the ability of IPS to accurately stratify ICI treatment outcomes in two independent cohorts representing traditionally ICI-resistant populations. **Methods:** From our multimodal real-world database, we used the ML-derived IPS algorithm to analyze two cohorts of high unmet need for which ICI is not approved: 1) microsatellite stable colorectal cancer (MSS CRC); and 2) rare solid cancer as defined by FDA ($<200,000$ cases/year) treated with off-label ICI. Pts were categorized as IPS-H and IPS-L using a previously independently validated and published threshold. Cox proportional hazards models were fit to demonstrate prognostic utility for real-world overall survival (rwOS). Association with time-to-next-treatment (TTNT) on prior chemotherapy (CT) was compared in the same pts to rwOS on subsequent ICI therapy to assess ICI-specific predictive value of IPS . **Results:** IPS-H consistently identified a subset of pts with improved clinical outcomes across both cohorts. In the MSS-CRC cohort (n = 46): IPS-H pts (6/46 = 13%) had longer rwOS than IPS-L pts (40/46 = 87%) (HR 0.22; 90% CI: 0.04-1.16). No difference was observed in TTNT between IPS-H and IPS-L for prior CT (HR 1.07; 90% CI: 0.60-1.91), while there was improvement in rwOS IPS-H vs IPS-L on subsequent ICI therapy (HR 0.21; 90% CI: 0.04-1.22). In the rare cancer cohort (n = 90): there were 26 solid tumor subtypes without an FDA-approved ICI label; carcinosarcoma (n = 19, 21%) and pancreatic ductal adenocarcinoma (n = 17, 19%) were the most commonly represented. IPS-H pts (16/90 = 18%) had longer rwOS than IPS-L pts (HR 0.26, 95% CI: 0.09-0.73). In this rare cancer cohort, IPS remained significant even when restricted to subtypes with representation from both IPS-H and IPS-L (HR = 0.18, 95% CI: 0.04-0.69). **Conclusions:** IPS is a novel multiomic genomic signature that identifies a subset of advanced MSS-CRC and rare solid cancer patients who may benefit from ICI therapy. By integrating multimodal genomic features, IPS emerged as a possible predictive biomarker in a population where ICI is not currently approved. IPS suggests a paradigm shift toward AI/ML-driven signatures to refine ICI candidate selection and personalize clinical decision-making in oncology. Research Sponsor: None.

AI-powered spatial tumor microenvironment analysis in metastatic microsatellite-stable colorectal cancer receiving immunotherapy.

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Background: Microsatellite-stable (MSS) colorectal cancer (CRC) is typically immune-cold, limiting the routine use of immune checkpoint inhibitors (ICIs). However, a subset of MSS CRC patients may still derive benefit from ICIs. Leveraging an AI-powered whole-slide image (WSI) analyzer applied to hematoxylin and eosin (H&E)–stained slides, we sought to identify subsets of MSS CRC more likely to benefit from ICIs. **Methods:** Between August 2016 and May 2024, pretreatment H&E–stained WSIs were collected from patients with metastatic MSS CRC treated at Asan Medical Center, Seoul, Korea. After quality control, 91 WSIs (93.8%) from 51 patients were included in the final analysis. Patients were treated with anti-PD-1/PD-L1 ICIs in clinical trials, with the majority treated in the third-line setting (n = 46, 90.2%). An AI-powered WSI analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) segmented cancer area (CA) and stromal area and identified tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS), fibroblasts, and endothelial cells within tumor tissue. We then evaluated the associations between CA-specific densities of TILs, macrophages, and endothelial cells, as well as the summed TLS area, and progression-free survival (PFS) and overall survival (OS). **Results:** Using maximally selected rank statistics based on PFS, patients were dichotomized into high and low groups according to the summed TLS area and the densities of TILs, macrophages, endothelial cells, and fibroblasts within the CA. Notably, patients with a high summed TLS area had significantly improved PFS and OS compared with those with a low TLS area (median PFS, 3.6 vs. 1.6 months; P=0.026; median OS, 11.6 vs. 6.6 months; P=0.024). High endothelial cell and fibroblast densities within the CA were not significantly associated with PFS (P=0.160, P=0.112, respectively), but were associated with worse OS, with a significant association for endothelial cells (median, 7.6 vs. 14.7 months; P=0.024) and a trend toward worse OS for fibroblasts (median, 8.9 vs. 12.2 months; P=0.056). Higher macrophage density within the CA showed a favorable trend toward improved PFS (median, 10.2 vs. 8.5 months, P=0.092), but was not associated with OS (P=0.399). In contrast, none of these biomarkers were associated with clinical outcomes in the first-line chemotherapy. **Conclusions:** Despite microsatellite-stable status, a higher summed TLS area was associated with improved progression-free and overall survival following immunotherapy, with endothelial cell and fibroblast densities providing additional prognostic information. AI-powered WSI analysis enabled effective stratification of these features. Research Sponsor: Lunit.

Multimodal immunoprofiling of peripheral blood using foundation models of the immune system for predicting immunotherapy response and toxicity in the RADIOHEAD pan-cancer cohort.

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Background: While immune checkpoint inhibition (ICI) is an emerging gold standard for cancer therapy, positive response is limited among treated patients and up to 70% experience toxicity. Early and accurate response prediction that accounts for immune-related adverse events (irAEs) is crucial for identifying patients who may benefit from ICI. We present AI-powered approaches for predicting ICI response by transcriptional and cellular profiling of blood immune cells from a pan-cancer cohort. **Methods:** Peripheral blood mononuclear cells (PBMC) were isolated at pre- (baseline) and early on-treatment for flow cytometry and RNA-seq profiling from the RADIOHEAD cohort *(Quandt et al. 2025)* receiving ICI (n=1,070). Patients were clustered based on variational autoencoder embeddings for real-world progression-free survival (rwPFS) and irAEs derived by a peripheral immune system encoder trained on the BostonGene patient database (n=45,000). The logrank test and Fisher's exact test were used to analyze survival and compare irAE frequencies between clusters, respectively. RNA-seq trajectory features were identified using hierarchical clustering, along with elastic net-regularized and simple multivariate Cox regression models for feature selection. **Results:** Pre-trained immunotype models (Dyikanov et al. 2024) applied to baseline PBMC revealed that G2-primed (memory CD4+ T cell-enriched) and G5-suppressive (monocyte enriched) immunotype scores stratified patients into responders (R) and non-responders (NR) ($p = 0.00001$). T cell receptor (TCR) dynamics revealed a significantly greater decrease in TCR diversity in NR during treatment ($p = 0.046$). We discovered a baseline gene set containing immune checkpoint and cancer antigen genes as well as a longitudinal trajectory set of monocyte and myeloid cell activation markers that both stratified patients by rwPFS ($p=0.006$; 0.03). Trained immune system embeddings identified a novel severe-risk patient group with both a high irAE incidence ($p = 0.025$) and short rwPFS. This group displayed both active inflammatory and tolerance pathways that stratified patients with irAEs by rwPFS ($p = 0.003$). **Conclusions:** Using pre-trained multimodal immune system projections, we 1) independently confirmed the association of peripheral immunotypes with ICI response; and 2) identified a novel severe-risk signature from patients with high irAE incidence (≥Grade 3) and short rwPFS. We also found that greater TCR diversity and T cell differentiation were associated with ICI response, while innate myeloid activation and trafficking correlated with non-response. Our unique AI-driven analytical framework underscores the potential of peripheral blood immunoprofiling for ICI treatment selection and patient stratification in prospective trials. Research Sponsor: None.

External validation of a deep learning CT biomarker to predict first-line immune checkpoint inhibitor monotherapy-associated survival in PD-L1–high metastatic non–small cell lung cancer.

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Background: Immune checkpoint inhibitor (ICI) monotherapy is a standard first-line treatment for patients with metastatic non–small cell lung cancer (mNSCLC) with high PD-L1 expression. However, 60% of patients treated with ICI monotherapy progress within 1 year of treatment. Imaging-based biomarkers from routine pretreatment computed tomography (CT) scans may provide a noninvasive approach to refine patient selection and guide treatment decisions. **Methods:** Enhanced CT Response Score (eCTRS v0.0.2; Sako et al, JCO CCI, 2024) is an imaging-based biomarker that stratifies patient survival among mNSCLC patients receiving ICI monotherapy. eCTRS is derived from pre-treatment CT scans, using deep-learning extracted imaging features, lesion features, and clinical variables of age and sex. eCTRS was previously trained on a diverse, real-world multi-institutional dataset of 1,058 mNSCLC patients. This retrospective study externally validated eCTRS using a deidentified, EHR-derived longitudinal database with imaging from Flatiron Health. Patients with PD-L1–high (PD-L1 tumor proportion score $\geq$ 50%) mNSCLC without actionable mutations who received first-line ICI monotherapy and had imaging from 12 weeks before to 2 weeks after treatment start were included. Patients were stratified into eCTRS High and eCTRS Low groups using a predetermined threshold. Survival analyses were conducted by an external, independent group. Kaplan-Meier and Cox proportional hazards analyses evaluated progression-free survival (PFS) and overall survival (OS) stratification. PFS was derived from RECIST 1.1 assessments by a centralized multi-reader radiologist adjudication process, and OS was defined as time from treatment start to death by any cause. **Results:** 205 patients met all inclusion criteria (median age 72 years, 48% female, 20% non-White). Eighty (39%) patients were classified as eCTRS Low and 125 (61%) as eCTRS High. PFS was improved among eCTRS High patients (Hazard Ratio [HR], 0.71; 95% CI, 0.51–1.00; p=0.048), with median PFS of 231 (95% CI: 133, 350) days versus 88 (95% CI: 57, 179) days in eCTRS Low patients. eCTRS High patients demonstrated significantly improved OS (HR, 0.56; 95% CI, 0.39–0.80; p=0.001), with median OS of 484 (95% CI: 361, NA) days for eCTRS High, versus 155 (95% CI: 75, 295) days for eCTRS Low. **Conclusions:** A deep learning–based imaging biomarker derived from routinely acquired pretreatment CT imaging identified survival benefit in patients with PD-L1–high metastatic NSCLC treated with first-line ICI monotherapy. These findings suggest that imaging-based biomarkers may serve as complementary, noninvasive tools to identify patients most likely to derive benefit from ICI monotherapy and to support risk-adapted treatment strategies. Research Sponsor: U.S. National Institutes of Health; 1R44CA291456.

Artificial intelligence (AI) foundation model as a predictor of efficacy of next-generation checkpoint inhibition with botensilimab (BOT) + balstilimab (BAL) in solid tumors using pretreatment H&E images.

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Background: Predicting immunotherapy response is challenging in treatment-refractory/resistant (R/R) tumors where heterogeneity limits conventional biomarker utility. BOT (Fc-enhanced anti–CTLA-4) augments T-cell priming, depletes Tregs, and activates antigen-presenting cells. BOT+BAL (anti–PD-1) has shown activity across "cold" and R/R tumors including PD-L1–low and tumor mutational burden–low disease; thus, non-conventional predictive biomarkers are needed. A self-supervised AI foundation model applied to routine pretreatment H&E images was used to infer spatial transcriptomics and identify features associated with therapeutic benefit from BOT+BAL in microsatellite-stable colorectal cancer (MSS CRC), sarcoma, and ovarian cancer. **Methods:** A self-supervised AI foundation model was trained to infer spatial transcriptome expression from H&E images using purpose-built multimodal training data from thousands of human tumors profiled with multimodal assays. Pretreatment H&E images (not used for training) from 121 BOT+BAL–treated patients (pts) with R/R MSS metastatic CRC (included 20 pts with liver metastases), sarcoma, and ovarian cancer from the phase 1b C-800-01 trial (NCT03860272) were analyzed. Pt-specific embeddings were used to fit cross-validated classifiers predicting BOT+BAL clinical benefit (defined as complete or partial response [CR/PR] or stable disease [SD]). **Results:** Fitted logistic regression classifiers separated responders and non-responders in all tumor types, as measured by area under the receiver operating characteristic curve (AUROC; ranges from 0.5 [chance] to 1.0 [perfect separation]). Cross-validated AUROC was 0.61 in MSS CRC, 0.67 in sarcoma, and 0.77 in ovarian cancer (table; shows all findings). The model-recommended population is predicted to have a higher rate of clinical benefit, as measured by cross-validated precision. Beyond this binary analysis, the concordance index (C-index; measures accuracy and ranges from 0.5 [chance] to 1.0 [perfect]) for predicting overall survival (OS; via Cox proportional hazards model) was >0.5 in all tumor types, and highest in ovarian cancer. **Conclusions:** A self-supervised AI foundation model applied to routine pretreatment H&E images predicted BOT+BAL responses in MSS CRC, sarcoma, and ovarian cancer. These findings support AI-derived, H&E–based biomarker strategies for BOT+BAL and warrant prospective validation. Research Sponsor: Agenus Inc.; Noetik Inc.

Sample characteristics and model predictions.

	MSS CRC	Sarcoma	Ovarian
Sampled population[a]			
No. of pt samples	67	30	24
Pts with CR/PR or SD	65%	57%	54%
Modeled population			
AUROC	0.61	0.67	0.77
OS prediction, C-index	0.58	0.69	0.78
Model recommended population			
Population size	43%	50%	46%
Estimated pts with CR/PR or SD	76%	67%	73%

[a]Data cutoff: Mar 13, 2025; analyses ongoing.

Clinical and translational results from the phase 1 portion of the phase 1/2 study to evaluate CHM-2101, an autologous cadherin 17 (CDH17) chimeric antigen receptor (CAR) T cell therapy for the treatment of relapsed or refractory gastrointestinal cancers.

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Background: CHM-2101 is a Cadherin 17 directed autologous CAR T-cell product being developed to address the continuing unmet medical need for effective therapy against relapsed or refractory gastrointestinal (GI) cancers. Solid tumors of the GI tract such as gastric cancer, colorectal cancer (CRC) and neuroendocrine tumors (NETs) are devastating diseases associated with poor outcomes and more than 1.3 million global deaths annually. Despite advances in surgical and medical treatment of these solid tumors, the prognosis for patients with relapsed or refractory disease remains poor. There remains a need for innovative and effective treatments for patients with advanced and treatment-recalcitrant GI malignancies. **Methods:** The ongoing clinical trial is a seamless Phase 1/2 study enrolling subjects with gastric cancer, CRC or NETs of the midgut or hindgut. Enrolled subjects undergo screening and apheresis to enable manufacturing of CHM-2101. After completing apheresis, bridging therapy is permitted to provide disease control. After confirming successful CHM-2101 manufacturing and washout of bridging therapy, study subjects receive 3 days of lymphodepleting chemotherapy (fludarabine 30mg/m2/day and cyclophosphamide 500mg/m2/day). After two days of rest, subjects receive a one-time IV infusion of CHM-2101. **Results:** As of October 24, 2025, 13 subjects have been enrolled with 2 screen failures. Eleven of eleven successful manufacturing runs enabled treatment of 9 subjects to date (4 subjects at Dose Level 1 and 5 subjects at Dose Level 2). Most AEs were Grade 1-2. Aside from lymphodepleting chemotherapy-related cytopenias, Grade 3 Treatment-Related Adverse Events (TRAEs) were Cytokine Release Syndrome (CRS) and Enterocolitis in 1 subject each. There have been no Grade 4 or 5 TRAEs or DLTs. After IV infusion, CHM-2101 was noted to expand and persist (by flow and ddPCR) in the peripheral blood of all treated subjects. **Conclusions:** CHM-2101 has demonstrated cellular expansion and persistence with clinical tolerability in study subjects with advanced GI cancers at two dose levels. Enrollment of patients at Dose Level 3 is ongoing at US Cancer Centers. Clinical trial information: NCT06055439. Research Sponsor: None.

Tumor infiltrating lymphocytes (LM103 infusion) in solid tumors: A phase I trial evaluating clinical and immunological anti-tumor activity.

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Background: Tumor-infiltrating lymphocyte (TIL) therapy has shown clinical promise in melanoma, but its applicability across diverse solid tumors in Asian patients remains unclear, and exploring molecular targets to improve anti-tumor responses of TIL are needed. **Methods:** In the phase I investigator-initiated trial, we evaluated the safety, feasibility, and preliminary efficacy of autologous TIL therapy in twelve patients with advanced melanoma, cervical, lung, or head and neck cancers. Twelve patients who failed with standard treatments were successfully enrolled in the trail from August 2022 to December 2024. The patients received a lymphodepletion therapy which consisted of cyclophosphamide (30mg/kg) for 2 days, followed by fludarabine (25mg/m^2) for 5 days, approximately 24 hours before receiving the intravenous autologous TILs infusion, and then received high doses of IL-2 for 6-12 days with the purpose of maintaining T cell survival and proliferation. After a 28 days safety observation, tumor assessment according to RECIST 1.1 was conducted every 6 weeks until 6 months followed by every 12 weeks long-term follow-up. T cell receptor (TCR) sequencing was performed to explore TIL persistence in vivo after TIL infusion. Differential genes were identified via Bulk-RNA sequencing on TILs of responders and non-responders. Target gene knocking out of TIL using CRISPR/Cas9 technology was performed to enhance its anti-tumor function. **Results:** The most common adverse observed events were fever, anemia, nausea, hypertension, and hyponatremia. The objective response rate (ORR) was 33.3% (4/12), including one complete response (CR) and three partial responses (PR), and the disease control rate (DCR) reached 75% (9/12). Infused TILs persisted in peripheral blood and induced reversed peripheral CD4+T and CD8+T percentages. T cell receptor (TCR) sequencing revealed dynamic clonal remodeling in responders. Transcriptomic profiling of infused TILs identified ASS1 and CEP20 as genes negatively associated with therapeutic activity. CRISPR/Cas9-mediated knockout of these targets enhanced TIL memory phenotypes, cytokine production, and tumor cytotoxicity *in vitro* and *in vivo*. **Conclusions:** Autologous TIL monotherapy is feasible and safe. This study reveals effective TIL therapy in diverse solid tumors of Asian patients and potent anti-tumor activity of genetically enhanced ASS1 KO and CEP20 KO TILs, which offer mechanistic insights that may guide optimization of TIL therapy for broader clinical application. Trial registration number: NCT05366478. Clinical trial information: NCT05366478. Research Sponsor: None.

Extended monitoring and biomarker analysis in metastatic melanoma patients treated with TIL therapy and conditioning-replacing igrelimogene litadenorepvec virotherapy: Pre-infusion immune cell and cytokine profiles associated with survival.

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Background: Adoptive transfer of tumor-infiltrating lymphocytes (TILs) can be effective in metastatic melanoma, but its routine use is limited by the need for lymphodepleting chemotherapy and systemic high-dose IL-2. To reduce toxicity while preserving antitumor activity, a strategy pairing TIL therapy with the oncolytic adenovirus igrelimogene litadenorepvec (TILT-123) was assessed. This virus selectively replicates in malignant tissue and drives local expression of TNF and IL-2 within tumors, functionally replacing the need for pre-infusion chemotherapy and post-infusion IL-2 administration. **Methods:** Seventeen patients with advanced melanoma resistant to immune checkpoint inhibitors were treated and sampled (NCT04217473). Treatment with igrelimogene litadenorepvec started upon tumor biopsy collection for TIL manufacturing took place and eventually followed by autologous TIL infusion around 36 days after. Hypotheses generated during data analysis were validated using additional patient datasets (NCT04695327, NCT05271318). **Results:** The regimen was well tolerated, with no dose-limiting toxicities. Objective response rate was 11.7%, with disease control in 35% by RECIST 1.1 and 47% by PET; metabolic responses were seen in 27%. Among those patients, higher baseline expression of epidermal and hepatocyte growth factors (EGF and HGF respectively) was associated with poorer prognosis. Higher than median HGF was negatively correlated with survival (p=0.032). Additionally, patients that achieved disease stabilization or better had a lower presence of circulating MDSCs (p=0.017). The link between growth hormones, MDSCs and disease progression was extrapolated to a larger dataset including other patients treated with igrelimogene litadenorepvec to find out the same trend for survival (HGF; p = 0.003, EGF; p = 0.029). In parallel, baseline circulating young memory T cells (CD27+CD28+CD8+) and an early expansion of NK cells (CD45+CD56+CD3-) correlated with a lower chance of progressing (T cells p=0.005, NK cells p=0.003). **Conclusions:** Combining TILT-123 with TIL therapy was safe and produced meaningful clinical activity in checkpoint inhibitor-refractory melanoma, especially in patients with lower HGF and EGF at baseline and a higher presence of young memory T cells and NK cells. In this clinical set-up, adapting the inclusion exclusion criteria to select patients with those defined immune system features, could help improve efficacy beyond. This approach may substantially broaden the feasibility and accessibility of TIL-based immunotherapy, especially due to the omission of the toxic conditioning regimens. Clinical trial information: NCT04217473. Research Sponsor: None.

Immunologic and clinical outcomes of perfluoroalkyl substances (PFAS) exposure in solid tumors treated with pembrolizumab.

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Background: Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are two major PFAS with persistent and widespread human exposure. Epidemiologic studies in non-cancer individuals suggest PFAS-associated immune dysregulation and anti-inflammatory effects. We assessed immunologic and clinical effects of PFAS on patients (pts) with advanced solid tumors treated with pembrolizumab. **Methods:** In the investigator-initiated INSPIRE study (NCT02644369) (n = 106) of advanced solid cancer pts treated with pembrolizumab (head and neck squamous cell cancer, triple-negative breast cancer, high-grade serous carcinoma, melanoma and other mixed solid tumors), we quantified baseline PFOS and PFOA via HPLC-tandem mass spectrometry. PFAS were evaluated as continuous variables and dichotomized at the median (< median vs > median; PFOS 3.6 ng/ml; PFOA 1.0 ng/ml). Associations with clinical and demographic factors were assessed using correlation/regression analyses. Association with toxicity and objective response (ORR) used Wilcoxon rank-sum tests; progression-free survival (PFS) and overall survival (OS) used Cox proportional hazards models. Immune correlates (immune infiltration measured by multiplex IHC, bulk-RNA sequencing of tumor tissue and plasma cytokine levels measured by Luminex multiplex cytokine assay) were evaluated using median-split Wilcoxon comparisons with Benjamini-Hochberg false discovery rate (FDR) control ($q < 0.2$). **Results:** Baseline PFOS and PFOA levels were moderately correlated (Pearson $r = 0.49$, $p < 0.001$). PFOS levels were significantly higher with increasing age (median age 59.4 years; range 21.1-81.8; $p = 0.016$). PFOA levels were significantly higher with increasing age ($p = 0.001$), in males ($p = 0.042$), and in the melanoma cohort ($p = 0.015$), and significantly lower in pts with prior systemic therapy ($p = 0.001$). For immune parameters, higher PFOA exposure was associated with reduced CD4 T-cell infiltration in tumor and stromal areas ($q = 0.07$). RNA sequencing of genes and immune signatures showed no associations reaching FDR significance. 10 cytokines were significantly lower in pts with high PFOA levels: IL-16, IL-2R, IL-3, HGF, IFN-γ, MCP-2/CCL8, MDC/CCL22, TNF-RII, TSLP, and BLC/CXCL13 (all $q = 0.15$) in ovarian cancer and melanoma pts. Neither PFOS nor PFOA levels showed significant associations with ORR, toxicity, PFS or OS. **Conclusions:** PFOS and PFOA levels vary by demographic and clinical factors but show no direct association with toxicity and treatment outcomes in pts treated with pembrolizumab. Elevated PFOA exposure correlates with reduced T-cell infiltration and cytokine suppression, potentially inducing systemic and local immune dysregulation. These findings highlight immunologic effects of PFAS and warrant mechanistic and longitudinal studies. Research Sponsor: None.

GK01 stemness-enriched tumor-reactive T-cell therapy plus IL-2 in advanced solid tumors: ORR and clonal persistence results in a first-in-human phase I study (GUARDIAN-01).

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Background: T-cell exhaustion and poor persistence limit tumor infiltrated lymphocytes (TILs) efficacy in solid tumors. GK01 is an autologous tumor-reactive T-cell product enriched for stem cell memory T cells (TSCM: $CD45RA^{+}CD62L^{+}$) and diverse T-cell receptor (TCR) clonotypes to promote durable engraftment. We conducted GUARDIAN-01 (NCT06954558), a phase I study of GK01 plus IL-2 in advanced solid tumors. **Methods:** This single-arm, open-label study enrolled patients with advanced solid tumors (ECOG PS 0-1; measurable disease per RECIST v1.1). Patients received standard lymphodepletion, GK01 (5×10^{9}-1×10^{11} cells per manufacturing yield), and IL-2 (300,000 IU/kg IV q12h, up to 5 days). Repeat infusion was permitted at investigator discretion based on clinical benefit. Primary endpoint was safety; secondary endpoints included objective response rate (ORR), disease control rate (DCR), and cellular kinetics via absolute lymphocyte count (ALC) and TCR sequencing. **Results:** From March 2025 to January 2026, 6 patients were enrolled (median age 53.5 years; median 2 prior lines; tumor types included gastric n = 3, pancreatic n = 1, penile SCC n = 1, and melanoma n = 1). Manufacturing succeeded in all patients; median time from tissue procurement to infusion was 28 days (range 25-39). Infused GK01 exhibited median TSCM frequency of 71% (range 42-92%) and demonstrated robust expansion and stemness properties. Upon tumor challenge, these T cells secreted IFN-γ at a median of 1,632 pg/mL (range, 35 - 4,886). Median dose was 2.8×10^{10} cells (range 1.4×10^{10}-8.8×10^{10}); 2 patients received repeat infusion. The median total IL-2 dose administered was 4 (range 1-5), with the first dose administered approximately 6 hours after GK01 infusion. No dose-limiting toxicities (DLTs) occurred. G3/4 adverse events were exclusively hematologic (neutropenia, thrombocytopenia, leukopenia, lymphopenia in all patients), attributable to lymphodepletion. Chills, fever, and erythroderma occurred in all patients but G1-2, resolving within 2 weeks. At median follow-up of 169 days (range 80-297), ORR was 66.7% (4/6 PR; 2/6 SD), and DCR was 100%. The median peak ALC reached at 11.3×10^{9}/L (range 4.9-22.7) at days 7-9 post-infusion, remained elevated at 3.1×10^{9}/L (range 2.0-6.4) at 1 month. Among patients with available peripheral-blood samples (n = 4), product-derived TCR clonotypes comprised 94% of the circulating repertoire at day 7 and 92% at 2 months. **Conclusions:** In this first-in-human study, GK01 plus IL-2 demonstrated a favorable safety profile with no DLTs and manageable toxicity. The TSCM-enriched product achieved a 67% ORR and 100% DCR, with product-derived clonotypes persisting at $>$ 90% of the T-cell repertoire at 2 months. These findings validate the stemness-enriched T-cell platform and support expansion cohorts in selected solid tumor indications. Clinical trial information: NCT06954558. Research Sponsor: Geekgene.

Longitudinal immune programs and association with toxicity burden and antitumor response during immunotherapy.

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Background: Immune-related adverse events (irAEs) and tumor responses often co-occur during immune checkpoint inhibitor (ICI) therapy. We investigated whether blood immune programs associated with toxicity can be temporally and biologically dissociated from response programs. **Methods:** ICI-naïve patients with advanced solid tumors (n=37; enriched for melanoma and NSCLC) were profiled at baseline (T0), early on-treatment (T1; week 4), and later timepoints (T2–T3); patients with irAEs had an additional sample at onset (Ttox) before immunosuppression. PBMCs were analyzed by multiparameter flow cytometry and plasma cytokines by 48-plex multiplex assay (log2). We compared timepoints and delta windows (ΔT1–ΔT3), controlled multiple testing with Benjamini–Hochberg ($q<0.1$), and evaluated baseline predictors from T0 alongside landmark Cox models from T1 for ΔT1 predictors to avoid immortal-time bias; baseline multiple-irAE signatures were tested in penalized multivariable models with clinical covariates. **Results:** irAEs occurred in 20/37 (54%) patients (grade ≥3: 8/37, 22%); multiple irAEs occurred in 14/37 (38%). Objective response occurred in 15/37 (41%), and 10/15 (67%) responders developed irAEs; median time to first irAE was 86 days (IQR 63–108). Baseline multiple-irAE susceptibility centered on Tfh states (higher Tfh1/Tfh17 PD1+ICOS− and lower Tfh1 PD1−ICOS+), and a MultiTox signature predicted multiple irAEs (OR 5.46; p=0.033). Early dynamics strengthened toxicity prediction: ΔT1 Tfh2 PD1+ICOS− decreased in AnyTox/MultipleTox and predicted subsequent irAEs (HR 0.41; p=0.0019), whereas ΔT1 PDGF-BB (log2) increased risk (HR 2.25; p=0.006). Approaching onset, activated regulatory compartments (activated Treg and Tfr) contracted, followed at Ttox by a surge in IFN-inducible CXCR3 chemokines (CXCL9/MIG $p=3.1\times10^{-5}$; CXCL10/IP-10 p=0.0021), consistent with a Th1/IFN axis. In contrast, response-associated programs emerged later and reflected a Tfh/B cell–activated CD8 axis (memory B at T1 p=0.036; ΔT2 Tfh2 PD1−ICOS− $q<0.1$, p=0.0010; ΔT2 eosinophils $q<0.1$, p=0.0071) and remained independently associated with response ($p\approx0.02$–0.03). **Conclusions:** Toxicity—particularly high-burden toxicity—appears to reflect a baseline susceptibility that is amplified by early on-treatment immune trajectories and culminates in a chemokine-rich onset state. In contrast, response-associated programs emerge later and are at least partly dissociable from high-burden toxicity. Distinct Tfh states—especially early Tfh2 dynamics—may support timing-informed monitoring and improved benefit–risk stratification during ICI therapy. Research Sponsor: None.

Phase 1 trial of a KRAS G12V/HLA-A*11:01–restricted TCR-engineered T-cell therapy in advanced solid tumors.

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Background: KRAS G12V is a prevalent oncogenic driver in solid tumors, particularly pancreatic cancer (PC), occurring in approximately 20-30% of patients (pts). Advanced solid tumors harboring this mutation carry a poor prognosis and limited treatment options following standard chemotherapy. This phase 1 study evaluates a novel TCR-engineered T cell (TCR-T) therapy derived from a naturally occurring, KRAS G12V/HLA-A*11:01–restricted T cell receptor (TCR) isolated from patient tumor-infiltrating lymphocytes. **Methods:** This open-label, single-arm, dose-escalation phase 1 trial assessed the safety, tolerability, and preliminary efficacy of autologous TCR-T cells in pts with advanced solid tumors. Eligible pts had confirmed KRAS G12V mutation and HLA-A*11:01 positivity. Using a standard 3+3 design, autologous T cells were transduced with a lentiviral vector encoding the TCR and a CD8 co-receptor. Pts received lymphodepletion with cyclophosphamide and fludarabine, followed by a single infusion of TCR-T cells at either 5×10^9 (DL1) or 1×10^{10} (DL2) cells, with adjunctive interleukin-2. **Results:** As of January 2026, 8 pts were enrolled; of whom 6 (median age 69.5 years, ECOG PS 1) received the planned infusion, including pts with colorectal cancer (n = 2), pancreatic cancer (n = 3), and endometrial cancer (n = 1). All pts had liver or lung metastases and $>$ 2 metastatic sites. No dose-limiting toxicities (DLTs) or grade $\geq$3 treatment-related adverse events (TRAEs) were observed. The treatment was generally well-tolerated; the most common ($\geq$50%) treatment-emergent adverse events (TEAEs) were pyrexia, cytokine release syndrome (CRS), neutropenia, anemia, and thrombocytopenia. Grade 1-2 CRS occurred in 4/6 pts and resolved without sequelae. No immune effector cell–associated neurotoxicity syndrome (ICANS) was observed. TCR-T cells peaked in peripheral blood at a median of day 4 (range, 1–10), with a median peak expansion of 61,863 copies/μg DNA (range, 40,394–80,824). The objective response rate (ORR) was 50.0% (3/6), with a disease control rate (DCR) of 83.3% (5/6). In the pancreatic cancer subset, the ORR was 66.7% (2/3) and the DCR was 100%. **Conclusions:** This KRAS G12V/HLA-A*11:01–restricted TCR-T therapy demonstrated a favorable safety profile and encouraging preliminary antitumor activity in advanced solid tumors. Notably, a high response rate was observed in heavily pretreated pancreatic cancer patients, supporting further clinical development of this novel cellular therapy. Clinical trial information: NCT06767046. Research Sponsor: Beijing CorreGene Biotechnology Co., Ltd; 2023YFC3403800, 2024ZD0520500, Z221100007922022.

Safety and preliminary efficacy of a novel armored mesothelin-targeted CAR-T therapy in advanced solid tumors.

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Background: UCMYM802 is an autologous mRNA-electroporated CAR-T cell therapy targeting mesothelin (MSLN), incorporating a lymphocyte-antigen-presenting cell costimulatory (LACO-Stim) molecule. This first-in-human study aimed to assess its safety, tolerability, preliminary efficacy, and pharmacokinetic/pharmacodynamic (PK/PD) profiles. **Methods:** This phase I study enrolled patients with metastatic or recurrent MSLN-positive solid tumors who failed standard therapies. Three dose levels were evaluated: 1×10^8 (n = 1), 5×10^8 (n = 1), and 1×10^9 CAR-T cells (n = 7). No lymphodepletion was required prior to infusion. Patients received up to 4 weekly infusions. Primary endpoints were safety and determination of the maximum tolerated dose (MTD). Secondary endpoints included objective response rate (ORR) by RECIST v1.1, disease control rate (DCR), and PK/PD parameters. **Results:** As of Nov. 2025, 9 patients were enrolled and treated (median age 67, range 52-67). Tumor types included pancreatic cancer (n = 3), peritoneal malignant mesothelioma (n = 1), adenocarcinoma of unknown primary, consistent with a gynecologic or peritoneal origin (n = 1), extrahepatic cholangiocarcinoma (n = 1), cholangiocarcinoma (n = 1), ovarian cancer (n = 1), and lung cancer (n = 1). All patients received at least one infusion. The 1×10^9 dose level was defined as the MTD, with one dose-limiting toxicity (DLT) observed (grade 4 cytokine release syndrome [CRS] with hypotension). Treatment-related adverse events (TRAEs) occurred in all patients, most commonly CRS (88.9%), fever (88.9%), decreased lymphocyte count (77.8%), anemia (77.8%), prolonged prothrombin time (66.7%), and hypoxia (55.6%). Grade $\geq$3 CRS occurred in 25% of patients. Among seven efficacy-evaluable patients, two patients achieved partial response (PR; one each in 5×10^8 and 1×10^9 cohorts), and two had stable disease (SD; one each in 1×10^8 and 1×10^9 cohorts). The ORR was 28.6% (2/7) and DCR was 57.1% (4/7). Notable responses included a PR in gynecologic or peritoneal origin adenocarcinoma and a PR at 6 months (converted to SD at 7.5 months) in extrahepatic cholangiocarcinoma. PK analysis showed peak CAR-T expansion (by copy number) at 1-hour post-infusion, with the highest and most sustained exposure after the first infusion. PD analysis indicated IFN-γ elevation correlating with CAR-T peak expansion. CAR-T exposure and activation marker expression showed a dose-dependent trend. **Conclusions:** UCMYM802 demonstrated a manageable safety profile consistent with expected CAR-T-related toxicities, primarily CRS. Preliminary anti-tumor activity was observed in heavily pretreated patients with MSLN-positive advanced solid tumors, with encouraging signals in gynecologic or peritoneal origin adenocarcinoma and biliary tract cancers. The recommended dose for expansion is 1×10^9 CAR-T cells. These results support continued investigation of UCMYM802. Clinical trial information: NCT06256055. Research Sponsor: None.

Phase 1 dose escalation study of CD34 selected CD19 directed CAR T with metabolic programming in relapsed/refractory B-cell lymphoma.

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Background: CD19 CAR T cell therapy (CAR-19) has been a breakthrough for relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-cell NHL). However, both relapse and toxicity remain major challenges. We utilized novel programming conditions aimed at enhancing the function and persistence of our CAR T products by improving metabolic fitness, via promotion of a hybrid Th1/Th17 phenotype. Additionally, CD34 selection was employed, via CD34 tag, to yield a more purified product and reduce potential toxicity. **Methods:** This single institution IRB approved phase 1B trial (NCT 05702853) evaluated a novel CD28 co-stimulated CAR-19 product, with metabolic programming and CD34 selection (CD19-CAR-CD34t hybrid T cells). Eligible patients had R/R B-cell NHL and were enrolled at dose level (DL) 1, 2, or 3 ($1x10^6$, $1.5x10^6$, $2x10^6$ CAR T cells/kg with max dose of $2.0x10^8$). Dose escalation (Desc) used a model-assisted keyboard design. Dose-limiting toxicity (DLT) evaluation occurred in the first 28 days following infusion per CTCAE v5.0, with CRS and ICANS assessed per ASTCT criteria. The primary objectives were to evaluate safety and determine recommended dose for expansion. **Results:** Desc completed enrollment with 15 patients across dose levels DL1-3, DL2-3, DL3-9. NHL subtypes included DLBCL (8), mantle cell (4), follicular (2), and marginal zone lymphoma (1). Patients received a median of two prior systemic therapies (range 1-5), and 11 (73%) received bridging therapy. All patients underwent successful leukapheresis, manufacturing, CAR T infusion, and completion of the 28-day DLT evaluation. Common AEs included neutropenia (100%), fatigue (53%), and nausea (47%). One DL3 patient experienced a DLT (grade 4 lung infection). CRS was noted in 9 patients (60%; (grade 1: 7 pts; grade 2: 2 pts), with no grade 3+ events. No ICANS was observed. Six patients (40%) received tocilizumab (toci) and two (13%) received corticosteroids for CRS management with cumulative administration of 8 doses of toci (mean 0.5 doses/patient) and 20 mg of dexamethasone (mean 1.3 mg/patient) for entire cohort. With 11.1-month median follow-up, ORR/CR rates were 73%/67% (1-year PFS 0.67; 95% CI 0.47-0.95). All 10 patients with CR remained relapse-free as of 1/1/26; 2 deaths occurred due to lymphoma progression. The median percentage of CD34 CAR T cells at infusion was 67%. Median total T-cell doses were 165.1 (DL1), 262.8 (DL2), and 236.2 (DL3) x 10^6. Data on persistence/expansion of Desc cohort are forthcoming. **Conclusions:** CD19-CAR-CD34t hybrid T cells showed promising efficacy and durability, with no relapses among patients with CR. There were no occurrences of either ICANS or grade 3+ CRS and limited CRS intervention needed. This is a promising toxicity profile for a CD28 co-stimulated CAR-19, likely owing to a more purified product via CD34 selection. DL3 was chosen for dose expansion and currently ongoing. Clinical trial information: NCT05702853.
Research Sponsor: None.

Effects of resorcinol isoprenyl benzene derivative IPI201 on natural killer cell cytotoxicity and tumor cell viability in human colorectal adenocarcinoma cells.

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Background: Natural killer (NK) cells play a critical role in anti-tumor immunity, yet their cytotoxic efficacy can be limited by tumor resistance. Resorcinyl isoprenyl benzene derivatives have previously shown anti-tumor activity, but effects on NK cell-mediated cytotoxicity remain unclear. IPI201 is a synthetic resorcinyl isoprenyl benzene derivative. We evaluated whether IP201 augments NK cell cytotoxicity and explored potential mechanisms. **Methods:** Cytotoxicity assays were performed using HT-29 colorectal carcinoma cells co-cultured with either standard NK cells or activated NK cells genetically modified to produce soluble IL-15 (sIL15 NK) under conditions of IPI201 pre-treatment or co-treatment. Cancer cell lysis was quantified over time to assess total cytolysis (AUC), maximum rate of killing (V_{max}), and time to 50% maximal cytolysis (T_{50}). NK activation markers were assessed by flow cytometry. NK cell survival following IPI201 exposure was assessed over 7 days using cell density quantification. **Results:** IPI201 enhanced NK cell-mediated cytotoxicity against colorectal cancer cells. Pre-treatment increased overall cytolysis and killing rates by 625% in standard NK cells and 50% in sIL15 NK cells ($P<0.05$). Co-treatment similarly increased tumor cell lysis ($P<0.05$). IPI201 alone induced rapid tumor cell death, outperforming standard NK cells alone in overall cytolysis, killing rate, and time to peak effect ($P<0.05$). Enhanced cytotoxicity was not associated with changes in NK activation markers. Instead, IPI201 increased NK cell survival across doses, with the highest dose increasing Day 7 density by 117% in standard NK cells and 214% in sIL15 NK cells ($P<0.05$). Further, IPI201 sensitized tumor cells to NK-mediated killing following tumor cell pre-treatment (+130% in both NK cell types; $P<0.05$). **Conclusions:** IPI201 induces tumor cell death independent of NK cells and enhances NK cell-associated cytotoxicity during pre- or -co-treatment. These effects may arise from increased NK cell survival and/or heightened tumor cell susceptibility to immune-mediated killing. To our knowledge, IPI201 is now the third known molecule alongside IL-2 and IL-15, that is independently sufficient to support NK cell survival. These findings support further investigation of IPI201 as a multifunctional immunomodulatory and cytotoxic agent in combination cell-based cancer therapies. Research Sponsor: None.

Epigenetic reprogramming of allogeneic NK cells via antigen-specific “training” to generate target-specific memory-like NK cells for B-cell lymphoma without genetic engineering.

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Background: Clinical application of CAR-NK cells is restricted by manufacturing complexity, cost, and potential genotoxicity. Furthermore, synthetic CAR expression may disrupt native NK biology and impose steric hindrance. We hypothesized that NK cells can be epigenetically reprogrammed ex vivo to acquire antigen-specific, memory-like cytotoxicity via a novel, non-genetic “Targeted Priming Platform” (TPP), bypassing the fundamental constraints of CAR engineering. **Methods:** Healthy donor NK cells were co-cultured with CD19+ Raji cells in the presence of a CD16xCD19 bispecific engager (BiKE) and IL-12/15/18 cytokines. After a 7-day priming phase and subsequent rest, cells were re-challenged to assess recall responses. Deep profiling was performed using mass cytometry, ATAC-seq, and ChIP-seq. In vivo efficacy was evaluated in NSG mice engrafted with CD19+ Raji lymphoma. Comparisons were made against cytokine-only primed (Cyt-NK) and naïve NK cells. **Results:** TPP-NK cells demonstrated a stable, antigen-specific recall response. Upon secondary challenge with CD19+ targets, TPP-NKs exhibited superior expansion, degranulation (CD107a), and IFN-γ production compared with Cyt-NK or naïve controls. This specificity was absent in mismatched target settings. Epigenetic analysis revealed that TPP induced durable chromatin remodeling, characterized by stable hypomethylation and open chromatin at critical cytotoxicity loci (e.g., IFNG, PRF1, GZMB), distinct from the transient changes observed in Cyt-NKs. In vivo, a single infusion of TPP-NKs combined with low-dose BiKE induced sustained remission and significantly prolonged survival compared with controls ($P < 0.001$). **Conclusions:** We demonstrate a paradigm-shifting strategy to generate “target-trained” memory NK cells without genetic engineering. TPP epigenetically imprints antigen specificity, combining the precision of antibody therapy with the persistence of cellular therapy. This scalable, “off-the-shelf” platform offers a safer, cost-effective alternative to CAR-based modalities for B-cell malignancies. Research Sponsor: None.

An LNP-mRNA–based in vivo cell engager as a producer of T macrophage tumor triads in situ for targeted anti-solid tumor therapies.

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Background: The solid tumor microenvironment promotes infiltration of myeloid cells, with tumor-associated macrophages as the most abundant innate immune population. A recent study showed tumor-reactive T cells enriched in functional clusters with tumor or antigen-presenting cells, and T cells expanded from these clusters ex vivo exhibit enhanced tumor-killing activity. Bispecific and trispecific antibodies have emerged to link T cells with tumor and myeloid cells, improving antitumor immunity. However, their clinical use is limited by structural complexity, manufacturing challenges, and immunogenicity risks. Here, we developed a "live-cell engager" by harnessing and engineering macrophages in vivo to form T-macrophage-tumor triads, activating both T cells and macrophages near tumor cells to boost antitumor responses. **Methods:** We engineered macrophages to express a single-chain variable fragment (scFv) targeting CD3 (αCD3), a tumor-specific chimeric antigen receptor (CAR) and CD80 on their surface. Each was encoded by separate mRNAs encapsulated within one lipid nanoparticle formulation (LNP-C-3-80). Mouse bone marrow-derived macrophages (BMDMs) were used ex vivo to evaluate T cell activation and antitumor function. The efficacy of LNP-C-3-80 was further tested in immunocompetent syngeneic models including ID8 ovarian cancer and Hepa1-6 hepatocellular carcinoma. **Results:** In vitro, BMDMs engineered with LNP-3-80 effectively engaged T cells with macrophages, significantly boosting T cell activation compared to LNP-3 alone, as shown by increased CD69 expression and elevated secretion of IFN-γ, IL-2, and Granzyme B. Furthermore, BMDMs engineered with LNP-C-3-80 were able to engage both T cells and tumor cells, and when co-cultured with T cells, showed tsuperior antitumor activity over control groups (LNP-3-80, LNP-3, LNP-GFP). The LNP-delivered αCD3 and CD80 mRNAs were mainly expressed on macrophages but not on T cells, facilitating macrophage-T cell-tumor cell cluster formation. This proximity enabled mutual activation and synergistic tumor cell killing. In vivo, LNP-C-3-80 achieved nearly complete tumor regression and strong prevention of recurrence in ovarian and liver cancer models after intraperitoneal or intravenous administration. Toxicity studies in healthy C57BL/6J mice showed no organ damage or adverse serum biochemical changes, indicating a favorable safety profile. **Conclusions:** In summary, in vivo macrophage engineering promotes the formation of T cell–macrophage–tumor cell clusters, reducing immune cell–cancer cell distance and concurrently activating T cells. LNP-C-3-80 shows significantly enhanced antitumor efficacy in syngeneic solid tumor models with minimal toxicity. These results highlight LNP-C-3-80's strong potential as a promising therapeutic strategy against diverse solid tumors. Research Sponsor: None.

Combining immune checkpoint inhibition and dendritic cell vaccination in advanced pleural and peritoneal mesothelioma: The phase 1b MESOVAX trial.

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Background: Mesothelioma (M) remains a rare malignancy with limited therapeutic options. While immunotherapy combinations have recently become the standard of care for non-epithelioid subtypes, further strategies are required to enhance clinical outcomes. Dendritic cell vaccines (DCvax) have demonstrated preliminary activity and a favorable safety profile in M. Preclinical data suggest that DCvax induces PD-L1 expression on tumor cells; therefore, combining DCvax with Pembrolizumab (P) may sensitize patients (pts) to PD-1 blockade. **Methods:** MESOVAX is a proof-of-concept, Phase Ib, study evaluating the safety of P 200 mg combined with an autologous anti-tumor DCvax administered every 3 weeks (Q3W) for 6 cycles, followed by P monotherapy until disease progression or up to 2 years. Subcutaneous IL-2 (3 MU) was administered for 5 days following each vaccination. The primary endpoint was safety. Secondary endpoints included: changes in PD-L1 expression evaluated in pre- and post-therapy tumor samples by immunohistochemistry (IHC); immunological efficacy evaluated *in vivo* by DTH test and *ex vivo* measuring the immune response against selected tumor antigens (i.e MESOTHELIN, WT1, 5T4, TWIST-1, KRT-18, THBS2) by Interferon gamma (IFNγ) Enzyme-Linked Immunosorbent Spot (ELISpot) Assay; and treatment activity (objective response rate [ORR], duration of response [DOR], progression-free survival [PFS], and overall survival [OS]). **Results:** As of 28/11/2025, 9 pts (median follow-up: 32.5 months (mths)) were evaluable for safety and efficacy. Median age was 62 years; 89% (n = 8) were male, and all had epithelioid histology. Treatment-related adverse events (TRAEs) of any grade occurred in all 9 pts, with the most frequent being injection site reactions, asthenia, and fever. No grade 3–4 TRAEs were reported. Regarding treatment exposure, 4 pts received 6 cycles of P+DC, 6 pts received maintenance P, and one pt completed the maintenance phase. Best overall responses included 1 partial response (PR), 4 stable diseases (SD), and 4 progressive diseases (PD), with a median PFS of 5.3 mths (95% CI 1.8–17.3). Notably, one pt with prolonged SD (duration 9 mths) exhibited a PD-L1 conversion in the tumor tissue (from negative to positive) following treatment. Regarding the immunological activity, 4 pts experienced a positive DTH test during treatment, and interestingly for 3 of them we were able to measure a concomitant increase of the *ex vivo* antitumoral immune response against the tested antigens. **Conclusions:** The combination of DCvax and P is safe and demonstrates encouraging clinical activity in pretreated epithelioid M. The observed PD-L1 induction at the tumor site supports the synergistic potential of this combinatorial immunotherapeutic strategy. This trial is supported in part by a research grant from Investigator-Initiated Studies Program of MSD Italia S.r.l. Clinical trial information: NCT03546426. Research Sponsor: MSD Italia S.r.l.

B cell responses in recurrent respiratory papillomatosis patients treated with DNA immunotherapy INO-3107.

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Background: Recurrent respiratory papillomatosis (RRP) is a chronic, debilitating disease of the airway primarily caused by infection with human papillomavirus (HPV) types 6 and/or 11 and characterized by recurrent, benign tumor growth with potential for malignant transformation. Current standard of care consists of repeated surgical removal of papillomas, which can lead to lasting airway damage and impaired vocal function. Thus, a non-surgical approach to treat RRP is paramount. Previously, we described T cell responses associated with an overall clinical response rate of 81% (26/32) to INO-3107, a DNA immunotherapy designed to generate T cells capable of targeting HPV-infected cells, in adult RRP patients during a Phase 1/2 trial (NCT04398433). Here, we describe B cell responses in these patients. **Methods:** INO-3107 was administered during study weeks 0, 3, 6 and 9. Peripheral blood mononuclear cells (PBMCs) were obtained at screening/day 0, weeks 6, 9, 11, 26 and 52. Formalin-fixed, paraffin-embedded papilloma tissue was obtained prior to INO-3107 treatment (Scr) and at the end of the 52-week study (EOS). Both PBMCs and tissue were subjected to RNA and BCR sequencing, which additionally underwent single sample gene set enrichment analysis and CloneTrack analysis, respectively. Clinical response was defined as any reduction in frequency of RRP surgical interventions in the 52 weeks following dose 1 of INO-3107 (Y1) compared to the 52 weeks prior. **Results:** Following INO-3107 treatment, 85% (23/27) of patients exhibited B cell expansion in PBMCs that was sustained through Y1 for responders, which in contrast began to contract at week 26 for non-responders. Enrichment of B cell signatures, inclusive of total, naïve, memory, and plasma B cells, in papilloma tissue increased significantly by EOS in responders compared to non-responders. Increases in tissue BCR clone counts from Scr to EOS correlated significantly with clinical response during Y1. BCR sequences detected in tissue taken at EOS displayed a low degree of overlap with those detected at Scr. Newly detected BCR sequences in EOS tissue were present in PBMCs prior to EOS. Some of these B cell clones were detectable in PBMCs and papilloma tissue only after INO-3107 treatment. **Conclusions:** B cell immunogenicity may play a role in mediating clinical responses to DNA immunotherapy INO-3107 for the treatment of RRP. INO-3107 treatment induced expansion and emergence of B cells in the blood of RRP patients, which trafficked to and infiltrated papilloma tissue by EOS as evidenced by increased B cell enrichment and clone counts. These immune responses were associated with improved clinical outcomes. These results suggest that INO-3107 engages B cells equipped with the potential to promote activation of T cell responses described previously (doi: 10.1038/s41467-025-56729-6) and that they may play a role in long-term immunity against RRP. Clinical trial information: NCT04398433. Research Sponsor: Inovio Pharmaceuticals, Inc.

Anitocabtagene autoleucel (anito-cel) clinical trial manufacturing experience in patients with relapsed/refractory (RR) or newly diagnosed (ND) multiple myeloma (MM).

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Background: Anito-cel is an autologous D-Domain–based anti-BCMA chimeric antigen receptor (CAR) T-cell therapy that demonstrated deep and durable efficacy and manageable safety in a Phase 1 study and a Phase 2 registrational study (iMMagine-1) in 4L+ RRMM (Bishop et al. ASH 2024; Patel et al. ASH 2025). The D-Domain has a fast off-rate and facilitates high transduction efficiency, high CAR expression, decreased risk of tonic signaling, and potential for enhanced manufacturing efficiency and optimal tumor cytotoxicity. Anito-cel is also being investigated in patients with RRMM with 1-3 prior therapies and in patients with NDMM. The anito-cel CAR T-cell therapy manufacturing process has been optimized by leveraging the learnings from the robust development process of another CAR T-cell therapy, axicabtagene ciloleucel (axi-cel). Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved in 2L large B-cell lymphoma based on the ZUMA-7 trial, with a demonstrated high manufacturing success rate (MSR) in both clinical trial and commercial real-world settings (100% and 99%, respectively; Alquist et al. TCT 2024). Here we report initial anito-cel manufacturing experience from 2 MM clinical trials. **Methods:** Pooled manufacturing outcomes from adults with MM enrolled and leukapheresed in iMMagine-3 or GEM-AnitoFIRST from 09/2024 to 10/2025 were included. First pass (FP)-MSR was defined as anito-cel lots manufactured on first attempt and within specification per total first attempt lots dispositioned plus lots not dispositioned due to termination in the period (excluding those terminated for patient withdrawal). The median turnaround time (mTAT) was defined as the time from leukapheresis to the quality release of final anito-cel product. **Results:** There was a total of 104 patients who were leukapheresed and whose lots were dispositioned as of October 31, 2025; anito-cel was successfully manufactured for 100% of these patients. The FP-MSR was 99.0% with 1/102 lots rejected on disposition (Table). The global mTAT was 18 days (interquartile range [IQR], 17-20 days) for the 101 lots released. Updated data to be presented. **Conclusions:** Our results demonstrate rapid and reliable anito-cel manufacturing for MM clinical trials globally, with high manufacturing success rates and consistent turnaround times. These results were consistent with axi-cel manufacturing outcomes and highlight the importance of leveraging axi-cel manufacturing experience in the development of anito-cel. Clinical trial information: NCT06413498 and NCT07045909. Research Sponsor: Arcellx Inc. and Kite, a Gilead Company.

FP-MSR, n/N (%)	101/102 (99.0)
Global mTAT, days (IQR)	18 (17-20)
Lots released, n	101

A phase 3 trial of adagloxad simolenin/OBI-821 in patients with high-risk early-stage triple-negative breast cancer.

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Background: Adagloxad simolenin (AS) is a therapeutic cancer vaccine composed of Globo H linked to the carrier protein keyhole limpet hemocyanin. OBI-821 is an adjuvant administered with AS to strengthen immune response. This phase 3 trial assessed safety/efficacy of AS/OBI-821 in patients with triple negative breast cancer (TNBC; NCT03562637). **Methods:** Eligible patients for this randomized, open-label trial were adults with high-risk (≥1cm residual primary, ≥1 residual axillary node after neoadjuvant chemotherapy, or stage IIB or III cancer treated with adjuvant chemotherapy alone), primary localized early-stage, Globo H-positive (H-score ≥15) TNBC. Patients were required to have received ≥4 cycles of standard taxane- and anthracycline-based chemotherapy. Patients were randomized 1:1 to receive standard of care (SOC; observation alone [29%], capecitabine [69%], or a checkpoint inhibitor ± capecitabine [2%]) or AS/OBI-821 and SOC (observation alone [26.6%], capecitabine [69.6%], or a checkpoint inhibitor ± capecitabine [3.8%]). Patients in the AS/OBI-821 arm received 4 weekly doses of study drug administered via subcutaneous injection, followed by 4 biweekly doses, 4 doses every 4 weeks, then doses every 8 weeks up to 100 weeks. The primary endpoint was invasive disease-free survival (IDFS); secondary endpoints included safety assessed via treatment-emergent adverse events (TEAEs) and overall survival (OS). Patients were followed for up to 5 years after randomization for OS. **Results:** The intent-to-treat (ITT) population was comprised of 575 patients, with 286 in the AS/OBI-821 arm, and 289 in the SOC arm. Patients were a median age of 51 years (range 24-85), all were female, and most were white (52.7%). A total of 5.2% of patients had stage I cancer, 50.3% had stage II, and 37.1% had stage III. IDFS in the AS/OBI-821 arm was not statistically different than in the SOC arm (IDFS hazard ratio [HR], 1.23 [95% CI: 0.88, 1.73]; *P*= 0.23). Three-year IDFS rate was 54.5% for AS/OBI-821 arm and 56.4% for the SOC arm. Similar pattern was observed for OS with HR = 1.36 [95% CI: 0.77, 2.38). TEAEs occurred in 79.6% of patients in the AS/OBI-821 arm and 66.7% in the SOC arm. The most common TEAEs in the AS/OBI-821arm were palmar-plantar erythrodysaesthesia syndrome (18.7%), fatigue (11.6%), and headache (11.3%). Serious TEAEs occurred in 5.3% of patients in the AS/OBI-821 arm vs 6.2% in the SOC arm. One patient (0.4%) in the AS/OBI-821 arm had a TEAE of interstitial lung disease, assessed as unlikely related to treatment and one patient (0.3%) in the SOC arm had acute coronary syndrome that led to death. **Conclusions:** In this phase 3, randomized, open-label trial, AS/OBI-821 was well-tolerated, with a safety profile similar to SOC. IDFS and OS were similar between the AS/OBI-821 and SOC arms. The trial was terminated per recommendation by the Data and Safety Monitoring Board as it met prespecified futility criteria. Clinical trial information: NCT03562637. Research Sponsor: None.

Phase 1 study of META 10-19, an IL-10-expressing, anti-CD19 CAR T cell product in patients with high-risk DLBCL.

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Background: Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of B cell lymphoma. However, limited duration of remission remains a significant challenge. We designed a metabolically armored anti-CD19 CAR T-cell product (META 10-19) that autocrine interleukin (IL)-10 to enhance antitumor activity, and assess the therapeutic potential in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). **Methods:** This phase 1 study is designed to evaluate the safety and preliminary efficacy of META 10-19 in relapsed/refractory DLBCL patients aged 3–70 years old. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by ASTCT criteria, and other adverse events (AEs) were evaluated according to CTCAE 5.0. Tumor response was assessed by investigators using Lugano 2014 criteria and IPCG criteria. **Results:** From December 2022 to December 2024, 14 patients with a median age of 54.5 years have been enrolled and received META 10-19 infusion at doses ranging from (0.002–0.1) $\times 10^6$ cells/kg, following a standard lymphodepletion regimen (30 mg/m^2/day Flu $\times$3 days, 300 mg/m^2/day Cy $\times$3 days). All patients had relapsed/refractory disease, with high-risk features including primary refractory (n = 9), nodal and extranodal involvement (n = 6), CNS lymphoma (n = 5), and bulky disease (n = 2). The most frequent Grade 3–4 AEs comprised neutropenia (100%, 14/14), thrombocytopenia (85.7%, 12/14), and anemia (71.4%, 10/14). CRS was predominantly manifesting as low-grade events (Grade 1–2, n = 13; Grade 3, n = 1). ICANS developed in 2 patients (14.3%) with primary CNS disease, manifesting as transient seizures and classified as Grade 3. At 3 months post-infusion, the overall response rate was 100%, including 13 patients (92.9%) achieved complete response (CR), and 1 patient achieved partial response. As of December 1, 2025, with a median follow-up of 23.3 months (range, 5.6–33.4), 9 patients maintained CR for over 1 year, 4 for over 2 years, and the earliest infused patient remains in remission at 33.4 months. The median progression-free survival (PFS) and overall survival (OS) have not yet been reached, while the 12-month PFS rate and 12-month OS rate were 71.4% and 92.9% , respectively. **Conclusions:** This first-in-human trial of META 10-19, an IL-10 expressing, anti-CD19 CAR T-cell product, for the treatment of relapsed/refractory DLBCL has exhibited manageable safety profile and durable efficacy at ultra-low doses in patients with high-risk features. Studies evaluating larger cohorts and longer follow-up are ongoing. Clinical trial information: NCT05715606. Research Sponsor: Research Funds of Centre for Leading Medicine and Advanced Technologies of IHM; National Natural Science Foundation of China.

Erythrocyte–anti–PD-1 conjugates in patients with advanced solid tumors resistant to anti–PD-1/PD-L1 therapy: Long-term follow-up of a phase I trial.

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Background: Despite the clinical success of immune checkpoint blockade, most patients with advanced solid tumors fail to achieve durable benefit due to limited efficacy and/or immune-related toxicities. αPD-1-Ery is an erythrocyte–antibody conjugate that covalently links an anti–PD-1 antibody to erythrocyte membranes. Unlike conventional antibodies, αPD-1-Ery preferentially accumulates in the spleen, where it remodels the splenic immune microenvironment by expanding effector T cells and reducing immunosuppressive myeloid cell reservoirs, thereby inducing systemic anti-tumor immunity. We previously reported favorable safety and preliminary efficacy of αPD-1-Ery in patients with PD-1/PD-L1–resistant solid tumors. Here, we report long-term follow-up results assessing durability of benefit and exploratory biomarkers. **Methods:** 14 heavily pretreated patients with 11 types of advanced solid tumors who had progressed on PD-1/PD-L1–containing regimens as their most recent line of therapy were enrolled. Patients received αPD-1-Ery monotherapy at 2×10^{11} or 3×10^{11} cells. Endpoints included safety, efficacy, and exploratory correlations between immune biomarkers and clinical outcomes. **Results:** As of October 31, 2025, all patients had completed treatment, with a median follow-up of 18.9 months. Treatment discontinuation occurred due to disease progression in 57.1% (8/14), CR in 7.1% (1/14), completion of planned treatment cycles in 21.4% (3/14), and other reasons (including AE or withdrawal) in 14.3% (2/14). No DLTs were observed. TRAEs occurred in 64.3% (9/14) of patients, with no grade >3 TRAEs, no grade ≥3 immune-related AEs, and no treatment discontinuations due to TRAEs. αPD-1-Ery demonstrated sustained anti-tumor activity, with a DCR of 78.6% (11/14) and an ORR of 42.9% (6/14; 1 CR, 1 uCR, 4 PR), with improved responses observed in the higher-dose cohort. mPFS was 5.6 months and mOS was 23.4 months. Durable benefit was observed in most responders, with 4/6 maintaining response after treatment discontinuation; 1 received no subsequent therapy and 3 resumed PD-1/PD-L1–based immunotherapy despite prior resistance. mDoR had not been reached (range, 4.8–24.7 months). Exploratory analyses indicated that clinical benefit was observed in both primary (n = 3) and acquired (n = 3) anti–PD-1/PD-L1–resistant patients. Responders had higher baseline circulating PMN-MDSCs and DCs and experienced rapid and sustained PMN-MDSC reduction following treatment. Tumor MMR status was available in 5 patients (all MSS), with objective responses observed in 3. **Conclusions:** Spleen-directed PD-1 blockade using erythrocyte–antibody conjugates induces durable clinical benefit. αPD-1-Ery represents a novel immunotherapeutic strategy for PD-1/PD-L1–resistant solid tumors and supports further clinical development. Clinical trial information: NCT06026605. Research Sponsor: None.

Single-cell multi-omics and TCR sequencing to identify early tumor cavity homing and phenotypic evolution of CAR-T cells in glioblastoma.

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy has shown remarkable efficacy in hematological malignancies but remains largely ineffective in glioblastoma. A systematic understanding of early CAR-T cell trafficking and phenotypic adaptation within the tumor immune microenvironment may provide critical insights into this limitation. **Methods:** We performed single-cell multi-omics profiling using the 10x Chromium Single-Cell 5' Immune Profiling platform on infused CAR-T cells and matched tumor cavity cerebrospinal fluid (CSF) obtained via an Ommaya reservoir at day 3 post-infusion. Paired transcriptome/TCR data enabled analyses of composition, clonal tracking, and phenotypic transitions within CAR-T populations following early tumor cavity homing. **Results:** Single-cell profiling of the infused CAR-T product revealed a T cell–dominant population, primarily composed of $CD8^+$ T cells (62.24%) and $CD4^+$ T cells (34.63%). Analysis of tumor cavity CSF demonstrated a heterogeneous immune landscape, including $CD4^+$ T cells (32.79%), $CD8^+$ T cells (20.83%), dendritic cells, monocyte/macrophage populations, and other innate immune subsets. Gene set variation analysis across all immune cell populations showed enrichment of memory-associated programs in the CSF, while exhaustion-related signatures were not prominent, indicating a relatively non-exhausted immune state at this early time point. TCR-based clonal tracking identified 188 CAR-T cells in the CSF that originated from the infusion product, corresponding to an early homing rate of 2.19%. These homed CAR-T cells were predominantly derived from cytotoxic and proliferating $CD8^+$ T cell subsets, as well as effector $CD4^+$ T cells. Notably, cytotoxic $CD8^+$ CAR-T cells exhibited pronounced clonal expansion in the CSF, whereas proliferating $CD8^+$ CAR-T cells underwent phenotypic transitions toward cytotoxic states following tumor cavity infiltration. In parallel, activated $CD4^+$ CAR-T cells preferentially adopted memory-like phenotypes. Consistently, TCR-tracked CAR-T cells in the CSF displayed significantly stronger memory-associated transcriptional signatures compared with their clonal counterparts in the infusion product (CSF vs. product, -0.187 vs -0.088 , $p = 2.48 \times 10^{-9}$). **Conclusions:** This study provides a single-cell and clonal-level view of early CAR-T cell trafficking and phenotypic adaptation within the glioblastoma tumor cavity. Early tumor cavity infiltration is a selective process driven by cytotoxic and proliferative CAR-T subsets and occurs in the context of preserved memory-associated programs with limited exhaustion. These findings suggest that the limited efficacy of CAR-T therapy in glioblastoma is likely to stem from barriers that emerge at later stages following initial tumor entry instead of immediate CAR-T dysfunction. Research Sponsor: None.

Rab11 family interacting proteins as regulators of T cell recognition and infiltration in triple negative breast cancer.

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Background: Triple negative breast cancer (TNBC) accounts for 10-15% of all breast cancer cases and has the worst prognosis (5 year relative survival rate of 78%). TNBC is defined by absent estrogen and progesterone receptors and lack of HER2 amplification. First-line treatment for metastatic TNBC has evolved in the past several years to include immunotherapy for PD-L1+ patients. Recent NCCN guidelines recommend antibody-drug conjugate (ADC) therapy as first line treatment for metastatic TNBC regardless of PD-L1 positivity. ADCs target cell surface proteins that are abundant on tumors and sparse on healthy cells, delivering cytotoxic payloads selectively to the tumor. ADC efficacy depends on surface localization of target antigens, whose localization is dictated by endosomal trafficking via Rab GTPases. We showed that Rab11b-mediated endosomal trafficking is required for breast cancer brain metastasis. Here we investigate how trafficking-mediated control of the cell surface dictates immune recognition and response. **Methods:** Using a CRISPR screen we found that Rab11 family interacting proteins, Rab11fip2 and Rab11fip3, are required for immunogenic breast cancer cells to be recognized by CD8+ T cells. Flow cytometry revealed that the loss of recognition is not due to changes in surface PD-L1 or MHC/antigen presentation. Knockout of either Rab11fip did not change cell proliferation or tumor burden in immunocompromised animals, but led to significantly increased tumor growth in immunocompetent animals. This suggests that knockout of either Rab11fip causes loss of immune recognition to allow faster tumor growth while control tumors are restrained by the immune system. IHC analysis revealed a significant decrease of tumor infiltrating T cells in Rab11fipKO tumors. Interestingly, immune disruption is systemic, as splenic architecture is disrupted in Rab11fipKO tumor bearing mice. **Results:** Since the primary function of Rab11fips is to mediate trafficking of Rab11 cargo proteins, our results suggest that surface localization of these cargo proteins is required for immune cell recruitment, recognition, or activation. **Conclusions:** We are currently focused on identifying these cargo proteins, determining whether Rab11 controls trafficking of Trop-2 the target of several current ADCs, and characterizing Rab11 control of the T cell-cancer cell interaction in human breast cancer cell lines. Our work holds the promise of finding novel targets for ADCs and biomarkers for responsiveness to immunotherapy. Research Sponsor: American Cancer Society; RSG-23-136584-01-MM; Mary Kay Ash Foundation; METAvivor.

Long-term follow-up of satricabtagene autoleucel (satri-cel) as sequential therapy after first-line treatment for advanced gastric cancer: A subgroup analysis.

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Background: Claudin18.2 (CLDN18.2) has emerged as a new target for the treatment of gastric cancer in the first-line (1L) setting with the approval of zolbetuximab. This long-term analysis reports the extended efficacy and safety of satri-cel (autologous CLDN18.2-specific CAR T cells) as sequential therapy after 1L treatment in patients with advanced gastric/gastroesophageal junction (G/GEJ) cancer, after the results of all cohorts published in 2024 (Qi C, et al. Nat Med. 2024;30(8):2224-2234. NCT03874897). **Methods:** This trial is an open-label, multi-cohort, phase 1 trial, which evaluated the safety and efficacy of satri-cel in patients with CLDN18.2-positive advanced gastrointestinal cancers. Cohort 3 in dose-expansion stage enrolled patients with advance G/GEJ cancer and were given satri-cel as sequential treatment after 1L therapy. The primary endpoint was safety; secondary endpoints included efficacy, pharmacokinetics and immunogenicity. **Results:** As of October 18, 2025, 5 patients with CLDN18.2-positive G/GEJ cancer received satri-cel infusion(s) of 250×106 cells, sequentially after 1L therapy. Each patient received a total of one (n=1), two (n=1), and three doses (n=3) of satri-cel. Patients had received a median of 5 cycles (range, 4-11) of 1L chemotherapy before satri-cel infusion, with 1 (20%) treated with PD-1 inhibitor. Notably, only 1 patient achieved PR after first-line therapy. Three patients (60%) were Lauren diffuse type and 1 (20%) with mixed type, 4 (80%) had signet ring cell carcinoma, and 4 (80%) had peritoneal metastases. Median follow-up from initial 1L therapy was 54.6 months (reverse KM, 95% CI: 51.1, NE). Among 4 patients with target lesions, confirmatory objective response rate was 100%, and median duration of response was not reached. One has maintained SD for 20.9 months and 2 received surgical resection after satri-cel therapy. Median progression-free survival and median overall survival since 1L therapy was 20.9 months (95% CI: 10.8, NE) and 22.1 months (95% CI: 10.8, NE), respectively. Two were still alive as of cutoff date, with a follow-up of 58.1 months and 51.1 months. Safety was manageable. No grade 3 or higher cytokine release syndrome (grade 1: n=1, 20%; grade 2: n=4, 80%), any grade immune effector cell-associated neurotoxicity syndrome, or treatment-related deaths occurred. Despite common hematologic toxicities, no severe infections (grade ≥3) or febrile neutropenia were reported. **Conclusions:** With an extended follow-up exceeding 4.5 years, satri-cel as first-line sequential treatment continues to demonstrate durable survival benefit with a manageable safety profile in patients with advanced G/GEJ cancer, supporting its highly promising potential in earlier lines of therapy. Clinical trial information: NCT03874897. Research Sponsor: None.

Concurrent chemoradiotherapy plus cytokine-induced killer cells therapy or observation in patients with locoregionally advanced nasopharyngeal carcinoma: A ten-year follow-up of a randomized, phase II study.

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Background: Concurrent chemoradiotherapy (CCRT) is the standard of care for patients with locoregionally advanced nasopharyngeal carcinoma (NPC). We aimed to evaluate the efficacy and safety of Cytokine-Induced Killer cells (CIK) consolidation therapy in combination with CCRT in these patients. **Methods:** Patients with locoregionally advanced NPC were randomized in a 1:1 ratio to receive concurrent chemoradiotherapy therapy plus CIK consolidation therapy or concurrent chemoradiotherapy alone in this single-center, randomized, phase II study. The primary endpoints were disease-free survival (i.e., survival period free from disease recurrence [distant metastasis and/or locoregional recurrence] or death from any cause) and overall survival in the intention-to-treat population. Safety was a secondary endpoint. **Results:** 58 patients were enrolled in this study (29 in the CIK therapy group and 29 in the control group). The median follow-up time was 144.70 months. In the CIK therapy group, the 10-year disease-free survival rate was significantly higher than that in the control group (82.5% versus 61.3%; hazard ratio for recurrence or death, 0.258; 95% confidence interval [CI], 0.094-0.712; P=0.005). The 10-year overall survival rate was 86.2% and 67.5%, respectively; (hazard ratio for death, 0.377; 95% CI, 0.131-1.087; P=0.06). The main adverse effects of CIK was fever which resolved after symptomatic treatment. In the CIK therapy group, 23.1% of patients experienced acute adverse events of grade 3 or 4 versus 17.2% in the control group during CCRT. The most frequent adverse events of grade 3 are mucositis, followed by decreased appetite, marrow suppression. **Conclusions:** CIK consolidation therapy plus CCRT significantly improved disease-free survival in patients with locoregionally advanced NPC. (This trial is registered with Chinese CilnicalTrial.gov, number ChiCTR-TRC-08000262). Clinical trial information: ChiCTR-TRC-08000262. Research Sponsor: None.

Optimization of tumor-infiltrating lymphocyte (TIL) manufacturing in non-small cell lung cancer (NSCLC) using an IL-7/IL-15/IL-2 expansion protocol.

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Background: Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) is a promising strategy in non-small cell lung cancer (NSCLC), although ex vivo expansion remains challenging due to variability in yield and product quality. Optimizing cytokine support during TIL expansion may improve manufacturing robustness while preserving a clinically relevant immunophenotype. **Methods:** Tumor tissue specimens were obtained from immediately resected NSCLC lesions and processed for TIL outgrowth and rapid expansion over 28 days using either standard IL-2 or an experimental IL-7/IL-15/IL-2 protocol. Manufacturing endpoints included expansion yield, viability and $CD3^+$ proportion. Multiparametric flow cytometry assessed memory differentiation subsets and exhaustion-associated markers at baseline, pre-REP and post-REP. Clinical-pathological variables included disease stage, PD-L1 expression and prior systemic treatment. **Results:** 11 NSCLC TIL expansions were analyzed (experimental: n=7; IL-2: n=4). Median age was 73.1 years (range 48.5–92.3) and ECOG was 0–1 in 91% of patients; 64% had early-stage disease and 27% had advanced-stage (III–IV). PD-L1 was <1% in 73%, 9% showed PD-L1 1–49%, and none ≥50%. The cohort included pretreated patients, including prior anti–PD-1 exposure. Compared with IL-2, IL-7/IL-15/IL-2 resulted in a modest reduction in expansion yield (15–28%) and a lower CD4+/CD8+ ratio (6.62 vs 19.86), but showed improved manufacturing robustness, with all expansions meeting predefined quality criteria, whereas standard IL-2 expansions showed more variable product quality. Immunophenotypic profiling showed a more stable memory-oriented differentiation pattern with IL-7/IL-15/IL-2, including reduced naïve and TEMRA subsets and increased CD4+ TCM cells; CD8+ TCM remained predominant in both protocols. A polarisation towards the effector memory phenotype ($CCR7^-CD45RA^-$) was observed in the experimental protocol. CD28 remained highly expressed in both protocols, while CD134 tended to decrease with IL-7/IL-15. During pre-REP, PD-1 and TIM-3 were reduced in several subpopulations under the experimental protocol, suggesting a transiently less exhausted phenotype. After REP, these differences disappeared, with comparable levels between protocols. During REP, Th1 and Tfh increased in both protocols, while Th2 and Th17 remained low. **Conclusions:** Supplementation with IL-7 and IL-15 during NSCLC-derived TIL expansion improves consistency of product quality and supports a favorable memory-oriented and functional phenotype without increasing exhaustion markers at the end of manufacturing. This approach may enable more reliable generation of clinically applicable TIL products in heterogeneous and pretreated NSCLC populations, facilitating broader implementation of TIL-based therapies. Research Sponsor: None.

Preliminary phase 1 results of a MICA/B-targeted CAR T cell designed to overcome solid tumor escape mechanisms and avoid the requirement for conditioning chemotherapy.

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Background: FT836 is a multi-engineered CAR T cell targeting the conserved α3 domain of MICA/B stress ligands, enabling recognition of diverse solid tumors with additional edits including, (i) the hnCD16a FC receptor to enable multi-antigen targeting in combination with monoclonal antibodies (mAb), (ii) Sword and Shield engineering consisting of alloimmune-defense receptor (ADR) expression and CD58 deletion to coordinately avoid host recognition eliminating the need for conditioning chemotherapy (CCT), and (iii) CXCR2 and TGFβ signal redirection receptors to maximize tumor trafficking and adaptability within an immunosuppressive tumor niche, respectively. Manufactured from an iPSC-master cell bank, it is available off-the-shelf and delivered on-demand to patients (pts). **Methods:** The Phase 1 trial of FT836 in pts with advanced solid tumors (NCT07216105) evaluates multiple regimens including monotherapy (Regimen A), combination with EGFR-targeting mAb cetuximab or HER2-targeting mAb trastuzumab (Regimen C or E, respectively). CCT is not required and FT836 is given twice during the treatment cycle, with retreatment available for eligible patients. First dose of FT836 is administered with a 24-hour hospital stay while the 2nd dose is given as outpatient. **Results:** First three pts (all MSS mCRC; median: age 45 y, prior therapies of 5, disease duration of 51 months) were treated in Regimen C dose level 1 (DL1 = 300 million cells/dose, Days 1 and 15 with cetuximab, no CCT) and completed dose limiting toxicity (DLT) evaluation (data cut-off 15 JAN 2026) with no DLTs, FT836-related serious adverse events, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) reported. One of the three pts demonstrated a CEA response with $>$50% reduction (480 ng/mL at BL; 230 ng/mL at 4 weeks after first FT836 infusion) that correlated to mass shrinkage in all target lesions in a week 7 CT scan (obtained after data cut-off date). Of the other two pts, one experienced PD while the other was not yet assessed at the time of abstract submission. FT836 was detected in peripheral blood (PB) following the first dose, with persistence observed up to 1 week. Notably, FT836 cells were detected beyond the initial PB detection in a tumor biopsy obtained at Day 22 ($\pm$3 days) indicating greater persistence in tissue compared to PB, supporting the value of additional engineered elements. EGFR and MICA/B antigens were identified in 3/3 baseline tumor biopsies, highlighting the relevance of multi-antigen targeting in driving patient outcome. **Conclusions:** FT836 Regimen C DL1 was well-tolerated and early clinical data supports anti-tumor activity in highly refractory mCRC where there is significant unmet need. This trial is actively enrolling and updated clinical and translational data will be presented. Clinical trial information: NCT07216105. Research Sponsor: Fate Therapeutics.

2561 Poster Session

Extreme persistence of polyclonal CD8⁺ CAR T cells as a driver of marrow failure, neurotoxicity, and fatal immune collapse after ciltacabtagene autoleucel.

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Background: BCMA-directed chimeric antigen receptor (CAR) T-cell therapies induce deep responses in relapsed/refractory multiple myeloma (MM), but increasing potency has expanded the spectrum of treatment-related toxicities. While cytokine release syndrome and immune effector cell–associated neurotoxicity are well characterized, the consequences of extreme and prolonged CAR T-cell persistence remain poorly understood, particularly as CAR T-cell strategies are extended to solid tumors. **Methods:** We performed longitudinal, multicompartment immunomonitoring in a patient with high-risk MM treated with ciltacabtagene autoleucel (cilta-cel) who developed an unusual leukemia-like clinical course. Peripheral blood (PB), bone marrow (BM), and cerebrospinal fluid (CSF) samples were analyzed by multiparameter flow cytometry, functional cytokine secretion assays, multiplex cytokine profiling, single-cell RNA sequencing with paired T-cell receptor (TCR) repertoire analysis, and lentiviral CAR integration site mapping. **Results:** Following cilta-cel infusion, the patient developed massive and persistent expansion of non-malignant CD8⁺ effector-memory CAR T cells, comprising >90% of circulating lymphocytes and ~95% of BM lymphocytes, with absence of detectable non-transduced T cells. Despite achieving complete remission of MM, extensive BM infiltration by CAR T cells was associated with marked marrow hypocellularity, trilineage hypoplasia, and prolonged pancytopenia. A distinct trafficking-competent CD8⁺ effector-memory subset (TEM5) was selectively enriched in CSF and associated with severe neurotoxicity and a local pro-inflammatory cytokine milieu. Single-cell transcriptomics demonstrated a highly migratory, cytotoxic effector program with suppressed proliferation, MAPK/TCR signaling, and tissue-residency signatures. TCR repertoire and integration site analyses confirmed polyclonality and excluded malignant transformation or insertional oncogenesis. Sustained CAR T-cell dominance coincided with profound hypogammaglobulinemia, failure of immune reconstitution, recurrent life-threatening infections, and ultimately fatal sepsis. **Conclusions:** These findings define a previously underrecognized toxicity paradigm of BCMA CAR T-cell therapy characterized by pathologic immune dominance and extreme persistence of cytotoxic CAR T cells, leading to marrow failure, neurotoxicity, and lethal immunosuppression. Extended multi-parametric immunomonitoring may identify patients at risk and inform risk-adapted management strategies, and this principle has potential implications for the design of next-generation CAR T-cell therapies, including for solid tumors. Research Sponsor: None.

Influence of onboard, tethered IL-12 on potency of the Tmod NOT gate and selectivity.

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Background: To realize the full therapeutic potential of engineered immune cells in solid tumors, high potency must be coupled with absolute selectivity. While synthetic NOT logic gates, such as the LIR-1 NOT gate (Tmod) system, effectively address non-specific cytotoxicity, overcoming the suppressive tumor microenvironment (TME) requires auxiliary stimulation. This study focused on Interleukin-12 (IL-12)—a potent pro-inflammatory cytokine—as an "armoring" strategy to bridge this gap. **Methods:** We designed an antigen-inducible, membrane-tethered IL-12 system to boost antigen-specific Tmod activity. The performance of this inducible IL-12 construct was evaluated across various long-term in vitro and in vivo assays to measure Tmod T cell exhaustion (specifically the upregulation of PD-1 and down-regulation of CD62L) and its ability to mitigate the immunosuppressive effects of TGFβ, a primary barrier in the solid tumor microenvironment. We further assessed the reversibility of IL-12 expression upon antigen clearance and monitored for IL-12 shedding both in vitro and in vivo. **Results:** The inducible IL-12 construct boosted antigen-specific Tmod activity, prevented T cell exhaustion, and effectively mitigated the immunosuppressive effects of TGFβ that typically hamper CAR-T persistence. Crucially, this potency boost did not "override" the LIR-1 blocker; the IL-12-enhanced cells remained selective, sparing normal cells. Furthermore, data showed that the expression of membrane-tethered IL-12 is reversible once the antigen is cleared. Minimal IL-12 shedding was observed, suggesting the pro-inflammatory signal remained localized to the immunological synapse. **Conclusions:** The antigen-inducible membrane-tethered IL-12 system enhances Tmod potency while maintaining a high degree of selectivity and an acceptable safety profile for clinical translation. An Investigational New Drug (IND) application for MSLN-targeted Tmod boosted by antigen-inducible membrane-tethered IL-12 has been approved by the FDA, and a Phase 1 clinical trial is currently ongoing.
Research Sponsor: None.

Novel transposon BAFF CAR-T cells (LMY-920) for non-Hodgkin lymphoma (NHL).

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Background: CAR-T cells targeting CD19 using scFv-based CARs have been effective and approved to treat lymphoma. Response rates are high, but a significant number of patients fail to respond or relapse. This has been linked to T cell exhaustion, immune dysregulation, and/or epitope loss. To overcome this, we developed a CAR-T cell product expressing a BAFF-ligand (LMY-920). The CAR consists of truncated human BAFF on a 3rd generation CAR backbone with CD28, OX40, and CD3z intracellular signaling domains. The BAFF-ligand domain confers ability to bind the 3 BAFF receptors (BAFFR/BR3, TACI and BCMA). These are attractive tumor-associated antigens being variably expressed in all B-lineage malignancies such as B cell NHL, chronic lymphocytic leukemia (CLL), hairy cell leukemia and multiple myeloma (MM), and are important for B-cell survival, reducing the chance of antigen escape. Additionally, they are expressed on B-lineage cells involved in antibody-mediated autoimmune diseases. BAFF ligand interactions are lower affinity than scFv interactions, potentially reducing T-cell exhaustion. The novel *TcBuster* transposon system is used to improve manufacturing time, efficiency, cost, and safety. **Methods:** Patients with refractory B cell NHL are treated in this study (NCT05312801). Autologous LMY-920 CAR-T cells are manufactured, then patients receive 3 days of fludarabine (30 mg/m^2/d) and cyclophosphamide (500 mg/m^2/d) lymphodepletion. LMY-920 is administered intravenously in a 3+3 dose escalation design from 1-8 x 10^6 BAFF-CAR-T cells/kg. Response is assessed using the Lugano criteria. CAR-T expansion and biologic characteristics are assessed. **Results:** Five patients have been treated with 1-2 x 10^6 BAFF-CAR-T cells/kg in this study, 2 patients each with mantle cell lymphoma (MCL), diffuse large B cell lymphoma (DLBCL), and one with marginal zone lymphoma (MZL). Patients had received 2 – 6 prior lines of therapy and all were refractory. One patient experienced grade 1 CRS (fever), but no ICANS was reported. All patients experienced grade 3 or higher hematologic toxicity that recovered prior to day 28, and grade 1-2 fatigue. There have been no dose limiting toxicities and dose escalation continues. Responses included 2 complete responses (CR) (DLBCL), a partial response (MZL), a mixed response (MCL) and one stable disease (MCL). Of note, one of the DLBCL patients in CR had received prior axicabtagene ciloleucel (anti-CD19) CAR-T cells as well as anti-CD20 bispecific antibodies, with lymphoma cells resulting in CD19 and CD20 antigen loss. **Conclusions:** The successful use of a novel transposon-engineered BAFF ligand-based CAR-T cell product demonstrates the potential of a new direction in CAR-T cell development. Safety and efficacy were seen, including patients with prior CAR-T failure and epitope loss, as hypothesized. This product is also being evaluated in patients with CLL, MM and systemic lupus erythematosus. Clinical trial information: NCT05312801. Research Sponsor: Luminary Therapeutics.

Depletion of T-regulatory cells by denileukin diftitox-cxdl (E7777) in combination with pembrolizumab in relapsed/refractory (r/r) gynecologic malignancies: Phase 1 study results.

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Background: Denileukin diftitox-cxdl (E7777) is an FDA-approved direct cytotoxic agent that depletes T-regulatory cells by targeting the IL-2 receptor. Pre-clinical studies have demonstrated synergistic activity between the immunomodulator E7777 and PD-1 immune checkpoint inhibitor (ICI). Here, we report positive results from a phase I study of E7777 + pembrolizumab (P) in r/r gynecological (GYN) malignancies. **Methods:** Phase I dose-escalation trial of E7777 given at 4 IV dose levels (DL): 3, 6, 9, and 12 mg/kg on days 1-3, combined with P (IV 200 mg, day 1) in a 21-day cycle x8, followed by maintenance P until progression. Dose-limiting toxicities (DLTs) were assessed during cycle 1 according to CTCAE v5 criteria. Responses were measured using the RECIST 1.1 criteria. Blood samples were collected for translational studies. **Results:** Pt demographics included: median age 64y (43, 88); race, 88% white; histology 40% endometrial, 36% ovarian. Of the 24/25 pts evaluable for DLTs, only 1 case of reversible capillary leak syndrome (CLS) was seen at DL4. Anemia, fatigue, chills, and hypoalbuminemia were the most common AEs. A comprehensive overview of AEs, SAEs, and immune-related adverse events (irAEs) will be presented at the annual meeting. Table 1 describes the 4 DLs and their responses in the 21 pts evaluable for efficacy. An ORR of 24% (5 PRs) was reported in this heavily pretreated patient population with a mDOR of 21.1m (4.2-35.0). E7777 + P responses were seen in patients who progressed on prior ICI therapy, and across different GYN histologies. The median Progression-free survival (mPFS) was 5.8 m (1.1 – 37), with 5 pts having a PFS of ≥20 months. The clinical benefit rate (CR; PR; SD ≥ 6 m) was demonstrated in 48% of pts (n=10), who achieved a mPFS = 17.4m (6.2 – 37); patients with documented PD had a mPFS = 2.1 m (1.1 – 4.7). **Conclusions:** The results from this Phase I study of two immunomodulatory agents in combination, E7777 + P, in patients with r/r GYN tumors was well tolerated and demonstrated promising efficacy. A max tolerated dose wasn't established. No new significant safety signals or irAEs were reported. ORR of 24 % was demonstrated. Responders achieved a mDOR of 21.1m (4.2 - 35.0) and a mPFS = 23 m (10.4 – 37.0). Thus, E7777 + P showed prolonged responses and clinical benefit in pts with r/r GYN malignancies and limited options. These results will inform a Phase II study. Clinical trial information: NCT05200559. Research Sponsor: Citius Oncology Inc.

Response- evaluable patients (RECIST v1.1)		DL1 (N=3)	DL2 (N=2)	DL3 (N=6)	DL4 (N=10)	Total (N=21)
Best response						
	CR	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PR	1 (33.3%)	0 (0%)	1 (16.7%)	3 (30.0%)	5 (23.8%)
	SD	1 (33.3%)	1 (50.0%)	2 (33.3%)	2 (20.0%)	6 (28.6%)
	PD	1 (33.3%)	1 (50.0%)	3 (50.0%)	5 (50.0%)	10 (47.6%)
CBR w/ Durable SD						
	(CR/PR/SD≥ 6m)	2 (66.7%)	1 (50.0%)	2 (33.3%)	5 (50.0%)	10 (47.6%)
	PD	1 (33.3%)	1 (50.0%)	4 (66.7%)	5 (50.0%)	11 (52.4%)

Transposon-engineered hypoxia-inducible T cells for treatment of solid tumors.

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Background: Engineered cell therapies expressing a chimeric antigen receptor (CAR) in human T cells have demonstrated significant promise for the treatment of hematological malignancies. However, translating CAR T cell therapies to solid tumors remains challenging due to two limitations: (1) specificity, as few antigens are truly unique to solid tumors, leading to off-target toxicities; and (2) suppression, as solid tumors establish immunosuppressive microenvironments that limit T cell survival and cytotoxicity. To address these challenges and improve the safety and potency of solid tumor cell therapies, we engineered cells with synthetic circuits designed to amplify hypoxia-induced signaling through feedback and synthetic transcriptional control, enabling augmented and tunable responses within both modestly and profoundly hypoxic environments. **Methods:** We evaluated circuit architectures in HEK293FT cells in which the HBS promoter drove either native HIF transcription factors or synthetic transcription factors and promoters controlling a fluorescent reporter. Circuits were stably integrated using PiggyBac transposon vectors, and cells were cultured under normoxic (21% O_2), modestly hypoxic (5% O_2), and profoundly hypoxic (1% O_2) conditions. Fluorescent reporter expression was quantified by flow cytometry over three days, and candidate circuits exhibiting high-output, low-background expression under hypoxia were identified. These candidate circuits were subsequently introduced into primary human T cells using transposon vectors. CAR expression in engineered T cells was measured by flow cytometry after culture for three days in modest or profound hypoxia, and cytotoxic activity was assessed in co-culture assays with BT-474 breast cancer and SKOV3 ovarian cancer cells. **Results:** We identified novel circuit architectures that produced rapid induction with minimal background under hypoxia and defined design rules governing transgene amplification. Circuit topologies incorporating synthetic transcription factor–mediated feedback exhibited markedly amplified expression relative to native HIF-based circuits. CAR-expressing T cells demonstrated cytotoxic activity compared with unmodified T cells in co-culture assays. **Conclusions:** We present a therapeutic platform that enables hypoxia-dependent sensing and high-output control of therapeutic gene expression within solid tumor microenvironments. This approach has the potential to improve the safety and efficacy of engineered cell therapies for solid tumors and to provide mechanistic insights that inform the development of hypoxia-responsive cell therapies. Research Sponsor: None.

Targeting MAN1A1 to address immune checkpoint inhibitors resistance: A novel mechanism of vascular-endothelial reprogramming in NSCLC.

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Background: Despite the efficacy of immune checkpoint inhibitors (ICIs) in NSCLC, resistance remains a major hurdle. The role of non-immune components, particularly vascular endothelial cells (VECs), is poorly understood. We aimed to identify key drivers of ICI resistance by focusing on VEC-mediated remodeling of the tumor microenvironment (TME). **Methods:** We integrated transcriptomic data from public cohorts of ICI-treated and treatment-naïve NSCLC patients (GSE225620), proteomic profiling from in-house whole blood samples, and peripheral blood lymphocyte subset analysis from NSCLC patients and healthy controls. Differential expression analysis and machine learning (LASSO, SVM-RFE) were employed to identify key resistance-associated genes, including MAN1A1. Functional validation was performed using shRNA-mediated MAN1A1 knockdown in A549 and H1299 NSCLC cell lines, with apoptosis measured by flow cytometry. Single-cell RNA-seq data (GSE207422) from pre- and post-treatment NSCLC tumors were analyzed using Seurat for cell annotation. Cell-cell communication (CellChat) and pathway activity (AUCell) analyses were used to investigate VEC-immune cell interactions and their association with treatment response. Statistical analyses included Kaplan-Meier survival, Cox regression, and ROC curves to assess the prognostic and predictive value of MAN1A1. **Results:** Multi-omics analysis identified MAN1A1 as a key candidate associated with ICI resistance. Elevated MAN1A1 expression predicted inferior clinical outcomes, including shorter mPFS (3.2 vs. 8.5 months; P=0.019) in our cohort and reduced OS (47.4 vs. 65.1 months; HR=0.95, P=0.017) in the TCGA dataset. MAN1A1 expression effectively distinguished ICI non-responders (AUC=0.784). MAN1A1 knockdown significantly induced apoptosis in NSCLC cell lines (A549, P=0.00022; H1299, P=0.0004). Increased peripheral B-cell counts post-chemotherapy correlated with treatment response, and MAN1A1 protein levels inversely associated with B-cell levels ($r=-0.38$, $P<0.05$). Single-cell RNA-seq analysis revealed VECs as the primary expressors and communication hubs of MAN1A1. In non-responders, MAN1A1-high VECs were reprogrammed to drive a pro-inflammatory feedback loop with neutrophils via ANXA1-FPR1/NAMPT-integrin signaling axes. In contrast, VECs from responders exhibited a shift towards T-cell-recruiting LGALS9-CD45 signaling. **Conclusions:** Our study identifies MAN1A1 as a novel driver of ICI resistance in NSCLC, mediating vascular-endothelial reprogramming that fosters an immunosuppressive TME characterized by pro-tumor neutrophil recruitment and impaired T- and B-cell immunity via the ANXA1-NAMPT axes. Targeting MAN1A1 represents a promising therapeutic strategy to overcome ICI resistance, providing a strong rationale for future translational development. Research Sponsor: None.

Circulating extracellular vesicles carrying PD-1, PD-L1, and CTLA-4 to inform resistance to immunotherapy in HCC.

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Background: First-line immune checkpoint inhibitor (ICI) therapy has contributed to improved outcomes in hepatocellular carcinoma (HCC). However, only around 30% of patients respond, highlighting the need for biomarker driven patient selection. Considering the lack of tissue acquirement in HCC in clinical routine, liquid biopsy holds great promise. In this study, we aimed at profiling immune checkpoints (IC) on circulating extracellular vesicles (EVs) as potential liquid biopsy-based biomarkers for prediction of treatment response. **Methods:** Three distinct cohorts were analyzed in this study: (1) *HCC Explorer Cohort* (n=40), testing the presence of membrane-bound ICs on EVs; (2) *early-stage HCC Cohort* (n=37 with paired blood and tissue), assessing the interplay between EV and tissue ICs alongside clinicopathological parameters and (3) *Treatment Cohort* (n=161 with 548 sequential blood samples), comprising a training (n=79,n=402 sequential samples) and a validation group (n=82, n=146 sequential samples), to identify predictors of immunotherapy response through IC profiling of circulating EVs via multiplex immunoassay. **Results:** PD-1, PD-L1 and CTLA-4 were enriched in EVs compared to EV-depleted serum. Baseline and early dynamics in EV-IC levels significantly discriminated between responders and non-responders in the training and validation cohort, while simultaneously predicting PFS and OS. In addition, dynamic changes of EV-IC levels during therapy in patients with initial response predicted acquired therapeutic resistance, approximately 36-42 weeks before progression was traceable on imaging. High serum EV-IC levels correlated with "cold" tumor features on paired tissue samples and single-EV profiling revealed various cells of origin of our EV-IC, e.g., PD-L1+ EV mainly derived from hepatocyte/HCC cells and antigen presenting cells, and PD-1+ EV mainly from T-cells and macrophages, as expected. **Conclusions:** EVs carrying PD-1, PD-L1 and CTLA-4 represent readily quantifiable, non-invasive biomarkers to predict response and survival in advanced HCC patients undergoing ICI therapy and serve to identify biological ICI resistance much earlier than current standards with imaging.
Research Sponsor: None.

Dataset on diverse clinical endpoints in training and validation cohorts.

Biomarker	Cohort	Objective Response p-value	mPFS High vs Low (months)	mOS High vs Low (months)
EV-PD-L1	Training	0.022	2.8 vs 10.8 (p<0.001)	13.7 vs 25.7 (p=0.021)
	Validation	<0.001	3.1 vs 5.8 (p=0.008)	10.4 vs 12.5 (p=0.97)
EV-PD-1	Training	<0.001	2.9 vs 15.9 (p<0.001)	6.4 vs 25.7 (p=0.002)
	Validation	<0.001	2.9 vs 8.4 (p=0.001)	7.3 vs 12.7 (p=0.056)
EV-CTLA-4	Training	<0.001	3.3 vs 16.1 (p<0.001)	20.2 vs 21.9 (p=0.081)
	Validation	<0.001	2.9 vs 9.0 (p<0.001)	8.8 vs 16.3 (p=0.003)

High vs low -> based on ideal cut-off.
NR = not reached.

Baseline peripheral blood activated-to-total CD8⁺ central memory T cell ratio to identify melanoma patients at high risk for severe toxicity but limited clinical benefit.

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Background: Immune-related adverse events (irAEs) represent a major clinical challenge that limits the usage of immune checkpoint blockade (ICB) for cancer therapy. The occurrence of irAEs often correlates with improved therapeutic response to ICB therapy, creating a therapeutic dilemma. Many known irAEs predictors correlate with treatment efficacy, further complicating clinical decision-making. Biomarkers that decouple severe irAEs risk from therapeutic benefit are thus urgently needed to guide clinical decision-making. **Methods:** We performed comprehensive peripheral blood immune profiling in two HCI (Huntsman Cancer Institute) clinical cohorts with 201 melanoma patients treated with ICB, analyzing 488-626 immune cell subsets and 1,463-2,926 plasma proteins at two timepoints: pretreatment and 3-6 weeks on therapy. Activated CD8+ T central memory (CD8Tcm) cells were defined by the expression of CD38, HLA-DR, or Ki67. Associations with severe irAEs, survival and treatment outcomes were evaluated across the largest test cohort composed of nine independent, multi-institutional clinical cohorts, two HCI cohorts, five Swiss cohorts, and two publicly available datasets. **Results:** Elevated pretreatment activated-to-total CD8+Tcm ratio robustly predicts severe irAEs. Patients with high versus low activated-to-total CD8+Tcm ratio showed two-fold or higher odds of developing severe irAEs across nine independent melanoma cohorts. Remarkably, this immune signature is associated with worse patient survival following ICB. These results suggest that there is a dedicated toxicity predictor in the peripheral blood. Incorporation of pretreatment plasma CXCL9 levels into a machine-learning regression model further improved irAEs predictive performance (mean AUC=0.78 across four independent cohorts). These baseline biomarkers outperformed previously reported irAEs predictors. **Conclusions:** The pretreatment activated-to-total CD8+Tcm ratio, alone or in combination with plasma CXCL9, identifies melanoma patients at high risk for severe irAEs who are not likely to respond to ICB treatment. This first of blood-based biomarker was tested and validated on many independent patients' cohorts and will allow to select patients based on the risk stratification prior to treatment initiation. Research Sponsor: None.

Impact of eftilagimod alfa, an APC activator via MHC class II, on lymphocyte activation and survival outcomes in metastatic cancer patients.

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Background: Immune activation is important for survival in cancer. Eftilagimod alfa (E), an antigen-presenting cell (APC) activator, binds to a subset of MHC class II molecules on APCs to mediate lymphocyte, e.g. T cell (CD4/CD8), recruitment/activation. Clinical studies of E in combination with a PD-1 antagonist (P) or chemotherapy (C) have shown promising results in phase 2 studies, and E is currently investigated in a phase 3 study in combination with P and C in first-line NSCLC (NCT06726265). We present cumulative correlation studies of immune activation in blood after administration of E with clinical efficacy in late-stage cancer patients (pts). **Methods:** Five (5) studies with 569 pts were evaluated. 30 mg E in combination with either P (pembrolizumab IV at 200 mg q3w or 400 mg q6w or 2 mg/kg q3w) or C (paclitaxel 80 mg/m^2 day 1, 8, 15, q4w) was administered SC biweekly for 6 months (mo), then every 2-4 weeks for 6-18 mo in pts with late-stage metastatic NSCLC, HNSCC, melanoma, or breast cancer. Absolute lymphocyte count (ALC) was taken before dosing (day 1 per cycle). ALC response was pre-defined as a change $\geq$0.2 x 10^9/L in $\leq$3 mo on study. Samples for gene expression profile (GEP) were taken pre-dose / 3 mo in a subset (N=111). IFN-g and CXCL10 were assessed pre-dose / after 1st E admin in a subset (N=79). Clinical efficacy was assessed by iRECIST and survival. **Results:** Treatment with E led to a rapid (3 mo) and sustained (~12 mo) stat. sign. (p=0.03) ALC gain versus control arm. 54.4% of all pts treated with E were ALC responders (53.6% for E+P; 55.1% for E+C). In ALC responders with E, overall survival (OS) was significantly improved (see Table 1) compared to non ALC responders. Effects were observed irrespective of the combination partner, P or C, with a median increase of 6.8 or 5.2 mo, respectively. In pts treated with P or C alone (control), 40.4% were ALC responders but with no sign. median OS gain. Clinical responders (iPR or iCR as BOR) exhibited consistent upregulation of immune pathways associated with T-cell functions, NK cell functions and cytotoxicity during treatment in GEP analysis. These functions were not upregulated in non-responders. IFN-g and CXCL10 concentrations increased quickly (~8h) and significantly post-first E dosing compared to baseline and levels remained elevated until next E dosing. This effect with E was consistent with P or C. **Conclusions:** E leads to immediate and sustained ALC increase and TH1 type reaction, which is associated with clinical efficacy in combination with P or C. Research Sponsor: None.

Treatment	Effects	Results
E (N=408)	ALC Responder with E	54.4% (N=222/408)
	Impact on survival: ALC responder vs. ALC non-responder	Median OS+ 7.7 mo(23.4 vs.15.7 mo) HR=0.69; p=0.002
Control arm (N=161)	ALC Responder in control arm	40.4% (N= 65/161)
	Impact on survival: ALC responder vs. ALC non-responder	Median OS+2.9 mo(20.4 vs. 17.4 mo) HR=0.98; p=0.93

Effects of a multimodal TCR/BCR repertoire foundation model on blood RNA-seq–based prediction of severe adverse event risk and rheumatoid arthritis.

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Background: Severe immune-related adverse events (irAEs) limit the use of immune checkpoint inhibitors (ICIs). Clinically, irAEs can resemble autoimmune diseases such as rheumatoid arthritis (RA), suggesting shared dysregulation of adaptive immune receptor repertoires (T-cell receptor [TCR] and B-cell receptor [BCR]). We developed a TCR/BCR foundation model to predict severe irAE risk prior to ICI treatment and to detect RA from peripheral blood. **Methods:** Peripheral blood RNA sequencing (RNA-seq) from cancer patients prior to ICI therapy, healthy donors, and RA patients was analyzed across six cohorts (Table 1). Severe irAEs were defined as grade $\geq$3. Gene expression quantification and signature scores were computed using kallisto and ssGSEA. Adaptive immune receptor repertoire (AIRR) features for TCR and BCR were derived from blood RNA-seq using an in-house pipeline (pyigmap). We trained neural network models to (i) estimate severe irAE risk in ICI-treated cancer patients and (ii) distinguish RA from healthy donors, using TCR/BCR embedding features alone or combined with gene signature scores. Performance was evaluated across multiple datasets to assess discrimination and cross-cohort robustness. **Results:** The model combining TCR/BCR embedding features with gene signature scores achieved improved discrimination for severe irAE risk prediction (AUC 0.78; $p=1\times10^{-5}$) and RA detection (AUC 0.70; $p=5\times10^{-14}$). This outperformed models based on gene signatures alone (irAE AUC 0.67; $p=8\times10^{-3}$; RA AUC 0.66; $p=4\times10^{-9}$), TCR/BCR diversity alone (irAE AUC 0.66; $p=2\times10^{-2}$; RA AUC 0.61; $p=6\times10^{-5}$), or signatures plus diversity (irAE AUC 0.70; $p=2\times10^{-3}$; RA AUC 0.69; $p=9\times10^{-13}$). Embedding-based representations were more robust to technical variation than conventional diversity metrics: batch-effect decomposition showed higher biological variability (0.012 vs 0.002) and lower technical variability (0.460 vs 0.861) for embeddings versus diversity features, consistent with improved cross-cohort generalization. **Conclusions:** A TCR/BCR foundation model integrated with gene signatures improves pre-treatment prediction of severe irAE risk and detection of autoimmune disease from peripheral blood RNA-seq. These repertoire-informed representations capture clinically relevant clonotype biology and support minimally invasive risk stratification and monitoring for patients receiving ICIs. Research Sponsor: None.

Cohort description.

Cohort	Source	N	Severe irAE	No severe irAE
#1 (irAE Train Set 1)	Internal	726	48	678
#1 (irAE Test Set 1)	Internal	187	12	175
#2 (irAE Test Set 2)	Internal	47	10	37
Cohort	**Source**	**N**	**Healthy**	**RA**
#3 (RA Train Set 1 / Validation Set)	Open source	211	97	114
#4 (RA Test Set 1)	Open source	101	50	51
#5 (RA Test Set 2)	Open source	24	12	12
#6 (RA Test Set 3)	Open source	140	20	120

Exploratory biomarker analysis of ociperlimab (OCI) plus tislelizumab (TIS) in patients (pts) with PD-L1–positive non–small cell lung cancer (NSCLC) in AdvanTIG-105.

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Background: OCI (anti-TIGIT) plus TIS (anti-PD-1) may enhance antitumor immune responses in advanced solid tumors. We present a retrospective biomarker analysis of pts in AdvanTIG-105 (NCT04047862), a phase 1/1b open-label study of OCI plus TIS for treatment-naïve metastatic non-squamous (NSQ) and squamous (SQ) PD-L1-positive (TC ≥1%) NSCLC. **Methods:** Pts in cohort 3 (n=46) were treated with 900 mg OCI plus 200 mg TIS. Pts in cohort 10 (n=68) were treated with 450 mg (Arm A), 900 mg (Arm B), or 1800 mg (Arm C) OCI plus 200 mg TIS. Baseline tumor tissue was used to measure PD-L1 and TIGIT expression (SP263 and SP410 IHC assays). Gene expression profiling (GEP) was performed using TrueSeq RNA Access (Illumina); gene signature scores were evaluated with ssGSEA. Progression-free survival (PFS) hazard ratio (HR) was calculated by Cox proportional hazards regression. **Results:** At Aug 2024 data cutoff, median follow-up was 19.7 months (range: 0.7-41.6 mo) for cohort 3 and 9.8 mo (range: 0.3-21.4 mo) for cohort 10. Baseline characteristics, overall response rate (ORR), and PFS were comparable across cohorts and between biomarker-evaluable and intent-to-treat (ITT) pts. PD-L1 ≥25% vs <25% and TIGIT ≥5% vs <5% subgroups were associated with a trend toward higher ORR and longer PFS, with greater increment in pts with NSQ- vs SQ-NSCLC (Table). PD-L1/TIGIT double high subgroup showed further enriched clinical efficacy in NSCLC (Table). Anti-TIGIT mechanism of action-related GEP signatures (NK cells, Treg, macrophages) were associated with a trend toward longer PFS primarily in pts with NSQ-NSCLC. **Conclusions:** Pts with NSCLC with PD-L1 ≥25%, TIGIT ≥5%, or PD-L1/TIGIT double high can achieve a trend toward longer PFS and higher ORR than PD-L1 low or TIGIT low subgroups when treated with OCI plus TIS. Longer PFS in PD-L1 ≥25% or TIGIT ≥5% subgroups in NSQ- vs SQ-NSCLC may be associated with biological differences in histology. Confirmation of these results will require prospective evaluation of OCI plus TIS in randomized studies. Clinical trial information: NCT04047862. Research Sponsor: BeOne Medicines Ltd.

	Subgroup	mPFS (mo)	ORR (%)
NSCLC	Evaluable pts (n=113)	5.5	34.5
	PD-L1 ≥25% vs <25%	6.9 vs 4.2	47 vs 22
	(n=57 vs 56)	HR 0.58 (95% CI: 0.37-0.9)	
	TIGIT ≥5% vs <5%	6.8 vs 4.1	45 vs 19
	(n=62 vs 48)	HR 0.64 (95% CI: 0.41-1)	
	PD-L1/TIGIT double positive vs other	8.3 vs 4.2	55 vs 22
	(n=38 vs 72)	HR 0.53 (95% CI: 0.33-0.86)	
NSQ-NSCLC	PD-L1 ≥25% vs <25%	8.3 vs 4.2	49 vs 19
	(n=35 vs 32)	HR 0.55 (95% CI: 0.32-0.98)	
	TIGIT ≥5% vs <5%	6.5 vs 4.1	50 vs 14
	(n=36 vs 29)	HR 0.53 (95% CI: 0.3-0.94)	
SQ-NSCLC	PD-L1 ≥25% vs <25%	5.5 vs 5.3	45 vs 25
	(n=22 vs 24)	HR 0.63 (95% CI: 0.35-1.29)	
	TIGIT ≥5% vs <5%	5.5 vs 5.5	38 vs 26
	(n=26 vs 19)	HR 0.93 (95% CI: 0.46-1.87)	

Molecular progression defined by longitudinal ctDNA dynamics for prediction of outcomes in immune checkpoint inhibitor–treated solid tumors.

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Background: Reliable early biomarkers of immune checkpoint inhibitor (ICI) resistance remain an unmet need due to delayed imaging and non-classical response kinetics. While ctDNA has shown promise, current methods often require tumor tissue or rely on static comparisons. We investigated whether longitudinal ctDNA dynamics measured using a tumor-naive, methylation-based assay could define molecular progression and predict outcomes in patients receiving ICIs. **Methods:** Patients with advanced solid tumors treated with ICI regimens were analyzed in a primary cohort (n=65) with serial plasma sampling. Tumor Methylation Scores (TMS) were generated using Northstar Response. Molecular progression based on ctDNA trajectory was assessed for associations with PFS and OS and compared with conventional landmark ctDNA approaches and RECIST v1.1. Independent validation was performed in a second cohort (n=72). **Results:** Molecular progression strongly stratified survival in the primary cohort (OS HR=4.9, $p<0.001$; PFS HR=5.3, p=0.0002) and demonstrated superior prognostic performance relative to RECIST. These results were independently validated (PFS HR=4.6, p=0.00004; OS HR=4.3, p=0.005). Notably, among RECIST-defined non-progressors at 6 months, molecular progression identified patients with markedly worse outcomes (PFS HR=6.7, p=0.002; OS HR=4.5, p=0.011). Molecular progression preceded radiographic and clinical progression by median lead times of 63.5 and 77 days, respectively. **Conclusions:** Longitudinal ctDNA dynamics measured using a tumor-naive methylation assay define molecular progression that robustly predicts survival and identifies early ICI resistance, including in RECIST-stable patients. This approach offers clinically meaningful lead time and supports integration of ctDNA dynamics into response assessment frameworks for immunotherapy. Research Sponsor: None.

2573 Poster Session

Molecular pathways of immune checkpoint inhibitor–induced hepatitis.

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Background: Immune checkpoint inhibitor (ICI) related hepatitis is a clinically significant immune-related adverse event (irAE) and a common cause of treatment interruption. It occurs in roughly 5 to 10 percent of patients receiving anti PD-(L)1 monotherapy and in up to one third of those treated with combination ICI therapy. Despite increasing clinical recognition, the molecular mechanisms and predictive factors underlying ICI hepatitis remain poorly defined. The Montreal Immune-Related Adverse Events (MIRAE)-led hepatitis project aims to characterize the immune cell populations and underlying transcriptional programs associated with ICI-hepatitis pathogenesis. **Methods:** This translational study is conducted within the MIRAE biobank, a prospective multicenter cohort of ICI-treated patients with and without irAEs. The hepatitis cohort includes patients with longitudinal plasma samples collected at baseline, on treatment, and at irAE onset. Ongoing immune profiling efforts include plasma-based cytokine and chemokine analysis, high-throughput plasma proteomics, and single cell RNA sequencing of PBMCs. Preliminary analysis focused on plasma proteomics. Five patients with high-grade ICI-hepatitis and five ICI-treated controls without irAEs were selected and matched by age, sex, and primary tumor. Plasma samples were analyzed using the SomaScan 11K assay to identify differentially expressed proteins and enriched immune pathways. **Results:** ICI-related hepatitis was clinically severe, requiring systemic corticosteroids in all cases and additional immunosuppressive therapies in most patients. ICI-hepatitis cases showed significantly higher plasma levels of liver injury markers, including ALT and AST, compared with matched controls. Widespread alterations were observed in the circulating proteome, with strong upregulation of liver-enriched proteins and inflammatory mediators. Gene set enrichment analyses revealed enrichment of liver-associated pathways including xenobiotic and bile acid metabolism, as well as IL-12 signaling, interferon-α and γ, neutrophil-associated pathways, and liver-resident macrophage signatures. Pathway analysis of single cell data revealed enhanced cytotoxic activity of CD8 T cells during ICI hepatitis, as exemplified by upregulation of the CTL and IL-6 pathways. **Conclusions:** ICI-hepatitis was associated with circulating immune signature characterized by liver injury markers, inflammatory mediators, and enrichment of innate immune pathways. These findings provide molecular insight into the immunopathogenesis of ICI hepatitis and inform future biomarker discovery, druggable pathways, and risk stratification. Research Sponsor: None.

Association of neutrophil percentage-to-albumin ratio with progression-free survival and overall survival in cancer patients treated with PD-1/PD-L1 inhibitors.

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Background: The Neutrophil Percentage-to-Albumin Ratio (NPAR) reflects systemic inflammation and nutritional status. Its prognostic and predictive value in cancer patients treated with PD-1/PD-L1 inhibitors remains unclear. We investigated the association of the baseline of NPAR with PFS and OS in cancer patients who received PD-1/PD-L1 inhibitors. **Methods:** A retrospective cohort of 532 patients treated with PD-1/PD-L1 inhibitors at the Second Xiangya Hospital of Central South University between 2018 and 2024 was enrolled. Participants were divided into tertiles based on the baseline of NPAR. PFS and OS were assessed using Kaplan–Meier method and log-rank tests. Univariable and multivariable Cox proportional hazards models were employed to examine the association between NPAR and survival outcomes, with sequential adjustment for clinically relevant confounders. **Results:** The median PFS and OS of total patients was 21.3 months (IQR, 10.5–32.7) and 24.7 months (IQR, 16.9–41.5), respectively. Individuals with elevated NPAR experienced significantly worse PFS and OS than those with low NPAR and medium NPAR (PFS: $p < 0.05$; OS: $p < 0.0001$). Subgroup analyses showed the consistent results in the lung cancer patients (PFS: $p < 0.05$; OS: $p < 0.01$). In univariate COX regression analyses, each one-unit increment in NPAR corresponded to hazard ratios (HRs) of 1.032 (95% CI, 1.004–1.062; $p < 0.05$) for PFS and 1.069 (95% CI, 1.035–1.104; $p < 0.001$) for OS. Multivariate Cox regression analysis identified that a high NPAR level remained independently associated with inferior survival outcomes after adjusting for confounders. Compared with the low NPAR group, the high NPAR group showed worse PFS (HR, 1.38; 95% CI, 1.03-1.84; $p < 0.05$) and OS (HR, 1.95; 95% CI, 1.36-2.79; $p < 0.001$) in the fully adjusted model (Model 4). **Conclusions:** Elevated NPAR can independently predict worse PFS and OS in cancer patients receiving PD-1/PD-L1 inhibitors and represents a simple, low-cost biomarker for clinical risk stratification. Research Sponsor: None.

Association between NPAR and PFS/OS of cancer patients.

	Model 1 HR (95%CI)		p-value		Model 2 HR (95%CI)		p-value		Model 3 HR (95%CI)		p-value		Model 4 HR (95%CI)		p-value	
	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS
NPAR Low group	ref	ref			ref	ref			ref	ref			ref	ref		
High group	1.40(1.06-1.85)	2.05(1.45-2.90)	0.018	<0.001	1.42 (1.07-1.89)	1.98 (1.40-2.82)	0.015	<0.001	1.40 (1.05-1.87)	1.99 (1.40-2.83)	0.023	<0.001	1.38 (1.03-1.84)	1.95 (1.36-2.79)	0.032	<0.001

Model 1: unadjusted. Model 2: adjusted for sex, diabetes, hyperlipidemia, cardiovascular disease, cerebrovascular disease, pulmonary tuberculosis and viral hepatitis type B. Model 3: adjusted for model 2 + single ICIs, chemotherapy, radiotherapy. Model 4: adjusted for model 3 + NSAIDS, PPI, β-blocker, hormone, whiteboard-raising drugs, anticoagulant and antithrombotic drugs.

2575 Poster Session

Plasma-TMB (pTMB) and circulating tumor fraction (ctF) dynamics as biomarkers of benefit from the addition of atezolizumab to first-line FOLFOXIRI/bevacizumab in metastatic colorectal cancer (mCRC): A translational analysis of the AtezoTRIBE study.

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Background: TMB-high pMMR mCRC patients (pts) do not seem to derive benefit from immune checkpoint inhibitors (ICIs). In the CO.26 trial, pMMR/MSS mCRC pts with high baseline pTMB had better outcome with ICIs than those with low pTMB. Moreover, in the AtezoTRIBE study, tissue TMB was identified as a promising biomarker able to identify a subgroup with potential benefit from the addition of atezolizumab to first-line FOLFOXIRI/bev. In that trial, the addition of atezolizumab did not improve ORR, and PFS curves separated only after approximately 6 months. Given this delayed treatment effect observed, we hypothesized that dynamic liquid biopsy biomarkers could identify early molecular changes associated with subsequent immune-sensitivity. Here we evaluated the prognostic and predictive role of both pTMB and on-treatment ctF dynamics in the AtezoTRIBE trial. **Methods:** Pts with untreated mCRC enrolled in the AtezoTRIBE trial (NCT03721653) and with available plasma at baseline (T0) and at the end of induction (T1) were included. Samples were analyzed using the Tempus xF assay, a 105-gene cell-free liquid biopsy panel, to determine ctF by Tempus xFv2 cTF algorithm, and pTMB. pTMB was assessed as a dichotomous variable (high: $\geq$26 mut/Mb). ctF dynamics between T0 and T1 identified molecular responders (MRs), i.e. pts with the top 30% relative ctF reduction including clearance below quantification/detection limits at T1, and non responders (nMRs). Cox models stratified by liver metastases, and including treatment-by-biomarker interaction when appropriate, were used for PFS analyses (likelihood ratio test, $p<0.15$). **Results:** pTMB was evaluable in 123/155 (79%) T0 samples, and 20 (16%) were classified as pTMB-high. Baseline characteristics were balanced between pTMB-high and pTMB-low groups. High pTMB was associated with longer PFS (HR: 0.69 [90%CI 0.43-1.10], p=0.095), while no interaction between pTMB and treatment arm was observed (p_{int}=0.871). Among 89 pts with evaluable ctF at T0 and T1, 63 (71%) were MRs. Baseline clinical and molecular characteristics did not differ in the MR and nMR groups. A significant interaction (p=0.132) between ctF dynamics and MR was reported, with nMRs achieving higher benefit from the addition of atezolizumab to FOLFOXIRI/bev (HR: 0.33 [90%CI: 0.16-0.69]) than MRs (HR: 0.76 [90%CI: 0.03- 3.95). A sensitivity analysis including 6 additional pts with undetectable ctF both at T0 and T1 provided consistent findings (p_{int}=0.108). **Conclusions:** The addition of ICI to first-line chemotherapy may be more efficacious among mCRC pts with lower molecular response to the upfront induction regimen, as measured by ctF dynamics. If independently validated, ctF molecular response biomarker might be useful for future trials' design. Research Sponsor: Tempus; GONO Foundation.

A phase 2, open-label, multi-center, single-arm study of atezolizumab and bevacizumab in the treatment of second line and beyond, recurrent/metastatic endometrial cancer.

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Background: The treatment paradigm for advanced/recurrent endometrial cancer (EC) is undergoing rapid transformation. Currently, use of immune checkpoint inhibitors (ICI) is standard of care for deficient mismatch repair (dMMR) tumors in the front line setting and ICI "can" be used in proficient MMR (pMMR). The purpose for this study is to evaluate an alternative ICI and anti-angiogenic regimen, atezolizumab plus bevacizumab in pts with recurrent EC with no prior ICI use and to identify blood-based correlates of non-responders early in treatment. **Methods:** This multicenter, single-arm, open label phase 2 trial (NCT03526432) enrolled pts with recurrent EC who had relapsed following platinum based chemotherapy. No prior ICI was allowed. Treatment consisted of atezolizumab 1,200 mg plus bevacizumab 15 mg/kg iv on day 1 every 21 days until progression or toxicity. The primary endpoint was objective response rate (ORR). Peripheral whole blood was collected at baseline and after 2 cycles of therapy, and high-dimensional immune profiling was performed. **Results:** Sixty-five pts were enrolled and received at least one dose of trial treatment. Fifty-six pts were response-evaluable (45 with pMMR tumors, 7 with dMMR tumors and 4 with unknown MMR status). Median age was 65 years. All pts had received at least one prior chemotherapy and 22 pts (39.3%) received prior radiation therapy. The ORR was 33.9%; 95% CI, 21.8 to 47.8; (19/56 patients), which include 5 complete and 14 partial responses; median duration of response (DOR) was 16 months. In addition, 63% of pts survived progression-free for at least 6 months. The median PFS was 8.8 months (95% CI, 5.5 to 12.0). The median OS was 41.55 months (95% CI, 27.0 – 57.5). The most common grade 3 or 4 adverse events were hypertension (21.5%), fatigue (7.7%) and diarrhea (7.7%). In peripheral blood analysis, non-responders demonstrated expansion of a suppressive myeloid population characterized by PD-L1^{+}CD16+ monocytes. There was an increase of ICOS^{+} Tregs consistent with an immunosuppressive phenotype. Within the effector T cell compartment, central memory CD8^{+} T cells expressing Fas and CD27 expanded in non-responders. **Conclusions:** The combination of atezolizumab and bevacizumab in patients with recurrent EC and post cytotoxic chemotherapy has efficacy in both dMMR and pMMR populations and a toxicity profile that appears more favorable than other treatments. This data suggests atezolizumab and bevacizumab could be considered as an alternative regimen in the recurrent, metastatic setting among pts who are ICI naïve and for whom there are concerns regarding the adverse events of treatment. Peripheral whole blood analysis of non-responders correlated with immune angiogenic escape mechanism with higher levels of ICOS+Tregs, Fas+CD27+ CD8T cells, and PDL1+ CD16+ monocytes. Clinical trial information: NCT3526432. Research Sponsor: Genentech.

Analysis of circulating small extracellular vesicle-associated miRNA in head and neck squamous cell carcinoma (HNSCC): Biomarker discovery in pre-operative neoadjuvant nivolumab.

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Background: Standard treatment options for HNSCC include chemotherapy, radiation, surgery, and immunotherapy. Immune Checkpoint Inhibitors (ICI) are safe and improve survival in platinum-refractory and metastatic HNSCCs. Further studies are needed to efficiently stratify patients who may benefit from ICIs. MYC-V1 is a family of oncogenes, induced by MYC signaling, that is negatively correlated with response to ICI in HPV+ HNSCC. Non-invasive Biomarkers (NiBs) identifying patients with low MYC-V1 expression may aid in predicting response to ICIs. Small extracellular vesicles (sEVs) are membrane-bound mediators of intercell communication that are present in circulation, serving as a promising source of NiBs. The Let-7 family of tumor suppressors are negative regulators of the MYC-V1 gene family and exhibit low expression in HNSCC compared to healthy controls. Let-7 family members, such as Let-7d and Let-7c, may play a role in ICI responsiveness via PD-L1 and MYC mRNA degradation, respectively. Here, we analyze the miRNA profile of sEVs from patients enrolled in a randomized Phase I clinical trial undergoing Neoadjuvant Nivolumab therapy. (NCT03238365). **Methods:** Plasma was collected before and after treatment (N=24) with ICI. 12 patients were included and stratified based on HPV status (6 HPV-, 6 HPV+) and pathologic treatment response (pTR) (6 Responders [R], 6 Nonresponders [NR]). pTR >20% of tumor surface area as graded by two pathologists was R; 0% was NR. sEVs were isolated via immunoprecipitation targeting tetraspanins CD63/9/81. miRNA was isolated and NGS was performed. Analysis was performed using Python and Biomni. Log2FC (FC) compared expression levels between groups and a False Discovery Rate (FDR) <.05 was significant. **Results:** 189 miRNAs were detected in HNSCC sEVs. Analysis comparing HPV+ R vs NR revealed 48 miRNAs with significantly different levels between these pretreatment groups. 47 were more abundant in R; 1 was less abundant. miRNAs found at higher levels in HPV+ R include the Let-7 family. Let-7d was most abundant (FC: 2.26, FDR 0.04), with a family (Let-7a,b,d,f,g,i) FC range of 1.63-2.26 (FDR 0.03-0.05). Following treatment with ICI, HPV+ patients had increased Let-7c levels (FC 4.71, FDR 0.02) compared to pretreatment. Analysis of HPV− R vs NR showed 0 miRNA that met statistical significance. **Conclusions:** Here, we show that ICI-responsive HPV+ HNSCC is associated with high levels of circulating, sEV-contained Let-7 family members and that Let-7c is increased in response to ICI in those same patients. We propose that a MYC-V1-suppresive, PD-L1-destabilizing mechanism may be present in patients with higher than average Let-7 expression, conferring sensitivity to ICI, and that sEV-associated Let-7 levels may serve as NiBs to identify these patients as favorable ICI candidates prior to treatment. Research Sponsor: U.S. National Institutes of Health.

T-cell stem-like memory cells as a novel biomarker to identify patients with sustained disease control during treatment with PD-(L)1 immunotherapy.

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Background: Reliable, clinically easily testable biomarkers to monitor the benefit of treatment with immune checkpoint inhibitors (ICI) remain limited. We performed comprehensive analysis of markers defining differentiation and functional status of different populations of peripheral blood T-cell in order to identify biomarkers associates to treatment response in treated patients. **Methods:** Peripheral blood was analyzed from metastatic patients receiving PD-(L)1–based therapy: anti–PD-(L)1 monotherapy (n=102), combination therapies (n=35), or chemo-immunotherapy (n=14). Sampling time on therapy was heterogeneous, recorded, and included in sensitivity analyses. All patients provided informed consent under IRB approval. A variety of CD4 andCD8 cell populations (naive, stem-like memory [SCM], central memory [CM], effector memory [EM], EMRA/TEMRA). were analyzed using -standardized multiparameter flow cytometry. Pre-specified stem-like–to–effector balance ratios were computed within CD4 and CD8 (SCM/CM and SCM/EM; SCM/EMRA exploratory). Markers analysis included CD45RA, CCR7, CD95, TCF1/TCF7, TOX, TIGIT, and Ki-67). Clinical benefit was assessed by disease control rate (DCR=CR+PR+SD) versus progressive disease (PD). Biomarkers were analyzed using Mann–Whitney U tests and clustered using unsupervised 1D k-means. Time-to-event analyses used univariable Cox models for time to disease control loss (DCL), defined from ICI initiation to first PD (or discontinuation for progression). **Results:** Among 151 patients, DCR n=89 and PD n=62, disease control was characterized by a stem-like/early memory blood T-cell profile. DCR showed higher CD4 and CD8 naive and SCM frequencies ($p<0.05$), whereas PD showed enrichment in differentiated T cell populations including CD4 CM/EM and CD8 EM ($p\leq0.01$ to $p<0.0001$). Stem-like–to–effector cell ratios were higher in DCR for both CD4 and CD8 (SCM/CM $p<0.001$; SCM/EM $p<0.01$) and for CD4 SCM/EMRA ($p<0.05$). In total CD3 T cells, DCR had higher CD45RA ($p<0.001$), CCR7 ($p<0.05$), and TCF1/TCF7 ($p<0.05$), with lower CD95 ($p<0.05$) and reduced TIGIT ($p<0.01$), TOX ($p<0.05$), and Ki-67 ($p<0.05$). In Cox models for DCL (inverse-coded; HR>1 favorable), significant associations were observed across subsets, ratio, and marker features (HR range 1.7–4.8; all $p<0.05$), with the strongest effects for stem-like–to–effector cell ratios and differentiated subset metrics. Associations were observed across PD-(L)1–based regimens. **Conclusions:** Stem-like memory CD4 and CD8 T cells represent a new marker associated with efficacious response to ICI and DCR while a dominant effector/terminal differentiation profile to DCL and PD. These findings underscore the importance of immune monitoring to identify patients at risk of early loss of treatment benefit and disease progression and to guide treatment modifications. Research Sponsor: None.

Real-world concordance of tumor mutational burden (TMB) between blood (circulating tumor DNA) and tissue, and its association with immunotherapy response.

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Background: Tissue-derived tumor mutation burden (tTMB) ≥10 mutations/Mb is a histology-agnostic predictive biomarker for the immune checkpoint inhibitor (ICI) pembrolizumab. It is unknown if circulating tumor DNA–derived TMB (bTMB) is also predictive and current ASCO guidelines recommend against using bTMB alone. Concordance between tTMB and bTMB is only moderate, with reported Pearson correlation coefficients between 0.54-0.70. In prior studies, bTMB was a median 2.4-fold greater than tTMB in matched samples. This study evaluated the correlation and predictive accuracy of immunotherapy response of bTMB vs. tTMB in solid tumors. **Methods:** 221 patients with solid tumors were included from the Cleveland Clinic genomics repository who had at least one tTMB and one bTMB result between July 1, 2021, and July 1, 2025. High TMB was defined as tTMB ≥10 mutations/Mb. For bTMB, thresholds of ≥10 and ≥16 mutations/Mb were evaluated, as prior studies suggest a bTMB threshold of 16 for Guardant 360 may be comparable to a tTMB of 10. Correlation between bTMB and tTMB was assessed using Pearson's correlation coefficient. Among patients treated with ICIs, treatment response and time to treatment failure (TTF) were analyzed using both bTMB thresholds and compared with tTMB. **Results:** Among the 221 patients included in the analysis, 80 received ICIs. Median bTMB was 2.3-fold higher than matched tTMB. A strong positive linear correlation was observed between bTMB and tTMB both among patients who received ICIs (R^2 = 0.845, $p < 0.001$) and across the full cohort of 221 patients (R^2 = 0.818, $p < 0.001$). High tTMB was associated with numerically longer TTF in those with both low bTMB (median 21.3 months) and high bTMB (median 15.2 months), as shown in Table 1. Those with high tTMB/low bTMB had numerically longer median TTF compared to those with low tTMB/high bTMB (21.3 vs. 7.0 months). Increasing the bTMB threshold from 10 to 16 was associated with improved median TTF from 3.5 to 7.0 months among patients with low tTMB. **Conclusions:** This study confirms that bTMB values are consistently higher than tTMB and demonstrates a strong positive correlation between the two measures. Raising the bTMB threshold appears to improve prediction of immunotherapy response in patients with low tTMB. However, tTMB continued to show evidence of predictive value for response to ICIs regardless of bTMB, although these subgroup analyses were limited by small sample sizes. Larger, disease-specific studies are needed to better define the independent clinical utility of bTMB. Research Sponsor: None.

Time to treatment failure in TMB-high vs. TMB-low patient pairs.

	bTMB -10=H Median TTF (months)		bTMB -16=H Median TTF (months)
tTMB-L, bTMB-L (n=35)	4.9	tTMB-L, bTMB-L (n=51)	3.9
tTMB-H, bTMB-L (n=3)	21.3	tTMB-H, bTMB-L (n=4)	21.3
tTMB-L, bTMB-H (n=32)	3.5	tTMB-L, bTMB-H (n=16)	7.0
tTMB-H, bTMB-H (n=10)	10.2	tTMB-H, bTMB-H(n=9)	15.2

Functional binding of PD-1 ligands: Overcoming PD-L1 staining limitations to predict therapy response.

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Background: Immune-checkpoint blockade (ICB) targeting the PD-1/PD-L1 axis has improved outcomes across multiple malignancies, yet response prediction remains unreliable due to fundamental limitations of PD-L1 immunohistochemistry (IHC). As a static expression assay, PD-L1 IHC does not capture functional ligand engagement, does not account for PD-L2 contributions to PD-1 signaling, and is confounded by N-glycosylation that masks epitopes and distorts measurable abundance. These mechanistic gaps undermine biomarker accuracy and impede appropriate patient selection. To overcome these limitations, we established IcAR-PD1, a functional reporter system designed to quantify the true biological availability of PD-L1 and PD-L2 for therapeutic blockade by anti-PD-1/PD-L1 ICBs. **Methods:** We conducted a double-blinded retrospective study spanning multiple tumor types. IcAR-PD1 scores from patient-derived samples were correlated with clinical outcomes to anti-PD1 therapy and benchmarked against PD-L1 IHC, evaluating predictive accuracy, response probability, and duration-of-response. To define how PD-L1 N-glycosylation modulates inhibitory signaling and drug susceptibility, IcAR-PD1 was combined with a full four-site glycosylation mutation array and validated using primary $CD8^+$ T-cell cytotoxicity assays. **Results:** IcAR-PD1 demonstrated markedly superior predictive power compared with PD-L1 IHC, achieving AUCs of 0.87–0.92 versus 0.55–0.62. High IcAR-PD1 scores aligned with >90% response probability and >3-fold longer median duration-of-response ($p<0.01$). Incorporation of PD-L2 activity and direct measurement of functional ligand availability explained the improved performance across tumor types. Glycosylation analysis showed that fully glycosylated PD-L1 reduced blockade efficiency, with anti-PD1 treatments markedly more sensitive to glycan status than anti-PDL1. Loss of the N35 site diminished anti-PD1 efficacy by increasing release of functional soluble PD-L1, partially affecting anti-PDL1 activity. The non-glycosylated Nx4 variant displayed enhanced susceptibility to both therapies, with a disproportionately greater improvement for anti-PD1 blockade. **Conclusions:** IcAR-PD1 resolves the major limitations of PD-L1 IHC by quantifying functional ligand activity, incorporating PD-L2 contribution, and revealing glycosylation-driven resistance mechanisms. These findings support IcAR-PD1 as a precise, mechanism-based biomarker for selecting patients most likely to benefit from anti-PD1 therapy. Research Sponsor: None.

Spatial immune profiling to identify GPNMB as a mediator of immune suppression that limits response to PD-1 blockade in TNBC.

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Background: Breast cancer (BC) is the leading cause of female cancer-related deaths. Triple-negative BC (TNBC), accounting for ~25% of BC-related deaths, carries the poorest prognosis due to limited targeted therapies and the significant, yet still modest overall, benefit achieved with immune checkpoint blockade (ICB). Identifying drivers of immune evasion is essential to expand patient benefit from ICB. Glycoprotein-NMB (GPNMB) is highly expressed in TNBC and associated with immune suppression, metastasis, and poor clinical outcomes. However, its role in shaping the TNBC immune landscape and contributing to ICB resistance remains unclear. We investigated the impact of tumor-derived GPNMB on the tumor immune microenvironment and whether its inhibition enhances ICB efficacy. **Methods:** Imaging mass cytometry, a high-dimensional spatial proteomics platform enabling simultaneous single-cell and spatial analysis of intact tissue, was used to map the immune landscape of GPNMB-proficient and -deficient EO771 tumors. Therapeutic relevance was evaluated by combining GPNMB loss with anti-PD-1 treatment. Associations between tumor GPNMB expression, immune infiltration, and clinical outcomes were evaluated in human TNBC tumors. **Results:** GPNMB loss in mammary tumor cells significantly impaired tumor growth in syngeneic, but not athymic (T cell-deficient) mice, suggesting a T cell-dependent mechanism. $GPNMB^{KO}$ tumors showed increased immune infiltration, notably $GZMB^{+}/PD\text{-}1^{+}CD8^{+}$ T cells, and enhanced formation of stimulatory $CD8^{+}$ T cell/$CD4^{+}$ T cell/$CD86^{+}$macrophage immune triads. GPNMB loss impaired tumor engraftment in an adoptive OT-1 T cell transfer model and significantly improved response to anti-PD-1 therapy in two independent TNBC models, reducing breast tumor growth and lung metastasis. Therapeutic benefit was accompanied by increased intratumoral T cell infiltration and functional reinvigoration, reflected by increased $GZMB^{+}CD8^{+}$ T cells. In human TNBC, high tumor GPNMB expression was associated with reduced intratumoral T cell infiltration and poorer clinical outcomes. $GPNMB^{high}$ tumors exhibited reduced infiltration of $CD8^{+}$, $GZMB^{+}CD8^{+}$, and $CD4^{+}$ T cells and were enriched in immune-desert and margin-restricted phenotypes. In contrast, $GPNMB^{low}$ tumors showed increased $CD8^{+}$ T cell/$CD4^{+}$ T cell/macrophage triads, indicating enhanced immune activation. Together, these data show that elevated GPNMB expression in human TNBC is associated with T cell exclusion, and an immune-excluded tumor architecture. **Conclusions:** Our findings identify tumor-derived GPNMB as a clinically relevant mediator of T cell exclusion and suppression in TNBC. Therapeutic targeting of GPNMB in combination with PD-1 blockade may enhance the efficacy of ICB and expand the subset of TNBC patients who derive meaningful clinical benefit, ultimately improving clinical outcomes. Research Sponsor: Canadian Institutes of Health Research (CIHR); 202211FBD.

Age-associated genomic instability and inflammatory pathway activation: A pan-cancer multi-omics analysis of the TITANIA framework.

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Background: Aging is associated with increased cancer incidence and altered tumor biology, yet molecular mechanisms underlying age-related differences remain poorly characterized at the multi-omics level. We hypothesized that elderly patients may exhibit coordinated increases in genomic instability and inflammatory pathway activation. **Methods:** We performed integrated multi-omics analysis comprising whole genome sequencing, RNA sequencing, and data-independent acquisition mass spectrometry-based proteomics on 153 treatment-naive patients across six cancer types (colorectal cancer n=52, gastric n=19, kidney n=32, non-small cell lung cancer n=27, ovarian n=19, liver n=4). The TITANIA study provided matched tumor and normal tissue specimens with standardized collection protocols (median cold ischemia time: 12 minutes). Patients were stratified by age (≤60 years, n=40; >60 years, n=113). Inflammation scores were calculated using ssGSEA of six Hallmark inflammatory pathways. Tumor microenvironment subtypes were identified using xCell deconvolution followed by k-means clustering (k=3). **Results:** Tumor mutation burden (TMB) showed a significant positive correlation with age (Spearman ρ=0.334, P<0.001), with elderly patients demonstrating higher median TMB than younger patients (4.55 vs 2.84 mut/Mb, P<0.001). Inflammation scores showed positive correlations with age in tumor tissues at both RNA (ρ=0.223, P=0.01) and protein (ρ=0.233, P=0.005) levels. Normal tissue inflammation correlated with paired tumor TMB (RNA: ρ=0.283, P=0.027; Protein: ρ=0.387, P<0.001), raising the possibility that systemic inflammaging may be associated with tumor genomic instability. TME clustering identified three subtypes: Immune-Hot (n=14), Immune-Cold (n=92), and Vascular-Rich (n=30). Notably, all patients in the Immune-Hot cluster were elderly (>60 years). TMB positively correlated with B cells, neutrophils, and M1 macrophages, while negatively correlated with stromal score and endothelial cells. The EPITHELIAL_MESENCHYMAL_TRANSITION pathway showed potential as a prognostic marker at both omics levels (C-index: RNA 0.63, Protein 0.61), though further validation is warranted. **Conclusions:** This pan-cancer multi-omics analysis demonstrates age-dependent genomic instability coupled with inflammatory pathway activation in both tumor and normal tissues, consistent with the inflammaging hypothesis. The novel finding that normal tissue inflammation correlates with tumor TMB suggests systemic inflammaging may contribute to tumor evolution, with potential implications for age-adapted immunotherapy strategies. Research Sponsor: None.

A new HLA genotyping algorithm to show accuracy and concordance between tumor and normal samples.

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Background: HLA genotyping, specifically HLA-A*02:01 is an actionable marker in uveal melanoma for Tebentafusp, a bispecific gp100 peptide-HLA-directed CD3 T cell engager, with ongoing clinical trials investigating its use in HLA-A*02:01 positive cutaneous and mucosal melanoma. However, prior work has shown a discrepancy in this marker between blood and somatic tumor testing (Seedor R et al ASCO 2023). Given therapeutic implications of these discordances, a better understanding of tumor versus normal HLA testing concordance is critical. **Methods:** The Tempus HLA genotyping algorithm was run on a cohort of 191 patients, each with a tumor and a normal sample. The reference HLA genotype was determined by an independent lab using the GenDx HLA genotyping kit and long read sequencing of the normal sample. Samples that failed sequencing in either lab were excluded from the analysis. Concordance between tumor and normal samples was additionally evaluated on a cohort of 7,821 solid-tumor samples from a variety of sites, selected from the Tempus multimodal database. **Results:** The Tempus HLA genotyping algorithm is highly accurate (>98.9% on all HLA genes except DQA1). Specifically, it has an accuracy of 100% on the HLA-A gene, using either the tumor or normal sample. On the larger tumor/normal comparison cohort (7,821 samples), the Tempus HLA genotyping algorithm is highly concordant (>99% for all genes except HLA-DQA1 [94.3%]). For the 183 melanoma samples in this cohort, concordance was similar with 100% for HLA-A and HLA-B and 99.5% (182/183) for HLA-C, further confirming that HLA genotyping can be performed accurately on melanoma tumor samples. Investigation of all discordances on HLA genes for which HLA LOH results were available (HLA-A, -B and -C) shows that 84% (88/105) of those discordant samples have somatically lost the allele responsible for the discordance. Of LOH positive discordant samples, 73% (64/88) had a tumor purity ≥70%. Thus, over half (64/105) of the discordances between tumor- and normal-HLA genotyping are caused by high tumor purity HLA LOH positive samples. On samples meeting these criteria, concordance drops to 86%-89%. **Conclusions:** The Tempus HLA genotyping algorithm is an extremely accurate laboratory developed test that provides accurate results, regardless of whether the normal or tumor sample is used. Concordance between normal- and tumor-based results is above 99.5% in a large-scale dataset, provided the sample does not have HLA LOH and a tumor purity over 70%. These findings suggest that this test can rapidly screen patients for HLA genotype and match them to appropriate clinical trials but emphasize the importance of a normal sample for high tumor purity specimens. Research Sponsor: Tempus AI, Inc.

	Accuracy (normal)	N (normal)	Accuracy (tumor)	N (tumor)
HLA-A	100.0%	189	100.0%	189
HLA-B	99.5%	187	99.0%	189
HLA-C	100.0%	185	98.9%	185
HLA-DQA1	99.5%	182	97.9%	189
HLA-DQB1	100.0%	186	99.5%	187
HLA-DRB1	98.9%	182	98.9%	182

Pan-cancer analysis of STAT6 expression and its relationship with tumor microenvironment characteristics and survival.

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Background: Co-targetable immune pathways influence cancer outcomes and responses to immune checkpoint inhibitors (ICIs). We examined the transcriptomic expression and clinical significance of signal transducer and activator of transcription-6 (STAT6), an immune-modulatory signaling factor activated by IL-4 and IL13 and involved in innate immunity in infection and cancer. **Methods:** Transcriptomic expression across 395 genes was measured in various solid tumors from 514 patients with advanced cancer, normalized to a reference population (n=735), and reported as percentiles (high defined as ≥75th percentile). We evaluated association between high STAT6 expression and transcriptomic expression of STAT6-related markers (IL4, IL13, TGFB1, IL10, CD8, CCL18, TNFRSF14 [HVEM], VISTA) and currently targetable immune checkpoints (PD-1, PD-L1, PD-L2, CTLA-4, LAG3). Genomic alterations were also assessed for the association with high STAT6 expression. Variables with $P<0.2$ in univariable analysis were included in the subsequent multivariable logistic regression model incorporating genomic, immunomic, and clinical factors. Clinical outcomes were evaluated using Kaplan–Meier method and Cox regression model. **Results:** High STAT6 expression was observed in 184 patients (35.8%); 2 (0.4%) had zero measurable expression. High STAT6 was associated with TMB <10 muts/Mb, high expression of LAG3, PD-L2, IL13, TNFRSF14 (HVEM), and VISTA (all immunosuppressive), and a diagnosis of colorectal cancer in multivariable analysis. Breast cancer was negatively associated with high STAT6. In univariable analysis, alterations in SMAD4, KRAS, and APC were significantly associated with high STAT6, though none remained significant in the multivariable model. In advanced cancer patients, high STAT6 was associated with shorter survival (N=489 with clinical data curated, Hazard ratio 1.44, 95% confidence interval 1.03–2.02, p=0.034). Among 217 ICI-treated patients, high STAT6 did not correlate with survival. **Conclusions:** High STAT6 expression associates with a biologically coherent tumor microenvironment characterized by factors mediating profound immune suppression. The STAT6-high phenotype is mechanistically linked to an exhausted immune landscape, evidenced by the co-expression of inhibitory checkpoints LAG3 and VISTA, and may be further driven by an IL13/STAT6 autocrine loop. Clinically, high STAT6 correlates with shorter survival in patients with advanced cancers. Prospective validation of this STAT6-driven signature is warranted to guide the development of precision therapy trials aimed at co-targeting this pathway to improve outcomes. Research Sponsor: None.

Beyond TMB: Characterizing tumor-intrinsic genomic architectures of immune resistance.

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Background: Immune checkpoint inhibitors (ICI) are increasingly selected based on tumor mutational burden (TMB); however, clinical benefit remains inconsistent. We hypothesized that tumor-intrinsic genomic alterations associated with immune suppression, immune exclusion, and antigen presentation failure frequently coexist with ICI-enabling biomarkers and define distinct resistance architectures. **Methods:** We analyzed tissue-based genomic profiling data from 7,773 solid tumors. TMB-high (TMB-H) tumors were evaluated for genomic alterations implicated in ICI resistance, including *PTEN* loss-of-function (LOF), *STK11* and *KEAP1* LOF, *WNT*/β-catenin pathway alterations (*CTNNB1* activating mutations, *APC* truncation/biallelic loss), *B2M* LOF (antigen presentation), *JAK1/2* LOF (interferon signaling), and *MDM2/MDM4* amplification. **Results:** Among 908 TMB-H tumors, 30.6% harbored at least one immune resistance–associated alteration. *PTEN* LOF was the dominant functional resistance event (7.6%) and represented the central hub in tumors with multiple resistance alterations (65.6%; 21/32). *WNT* pathway alterations were frequent, with *APC* truncation (15.9%; 144/908) exceeding *CTNNB1* mutations (2.6%; 24/908), indicating heterogeneous modes of *WNT* activation. Importantly, *WNT*-driven tumors demonstrated divergent immune escape architectures: *CTNNB1*-mutant tumors were enriched for *B2M* LOF (16.7%; 4/24), whereas *APC*-mutant tumors rarely harbored *B2M* loss (0.7%; 1/144), suggesting antigen presentation-dependent versus immune-exclusion-dominant resistance, respectively. Across the TMB-H cohort, increasing mutational burden was significantly associated with higher *B2M* LOF frequency (Wilcoxon rank-sum $p = 3.6 \times 10^{-6}$), consistent with immune editing under high neoantigen pressure. Interferon signaling alterations were rare (*JAK1*: 0.2%; 2/908; *JAK2*: 0.0%; 0/908). **Conclusions:** TMB identifies immune pressure but not immune competence. Intrinsic ICI resistance in TMB high tumors is structured around a *PTEN-WNT-B2M* genomic axis, with distinct immune escape architectures determined by the mode of *WNT* activation. Integrating negative genomic predictors of immune response with established biomarkers may improve immunotherapy stratification and inform development of rational combination strategies. Research Sponsor: None.

Prevalence of genomic alterations associated with intrinsic ICI resistance in TMB-high solid tumors.

ICI resistance marker	Prevalence in TMB-High Tumors
STK11	2.4%
KEAP1	0.3%
PTEN	7.6%
CTNNB1	2.6%
APC	15.9%
B2M	2.4%
JAK1	0.2%
JAK2	0.0%
MDM2	2.5%
MDM4	0.4%

Safety, PK/PD, and efficacy results from Expand-1: A phase 1 dose escalation study of the novel PD-1 targeted IL-2R-βγ agonist sunekafusp alpha (ANV600) as a single agent and in combination with pembrolizumab in patients with advanced solid tumors.

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Background: Sunekafusp alpha (ANV600) is a novel PD-1-targeted, IL- 2Rβ/γ agonist, which binds, without blocking, a unique epitope distinct from pembrolizumab, or other PD-1 checkpoint inhibitors. **Methods:** In this phase 1 study, safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of increasing doses of ANV600 administered intravenously in two different dosing regimen were investigated in patients with advanced solid tumors as monotherapy and in combination with pembrolizumab. A Bayesian Optimal Interval design guided the dose escalation to determine the MTD and RP2D. **Results:** 63 patients were treated: 44 in monotherapy at 10 to 150 μg/kg ANV600 and 19 in combination therapy at 30 to 90 μg/kg ANV600. The median (range) number of previous lines of treatment was 4 (1-16) in monotherapy and 4 (2-10) in combination therapy. In mono- and combination therapy 27 (61%) and 9 (47%) patients were previously treated with a checkpoint inhibitor (CPI). ANV600 was generally well tolerated. Most common treatment related adverse events were pyrexia, transient and self-limiting transaminase elevations, and low-grade (≤G2) cytokine release syndrome. No treatment-related death was reported. The recommended phase 2 dose of ANV600 was determined to be 90 μg/kg Q1W as starting dose for 4 weeks followed by 150 μg/kg Q2W as maintenance dose. Selective targeting of PD-1-expressing cells was demonstrated, with preferential induction of proliferation of PD-1^{+} CD8^{+} T cells compared to PD-1^{-} CD8^{+} T cells. In the monotherapy setting, 12 patients (32%) experienced target lesion shrinkage; 4 of these (33%) were CPI treatment-naïve. Disease control was observed in 16 patients (42%). Clinical benefit was in general long lasting. A complete response was confirmed in 1 patient with bronchial adenocarcinoma, starting at 6 months after initiation of monotherapy treatment and still ongoing after 9 months of treatment. The patient was previously progressing under 1st line anti-PD-L1 therapy and 2nd line chemotherapy with carboplatin and paclitaxel. Similarly, in the combination therapy setting, 4 patients (24%) experienced target lesion shrinkage; 2 of these (50%) were CPI treatment-naïve. Disease control was observed in 10 patients (59%). **Conclusions:** ANV600 as monotherapy and in combination with pembrolizumab showed a favorable safety profile. Highly promising efficacy signals with one ongoing complete response, several long-lasting partial responses and stable diseases were reported in CPI-naïve and CPI pretreated patients, including CPI-resistant tumors. Clinical trial information: NCT06470763. Research Sponsor: Anaveon AG.

Multi-omics analysis from the IMMUcan consortium to identify predictors of chemo-immunotherapy response in early-stage triple-negative breast cancer.

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Background: Combining PD-1/PD-L1 immune checkpoint blockade (IO) with neoadjuvant chemotherapy (CT) is now a standard treatment for early-stage triple-negative breast cancer (eTNBC). However, no validated biomarker is currently used to guide patient selection for CT-IO benefit. We aimed to define baseline tumor–immune–stroma ecosystem states that explain differential responses and could inform future biomarker-driven trial designs. **Methods:** The IMMUcan consortium prospectively enrolled 422 patients with eTNBC treated with CT alone (n=221) or CT-IO (n=201). Pretreatment FFPE biopsies underwent whole-exome sequencing (n=397), RNA sequencing (n=360), multiplex immunofluorescence (2 panels, n=353/368), and imaging mass cytometry (n=341). Response was assessed as pathological complete response (pCR) versus residual disease (n=400). Clinical, genomic, transcriptomic, and spatial features were analyzed for associations with pCR and treatment interaction. Multi-omics integration was performed using Multi-Omics Factor Analysis (MOFA) to derive latent factors and ecosystem states. **Results:** Baseline clinicopathological characteristics were balanced between groups, while the pCR rate was higher with CT-IO than CT alone (73.1% vs 54.8%; Δ=20.4%; $p<0.01$). High tumor grade and tumor-infiltrating lymphocytes predicted pCR in both groups without IO-specific predictive value. Among transcriptomic TNBC subtypes, immunomodulatory, mesenchymal (M), and luminal androgen-receptor (LAR) derived the greatest benefit from CT-IO. Spatial profiling identified as key CT-IO responsive feature the enrichment of activated PD-1^{+}GZMB^{+}CD8^{+} T cells in proximity to tumor cells. MOFA identified biological axes with predictive value, including organized adaptive immunity, effector functions, immune-memory, stromal/angiogenic barrier, and luminal-metabolic lineage. Organized adaptive immunity predicts CT-IO benefit in M and LAR subtypes (OR: 5.42; 95% CI 0.87-33.6; p interaction = 0.048; and OR: 2.97; 95% CI 0.98-8.9; p interaction = 0.036, respectively). Conversely, LAR tumors characterized by luminal–metabolic lineage showed no benefit from CT-IO. **Conclusions:** Integration of multi-omics data revealed distinct baseline biological ecosystem states capable of identifying patients most likely to benefit from, or exhibit resistance to, CT-IO. These findings provide a comprehensive framework for designing biomarker-driven therapeutic strategies in next-generation neoadjuvant trials for early-stage TNBC. Research Sponsor: EU's Horizon 2020 and EFPIA; IMI2 JU grant agreement 821558; Fondation contre le cancer - Belgium.

Chemotherapy-induced gut microbiota taxonomic deviation and its association with outcomes and toxicities in breast cancer: CANTO microbiota.

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Background: Gut microbiota (GM) modulates immunotherapy (IT) efficacy and toxicity, but its impact on outcomes in breast cancer (BC) patients (pts) remains unclear. TOPOSCORE is a GM-derived score reflecting the ecosystem structure that classifies pts into SIG1+ or SIG2+ profiles, the latter being enriched in obligate anaerobes with immunostimulatory proprieties and associated with favorable IT outcomes. **Methods:** CANTO-Microbiota (target N=1000) is an ongoing substudy of the prospective CANTO cohort (NCT01993498). Stool samples were available from 209 pts (202 pre-treatment (Tx) and 94 post-Tx [after surgery, chemotherapy (CT) ±targeted-, and/or radiotherapy]), enrolled 2015-2024. GM was profiled by shotgun metagenomics and assessed as TOPOSCORE (SIG1+ vs. SIG2+) pre- and post-Tx. Associations of GM with invasive (iDFS), distant disease-free (DDFS), and overall survival (OS) (Kaplan–Meier and Cox regression models), and with treatment-related toxicities (multivariable logistic regression). Post-treatment analyses were landmark-based. **Results:** Median age was 46.6 years, 72% were premenopausal, 79% had stage II-III, 36% HER2+, 34% HR+/HER2-, and 30% TN, 89% received (neo)adjuvant CT, 15% IT and 33% anti-HER2-therapy. Median follow-up was 2.2 years. At baseline, 74% of pts had a SIG2+ profile. This profile was not associated with clinicopathologic features or clinical outcomes; however, SIG2+ was associated with a reduced incidence of post-treatment diarrhea and long-term neuropathy, and remained independently protective against neuropathy (OR 0.25, 95% CI 0.09–0.64; p=0.005). Paired analyses (n=87) revealed a significant shift in TOPOSCORE signatures post-treatment, resulting in an increase in SIG1+ prevalence from 28% to 47% (p=0.004), In univariable landmark Cox analyses, post-treatment SIG1+ was associated with worse iDFS (HR 5.0, 95% CI 1.1–4.2; p=0.04), DDFS (p=0.0053) and OS (p=0.04). In multivariate model adjusted for age, stage, and subtype, post-treatment SIG2+ remained independently protective for iDFS (HR 0.17, 95% CI 0.03–0.88; p=0.035). Assessing longitudinal GM trajectories, worsening patterns (SIG2+→SIG1+ in 28% and persistent SIG1+→SIG1+ in 20% of pts) were associated with an increased risk of iDFS (HR 5.25, 95% CI 1.11–24.7; p = 0.036). Post-treatment TOPOSCORE associations with outcomes were validated in two independent prospective cohorts outside France. **Conclusions:** Chemotherapy is associated with measurable shifts in GM composition that correlated with treatment-related long-term toxicity and outcomes. These findings support the evaluation of microbiota centered interventions during treatment in eBC. Research Sponsor: None.

Safety and preliminary efficacy of OH2 combined with BS006 sequential intratumoral injection in patients with advanced solid tumors: An open-label, dose-escalation phase Ib/II study.

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Background: The immunosuppressive ("cold") tumor microenvironment (TME) limits patient response to checkpoint inhibitors. Oncolytic viruses (OVs) can selectively replicate in tumor cells, leading to robust TME-remodeling. Reported here is the first clinical evaluation of a dual TME-modulating strategy based on an oncolytic HSV2 platform, whereby OH2, a clinically validated oncolytic HSV2 expressing GM-CSF, which enhances tumor lysis, antigen release, and dendritic cell recruitment in the TME, is co-injected with BS006, a second HSV2-based OV, which expresses a PD-L1/CD3 bispecific antibody that can redirect bystander T cells to tumor cells in the TME. **Methods:** BS008-001 is a multicenter, open-label phase Ib /II trial in heavily pre-treated patients with advanced solid tumors. Patients received biweekly sequential intratumoral injections of OH2 (fixed dose: 10^7 $CCID_{50}$/mL) followed by BS006 (dose escalation: 10^6–10^7 $CCID_{50}$/mL), with identical volumes being injected at the same lesion. The primary endpoint is safety and tolerability; secondary endpoints included efficacy outcomes assessed by RECIST 1.1/iRECIST. **Results:** As of January 5, 2026, a total of 15 patients with a mean age of 59.3 were enrolled (4 soft tissue sarcoma, 3 colorectal cancer, 2 melanoma, 2 biliary tract tumors, 2 breast cancer, 1 pancreatic cancer, and 1 liver cancer). 93.3% of the patients had a baseline ECOG score of 1. The mean maximum diameter of the target lesion at baseline was 91.3 mm. 100% of the patients had distant metastases to internal organs such as the liver and lungs. Safety: Incidence of TRAEs in the Safety Set was 53.3% (8/15) with mild grade 1-2 reactions, including fever (40.0%) and decreased lymphocyte count (20.0%). 1 patient developed Grade ≥3 TRAE (6.7%), but no DLT-causing AEs or premature withdrawal from the trial occurred. Efficacy: In the 13 patients with evaluable advanced multi-line solid tumors, ORR was 7.7% and DCR 38.5%. 1 melanoma patient achieved 1 PR after 11 treatments, with the total diameter of the target lesions significantly decreasing by 70.8% to 30.4 mm; another melanoma patient received 39 doses over a treatment duration of 18.9 months (SD), whereas 1 subject with leiomyosarcoma achieved SD and survived for 27.1 months. While the mOS of the 15 patients has not yet been reached, landmark 1-year OS is 78% (95% CI: 47%-92%), with 3 patients still on treatment. **Conclusions:** Sequential intratumoral administration of OH2 and BS006 in heavily pre-treated patients is feasible and safe and results in reasonable DCR, with some patients achieving long-term clinical benefits. This study supports the clinical relevance of an HSV2-based platform combination of 2 oncolytic viruses encoding GM-CSF and T-cell redirected bispecific antibodies to warm up the cold TME. Further clinical research of the platform is warranted. Research Sponsor: None.

Association of SARS-CoV-2 vaccination with survival outcomes in patients with metastatic solid tumors treated with immune checkpoint inhibitors.

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Background: Patients with cancer experience disproportionately high morbidity and mortality from SARS-CoV-2 infection, and COVID-19 vaccination is recommended for all patients with cancer. Although vaccines primarily reduce infection related complications, emerging data suggest SARS-CoV-2 mRNA vaccines may also enhance antitumor immune responses and potentially synergize with immune checkpoint inhibitors (ICIs). We evaluated survival outcomes in vaccinated versus unvaccinated patients with metastatic solid tumors treated with immunotherapy. **Methods:** Data for adults with metastatic cancers for which ICIs are indicated were obtained from the TriNetX Research Network (2019–2024). Patients were classified by receipt of ≥1 SARS-CoV-2 mRNA vaccine around the time of ICI initiation (±1 year) and compared with unvaccinated patients. Those with prior systemic antineoplastic, endocrine, or immunosuppressive therapy before ICI initiation or who developed COVID-19 were excluded. Cohorts were propensity matched for demographics, cancer type, comorbidities, and laboratory values. Outcomes included overall survival at 90 days, 1 year, and 5 years using Kaplan–Meier analyses, and all-cause hospitalization and immune-related adverse events (irAEs) within 90 days. **Results:** After matching, 543 vaccinated and 543 unvaccinated patients were well balanced. Vaccination was not associated with increased irAEs, with similar rates of any irAE (19.0% vs 17.9%, p=0.64), gastrointestinal (3.87% vs 3.87%, p=1.00), dermatologic (11.8% vs 10.7%, p=0.56), and neurologic events (2.76% vs 2.39%, p=0.70); pulmonary and hepatic irAEs were rare. Hospitalization rates were comparable (24.9% vs 23.9%, p=0.72). Vaccinated patients demonstrated improved intermediate-term survival, with higher 1-year survival (73.35% vs 64.12%; HR 0.70, 95% CI 0.56–0.87, p=0.001), with trends toward benefit at 90 days (HR 0.69, p=0.053) and 5 years (HR 0.85, p=0.066). Landmark analysis from 1 to 5 years showed no significant survival difference (HR 1.15, p=0.34). Consistent 1-year survival benefits were observed in lung cancer (65.93% vs 52.56%; HR 0.63, p=0.0005) and melanoma (80.25% vs 68.65%; HR 0.56, p=0.0355). **Conclusions:** In this large propensity-matched real-world cohort of metastatic solid tumor patients receiving immune checkpoint inhibitors, COVID-19 vaccination was not associated with increased immune-related toxicity or hospitalization and was associated with significantly improved 1-year overall survival. Attenuation of the survival association in landmark analyses suggests potential time-related bias, supporting the need for further studies with precise exposure timing. Research Sponsor: None.

An exploratory, single-center, single-arm trial of R-ISV-FOLactis in situ vaccination for advanced soft tissue sarcoma.

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Background: Advanced soft tissue sarcomas (STSs) have limited treatment options and exhibit low responsiveness to immunotherapy, largely due to an immunosuppressive tumor microenvironment (TME). In situ vaccination (ISV) represents a promising strategy to convert immunologically "cold" tumors into "hot" ones. FOLactis, a food-grade probiotic Lactococcus lactis engineered to express a fusion protein of Fms-like tyrosine kinase 3 ligand (Flt3L) and OX40 ligand (OX40L), has shown antitumor immune activity in preclinical models. This study investigates the synergistic antitumor effect and safety of intratumoral FOLactis in combination with hypofractionated radiotherapy and anti-PD-1 therapy in clinical settings. **Methods:** In this investigator-initiated, single-arm trial, patients with advanced STS who had failed standard therapies received intratumoral injections of FOLactis combined with hypofractionated radiotherapy and PD-1 blockade. Primary endpoints included safety and efficacy, secondary endpoints encompassed abscopal responses and mechanistic exploration of treatment efficacy. **Results:** Between July 2022 to July 2025, 16 advanced STS patients were enrolled. The R-ISV-FOLactis regimen was well-tolerated, with grade 3 adverse events occurring in 37.5% of patients. Injected lesions showed a best objective response rate (ORR) of 56.25% and a disease control rate (DCR) of 100%. Median progression-free survival (mPFS) for all lesions was 6.3 months, while mPFS for injected lesions was not reached. Abscopal responses were observed in 56.25% of patients. Immunological analyses revealed increased frequencies of peripheral memory $CD8^+$ T cells, PD-1^+ $CD8^+$ T cells, and dendritic cells (DCs), alongside decreased regulatory T cells (Tregs) and tissue-resident $CD103^+CD4^+$ T cells in responders, indicating systemic immune activation. Furthermore, reshaped TME with reduced fibroblasts and increased immune cell infiltration were associated with enhanced antitumor immunity. Moreover, significant increase of $CD8^+$ T cell density in regions distal to neutrophil clusters, along with elevated 4−Cresol Sulfate levels suggesting neutrophil modulation. **Conclusions:** R-ISV-FOLactis exhibited a favorable safety profile and encouraging efficacy against both local and distant tumors. The treatment induced systemic immune activation and metabolic remodeling, supporting its further development as a novel ISV strategy for advanced STSs. Clinical trial information: ChiCTR2200060660. Research Sponsor: None.

Quality of life in cancer patients treated with anchored interleukin-12 (IL-12) immunotherapy: Results from a first-in-human phase 1 trial of tolododekin alfa (ANK-101).

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Background: Anchored immunotherapy is a novel method for retaining high concentrations of anti-tumor drugs in established tumors with limited systemic exposure. The integration of quality-of-life (QOL) assessment in a phase 1 study of anchored IL-12, tolododekin alfa (ANK-101), provided an opportunity to gather baseline QOL data, longitudinally measure patient well-being during drug exposure, identify associations between adverse events and patient well-being, and generate additional clinical benefit information. **Methods:** All patients enrolled in the phase 1 clinical trial of ANK-101 for patients with advanced/metastatic solid tumors were eligible and provided written informed consent. Patients were treated with direct intratumoral injection every 3 weeks up to 8 cycles over 6 months. QOL was measured by the validated FACT-G survey, which collects scores across a 27-item questionnaire that measures physical, family/social, emotional, and functional well-being. Subjects were asked to complete the FACT-G at baseline every 3 weeks during treatment and at end-of-treatment. QOL scores were evaluated by paired-sample t-tests to evaluate differences in QOL at various time intervals. Data cut-off was on October 21, 2025. **Results:** 39 of 40 (98%) patients completed at least two FACT-G surveys. The median age was 68 and 44% were female. Patients had a median of 5 lines of prior therapy (range 1-18). The most common cancer types included were melanoma (33%), head and neck (18%), cutaneous squamous cell carcinoma (8%), and colorectal cancer (8%). There were no dose-limiting toxicities but there were 42 grade 2 events in 13 subjects and five grade 3 events in 3 subjects (elevated liver transaminases, abdominal pain, neutropenia, stomatitis). At baseline, the median of QOL score was 80.5 (range 51-106). After two and four cycles, there was no decrease in QOL scores across any of the functional domains. For patients who developed grade 2 or 3 adverse events, there was a trend toward decreased QOL in social well-being (median 25.5 at baseline to 23 after two cycles; median change -2.0; p=0.08) and in physical well-being (median 24 at baseline to 20 after four cycles; median change -5.5; p=0.06 after four cycles). Patients who completed all 8 cycles of treatment demonstrated no change in any QOL measure (p range 0.14-0.70). **Conclusions:** ANK-101, the first anchored immunotherapy, was associated with QOL scores that were not significantly diminished in heavily pre-treated advanced cancer patients with a non-significant decrease in social and physical well-being among those who developed grade 2 or greater adverse events. Further, patients with visceral tumors had no difference in QOL compared to superficial lesions. Early implementation of QOL data is feasible in phase 1 trials and may be of use to identify drug impact on clinical and safety measures. Clinical trial information: NCT06171750. Research Sponsor: Ankyra Therapeutics.

Intratumoral dendritic cell (DC1) therapy prior to neoadjuvant chemotherapy in HER2-positive breast cancer (NATASHA trial).

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Background: Enhancing the efficacy of neoadjuvant therapy (NAT) while minimizing treatment-related toxicity remains a critical unmet need for patients (pts) with HER2-positive (HER2+) breast cancer (BC). We previously reported intratumoral (IT) delivery of increasing doses (50 million and 100 million cells) of conventional type I dendritic cells (DC1) combined with anti-HER2 antibodies is safe and effective in altering the tumor microenvironment (TME) and inducing tumor regression in early-stage HER2+ BC. We conducted a phase II neoadjuvant clinical trial of IT DC1 (NCT05325632). **Methods:** Pts with early-stage HER2+ BC with tumor ≥ 1cm were eligible. Treatment included initial immunotherapy with IT DC1 weekly x6 (100 million) followed by paclitaxel 80 mg/m^2 IV weekly x12. Starting from day 1, pts also received trastuzumab (H) IV (8 mg/kg loading dose, then 6 mg/m^2) and pertuzumab (P) IV (840 mg loading dose, then 420 mg) every 3 weeks x 6 cycles. Core needle biopsies were obtained at baseline and at week 6 following the last DC1 injection and analyzed by multiplex immunofluorescence (mIF) to assess immune cell infiltration. At these timepoints and post-chemotherapy, radiologic response was assessed by breast MRI and blood was collected for biomarker and ctDNA analysis using a personalized, tumor-informed test (Signatera, Natera, Inc.). The primary end point of this study is pathologic complete response rate (pCR). **Results:** A total of 47 pts (24 HR+/HER2+, 23 HR-/HER2+) were enrolled between 5/2022 and 10/2025. Median age was 54 years (range 27-82). 21 pts had biopsy-proven axillary node positive disease with clinical stage I/II/III (7/30/10). All pts completed NAT, and 42 pts underwent surgery as of 1/22/2026. The pCR rates for HR+/HER2+ and HR-/HER2+ were 50% (12/24) and 89% (16/18), respectively. The most frequent toxicities related to DC1 were grade 1/2 chills, flu-like symptoms, headache, nausea, fever, and injection site reaction. IT DC1 + HP therapy was associated with a significant increase in intratumoral CD3$^+$ T cell infiltration and a decrease in tumor cells assessed by mIF. ctDNA levels were evaluable for 25 patients (13 HR+ and 12 HR-). Sixteen pts (64%) had positive ctDNA (6 HR+ and 10 HR-) at baseline and 14/16 cleared ctDNA with NAT (13/16 cleared ctDNA post- IT DC1+HP, prior to chemotherapy). At present (median post-surgery follow-up: 15.1 mos.; median follow-up from last ctDNA test: 8.7 mos.), no pts have experienced disease recurrence. **Conclusions:** IT DC1 + HP prior to neoadjuvant paclitaxel + HP in HER2+ BC pts was well tolerated with manageable toxicities. IT DC1 led to immune cell infiltration and ctDNA clearance with improved pathologic tumor response rates, particularly in HR-/HER2+ BC. Updated surgical outcomes and biomarker results (mIF, MRI and ctDNA) will be presented at the meeting. Clinical trial information: NCT05325632. Research Sponsor: None.

First-in-human evaluation and preclinical mechanistic studies of targeted hyperthermia therapy.

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Background: Photothermal conversion of near-infrared (NIR) light using specifically tuned, directly delivered gold nanorods produces controllable hyperthermia in tumor microenvironments. Precisely controlled, targeted hyperthermia therapy (THT) induces immunogenic cell death (ICD) and remodels the tumor microenvironment, promoting immune activation in otherwise poorly inflamed tumors. Here, we report an early clinical evaluation of THT integrated with mechanistic preclinical analyses. Preclinical studies: In B16F10 melanoma and CT26 colorectal models, controlled thermal dosing induced a 24–48 h ICD response marked by calreticulin and HSP70 exposure, chemokine and complement activation, and early T-cell receptor remodeling. Transcriptomic analyses revealed a dose-dependent transition from innate immune activation to a coordinated tissue repair program involving extracellular matrix remodeling. Lower thermal doses in the hyperthermic window decreased regulatory pathways and induced antigen presentation. Modulation of myeloid signaling limited macrophage accumulation, prevented tumor regrowth, and sustained antitumor inflammation. **Methods:** In a first-in-human, open-label, early feasibility study (NCT06894407), ten patients with stage IIIc/IIId/IV M1 cutaneous metastatic melanoma progressing on checkpoint inhibitor therapy received intratumoral gold nanorods (Sona Nanotech Inc.) followed by NIR-mediated heating on days 1 and 8. Up to four lesions per patient were treated, with intratumoral temperatures maintained at 42–48 °C for 5 minutes. Safety, feasibility, and early biological activity were assessed through adverse-event monitoring, clinical photography, and tumor biopsies obtained on days 15 and 29. **Results:** Clinical: THT was well tolerated, with no treatment-related serious adverse events observed. By day 15, 8 of 10 patients demonstrated regression in treated lesions. Histologic assessment showed complete tumor clearance in 6 patients, partial regression in 2 patients, and no response in 2 patients. **Conclusions:** THT-induced ICD progresses through temporally regulated immune states, including a reparative myeloid-associated phase that limits durability. Defined thermal-dose parameters provide a framework for rational integration of THT with macrophage-modulating and checkpoint-based immunotherapies. THT is safe, feasible, and biologically active in immunotherapy-refractory metastatic melanoma. Further clinical studies are needed to evaluate the efficacy of THT in immune-refractory cancers. Clinical trial information: NCT06894407. Research Sponsor: Sona Nanotech Inc.

Evaluation of adnexal features and histological response to intralesional SP-002 in nodular basal cell carcinoma.

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Background: No FDA approved nonsurgical therapies exist for primary nBCC at high-risk sites, e.g., H-zone, representing a significant unmet medical need. Recombinant IFN-alfa-2b previously achieved ~85% complete histologic clearance in superficial and nBCC, but required multiple (9-12) injections and was associated with systemic toxicity. SP-002 encodes human IFN-γ and enables sustained, localized cytokine expression with anti tumor activity, achieved with a once weekly, three dose regimen that demonstrates a superior therapeutic index. **Methods:** Two early phase clinical studies of SP-002 in nBCC were completed: a single lesion study (ASN-002-001, NCT02550678, n=16), and a combination multilesion study with 4 weeks of vismodegib (ASN-002-003, NCT04416516, n=21, 46 lesions). Pretreatment biopsies from ASN-002-001 served as discovery specimens, while pretreatment biopsies from ASN-002-003 were prospectively assessed by central review for adnexal features (AdnF; follicular or eccrine differentiation) using standardized criteria. Post-treatement excision specimens were evaluated by local histopathology laboratories for CHC per protocol-defined criteria. CHC rates were calculated by AdnF. **Results:** ASN-002-001: sporadic low frequency/risk BCC, AdnF(+) rate was 20%. CHC rates were 33% (5e10vp), 83% (1.5 and 3.0e11vp). ASN-002-003: high-frequency multilesion BCC, AdnF(+) rate was ~50%. CHC rates were 75% (1 nBCC)/52.9% (3 nBCC) (1.0e11vp) and 52.4% (3 nBCC) (1.5e11vp)-ITT. When analyzed by AdnF status, CHC rates were 97% in AdnF(-) lesions and 11.5% in AdnF(+) lesions. Baseline biopsies in non-responders demonstrated follicular/eccrine structures especially papillary mesenchymal bodies, harboring CKT15(+) stem cells (SC) and nuclear β-catenin, indicating active WNT signaling. Dual repression of programmed cell death effectors, CASP8/RIPK3, was also observed at baseline in lesions with residual disease with focal loss or widespread loss across tumor islands in β-catenin active regions. Either or both CASP8/RIPK3 were present in all complete responders at baseline and their absence may indicate risk for incomplete response to SP-002. **Conclusions:** SP-002 achieved high CHC rates at doses of 1.5e11vp/3.0e11vp and AdnF(-) lesions (most nBCC) had clearance rates comparable to surgical excision (>90%).Adnexal differentiation identifies a biologically distinct, treatment-resistant subset with WNT pathway activation, adnexal niches harboring CKT15(+) SC, and impaired IFN-γ cell death. These findings support AdnF as a predictive biomarker and position SP-002 as a promising non-surgical option for selected patients with nBCC. Clinical trial information: NCT02550678, NCT04416516. Research Sponsor: Ascend Biopharmaceuticals Ltd, Level 1 159 Dorcas Street, South Melbourne VIC 3205.

	CHC rate AdnF(-) n/N lesions (%)	CHC rate AdnF(+) n/N lesions (%)
ASN-002-001 (n=15, 15 lesions)	11/12 (91.6%)	0/3 (0%)
ASN-002-003 (n=21, 46 lesions)	23/23 (100%)	3/23 (13%)
	34/35 (97.1%)	3/26 (11.5%)

Safety and feasibility of intratumoral injection of RP1 or RP2 oncolytic immunotherapies in visceral metastases.

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Background: RPx is an investigational HSV-1-based oncolytic immunotherapy platform including RP1 (vusolimogene oderparepvec) and RP2. RP1 expresses GM-CSF and a fusogenic glycoprotein (GALV-GP-R$^-$); RP2 also expresses an anti–CTLA-4 antibody-like molecule. We report safety data from patients (pts) who received intratumoral (IT) injections of RP1/2 into visceral metastases (mets). **Methods:** Pts with advanced/metastatic solid tumors were enrolled into RP1/2 clinical trials (RP1: NCT03767348; RP2: NCT04336241). RP1/2 was injected into visceral tumors using CT or ultrasound guidance. The recommended needle gauges ranged from 17-27G. Pts received RP1/RP2 for up to 8 doses as monotherapy or in combination with nivolumab IV starting at cycle 2 or 4 for up to 2 years. Additional RP1/2 doses could be given if protocol-specified criteria were met. This analysis evaluated safety among pts receiving IT RP1/2 injections to visceral mets (defined as lung or liver mets). All safety data presented includes events occurring within 7 days after injection (except where noted). **Results:** As of data cutoff (RP1: 15OCT2024; RP2: 29AUG2025), there were a total of 665 RP1/2 injections into the lung (n = 125; median lung injections/pt/treatment course [c]: RP1 = 5.5 and RP2 = 8) and liver (n = 540; median liver injections/pt/c): RP1 and RP2 = 5) among 105 pts. The most common treatment-related adverse events (AEs) were pyrexia, chills, and fatigue (Table). A total of 9 pneumothorax (PTX) events occurred (within 3 days after injection) out of 125 lung injections (7.2%) in 19 pts receiving RP1/2; all cases were Grade (G) 1/2 and resolved. Only 1 pt required a chest tube for a G2 PTX event and the pt continued to receive RP1 after resolution. There were 3 bleeding events within 3 days after injection among 665 injections (0.5%) in the lung or liver in 105 pts receiving RP1/2. All bleeding events occurred in pts receiving RP2 liver injections and resolved (2/3 events resolved by the following day). **Conclusions:** RP1/2 injections into visceral mets were well tolerated, with a comparable safety profile to liver and lung biopsies performed in other clinical settings. The observed RPx safety profile supports the incorporation of IT injections into deep visceral tumors as part of cancer therapy. Clinical trial information: NCT03767348; NCT04336241. Research Sponsor: Replimune, Inc.

All-grade treatment-related adverse events (>15%).

	RP1				RP2			
	Monotherapy		Combination therapy		Monotherapy		Combination therapy	
n (%)	Injected visc mets (n = 11)	Total (n = 19)	Injected visc mets (n = 46)	Total (n = 151)	Injected visc mets (n = 14)	Total (n = 20)	Injected visc mets (n = 34)	Total (n = 47)
Pyrexia	9 (82)	12 (63)	22 (48)	51 (34)	6 (43)	9 (45)	18 (53)	25 (53)
Chills	6 (55)	6 (32)	20 (44)	43 (28)	3 (21)	5 (25)	13 (38)	19 (40)
Fatigue	3 (27)	7 (37)	8 (17)	39 (26)	1 (7)	3 (15)	4 (12)	7 (15)
Influenza-like illness	1 (9)	2 (11)	12 (26)	31 (21)	0	0	2 (6)	8 (17)
Nausea	1 (9)	1 (5)	13 (28)	26 (17)	1 (7)	1 (5)	5 (15)	8 (17)

mets, metastases; visc, visceral.

STING agonist JMKX000197 infusion in patients with malignant pleural effusion: Preliminary results from a prospective phase Ib study.

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Background: Indwelling pleural catheter (IPC) is frequently used for symptomatic malignant pleural effusion (MPE), its therapeutic benefits remain limited. JMKX000197 is a novel small molecule stimulator of interferon genes (STING) agonist that activates STING to induce type I interferons and pro-inflammatory cytokines and may have a promising clinical prospect for the treatment of MPE. **Methods:** Eligible patients had advanced solid tumors with moderate-to-large MPE and had progressed on systemic therapy or had poorly controlled effusion. Patients were randomized assigned in a 1:1:1 ratio to receive intrapleural infusions of JMKX000197 (150 μg or 300 μg) combined with IPC or IPC alone (control) on day 1 and day 8. Here, we report safety, tolerability, preliminary efficacy, and PK/PD characteristics from the phase Ib study of JMKX000197 (NCT06740019). **Results:** As of October 15, 2025, 35 patients were enrolled (45.7% female, median age 59 years, 71.4% with lung adenocarcinoma). 2 patients withdrew from the study without receiving any treatment after randomization, thus, the safety and efficacy analysis was based on 33 patients who received treatment. Among 33 patients, 1 patient in the 300 μg group withdrew the informed consent after one dose while 32 patients (97%) completed the two-dose regimen (11 in 150 μg group [N=11], 9 in 300 μg group [N=10], and 12 in control group [N=12]). Treatment-emergent adverse events (TEAEs) occurred in 100%, 90%, and 83.3% of patients in the 150 μg, 300 μg, and control groups, respectively. Grade ≥3 TEAEs occurred in 3(27.3%), 1 (10%) and 1 (8.3%) patients in each group. 2 patients in 150 μg group and 5 patients in 300 μg group experienced grade 1–2 cytokine release syndrome (CRS), which were adverse event of special interest, all resolved with supportive care. No TEAE led to treatment discontinuation or death. Puncture-free survival (PuFS) was defined as the period from the removal of the IPC immediately after the last dose of treatment to the next therapeutic puncture and/or drainage or death, whichever occurs first. The median PuFS was 37 days, 116 days, and 56 days in the 150 μg, 300 μg, and control groups, respectively. Limited exposure of JMKX000197 in plasma was observed (>700 fold lower than that in pleural effusion). PD analysis showed significant elevation of IFN-β in both plasma and pleural effusion (higher in pleural effusion), along with increased TNF-α, IP-10, MCP-1, and IL-6. Immunophenotyping demonstrated enhanced CD8+ T-cell activation and reduced Treg cell proportions post-treatment (both in peripheral blood and pleural effusion). **Conclusions:** Intrapleural JMKX000197 exhibited a manageable safety profile and promising preliminary efficacy in MPE patients, with a better efficacy at the 300 μg dose. JMKX000197 may induce the production of pro-inflammatory cytokines and subsequently activate the tumor microenvironment. Clinical trial information: NCT06740019. Research Sponsor: Shanghai Jeyou Pharmaceutical Co., Ltd.

Clinical efficacy and safety of BM201 intra-tumoral injection and radiotherapy in advanced solid tumors: Results from the phase I/IIT study.

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Background: For vaccine design, an antigen and an adjuvant are necessary for an effective immune response. In the context of therapeutic tumor vaccination, in situ vaccination has garnered increasing attention as it enables tumors to provide antigens through radiotherapy or intra-tumoral (i.t.) delivery of immunomodulators. BM201, a selective TLR7/8 agonist uniquely designed for intra-tumoral (i.t.) administration, aims to effectively activate antigen-presenting cells and enhance immunogenicity through combination with radiotherapy by more effectively presenting the tumor antigens exposed to T cells. When combined with intravenous (i.v.) infusion of αPD-1 monoclonal antibody (mAb), it relieves tumor immunosuppression and exerts synergistic anti-tumor effects. **Methods:** This is an open-label, exploratory, and phase I/IIT study. Phase I portion was a dose-escalation study designed to investigate BM201 (dose range: 24-240mg, i.t. every 2 weeks) in combination with hypofractionated radiotherapy (5-8Gy, 4 fractions) (R-ISV-BM201) in patients with refractory or metastatic solid tumors. Phase IIT portion was designed to investigate BM201 (dose range: 24-240mg, i.t. every 3 weeks) in combination with hypofractionated radiotherapy (5-8Gy, 4 fractions) plus αPD-1 (200mg, i.v. every 3 weeks) (R-ISV-BM201 + αPD-1) in patients with refractory or metastatic soft tissue sarcomas. Primary objective of both 2 studies was safety and tolerability. Secondary endpoints included PK and preliminary anti-tumor activity according to RECIST 1.1 in Phase I, while anti-tumor activity according to irRECIST 1.1 in Phase IIT. **Results:** Till December 05, 2025, 29 patients had been treated with BM201 (19/29 in Phase I, 10/29 in Phase IIT). Among the 29 patients, 51.7% had been unresponsive to immunotherapy (prior αPD-1). Plasma exposure increased with dose. A sustained-release PK characteristic was observed in most patients experiencing tumor shrinkage. Abscopal effects were observed in 31.6% (6/19) and 50% (5/10) of patients in Phase I and Phase IIT, respectively. In Phase I, the objective response rate (ORR) was 5.2%, and the disease control rate (DCR) was 84.2%; while these were 10.5% and 84.2% in injected lesions. In Phase IIT, the ORR was 20%, and the DCR was 100.0%; while these were 46.1% and 92.3% in injected lesions. The median progression-free survival was 7.7 months, the median overall survival was 17.0 months, and the median duration of response in injected lesions was 5.6 months. The majority of TRAEs were grade 1-2. Grade 3-4 TRAEs mainly included lymphocytopenia, anemia, thrombocytopenia, and hypertension. No grade 5 TRAEs or dose-limiting toxicity was observed. **Conclusions:** R-ISV-BM201 has a manageable safety profile and has shown encouraging anti-tumor activity. A trigger systemic immune response would be expected when it is synergized with αPD-1 mAb. Clinical trial information: Phase I: NCT06368960; Phase IIT: ChiCTR2300077953. Research Sponsor: National Natural Science Foundation of China; Foundation for studies of Clinical Trials, Drum Tower Hospital; Science Fund for Distinguished Young Scholars of Jiangsu Province; Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University; Nanjing Medical Science and Technology Development Foundation; InnoBM Pharmaceutics Co. Ltd.

Hepatic arterial infusion chemotherapy combined with immunotherapy for unresectable intrahepatic cholangiocarcinoma: A single-arm, open-label, prospective clinical trial.

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Background: In recent years, immune checkpoint inhibitors (ICIs) have demonstrated substantial clinical advances in the treatment of intrahepatic cholangiocarcinoma (ICC). However, the efficacy of first-line systemic chemotherapy remains suboptimal for patients with unresectable ICC. Hepatic arterial infusion chemotherapy (HAIC) can markedly elevate local drug exposure, enhance tumor cytotoxicity, and minimize systemic adverse effects. Whether the combination of HAIC and immunotherapy confers a clinical benefit for patients with unresectable ICC remains an urgent clinical issue to be addressed. **Methods:** This is a single-arm, open-label, prospective clinical trial designed to evaluate the efficacy and safety of HAIC combined with ICIs in the treatment of patients with unresectable ICC. The HAIC regimen consists of gemcitabine plus cisplatin (GC-HAIC), while programmed death-1 (PD-1) inhibitors are administered for immunotherapy, with either camrelizumab or sintilizumab chosen on a patient clinical characteristics basis. The trial was planned to enroll 30 participants. The primary endpoint was the objective response rate (ORR). Secondary endpoints included overall survival (OS), progression-free survival (PFS), and disease control rate (DCR). Safety was assessed through the monitoring and grading of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. **Results:** From August 2022 to January 2025, a total of 31 patients with unresectable ICC were enrolled and received the protocol-defined treatment. The ORR was 41.9% according to RECIST 1.1 criteria, while the ORR assessed per mRECIST criteria was 71%. The median follow-up time was 22.0 months (95% CI, 17.9–26.7 months). The median OS was 20.0 months (95% CI, 15.7–28.6 months), and the median PFS was 12.3 months (95% CI, 10.9–21.3 months). The DCR reached 93.5%. Treatment-related AEs of any grade occurred in 83.9% of patients, whereas grade 3 or 4 AEs were observed in only 16.1% of participants. **Conclusions:** This study evaluated the efficacy and safety of GC-HAIC combined with anti-PD-1 immunotherapy in the treatment of patients with unresectable ICC. The results demonstrated that this regimen exhibited promising efficacy, with manageable adverse events and complications. Additionally, these results also offer a potential novel first-line treatment option for this patient population. Based on the results of this study, future phase III clinical trails are warranted to validate the outcomes. Clinical trial information: ChiCTR2500112123. Research Sponsor: Haiyan Foundation; Beijing Medical Award Foundation.

Tumor response.

	RECIST 1.1		mRECIST	
Efficacy	**%**	**N**	**%**	**N**
CR	0	0	3	9.7
PR	13	41.9	19	61.3
SD	16	52.6	7	22.6
PD	2	6.5	2	6.5
ORR	13	41.9	22	71.0
DCR	29	93.5	29	93.5

CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, Objective response rate; DCR, Disease control rate.

A phase I trial on the safety, tolerance, and preliminary efficacy of intracavitary injection of in situ vaccines (FOLactis) in patients with advanced solid tumors complicated with malignant pleural effusion.

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Background: Malignant pleural effusion (MPE) is caused by the metastasis of malignant tumors to the pleura. Traditional treatment have limited efficacy. In our preliminary research, a recombinant lactobacillus expressing the fusion protein Flt3L-OX40L (enhancing antigen-presenting function of dentritic cells and activation of antigen-specific T cells) named FOLactis was proved to have strong anti-tumor effect in early clinical trials. This clinical study was designed to explore the safety and efficacy of intracavitary injection of FOLactis for the treatment of malignant pleural effusion (NCT06512896). **Methods:** This is a single arm, single center study. In addition to systemic treatment, participants received intracavitary 2-4 injections of FOLactis. Primary endpoint was safety; secondary endpoints included Objective response rate of pleural effusion and the duration time of pleural effusion control. **Results:** From June 2023 to Oct 2025, a total of 38 patients were intracavitary injected with FOLactis, of which 29 patients completed more than 2 injections. Among these patients, the adverse reactions included Grade I-II fever (12/38, 31.6 %), chest wall pain (9/38, 23.68%), fatigue (2/38, 5.26%), and pneumothorax (1/38, 2.63%), while no adverse events above grade III were observed. Among the 38 patients with local treatment efficacy evaluation, 10 patients had complete disappearance of pleural effusion (10/38, 26.32%), 24 patients had reduction of pleural effusion (24/38, 63.16%), 4 patients had no significant change in pleural effusion (4/38, 10.53 %). Up to the current date, there are 21 patients whose pleural effusion has been controlled for more than one year. Among them, one patient with with advanced lung adenocarcinoma have had their pleural effusion controlled for over 30 months and is still under follow-up. It was found that patients with reduced pleural effusion had higher baseline secretion levels of IL-5 (P=0.0217), TNF-a (P=0.0178) and IFN-a (P=0.0278) in pleural effusion, while those with significantly increased levels of IL-6 (P=0.0076), IL-1B (P=0.0009) and IL-8 (P=0.0198) after treatment also had better control of pleural effusion. Further analysis of RNA sequencing in the pleural fluid of 15 patients revealed that patients with better therapeutic effects showed upregulation of $CD4^+$memory T cells, lymphoid precursor cells, $CD8^+$effector memory T cells and an upward trend in immune microenvironment scores after treatment. **Conclusions:** This ongoing phase I study with intracavitary injection of FOLactis in patients with malignant pleural effusion has preliminarily confirmed safety and clinical efficacy, which suggested to be a promising immunotherapeutic strategy for the effective control of malignant pleural effusion. Clinical trial information: NCT:06512896. Research Sponsor: None.

Safety and efficacy of intratumoral (IT) ruxotemitide (LTX 315) in combination with pembrolizumab in patients with unresectable advanced melanoma or triple-negative breast cancer (TNBC).

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Background: Advanced unresectable cutaneous melanoma or TNBC are associated with poor prognosis and limited treatment options. Ruxotemitide is an oncolytic peptide that induces immunogenic cell death and reshapes the tumor microenvironment to boost antitumor immune responses. We report aggregate safety and efficacy from two trials that assessed intratumoral ruxotemitide combined with pembrolizumab in patients with advanced or metastatic melanoma or TNBC. **Methods:** Two studies enrolled respectively patients with melanoma stage IIIB–IV (M1b) or unresectable TNBC and at least one injectable lesion (as cutaneous, subcutaneous or lymph node). Patients with melanoma were required to have failed prior PD-1\PD-L1 blockers treatment while TNBC patients were naïve of immunotherapy. Patients were required to have adequate organ function. Patients received IT ruxotemitide (up to seven injections during the first 29 days) in combination with pembrolizumab 200 mg IV every 3 weeks until disease progression or for up to 24 months. Safety and efficacy were analyzed across both studies. Tumor assessments were based on RECIST v1.1. **Results:** 41 patients were enrolled, with a median age of 61 years. 26 of pts (63.4%) had received three or more prior lines of therapy, and 22 pts (53.7%) had previous checkpoint blockade treatment. 22 patients (53.7%) had melanoma, 18 patients TNBC (43.9%) and 1 patient (2.4%) a carcinoid tumor. 4 patients had a partial response (2 with melanoma and 2 with TNBC). All responses in melanoma patients were durable, lasting more than 24 months. 1 patient with TNBC achieved a PR for one year. The safety profile was consistent with known effects of IT immunotherapy and pembrolizumab. The most common treatment emergent adverse events (TEAEs) related to ruxotemitide were injection-site reactions (78%), injection site erythema (26.8%), fatigue (22%), hypotension, injection site swelling or pruritus (14.6% each). Grade 3 TEAEs related to ruxotemitide included injection site pain (19.5%) and hypertension (4.9%). There were no related grade 4 TEAEs or deaths. **Conclusions:** IT ruxotemitide plus pembrolizumab demonstrated durable antitumor activity and manageable safety in heavily pretreated patients with advanced or metastatic melanoma or TNBC with injectable disease. These findings support further clinical evaluation of this combination in melanoma and TNBC. Clinical trial information: NCT01986426 and NCT04796194. Research Sponsor: None.

A phase I window-of-opportunity trial of intraperitoneal, intratumoral lipopolysaccharide in peritoneal metastases: Safety and immune remodeling from the RIOT-1 study.

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Background: Peritoneal metastases (PM) from gastrointestinal malignancies exhibit immune exclusion and limited responsiveness to systemic immunotherapy. Regional intratumoral immune activation may reprogram the tumor microenvironment (TME). RIOT-1 evaluated the safety, feasibility, and biological effects of intraperitoneal intratumoral lipopolysaccharide (LPS), a Toll-Like Receptor-4 (TLR4) agonist, administered during diagnostic laparoscopy. **Methods:** RIOT-1 (NCT05751837) was a single-center, open-label Phase I window-of-opportunity trial. Twelve patients with appendiceal or colorectal PM received paired intratumoral injections of 1 μg E. coli O113-derived LPS and normal saline into spatially distinct tumor deposits at laparoscopy, followed by planned cytoreductive surgery 14 days later. The primary endpoint was safety. Secondary endpoints included immune and molecular remodeling assessed by immunohistochemistry (IHC), PhenoCycler multiplex immunofluorescence, spatial neighborhood analysis (CytoMAP), and high-resolution mass-spectrometry proteomics. Key proteomic findings were validated by targeted IHC staining. **Results:** Intratumoral LPS administration was feasible and well tolerated, with no grade $\geq$3 adverse events and no interference with subsequent cytoreductive surgery. IHC demonstrated significant post-LPS increases in M1-like macrophages ($CD68^+CD86^+$), M2-like macrophages ($CD68^+CD206^+$), and $CD1a^+$ antigen-presenting cells (all $p<0.05$). PhenoCycler and CytoMAP analyses revealed LPS-specific reorganization of the immune microenvironment, characterized by enrichment of myeloid- and APC-dominant neighborhoods and altered tumor–immune spatial relationships compared with saline-injected controls. Proteomic profiling quantified 5,178 proteins and revealed LPS-specific enrichment of neutrophil degranulation, cytokine-mediated signaling, RNA translation, and autophagy–lysosomal pathways, distinct from biopsy/carrier-associated structural remodeling observed with saline. Upregulated proteins including LYZ, FCER1G, NAIP, and CD68 were confirmed by IHC, supporting localized innate immune activation and metabolic reprogramming. **Conclusions:** Intraperitoneal intratumoral LPS delivery in PM is safe and biologically active, inducing reproducible innate-dominant immune and metabolic remodeling validated across spatial, proteomic, and histologic platforms. These data establish clinical proof-of-mechanism for regional TLR4 agonism and support further dose-optimization and rational combination strategies in peritoneal malignancies. Clinical trial information: NCT05751837. Research Sponsor: ACPMP.

Clinical translation of PeptiCRAd-1: Interim clinical evaluation of a modular oncolytic adenovirus vaccine platform targeting NY-ESO-1 and MAGE-A3 in advanced solid tumors.

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Background: Oncolytic viruses can convert poorly immunogenic tumors into inflamed, immune-responsive lesions, but clinical benefit is often limited by insufficient induction of tumor antigen–specific T cells. PeptiCRAd-1 is a novel peptide-guided oncolytic adenoviral immunotherapy designed to deliver tumor antigens while providing intrinsic immune stimulation. It consists of a conditionally replicating adenovirus expressing CD40L and OX40L and coated with NY-ESO-1 and MAGE-A3 peptides to enhance priming of antigen-specific adaptive immunity. **Methods:** VALO-001 (NCT05492682) is an ongoing, open-label, non-randomized phase 1 trial enrolling adults with injectable advanced solid tumors expressing NY-ESO-1 and/or MAGE-A3, including melanoma, TNBC, NSCLC, sarcomas, and colorectal cancer. Treatment includes low-dose cyclophosphamide followed by intratumoral PeptiCRAd-1 prime/boost injections combined with pembrolizumab. Primary objectives are safety and tolerability; secondary/exploratory endpoints assess innate and adaptive immune activation: antigen-specific T-cell induction, tumor-infiltrating lymphocyte (TIL) density, viral shedding, and preliminary antitumor activity. Immune monitoring includes cytokine profiling, ELISpot for NY-ESO-1/MAGE-A3 responses, and paired biopsies for multiparametric immunophenotyping. **Results:** Seven patients have been enrolled and treated in the START Phase 1 evaluation of PeptiCRAd-1: five in the intratumoral (i.t.) cohort and two in the combined intratumoral plus subcutaneous (i.t. + s.c.) cohort. Across both groups, study treatment has been feasible and well tolerated, with no dose-limiting toxicities, treatment-related serious adverse events, or unexpected safety signals reported to date. In the i.t. cohort, innate immune activation occurred in 3/5 patients; NY-ESO-1/MAGE-A3-specific T-cell responses in 3/5; and increased TILs in 4/5. Clinical responses were observed in 2/5, with disease control in 3/5 patients. Early i.t. + s.c. data show markedly stronger peptide-specific T-cell responses than i.t. alone, supporting combined local–systemic immunization. This cohort remains open, with eight additional patients required. Across evaluable patients, biopsies demonstrated increased TIL density, and early antitumor activity—including partial responses and durable stable disease—was observed across multiple tumor types. **Conclusions:** PeptiCRAd-1 shows a favorable safety profile and induces coordinated systemic and intratumoral immune activation in advanced solid tumors. Robust antigen-specific T-cell responses and enhanced TIL infiltration support its potential to strengthen antitumor immunity and justify continued evaluation, including combination with PD-1 blockade. Clinical trial information: NCT05492682. Research Sponsor: None.

BI-1808 + pembrolizumab: Responses to a chemotherapy-free regimen in advanced ovarian cancer.

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Background: Up to 80% of individuals with advanced ovarian cancer experience disease progression after standard platinum-based chemotherapy, leaving few approved therapeutic options and poor prognosis. Anti-PD-1 therapies such as pembrolizumab have shown modest efficacy in recurrent ovarian cancer as single agent therapy with an ORR of 8% (KEYNOTE-100), while adding pembrolizumab to weekly paclitaxel±bevacizumab regimen (KEYNOTE-B96) demonstrates statistically meaningful improvement in OS and PFS in all comers and the PD-L1 CPS ≥1 population. BI-1808 is an IgG1 mAb targeting TNFR2. It blocks TNF-α binding and, via FcγR engagement, depletes Tregs and reprograms myeloid cells, expanding antitumor CD8+ T cells. These mechanisms of action differentiate BI-1808 from the relief of T cell suppression mediated by anti-PD1. Accordingly, in preclinical models BI-1808 synergizes with anti-PD-1 leading to an additive tumor inhibition. During BI-1808 monotherapy exploration, one case of complete response in a platinum-resistant patient was observed. The combination of BI-1808 and pembrolizumab could offer a chemotherapy-free treatment alternative in ovarian cancer. **Methods:** Safety and efficacy of BI-1808 plus pembrolizumab are being evaluated in patients with advanced pretreated ovarian cancer in a sub-cohort of the ongoing Phase 2a trial (19-BI-1808-01). The signal-seeking cohort aimed to enroll 20 patients at BI-1808 1000 mg Q3W plus pembrolizumab 200 mg Q3W, followed by dose optimization. **Results:** As of Dec 18, 2025, 24 subjects received BI-1808 plus pembrolizumab. Among 17 response-evaluable patients, 4 achieved confirmed partial response (ORR 24%). Disease control rate was 65%, with 7 patients showing prolonged stable disease, several ongoing beyond 10 months. Strong activity was observed in both high-grade serous and clear cell subtypes. The combination was generally safe and well tolerated; immune related events were manageable and did not lead to treatment discontinuation. Analysis of circulating immune cells shows significant T reg depletion and strong signs of $CD8^+$ T cell activation. **Conclusions:** Early data from this cohort are highly encouraging, with ORR 24% and DCR 65%. BI-1808 plus pembrolizumab demonstrated a manageable safety profile and promising activity in advanced heavily pretreated ovarian cancer. Based on these findings, the cohort will expand by 20 additional patients focusing on clear cell and high-grade serous subtypes. Further data, including biomarker analyses, will be presented on poster. Clinical trial information: NCT04752826. Research Sponsor: None.

Neoadjuvant chemokine modulation of the tumor microenvironment (TME) in resectable metastatic colorectal cancer: Results from a phase I study.

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Background: Our preclinical studies using ex vivo explant cultures of resected metastatic colorectal cancer (CRC) tissues and in vivo mouse models showed that the combination of interferon alpha (IFNα) with toll-like receptor-3 (TLR-3) ligands and inhibitors of prostaglandin synthesis selectively induces effector T cell-attracting chemokines (CXCL9, CXCL10, CXCL11, and CCL5) in tumor microenvironments (TME), but not in adjacent healthy tissues, allowing for their systemic application to modulate TME. The chemokine-modulating (CKM) regimen, consisting of IFNα, rintatolimod (a selective TLR3 agonist), and celecoxib (a COX-2 inhibitor), also suppresses CCL22, a Treg-attracting chemokine in the TME. Based on these preclinical data, we hypothesized that a systemic CKM regimen would be safe and effective in modulating the TME of metastatic CRC. **Methods:** Nine chemotherapy-naïve patients with metastatic or recurrent CRC confined to the abdomen/pelvis and expected to have a complete resection received increasing doses of IFNa2b in a Phase I study to establish a recommended phase II dose of CKM for efficacy studies. The adaptive dose-escalation evaluated IFNα2b at 5, 10, and 20 million units (MU)/m2/day IV (Monday–Friday for 1 week pre-surgery), in combination with fixed doses of rintatolimod (200 mg IV; Monday–Friday) and celecoxib (200 mg orally twice daily; Monday–Friday). **Results:** No dose-limiting toxicities were observed, and 20 MU/m^2 of IFNα2b was identified as the recommended Phase II dose. All treated patients underwent R0 resection, as planned. Common treatment-related adverse events were flu-like symptoms (chills, fever, fatigue) and transient laboratory abnormalities (anemia, leukopenia), mostly grade 1–2. Two patients (13%) developed grade 3–4 neutropenia, which resolved without sequelae. There were no unexpected perioperative complications attributable to the regimen. Preliminary analysis of resected tumor tissues showed evidence of immune modulation in CKM-treated patients: increased ratios of CD8+ CTLs to FoxP3+ Tregs, with concomitant elevation of the effector chemokines (CCL5 and CXCL10), along with reduced expression of the Treg-recruiting chemokine CCL22, compared to 77 patients undergoing upfront tumor resections. **Conclusions:** Neoadjuvant CKM regimen is safe and feasible in resectable metastatic CRC and is associated with improved ratios of CD8+ CTLs to FoxP3+ Tregs in the TME. Further studies combining CKM with immune checkpoint inhibitors and/or chemotherapy are warranted to evaluate the impact of preoperative TME modulation on long-term oncologic outcomes in CRC. Clinical trial information: NCT01545141. Research Sponsor: National Cancer Institute; P01CA132714; National Cancer Institute; P01CA234212.

Safety and efficacy results from a first-in-human, phase 1/2 study of ASKG915, an anti-PD-1/pro-IL-15 bifunctional fusion protein, for patients with advanced solid tumors.

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Background: ASKG915 is a bifunctional fusion protein of PD-1 antibody fused with an IL-15 prodrug. Preclinical studies demonstrated the efficacy of ASKG915 in neoplastic models. Here, we present updated safety and efficacy results from a first-in-human, dose escalation and dose expansion of ASKG915 monotherapy in patients (pts) with advanced solid tumors. **Methods:** This open-label, multicenter, Phase 1/2 study in adult pts with advanced unresectable or metastatic solid tumors (NCT05867420) comprised two parts: dose escalation (Part 1) and dose expansion (Part 2). Pts with advanced solid tumors that were resistant/refractory to current standard treatment, and with at least 1 measurable lesion per RECIST 1.1, were eligible. The primary objective was safety. Secondary objectives included efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity. **Results:** As of December 30, 2025, we have treated 104 pts at dose-escalation phase (n=19) and dose expansion phase (n=85). Primary tumor types included NSCLC (n=48, 46.2%), CRC (n=35, 33.6%), ovarian cancer (n=11, 10.6%), cervical cancer (n=4, 3.8%) and others (n=6, 5.8%). Most pts (83/104, 79.8%) had received two and more lines of prior treatment, and 71 pts (68.3%) had undergone previous immunotherapy. No dose-limiting toxicities was observed in dose escalation phase, and the maximum tolerated dose has not been reached up to 3 mg/kg. In SS set, any-grade treatment-related adverse events (TRAEs) were reported in 98/104 (94.2%) pts, with the most common being rash (39/104, 37.5%), anemia (37/104, 35.6%), and elevated aspartate aminotransferase (19/104, 18.3%). ASKG915 monotherapy exhibited dose-dependent efficacy across dose levels. In the EFR cohort, encouraging antitumor activity was observed at the mid-dose level or above in both late-line NSCLC that had progressed on prior immunotherapy and MSS CRC: a 30% confirmed partial response (PR) rate (3/10) in non-liver metastatic MSS CRC at the mid-dose level or above, and a 30% PR rate (3/10) in NSCLC patients at the high-dose level. Further efficacy data will be presented at the time of the conference. CD8+ T and NK cells demonstrated proliferative expansion at mid-to-high doses. Drug plasma exposure increased dose-dependently with low activated ASKG915 levels and no ADA impact after repeat dosing. **Conclusions:** ASKG915 demonstrated a promising clinical efficacy in pts with MSS CRC and NSCLC, with a well-tolerated safety profile. These results support further evaluation of ASKG915 as a monotherapy and in combination therapies. Clinical trial information: NCT05867420. Research Sponsor: None.

RAISIC-1: A phase 1/2 clinical trial of the GPR65 inhibitor PTT-4256—Preliminary safety, tolerability, pharmacokinetic, and pharmacodynamic results.

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Background: The acidic tumor micro-environment is linked to immune suppression and insensitivity to immunotherapy. The G protein-coupled receptor, GPR65, is activated in this low pH environment, driving the increased transcription of myeloid immune-suppressive genes and reduced transcription of T- and NK-cell functional and effector genes. Against the backdrop of this target validation, PTT-4256, a first-in-class, potent, orally-bioavailable, allosteric, small molecule inhibitor of GPR65, is being developed as a potential treatment of solid tumors. In mouse syngeneic cancer models, oral administration of PTT-4256 as monotherapy delivers pronounced efficacy, which is enhanced in combination with an anti-PD-1 antibody. Transcriptomic analysis shows that PTT-4256 effectively reverses the acidic immune suppression in mice tumors. **Methods:** RAISIC-1 is a multi-modular Phase 1/2 clinical trial in adults with histologically confirmed advanced/metastatic solid malignancies who have previously received standard of care therapies. Phase 1 (Module A) is aimed to evaluate safety (treatment emergent and related adverse events – TEAE/TRAE; dose limiting toxicity – DLT; maximum tolerated dose-MTD), pharmacokinetics, pharmacodynamics, preliminary efficacy (as per RECIST 1.1) and estimate the optimal biological dose (OBD) / recommended Phase 2 dose (RP2D). PTT-4256 is administered orally in 21-day cycles until disease progression or unacceptable toxicity. A comprehensive biomarker program is included to detect immune-related changes in blood/plasma. **Results:** As of 7 January 2026, 14 participants (3 ongoing) have been treated with one of 5 dose-levels (10, 20, 40, 80 and 160 mg/day). PTT-4256 was well-tolerated with no DLTs. TRAEs were reported in ten participants, with fatigue (n = 8), nausea (n = 4), rash (n = 4), reduced appetite (n = 4), vomiting (n = 2) reported in more than 1 participant. All were grade 1 or 2 except one transient episode ($<$ 1 day) of grade 3 hypertension. Tumor shrinkage and stable disease have been observed at doses 40mg and above in six participants, of which two (nasopharyngeal cancer and renal cell cancer (RCC)) are ongoing in treatment $>$ 5 months. Transcriptomics and proteomics analyses show dose-dependent changes in immune-related markers in blood/plasma following PTT-4256 treatment that are consistent with preclinical data and the mode of action. **Conclusions:** Enrollment at dose levels $\geq$ 300 mg is ongoing. Phase 2 (Module B) as PTT-4256 monotherapy or in combination with anti-PD1 in RCC and head & neck squamous cell cancer (HNSCC) will commence upon identification of RP2D. Clinical trial information: NCT06634849. Research Sponsor: Pathios Therapeutics Limited.

Influence of pirfenidone on checkpoint inhibitor pneumonitis and antitumor efficacy in NSCLC: A multicenter study and mechanistic exploration.

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Background: Checkpoint inhibitor pneumonitis (CIP) is a major fatal immune-related adverse events (irAEs) in immune checkpoint inhibitor (ICI) therapy, accounting for ~35% of fatal irAE-related deaths. Patients with pre-existing interstitial lung disease (ILD) face markedly higher CIP risk and are routinely excluded from ICI treatment, depriving them of antitumor benefits. Current first-line glucocorticoid therapy for CIP are limited by inadequate efficacy in fibrotic-stage or steroid-resistant CIP and impaired ICI activity. As a drug-induced interstitial pneumonitis, CIP shares pathological similarities with ILD. Pirfenidone, an approved ILD drug, showed potential efficacy in CIP case reports, but its systematic clinical value and mechanisms remain unvalidated. This study aimed to elucidate pirfenidone's role in full-cycle CIP management and its synergistic antitumor effect with ICIs. **Methods:** A multicenter retrospective study enrolled advanced non-small cell lung cancer (NSCLC) patients receiving first-line ICI-based therapy from three hospitals between 2018 and 2024, stratifying into pirfenidone+ICI+chemotherapy (Pirf+ICI+chemo) and ICI+chemotherapy (ICI+chemo) groups. Primary endpoint was CIP incidence, secondary endpoints objective response rate (ORR) and progression-free survival (PFS). For mechanistic studies, bleomycin and ICI were administered to spontaneous NSCLC mice to mimic clinical ICI treatment in ILD-high-risk patients, generating a CIP mouse model. Lung scRNA-seq defined pirfenidone's role in CIP management and synergistic antitumor activity. **Results:** Of 141 enrolled patients, Pirf+ICI+chemo had significantly lower CIP incidence vs. ICI+chemo (34.01% vs. 59.57%, p=0.0070), with synergistic antitumor effects manifested as higher ORR (78.72% vs. 60.64%, p=0.0376), and longer median PFS (9.97 vs. 5.47 m, p=0.0120). CIP shows a biphasic inflammation-fibrosis pathology. scRNA-seq of 62,335 lung cells identified ISG^+ aged neutrophils (ISG^+ Na) as the key pathogenic driver of CIP progression. ICI-induced excessive immune activation triggers lung damage, activating the IFN-I-IRF9/STAT1 axis to promote ISG^+ Na differentiation. These cells secrete IL-6, IL-8, TNF-α to amplify inflammation, and TGF-β to induce fibroblast proliferation and activation, all of which pirfenidone blocks, supporting its full-cycle CIP efficacy mechanistically. Animal experiments further confirmed pirfenidone's robust efficacy in CIP prevention, treatment and synergistic antitumor activity with ICI. **Conclusions:** Pirfenidone reduces CIP incidence and synergizes with ICI therapy to enhance antitumor efficacy. Mechanistically, it targets IFN-I-IRF9/STAT1-ISG^+ Na axis for dual clinical benefits. These findings confirm pirfenidone as a translatable strategy to balance CIP control and antitumor activity. Research Sponsor: None.

Intratumoral injection of IP-001 following thermal ablation in patients with advanced solid tumors: A multicenter phase Ib/IIa trial with expansion cohorts in melanoma and soft tissue sarcoma patients (SAKK 66/17).

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Background: This trial combines the novel adjuvant immunomodulator IP-001, a glycan polymer, with laser ablation in patients with relapsed solid tumors. **Methods:** This is a non-randomized, open-label multicenter phase Ib/IIa trial with a dose-finding part 1 and a dose expansion part 2 in advanced melanoma and soft tissue sarcoma (STS). Primary objectives include the safety and tolerability of up to six 4-weekly cycles of intratumoral IP-001 following laser ablation (TRANBERG Thermal Therapy System, Clinical Laserthermia System AB), and 12-week disease control rate (12w-DCR) according to RECIST v1.1 in advanced melanoma. The dose-finding part used 4 mL of IP-001 (10 mg/mL). The activity endpoint for advanced melanoma used the 1st stage of a Simon 2-stage design, with 12w-DCR ≤20% (H0) vs. ≥40% (H1) (type-I error 0.05, power 80%). **Results:** We treated 15 melanoma and 10 STS patients, including 4 in part 1 (n=28). Median age was 62 years, 57% were male, all patients had metastatic disease, including 60% with liver metastases. Most patients (78%) had received ≥3 prior lines of systemic treatment, including 79% with prior immunotherapy. Treatment was well tolerated with no dose-limiting toxicity, and a recommended IP-001 dose of 4 mL. Patients received a median of 2 (range 1 to 6) cycles of study treatment. Reasons for treatment discontinuation included physician's decision (39%) and disease progression (25%). 27 patients (96%) experienced treatment-emergent adverse events (TEAE). IP-001-related TEAE occurred in 16 (57%) patients, including 5 (17%) patients with severe IP-001-related TEAE. Severe TEAE occurred in 20 (71%) patients overall. Most frequent mild IP-001-related TEAE included fever (36%), fatigue (21%), rash (14%), hypotension (11%), injection site reactions (11%) and flu-like symptoms (7%); 2 cases (7%) of severe allergic reactions were reported, including one serious reaction. Allergic reactions occurred at cycle 3 in both patients and resolved without sequelae. Treatment discontinuation for TEAE occurred in a single patient (4%). 12w-DCR in advanced melanoma was 21% (3/14 evaluable patients) (2-sided 90% CI: 6%, 46%), with stable disease in 50% and partial remission (PR) in one (7%) melanoma patient. 15 (53%) patients had radiological tumor shrinkage in ≥1 untreated tumor lesion. Median progression-free survival (PFS) in advanced melanoma was 3 months, with a 12-month PFS rate of 33%, indicating preliminary evidence of disease control beyond the 12-week primary endpoint window. **Conclusions:** Intratumoral IP 001 at a dose of 4 mL following thermal ablation is well tolerated, with mainly mild, transient immune-related events. Although the pre-specified activity endpoint was not met, the observed DCR and PFS support further evaluation of this novel immuno-oncologic strategy. Clinical trial information: NCT03993678. Research Sponsor: Immunophotonics, Inc., St. Louis MO, 63110, U.S.

Potential effects of TGF-β inhibition on immune resistance by targeting immunosuppressive microenvironment in advanced gastric cancer (AGC): Multi-omics post-hoc analysis of the K-Umbrella-06 trial.

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Background: TGF-β signaling promotes immune exclusion by driving fibrosis and hindering T-cell infiltration. We performed multi-omics post-hoc analyses of K-Umbrella-06 to identify mechanisms and predictive biomarkers for TGF-β/PD-L1 dual blockade in HER2-negative AGC. **Methods:** K-Umbrella-06 (NCT04835896) was an investigator-initiated, single-arm, phase Ib/II study enrolling HER2-negative AGC pts who had progressed on 1st-line treatment. Pts received bintrafusp alfa (TGF-β trap/anti–PD-L1) and weekly paclitaxel. Pretreatment H&E whole-slide images (WSIs) were analyzed with an AI-powered WSI analyzer to quantify fibroblast and endothelial cell (EC) densities and immune phenotypes. A separate cohort treated with nivolumab + paclitaxel (n=26) served as a control. Integration of baseline tissue transcriptomics and serial ctDNA sequencing (baseline, 1st RECIST assessment, and progression) was performed to identify predictive biomarkers and resistance mechanisms. **Results:** At a median follow-up of 46 months in 30 enrolled patients, the mPFS and mOS were 3.8 and 8.9 months, respectively; notably, 5 patients achieved durable responses with PFS exceeding 3 years. AI-WSI analysis revealed that high fibroblast density (≥median) was a significant predictor of superior outcomes (mPFS: 4.3 vs. 2.0 months, HR 0.29, P=0.007; mOS: 20.4 vs. 5.8 months, HR 0.28, P=0.012). Conversely, patients with higher intratumoral EC density had shorter mPFS (2.0 vs. 5.9 months, HR 2.29, P=0.058) and mOS (4.0 vs. 8.9 months, HR 1.61, P=0.285). Notably, patients with the immune-excluded phenotype achieved a higher ORR (60.0% vs. 18.2%) and prolonged survival compared to inflamed/desert types. These biomarkers were not predictive in the nivolumab + paclitaxel cohort, suggesting a TGF-β specific effect. Transcriptomic profiling of responders showed enrichment in TGF-β signaling (normalized enrichment score [NES] 2.87, P<0.001) and SMAD2/3 activity (NES 2.99, P<0.001), alongside increased naive CD8+ T cells and inflamed EC cells. Conversely, non-responders exhibited higher M2 macrophage and abundant angiogenic tip cells. Serial ctDNA analysis identified emergent TGF-β pathway alterations as a potential mechanism of acquired resistance (OR 7.30, P=0.08). **Conclusions:** Integrated AI-WSI, transcriptomic, and longitudinal ctDNA analyses suggest that TGF-β pathway activation and an immune-excluded phenotype are associated with clinical benefit from bintrafusp alfa plus paclitaxel, and may identify a responder subset distinct from conventional PD-1/PD-L1–based therapy. These findings support further evaluation of anti–TGF-β strategies for AGC with an immunosuppressive tumor microenvironment. Clinical trial information: NCT04835896. Research Sponsor: Merck KGaA.

Effects of SECN-15, a neuropilin-1–targeting antisense oligonucleotide, on resistance to immune checkpoint inhibitors in preclinical tumor models.

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Background: Neuropilin-1 (NRP1) is a transmembrane co-receptor implicated in tumor growth, metastasis, angiogenesis, and immune suppression. High NRP1 expression is associated with poor prognosis in multiple solid tumors, including gastric cancer (GC) and breast cancer. SECN-15 is a high-affinity antisense oligonucleotide (ASO) designed to selectively downregulate NRP1. In light of recent clinical success of combined PD-1/PD-L1 and anti-angiogenic strategies and given its dual role in angiogenesis and immune suppression, NRP1 represents an attractive target to overcome resistance to immune checkpoint inhibition. **Methods:** NRP1-specific ASOs were identified using the OligoCreator platform. Anti-tumor efficacy was assessed following systemic administration in multiple syngeneic mouse tumor models, both as monotherapy and in combination with immune checkpoint inhibitors. Target engagement was evaluated at the RNA level in tissues and at the protein level in plasma via soluble NRP1 quantification. In silico analyses of patient transcriptomic datasets were conducted to prioritize indications for clinical development. PK/PD characterization and dose optimization studies are currently underway to support dose selection for GLP toxicology studies and first-in-human evaluation. **Results:** Systemic administration of SECN-15 achieved robust target knockdown in tumors across multiple cell populations and modulated the tumor microenvironment, including downregulation of extracellular matrix and EMT genes. A single dose resulted in near-complete and sustained suppression of plasma soluble NRP1 levels for up to 28 days, consistent with durable target engagement. SECN-15 delayed tumor growth as monotherapy, with complete regressions observed in a subset of animals, and significantly enhanced anti-tumor activity in combination with immune checkpoint inhibitors in models with limited responsiveness to checkpoint blockade alone. Single-cell RNA-seq analyses from gastric cancer patients identified endothelial cells and macrophages as major NRP1-expressing populations, with NRP1high subsets exhibiting TGF-β, hypoxia, and EMT pathway activation and suppression of allograft rejection signatures, consistent with an immunosuppressive, pro-angiogenic tumor microenvironment. In silico analyses showed that high NRP1 expression correlates with poor survival and advanced disease stage in gastric cancer, supporting its prioritization for clinical development. **Conclusions:** Targeting Neuropilin-1 with the ASO SECN-15 remodels the tumor microenvironment and enhances responsiveness to immune checkpoint blockade, supporting NRP1 inhibition as a strategy to overcome resistance to ICI therapy in solid tumors. The program is approaching IND-enabling development to support the clinical translation of SECN-15. Research Sponsor: Secarna Pharmaceuticals GmbH & Co. KG.

Non-invasive characterization of intratumoral CD8+ T cells using standard-of-care (SOC) CT and ^{89}Zr-crefmirlimab berdoxam PET (CD8-PET) radiomic signature in solid tumors.

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Background: Noninvasive estimation of intratumoral CD8+ T-cell density using radiomics may enhance comprehensive immune profiling and support immuno-oncology development and treatment decisions. We evaluated the feasibility of using a multimodality radiomic approach incorporating SOC CT and CD8-PET/CT to characterize CD8+ T-cell density in solid tumor lesions. **Methods:** 71 soft-tissue lesions from 52 patients with solid tumors enrolled in a Phase II iCorrelate trial (NCT03802123) were retrospectively analyzed. Patients received a pre-treatment CD8-PET/CT scan (ImaginAb, Inc) before initiating SOC immunotherapy (IOT) and a second CD8-PET/CT scan on-treatment 4-8 weeks later, with selection of biopsied tumor lesions of known CD8+ T-cell density for radiomic analysis. Radiomic features were extracted from volumetric segmentations of these tumor lesions using 3D Slicer on Diagnostic contrast CT (DCT, n=27), CT attenuation correction (CTAC; n=71), and CD8 PET (n=71) images. Features were integrated with acquisition parameters, lesion location, and adenopathy status. Feature selection used maximum relevance–minimum redundancy and variance inflation factor methods. Elastic-Net classifiers were trained to predict binarized (median split at the 328 cells/mm^2 level) CD8+ T-cell density, with hyperparameter optimization via grid search and 5 fold Cross-Validation (CV). In each iteration of the CV, 1 fold (20%) was left out and models were trained on the remaining 4 folds (80%). Model performance was assessed using AUC and F1 score. **Results:** In the test set, Multimodality models (CTAC+DCT+PET) outperformed single-modality (AUC up to 0.94 vs. 0.80), with improved AUC and F1 scores and robust performance across endpoints. Single-modality models achieved AUCs of 0.76 (F1 0.55) for DCT, 0.80 (F1 0.72) for CTAC, and 0.80 (F1 0.70) for PET. The combined CTAC+DCT+PET model demonstrated superior performance with a test AUC of 0.85 (F1 0.79) and training AUC of 0.94 (F1 0.89). Application of previously reported DCT radiomic weights (Sun et al.) to this cohort yielded a lower AUC of 0.68, compared with the multimodality model. **Conclusions:** This study demonstrates robust radiomics-based characterization of intratumoral CD8+ T-cell density in patients with solid tumors is feasible using non-invasive multi-modality approach utilizing CD8-PET and SOC CT scans. These findings may lead to further clinical adoption and non-invasive monitoring of the tumor immune microenvironments with CD8-PET and SOC CT scans using radiomics, informing IOT decision-making, and enhancing patient stratification in both clinical development and routine oncology practice. Validation in larger, multicenter cohorts is still required to confirm generalizability and robustness of these radiomic signatures. Clinical trial information: NCT03802123. Research Sponsor: None.

PhaseX as a phase 0.9 translational platform to de-risk BiTE immunotherapy through mechanistic patient explant profiling.

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Background: Bispecific T-cell engagers (BiTEs) redirect cytotoxic T cells to tumor cells, but responses in solid tumors remain heterogeneous due to antigen variability, T-cell exclusion, stromal barriers, and immunosuppressive cues within the tumor microenvironment (TME). PhaseX (patient-derived hydrogel-assisted explants) preserves native tissue architecture and endogenous immune composition ex vivo, enabling mechanistic, patient-specific interrogation of immunotherapies in a physiologically relevant context. We used PhaseX to define BiTE mechanism of action (MoA) and resolve response phenotypes in head and neck squamous cell carcinoma (HNSCC). **Methods:** Tumor explants from ~25 HNSCC patients were ex-vivo cultured in PhaseX and treated for 6 days with CD3×B7-H3 or CD3×EpCAM BiTEs with matched controls. Supernatants were collected longitudinally for multiplex secretome profiling. At endpoint, explants were dissociated and subjected to flow cytometry, while some explants were fixed and processed to FFPE sections for multiplex immunofluorescence (mIF). Cancer cells were quantified using epithelial markers (PanCK and p60). Tumor response states were classified as tumoricidal (increased tumor-cell CC3 [cleaved caspase-3] with reduced $PanCK^+/p60^+$ cancer cell burden) versus tumorostatic (preserved $PanCK^+/p60^+$ cancer cell burden with reduced Ki-67 in $PanCK^+/p60^+$ cancer cells). **Results:** Across both CD3×B7-H3 and CD3×EpCAM BiTE-treated explants, PhaseX captured core BiTE MoA: (i) TCR-driven activation with expansion of activated $CD8^+$ T cells ($CD137^+$) and enrichment of tumor-reactive $CD8^+$ subsets ($CD137^+CD103^+CD39^+$); (ii) immune trafficking and inflammatory programming consistent with IFNγ signaling, evidenced by increased CXCL9/10/11 and coordinated effector cytokine signatures; and (iii) effector execution in tissue, integrating increased cytotoxic mediators (perforin, granulysin) with spatial mIF evidence of enhanced intratumoral CD8+ infiltration. Tumoricidal responders showed elevated tumor-cell CC3 with concomitant loss of $PanCK^+/p60^+$ tumor area, whereas tumorostatic responders showed decreased tumor-cell Ki-67 expression with comparatively limited CC3 induction, supporting biologically distinct on-treatment states. **Conclusions:** PhaseX serves as a "Phase 0.9" translational platform that preserves the TME and resolves BiTE MoA from activation to trafficking to effector execution, while distinguishing tumoricidal and tumorostatic response phenotypes. This framework supports mechanistic deconvolution, biomarker discovery, and patient stratification to de-risk bispecific antibody development. Research Sponsor: National Medical Research Council; MOH-STAR24jul-0002; National Medical Research Council; MOH-001212-01.

Phase 1A/B study of AB248, a CD8+ selective IL-2 mutein fusion protein, alone or in combination with pembrolizumab, in patients with advanced solid tumor malignancies.

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Background: High-dose IL-2 demonstrates modest activity in melanoma and RCC but its use is limited by severe toxicity. AB248 is a novel IL-2 fusion protein of an attenuated IL-2 mutein linked to an antibody targeting CD8β that features >500-fold selectivity for CD8+ T cells and shows strong anti-tumor activity both alone and with anti-PD1 in preclinical models. In addition to CD8+ T cell expansion and activation, the drug avoids NK cell toxicity and Treg-mediated immunosuppression. **Methods:** NCT05653882 is a phase 1A/B study investigating the safety, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of AB248 alone or with pembrolizumab in locally advanced/metastatic solid tumor malignancies, including melanoma, having previously progressed through PD-1/PD-L1 checkpoint blockade. The study's primary objective was to assess the safety and tolerability of AB248 alone and in combination with pembrolizumab. **Results:** As of December 1, 2025, 61 patients (pts.) were treated with monotherapy (MT) at 6 dose levels across 3 schedules (Q2W at 0.02mg/kg-0.75mg/kg; QW at 0.15mg/kg; Q3W at 0.3mg/kg). 68 additional pts. were treated with combo therapy (CT) at Q3W 0.15-0.3mg/kg and step-up dosing. The most common TEAEs (> 95% G1-2) among all pts. were fatigue (50%), rash (49%), nausea (43%), chills (33%), pyrexia (32%), vomiting (32%) and diarrhea (30%). Maximum tolerated doses (MTDs) were 0.5 mg/kg for MT Q2W and 0.15 mg/kg for CT Q3W. An MTD was not reached for CT step-up dosing. 41 cutaneous (cut) and mucosal (muc) melanoma pts. were evaluable for response across MT and CT dose cohorts, with 95% of pts. having received prior IO doublet therapy (anti-PD1 + anti-CTLA or anti-LAG3) and 83% having received ≥ 2 anti-PD1 regimens. Among evaluable cut melanoma pts., 2 confirmed PRs (18%) were observed among 11 pts. enrolled at higher MT dose levels (net tumor reductions of 78.8% and 87.2%) and 2 confirmed PRs (12%) were observed among 16 CT pts. (37.5% and 57.5%). Among 11 muc melanoma pts., 3 confirmed PRs (27%) were observed in CT dosing. One additional muc melanoma pt. received 0.5 mg/kg MT and remained on study with SD > 15 mos. AB248 exhibited dose-proportional PK that is comparable between MT and CT dosing. Peripheral PD data demonstrated robust and preferential CD8+ T cell expansion, with >20X expansion in MT (0.3 mg/kg and above) and >11X expansion in CT dosing (0.15 mg/kg and above). Further data on safety, PK, PD, and preliminary anti-tumor activity will be presented. **Conclusions:** AB248 demonstrates robust anti-tumor activity across heavily IO-pretreated patients with metastatic melanoma (incl. mucosal melanoma). Combined with an acceptable safety profile, favorable PK and differentiated PD, the drug's anti-cancer activity merits further investigation. Clinical trial information: NCT05653882. Research Sponsor: Asherbio Therapeutics.

First-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody IBI363 (TAK-928) in patients (pts) with advanced immunotherapy-resistant non–small cell lung cancer (NSCLC): Updated results from a phase I study.

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Background: IBI363 is a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein designed to block the PD-1/PD-L1 pathway and simultaneously activate the IL-2 pathway. IBI363 selectively expands and rejuvenates exhausted tumor-specific T cells by cis-activating IL-2 receptors. It has shown a manageable safety profile and encouraging efficacy in NSCLC (No. 8509, 2025 ASCO). The updated findings are reported here with a longer follow-up. **Methods:** Pts with advanced NSCLC who had progressed on standard therapy were enrolled and received IBI363 at dose levels of 0.002/0.01/0.3/0.6 mg/kg every week, 0.3/0.6/1 mg/kg Q2W or 1.5/2/3/4 mg/kg Q3W. Endpoints included safety, ORR, DCR, DOR and PFS assessed by investigator per RECIST v1.1, and OS. **Results:** As of Nov 20, 2025, 136 pts with NSCLC were enrolled (prior treatment lines ≥2 72.1%; including 67 with squamous NSCLC [sqNSCLC] and 66 with adenocarcinoma). The median follow-up was 14.4 months (mos, range 0.8–30.6). Both the ORR and DCR in sqNSCLC or adenocarcinoma were consistent with those reported previously. In pts with sqNSCLC at 1/1.5 mg/kg (n=28) and 3 mg/kg Q3W (n=31) (58/59 with prior IO therapy), median PFS was 5.5 (95% CI 1.5, 8.3) and 10.1 mos (6.0, 14.0), median OS was 12.5 (7.6, 22.2; maturity 71.4%) and 18.2 mos (10.7, not calculable [NC]; maturity 48.4%), with 24-month OS rate of 29.9% (14.2, 47.3) and 47.8% (28.7, 64.7), respectively. Among those who had a confirmed complete response (n=1) or partial response (PR, n=17), the overall DOR was 10.3 mos (7.0, 13.4; maturity 72.2%). In pts with *EGFR*^{wt} adenocarcinoma at 0.6/1/1.5 mg/kg (n=30) and 3 mg/kg Q3W (n=25) (all with prior IO therapy), median PFS was 2.7 (1.4, 5.1) and 4.2 mos (3.0, 7.0), median OS was 17.5 (7.1, NC; maturity 56.7%) and 15.2 mos (9.6, NC; maturity 56.0%), with 24-month OS rate of 40.2% (22.2, 57.7) and 42.7% (23.1, 61.0), respectively; the overall DOR reached 21.3 mos (4.0, 21.3; maturity 40.0%) in those achieving a confirmed objective response (n=10, all PRs). Smoking is a major factor affecting treatment efficacy in adenocarcinoma. In smokers (n=31) and non-smokers with adenocarcinoma (n=24), the median OS was 23.4 (11.3, NC; maturity 48.4%) and 11.5 mos (5.6, 19.6; maturity 66.7%), respectively. In the overall population (n=136), treatment-emergent adverse events (TEAEs) occurred in 135 pts (99.3% any grades; 48.5% ≥G3). TEAEs led to treatment discontinuation in 11 (8.1%) pts. TEAEs led to death in 5 pts (3.7%) with only 1 event (0.7%) considered treatment-related (unexplained death). The most common TEAEs were arthralgia (52.2%; 3.7% ≥G3), anemia (46.3%; 4.4% ≥G3), and rash (39.0%; 8.8% ≥G3). **Conclusions:** IBI363 was well tolerated with a manageable safety profile consistent with earlier reports, and continued to show strong and durable efficacy in pts with heavily pretreated NSCLC. Clinical trial information: NCT05460767.
Research Sponsor: This study was funded by Innovent Biologics, Inc.

Alirocumab plus cemiplimab in immuno-refractory metastatic NSCLC: A single-arm, multi-center, phase 2 study.

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Background: Immunotherapy resistance remains a significant unmet clinical need for most non-small cell lung cancer (NSCLC) patients. PCSK9 was shown in preclinical models to mediate cancer immunotherapy resistance and may serve as a novel immuno-inhibitory target. **Methods:** This is a first-in-class, multi-center, single arm, phase II study evaluating the clinical activity and safety of the PCSK9 inhibitor, alirocumab, in combination with the anti-PD1 antibody cemiplimab, in non-small cell lung cancer (NSCLC) patients whose tumors were previously resistant to immune checkpoint blockade. The primary endpoint was objective response rate (ORR). Secondary endpoints were safety, progression free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR). The correlative objective was to analyze the biomarkers of response. **Results:** A total of 60 patients were enrolled between May 2023 and August 2025. In the 58 evaluable patients, the estimated ORR for the two-stage design was 14.98% (90% CI, 5.45, 25.52). The median duration of response was not estimable. The median OS was 7.2 months (95% CI, 5.3 – 13.6). No new safety signals were seen. Non-hematologic adverse events (AEs) were more prevalent than hematologic AEs and were predominantly grade 2 or less. Two grade 3 events were seen. Biomarker analysis identified superior outcomes in NSCLC harboring *PIK3CA, AKT1*, or *PTEN* alterations, with ORR of 31.5% (95% CI,13.9%, 68.4%,), significantly associating with response, p 0.0008 (two-sided, Fisher's exact). No objective responses were observed in the absence of *PIK3CA, PTEN* or *AKT1* alterations. Median OS was numerically longer in the altered group was 13.64 months (95% CI, 3.1 – NR) compared to 7.2 months (95% CI, 5.2-12.8) in the unaltered group. Analysis of the cancer genome atlas (TCGA) in NSCLC cohorts demonstrated a correlation between *PIK3CA, PTEN* and *AKT1* expression and PCSK9 expression. Preclinical translational studies further elucidated the impact of *PIK3CA, PTEN* or *AKT1* in intratumoral PCSK9 secretion, a novel immune-oncological finding for this pathway, and provided a biological rationale for the observed pattern of response. **Conclusions:** These findings provide clinical proof-of-principle that PCSK9 inhibition can overcome immunotherapy resistance in a subset of patients and suggest that *PIK3CA/PTEN/AKT1* pathway may play a significant role in PCSK9 mediated immune evasion and could be a biomarker of response. These findings warrant further investigation in a larger confirmatory study. Clinical trial information: NCT05553834. Research Sponsor: None.

Targeting PI3K-β to develop novel combinational therapies for melanoma.

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Background: Melanoma is the deadliest skin cancer, and more than 100,000 people in the United States were diagnosed in 2024. While the 5-year survival rate is 99% for localized disease, it is just 10-25% in metastasis. Treatment for metastatic melanoma often involves powerful immunotherapies (e.g. checkpoint inhibitors). However, approximately 55% of patients have innate resistance and 25% of responders develop resistance within two years. Immunotherapy resistance is due to continued checkpoint protein expression and antagonization of T-cell activation – processes controlled by the phosphatidyl inositol 3-kinase (PI3K) system. Of the four PI3K kinases (α, β, δ and γ), recent work from the Sheng lab suggests that PI3Kβ has the largest role in the growth of $BRAF^{V600E}/PTEN^{null}$ (PI3K inhibitor) melanoma and is a prime drug target. There is an 18-residue motif found only in PI3Kβ that has close interactions with p85 - a key regulatory protein responsible for kinase activation. The Sheng lab harnessed this motif and developed a novel peptide (CPP-β18) that selectively blocks PI3Kβ with high affinity and decreases viability in cells that hyper-express PI3Kβ. Given the vital role of PI3K in immunosuppression, further investigation into CPP-β18's sensitizing effects on checkpoint inhibitors is urgently needed to lead to new therapies. **Methods:** PI3K inhibition in $BRAF^{V600E}/PTEN^{null}$ YUMM1.7 and $BRAF^{V600E}/PTEN^{WT}$ YUMM5.2 murine cell lines was validated by exposing cells to various commercial PI3K inhibitors and CPP-β18. Cell viability was measured via MTS colorimetric response. Advanced live-cell imaging techniques were employed to assess apoptosis when melanoma cells were treated with these selective inhibitors. Both cell lines were fluorescently labeled to differentiate cells from cytotoxic T-cells in future co-culture work. **Results:** MTS colorimetric assays reveal decreased YUMM1.7 cell viability with various PI3Kβ inhibitors (IC_{50} values = 6-10 μM) in comparison to increased YUMM5.2 cell viability (IC_{50} values = 21-30 μM). PI3Kδ and PI3Kγ inhibition had negligible effect on cell survival. YUMM1.7 cell death (>70%) was also demonstrated when treated with the novel CPP-β18 peptide inhibitor. Live cell imaging studies confirm feasibility to investigate interactions between drug therapy and melanoma cells and to appreciate early and late stages of apoptosis on a cellular level. Both cell lines are successfully fluorescently labeled to undergo further drug challenge experiments. **Conclusions:** Our data strongly supports CPP-β18 as a potential drug therapy to augment checkpoint inhibitor efficacy and mitigate the development of resistance. Cell line validation demonstrates increased PI3K activity with deleted PTEN and decreased viability when challenged with PI3Kβ inhibitors. Selectively blocking PI3Kβ via CPP-β18 may augment checkpoint inhibitors and mitigate resistance, giving patients improved treatment options. Research Sponsor: None.

Phase I/II study of concurrent intrathecal toripalimab and pemetrexed (PM) for leptomeningeal metastases (LM) from solid tumors.

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Background: Intrathecal (IT) programmed death-1 (PD-1) inhibitors have demonstrated safety and feasibility in leptomeningeal metastases (LM) from melanoma or lung cancer. However, no studies have yet reported on the combination of IT PD-1 inhibitors with IT chemotherapy for LM from solid tumors. This study evaluated the feasibility and potential clinical benefit of combining IT toripalimab with pemetrexed (PM) in this patient population. **Methods:** Phase I followed a 3+3 dose de-escalation design to determine the dose-limiting toxicity (DLT) and the recommended phase II dose (RP2D). Patients received IT PM (15 mg flat dose) twice weekly for 2 weeks (induction), then weekly for 4 weeks (consolidation), followed by monthly maintenance. The administration of IT toripalimab (40 mg initial dose) was initiated concurrently with the fourth dose of IT PM, on an every-two-week schedule for 6 weeks (induction/consolidation), switching to monthly dosing during the maintenance phase. Continuation of previously administered systemic therapies was permitted during the study. The primary endpoints were RP2D and safety. Secondary endpoints included clinical response rate (CRR), disease control rate (DCR) and overall survival (OS). **Results:** From June 2024 to September 2025, 45 patients were enrolled (40 non-small cell lung cancer, 4 breast cancer, and 1 small cell lung cancer). Median age was 52 years (range 30–69), and 35 patients were female. In phase I, no DLTs were observed; the RP2D was established as toripalimab 40 mg plus PM 15 mg. All patients completed induction therapy, 42 completed consolidation therapy, and 41 received maintenance therapy. No treatment-related deaths occurred. All grade ≥3 adverse events (AEs) were attributable to IT PM, with an overall incidence of 55.6% (25/45), including leukopenia (n = 16), thrombocytopenia (n = 10), decreased hemoglobin (n = 7), and elevated hepatic aminotransferases (n = 5). Immune-related AEs were limited to grades 1-2, occurring in 24.4% (11/45) of patients, and included rash (n = 5), fever (n = 3), hypothyroidism (n = 3), and pneumonia (n = 1). According to Response Assessment in Neuro-Oncology (RANO) criteria, the CRR was 66.7% (30/45), including 11 patients with neurological dysfunction improvement, 16 with CSF cytological response, and 18 with neuroimaging improvement. The DCR was 93.3% (42/45). As of January 20, 2026, 19 patients had died. Median follow-up was 11.1 months (95% CI: 7.7–17.0). Median OS was 13.1 months (95% CI: 9.9–not applicable). **Conclusions:** IT toripalimab combined with PM showed a manageable safety profile and promising clinical activity in patients with LM from solid tumors. Based on the encouraging interim OS observed, further clinical investigation of intrathecal immunotherapy is warranted for patients with LM. Clinical trial information: NCT06462222. Research Sponsor: Huizhou Science and Technology Innovation Team Project; 2023EQ050012; Huizhou Outstanding Young Scientific and Technological Talents Program; 2025EQ050018.

Sequential or concurrent immunotherapy with locoregional radiotherapy in de novo metastatic nasopharyngeal carcinoma.

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Background: First-line chemotherapy combined with immunotherapy (CT-IO), followed by selective locoregional radiotherapy (LRRT), has emerged as the mainstay treatment for de novo metastatic nasopharyngeal carcinoma (dmNPC). However, the efficacy of adding concurrent immunotherapy to LRRT remains controversial. **Methods:** This study enrolled patients with dmNPC who received platinum-based chemotherapy, anti–PD-1 immunotherapy, and definitive LRRT. Survival outcomes were assessed using a 12-month landmark analysis to minimize immortal time bias. Inverse probability of treatment weighting (IPTW) was employed to balance baseline characteristics between the CCRT+IO (LRRT with concurrent immunotherapy) and CCRT-IO (LRRT without concurrent immunotherapy) groups. Recursive partitioning analysis (RPA) utilizing baseline and post-CT-IO factors was applied to stratify patients into low- or high-risk groups to evaluate the benefit of concurrent IO. Absolute lymphocyte count (ALC) was monitored during and up to 6 months post-LRRT. **Results:** A total of 238 patients were included (185 receiving concurrent IO and 53 without). In the IPTW-adjusted Kaplan-Meier analysis at the 12-month landmark, the addition of concurrent IO was associated with significantly inferior progression-free survival (PFS) (Hazard Ratio [HR]: 3.189; 95% CI, 1.352–7.524; p = 0.008). The "Sandwich" mode—comprising 4-6 cycles of induction CT-IO, followed by LRRT, and subsequent IO maintenance—yielded the optimal survival outcomes (HR: 0.288; 95% CI, 0.106–0.786; p = 0.015). An RPA model incorporating five prognostic factors (the number of metastatic lesions, pretreatment LDH level, post-CT-IO Epstein-Barr virus DNA, and radiological response post-CT-IO) stratified patients into two risk subgroups. Low-risk patients derived no clinical benefit from concurrent IO (p = 0.134), whereas high-risk patients exhibited significantly worse 12-month landmark adjusted PFS (p = 0.031). Notably, subgroup analysis showed that patients with persistent radiation-induced lymphocytopenia at 3 months post-RT demonstrated the most unfavorable survival outcomes after concurrent immunotherapy ($p < 0.001$). **Conclusions:** DmNPC patients receiving first-line CT-IO followed by LRRT did not benefit from concurrent immunotherapy during RT, particularly those identified as high-risk by the prognostic model and those with persistent lymphocytopenia at 3 months post-RT. Research Sponsor: None.

Efficacy and safety of cadonilimab in patients with MSI-H/dMMR locally advanced or metastatic gastrointestinal malignancies: A real-world retrospective study.

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Background: Immunotherapies targeting PD-1 and CTLA-4 have emerged as promising therapeutic strategies for gastrointestinal malignancies (GIM), particularly those dMMR or MSI-H phenotypes. Cadonilimab, a novel bispecific antibody co-targeting PD-1 and CTLA-4, has showed potent anti-tumor effect across multiple cancer types. This real-world retrospective study systematically evaluated the efficacy and safety of cadonilimab in patients with MSI-H/dMMR locally advanced or metastatic GIM. **Methods:** This study retrospectively included patients with MSI-H/dMMR unresectable locally advanced or metastatic GIM who administered cadonilimab(6 mg/kg Q2W) since November 2022 in The Affiliated Hospital of Qingdao University. The primary endpoint was ORR as assessed by investigators per RECIST v1.1. Secondary endpoints included DCR, PFS, DoR, safety profile, and exploratory biomarker analysis (interleukins [IL-2, IL-6, IL-8, IL-10]) was performed on blood samples collected at baseline and before each treatment cycle. **Results:** As of November 7, 2025, a total of 21 patients were enrolled. The median follow-up duration was 19.4 months. The ORR was 76.19% and DCR was 100%. Median PFS and median DoR were not reached. The 12-month PFS rate was 74.9% (95% CI, 49.6%-88.8%) and 18-month PFS rate was 68.1% (95% CI, 41.6%-84.5%). Among 14 gastric cancer (GC) patients, ORR was 78.57% (5 CR, 6 PR), median PFS was not reached, 12-month PFS rate was 77.9% (95% CI, 58.6%-100%), and 18-month PFS rate was 68.2% (95% CI, 46.3%-100%). The ORR of GC treated in 1^{st} line was 80%, 4 achieved CR (40%). Among 7 colorectal cancer (CRC) patients, ORR was 71.43% (2 CR, 3 PR), median PFS was not reached, 12-month PFS rate was 71.4% (95% CI, 49.6%-88.8%), and 18-month PFS rate was 71.4% (95% CI, 29.4%-91.9%); the ORR of 1^{st} line treatment was 83.33%. By metastatic site: ORR was 85.71% in patients with peritoneal metastasis and 100% in those with pelvic metastasis. Notably, one patient achieved pCR after cadonilimab conversion therapy, and another patient receiving cadonilimab as fourth-line monotherapy achieved PFS of 25.4 months. As of data cutoff, 5 patients remained on treatment. Regarding safety, 33.33% of patients experienced grade 1-2 immune-related adverse events (irAEs), and 4.76% had grade $\geq$3 irAEs. No treatment discontinuation due to adverse events. Exploratory biomarker analysis showed that ORR was 90.91% in patients with high IL-2 expression, 91.67%,92.86% and 81.82% in patients with normal IL-6, IL-8 and IL-10 levels, respectively. **Conclusions:** Cadonilimab demonstrates potent and durable anti-tumor activity with a favorable safety profile in MSI-H/dMMR locally advanced or metastatic GIM. Additionally, interleukins may serve as potential predictive biomarkers for cadonilimab efficacy, providing insights for precision medicine in this patient population. Research Sponsor: None.

Intrathecal (IT) PD-1/CTLA-4 antibody combined with pemetrexed (PM) for leptomeningeal metastases (LM) from solid tumors: Preliminary results of two single-center phase I studies.

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Background: IT PD-1 inhibitors, alone or combined with IT PM, have shown safety and feasibility in LM from solid tumors. Cadonilimab (AK104) and iparomlimab/tuvonralimab (QL1706) are novel bispecific PD-1/CTLA-4 antibody. Our preclinical animal studies demonstrated the safety of IT administration of these agents. This study evaluated the feasibility and potential clinical benefit of combing IT PD-1/CTLA-4 antibody with PM in patients with LM from solid tumors. **Methods:** Eligible patients had histologically confirmed solid tumors and positive CSF cytology. A rapid dose-escalation design was employed across three dose levels: AK104 at 15.625 mg, 31.25 mg and 62.5 mg; QL1706 at 25 mg, 37.5 mg and 50 mg. One patient was enrolled in each of the first two dose cohorts, while six were enrolled at the third dose cohort. The protocol would revert to a standard 3+3 design if any dose-limiting toxicities (DLT) occurred. IT PM was given at a fixed dose of 15 mg twice weekly for two weeks (induction), then weekly for four weeks (consolidation), followed by monthly maintenance until progression or death. IT PD-1/CTLA-4 antibody began at the fourth IT PM dose, administered every two weeks for six weeks, then monthly until progression or death. Continuation of previously administered systemic therapies was permitted during the study. **Results:** A total of 17 patients were enrolled (AK104: n=8; QL1706: n=9). Median age was 54 years (range 37–73); 13 were female. Primary tumors included lung adenocarcinoma (n=13) and breast cancer (n=4). 16 patients (94.1%) completed induction and consolidation therapy. No DLT occurred. Grade ≥3 adverse events (AEs) occurred in 64.7% (11/17) of patients. Specifically, grade ≥3 AEs attributed to IT PM were observed in 58.8% (10/17), primarily hematological toxicity (n=10), elevated hepatic aminotransferase (n=1) and fatigue (n=1). For IT PD-1/CTLA-4 antibody-related AEs, grade ≥3 occurred in 11.8% (2/17; rash n=1, diarrhea n=1), and grade 1-2 in 17.6% (3/17; rash n=3, fever n=1, diarrhea n=1). Clinical response rate was 41.2% (7/17) by RANO-LM criteria. Disease control rate was 82.4% (14/17). As of January 15, 2026, 8 patients had died, with 1 due to LM, 3 due to systemic progressive disease, and 4 due to non-cancer-related causes. Median follow-up time was 8.53 months (95%CI: 8.07-NA), and median overall survival was 8.53 months (95%CI: 6.3-NA). **Conclusions:** The study demonstrates the manageable safety and feasibility of IT PD-1/CTLA-4 antibody combined with PM, with no unexpected systemic or neurological toxicities observed. Preliminary results suggest potential clinical benefits, with a high clinical response rate and notable treatment responses even among those with severe conditions. ClinicalTrials.gov registration: NCT06762080/NCT06809530. Clinical trial information: NCT06809517/NCT06809530. Research Sponsor: Huizhou Science and Technology Innovation Team Project; 2023EQ050012; Huizhou Outstanding Young Scientific and Technological Talents Program; 2025EQ050018.

Evaluation of intravenous IPI201 in combination with anti–PD-1 therapy in a colorectal cancer mouse model.

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Background: Immune checkpoint inhibitors targeting PD-1 improve outcomes in colorectal cancer (CRC) but are limited by intrinsic and acquired resistance. Resorcinyl isoprenyl benzene derivatives have previously shown anti-tumor activity in multiple models, including remodeling of the tumor microenvironment (TME). IPI201 is a novel, synthetic resorcinyl isoprenyl benzene derivative administered intravenously. Here, we evaluated whether IPI201 combined with anti-PD-1 therapy alters tumor and immune outcomes in a murine model of CRC. **Methods:** MC38 colon tumors were implanted subcutaneously in mice and treated with vehicle, IPI201 (i.v.), anti-PD-1 (BE0156; i.p.), 5-fluorouracil (5-FU) (i.p.), or IPI201 plus anti-PD-1 at varying dose combinations once the implanted tumor reached a size of 75 mm^3. Change in tumor volume and subject survival were assessed over 30 days. Tumor necrosis was evaluated by blinded histopathology. Tumor gene expression was analyzed using NanoString nCounter immune-focused panels with pathway and network analyses comparing combination therapy to monotherapies and vehicle controls. **Results:** While IPI201 or anti-PD-1 monotherapy demonstrated limited activity, combination treatment produced enhanced anti-tumor effects. The optimal dose combination resulted in a 66% reduction in tumor growth compared with anti-PD-1 alone, with a significant treatment interaction (P=0.03). Combination therapy significantly improved survival relative to monotherapies and 5-FU (50% vs 0%, adjusted $P<0.02$), yielding the highest survival among treatment groups. Tumor necrosis scores were increased with combination therapy, with necrosis twofold higher than anti-PD-1 alone ($P<0.01$). Transcriptomic profiling revealed differential regulation of 771 genes across 51 biological pathways, including VEGF, EGFR, MAPK/ERK, and PI3K/Akt/mTOR signaling, as well as immune-associated pathways related to antigen presentation, cytotoxic lymphocyte activation, and myeloid cell recruitment. This transcriptional signature is consistent with a pro-immune, anti-tumor TME. **Conclusions:** IPI201 and PD-1 blockade combination improves survival, promotes tumor necrosis, and remodels the tumor microenvironment in a preclinical CRC model. These findings support further development of IPI201 as a combination immunotherapy strategy and provide a mechanistic rationale for evaluating resorcinyl isoprenyl benzene-based enhancers of checkpoint inhibition in CRC. Research Sponsor: None.

Phase I/II study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in combination with LB4330, a long-acting IL-10, in patients with advanced solid tumors.

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Background: LB1410 is an anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Bio Co., Ltd., Shanghai, China. In an ongoing phase I study in patients (pts) with advanced solid tumors (NCT05357651), LB1410 demonstrated an excellent safety profile (RPIID 20 mg/kg) and promising efficacy in various anti-PD-1-resistant solid tumors: ORR 9.1%; DCR 54.5%; n = 66 as of Jan 4, 2026. Antitumor activity was especially notable in anti-PD-1-resistant ccRCC (ORR 11.1%; DCR 77.8%; n = 9) and anti-PD-1-resistant CC (ORR 38.5%; DCR 69.2%; n = 13). LB4330 is a novel, long-acting IL-10 developed by L&L Bio Co., Ltd., Shanghai, China. It is generated by fusing IL-10 to a high-affinity anti-CLDN18.2 antibody and exhibits a significantly extended $T_{1/2}$ of 2.3 days. In a completed phase I study (NCT05707676), LB4330 effectively enhanced CD8+ T cell proliferation and activation in cancer pts and achieved a DCR of 36.4% (12/33) in pts with PDAC, CRC and other anti-PD-1-resistant tumors. Given their complementary mechanisms and potential to better enhance antitumor immune activity, a phase I/II study has been launched to evaluate LB1410 in combination with LB4330 in pts with advanced solid tumors. **Methods:** Eligible pts were ≥18 yrs old with ECOG PS 0-1. Pts received LB1410 at 15 or 20 mg/kg in combination with LB4330 at 0.2-0.4 mg/kg IV Q2W, with a maximum of 6 doses of LB4330. A 3+3 dose-escalation design was used to assess safety and tolerability. The selected doses of LB1410 at 15 or 20 m/kg plus LB4330 at 0.4 mg/kg were used for the efficacy expansion study in pts with anti-PD-1-resistant ccRCC and HCC. **Results:** As of Jan 14, 2026, 15 patients (1 CRC, 1 HCC, 3 NSCLC, 4 CC and 6 ccRCC) had been enrolled: median age 58.5 yrs (42-71 yrs); 57.1% male; 85.7% with prior anti-PD(L)1-based therapies. TRAEs occurred in 13 pts (92.9%), the most common (≥ 20%) being fever, platelet count decreased, pruritus, elevated ALT, elevated AST, elevated creatinine, cough, rash and anemia. Most TRAEs were related to the MOA of LB4330 and were manageable. Grade 3-4 TRAEs occurred in 5 pts (35.7%), including decreased platelet count in 2 pts and IRR, shock symptom and immune-mediated myocarditis in 1 pt each. No DLTs were observed. Among all pts with on-treatment scans, the overall ORR per RECIST 1.1 was 15.4% (2/13) with 2 confirmed PR ; DCR was 30.8% (4/13). Notably, the 5 pts with anti-PD-(L)1-refractory favorable-risk ccRCC showed an ORR of 40.0% and a DCR of 80.0%. 50% ccRCC pts with PR/SD (2/4) had been on treatment for nearly one year or longer. **Conclusions:** The combination of LB1410 and LB4330 exhibited a manageable safety profile consistent with that observed with each monotherapy. Clinical data in pts with favorable-risk ccRCC support the characteristics and efficacy of LB4330 as an immune-enhancing agent. Efficacy expansion studies are ongoing. Clinical trial information: NCT06468358. Research Sponsor: L&L Bio Co., Ltd., Shanghai, China.

Low-dose intestinal irradiation to enhance the efficacy and prognosis of PD-1 blockade in metastatic non-small cell lung cancer.

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Background: Intestinal low-dose irradiation (ILDR) has been shown to enhance the efficacy of immunotherapy in advanced solid tumors by modulating the gut microbiota and metabolism. However, its role in metastatic non-small cell lung cancer (mNSCLC), particularly in the first-line treatment setting, remains unclear. Therefore, this study investigated the impact of intestinal radiation dose on the efficacy and prognosis of programmed cell death protein 1 (PD-1) blockade in patients with mNSCLC. **Methods:** This multicenter retrospective and prospective study included patients with mNSCLC who received first- or second-line PD-1 inhibitors combined with abdominopelvic radiotherapy between 2018 and 2025. Patients were stratified into three groups according to the mean intestinal radiation dose: <1 Gy, 1–3 Gy, and >3 Gy, and treatment outcomes were compared among groups. In addition, blood and fecal samples prospectively collected were subjected to multi-omics analyses. **Results:** A total of 301 patients were included in the retrospective analysis, among whom 105 patients (34.9%) had a small intestinal mean radiation dose (SIMRD) <1 Gy, and 84 patients (27.9%) had a SIMRD of 1–3 Gy. Overall, 183 patients (60.8%) received first-line PD-1 blockade, and 118 patients (39.2%) received second-line treatment. The median follow-up time was 27.2 months. The results showed that patients with a SIMRD of 1–3 Gy achieved the highest objective response rate (21.0% vs. 48.8% vs. 6.3%). Compared with the <1 Gy and >3 Gy groups, the 1–3 Gy group also demonstrated significantly prolonged progression-free survival (PFS, 10.2 months) and overall survival (OS, 23.7 months) ($P < 0.01$), with consistent findings across all subgroup analyses. Compared with the 1–3 Gy group, SIMRD >3 Gy (HR = 4.96, $P < 0.001$) and SIMRD <1 Gy (HR = 1.90, $P < 0.001$) were both independent predictors of worse OS. Thirty patients who recevied first-line PD-1 inhibitors combined with abdominopelvic radiotherapy were included in the prospective analyses. With a median follow-up of 17.5 months, patients with a SIMRD of 1–3 Gy achieved the best disease control rate (1-3 Gy vs. <1 Gy vs. >3 Gy: 90.0% vs. 63.7% vs. 33.3%; P = 0.041) and the longest median PFS (1-3 Gy vs. <1 Gy vs. >3 Gy: not reached vs. 9.3 months vs. 5.8 months; P = 0.120). Multi-omics analyses revealed that responders were enriched in *Bacillota*, *Clostridia*, and indole-derived metabolites, particularly indole-3-carboxylic acid. Moreover, patients in the 1–3 Gy group exhibited increased circulating macrophage inflammatory protein-3α levels and a reduced proportion of $\alpha4\beta7^{+}$ regulatory T cells. **Conclusions:** ILDR influences the efficacy of PD-1 inhibitor therapy in patients with mNSCLC, with the most pronounced benefit observed when SIMRD is maintained within the 1–3 Gy range. This effect may be mediated through modulation of the gut microbiota–metabolite–immune axis. Research Sponsor: National Natural Science Foundation of China; 82573453; National Natural Science Foundation of China; 82403791; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2024ZD0525902; Natural Science Foundation of Shandong Province; ZR2024QH459; CSCO-Nav HER2-related Solid Tumors Research Foundation; Y-2022HER2AZMS-0291; Collaborative Academic Innovation Project of Shandong Cancer Hospital; ZF001; Project supported by ShanDong Provincial Medical Association; YXH2025YS042; Shan-dong Province University "Youth Innovation Team Program"; 2024KJJ027.

Personalized N-of-1 combinations based on molecular profiles in advanced malignancies: Immunotherapy group analysis of the I-PREDICT N-of-1 precision oncology study.

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Background: While current precision oncology typically targets a single biomarker, most cancers have multiple pathogenic alterations that often differ from patient to patient. We evaluated whether individualized, N-of-1 biomarker-based combinations that included immune checkpoint inhibitors (ICIs) would improve outcomes in patients (pts) with advanced cancers. **Methods:** In the I-PREDICT prospective trial (NCT02534675), 70 pts with advanced poor-prognosis cancers received ICI-based regimens. Personalized combinations were based on tissue/ctDNA next-generation sequencing (NGS) and Molecular Tumor Board review. An "i-Matching Score" was developed using TMB ≥16 mut/Mb—selected because analysis showed it was a more robust outcome predictor than TMB ≥10 or continuous TMB (though both correlated with some outcome parameters)—alongside scores reflecting the matching of other targeted therapies (TT) to tumor alterations. Regimens used individualized dose reductions and intra-patient dose titration for safety. **Results:** Tumors harbored a median of five pathogenic alterations (range, 1–18); 97% of pts had unique molecular profiles. To optimize biomarker-matching, pts received 48 distinct therapy regimens, many previously unstudied; for the first-in-human (FIH) combinations, initial doses were lowered, and intra-patient dose modifications were made for tolerance. Regimens included ICI monotherapy (20%), ICI + TT (61%), and others. Mean initial dose was 79.5% of the FDA-approved dose; 26% of pts had dose adjustments (6% increase; 20% decrease). Initial doses were lower for multi-drug regimens (P=0.002), ICI+TT (P<0.001), and FIH regimens (P=0.005) vs. established regimens. Grade ≥3 treatment-related serious adverse events (SAEs) occurred in 14% of 70 pts; notably, the SAE rate for ICI monotherapy (established safety profile) was 15%, and no combination subgroup significantly exceeded this rate. FIH regimens and high i-Matching groups (>50% vs. ≤50%) trended towards fewer SAEs (P=0.06/0.08). TMB ≥16 independently predicted improved disease control rate (DCR; SD ≥6mo/PR/CR), PFS, and OS (P=0.006/0.001/0.016); i-Matching Score >50% vs. ≤50% significantly correlated with higher DCR (74% vs 27%, P<0.001), longer PFS (10.4 vs 3.8 mo, P<0.001) and OS (19.1 vs 9.1 mo, P=0.016). In pts receiving ICI+TT (n=51), the i-Matching Score outperformed TMB as an outcome predictor. **Conclusions:** Individualized, N-of-1 ICI-based combinations, molecularly matched to complex genomic profiles, can be safely given with initial dose reduction and intra-patient dose modification. Higher TMB and higher degrees of biomarker matching (i-Matching Score) correlated with improved outcomes, with the latter performing best in pts receiving ICI+TT combinations. This molecularly guided multi-agent therapy paradigm warrants further study. Clinical trial information: NCT02534675. Research Sponsor: U.S. National Institutes of Health; 5UG1CA233198-05; U.S. National Institutes of Health; 5U01CA180888-08.

Phase 1 dose escalation of CTX-8371, a novel PD-1×PD-L1 bispecific antibody, in patients with advanced malignancies post checkpoint inhibition.

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Background: CTX-8371 is a novel bispecific antibody targeting both programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). In addition to potent PD-1 and PD-L1 blockade, CTX-8371 uniquely enables CD80-CD28 engagement and facilitates the cleavage of PD-1 from the surface of activated T-cells. Preclinically, CTX-8371 exhibited greater potency than singular blockade with either anti-PD1 or anti-PD-L1 alone. **Methods:** In this first-in-human study (NCT06150664) with a 3+3 dose-escalation design, patients (pts) with metastatic melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma (HL), and triple-negative breast cancer (TNBC) in whom standard treatments including prior immune checkpoint inhibitors (ICI) had failed, were eligible. CTX-8371 was administered intravenously every two weeks at 5 dose levels ranging from 0.1 to 10.0 mg/kg. The primary objectives were to evaluate the safety and tolerability of CTX-8371 and determine doses to be evaluated in expansion. Secondary objectives included assessment of anti-tumor activity, pharmacokinetics, pharmacodynamics, and immunogenicity of CTX-8371. **Results:** Between 15 Apr 2024 and 12 Aug 2025, 17 pts were enrolled; 15 pts completed the dose-limiting toxicity (DLT) period and had post-baseline imaging: NSCLC n=7, melanoma n=3, HNSCC n=2, TNBC n=2, HL n=1. All 15 pts had received a minimum of 2 prior therapies including checkpoint inhibitors. Median duration on study was 9.8 months; CTX-8371 treatment is ongoing in 3 pts. CTX-8371 was well tolerated with no DLTs. The maximum tolerated dose (MTD) was not reached. All treatment-related adverse events (AEs) were Grade 1/2, except one Grade 3 AE of asymptomatic lipase increase which resulted in the only dose interruption. There were no dose reductions. Dose-dependent increases in CTX-8371 serum concentrations (AUC and Cmax) were observed. In the 15 pts with post-baseline imaging, the overall response rate (ORR) was 20% (one pt each with NSCLC [irPR], TNBC and HL) and the disease control rate (DCR) was 60%. The responses were 2.3 months NSCLC; 6.4+ months TNBC; 3.6+ months HL with greater depth and longer durability at the recommended doses for further study ($\geq$ 3 mg/kg). The two ongoing responders are in pts treated at 3 mg/kg (TNBC: $>$90% reduction in overall tumor volume) and 10 mg/kg (HL: metabolic partial response). **Conclusions:** CTX-8371, a novel bispecific antibody targeting both PD-1 and PD-L1, was well tolerated and demonstrated promising clinical activity as a monotherapy in advanced pts resistant to prior ICI. Dose expansion in pts with NSCLC and TNBC in 2 dosing cohorts (3 and 10 mg/kg) is underway. Future development in treatment refractory HL is planned. Clinical trial information: NCT06150664. Research Sponsor: Compass Therapeutics.

Clinical efficacy of tislelizumab in combination with gemcitabine and nab-paclitaxel and chemoresistance analysis in borderline resectable pancreatic cancer: A prospective pilot study.

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Background: Neoadjuvant therapy has been demonstrated to improve the survival outcomes of patients with borderline resectable pancreatic cancer (BRPC). While neoadjuvant therapy is increasingly utilized, exploring novel combination strategies, such as immunotherapy plus chemotherapy, is essential to further enhance surgical resectability and survival outcomes. This study investigated the clinical feasibility of tislelizumab in combination with gemcitabine and nab-paclitaxel for BRPC in a neoadjuvant setting. **Methods:** In this prospective study, patients diagnosed with BRPC were enrolled. Preoperatively, intravenous injection of tislelizumab (200 mg per time, Q3W) was used for 3 cycles, in combination with gemcitabine (1 000 mg/m^2, d1, d8) and nab-paclitaxel (125 mg/m^2, d1, d8). Postoperatively, this regimen continued to be used. The primary endpoints were the margin-negative (R0) resection rate and treatment-related adverse events (TRAEs). Exploratory objectives were resistance to this neoadjuvant regimen. **Results:** Totally 30 patients were enrolled in this study, among whom 80.0% (24/30) completed neoadjuvant therapy and underwent surgical resection. R0 resection was achieved in 80.0% of the patients (24/30) and in 100.00% of the patients with surgical resection (24/24). Most patients experienced grade I-II TRAEs, and no serious TRAEs occurred. Through the quantitative proteomics and machine learning algorithms for differentially expressed proteins, NT5DC2, FAM3D, CXCL5 and TMT1B were identified to play crucial roles in resistance to the neoadjuvant regimen in pancreatic cancer. **Conclusions:** Neoadjuvant therapy with tislelizumab plus gemcitabine and nab-paclitaxel demonstrated clinical feasibility and encouraging antitumor activity in BRPC patients, with a favorable safety profile. NT5DC2, FAM3D, CXCL5 and TMT1B may be the biomarkers for preoperative drug resistance in pancreatic cancer. Clinical trial information: ChiCTR2200063680. Clinical trial information: ChiCTR2200063680. Research Sponsor: None.

A phase 2 study of fruquintinib combined with sintilimab and chidamide in refractory MSS metastatic colorectal cancer: Preliminary efficacy and safety.

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Background: Microsatellite stable (MSS) metastatic colorectal cancer (mCRC) has limited response to immune checkpoint inhibitors. Preliminary evidence from preclinical studies and the CAPability-01 trial suggest that combining anti-angiogenic therapy with epigenetic drugs such as histone deacetylase inhibitors can favorably remodel the tumor immune microenvironment and enhance the efficacy of PD-1 immune checkpoint blockade for advanced MSS-type mCRC. This study evaluates the efficacy and safety of the triple combination of fruquintinib, sintilimab, and chidamidein patients with refractory MSS mCRC. **Methods:** This is a single-arm, open-label phase 2 study. Eligible patients had histologically confirmed MSS-type mCRC, disease progression after ≥2 prior lines of therapy, ≥1 measurable lesion (RECIST v1.1), and ECOG 0–1. Patients received fruquintinib (5 mg orally on days 1–14, Q3w), sintilimab (200 mg IV on day 1, Q3w), and chidamide (30 mg orally twice weekly). The primary endpoint was mPFS. Secondary endpoints included ORR, DCR, mOS, DOR and safety. Tumor assessments were performed every 9 weeks. With a statistical hypothesis of improving the median PFS from 3.7 (historical control) to 6.0 m, a sample size of 46 patients was planned. **Results:** From January to December 2025, a total of 9 patients were enrolled. The median age was 60.0 years (39–72). All patients had MSS-type tumors, with a median of 2 prior lines of therapy (range: 2–4). Preliminary efficacy analysis showed that 4 patients achieved PR and 2 achieved SD, resulting in an ORR rate of 44.4% and a DCR rate of 66.7%. Given the limited sample size and relatively short follow-up of 9.1m at this preliminary analysis, mPFS and mOS were not yet reached. Treatment was generally tolerable. TRAEs of any grade occurred in all 9 patients. The most common TRAEs included hematological toxicities such as thrombocytopenia (66.7%), neutropenia (44.4%), and leukopenia (33.3%); hepatic laboratory abnormalities including elevated ALT 33.3%), and elevated AST (33.3%); as well as proteinuria (66.7%), hyperlipidemia (55.6%), increased blood creatine kinase (55.6%), and fatigue (1/9 with Grade 3). Grade ≥3 TRAEs were observed in 5 patients (55.6%), including Grade 3 neutropenia (2 patients), fatigue (1 patient), cutaneous adverse reactions (1 patient), and cholecystitis (1 patient). No treatment-related deaths occurred. **Conclusions:** Preliminary results indicate that the triple therapy of fruquintinib, sintilimab, and chidamide demonstrates promising response rate, disease control and a manageable safety profile in patients with refractory MSS-type mCRC. This combination strategy represents a potential therapeutic option for this population, who currently have limited treatments available. Further follow-up with a larger sample size and longer duration is needed to confirm its survival benefit. Clinical trial information: NCT06979908. Research Sponsor: None.

A phase II study to evaluate the safety and efficacy of BB-1701 in combination with sintilimab in patients with HER2 expression or mutation in locally advanced/ metastatic breast cancer or NSCLC.

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Background: BB-1701, a HER2-targeting antibody-drug conjugate (ADC) containing eribulin, has demonstrated promising antitumor activity in the clinical studies in breast cancer (BC) patients with HER2 low expression and non-small cell lung cancer (NSCLC) patients with HER2 mutation. Currently, there are no approved treatment options of ADC in combination with anti-PD-1 antibody for metastatic BC patients with HER2 low expression and NSCLC patients with HER2 mutation. We report the preliminary efficacy and safety results from the ongoing phase 2 study (including dose escalation and dose expansion) of BB-1701 in combination with Sintilimab (an anti-PD-1 antibody) in advanced or metastatic BC patients with HER2 low expression and NSCLC patients with HER2 mutation. **Methods:** Patients enrolled were ≥18 years of age; had confirmed locally advanced/metastatic HER2 low-expressing BC or HER2 mutated NSCLC, an ECOG PS <2 and measurable lesion(s) (per RECIST v1.1); and disease progression after ≥1 lines of prior standard therapies. HER2 expression was confirmed by IHC or NGS/PCR before patient enrollment. BB-1701 was administered at 1.2 mg/kg Q3W or 1.6 mg/kg Q3W, and sintilimab is administered at 200 mg Q3W. **Results:** As of 26 January 2026, a total of 12 patients with HER2 low-expressing BC or HER2 mutated NSCLC have been enrolled and treated, 6 patients at each dose level of BB-1701 during dose escalation. Median age is 63 years, 91.7%/8.3% patients were female/male, and 16.7%/83.3% patients have ECOG PS 0/1. The median number of prior systemic therapy lines was 2.0/1.0 for BC and NSCLC. All patients experienced at least one treatment-emergent adverse events (TEAEs). The most common (≥20%) reported all grade TEAEs are alanine aminotransferase increased, aspartate aminotransferase increased, γ-glutamyltransferase increased, hypercholesterolemia, peripheral neuropathy, anemia and Urinary tract infection. Three grade 3 TEAEs are γ-glutamyltransferase increased, pneumonia and open globe injury. There has been no grade 4 or grade 5 events as of data cut-off date. One treatment emergent serious adverse event is open globe injury. All patients were evaluable for efficacy. Among 5 BC patients, 4 patients achieved partial response (PR) with disease control rate (DCR) of 80.0%. Among 7 NSCLC patients, 2 patients achieved PR and 2 patients had stable disease (SD) with DCR of 57.1%. Details of data will be presented at the ASCO meeting. **Conclusions:** BB-1701 in combination with Sintilimab shows encouraging antitumor activity and a manageable safety profile in HER2 low-expressing BC patients and HER2 mutated NSCLC patients. The further dose expansion study is guaranteed based on the preliminary data from dose escalation study. Clinical trial information: CTR20241422. Research Sponsor: None.

Outcomes of patients with rare cancers treated with combination immune checkpoint inhibitors with and without lung and/or liver metastases (NCI/SWOG S1609).

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Background: Limited prior retrospective data, primarily among patients with lung cancer, liver cancer, and melanoma, has indicated that liver metastases are associated with poorer outcomes with chemotherapy, targeted agents, and checkpoint inhibitor therapy. We used a unique clinical trial resource to evaluate whether liver and/or lung metastases were associated with outcomes among patients with rare tumors treated with combination anti-PD-1 and anti-CTLA-4 therapy. **Methods:** The basket trial, SWOG trial S1609 (NCT02834013, DART trial), treated 655 eligible patients without lung or liver primary cancers. Associations with progression-free and overall survival were evaluated with Cox regression models; multivariable models controlled for age at trial registration, sex, performance status, race, ethnicity, primary tumor organ. Associations with clinical benefit rate (confirmed complete and partial response or stable disease for six months or longer) and treatment-related adverse events were evaluated using Fisher's exact test. **Results:** There was no significant difference in rates of grade 3 or higher treatment-related adverse events across the groups. Participants with liver metastases, with or without lung metastases, had a lower likelihood of experiencing clinical benefit (11% and 18%, respectively) compared to participants with lung but not liver metastases or participants with neither lung nor liver metastases (26% and 30%, respectively, p=0.003). On multivariable analysis, both lung and liver metastases were associated with shorter progression-free and overall survival compared to presence of neither liver nor lung metastases. **Conclusions:** In a diverse cohort of participants with advanced rare tumors treated with combination anti-CTLA-4 and anti-PD-1 therapy, we found that both lung and liver metastases were associated with shorter progression-free and overall survival. Research Sponsor: US National Cancer Institute; U10CA180888 and U10CA180819.

Multivariable Cox regression models for progression-free survival and overall survival.

Covariate	Progression-free survival	Overall survival
Lung but not liver metastases (N=175) (reference = neither liver nor lung, N=269)	1.40 (1.13-1.72) **0.0019**	1.24 (1.00-1.55) 0.053
Liver but not lung metastases N=154) (reference = neither liver nor lung, N=269)	1.73 (1.38-2.17) **<0.001**	1.33 (1.05-1.68) **0.017**
Liver and lung metastases N=57) (reference = neither liver nor lung, N=269)	1.96 (1.44-2.65) **<0.001**	1.91 (1.40-2.61) **<0.001**
Liver but not lung metastases N=154) (reference = lung but not liver, N=175)	1.24 (0.96-1.60) 0.095	1.07 (0.83-1.38) 0.62
Liver and lung metastases N=57) (reference = lung but not liver, N=175)	1.40 (1.02-1.92) **0.037**	1.54 (1.11-2.12) **0.009**
Liver and lung metastases N=57) (reference = liver but not lung, N=154)	1.13 (0.83-1.55) 0.45	1.44 (1.04-1.99) **0.030**

Hazard ratio (95% confidence interval) p-value reported.

Prior CTLA-4 blockade as associated with a hyperactive immunosuppressive signature and limited response to subsequent immunotherapy in melanoma.

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Background: Checkpoint blockade achieves durable long term responses in about 30-50% of patients with malignant melanoma (MM). However, a substantial proportion of patients either fail to respond or develop resistance after initial response. As a result, many MM patients undergo multiple sequential immunotherapeutic treatments in an attempt to achieve clinical benefit. However, the effects of repeated rounds of immunotherapy on the immune system remain poorly understood. We herein report that prior anti-CTLA-4 blockade within 12 months of analysis associated with a hyperactive immunosuppressive immune signature involving IL-6, in 24 patients with anti-PD-1 refractory metastatic MM enrolled in a Phase I/II trial. **Methods:** The patients received continued checkpoint inhibition with an anti-PD-L1 antibody in combination with an immunostimulatory gene therapy based on replication-competent adenovirus targeting the CD40 and 4-1BB pathways (LOKON003, NCT04123470). Using unsupervised clustering, plasma biomarker profiles at baseline and post treatment initiation was evaluated and correlated to clinical parameters. **Results:** Two plasma protein profiles were identified at baseline among enrolled patients and one of those included immunosuppressive biomarkers. While patients with this hyperactive immunosuppressive signature (n=8) at baseline experienced a median overall survival (mOS) of 4.0 months, patients without this baseline signature (n=15) had a mOS of 28.1 months. The hyperactive immunosuppressive signature was not related to M1 status, sex, age, or number of prior treatments, but prior anti-CTLA-4 treatment within a year of enrollment was more prevalent in patients with this signature. If dividing the patients only based on receiving anti-CTLA-4 therapy within 12 months (n=10) versus later or not at all (n=14), mOS was 5.3 and 30.7 months, respectively. Patients that had received recent anti-CTLA-4 treatment, presented with a plasma protein signature resembling the hyperactive immunosuppressive signature with IL-6 as a central node among the upregulated proteins. Patients who did not receive anti-CTLA-4 blockade during the past 12 months responded to the combination of the immunostimulatory gene therapy and continued checkpoint blockade with upregulation of biomarkers associated with T cell activation and cell killing capacity, which may have supported the better survival outcome in this patient group. **Conclusions:** The findings highlight the need for further clinical evaluation of the consequences of repeated immunotherapeutic treatments, IL-6 inhibition in this population, and consideration for a wash-out period from further immunotherapy to allow for immune system recovery post anti-CTLA-4 treatment. Clinical trial information: NCT04123470. Research Sponsor: The Swedish Cancer Society; The Swedish Research Council; Lokon Pharma.

Phase IIa study of tosposertib, a dual TGFβRI and VEGFR2 inhibitor, in combination with pembrolizumab in recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

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Background: Tosposertib (TU2218) is a highly potent dual inhibitor of the transforming growth factor-β type I receptor (TGFβRI/ALK5) and vascular endothelial growth factor receptor 2 (VEGFR2), designed to simultaneously target immunosuppressive tumor microenvironment signaling and angiogenesis. This open-label, multicenter, non-randomized phase IIa trial evaluated the efficacy and safety of tosposertib in combination with pembrolizumab in patients with R/M HNSCC (NCT05784688). **Methods:** Eligible patients included anti–PD-(L)1–naïve patients with PD-L1 combined positive score (CPS) ≥1. Tosposertib (97.5 mg twice daily; 2 weeks on/1 week off) was administered orally in combination with pembrolizumab (200 mg intravenously every 3 weeks). **Results:** As of December 31, 2025, 29 patients (median age, 61 years; 76% male) had been enrolled, with a median follow-up duration of 6.0 months (range, 8–401 days). Primary tumor sites included the oral cavity (n=11, 37.9%), oropharynx (n=6, 20.7%), larynx (n=3, 10.3%), and nasal/paranasal regions (n=3, 10.3%). HPV positivity was observed in 13.8% (4/29) of patients. Among 26 efficacy-evaluable patients, responses were assessed by treatment line. In the first-line setting, 9 of 12 patients achieved an objective response (ORR, 75.0%), including 1 confirmed complete response (CR) and 8 partial responses (PRs; 6 confirmed, 2 unconfirmed). Among the 14 patients who had received at least one prior systemic therapy, the ORR was 42.9%, with 1 confirmed CR and 5 confirmed PRs. A numerically higher ORR was observed in patients with PD-L1 CPS ≥20 compared with those with CPS 1–10 (66.7% vs 52.9%). The most frequent any-grade treatment-emergent adverse events (TEAEs), (≥20%) [and ≥ Gr3 TEAEs], were rash (48.3% [20.7%]), mucosal inflammation (34.5% [13.8%]), pruritus (27.6% [3.4%]), weight loss (27.6% [0%]), and elevations in aspartate aminotransferase (AST; 20.7% [3.4%]) or alanine aminotransferase (ALT; 20.7% [3.4%]). Discontinuations due to TEAEs occurred in three patients. No treatment-related deaths were reported. **Conclusions:** Tosposertib in combination with pembrolizumab demonstrated a manageable safety profile and encouraging antitumor activity in patients with R/M HNSCC, with particularly robust efficacy observed in the first-line setting and a favorable trend in PD-L1–high tumors. Clinical trial information: NCT05784688. Research Sponsor: TiumBio Co., Ltd.

Best overall response by subgroups.

Best Overall	ALL (n=26)	Prior lines of therapy	Prior lines of therapy	PD-L1status, n (%)	PD-L1status, n (%)
Response, n (%)		None (n=12)	≥1 (n=14)	CPS 1-19 (n=17)	CPS ≥20 (n=9)
Complete Response	2 (7.7)	1 (8.3)	1 (7.1)	1 (5.9)	1 (11.1)
Partial Response	13 (50.0)	8 (66.7)	5 (35.7)	8 (47.1)	5 (55.6)
Stable Disease	5 (19.2)	2 (16.7)	3 (21.4)	3 (17.6)	2 (22.2)
Progressive Disease	6 (23.1)	1 (8.3)	5 (35.7)	5 (29.4)	1 (11.1)
Response Rate (%)	57.7	75.0	42.9	52.9	66.7

Association of mRNA COVID-19 vaccination near immune checkpoint inhibitor initiation with outcomes: A real-world analysis.

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Background: Prior study showed mRNA COVID-19 vaccines can activate innate and adaptive immune pathways and have been hypothesized to "prime" anti-tumor immunity via increased tumor PD-L1 expression when administered near immune checkpoint inhibitor (ICI) initiation. We performed a real-world validation to evaluate the association between COVID-19 vaccination around ICI initiation and outcomes among patients with 4 advanced/metastatic solid tumors. **Methods:** Using ConcertAI Patient360 (US-based, de-identified, human-abstracted oncology EHR linked to medical/pharmacy claims and third-party mortality), we identified adults (≥18 years at diagnosis) with advanced/metastatic bladder cancer, melanoma, non-small cell lung cancer (NSCLC), or renal cell carcinoma (RCC) who initiated an ICI between Jan 2021 and Mar 2024. Exposure was receipt of ≥1 mRNA COVID-19 vaccine within 100 days of ICI initiation. Exposed patients were propensity score–matched 1:1 to unexposed patients on demographics (age, sex, race, ethnicity) and clinical factors (baseline steroid use, ICI initiation year, Charlson Comorbidity Index, ECOG performance status, BMI, and tumor type). Real-world OS (rwOS) and real-world PFS (rwPFS) were estimated by Kaplan-Meier; hazard ratios (HRs) were estimated using univariate Cox models (post-match) and multivariable Cox models (residual confounding sensitivity), overall and by tumor type. **Results:** Among 7085 eligible patients, 1,513 were vaccinated around ICI initiation. After matching, 3,018 patients (1,509 per group) had evaluable time-to-event data and were included in Kaplan-Meier and Cox analyses (tumor mix: NSCLC 73.6%, RCC 11.7%, bladder 8.5%, melanoma 6.3%). Overall, vaccination was associated with improved rwOS and rwPFS: median rwOS 19.52 vs 15.31 months ($p<0.001$) and median rwPFS 7.95 vs 6.37 months ($p=0.002$). Univariate Cox models favored vaccination for rwOS (HR 0.82; 95% CI 0.75–0.90; $p<0.001$) and rwPFS (HR 0.88; 95% CI 0.81–0.95; $p=0.002$), with consistent findings in multivariable models (rwOS HR 0.81; 95% CI 0.74–0.89; $p<0.001$; rwPFS HR 0.87; 95% CI 0.80–0.95; $p=0.001$). Twelve-month rwOS was 64.87% vs 54.45% (vaccinated vs unvaccinated). By tumor type, univariate (post-match) associations were directionally favorable and strongest in NSCLC (rwOS HR 0.79; 95% CI 0.71–0.87; $p<0.001$; rwPFS HR 0.85; 95% CI 0.77–0.93; $p<0.001$). Similar, non-significant trends were observed in smaller bladder and RCC cohorts; melanoma showed no association with rwOS. **Conclusions:** In this large propensity score–matched real-world cohort of ICI-treated patients, COVID-19 vaccination within 100 days of ICI initiation was associated with significant improvements in rwOS and rwPFS, particularly in NSCLC. Prospective validation and randomized clinical trials are warranted to confirm these findings. Research Sponsor: UTSW.

Impact of COVID-19 mRNA vaccines on survival outcomes in patients with solid tumors receiving immunotherapy: A large-scale retrospective study.

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Background: Immune checkpoint inhibitors (ICIs) became the cornerstone in the treatment of solid tumors. While personalized cancer vaccines have yet to overcome complex scalability and manufacturing challenges, preclinical data suggests SARS-CoV-2 mRNA vaccines prime innate immunity, potentially enhancing ICI efficacy. A study by Grippin et al. evaluated the use of mRNA vaccine in NSCLC and melanoma patients receiving ICI and showed improved median and three-year overall survival (OS). We conducted a multicenter retrospective study to determine if this survival benefit extends across a broader range of ICI-treated solid tumors. **Methods:** Using the TriNetX global network, we identified adults (≥18) with solid tumors (NSCLC, melanoma, colorectal, hepatobiliary, gallbladder, gastric, bladder, pancreatic, renal, breast, head and neck, and esophageal) who received ICI treatment. The experimental group received SARS-CoV-2 mRNA vaccine within 100 days of ICI initiation; controls received no mRNA vaccine from 100 days pre-index through follow-up. Exclusion criteria: COVID-19 infection within 100 days and through the follow-up period. 1:1 propensity score matching (PSM) balanced demographics and comorbidities. Primary endpoint was median OS, including tumor-specific subgroup analyses. Survival was assessed via Kaplan-Meier and log-rank tests. **Results:** After PSM, we had 15,374 matched patients (7,687 per group). Vaccination within 100 days of ICI was associated with improved median OS (1,421 vs 667 days; HR 0.63; 95% CI 0.60-0.66; $p<.001$). Benefit was observed in 10 of 12 tumor types. Strongest effects were in NSCLC (n=7,350; HR 0.64), melanoma (n=2,684; HR 0.61; landmark survival 62.1% vs 50.3%), hepatobiliary (n=1,428; HR 0.64), colorectal (n=1,068; HR 0.67), gastric (n=792; HR 0.68), bladder (n=1,398; HR 0.63), pancreatic (n=240; HR 0.65), renal (n=1,996; HR 0.64), head and neck (n=964; HR 0.68), and esophageal (n=828; HR 0.63). No significant benefit was seen in breast (n=1,412; HR 0.85) or gallbladder cancer (n=58; HR 0.88). **Conclusions:** SARS-CoV-2 mRNA vaccination within 100 days of ICI therapy was associated with improved survival across solid tumors. These results suggest off-the-shelf RNA therapeutics may be scalable, cost-effective enhancers of cancer immunotherapy. Prospective studies are needed to confirm these findings and define the impact of universal mRNA strategies. Research Sponsor: None.

Distinct T-cell subsets as drivers of response to different neoadjuvant treatments in esophageal squamous cell carcinoma.

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Background: The optimal integration of immunotherapy with chemoradiotherapy (CRT) in the neoadjuvant treatment of esophageal squamous cell carcinoma (ESCC) remains unclear, largely due to limited mechanistic insight into immune determinants of response. **Methods:** we performed paired single-cell RNA and TCR sequencing of ESCC tumor samples collected before and after treatment across three neoadjuvant modalities—immunochemotherapy (NICT), chemoradiotherapy (NCRT), and immuno-chemoradiotherapy (NICRT)—to dissect intratumoral $CD8^+$ T cell dynamics. **Results:** We identified two distinct immune response programs. In NICT responders, pre-existing immunoresponsive $CXCL13^+PD\text{-}1^+CD8^+$ T cells underwent clonal expansion and transcriptional reprogramming into a less exhausted yet CXCL13+ progenitor-like state (CD8Tex_CXCR4), accompanied by the formation of tertiary lymphoid structures. Conversely, CRT responders exhibited depletion of the subset of $CXCL13^+$ $CD8^+$ T cells and enrichment of $PD\text{-}1^-$ cytotoxic CD8Teff_NIBAN1 cells, which originated from the peripheral blood and were characterized by robust clonal expansion, high effector gene expression, and association with tumor regression. We validated the association of these two T cell subsets with distinct neoadjuvant modalities and treatment responses using public datasets and independent prospective cohorts encompassing NICT, NICRT, and NCRT. Mechanistically, conventional radiotherapy suppressed $PD\text{-}1^+$ T cell expansion—even in the presence of ICB—while a sequential strategy of induction ICB followed by delayed radiotherapy preserved the process of clonal expansion in exhausted T cell populations and achieved superior tumor control in vivo. **Conclusions:** These findings reveal divergent $CD8^+$ T cell–mediated immune programs driving response to neoadjuvant therapies in ESCC and identify CD8Teff_NIBAN1 as a key effector population following CRT. Our study provides mechanistic insight into ICB–radiotherapy interactions and supports the rational design of temporally optimized combination strategies in solid tumors. Research Sponsor: None.

Phase I study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in patients with advanced solid tumors.

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Background: LB1410 is a recombinant humanized anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Bio Co., Ltd, Shanghai, China for patients (pts) resistant/refractory (R/R) to anti-PD-(L)1 therapies. Pre-clinical studies revealed superior T cell and DC activity and *in vivo* antitumor efficacy compared to the combined use of TIM-3 and PD-1 monoclonal antibodies. This ongoing open-label phase I trial evaluates LB1410 monotherapy in pts with advanced solid tumors. **Methods:** Eligible pts were ≥18 yrs old with ECOG PS 0-1. Dose ranged from 0.001 to 20 mg/kg IV Q2W or 2000 mg/kg IV Q3W in an accelerated titration or a traditional 3+3 design. The RPIID of 20 mg/kg was used for efficacy expansion in pts with advanced clear cell renal cell carcinoma (ccRCC), cervical cancer (CC) and hepatocellular carcinoma (HCC). The primary objective was safety, including dose-limiting toxicities (DLTs); secondary objectives included efficacy, pharmacokinetics (PK) and immunogenicity. **Results:** As of Jan 4, 2026, 94 pts were enrolled: median age 59 yrs (31-73 yrs); 64.9% male; 84.0% ECOG PS 1. Tumor types included NSCLC (26.6%), CRC (21.3%, all non-MSI-H), CC (14.9%), ccRCC (11.7%), HCC (9.6%) and others (16.0%). 77 pts (81.9%) had received ≥ 2 prior lines of therapy. 98.6% non-CRC pts (73/74) were R/R to anti-PD-(L)1 therapies. 72 pts (76.6%) experienced TRAEs. The most common TRAEs (≥ 10%) included anemia (25.5%), proteinuria (11.7%), elevated ALT (11.7%), elevated AST (11.7%) and elevated lactate dehydrogenase (10.6%). Only 10 pts (10.6%) experienced Grade 3-4 TRAEs, most frequently hypertension (4.3%) and hypokalemia (2.1%). Only 1 hypertension and 1 elevated GGT in 1 pt were Grade 4. Serious TRAEs occurred in 3 pts (3.2%). No DLTs were observed. Among pts with available on-treatment scans, the overall ORR per RECIST 1.1 was 7.1% (6/85) with 5 confirmed PRs and 1 confirmed CR; the DCR was 48.2% (41/85). Notably, among CC pts previously treated with anti-PD-(L)1 therapies, there were 4 confirmed PRs and 1 confirmed CR: ORR 38.5% (5/13); DCR 69.2% (9/13); mPFS 7.5 months. 5 pts with CR/PR/SD remained on treatment (max. 16 treatment cycles; max. follow-up 14.4 months). The CR patient had received 5 prior lines of therapy, including PD-1/CTLA-4 BsAb. In anti-PD-1-resistant ccRCC, LB1410 monotherapy had an ORR of 11.1% (1/9) and a DCR of 77.8% (7/9). **Conclusions:** LB1410 showed an excellent safety profile and promising antitumor efficacy in pts with immune-oncology (IO)-R/R CC. Further studies of LB1410 as monotherapy and in combination with lenvatinib in pts with IO-R/R CC are ongoing. Clinical trial information: NCT05357651. Research Sponsor: L&L Bio Co., Ltd., Shanghai, China.

Immune checkpoint inhibitor (ICI) toxicity in a large prospective cohort of patients with solid tumors: The I-CHECKIT study (SWOG S2013).

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Background: Based on clinical trials, the expected rate of ≥ grade 3 iRAEs is ~15% for single agent ICIs and ~30-50% for ipilumimab (ipi) plus nivolumab (nivo). Predictors of irAEs remain poorly defined, limiting clinicians' ability to anticipate and manage irAEs especially in patients treated in community practices. We conducted a prospective study to quantify the incidence and severity of irAEs across a large, diverse population of patients receiving ICI therapy and to identify clinical predictors of irAE development. **Methods:** S2013 enrolled adult patients planning to receive standard of care ICI-based therapy in two separate cohorts; only results from the completed first cohort, which received either single drug or combination (combo) ICI therapy, are reported here. Eligibility criteria were few and study included patients with active autoimmune disease, decreased performance status, and any stage of cancer. No chemo, biological or targeted therapy were permitted. Patients were followed for 1 year for the occurrence of irAE. The primary objective was to assess the occurrence of Grade >3 non-hematologic irAEs per CTCAE v5. Evaluable patients had 1 or more toxicity assessment. irAE events were centrally reviewed by the study team. **Results:** 2084 patients were enrolled and N=2,020 patients were eligible (96.9%). Mean (SD) age was 68.7 (12.5) years, 35.8% were female, 5.2% Black, and 8.0% Hispanic. Most patients received single drug (1,684; 83.4%), while 336 (16.6%) received combo. Majority of single drug patients received pembrolizumab (50.6%), followed by nivo (29.6%), durvalumab (14.0%), and ipi (13.8%). Combinations were mostly ipi plus nivo. Within the first year, 269 (13.3%) patients experienced Grade ≥3 non-hematologic irAE. The most common irAEs were hepatitis, 21.2%; gastrointestinal disorders, 19.3%; and respiratory, 10.0% (Table). IrAE incidence was higher in patients receiving combinations (27.4%) compared to single drug (10.5%; Chi-square p<.001). **Conclusions:** In this large prospective cohort with unrestrictive enrollment criteria, irAE incidence was similar to that seen in more restrictive clinical trial populations. Analysis of the clinical predictors of irAEs is in progress. Grant: NIH/NCI UG1CA189974. Clinical trial information: NCT04871542. Research Sponsor: National Cancer Institute; NIH/NCI UG1CA189974.

Grade ≥3 non-hematologic irAEs, by category.

irAE	n	%	irAE	n	%
Hepatitis	57	21.2	Metabolism/nutrition	19	7.1
Gastrointestinal	52	19.3	Musculoskeletal	12	4.5
Skin	32	11.9	Cardiac	9	3.3
Respiratory	27	10.0	Hepatobiliary	7	2.6
Endocrine	22	8.2	Nervous system	7	2.6

COVID-19 mRNA vaccination and risk of immune-related adverse events in ICI-treated cancer patients.

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Background: Immune checkpoint inhibitors (ICIs) are now standard-of-care in cancer therapy; however, concerns persist regarding whether COVID-19 mRNA vaccination may enhance immune activation and exacerbate immune-related adverse events (irAEs). We evaluated the association between COVID-19 mRNA vaccination and irAE risk among patients initiating ICI therapy and assessed toxicity and survival outcomes. **Methods:** We conducted a retrospective cohort study using target trial emulation with 1:1 propensity score matching based on data from the TriNetX Research Database (January 2021–December 2025). Adult patients with metastatic cancer initiating their first ICI therapy were included. Patients with prior ICI therapy, active irAE within 30 days before ICI initiation or immunosuppressive conditions were excluded. Vaccinated patients who received COVID-19 mRNA vaccination within 100 days prior to ICI initiation were matched to unvaccinated controls. The primary outcome was composite irAE incidence over 36 months. Secondary outcomes included severe irAEs, organ-specific irAEs, all-cause mortality, pneumonia, and intensive care unit (ICU) admission. Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs). E-values and quantitative bias analyses assessed robustness to unmeasured confounding. **Results:** The matched cohort included 7,218 patients (3,609 vaccinated; 3,609 unvaccinated). Vaccinated patients had a higher risk of overall irAEs (HR 1.22, 95% CI 1.17–1.28; E-value 1.74) and severe irAEs (HR 1.11, 95% CI 1.04–1.18; E-value 1.45). Organ-specific analyses demonstrated a significant increase in ocular irAEs (HR 1.48, 95% CI 1.17–1.87; E-value 2.33), with non-significant associations for dermatologic (HR 1.08, 95% CI 0.97–1.21) and rheumatologic irAEs (HR 1.12, 95% CI 0.96–1.32). No significant increases were observed for cardiac, endocrine, gastrointestinal, hematologic, or pulmonary irAEs. Despite higher irAE risk, vaccination was associated with lower all-cause mortality (HR 0.86, 95% CI 0.80–0.93) and fewer ICU admissions (HR 0.43, 95% CI 0.25–0.73). Subgroup analyses showed stronger overall irAE associations in females and patients aged ≥50 years. Quantitative bias analysis indicated moderate robustness, with a 74.8% probability that HR>1.0 persists despite plausible unmeasured confounding. All $P<0.001$. **Conclusions:** COVID-19 mRNA vaccination among patients receiving ICIs is associated with a modest increase in irAEs, particularly ocular toxicities, but may offer survival and critical illness benefits. These findings support continued vaccination in eligible ICI-treated patients, along with enhanced irAE monitoring, including ophthalmologic surveillance in higher-risk groups. Research Sponsor: None.

Analysis of delta-like ligand 3 (DLL3) expression levels and characteristics of patients (pts) with advanced extrapulmonary neuroendocrine carcinomas (epNECs) from an ongoing phase I trial.

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Background: Specific DLL3 expression on the surface of epNEC tumor cells makes it a promising therapeutic target, but there is a lack of prospective data on DLL3 expression patterns in pts with epNEC. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager. The first-in-human phase I trial (NCT04429087) showed obrixtamig activity in pts with DLL3-positive epNEC, especially pts with DLL3-high tumors (Capdevila et al, ASCO 2025, #3004). We report updated DLL3 expression data and pt/tumor characteristics in pts with epNEC from NCT04429087. **Methods:** DLL3 IHC was performed with an investigational DLL3 antibody (SP347) at the Roche CDx CAP/CLIA Laboratory. DLL3 expression was categorized as: negative (absent or weak tumor cell [TC] membrane/cytoplasm staining), positive (moderate-to-strong staining in any TCs), high (≥50% moderate-to-strong TC staining), or low (<50% moderate-to-strong TC staining). **Results:** As of Sept 4, 2025, 282 of 365 screened pts with epNEC were DLL3-evaluable, of whom 235 (83.3%) had DLL3-positive tumors (DLL3-high: n=120 [42.6%], DLL3-low: n=115 [40.8%]); 47 (16.7%) were DLL3-negative. In the DLL3-positive treated set (n=93), 51 pts (54.8%) had DLL3-high and 42 (45.2%) had DLL3-low tumors. The prevalence of DLL3-high tumors in male/female pts was 47.5%/68.8%, and prevalence in pts with liver/brain metastases was 57.1%/70.0%. DLL3-high prevalence by primary tumor site, GI/GU/cancer of unknown primary site (CUP), was 44.9%/67.7%/60.0%. Pt characteristics in obrixtamig-treated DLL3-high and -low epNEC subgroups are in Table 1. **Conclusions:** In the largest prospectively screened cohort of pts with epNEC, high (83.3%) prevalence of DLL3 expression was seen, underscoring DLL3 as a promising target for clinical development of DLL3-targeted therapies such as obrixtamig. Obrixtamig safety and efficacy in pts with DLL3-positive epNEC are being assessed in several ongoing trials, including DAREON-5 (NCT05882058), with the data expected to inform and support Phase III development. Clinical trial information: NCT04429087. Research Sponsor: Boehringer Ingelheim.

	DLL3-high (n=51)	DLL3-low (n=42)
Male / female, n (%)	29 (56.9) / 22 (43.1)	32 (76.2) / 10 (23.8)
Primary tumor site: GI / GU / CUP, n (%)	22 (43.1) / 21 (41.2) / 6 (11.8)	27 (64.3) / 10 (23.8) / 4 (9.5)
Lactate dehydrogenase ≤ULN / >ULN, n (%)	22 (43.1) / 29 (56.9)	16 (38.1) / 26 (61.9)
Prior lines of therapy: 1 / 2 / 3 / >3	12 (23.5) / 17 (33.3) / 9 (17.6) / 13 (25.5)	11 (26.2) / 12 (28.6) / 10 (23.8) / 9 (21.4)
Median duration of prior anticancer treatment, weeks (range)	22 (5–349)	22 (8–148)
Prior radiotherapy / surgery / anti PD-(L)1, n (%)	22 (43.1) / 28 (54.9) / 14 (27.5)	11 (26.2) / 24 (57.1) / 9 (21.4)
Liver / brain metastases, n (%)	40 (78.4) / 7 (13.7)	30 (71.4) / 3 (7.1)
Median sum of diameters of target lesions, mm (IQR)	87.5 (64.0–123.0)	117.3 (66.2–176.0)

Engineering tumor-infiltrating lymphocytes (TILs) via the T-Editor platform to enhance antitumor activity.

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Background: Tumor-infiltrating lymphocyte (TIL) therapy has demonstrated clinical potential in melanoma, cervical cancer, and non-small cell lung cancer following failure of standard-of-care therapies, achieving objective response rates of 25-40%. However, two major challenges remain: the limited understanding of biological mechanisms underlying differential patient responses, and the absence of robust engineering technologies for manipulating fragile TIL populations. These limitations have constrained the application of genetic modification strategies to improve TIL therapeutic efficacy. **Methods:** By comparing transcriptomic profiles of infused TILs from responders (R) and non-responders (NR) in a Phase I investigator-initiated trial evaluating TIL therapy for solid tumors, we identified more than 10 differentially expressed genes as candidate therapeutic targets. We established the T-Editor platform, a CRISPR-mediated gene editing system optimized for TIL engineering, through systematic optimization of stimulation conditions, electroporation parameters, and CRISPR/Cas9 component dosing. Functional validation was performed by generating knockout (KO) constructs for each candidate gene using T-Editor, assessing their impact on TIL expansion, cytokine secretion, and cytolytic activity. The most promising target was selected for advanced cytosine base editing (CBE) studies, employing sgRNA designs to minimize Cas9-induced double-strand break risks. Base-edited TILs were comprehensively compared with Cas9-KO counterparts in vitro, while in vivo efficacy was evaluated using patient-derived xenograft (PDX) mouse models. **Results:** The T-Editor platform we established achieved optimal gene editing efficiency with defined stimulation condition, electroporation program and CRISPR/Cas9 doses. Functional screening revealed four critical regulatory genes, with FAM84B emerging as the most significant target where knockout demonstrated an increase in cytolytic activity compared to controls. CBE-mediated C·G→T·A conversion at FAM84B exon achieved high editing efficiency with minimal insertion-deletion events. Base-edited TILs showed comparable expansion kinetics, phenotypic stability, and cytokine production to Cas9-KO counterparts. In vivo studies demonstrated increased tumor growth inhibition in PDX models with FAM84B-edited TILs, which exhibited enhanced memory phenotype, superior effector function and elevated IFN-γ secretion. **Conclusions:** The T-Editor platform represents a rapid, efficient, and safe CRISPR-based system for TIL engineering, enabling both gene knockout and precise base editing applications. Our discovery of FAM84B as a potential novel inhibitory regulator of TIL function establishes a promising therapeutic target for improving adoptive cell therapy outcomes in solid tumor treatment. Research Sponsor: None.

Atezolizumab (A) plus pertuzumab/trastuzumab/hyaluronidase (PHESGO) in patients (pts) with solid tumors with *ERBB2* alterations (alt): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating the antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alts. Results of a cohort of pts with solid tumors with *ERBB2* alts treated with A+PHESGO are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no remaining standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited labs. Dosing for A was 1200 mg IV delivered every 3 weeks (wks). PHESGO was dosed every 3 wks, with a loading dose of 1200 mg/600 mg/30,000 units, then 600 mg/600 mg/20,000 units, until progression. Primary endpoint was disease control (DC) per investigator defined as objective response (OR) or stable disease (SD) of at least 16 wks duration (SD16+) per RECIST v.1.1. Simon 2-stage design tested null DC rate of 15% vs. 35% (power = 0.85; α = 0.10). If $\geq$2/10 pts in stage 1 had DC, cohort expanded to stage 2; otherwise, the cohort was closed. Cohorts closed prior to reaching the protocol-specified sample size of 28 used alternative thresholds set forth in the protocol to maintain the α level. For n=20, 6 pts had to have DC to reject the null (power = 0.74). Secondary endpoints were OR, progression-free survival (PFS), overall survival (OS), duration of response and SD, and safety. **Results:** The cohort expanded to stage 2 but closed before reaching the planned sample size. 23 pts with 6 tumor types (colorectal [CRC; 14], gallbladder [GB; 3], stomach [3], breast [1], pancreas [1], small intestine [1]) with *ERBB2* amplification (amp; n=16), *ERBB2* overexpression (n=2), *ERBB2* mutation (mut; n=2), and *ERBB2* amp and mut (n=3) were enrolled. 3 pts were not evaluable. 2 partial responses (both GB, *ERBB2* amp) and 2 SD16+ (both CRC, *ERBB2* amp) were observed for a DC rate of 25% (1-sided 90% CI, 10 to 100) and an OR rate of 10% (95% CI, 1 to 32). The null hypothesis was not rejected (p=0.26). 6 pts had tx-related grade 3 AE/SAEs: acute kidney injury, ALP increase, dehydration, diarrhea, infusion related reaction, lymphopenia, maculo-papular rash, pneumonitis and sepsis. **Conclusions:** A+PHESGO did not demonstrate sufficient antitumor activity in pts with *ERBB2*-altered solid tumors to warrant further study. However, the cohort did not reach its planned accrual, limiting statistical power for demonstrating efficacy. Other tx should be considered for these pts, including tx offered in clinical trials. Clinical trial information: NCT02693535. Research Sponsor: Genentech; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck, Pfizer, Seagen (now a wholly owned subsidiary of Pfizer Inc.), Taiho Oncology.

Demographics (N=23) and efficacy outcomes (n=20).		
Median (Med) age, years (range)		61 (43, 90)
ECOG PS, No. (%)	0	10 (44)
	1	11 (48)
	2	2 (9)
Prior systemic regimens, No. (%)	0-2	16 (70)
	$\geq$3	7 (30)
DC (OR plus SD16+) rate, % (1-sided 90% CI), p-value		25 (10, 100), p=0.26
OR rate, % (95% CI)		10 (1, 32)
Med PFS, wks (95% CI)		9 (8, 16)
Med OS, wks (95% CI)		35 (16, 52)

Functional assessment of polymerase proofreading variants to define sensitivity to immune checkpoint blockade (ICB) pan-cancer.

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Background: Cancers with inactivating alterations in DNA proofreading polymerases POLE and POLD1 (POLd) are ultra-hypermutated and benefit from ICB. Most mutations in DNA polymerases are synonymous; discerning pathogenic (P) vs variants of unknown significance (VUS) remains challenging. A strategy to define functional mutations in POL with mutational signature deconvolution and AI- protein conformational modeling could better predict ICB benefit. **Methods:** Solid tumors from patients at MSK and DFCI were selected with DNA panel sequencing datasets to enrich for somatic POL P/likely-P(LP) variants or VUS. Co-mismatch-repair deficiency (MMRd) was defined with MSIsensor and IHC. Tumors were assigned as POL high (>50%), intermediate ([int] 1-49%), or null (0%) based on the proportion of single-base-substitutions (SBS) aligning with POLd COSMIC signatures via the mutational-patterns algorithm. *POLE/D1* VUS were functionally evaluated with Swiss-PdbViewer and AlphaFold-derived AI models to infer proofreading efficiency impact. Patient overall survival (OS) from stage IV diagnosis and progression-free survival from ICB start (PFS-ICB) were evaluated with multivariable (MV) Cox regression including MMRd status. **Results:** POL variants were found in 546 patients across 18 diverse cancers. 84% were P/LP POL alterations, 16% were POL VUS, and 36% overall had concomitant MMRd. Tumors with P/LP variants had high (69%), int (23%), or null (8%) POLd signature intensities, while 62% of tumors with VUS had int POLd signatures. For the subgroup of patients with POL P/LP variants, OS from diagnosis significantly differed based on POLd signature intensity: not reached [NR], 94.5 months [mo], and 32.9 mo for POLd signature high, int, and null, respectively. In MV analysis of POL P/LP tumors, patients with POL signature-null tumors had significantly worse OS than POL-int (HR 0.35, 95%CI 0.16-0.80; p=0.01) and POL-high (HR 0.18, 95%CI 0.08-0.42; p<0.001) patients. POLd signature intensity predicted ICB benefit. Patients with POL P/LP tumors with high and int signatures exhibited favorable PFS-ICB (NR in both) versus POL P/LP–null-signature tumors (12.7 months). In MV model including MMR status, patients with POL-null SBS exhibited significantly worse PFS-ICB versus pts with combined POL signature high or int (HR 0.31, 95% CI 0.10-0.98; p=0.047). Study findings were consistent after adjustment for cancer type. Tumors with POL VUS predicted to be inactivating based on mutational signature deconvolution combined with Swiss-PdbViewer and AlphaFold AI models demonstrated similar OS/PFS to patients with tumors with P/LP variants and high/int signature scores. **Conclusions:** A strategy combining mutational signature deconvolution with AI proteomic functional assessment predicts survival and ICB benefit in tumors with functional DNA polymerases *POLE* and *POLD1* mutations. Research Sponsor: None.

Development and testing of an ex vivo, live tumor fragment platform for the prediction of immune checkpoint inhibitor response and relationship to approved biomarkers.

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Background: Immune checkpoint inhibitors (ICIs) have transformed the management of many advanced cancers but identifying patients who are likely or unlikely to benefit from ICI treatment remains a critical challenge. Biomarkers, such as PD-L1, mismatch repair deficiency, and tumor mutational burden, capture only static, unidimensional features of the complex tumor microenvironment, and therefore inadequately predict response to immunotherapy in patients. In contrast, live tumor fragments (LTFs) preserve the full complexity of the tumor microenvironment and enable functional ex vivo assessments of ICI activity. Previous efforts have had limited clinical applicability because they required larger resection specimens often collected at a single academic center. Here, the predictive capability of an ex vivo platform using core needle and forceps biopsies from multiple clinical sites was assessed and compared to approved biomarkers. **Methods:** Patients with eligible solid tumors (where ICI has an indication, including renal, non-small cell lung, bladder, colorectal, and triple-negative breast cancer, and others) were enrolled in ongoing, prospective observational trials (NCT05478538, NCT05520099, NCT06349642). Biopsies were cut into LTFs, encapsulated in hydrogel, and treated sequentially with IgG antibody followed by ICI (αPD-[L]1 with or without αCTLA-4). Cytokine production was assessed by a multiplexed bead-based immunoassay at multiple time points during ex vivo treatment. Using receiver operating characteristic and precision recall analyses, we identified 9 predictive cytokines (including IFN-γ, granzyme B, and CXCL9/10), which were used to develop the Elephas score (ELP-score) to assess cytokine response to ex vivo ICI treatment. **Results:** Of 167 eligible patient specimens, 85% (n = 142) passed quality control metrics and 130 were used for model development. Hierarchical clustering of cytokine production revealed that 27% (n = 35) of patient specimens exhibited a cytokine response to ICI. In a validation set of 20 tumors, collected from patients who were subsequently treated with ICI, ELP-score positivity correctly identified 9 of 11 patients (82%) who had an objective response (PR/CR) to ICI, including 2 patients who were negative for FDA-approved standard-of-care ICI biomarkers. Furthermore, 5 of 5 patients (100%) with clinical progressive disease were correctly characterized as ELP-score negative. **Conclusions:** Using routine biopsy specimens, the ex vivo live tumor platform accurately identifies patients with clinical response to ICI therapy, including those incorrectly identified by conventional biomarkers. Ongoing efforts will test these findings in an additional validation set. If confirmed, the ex vivo LTF platform could enable the identification of patients likely to benefit from ICI therapy. Clinical trial information: NCT05478538, NCT05520099, NCT06349642. Research Sponsor: Elephas.

Mitochondrial DNA (mtDNA) expression as used to define metabolic and immune states in colorectal cancer (CRC).

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Background: CRC exhibits metabolic reprogramming driven by the Warburg effect; however, active mitochondria and oxidative phosphorylation (OXPHOS) often remain crucial for tumor growth. mtDNA encodes critical OXPHOS components and influences the balance between OXPHOS and glycolysis, with effects on tumor microenvironment and response to immune checkpoint inhibitors (ICIs). We evaluated whether mtDNA gene expression predicts metabolic phenotype, immune contexture and benefit from ICIs. **Methods:** 30,887 CRC cases with DNA/RNA sequencing were analyzed from Caris Life Sciences. Expression of mtDNA-encoded OXPHOS genes (*MT-ND1–6*, *MT-ND4L*, *MT-CO1–3*, *MT-ATP6*, *MT-CYB*) was summarized as a composite Z-score due to correlation ($r>0.9$). Tumors were stratified into quartiles (n=7,722 each), mtDNA-high (MT-H, top quartile) and mtDNA-low (MT-L, bottom quartile) cohorts. Overall Survival (OS) was calculated in months (m) from first treatment to last contact. Hazard ratios (HRs) were calculated using Cox proportional hazards models and p-values by log-rank tests. Gene set enrichment analysis (GSEA) was performed to evaluate pathway differences. **Results:** MT-H tumors were enriched for Consensus Molecular Subtype (CMS) 2 compared to MT-L (44.2% vs 21.9%) and CMS3 (24.5% vs 8.7%), whereas CMS4 was markedly enriched in MT-L tumors (MT-H 16.5% vs MT-L 52.2%); all $p<0.001$. GSEA showed a trend toward higher OXPHOS activity in MT-H tumors (NES 1.19, FDR q=0.472), while glycolysis was significantly downregulated (NES -2.43, FDR q=0.002), with low immune/inflammatory signaling (interferon signaling and inflammatory response, among others) and reduced immune cell infiltration. These associations persisted in microsatellite stable (MSS) CRC, including CMS (CMS2/CMS3 46.3%/24.9% in MT-H vs CMS4 55.6% in MT-L) and immune signatures (all $q<0.05$). MT-L was prognostic for improved OS vs MT-H (median OS [mOS] 30.1 vs 27.2 m; HR 0.87, 95% CI 0.84-0.91, $p<0.001$). In ICI-treated patients (pts), MT-L showed amplified effect (mOS 24.3 vs 13.5 m; HR 0.69, 95% CI 0.58-0.83, $p<0.001$), including in CMS1 (mOS 39.3 vs 26.0 m; HR 0.71, 95% CI 0.53-0.96, p=0.024), CMS4 (mOS 19.3 vs 10.7 m; HR 0.61, 95% CI 0.40-0.94, p=0.024), MSS (mOS 13.8 vs 9.02 m; HR 0.67, 95% CI 0.54-0.84, $p<0.001$) and in pts with liver metastases (mOS 13.4 vs 7.93 m; HR 0.65, 95% CI 0.44-0.97, p=0.034). Multivariate analysis adjusting for age (>65 years), sex, liver metastases, MSI status, *BRAF V600E* status and CMS confirmed MT-L to be independently associated with improved OS in ICI-treated pts (p=0.01). No survival association was observed in pts treated with other therapies. **Conclusions:** mtDNA-encoded OXPHOS expression defines biologically distinct CRC subsets with distinct metabolic states and immune infiltration, with MT-L linked to improved OS and enhanced benefit from immunotherapy, including in MSS and liver metastases where ICI sensitivity is limited. Research Sponsor: None.

Pan-cancer long mononucleotide repeat microsatellite instability testing for detection and immunotherapy selection.

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Background: Microsatellite instability (MSI) and mismatch repair deficiency (dMMR) are crucial biomarkers to inform potential for hereditary risk and eligibility for immunotherapy across multiple cancers. While current standard of care testing can identify most MSI-high (MSI-H)/dMMR patients, improved testing sensitivity for MSI-H status could identify more patients who may benefit from immunotherapy. Recent studies have indicated potential for more sensitive testing using a long mononucleotide repeat (LMR)-based multiplex MSI-detection assay. **Methods:** Patients were identified and consented as part of an IRB-approved protocol (UW15068) based on MSI status, MMR gene variants, or high tumor mutation burden (TMB). Patient tissues, normal and tumor, were formalin-fixed and slides were prepared for pathologist annotation and immunohistochemistry (IHC) for CD8. CD8+ tumor infiltrating lymphocytes (TILs) were quantified/high powered field (HPF). Slides were scraped for DNA isolation. MSI testing was performed on the resultant DNA using the LMR MSI Analysis System (Promega, Madison, WI) and the OncoMate MSI Dx Analysis system (OM, Promega) per manufacturer protocols. LMR MSI status and score were compared with other testing methods, TMB, CD8+ TILs/HPF, immunotherapy response, progression-free survival (PFS), and overall survival (OS). **Results:** A cohort of 202 patients (median age: 64 (range: 24-80+)) with 20+ different cancer types (lung 27.2%, colorectal 18.8%, skin 9%, esophageal 5.9%, uterine 5.9%) and across disease stages, mutation profiles, and immunotherapy treatment regimens were consented. At least one test identified a case as dMMR/MSI-H in 31.6% of cases. In 9.4% of cases, a discrepancy between testing methods was observed. LMR detected 9 cases as MSI-H that were not detected by clinical NGS or OM. 4 cases were detected as MSI-H by LMR and OM alone, one case by OM alone, and one case by LMR and clinical NGS alone. Additionally, 2 cases were dMMR by IHC but not LMR, OM, or clinical NGS and 2 cases were dMMR by IHC and MSI-H by clinical NGS, but not LMR or OM. LMR score positively correlated with TMB (r^2 = 0.57) for MSI-H, but not MSS patients (r^2 = 0.002). LMR score weakly correlated with CD8+ TILs/HPF (r^2 = 0.16) in MSI-H, but not MSS cases (r^2 <0.001). LMR MSI-H cases have a 52.6% complete response rate compared to 6.12% of LMR MSS subjects ($p<0.001$). Patients identified as MSI-H by LMR testing had an increased PFS (median PFS (days) MSI-H: 711, MSS: 178; hazard ratio (HR) 0.25 [95% CI 0.13-0.50; $p<0.001$]) and OS (median OS (days) MSI-H: 926, MSS: 402; HR 0.43 [95% CI 0.22-0.82; p=0.015]) compared to LMR MSS patients. **Conclusions:** Variability can be observed between dMMR/MSI testing methods indicating that multiple methods should be considered for each patient. LMR testing demonstrates promising sensitivity and correlation with immunotherapy efficacy. Research Sponsor: Promega.

Are all tumor-agnostic biomarkers equally tissue-independent? Comparative cross-histology efficacy analysis of MSI-H/dMMR versus *BRAF* V600E.

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Background: FDA tumor-agnostic approvals for pembrolizumab/dostarlimab (MSI-H/dMMR) and dabrafenib-trametinib (BRAF V600E) assume uniform cross-histology efficacy. However, MSI-H/dMMR depends on immune checkpoint blockade—potentially influenced by tissue-specific microenvironments—while BRAF V600E represents oncogene addiction with essential MAPK dependencies. We hypothesized these biomarkers differ in tissue independence, with MSI-H/dMMR demonstrating greater histology-dependent response variability. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed, Embase, and the Cochrane Central Register owere searched from inception to January 2026 to identify prospective basket trials enrolling adults (≥18 years) with advanced or metastatic solid tumors harboring FDA-approved tumor-agnostic biomarkers. Eligible trials evaluated pembrolizumab or dostarlimab in MSI-H/dMMR tumors, or dabrafenib plus trametinib in BRAF V600E-mutant tumors, and reported objective response rates (ORR) stratified by tumor histology. Studies were required to include ≥3 distinct tumor histologies (not subtypes) with a minimum of 10 patients per histology cohort. Phase I trials, retrospective case series, pediatric-only populations, and studies without histology-specific efficacy data were excluded. Primary outcome was ORR heterogeneity across tumor types within each biomarker platform, quantified using the I^2 statistic and coefficient of variation (CV). Pooled analyses were performed using random-effects models. Effect estimates are expressed as ORR percentages with 95% confidence intervals. **Results:** Four trials included: KEYNOTE-158 (pembrolizumab, n=373), GARNET (dostarlimab, n=363), ROAR (dabrafenib-trametinib, n=215), VE-BASKET (vemurafenib, n=62); 1,013 patients across 12 tumor histologies. MSI-H/dMMR platform (n=736, 8 tumor types): mean ORR 35.1% (range 0-57.1%); endometrial 57.1%, gastric 45.8%, colorectal 43.5%, small intestine 42.1%, cholangiocarcinoma 40.9%, ovarian 33.3%, pancreatic 18.2%, brain 0%; CV=0.513. BRAF V600E platform (n=277, 4 tumor types): mean ORR 45.0% (range 37.1-53%); anaplastic thyroid 53%, biliary tract 47%, glioma 42.9%, NSCLC 37.1%; CV=0.149. MSI-H/dMMR demonstrated 3.4-fold greater heterogeneity than BRAF V600E (CV 0.513 vs 0.149). **Conclusions:** Tumor-agnostic biomarkers exhibit differential tissue independence. MSI-H/dMMR showed 3.4-fold greater response heterogeneity (CV=0.513) than BRAF V600E (CV=0.149), indicating immune checkpoint efficacy remains tissue-dependent while oncogene addiction confers uniform predictivity. These findings challenge the assumption of biomarker-driven tissue-agnostic efficacy and necessitate histology-specific outcome counseling and trial stratification. Research Sponsor: None.

Pan-cancer landscape of oncogenic POLE and POLD1 alterations.

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Background: POLE and POLD1 encode key enzymes for DNA proofreading. Oncogenic alterations in POLE and POLD1 associated with defective proofreading can lead to tumor hypermutation and increased sensitivity to immune checkpoint inhibition. Prior studies have identified enrichment of POLE and POLD1 alterations in colorectal and endometrial cancers. However, characterization of POLE and POLD1 alterations in the pan-cancer setting has been limited. Utilizing the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) v19.0, we performed a comprehensive analysis of oncogenic POLE and POLD1 alterations across tumor types. **Methods:** The AACR GENIE v19.0 database was used to select tumor samples that were profiled for molecular alterations (somatic mutations, structural variants, copy number alterations) in POLE or POLD1. POLE and POLD1 alterations were annotated by OncoKB to determine if they were oncogenic. Tumor samples were analyzed for co-occurring molecular alterations. Categorical variables were compared using chi-square or Fisher exact tests, as appropriate. P-values were adjusted with Benjamini-Hochberg correction to control false discovery rate (significance for $q<0.05$). **Results:** Across 188,863 tumor samples that were profiled for POLE or POLD1, there were known oncogenic alterations in 786 samples (0.4%). Of note, there were 18,170 molecular alterations in POLE and POLD1 that were classified as variants of unknown significance at time of analysis. The most common tumor types with oncogenic alterations were endometrial (n=374 of 7573 samples profiled; 4.9%), colorectal (143/17821; 0.8%), glioma (49/12795; 0.4%), NSCLC (35/30542; 0.1%), ovarian (26/7728; 0.3%), breast (25/16813; 0.2%), bladder (25/6433; 0.4%), cancer of unknown primary (19/6544; 0.3%), melanoma (13/7965; 0.2%), and pancreatic (10/10369; 0.1%), and esophagogastric (9/6503, 0.1%). The most common mutations in POLE were V411L, E18K, P286R, S297F, and A456P. The most common mutations in POLD1 were R1016H, R1016C, R689W, L606M, and D402N. Oncogenic alterations in POLE and POLD1 were enriched in endometrial cancer (OR 22.8; $q<0.001$) and colorectal cancer (OR 2.14; $q<0.001$), with no other tumor types showing enrichment. Within the oncogenic POLE/POLD1 cohort, the most common co-occurring molecular alterations were in PIK3CA (n=561, 71.4% in altered vs 12.9% in unaltered, $q<0.001$), APC (n=526, 68.7% vs 11.8%, $q<0.001$), ATM (n=523, 67.8% vs 7.3%, $q<0.001$), and PTEN (n=523, 66.5% vs 8.7%, $q<0.001$). **Conclusions:** To our knowledge, this study represents the largest molecular analysis of oncogenic POLE and POLD1 alterations in a pan-cancer setting. These findings suggest that oncogenic POLE and POLD1 alterations may be rarely identified in a broad range of tumor types. Further studies are needed to classify the functional implication of many variants of unknown significance in POLE and POLD1. Research Sponsor: None.

Phase Ib evaluation of a recombinant overlapping peptide survivin immunotherapy: Safety, immunogenicity, and immune–clinical associations in advanced solid tumours.

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Background: Survivin (BIRC5) is a tumour-associated self-antigen broadly expressed in solid malignancies but subject to immune tolerance, limiting its value as an immunotherapy target. OVM-200 is a recombinant overlapping peptide (ROP) survivin immunotherapy designed to enhance antigen processing and presentation through both MHC class I and II pathways, thereby overcoming HLA restriction. A Phase Ia study established safety and the recommended regimen. Here we report novel Phase Ib data evaluating extended immunisation and immune–clinical associations. **Methods:** Phase Ib enrolled a total of 24 patients with advanced NSCLC, ovarian, or prostate cancer who had progressed on standard therapies. Patients received OVM-200 at the recommended regimen (2 mg) with extended immunisation schedules (3–11 immunisations). The primary endpoint was safety and the secondary endpoint was immunogenicity. Survivin-specific antibodies were measured by IgG ELISA and T-cell responses by IFN-γ ELISpot. Tumour response was assessed using RECIST 1.1, with best overall response (BOR) classified as stable disease (SD) or progressive disease (PD). Immune responses were analysed longitudinally and in relation to BOR. **Results:** The primary endpoint of safety was met, with OVM-200 well tolerated and no dose-limiting toxicities or treatment-related serious adverse events. Survivin expression was detected in tumour tissue in 17 patients prior to immunisation; however, baseline survivin-specific antibody and T-cell responses were low or undetectable, consistent with immune tolerance. The secondary endpoint of immunogenicity was achieved. Mean peak anti-survivin antibody titres increased from 1:143 pre-treatment to >1:160,000 post-treatment ($p < 0.001$), and mean peak T-cell responses increased from 211 to 859 net SFU/10^6 PBMCs ($p < 0.00001$). Antibody responses were durable, rising through Days 113–169, whereas T-cell responses peaked at Day 57 and remained significantly above baseline. Extended immunisation (>5 immunisations) maximised humoral responses, while T-cell magnitude was comparable across schedules. Patients with BOR of SD showed higher and more sustained survivin-specific humoral and cellular immune responses than those with PD. **Conclusions:** Phase Ib results demonstrate that OVM-200 is safe and immunogenic, achieving both the primary safety and secondary immunogenicity endpoints. OVM-200 overcomes immune tolerance to survivin and induces durable humoral and cellular immune responses. The observed association between stronger immune responses and BOR of SD supports further clinical evaluation and rational combination strategies. Clinical trial information: NCT05104515. Research Sponsor: Oxford Vacmedix.

Monitoring blood-based biomarkers as early predictors of progression-free survival in a randomized Bria-ABC phase 3 trial for advanced metastatic breast cancer: An ongoing analysis.

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Background: Circulating Tumor Cells (CTCs) are prognostic for poor outcomes in metastatic Breast Cancer (mBC), however CTCs are uncommon in mBC (<20%) and many pts without CTCs often progress. Cancer associated macrophage-like cells (CAML) are prognostic inflammatory pro-tumorigenic PD-L1 expressing macrophages common in mBC pt blood (>90%). In a previous randomized phase II trial, CTC & CAML decreases post Bria-IMT induction correlated with clinical benefit. Bria-IMT is an allogenic whole cell vaccine engineered to express tumor associated antigens & GM-CSF, promoting adaptive & innate immune responses. The ongoing Bria-ABC (NCT06072612) phase 3 study compares Bria-IMT to physician's choice (TPC) in late stage mBC. We present interim results, without treatment arm comparison, for Progression Free Survival (PFS) by CTC & CAML changes as the exploratory part of the trial. **Methods:** This still blinded ongoing multicenter randomized open label Phase 3 trial evaluates Bria-IMT+ checkpoint inhibitor (CPI) vs TPC in mBC pts lacking approved therapies. Pts are randomized 1:1:1 to Bria-IMT+CPI, TPC, or Bria-IMT monotherapy (discontinued after 150 pts). The Bria-IMT consists of cyclophosphamide, irradiated SV-BR-1-GM cells, micro-dose pegylated α IFN at each inoculation site. CPI is administered day -3 to 3. TPC followed standard of care. Blinded anonymized blood was taken at baseline (BL), prior to therapy & 2nd (T1) taken at cycle 3 (~4 weeks post initiation). CTCs & CAMLs, and PD-L1 expressions, were quantified using LifeTracDx liquid biopsy with analysis of PFS by censored univariate analysis. **Results:** At time of analysis, >250 consented, >170 randomized, 119 had BL and 78 had T1. Median age 56 yrs [34–83], median 6 [2–13] prior lines of therapy, 31% TNBC, 62% ER+/PR+, & 15% HER2+. ≥1 CTCs were found in 25% (30/119) at BL & 22% (17/78) at T1. ≥1 CAMLs were found in 93% (111/119) at BL & 95% (74/78) at T1. At BL, ≥1 CTC was not significant for PFS (HR=1.7, CI95% 1.0-2.9, p=0.0513), but ≥2 CTCs was significant for worse PFS (HR=1.8 CI95% 1.1-3.1, p=0.0480). At T1, ≥1 CTCs nor ≥2 CTCs correlated with PFS (HR=0.9, p=0.8392) & (HR=1.6, p=0.1079), respectively. Further, a decrease in CTCs was seen in 11 pts but did not correlate with PFS (HR=0.7, p=0.6552). ≥1 CAML at BL nor T1 correlated with PFS (HR=1.2 CI95% 0.7-2.0, p=0.6811) or (HR=0.9 CI95% 0.7-2.5, p=0.5307), respectively. However, 51 pts (65%) had a decrease or stable CAML counts between BL & T1 which did significantly correlate with better PFS (HR=2.2 CI95% 1.2-3.9, p=0.0154). **Conclusions:** In an ongoing analysis of a heavily treated mBC pts, we observed that in the entire blinded population, 65% of pts had stability/drop in CAMLs significantly correlated with better PFS. Treatment arm specific comparisons will not be unblinded until completion of the designated milestone (144 mortalities). Clinical trial information: NCT06072612. Research Sponsor: Creatv Microtech; BriaCell Therapeutics Corp.

Off-target HLA matches for prediction of response in personalised cancer vaccines: A multi-trial retrospective analysis.

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Background: Personalized neoantigen vaccines aim to match epitopes to a patient's HLA genotype, yet many peptides bind promiscuously across multiple HLA alleles. Promiscuous binding may reflect intrinsic peptide properties, including enhanced processing efficiency and structural stability, that drive immunogenicity independent of any single HLA match. We hypothesized that peptides with broader HLA binding profiles would show higher clinical immunogenicity, even when restricted to the patient's own HLA alleles. **Methods:** We curated 17 neoantigen vaccine trials (174 patients) and selected five with per-epitope $CD8^+$ T cell immunogenicity data for primary analysis. Across 571 neoantigen sequences (3,806 derived peptides), we predicted binding and presentation using NetMHCpan-4.2, MHCflurry 2.0, and PRIME-2.0, and estimated peptide–MHC stability with NetMHCstabpan. A reference panel of 62 common HLA class I alleles (>95% global coverage) was used to quantify incidental coverage, defined as predicted binding (IC50 <500 nM) to non-patient HLA alleles. Mixed-effects models adjusted for patient-specific binding affinity, predicted stability, mutation type, neoantigen length, and trial structure, with Bonferroni correction for 5 pre-specified hypotheses. **Results:** Off-target HLA binding independently predicted clinical immunogenicity. Among peptides selected for vaccination, 35.2% bound at least one non-patient HLA allele, with the most promiscuous peptides binding up to 37 alleles. After adjusting for patient-specific binding affinity and stability, peptides from immunogenic neoantigens showed greater incidental coverage than non-immunogenic peptides (mean 2.46 vs 1.80 additional HLAs; p=0.0034). This association was consistent across tumour types and prediction methods. Among immunogenic peptides, the breadth of off-target binding correlated with response magnitude (Spearman ρ=0.46, p=0.034), with the strongest effect observed in glioblastoma. High-affinity off-target matches (IC50 <50 nM) and high-stability interactions showed the most robust associations with immunogenicity. **Conclusions:** Promiscuous HLA binding independently predicts neoantigen immunogenicity in clinical trials, beyond binding affinity and stability to the patient's own HLA alleles. These results point to peptide-intrinsic properties linked to MHC stability and processing that are overlooked by current selection pipelines. Explicit modelling of HLA promiscuity and stability may improve neoantigen prioritisation, particularly in low–mutation burden tumours and patients with rare HLA genotypes. Research Sponsor: None.

Ranking neoantigens for escape-resilience rather than predicted immunogenicity: Associated changes in vaccine design.

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Background: Personalised neoantigen vaccines induce detectable $CD8^+$ T cell responses for fewer than one-third of selected peptides. Current pipelines prioritise candidates by predicted immunogenicity and select peptides independently, overlooking two constraints: efficacy depends on the peptide set as a whole, and tumours adapt antigen processing under immune pressure. We developed a framework that optimises peptide combinations for resilience to tumour escape and tested whether escape-resilience predicts clinical immunogenicity. **Methods:** We modelled peptide susceptibility to five antigen-processing escape mechanisms: TAP downregulation, immunoproteasome-to-constitutive proteasome switching, aminopeptidase upregulation, tapasin loss, and HLA loss of heterozygosity. Selection was formulated as a minimax optimisation, maximising predicted efficacy under worst-case tumour adaptation. We analysed five neoantigen vaccine trials with per-epitope $CD8^+$ T cell response data, consisting of 571 neoantigens, 3,806 peptides, and 174 patients. Mixed-effects models tested associations between escape-resilience and immunogenicity, adjusting for binding affinity (NetMHCpan-4.1 %rank), pMHC stability (NetMHCstabpan), mutation type, and clonality. Six hypotheses were pre-registered with Bonferroni correction. **Results:** Escape-resilience predicted immunogenicity independently of established features. After adjustment, vulnerability to TAP loss (OR 0.42 per SD, 95% CI 0.24–0.71, p=0.0018) and proteasome switching (OR 0.54 per SD, 95% CI 0.34–0.86, p=0.0089) were associated with failure to elicit $CD8^+$ responses. Among peptides with comparable predicted binding affinity, escape-resilient peptides were significantly more likely to be immunogenic. Composite escape-resilience scores discriminated immunogenic from non-immunogenic peptides (AUC 0.71, 95% CI 0.66–0.76), outperforming binding affinity alone (AUC 0.58) and an affinity-stability model (AUC 0.64). Adding escape-resilience improved discrimination (ΔAUC 0.07, p=0.003). Retrospective re-ranking altered 38% (95% CI 31–45%) of vaccine compositions, replacing high-affinity but escape-vulnerable peptides with lower-affinity, processing-robust alternatives. Associations were stronger for truncal mutations (OR 2.8, 95% CI 1.6–4.9) than subclonal mutations (OR 1.4, 95% CI 0.8–2.4; interaction p=0.041), indicating that processing robustness is most consequential for clonally dominant neoantigens. **Conclusions:** Optimising neoantigen selection against tumour escape identifies peptides more likely to elicit $CD8^+$ T cell responses, independent of binding affinity and stability. The stronger effects in truncal mutations suggest escape-aware ranking may be particularly valuable for durable, clone-targeted vaccination strategies. Prospective trials are needed to assess clinical impact. Research Sponsor: None.

The differentiated SIRPα–IgG4 Fc fusion protein HCB101 in monotherapy and combination therapy.

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Background: The CD47–SIRPα axis is a central innate immune checkpoint that enables tumor immune evasion. No prior CD47-directed program has demonstrated meaningful monotherapy activity, limited by on-target hematologic toxicity, constraining development. HCB101 is a differentiated SIRPα–IgG4 Fc fusion protein engineered to maintain macrophage-mediated phagocytosis while reducing red-blood-cell binding. This study assesses whether HCB101 can overcome historical class limitations by achieving a wide therapeutic safety margin and durable monotherapy antitumor activity, while also serving as a backbone for combination immunotherapy efficacy across standard-of-care (SOC) regimens. **Methods:** HCB101-101 (NCT05892718) is a first-in-human Phase 1 monotherapy dose-escalation study evaluating weekly IV dosing from 0.08 to 36 mg/kg. HCB101-201 (NCT06771622) is a Phase 1b/2a multicohort trial assessing HCB101 combined with SOC agents across 9 solid tumor types, including gastric cancer (GC), triple-negative breast cancer (TNBC), colorectal cancer, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma, ovarian cancer, and small cell lung cancer. Primary endpoints are safety, tolerability, and determination of the recommended Phase 2 dose; secondary and exploratory endpoints include pharmacokinetics (PK), pharmacodynamics, efficacy, and biomarkers. **Results:** In HCB101-101, 36 mg/kg has been reached. To 09JAN2026, 2 confirmed partial responses (HNSCC: −42% at 5.12 mg/kg, durable > 44 weeks; marginal zone lymphoma), and 9 stable diseases (SD) have been observed. PK was dose-proportional ($T_{1/2}$ ~2.9 days) with receptor occupancy plateauing at > 99% by ≥8 mg/kg. In HCB101-201, 2L-GC treated with HCB101 plus ramucirumab and paclitaxel demonstrated 8 PRs and 5 SDs, with two additional patients at 12 mg/kg pending first assessment. In mid-dose cohorts (5.12–8 mg/kg), 8 of 10 subjects achieved PRs and 100% achieved disease control, with regressions up to −78.2%. In 1L HER2+ GC, 4 subjects showed 3 PR (up to −57.6%) and 1 SDs. In 1L-TNBC, 6 of 6 subjects achieved disease control, including 3 PRs. Across cohorts, HCB101 demonstrated manageable safety with reversible cytopenias and no unexpected immune-mediated toxicities. **Conclusions:** HCB101 demonstrates a class-distinguishing profile for a macrophage checkpoint inhibitor, with durable monotherapy antitumor activity and a wide therapeutic window up to 36 mg/kg, addressing long-standing limitations of CD47-directed therapies. The early and reproducible combination activity across multiple solid tumors, including GC, HER2+ GC, and TNBC, has supported rapid cohort expansion. These data position HCB101 as a next-generation innate immune checkpoint backbone with broad clinical applicability and a clear rationale for future combination-based registrational development. Clinical trial information: NCT05892718. Research Sponsor: None.

Low-dose nivolumab in patients at high risk of immune-related adverse events: A retrospective cohort study.

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Background: Immune checkpoint inhibitors (ICIs) are relatively contraindicated in patients with prior severe immune-related adverse events (IRAEs) and/or have pre-existing serious auto-immune diseases (AID). Such patients are generally excluded from immunotherapy trials due to toxicity concerns, and data on ICI (re)exposure is limited. Our correlative data [Tachiki L 2024 SITC] suggest that low-dose (LD) nivolumab (Nivo; 40 mg) achieves PD-1 receptor occupancy comparable to standard-dose (SD) Nivo (240 or 480 mg), suggesting a potentially similar risk of developing IRAEs. However, faster serum clearance observed with LD Nivo may allow easier management of IRAEs when they occur. Based on this rationale, we have offered LD Nivo to high-risk patients after careful clinical discussion. In this study, we present the outcomes of our institutional experience. **Methods:** This single institution, retrospective cohort study included patients with advanced skin cancers who received LD Nivo (40 mg) due to a high-risk of IRAEs, including those with a previous history of IRAEs from SD ICIs or ICI-naïve patients with pre-existing AID. We analyzed efficacy and safety endpoints, including best objective response rates (BORR) per RECIST v1.1 and rates of IRAE with SD and LD ICIs. Outcomes were analyzed using descriptive statistics and stratified Cox models. **Results:** From 2015 – 2025, 23 patients with advanced skin cancers (22-Melanoma; 1-Merkel cell carcinoma) received LD Nivo due to an elevated IRAE risk. Sixteen patients had a history of treatment-limiting IRAEs on SD ICIs (“Prior-IRAE” cohort: 7 SD anti-PD-1 monotherapy; 9 SD combination ICI), and 7 patients were ICI-naïve with pre-existing AID (“AID” cohort). In the Prior-IRAE cohort, treatment hold/discontinuation due to IRAEs occurred in 100% with SD ICI versus 43.8% with LD Nivo ($p = 0.032$). Among the 7 patients previously treated with SD anti-PD-1 monotherapy, the incidence of grade $\geq$2 IRAEs was 100% (median duration 75 days; range, 12–217) on SD therapy versus 42.8% (median duration 43 days; range, 23–146) on LD Nivo. In the AID cohort, 100% patients experienced at least one grade 2 IRAE, but no grade 3 or 4 events were observed. In patients with evaluable disease (measurable and progressing at LD Nivo initiation), BORR was 57.1% (4/7; 1 complete response [CR], 3 partial responses) in the Prior-IRAE cohort and 33.3% (2/6; both CR) in the AID cohort. **Conclusions:** LD Nivo demonstrates biological activity, as evidenced by both anti-tumor responses and toxicities, in patients at high risk of IRAEs. Compared to SD ICI, LD Nivo may offer an advantage in toxicity management, potentially enabling more consistent treatment delivery with fewer interruptions and reduced need for immunosuppressive interventions. This strategy warrants further evaluation in prospective clinical trials. Research Sponsor: Winn Career Development Award; Kuni Foundation.

Association of PCSK9 inhibitors with clinical outcomes in patients with cancer receiving immune checkpoint inhibitors: A real-world analysis.

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Background: Although developed as lipid-lowering agents, PCSK9 inhibitors (PCSK9i) have shown preclinical potential to synergize with immune checkpoint inhibitors (ICIs) by increasing tumor antigen presentation and overcoming ICI resistance. However, there is limited evidence describing their use and associated outcomes in real-world oncology practice. We aimed to explore the clinical outcomes in relation to PCSK9i use in patients with cancer receiving ICIs. **Methods:** This propensity score-matched (PSM) cohort study utilized the TriNetX research network, encompassing real-time electronic health records from > 70 U.S. healthcare organizations. The study population included adults (aged ≥18 years) diagnosed with non-small cell lung cancer, melanoma, renal cell carcinoma, or breast cancer, who underwent concurrent ICI therapy (e.g., pembrolizumab, nivolumab, atezolizumab, durvalumab) plus PCSK9i (e.g., evolocumab, alirocumab; with or without statins) or high-intensity statins alone (atorvastatin ≥ 40 mg, or rosuvastatin ≥ 20 mg) between 01/01/2011 (the earliest year of ICI approval) and 01/01/2025 for hyperlipidemia. The primary outcome was overall survival (OS). Secondary outcomes included emergency room (ER) visits, all-cause hospitalization, ICU admission, and 4-point (acute myocardial infarction, heart failure, stroke, and unstable angina) major adverse cardiovascular event (MACE). A 1:1 PSM was applied to balance potential confounders, including demographics, socioeconomic status, cancer site, Charlson-Comorbidity-Index comorbidities, and laboratory parameters [Albumin, LDL, AST/ALT, and BMI]. Time-to-event analyses were performed using Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with log-rank test for significant survival differences. Follow-up began at the initiation of concurrent ICI plus PCSK9i or statin and continued until 01/05/2025, or until the occurrence of the study outcomes. **Results:** A total of 254 patients in PCSK9i cohort were matched to 254 patients from the statin-only cohort (n = 13734). Patients receiving PCSK9i demonstrated significantly improved OS compared with those receiving statins alone (HR 0.67, 95% CI 0.52-0.88) and associated with lower risk of ER visits (HR 0.64, 95% CI 0.49-0.83), hospitalization (HR 0.68, 95% CI 0.54-0.85), and ICU admission (HR 0.69, 95% CI 0.50-0.95; all $p<0.01$). No significant difference was observed for MACE outcomes (HR 0.79, 95% CI 0.59-1.07, p=0.13). **Conclusions:** In this large, real-world analysis, the use of PCSK9i in patients with cancer and hyperlipidemia treated with ICIs was associated with improved overall survival and reduced healthcare utilization. These findings support ongoing prospective clinical trials evaluating the potential synergistic effects of PCSK9 inhibition with ICI therapy. Research Sponsor: None.

Modulation of PD-1 and PD-L1 expression on peripheral blood T-cells by novel rotavirus variants.

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Background: Promising oncolytic viruses are typically evaluated based on their direct cytotoxic effects on cancer cells. However, the therapeutic benefit of virotherapy may also stem from its immunomodulatory actions, particularly through influencing immune checkpoint molecules like PD-1 and PD-L1. This study aimed to investigate the effect of unclassified apathogenic rotavirus strains RVK100 and RVK228 on the expression of PD-1 and PD-L1 on T-cells derived from the peripheral blood of patients with breast cancer. **Methods:** Mononuclear cells of peripheral blood were isolated on a ficoll gradient, cultured in RPMI 1640 (Gibco, USA) without serum at 37 °C, 5.0% CO2 in 4 variants of the experiment: 1) negative control without viruses; 2) positive control of activation with the addition of PHA; 3) experience with the addition of 107 particles per 1 ml of the RVK100 strain; 4) experience with the addition of 107 particles per 1 ml of the RVK100 strain RVK228. After 24 and 72 hours of cultivation, the expression of PD-1 (CD279) and PD-L1 (CD274) was determined on T cells by flow cytometry. The study used antibodies conjugated with fluorochromes: anti-CD4 (PE), anti-CD8 (APC Cy7), anti-CD279 (FITC), anti-CD274 (PerCP-Cy5–5) (Becton Dickinson, USA). **Results:** After 24 hours, we observed increases in PD-1 expression on CD4+ (PHA—40.5%, RVK100—42.3%, RVK228—37.5%; vs. control—18.1%) and CD8+ cells (PHA—41.7%, RVK100—46.4%, RVK228—42.6%; vs. control—27.7%). Similarly, PD-L1 expression rose on CD4+ cells (RVK100—67.0%, RVK228—58.6%, PHA—75.1%; vs. control—44.8%) and CD8+ cells (RVK100—63.4%, RVK228—58.4%, PHA—52.8%; vs. control—46.2%). At 72 hours, PD-1 levels decreased significantly in CD4+ cells exposed to RVK100 (from 42.3% to 21.6%) and CD8+ cells (from 46.4% to 17.4%). Conversely, PD-L1 expression increased across all groups on CD8+ cells, reaching 67–79%, while minimal change occurred on CD4+ cells except for a minor decline in the RVK100 group. **Conclusions:** Both strains, like the non-specific T-mitogen PHA, caused the stimulation of the expression of immune checkpoint receptors PD-1 and PD-L1 on T-helpers and CTL after 24 hours of cultivation. After 72 hours of cultivation, RVK100, unlike RVK228, was revealed ability to reduce the expression of PD-1 on these cells. Research Sponsor: None.

Preclinical investigations and first-in-human phase I trial of KP-483 in solid tumors: Safety, antitumor activity, and preliminary efficacy.

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Background: KP-483 is a novel small-molecule antagonist of the E-type prostanoid receptor 4 (EP4) that potentially exerts antitumor effects by modulating the tumor microenvironment and restoring antitumor immunity. Based on preclinical and phase I studies, this report presents the pharmacological properties, safety, and preliminary efficacy of KP-483. **Methods:** In preclinical studies, the pharmacodynamic profile of KP-483 was characterized *in vitro* and *in vivo*. Antitumor activity was evaluated in tumor-bearing mice, and tumor infiltrating $CD8^+$ and $CD163^+$ cells were quantified. A first-in-human phase I study (jRCT2031220311) using a 3+3 dose-escalation design enrolled patients with solid tumors who had progressed after standard treatments or for whom no appropriate standard treatment was available. KP-483 was administrated orally once daily, with dose escalation across five cohorts (50, 100, 200, 400, and 800 mg). The primary endpoints were dose-limiting toxicities (DLTs) and safety profiles. Plasma concentrations of KP-483 were also measured. Preliminary efficacy was evaluated according to RECIST criteria, and the antitumor mechanisms were explored by flow cytometry analysis of tumor tissue. **Results:** KP-483 exhibited greater EP4 antagonist activity than existing antagonists (IC_{50}: 1.0 nmol/L in human) and had higher binding affinity to the EP4 receptor and a longer dissociation half-life than PGE_2 *in vitro*. In mouse models, KP-483 exhibited dose-dependent antitumor effects following 14 days of oral administration at doses of 3, 30, and 300 mg/kg once daily. The number of $CD8^+$ T cells in tumor tissue increased while that of $CD163^+$ cells decreased in a dose-dependent manner. In addition, combination treatment with KP-483 (15 mg/kg, twice daily) and either anti-PD-1 or anti-PD-L1 antibodies enhanced antitumor effects compared with either monotherapy. In the phase I study, safety was assessed in a total of 19 patients. The median treatment duration was 43 days (range: 24–713 days), and no DLTs were observed. The most common treatment-emergent adverse events were anemia and nausea (each 26.3%), with only one study-drug-related grade ≥3 event (anemia). Systemic exposure to KP-483 increased with dose, and the plasma half-life of KP-483 ranged from 7.9 to 12.8 hours on treatment day 15. Best overall responses included stable disease in four patients and partial response in one patient. Flow cytometry analysis of tumor tissue showed a trend toward increased activated cytotoxic T cells, dendritic cells, and M1-like macrophages. **Conclusions:** KP-483 is a potent EP4 antagonist that exerts antitumor effects through modulation of the tumor immune microenvironment. Given its favorable safety and pharmacokinetic profiles, KP-483 represents a promising EP4 receptor–targeted therapeutic strategy with potential for combination with immune checkpoint inhibitors. Clinical trial information: jRCT2031220311. Research Sponsor: KAKEN Pharmaceutical Co., LTD.

Enrichment of the germline *NLRC5*^{Pro191Leu} variant in patients with immune checkpoint inhibitor–induced hepatitis.

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Background: Immune checkpoint inhibitor–induced hepatitis (ICI-hepatitis) is a clinically significant immune-related adverse event (irAE) that may require treatment interruption and immunosuppressive therapy. Predictors of susceptibility to irAEs remain poorly defined. NLRC5 is a key regulator of MHC class I antigen presentation and $CD8^+$ T-cell–mediated immune activation. We previously identified a germline missense variant at the NLRC5 gene (*NLRC5*^{Pro191Leu}) that is associated with ICI-related endocrinopathies, and increased expression of downstream genes involved in antigen presentation. Our purpose was to determine whether the variant has a broader role in immune-related toxicity. **Methods:** We evaluated the prevalence and clinical associations of the germline *NLRC5*^{Pro191Leu} variant in patients with grade ≥2 ICI-hepatitis. Sanger sequencing was performed to assess the *NLRC5*^{Pro191Leu} (rs74439742) germline variant. Hepatitis severity was graded according to CTCAE criteria. Clinical data included irAE co-occurrence, duration of corticosteroid therapy, and requirement for additional immunosuppression. Variant prevalence was compared with the general population using data from the 1000 Genomes Project. **Results:** Among 39 patients with ICI-hepatitis, the cohort was predominantly composed of patients with metastatic melanoma receiving ipilimumab plus nivolumab. The variant was significantly enriched in the ICI-hepatitis cohort compared with the general population (30.0% vs 12.8%; p = 0.007, odds ratio [OR] = 2.9). Variant carriers also more frequently developed co-occurring endocrine irAEs, particularly thyroid dysfunction and hypopituitarism. Conversely, co-occurrence of hepatitis and colitis was more frequent among wild-type patients (p = 0.06, OR = 7.6), suggesting distinct immunopathogenic toxicity patterns. The severity of hepatitis was assessed by a composite outcome of maximal grade 4 hepatitis and prolonged steroid use (≥120 days). Variant carriers showed a trend toward increased hepatitis severity that did not reach statistical significance (Fisher's exact p = 0.06; OR = 4.9). **Conclusions:** Germline *NLRC5*^{Pro191Leu} is significantly more common in patients who develop ICI-hepatitis than in the general population and is associated with distinct immune-related toxicity patterns. This suggests that host genetic factors may inform toxicity surveillance and early management strategies. Larger multi-center studies are needed to validate these observations and define the clinical utility of *NLRC5*^{Pro191Leu} as a predictor of immune-related toxicity risk. Research Sponsor: Davidoff Fund.

Prevalence of *NLRC5*^{Pro191Leu} variant in the ICI-hepatitis cohort.

Group	NLRC5 WT, n (%)	*NLRC5Pro191Leu*, n (%)
ICI-hepatitis cohort (n=39)	27 (70.0)	12 (30.0)
Odds ratio		2.9
p value		0.007
General population (1000 Genomes Project) (n=694)	605 (87.2)	89 (12.8)

Systemic third generation allosteric STING agonist CRD3874-SI, a novel immunotherapy, in patients with advanced solid tumors: Results from a single-agent phase I study.

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Background: CRD3874-SI is a first in class, systemically administered, allosteric STING agonist that blocks STING's proton channel activity differentiating it from previously developed STING agonists. The drug has demonstrated pre-clinical anti-cancer activity in several murine tumor models and has pharmacological properties distinct from earlier generation STING agonists. **Methods:** This is a single institution, open-label, phase I study of CRD3874-SI in patients with advanced solid tumors. The dose escalation study follows a standard 3+3 design. CRD3874-SI is administered intravenously once per week for 2 cycles. Cycle duration is 28 days. From cycle 3 onwards, continuous weekly treatment +/- one week break (week 4) may be considered. The primary objective is to assess the safety of CRD3874-SI by determining the maximum tolerated dose, recommended phase 2 dose and schedule of administration. Secondary objectives include examining the pharmacokinetics and pharmacodynamics (IP10 analysis) of CRD3874-SI and evaluating the efficacy of CRD3874-SI as determined by best objective response rate per RECIST v1.1. Clinical trial information: NCT06021626. Research sponsor: Curadev Pharma, Inc. **Results:** As of January 5th 2026, 21 patients (sarcoma n=20, adenoid cystic carcinoma n=1) received treatment at four escalating dose levels (0.1-1.8mg/kg). The median number of prior lines of treatment was 4 (1-11). The median duration of treatment was 7 weeks (range: 1-32 weeks). 2 patients continue treatment. Reasons for treatment discontinuation include: progression of disease (n=16), toxicity (n=2), patient withdrawal (n=1). Treatment emergent adverse events (TEAEs) were manageable and reversible. Only low-grade cytokine related symptoms were reported. TEAEs possibly related to study treatment reported in >20% of participants and were mostly low grade include: fatigue (43%), chills (38%), nausea (38%), diarrhea (33% (G3 (10%)), headache (29%) and flu-like symptoms (24%). Low grade colitis not typical of auto-immune mechanism, responding well to temporary treatment pause +/- oral budesonide, were reported in 4 patients. One DLT at dose level 4 (G3 dyspnea) was observed. 19 patients are evaluable for efficacy. The best objective response per RECIST v1.1: confirmed partial response, n=1 (malignant phyllodes tumor); stable disease, n=9; progressive disease, n=9. Dose level 3 (0.9mg/kg) represents a biologically active dose (one confirmed PR and a second case with -27% tumor regression was observed). Dose proportional increase in AUC with concomitant increase in plasma CXCL10 levels were observed. **Conclusions:** CRD-3874-SI has demonstrated clinical activity with manageable safety. Dose level 0.9mg/kg is biologically and clinically active. A dose expansion phase at this dose level in is planned in >5 histology specific cohorts. Clinical trial information: NCT06021626. Research Sponsor: Curadev Pharma.

Effect of IL7 on ImmTAC-mediated killing by T cells in vitro and T-cell fitness in patients.

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Background: A blood T cell fitness (TCF) signature, reflecting properties of naïve and stem cell memory T cells, was strongly associated with clinical benefit from tebentafusp (gp100 × CD3) and brenetafusp (PRAME × CD3) ImmTAC bispecific therapies[1]. Here, we assessed whether TCF could be enhanced by IL7, a cytokine that plays a key role in T cell homeostasis and promotes the proliferation and survival of naïve and stem cell memory T cells. **Methods:** T cell exhaustion was induced in vitro by four weekly ImmTAC stimulations against the Non-Small Cell Lung Cancer (NSCLC) cell line NCIH1755 with or without IL7. Tumor killing, T cell cytokine secretion, and T cell phenotype were assessed using standard methods. Data are given as mean ± SEM; groups were compared using paired t test. *IL7R* gene expression and TCF (mean expression of *TESPA1*, *CD28* and *GPR183*) were measured in baseline whole blood from patients with unresectable or metastatic uveal melanoma (mUM) treated with tebentafusp (n=132 NCT02570308) or brenetafusp (N=37 NCT04262466) as previously described[1]. TCF high/low threshold was cut at the median. TCF was also assessed in baseline and on-treatment PBMC from patients with NSCLC and Triple-Negative Breast Cancer (TNBC) (n=15) receiving NTI7, a long acting recombinant human IL7 (rhIL7, NCT03752723, NCT04984811). **Results:** In vitro, repeated re-direction of T cells by ImmTAC resulted in reduced tumor cell lysis from 46±9% after a single stimulation to 3±1% after 4 weekly stimulations. In contrast, T cells cultured with IL7 retained tumor cell lysis after 4 stimulations (58±2% ImmTAC-redirected cytolysis compared with 3±1% in IL7-untreated T cells, p = 0.02), accompanied by a 14.3-fold increase in IFNγ secretion (p = 0.04). The proportion of naïve/stem cell memory T cells increased in response to IL7 treatment from 37±5% to 57±8% (p=0.009). In mUM patients, gene expression of *IL7R* strongly correlated with TCF signature in peripheral blood (R = 0.91, $p < 0.001$). As early as 3 weeks following a single dose of NTI7, TCF increased by ~3-fold in PBMC from NSCLC and TNBC patients. The proportion of TCF high patients increased from 36% at baseline to 93% post NTI7 monotherapy. This increase in TCF signature was sustained for at least 12 weeks. **Conclusions:** Despite repeated antigen stimulation in vitro, IL7 sustained naïve/memory T cells, enhanced ImmTAC-redirected T cell cytotoxicity and IFNγ production, and reduced T cell exhaustion. A single dose of rhIL7 resulted in a sustained increase in TCF signature and converted patients with low TCF signature into high TCF. These findings support combination with IL7 as a rational strategy to augment T cell fitness and potentially improve efficacy of ImmTAC bispecific T cell therapies. 1) Sacco et al ESMO 2024. Research Sponsor: Immunocore Ltd.

A phase I study of pomalidomide and nivolumab (Pom/Nivo) in patients with virus-associated malignancies with and without HIV.

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Background: Up to 15% of cancers worldwide are associated with oncogenic viruses and disproportionately affect people with HIV (PWH). Epstein–Barr virus (EBV) is linked to several malignancies, particularly lymphomas; Kaposi sarcoma herpesvirus (KSHV) to Kaposi sarcoma (KS) and primary effusion lymphoma (PEL); and human papillomavirus (HPV) to anogenital and head and neck cancers. Virus-associated tumors evade immune surveillance through mechanisms such as T-cell exhaustion. In vitro studies show that pomalidomide (Pom), an immunomodulatory drug, enhances T-cell co-stimulation and increases immune surface marker expression in virus-infected cell lines. Pom may synergize with nivolumab (Nivo), an anti-PD-1 monoclonal antibody, to reverse immune exhaustion and enhance antitumor immunity. **Methods:** This phase I study enrolled participants (pts) with advanced virus-associated malignancies (EBV, KSHV, HPV). PWH were required to receive antiretroviral therapy for ≥4 weeks with an HIV viral load (VL) ≤400 copies/mL. There was no CD4 T-cell requirement; however, major opportunistic infections (with limited exceptions) were not permitted within 6 months of enrollment. Intravenous Nivo (480 mg) was administered every 28 days with Pom given once daily on days 1-21 of a 28-day cycle using a 3+3 dose-escalation design (DL1=3 mg, DL2=4 mg, optional DL-1=2 mg) for up to 24 cycles. The primary objective was safety and tolerability of the combination (using CTCAE v5.0). The secondary objective was to evaluate the anti-tumor activity of Pom/Nivo using disease-specific criteria (RECIST 1.1, Lugano criteria, or modified ACTG criteria for KS). **Results:** Sixteen pts (75% male, 56% White and 37% Hispanic) were enrolled, including 9 PWH with a baseline median (med) CD4 T-cell of 253 cells/mm^3 (range 61-616) and HIV VL 37 copies/mL. After a med of 7 cycles (range 1-24), the most common Grade (G) 1/2 toxicities were anemia, lymphopenia, and maculopapular rash. Five pts had G3 or G4 neutropenia that was managed with growth factor support and Pom dose reductions. The only dose-limiting toxicity was observed in 1 pt with metastatic anal cancer in DL1 who developed G3 dyspnea; the maximum tolerated dose of Pom was 4 mg. Five pts were not evaluable for an objective response (2 died from progressive disease (PD), 2 declined further treatment, 1 was deemed ineligible), among 11 pts who received ≥3 cycles, all 4 pts with KS had a response (2 partial and 2 complete responses), 1 pt with PEL had stable disease (SD), 1 of 4 pts with HPV-malignancies had SD and 1 of 2 with nasopharyngeal carcinoma had SD, and 4 pts had PD. Among PWH, CD4 T-cell count did not change from baseline to the end-of-treatment (p=0.46). **Conclusions:** Pom/Nivo is a chemotherapy-sparing regimen with acceptable safety in advanced virus-associated cancers and promising activity in KS. Based on these results, an expanded KS cohort will be added to the trial. Clinical trial information: NCT04902443. Research Sponsor: None.

Influence of pelareorep on mutant KRAS-specific blood TIL clonal expansion.

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Background: Pelareorep (pela) is an intravenously delivered unmodified oncolytic reovirus that selectively infects cancer cells and is being developed as an immunotherapy for multiple cancers. We report here the analysis of tumor and blood samples from breast and pancreatic cancer patients that demonstrate a multi-step process of innate, viral, and tumor-specific immune activation culminating in the expansion of tumor-specific mutant KRAS (mKRAS) T cell clones that are associated with reductions in tumor volume. **Methods:** Translational samples were obtained from subjects enrolled in breast cancer (AWARE-1 ClinicalTrials.gov ID NCT04102618) and pancreatic (PDAC) cancer trials (GOBLET ClinicalTrials.gov ID NCT07280377). Analysis of tumor gene expression was performed on extracted RNA from Formalin-Fixed Paraffin-Embedded (FFPE) obtained from AWARE-1 clinical samples collected at baseline, day 3 and day 21 of therapy. Changes in tumor gene expression were determined using a customized code-set including the 50 PAM50 genes + other genes (as immune panels). Translational data from GOBLET PDAC subjects included anti-reovirus T cell responses, which were assessed by ELISPOT using whole inactivated reovirus antigen stimulation. Enumeration of the T cell fractions was performed by Adaptive Biotechnologies (Seattle, WA, USA). TCRβ CDR3 DNA was isolated from tissue and blood at baseline and from blood collected post-treatment from both studies. Antigenic specificity of selected T cell clones for mKRAS was determined by the MIRA assay (Adaptive Biotechnologies). **Results:** Sequential genetic analyses of breast cancer tumor biopsies pre- and post-pelareorep therapy demonstrated significant increases in anti-viral and immune gene expression consistent with the activation of toll-like receptor 3 (TLR3). Activation of TLR3 also induced the production of CXCL13, a chemokine critical for the formation of tertiary lymphoid structures (TLS). TLS in the tumor were confirmed by imaging mass cytometry of tumor biopsies following pelareorep treatment. Expansion of tumor-infiltrating lymphocytes (TILs) in both tumor and blood was also observed. Analysis of serial blood samples from a cohort of pelareorep-treated pancreatic cancer patients showed expansion of anti-viral T cells by ELISPOT. In addition, clonal expansion of tumor-specific T cells was observed after one cycle of treatment. The expansion of pre-existing TIL clones in the blood correlated with reductions in tumor volume in pancreatic cancer. Analysis of TCR sequences for antigen specificity confirmed the expansion of mKRAS clones in these samples. **Conclusions:** These findings suggest that pelareorep immunotherapy, through the combined activation of TLR3 and infection of the tumor, induces innate and adaptive antiviral and anti-tumor-specific immune responses capable of controlling tumor growth. Research Sponsor: None.

TPS2665 Poster Session

ASP2998, a trophoblast cell-surface antigen 2 (TROP2)–targeted immunostimulatory antibody-drug conjugate with dual payloads, in patients with locally advanced unresectable or metastatic solid tumors: A phase 1b/2 study.

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Background: TROP2 is a type I transmembrane glycoprotein involved in cell proliferation, migration, and survival, that is upregulated in and is associated with poor prognosis in patients (pts) with several malignancies including urothelial carcinoma, non-small cell lung cancer, gastric cancer and breast cancer. TROP2 antibody drug conjugates (ADCs) have demonstrated clinical efficacy and are approved for metastatic breast cancer and epidermal growth factor receptor-mutated non-small cell lung cancer. ASP2998 is a dual-payload (topoisomerase I inhibitor plus stimulator of interferon genes [STING] agonist) immunostimulatory ADC targeting TROP2. ASP2998 monotherapy has shown preclinical antitumor activity in a syngeneic mouse model bearing human TROP2-expressing tumors that was superior to single-payload topoisomerase I inhibitor TROP2 ADCs. **Methods:** This first-in-human, multicenter, open-label, phase 1b/2 dose escalation (DESC) and expansion (DEXP) study, is evaluating the safety, tolerability, recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD), preliminary antitumor activity, and pharmacokinetic profile of ASP2998 in pts with locally advanced unresectable or metastatic solid tumors. Initial DESC of ASP2998 includes 6 dose levels (n≥3 per dose level) to determine the RP2D and/or MTD. Eligible pts (aged ≥18 years) include those with urothelial carcinoma, non-small cell lung cancer, gastric/gastroesophageal junction cancer, or locally confirmed human epidermal growth factor receptor 2-negative breast cancer, who have progressed on, are ineligible for, or have refused all available standard therapies per investigator's decision. At DEXP, multiple dose levels of ASP2998 may be evaluated based on the totality of data to optimize dosage in at least one tumor type (n≤40 per dose level per tumor type). Eligible DEXP pts with non-small cell lung include those who have received ≤3 prior lines of therapy and known programmed death-ligand 1 status, without actionable oncogenic alterations, who have progressed on or after platinum-based chemotherapy and/or checkpoint inhibitors. Eligible DEXP pts with urothelial carcinoma include those who have received ≤3 prior lines of therapy and progressed on or after enfortumab vedotin plus pembrolizumab. Prior exposure to TROP2, STING agonists or topoisomerase I inhibitor-directed therapy is permitted at DESC but not DEXP. Tumor-specific backfill pts can be enrolled in the DESC cohorts at dose levels that are deemed safe and tolerable, and will be counted towards the corresponding tumor-specific DEXP cohorts. Recruitment is ongoing with 196 planned pts (36 in DESC; 160 in DEXP). ClinicalTrials.Gov Identifier: NCT07287995. Clinical trial information: NCT07287995. Research Sponsor: Astellas Pharma Inc.

TPS2666 Poster Session

Phase I/II study of AZD6750, a CD8-guided interleukin-2 agent, alone and in combination with other anti-cancer agents in participants with advanced or metastatic solid tumors.

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Background: Interleukin-2 (IL-2) has antitumor activity through stimulation of proliferation and differentiation of cytotoxic T lymphocytes, but toxicity due to systemic immune system activation limits its clinical use. AZD6750 comprises two CD8 human IgG1 binding domains and two IL-2 mutein domains and uses cis-guiding to deliver IL-2 mutein preferentially to CD8+ T cells, with the goal of increasing antitumor activity while limiting toxicity. It has high affinity for CD8α and the CD122/CD132 IL-2R complex, and reduced affinity for CD25 (IL-2Rα). In preclinical studies, AZD6750 has been shown to cause preferential proliferation of CD8+ T cells without increasing cytokine release from peripheral blood mononuclear cells; improve antigen-specific tumor cytolysis; increase IFN-γ secretion, a sign of productive responses in tumor-infiltrating lymphocytes; and inhibit growth of a tumor model in vivo. We describe the design of a phase I/II trial of AZD6750 in patients with metastatic solid tumors (NCT07115043).
Methods: This first-in-human, open-label, phase I/II, multicenter clinical trial is evaluating AZD6750 as monotherapy (Module 1, dose escalation) and combined with rilvegostomig (Module 2) in patients with selected locally advanced or metastatic solid tumors. All patients must have ECOG performance status of 0/1 and $\geq$1 measurable lesion per RECIST v1.1. In Module 1, patients must have received prior standard-of-care therapy and have a tumor type for which immune checkpoint inhibitors are known to be effective or in which IL-2 potentially has benefit. Dose escalation starts with an accelerated titration design and switches to a modified toxicity probability interval-2 (MTPI-2) design after the first 2 dose cohorts or earlier sign of grade $\geq$2 toxicity. Module 2 will enroll patients with stage IV NSCLC who have either received $\geq$1 line of therapy in the metastatic setting (including targeted therapy if actionable mutations are present) (Module 2A, dose escalation) or are metastatic treatment naïve and have tumor PD-L1 expression $\geq$1% (Modules 2A and 2B). Patients who have autoimmune or inflammatory disorders within 3 years of study or toxicity that led to discontinuation of prior immunotherapy are not eligible for Module 2. In Module 2A, dose escalation will use MTPI-2. Module 2B will be a dose expansion module. The primary endpoints of Modules 1 and 2A are the incidence of adverse events (AEs), serious AEs, and dose-limiting toxicities, which will be used to determine the maximum tolerated dose/recommended phase 2 dose. In Module 2B (dose expansion), the primary endpoint will be preliminary antitumor activity. Secondary endpoints include pharmacodynamics (PD-L1), immunogenicity (anti-drug antibodies), and pharmacokinetics. The study is actively recruiting globally, with 3 patients enrolled as of December 2025. Clinical trial information: NCT07115043. Research Sponsor: AstraZeneca.

TPS2667 Poster Session

A phase I trial evaluating an optimized B7-H3xCD3 T cell engager for treatment of solid cancer.

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Background: T cell-based immunotherapy has revolutionized oncological treatment of various malignancies. However, many patients still do not respond to immunotherapy, and long-term remissions remain rare, particularly in solid tumors. B7-H3 (CD276) is overexpressed in multiple cancer entities on both tumor cells and tumor microenvironment, the latter facilitating access of effector cells into the tumor site as prerequisite for success of therapeutically targeting solid cancers. To address the high medical need of patients with colorectal cancer (CRC), breast cancer (BC), penile cancer as well as bone and soft tissue sarcoma, we developed and validated a CD276xCD3 T cell engager (TCE) termed CC-3. CC-3 mediated pronounced antitumor activity in vitro and displayed the expected long half-life and potent antitumor activity in murine models using immunocompromised mice adoptively transferred with human effector cells with regard to prevention of lung metastasis and flank tumor growth as well as elimination of large established tumors (Zekri et al, Mol Ther, 2023). **Methods:** This is an ongoing open label, multi-center phase I clinical trial evaluating CC-3 in patients with metastatic CRC, BC, penile cancer as well as bone and soft tissue sarcoma. Key eligibility criteria include diagnosis of progressive metastatic disease and exhaustion of standard of care. The trial comprises a dose escalation part to determine the maximum tolerated dose followed by a dose expansion part to define the recommended phase II dose and collect first signs of efficacy. During the dose escalation, initially an accelerated titration design with single patient cohorts is employed. Here, each patient receives a fixed dose level (starting with 50μg for the first patient). Dose levels are increased by up to 100%, based on the decision of a safety review committee (SRC). Upon occurrence of adverse events (AEs) grade $\geq$2, dose limiting toxicity (DLT), or reaching a dose level of $\geq$800μg, treatment switches to a standard 3+3 dose escalation design. After maximum tolerated dose (MTD) is determined, defined as no more than one of six patients experiencing DLT, an additional 14 patients receive CC-3 at the MTD level in the dose expansion phase. Primary endpoints are incidence and severity of AEs, as well as the best objective response to treatment according to RECIST 1.1. Secondary endpoints include overall safety, efficacy, survival, quality of life, and pharmacokinetic investigations. At present, the accelerated titration phase employing cohorts 1 - 4 has been completed without DLT; likewise, in the so far completed cohorts 5-8 of the standard titration phase, no DLT was observed. Enrollment to cohort 9 began in May 2025. Clinical trial information: NCT05999396. Clinical trial information: 2022-503084-15-00. Research Sponsor: German Cancer Consortium (DKTK).

TPS2668 Poster Session

First-in-human phase 1a/1b study of LB-LR1109, an anti-LILRB1 monoclonal antibody, as monotherapy in advanced solid tumors and in combination with atezolizumab in advanced NSCLC.

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Background: LB-LR1109 is a human IgG4 monoclonal antibody targeting LILRB1, an inhibitory receptor expressed on multiple immune cell subsets. LILRB1 binds HLA-G, delivering suppressive signals that enable tumor immune evasion. Blocking this axis may restore immune activation within the tumor microenvironment and promote both innate and adaptive antitumor responses. Phase 1a tumor types were selected through TCGA analyses showing high LILRB1/HLA-G expression and increased infiltration of LILRB1+ NK cells, T cells, and monocytes in RCC, NSCLC, HNSCC, urothelial carcinoma (UC), and melanoma. High LILRB1 expression correlates with poor overall survival in RCC, UC, and lung SCC, supporting clinical relevance. Preclinical data (AACR2026 #1243) demonstrated that LB-LR1109 binds LILRB1 with high affinity, blocks HLA-G interactions, restores NK and T-cell function, and induces strong anti-tumor activity in human LILRB1 transgenic mouse models. LB-LR1109 also showed synergy with PD-L1 blockade, favorable PK, and an excellent safety profile, supporting clinical development as monotherapy and in combination. Public transcriptomic data also support combining LB-LR1109 with atezolizumab in NSCLC based on correlated LILRB1 and PD-L1 expression. **Methods:** This ongoing first-in-human, multicenter, open-label Phase 1 study (NCT06332755) evaluates LB-LR1109 as monotherapy (Phase 1a) and in combination with atezolizumab (Phase 1b). The study began in September 2023; Phase 1b enrollment started December 2025. Phase 1a includes monotherapy dose escalation (DL1–DL8, IV Q2W) using BLRM, enrolling patients with advanced/metastatic RCC, NSCLC, HNSCC, UC, or melanoma who relapsed from or are intolerant to approved therapies. Phase 1b evaluates LB-LR1109 (IV Q2W) plus atezolizumab 840 mg Q2W in advanced/metastatic NSCLC without actionable mutations. Patients must have received prior approved therapies including anti-PD-1/PD-L1 with ≥12 weeks of response, to test whether LILRB1 blockade may restore immune surveillance after checkpoint inhibitor resistance. Primary objectives: safety, tolerability, and determination of MTD/RP2D. Secondary endpoints: antitumor activity, PK, immunogenicity. Exploratory endpoints: correlations between LILRB1/HLA-G expression and clinical response, longitudinal immune profiling, and receptor occupancy in peripheral monocytes. The study is conducted at eight sites in Korea and the United States. Phase 1a has escalated to DL7 with no DLTs, and enrollment into the combination DL5 cohort began January 2026. Clinical trial information: NCT06332755. Research Sponsor: LG Chem Lifescienes.

TPS2669 Poster Session

Phase 1 first-in-human trial of AG01, a recombinant humanized monoclonal antibody to progranulin/glycoprotein 88 (GP88) to determine the safety, tolerability, pharmacokinetics, and preliminary antitumor activity in subjects with advanced solid tumor malignancies.

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Background: Progranulin also called GP88/PGRN plays a major role as an autocrine growth & survival factor associated with resistance to standard of care (SOC) targeted and chemo therapies in several cancers including breast cancer (BC) & non-small cell lung carcinoma (NSCLC): 1) GP88 is expressed in 80% breast invasive ductal carcinomas & is negative in normal mammary tissue; 2) GP88 tumor expression is a prognostic indicator of recurrence & survival in BC, NSCLC & prostate cancer patients (pts) 4) Elevated serum GP88 levels are present in several cancers including metastatic breast cancer (MBC), lung & prostate cancer pts compared to healthy subjects; 5) Elevated/rising GP88 serum levels in MBC pts are associated with disease progression & inferior survival. These results make GP88 an ideal therapeutic & diagnostic target in solid tumors. An anti-human PGRN/GP88 monoclonal antibody inhibiting PGRN/GP88 action was developed & expressed in CHO cells. Pharmacology, GMP manufacturing, formulation, stability studies & GLP toxicology studies in non-human primates were done. The IND application cleared by the US FDA led to the FIH AG01 study in adults with advanced solid tumors lacking effective therapies. **Methods:** A Phase 1 FIH dose-escalation study was designed in pts with advanced solid tumor malignancies, the study is approved by the University of Maryland IRB. AG01 monoclonal antibody is administered intravenously (IV) over 90 minutes every 14 days +/- 1 day; DLT observation period is the 1st cycle=28days, with AG01 Dose levels of,1mg/kg, 2mg/kg, 4mg/kg, 6mg/kg, 8 mg/kg. Initially accelerated titration design (1pt/dose level) was followed by 3+3 design). Eligibility criteria include pathologically confirmed diagnosis of advanced/relapsed/refractory solid tumor malignancy; failed >=1 SOC therapy or not a candidate/declines SOC therapy, ECOG <=2, adequate organ/bone marrow function, at least 1 RECIST 1.1 measurable and/or evaluable lesion. Tumor imaging-every 2 cycles (8 weeks) is used for response assessment. Primary objective is to determine the maximum tolerated dose MTD and/or maximum administered dose MAD of AG01 in the target population. Secondary objectives are to determine the RP2D, safety, tolerability, PKs, immunogenicity (ADA) & the preliminary anti-tumor activity of AG01 in pts with advanced solid tumors. Exploratory objectives will determine PGRN/GP88 expression in tumor tissue & PGRN/ GP88 blood levels (A&G's IHC & ELISA test). The study is ongoing; & pts are currently enrolled. A parallel prospective study investigates the association of serum GP88 in MBC pts with response to SOC therapy and progression of disease based on RECIST 1.1 criteria. These studies are supported by NCI grants R44CA224718 and CA210817. Clinical trial information: NCT05627960. Research Sponsor: None.

TPS2670 **Poster Session**

A first-in-human phase I clinical trial evaluating the safety, tolerability, and preliminary efficacy of the novel fas ligand (FasL) inhibitor M3T01 in adults with advanced solid tumors.

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Background: Tumor-specific T cells undergo apoptotic cell death following FasL binding to the fas (CD95) receptor. FasL is upregulated in many advanced cancers and is expressed by tumor endothelial cells, macrophages, and activated T and natural killer (NK) cells. Consequently, FasL contributes to tumor progression through deletion of tumor-specific T cells and impaired T cell tumor infiltration. Preclinical studies demonstrate that FasL blockade facilitates increased T cell tumor infiltration and enhances efficacy of immune checkpoint inhibitors and adoptive cell therapies. M3T01 is a fully human IgG4/kappa monoclonal antibody that potently inhibits FasL. This is an ongoing first-in-human phase I clinical trial (NCT06719362) evaluating the safety, tolerability and preliminary antitumor efficacy of M3T01 as monotherapy and in combination with pembrolizumab in adults with advanced solid tumors. **Methods:** The primary objectives are to evaluate the safety/tolerability, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of M3T01. Secondary objectives are to characterize the pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary antitumor efficacy of M3T01 as monotherapy and in combination with pembrolizumab. A sub-study will evaluate paired tumor biopsies (pre-treatment and cycle 2 day 8) to evaluate for changes in the tumor microenvironment induced by FasL inhibition. Eligible patients have unresectable or metastatic solid tumors that are refractory to standard systemic therapy. Patients must have adequate organ function, measureable disease per RECIST v1.1 or RANO 2.0, and an ECOG performance status of 0-1. Dose escalation through a 3 + 3 design will evaluate M3T01 as monotherapy and in combination with pembrolizumab (administered intravenously every 3 weeks). Monotherapy cohorts 1-4 (100 to 600 mg) have been completed without DLT. After completion of the dose escalation portion of the trial, dose expansion cohorts will open to evaluate M3T01 in combination with standard systemic therapies in the treatment of patients with glioblastoma, gastric/esophageal adenocarcinoma, and head and neck squamous cell carcinoma. Clinical trial information: NCT06719362. Research Sponsor: None.

TPS2671 Poster Session

A phase I/IIa dose-escalation, dose-optimization, and dose-expansion study to evaluate the safety and preliminary efficacy of tri-specific antibody (SOA101) in subjects with advanced solid tumors.

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Background: SOA101 is a nanobody (VHH)-based tri-specific T cell engager targeting programmed death-ligand 1 (PD-L1), Human Leukocyte Antigen G (HLA-G), and Cluster of Differentiation 3 (CD3) to modulate the immunosuppressive tumor microenvironment and enhance T-cell activation and recruitment. In vitro, SOA101 showed potent, broad-spectrum anti-tumor activity, enhancing peripheral blood mononuclear cells mediated cytotoxicity against non–small cell lung cancer (NSCLC) cells with varying PD-L1/HLA-G expression. In vivo, SOA101 demonstrated superior anti-cancer efficacy compared with relevant monoclonal antibodies and bispecific T-cell engagers in a humanized NSCLC mouse model, achieving effective tumor control and prolonged survival. The pharmacologically active dose did not increase cytokine secretion ex vivo, indicating a manageable safety profile with low cytokine release syndrome risk. **Methods:** This first-in-human clinical study, regulated by FDA and TFDA, is being conducted in subjects with locally advanced or metastatic solid tumors, including NSCLC ovarian cancer, head and neck cancer, breast cancer, and colorectal cancer with PD-L1 expression ≥1%. The dose-escalation phase is a six-cohort study designed to determine the maximum tolerated dose or pharmacoactive dose, enrolling up to 36 subjects who receive bi-weekly SOA101 for up to six doses. The dose-optimization phase randomizes approximately 40 subjects into low- or high-dose cohorts to further evaluate safety, pharmacokinetics, preliminary antitumor activity, and to determine the recommended Phase 2 dose. Part 2 may include up to four disease-specific expansion cohorts (up to 27 subjects each) to further characterize safety and antitumor activity. The study is currently in the dose-escalation phase. Cohort 1 has been completed without DLT, and enrollment for Cohort 2 has begun following approval by the independent Safety Review Committee. Clinical Trial Registry Number: NCT07055594. Clinical trial information: NCT07055594. Research Sponsor: None.

TPS2672 Poster Session

Phase 1, open-label clinical trial to treat stage IV cancer patients harboring multiple patient-specific mutated cell surface proteins with chimeric antibodies.

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Background: Despite the advent of multiple classes of systemic cancer treatments, tumor recurrence and subsequent resistance to systemic therapy remain a persistent challenge. Thus, newer treatment strategies are needed for metastatic cancer refractory to extant therapies. Leveraging the vast landscape of targetable tumor-specific mutated peptides (TSPs) on the surface of malignant cells offers an opportunity for individualized antibody therapy. These surface TSPs arise due to genetic instability and progressive accumulation of random missense mutations in cancer cells, resulting in dozens to hundreds of substituted amino acids in proteins at the cancer cell surface. We refer to surface proteins harboring substituted amino acids as Mutated cell Surface Proteins (MSPs). Antibodies generated against short TSPs preferentially bind to the mutated peptide compared to the nonmutated peptide. Notably, most cancers harbor several distinct MSPs. For instance, of 100 colon cancer cases, 96% harbored ≥10 MSPs, with similar findings in lung cancer (97%), melanoma (93%), lymphoma (92%), bladder cancer (85%), and stomach cancer (84%). While the presence of many MSPs is common, each patient harbors a unique set of MSPs. Study sponsor has developed a means of preparing custom antibodies against the TSPs present in multiple MSPs to inhibit cancer growth in several preclinical models, prompting a pan-tumor Phase I study evaluating the safety and feasibility of such therapy in refractory cancer patients. **Methods:** This is a phase I first-in-human study aiming to enroll up to 12 eligible subjects. Primary objective: Safety and tolerability. Secondary objectives: Feasibility of producing and administering the protocol-directed treatment to the patient population; progression-free survival; response rate. Key Inclusion Criteria: a) Stage IV refractory cancer (breast, colon, esophageal, kidney, lung, ovarian, bladder urothelial, stomach, or pancreatic cancers, melanoma, or lymphoma); b) availability of tumor and matched normal tissue sequence data. Treatment: Custom-manufactured chimeric antibodies are being used to target a minimum of 2 to 8 MSPs per patient. An interval of 4- to 6-month antibody production interval is required from initial consent to the start of treatment. The dose-limiting toxicity (DLT) period is 4 weeks; thereafter, in addition to antibody treatment, subjects can receive standard of care [immunotherapy, targeted therapy or hormonal therapies]. Treatment schedule: Week 1, 100 mg i.v.; week 2, 200 mg i.v.; week 3 400 mg; and then 400 mg i.v. every other week for total of 10 doses. We have enrolled 3 subjects and have completed treatment of Subject #1 (bladder cancer), with no DLT to date. The study is ongoing since 12/2025. Clinical trial information: NCT06674538. Research Sponsor: Moonshot Antibodies, Inc.

TPS2673 Poster Session

A logic-gated chimeric antigen receptor T-cell (CAR T) therapy with an armored, membrane-tethered IL-12 booster in patients with advanced solid tumors with HLA-A*02 loss of heterozygosity (LOH): EVEREST-2, a phase 1/2 study.

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Background: The main challenge for developing CAR T therapies for solid tumors is the lack of targets that distinguish tumor from normal cells, resulting in on-target, off-tumor toxicity. Tmod logic-gated CAR T therapy addresses this challenge by incorporating 2 CARs on the same T cell: an activator targeting a marker on both tumor and normal cells, and a blocker targeting HLA-A*02 that inhibits CAR T activity against normal cells while allowing activation against tumor cells (with HLA-A*02 LOH), improving tumor selectivity and decreasing toxicity. Early safety results from 3 ongoing phase 1/2 clinical trials of logic-gated, Tmod CAR T therapy (EVEREST-1, EVEREST-2, and DENALI-1) have demonstrated manageable safety and tolerability in patients with advanced solid tumors (Grierson et al, *SITC*, 2024; Ward et al, *SITC* 2025; Specht et al, *SABCS*, 2025). Early efficacy results include the first ever reported complete response in a patient with non-small cell lung cancer following treatment with a CAR T-cell therapy (A2B694). A2B543 is an autologous Tmod CAR T therapy that contains the same Tmod construct as A2B694 with an added membrane-tethered IL-12 (memIL12) booster. Specifically, A2B543 is comprised of autologous Tmod cells transduced with 2 lentiviral vectors: one expressing both the HLA-A*02-targeted blocker and the mesothelin-targeted CAR activator; and a second expressing the memIL12 booster. Interleukin 12 (IL-12) is a potent, pro-inflammatory cytokine that plays a crucial role in inducing antitumor immune responses; however, systemic IL-12 can be prohibitively toxic (Jia et al, *Front Immunol*, 2022). In A2B543, expression of the memIL12 cassette is under the control of an NFAT promoter and is induced during antigen engagement or T cell activation. This inducible memIL12 is designed to reduce the toxicity associated with systemic IL-12 while enhancing the long-term potency and persistence of Tmod (Zhang et al, *J Immunother Cancer*, 2025). **Methods:** EVEREST-2 (NCT06051695) is a phase 1/2, open-label, nonrandomized study evaluating the safety and efficacy of A2B543 in adults with recurrent/metastatic mesothelin-expressing cancers with tumor-associated HLA-A*02 LOH, including mesothelioma, colorectal, non-small cell lung, pancreatic, or ovarian cancer. Patients are enrolled through BASECAMP-1 (NCT04981119), a master prescreening study that identifies patients with HLA LOH via next-generation sequencing and cryopreserves leukapheresis product. Upon progression, A2B543 is manufactured and then administered after lymphodepletion. The phase 1 primary objective is to evaluate the safety and tolerability of A2B543 and identify a recommended phase 2 dose (RP2D). The phase 2 primary objective is to assess overall response rate. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

TPS2674 Poster Session

A phase I, open-label, dose-escalation study of CAR001 (mRNA-engineered Nb-CAR.BiTE-γδ T cells) in patients with relapsed or refractory solid tumors.

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Background: Solid tumors are characterized by a highly immunosuppressive tumor microenvironment (TME). Key immune checkpoint molecules, such as HLA-G and PD-L1, are frequently expressed and act as barriers that limit the infiltration and efficacy of conventional CAR-T cell therapies. CAR001 is an investigational, allogeneic, mRNA-engineered Nb-CAR.BiTE-γδ T cell therapy. By utilizing the innate homing capabilities of γδ T cells and a dual-targeting mechanism, direct binding of HLA-G by T cells and secreting PD-L1 bispecific T-cell engagers from T cells, CAR001 is designed to overcome TME-mediated resistance. This study evaluates the safety and potential activity of repeat intravenous dosing of CAR001 in patients with advanced solid tumors. **Methods:** Study Design: This is an ongoing, multicenter, open-label, phase I dose-escalation study utilizing a standard 3+3 design or similar escalation schema. Patient Population: Adults with histologically confirmed refractory or relapsed solid tumors (including, but not limited to, colorectal cancer, glioblastoma, and triple-negative breast cancer) who have exhausted standard of care. Intervention: Patients receive escalating doses of CAR001 via intravenous infusion. The protocol allows for repeat dosing to enhance therapeutic persistence. Objectives: The primary objective is to evaluate the safety and tolerability of CAR001 and to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Secondary objectives include assessing preliminary antitumor activity per iRECIST or RANO criteria, as well as characterizing the pharmacokinetic profile of the Nb-CAR.BiTE-γδ T cells. Safety Monitoring: Adverse events (AEs) are monitored using CTCAE v5.0, with specific focus on dose-limiting toxicities (DLTs), cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). Trial Status: This trial is currently active and enrolling patients. As of the submission deadline, dose-escalation cohorts are ongoing. To maintain the integrity of the study and comply with ASCO Trials in Progress guidelines, no formal analysis of clinical endpoints or treatment outcomes is provided. Clinical trial information: NCT06150885. Research Sponsor: None.

TPS2675 Poster Session

A phase 1/2 dose-escalation/expansion study of REGN10597 (anti–PD-1–IL2Rα-IL2) in patients with advanced solid tumors.

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Background: Interleukin 2 (IL-2) is a cytokine involved in lymphocyte expansion and differentiation during the anticancer immune response. Aldesleukin, an approved recombinant high-dose IL-2 therapy, has shown complete and durable responses in some cases; however, high-dose IL-2 is associated with severe toxicity, including vascular leak syndrome and pulmonary edema. Despite clinical advances with checkpoint inhibitor therapies, many advanced solid tumors continue to respond poorly to these treatments. REGN10597 is an antibody–cytokine fusion protein comprising a human anti–programmed cell death-1 antibody fused with a receptor-masked cytokine, IL2Rα-IL2. REGN10597 has demonstrated tumor inhibition, enhanced specificity, and reduced toxicity versus recombinant high-dose IL-2 in preclinical mouse models (Wu et al. Cell Rep Med 2024;5:101747). Here we describe BrILliance (NCT06413680), a study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of REGN10597 in patients with advanced solid tumors. **Methods:** This is an open-label, Phase 1/2, dose escalation/expansion, first-in-human, multicenter study evaluating REGN10597 in advanced or metastatic solid tumors. Patients must be aged ≥18 years with histologically or cytologically confirmed locally advanced or metastatic tumors and confirmed disease progression on standard-of-care therapy. During the dose escalation phase, patients will be enrolled to receive REGN10597 by intravenous infusion at the assigned dose level and schedule (additional dose schedules are available for further exploration). When the recommended Phase 2 dose level and schedule are determined, additional patients will be enrolled across two dose expansion cohorts: patients with locally advanced or metastatic melanoma (Cohort 1) and those with advanced or metastatic clear cell renal cell carcinoma (Cohort 2). Dose escalation primary endpoints include incidence of dose-limiting toxicities, incidence of treatment-emergent adverse events (including those leading to treatment discontinuation or death), incidence of serious adverse events, and the number of patients with Grade ≥3 laboratory abnormalities. The dose expansion primary endpoint is objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by investigator assessment. Secondary endpoints for both phases include additional efficacy measures (best overall response, duration of response, disease control rate, time to response, and progression-free survival, all per RECIST 1.1), and pharmacokinetics and immunogenicity of REGN10597. Trial enrollment for the dose escalation phase began on October 1, 2024; as of January 27, 2026, 22 patients have been enrolled. Clinical trial information: NCT06413680. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS2676 **Poster Session**

Biomarker study of BND-22 in combination with cemiplimab in solid tumors.

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Background: Immune checkpoint inhibitors benefit only a subset of patients, indicating a need to identify other therapeutic targets and understand the role of tumor microenvironment in shaping immune response. Immunoglobulin-like transcript-2 (ILT2) is an inhibitory receptor expressed on monocytes, dendritic cells, NK cells, and subset of T cells. ILT2 binds multiple MHC class-I molecules, with highest affinity for HLA-G, which is frequently overexpressed in solid tumors. Engagement of HLA-G/ILT2 pathway inhibits key immune functions, including cytotoxicity, cytokine production, antigen presentation, phagocytosis and proliferation. ILT2 expression can be upregulated following anti PD-1 therapy, suggesting a mechanism of resistance to checkpoint blockade. Inhibition of this pathway could potentially promote antitumor immune responses. BND-22, a first-in-class humanized IgG4 mAb, selectively binds to ILT2 on NK/T cells/macrophages, blocking its interaction with HLA-G. In preclinical studies and in a phase I trial, BND-22 alone and in combination with a PD-1 inhibitor demonstrated enhanced anti-tumor activity. The study revealed a dose-dependent activation in immune markers. Building on this finding, we initiated a phase II biomarker study (NCT06651593) of BND-22 in combination with cemiplimab, a recombinant human IgG4/kappa anti–PD-1 mAb, to further understand immune biology and explore the tumor microenvironment. **Methods:** The study has 2 patient cohorts: Cohort 1: patients with cholangiocarcinoma, who have had prior immunotherapy and Cohort 2: patients with microsatellite stable colorectal cancer and ovarian cancer who are anti–PD-1/PD-L1 naïve. Approximately 40 patients will be enrolled (10 per indication and an additional 10 to the best performing indication). The dose of BND-22 is 10 mg/kg IV on Day 1 every 3 weeks (Q3W), based on the dose escalation trial (NCT04717375). The dose of cemiplimab is the FDA-approved dose of 350 mg IV on Day 1 Q3W, starting at C2D1. Each cycle = 21 days. The combination will be administered for a max of 24 months in the absence of progression or until progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation. Biopsy tissues and peripheral blood samples for biomarker analyses will be collected at baseline, on treatment, and at progression (for patients with CR, PR, or SD≥6 months). The primary objective is 1) to identify biomarkers related to mechanism of action and predictors of response, resistance, and survival 2) evaluate the association between the biomarkers and outcomes. The secondary objective is to evaluate efficacy, safety, and tolerability of this combination; identify imaging characteristics predictive of response and toxicity; and, evaluate TCR beta variable polymorphism and its relationship with immune-related adverse events. Enrollment is ongoing; 2 patients in Cohort 1 and 10 patients in Cohort 2 have been treated. Clinical trial information: NCT06651593. Research Sponsor: Sanofi; Regeneron.

TPS2677 **Poster Session**

The TIME trial: Phase II randomized controlled trial of time-of-day–specified nivolumab and ipilimumab for advanced melanoma.

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Background: Nivolumab/ipilimumab is standard of care for advanced melanoma patients based on Phase III randomized data from the CheckMate 067 trial. The recent 10-year outcomes results were reported with a melanoma specific survival for Nivolumab/ipilimumab of 52%. These data are very encouraging, but 50% of patients still succumb to their disease by 10-years. Preclinical data suggests that the circadian rhythm may influence the anatomic localization, function and activity of T cells, the target of immunotherapy. More T cells in the tumor or tumor-draining lymph node during initial immunotherapy administration may improve clinical responses and long-term outcomes. To investigate this idea, we performed a retrospective analysis, the MEMOIR study, finding that more evening infusions of immunotherapy were associated with significantly worse progression free and overall survival for metastatic melanoma patients. These findings have now been reproduced in other cancer histologies, in a larger meta-analysis, and in pre-clinical mechanistic studies. Considering these data, we hypothesize that evening infusions of immunotherapy will have worse progression free survival than either morning or midday infusions. **Methods:** The TIME trial is a three-arm phase II study of time-of-day specified administration of standard dose nivolumab/ipilimumab for metastatic melanoma. For newly diagnosed metastatic melanoma patients enrolled on study, they will be randomized to receive 4 cycles every 3 weeks of nivolumab/ipilimumab between 8:00-11:00 (Arm A), 11:00-14:00 (Arm B), or 14:00-17:00 (Arm C). Following these 4 cycles, they will receive standard of care maintenance nivolumab in a time-of-day agnostic fashion. Eligible patients must have stage IV unresectable cutaneous, acral or mucosal melanoma, no prior immunotherapy within 1 year, ECOG performance status of 0-1, age $\geq$ 18, no symptomatic or hemorrhagic brain metastases with none greater than 2 cm. The primary objective is to determine whether progression free survival for Arm A or Arm B is superior to Arm C. Secondary objectives include assessments of adverse events, melanoma specific survival and overall survival. We will evaluate the immune profiles of blood and tumor to assess the impact of time of drug administration on the circulating immune responses and the tumor immune microenvironment. 99 patients will be enrolled to detect a HR of 0.50 with at least 80% power and a Type 1 error rate of 0.1 (2-sided) for a comparison of A vs. C, and B vs. C. The study is open at Emory and has enrolled 3 patients; the study is undergoing regulatory review at MGH and Cedars-Sinai. Clinical trial information: NCT07155317. Research Sponsor: None.

TPS2678 Poster Session

A phase 1b, two-arm study of tolododekin alfa (ANK-101) in combination with an anti–PD-1/PD-L1 antibody in participants with advanced non–small cell lung cancer (NSCLC).

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Background: Tolododekin alfa (ANK-101) is an anchored immunotherapy linking IL-12 to aluminum hydroxide through an alum-binding protein (ABP). Direct delivery to tumors results in prolonged IL-12 local retention and limited systemic absorption. A Phase 1 study in advanced solid tumors demonstrated ANK-101 was well tolerated with evidence of antitumor activity, recruitment of CD8+ T cells, and induction of local programmed cell death ligand 1 (PD-L1) expression. ANK-101 is now being evaluated in combination with PD-1/PD-L1 checkpoint blockade (ICB) in patients with non-small cell lung cancer (NSCLC). **Methods:** This study is a Phase 1b, two-arm, open-label study of direct injection (IT) of tolododekin alfa administered in combination with an anti-PD-1/PD-L1 antibody in participants with locally advanced or metastatic NSCLC. Cohort A will be conducted in participants who have progressed on prior standard of care treatment with ICB and platinum-based chemotherapy, either in combination or sequentially. Cohort B will enroll participants with untreated locally advanced or metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 50%. Participants with targetable EGFR mutations or ALK rearrangements are excluded. In Cohort A, participants will receive tolododekin alfa at 250 μg/mL IT in combination with cetrelimab (anti-PD-1) intravenously (IV) Q3W at a dose of 360 mg for up to 8 cycles, followed by cetrelimab monotherapy for up to one year, unless they have unacceptable toxicity, clinical deterioration, confirmed tumor progression, or have withdrawn consent. In Cohort B, participants will receive tolododekin alfa at 250 μg/mL IT in combination with investigator's choice of an FDA-approved ICB for first-line use as monotherapy in patients with TPS ≥" role="presentation" tabindex="0">≥ 50% IV Q3W at the approved dose for up to 8 cycles, followed by continued ICB according to the FDA-approved label. The primary objective is objective response rate by RECIST 1.1. Secondary endpoints include safety, duration of response, disease control rate, progression-free survival, and overall survival. In addition, lesion-level responses, serum PK analyses, and anti-drug antibody (ADA) levels will be assessed. Exploratory endpoints include measurements of selected serum cytokine levels and characterization of the composition of the tumor microenvironment before and on-treatment. This clinical trial is in progress. Clinical trial information: NCT07027514. Research Sponsor: Ankyra Therapeutics.

TPS2679 Poster Session

OP-NEU-101: A phase 1/2 open-label, dose finding and expansion study to investigate the safety and effectiveness and determine the optimal dose of N17350 administered intratumorally in participants with advanced solid tumors.

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Background: Despite advances in targeted therapies and immunotherapy, many patients with advanced solid tumors have limited treatment options. N17350 is a first-in-class, optimized therapeutic elastase designed for intratumoral administration that selectively induces cancer cell death by activating the neutrophil elastase (ELANE) pathway while preserving immune cell viability. Preclinical studies demonstrated broad antitumor activity across 30 cancer cell lines, 15 in vivo models, and 45 patient-derived tumor samples, as well as induction of antitumor immunity in both immunologically cold and hot tumors (Gujar et al., 2025; doi:10.1016/j.xcrm.2025.102446. Together with preclinical toxicology studies supporting a starting dose within the therapeutic range, these findings support the clinical evaluation of N17350. **Methods:** This first-in-human, multicenter, open-label Phase 1/2 study (OP-NEU-101) is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of intratumorally administered N17350 in adults with advanced solid tumors. The study consists of a dose-finding and dose-optimization phase (Parts A1 and A2) followed by monotherapy expansion cohorts (Part A3). Dose-finding in participants with superficial (Part A1) and visceral lesions (Part A2) is guided by a Backfill Bayesian Optimal Interval (BF-BOIN) design to determine the maximum tolerated dose, optimal biologic dose, and/or recommended Phase 2 dose (RP2D). Once optimal dose(s) are identified, up to five tumor-specific expansion cohorts (data dependent: SCCHN, NSCLC, TNBC, cuSCC, Melanoma) may be opened to further characterize safety and clinical activity. Key Eligibility Criteria: Eligible participants are adults with advanced or metastatic solid tumors who have progressed on or are intolerant to standard therapies, have ECOG performance status 0–1, adequate organ function, and at least one superficial or visceral lesion suitable for intratumoral injection. Endpoints: The primary endpoints of the dose-finding phase are safety and tolerability, including the incidence of dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints include PK, immunogenicity, and preliminary antitumor activity assessed per RECIST v1.1 and/or itRECIST. Exploratory endpoints include evaluation of ELANE pathway activation, immune modulation, circulating tumor DNA, and multiomic analyses of tumor tissue and peripheral blood. The study has been initiated and will be enrolling participants at sites in the United States and Australia. Clinical trial information: NCT07339176. Research Sponsor: None.

TPS2680 Poster Session

A phase 1, first-in-human study of DS5361, a small-molecule, nonsense-mediated mRNA decay (NMD) inhibitor in patients with advanced/metastatic solid tumors (parts 1 and 2).

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Background: Despite the profound impact of immune checkpoint inhibitors (ICIs) on the treatment of patients with advanced or metastatic solid tumors, only a small proportion of patients experience meaningful responses, underscoring the need for novel therapies to maximize clinical benefit. High tumor mutational burden (TMB-H) and high microsatellite instability (MSI-H) are associated with improved efficacy of ICIs due to an increase in neoantigens, tumor-specific peptides displayed on tumor cell surfaces that are critical for antitumor immune responses. mRNAs harboring premature termination codons, including neoantigenic transcripts derived from frameshift mutations, are recognized and degraded by NMD. DS5361 is a potentially first-in-class, orally available, small-molecule inhibitor targeting the serine/threonine kinase SMG1, a key component of the NMD mechanism. DS5361 is designed to activate antitumor immunity by increasing neoantigen expression and, when administered in combination, to enhance ICI efficacy. **Methods:** DS5361-061 (NCT07182591) is a Phase 1, first-in-human, open-label, multicenter study (N≈66 for Parts 1 and 2) of DS5361 as monotherapy (Part 1) and in combination with pembrolizumab (Part 2). Patients must be adults, have measurable disease per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with advanced or metastatic TMB-H and/or MSI-H solid tumors who are unable to tolerate standard treatment or have disease that is refractory to standard treatment, or for which no such treatment is available, will be enrolled across both parts. The primary objectives in Parts 1 and 2 (dose escalation) are to evaluate the safety and tolerability, and determine the maximum tolerated dose, of DS5361 as monotherapy in Part 1 and in combination with pembrolizumab in Part 2, and/or determine the recommended dose(s) for expansion in combination with pembrolizumab (Part 2 only). Safety endpoints include dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints include objective response, disease control, and duration of response, all assessed by the investigator per RECIST 1.1, as well as pharmacokinetics. Enrollment is ongoing. Clinical trial information: NCT07182591. Research Sponsor: Daiichi Sankyo.

TPS2681 Poster Session

Updated design of INVOKE: A phase 1 study of OKN4395, a first-in-class EP2/EP4/DP1 triple prostanoid receptor antagonist, in patients with advanced solid tumors.

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Background: The immunosuppressive pathway of prostaglandin E_2 (PGE_2), part of the cyclo-oxygenase (COX) pathway, is upregulated in certain cancers and has been implicated in tumor evasion of CD8 T, NK, and dendritic immune cells, allowing tumor growth and metastasis (Jin et al., 2023). COX2 inhibitors, aspirin and nonsteroidal anti-inflammatories (NSAIDS) have shown some survival benefit in patients with gastrointestinal cancer and others (Cao et al., 2016; Martling et al., 2025; Takiuchi et al., 2018; Zhang et al., 2025); however, results are inconsistent, likely due to toxicity limiting complete blockade of the pathway, highlighting the need for more potent but selective inhibitors. OKN4395 is a first-in-class, highly selective, equipotent inhibitor of EP2, EP4, and DP1, downstream receptors for COX-derived PGE_2, and PGD_2, respectively. DP1 has described roles in immunosuppression and inhibition of apoptosis, supporting the therapeutic rationale (Luo et al., 2024; Peinhaupt et al., 2017). OKN4395 is hypothesized to modulate the tumor microenvironment to allow an effective immune response as monotherapy, and to potentiate the effect of immunotherapies such as checkpoint inhibitors, both of which are evaluated in INVOKE. Tumor types for INVOKE were selected using previously presented multimodal artificial intelligence (AI) drug-matching algorithms (Grimaldi, et al., 2025). **Methods:** INVOKE (OKN-4395-121; NCT06789172) is a Ph1a/1b, first-in-human study of OKN4395 (oral, BID) as monotherapy (mono) or in combination with a PD1 checkpoint inhibitor (combo), in patients with advanced solid tumors. Ph1a is a Bayesian dose escalation in mono with a new parallel substudy, followed by combo dose confirmation, primarily assessing safety, establishing the Ph1b dose. Response will be assessed in updated Ph1b (cohorts of n=20): select sarcomas (mono), non-small cell lung (combo), colorectal (combo), and gastric cancer (combo). Key inclusion criteria include COX-active (Ph1a) or above-listed (Ph1b) tumors, performance status 0-1, biopsy-amenable lesions, and adequate organ function. Active CNS metastases, upper GI bleed risk factors, untreated H. pylori infection, and concomitant NSAIDs/COX inhibitors/prostaglandins are exclusionary. A new and innovative 3-period, crossover substudy in parallel with Ph1a will explore the intra-participant effects of food and gastric pH on OKN4395 pharmacokinetics. Trial data, paired pre- and on-treatment biopsies, and exploratory biomarkers will be used to enhance development using advanced agentic AI systems, including a synthetic digital twin control arm, novel methodology of which is submitted to this meeting as well. Ph1a of the study is currently recruiting in the US, UK, and Australia. Dose Level 5 concluded in December 2025 with no DLTs to that date. Clinical trial information: NCT06789172. Research Sponsor: None.

TPS2682 **Poster Session**

Eiu-104101: A first-in-human phase 1a/1b study of EVOLVE104, a trispecific CD3×CD2×ULBP2/5/6 T-cell engager, in advanced urothelial and squamous cell carcinomas.

Tony Fiorino, Manish R. Sharma, Meredith McKean, Jacqueline T. Brown, Jacob Stephen Thomas, Thomas Urban Marron, Shaun O'Brien, Xiaowei Guan, Astha Bhatia, Keri Urwin, Oksana Sergeeva, Jay Fine, Alexander I. Spira; EvolveImmune Therapeutics, Branford, CT; The START Center for Cancer Research – Midwest, Grand Rapids, MI; Sarah Cannon Research Institute, Nashville, TN; Winship Cancer Institute of Emory University and Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA; Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; Virginia Cancer Specialists and NEXT Oncology, Fairfax, VA

Background: EVOLVE T cell engagers (TCEs) bind to a tumor antigen and to both CD3 and CD2 on T cells, thereby providing integrated costimulation via CD2 binding. EVOLVE TCEs demonstrate superior T cell activation and tumor cell killing compared to first generation TCEs, without excess cytokine release or tonic T cell activation, and may offer clinical benefits such as enhanced potency and duration of activity. UL16 binding proteins 2, 5 and 6 (ULBP2/5/6) belong to a family of cell surface proteins that are ligands for the NKG2D receptor. We have previously reported that cell-surface ULBP2/5/6 is not present in vital organs and found in some mucosal epithelia. Cell surface ULBP2/5/6 is found in urothelial carcinomas and squamous cell carcinomas (SCCs). With high expression on malignant cells and limited normal tissue expression, ULBP2/5/6 are intriguing targets for cancer immunotherapy. EVOLVE104 is a trispecific TCE that binds ULBP2/5/6 and both CD3 and CD2 on T cells. Preclinical studies with EVOLVE104 demonstrated enhanced T cell activation and killing of ULBP2/5/6-positive tumor cells compared to bispecific TCEs, and no safety concerns were identified in preclinical toxicity studies. With this encouraging preclinical profile, EVOLVE104 represents a novel approach to redirected T cell therapy in solid tumors. **Methods:** EIU-104101 is a first-in-human phase 1a/1b study evaluating EVOLVE104 monotherapy in adults with advanced solid tumors. Eligible tumor types include urothelial carcinoma of the bladder and SCCs of the bladder, lung, esophagus, tongue, skin, and anogenital region (penis, anus, vagina, vulva, cervix, and urethra). Subjects must have locally advanced or metastatic disease that has relapsed from, or is refractory to, standard-of-care therapies. Study objectives include assessing the safety, efficacy, pharmacokinetics and pharmacodynamics of EVOLVE104 and identifying the recommended phase 2 dose (RP2D). The phase 1a portion of the study will enroll up to 80 subjects using a Bayesian optimal interval (BOIN) dose-escalation scheme including backfill at dose levels deemed safe, with a key objective to identify one or more recommended doses for expansion (RDEs). Phase 1b includes two expansion cohorts: Cohort A, which will be a dose optimization cohort in a single indication (to be determined based on the phase 1a observations) in which 40 subjects will be randomized 1:1 to two RDEs to determine the RP2D; and Cohort B, which will enroll up to 40 subjects in other relevant indications. The study opened in October 2025 and is actively enrolling at US sites. ClinicalTrials.gov Identifier: NCT07217171. Clinical trial information: NCT07217171. Research Sponsor: EvolveImmune Therapeutics.

TPS2683 Poster Session

POLARIS: Polymetastatic lesion ablative radiotherapy with immunotherapy study.

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Background: Patients with polymetastatic disease, most commonly defined as >5 metastatic lesions, often have limited treatment options and poor overall prognosis[1,2]. The emergence of immunotherapy (IO) has slowed disease progression in some patients; however, its efficacy is limited by tumor heterogeneity and patient-specific factors, including baseline health status[3]. Emerging data suggest a synergistic effect when combining IO with radiotherapy (RT), a strategy that has led to FDA-approved treatment approaches in non-small cell lung cancer (NSCLC)[4–6]. As multimodal cancer therapies evolve, robust methods to assess treatment response are increasingly important. Circulating tumor DNA (ctDNA) is a minimally invasive biomarker that has been shown to correlate with clinical response to therapy[7,8]. However, the kinetics and clinical significance of ctDNA in patients receiving combined IO and ablative RT remain poorly characterized. **Methods:** POLARIS is a pilot phase II, double-arm clinical trial evaluating the addition of ablative radiotherapy in patients with polymetastatic disease receiving immunotherapy. Twenty-eight patients with polymetastatic disease, defined as having at least 3 and no more than 10 metastatic lesions, and receiving immunotherapy alone for at least 30 days prior to registration will be enrolled at the University of Illinois Hospital & Health Sciences System (UIH). Patients will be stratified into two cohorts based on their response to immunotherapy after ≥3 months: Cohort A includes patients with investigator-assessed stable disease or partial response, while Cohort B includes patients with oligoprogression, defined as 1–5 sites of progressive disease within 3 months of registration. Both cohorts will receive ablative RT targeting up to 10 metastatic lesions in combination with ongoing immunotherapy. The primary endpoint is the proportion of patients achieving a molecular response, defined as a >50% reduction in ctDNA levels, at 8 weeks following ablative RT. Secondary endpoints include overall survival and progression-free survival at 6 and 12 months, objective response rate, and treatment-related adverse events (TRAEs). This trial is the first to prospectively evaluate ablative radiotherapy as an adjunct to immunotherapy while integrating ctDNA as a biomarker of treatment response in polymetastatic disease. Clinical trial information: NCT07269080. Research Sponsor: University of Illinois Chicago.

TPS2684 Poster Session

Pharmacokinetics and pharmacodynamics evaluation in phase I trial of APX-343A, selective NOX inhibitor targeting CAF-mediated immunosuppression in patients with advanced solid tumors.

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Background: Cancer-associated fibroblasts (CAFs) drive fibrotic remodeling and immune exclusion in solid tumors and contribute to resistance to immune checkpoint inhibitors (ICIs). CAF-mediated immune suppression is regulated by upstream oxidative signaling pathways. NADPH oxidases (NOXs) are upregulated in CAFs and promote fibrotic remodeling and myeloid cell–mediated inhibition of cytotoxic T-cell function, linking CAF activity to immune exclusion and immunotherapy resistance. APX-343A is a selective NOX1/2/4 inhibitor designed to modulate CAF-associated tumor biology. This ongoing Phase 1 study evaluates pharmacokinetic (PK) and pharmacodynamic (PD) components to assess translational biomarkers of NOX target engagement and CAF-driven immune modulation supporting dose selection and rational combination strategies with immunotherapy. **Methods:** This is a Phase 1, dose-escalation study (NCT07123415) evaluating the safety, tolerability, PK, PD, and preliminary antitumor activity of orally administered APX-343A as monotherapy (Part A; 100–600 mg BID) and in combination with pembrolizumab (Part B; 200–600 mg BID) in patients with advanced solid tumors. Dose escalation is conducted independently using dose-limiting toxicity–based escalation in Part A and a Bayesian Optimal Interval (BOIN) design in Part B to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). PK assessments are conducted in Part A to evaluate dose proportionality and support RP2D determination, including Cmax, Tmax, area under the concentration–time curve (AUC), and accumulation. PD assessments use peripheral blood and tumor tissue samples to evaluate biomarkers of NOX pathway inhibition and CAF-driven immune modulation, including NOX isoforms (NOX1/2/4), CAF-associated markers, and immune-related cytokines and chemokines (e.g., interleukins, CCL2). Integrated PK/PD analyses explore exposure–biomarker relationships. This ongoing Phase 1 trial of APX-343A is actively enrolling, with Part A dose-escalation cohorts underway. Integrated PK and PD assessments are designed to establish translational evidence of NOX target engagement and CAF modulation, providing a mechanistic foundation for dose selection and rational combination strategies with ICI. Clinical trial information: NCT07123415. Research Sponsor: None.

TPS2685 Poster Session

A phase 1 study of PHST001, an anti-CD24 monoclonal antibody, in adult patients with advanced relapsed and/or refractory solid tumors.

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Background: Macrophages are the most abundant immune cells in tumors and can directly phagocytose tumor cells and promote broad anti-tumor immunity. However, phagocytosis can be inhibited by macrophage checkpoints, also known as 'don't eat me' signals. One such checkpoint is the immunomodulatory protein CD24 that is overexpressed in many tumors and associated with poor clinical prognosis. CD24 inhibits macrophage phagocytosis of tumor cells via binding to Siglec-10 on macrophages. PHST001 is a high affinity anti-CD24 IgG4 antibody that blocks multiple glycoforms of CD24 and induces macrophage phagocytosis of tumor cells in a wide range of preclinical models. In addition, PHST001 improves tumor control and survival in murine models when combined with multiple chemotherapies as chemotherapy-induced tumor cell stress may improve macrophage phagocytosis of tumor cells when combined with CD24 blockade. Thus, CD24 blockade has potential as monotherapy and in combination with other cancer therapies to enhance tumor cell phagocytosis and improve patient survival. **Methods:** PHST001-101 is an open-label, first-in-human, Phase 1 study in patients $\geq$ 18 years of age with advanced relapsed and/or refractory solid tumors (NCT06840886). In Phase 1a, patients receive escalating doses of PHST001 administered Q3W as an IV infusion at one of nine dose levels. Phase 1b combines PHST001 with chemotherapy in patients with ovarian cancer, endometrial cancer, or cholangiocarcinoma in safety run-in groups and tumor-specific expansion cohorts. Key inclusion criteria include age $\geq$ 18 years, evidence of measurable disease, an ECOG performance status of 0 or 1, and adequate organ function. Key exclusion criteria include a diagnosis of immunodeficiency, active CNS disease, or active autoimmune disease. The primary objective is to assess the safety and tolerability of PHST001 as monotherapy and in combination with chemotherapy, and to assess the preliminary antitumor activity of PHST001 in combination with chemotherapy. Secondary objectives include assessing antitumor activity of monotherapy and pharmacokinetics (PK) of PHST001. Exploratory objectives include evaluating the relationship between PK and pharmacodynamics (receptor occupancy, cytokine profiling, changes in ctDNA, and immune cell subsets in the tumor), immunogenicity of PHST001, antitumor activity in patients treated beyond progression, and patient-reported outcomes. The study enrolled the first patient treated in April 2025 and is currently enrolling patients in Phase 1a at Dose Level 8 (18 mg/kg) with no DLTs to date. Enrollment in Phase 1b is anticipated to begin in early 2026. Clinical trial information: NCT06840886. Research Sponsor: Pheast Therapeutics.

TPS2686 **Poster Session**

A phase 1/2a, multicenter, first-in-human, open-label clinical trial evaluating MDX2004 monotherapy in patients with advanced tumors.

Jordan Ellis Cohen, Udit Nindra, Ruth Perets, Ravit Geva, Yakir Rottenberg, Kenneth John O'Byrne, Lukas Makris, Alicia McConnell, Anne-Laure Goenaga, Dalia Burzyn, Kerry Culm, Giovanni Abbadessa; Calvary Mater Newcastle, Newcastle, NSW, Australia; Liverpool Hospital, Liverpool, Australia; Oncology Department, Rambam Health Care Campus, Haifa, Israel; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Hadassah Medical Center, Jerusalem, Israel; Princess Alexandra Hospital, Translational Research Institute and Queensland University of Technology, Brisbane, Australia; Stathmi, Inc., New Hope, PA; ModeX Therapeutics, Weston, MA; ModeX Therapeutics, An OPKO Health Company, Weston, MA

Background: MDX2004 is a trispecific antibody–fusion protein developed as an immunotherapy for advanced cancers. It is designed to stimulate T cells through engagement of CD3, CD28, and 4-1BB, thereby enhancing immune activation. MDX2004 is expected to promote activation and expansion of T lymphocytes, including stem and memory T-cell populations. **Methods:** This Phase 1/2, multicenter, first-in-human, open-label clinical trial evaluates MDX2004 in patients with advanced or metastatic solid tumors (NCT07110584). The study includes a Phase 1a dose-escalation stage guided by a Bayesian Optimal Interval (BOIN) design targeting a maximum tolerated dose toxicity rate of 30%; a Phase 1b indication-optimization stage in up to five tumor types; a Phase 1c dose-optimization stage in up to three indications; and a Phase 1d/2a expansion at the recommended Phase 2 dose (RP2D) in a single indication. In Phase 1a, patients with advanced solid tumors receive escalating intravenous doses of MDX2004. Phase 1b evaluates a selected dose in patients with homogeneous indications to assess preliminary efficacy. In Phase 1c, patients with selected indications are randomized 1:1 to two dose cohorts using a Bayesian Optimal Phase 2 (BOP2) design. Once the RP2D is established, Phase 1d/2a will enroll approximately 30 patients into a single cohort using a BOP2 design. The primary objectives across study phases are to characterize the safety, tolerability, and antitumor activity of MDX2004. Secondary endpoints include time to response, disease control rate, duration of response, pharmacokinetics, and immunogenicity. Radiologic tumor assessments are performed every 8 weeks, and treatment continues until disease progression per RECIST v1.1 (investigator assessed), unacceptable toxicity, withdrawal of consent, or another protocol-defined discontinuation criterion. The study is planned to be conducted in Australia, Israel, Moldova; patient recruitment is ongoing. Clinical trial information: NCT07110584. Research Sponsor: None.

TPS2687 Poster Session

Phase 1 clinical trial investigating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of AB821 in adult patients with locally advanced or metastatic melanoma and other solid tumor malignancies (NCT 07027488).

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Background: In recent years, T-cell enhancement strategies have achieved notable survival benefits in patients with cancer. While cytokine therapy with both IL-2 and IL-21 demonstrate anti-cancer activity through enhanced proliferation, survival and function of antigen specific CD8+ T cells, their use is limited by off-target effects and rapid clearance. AB821 is a fusion of a CD8-targeting antibody that binds to the CD8$\alpha\beta$ heterodimer on CD8+ T cells and an IL-21 mutein containing a mutation that attenuates affinity for the IL-21receptor. In pre-clinical experiments, AB821 promotes CD8+ T-effector cell cytotoxicity and CD8+ T-cell memory and demonstrates both robust tumor growth inhibition and minimal toxicity in immune checkpoint inhibitor refractory tumor models. Notably, AB821 avoids activation of other IL-21R-expressing cell types, including CD4+ T cells, NK cells, B cells, dendritic cells, intermediate monocytes, and nonclassical monocytes, that can act as pharmacologic sinks or contribute to off-target toxicity. **Methods:** This first-in-human phase 1 dose-escalation clinical trial is designed to assess the safety, pharmacokinetics, pharmacodynamics, immunogenicity and preliminary anti-tumor activity of AB821 monotherapy administered every 2 weeks (Q2W) in patients (pts.) with recurrent locally advanced or metastatic melanoma and other immune-responsive solid tumor malignancies. Pts. with melanoma are required to have previously been treated with an inhibitor of PD1/L1 while pts. with other cancer types are required to have received a previous systemic treatment regimen. The primary objective of the study is to assess the safety and tolerability of AB821 and identify a candidate recommended phase 2 dose for further evaluation. AB821 is being administered as a 30-minute IV infusion on day 1 of each 2-week treatment cycle with therapy continued for a maximum duration of two years (52 cycles) or as long as participants experience clinical benefit as determined by the treating investigator. Dose-escalation and/or de-escalation decisions is being guided by a BF-BOIN design (Liu 2015; Yuan 2016) employing a target toxicity probability of 0.30 with up to 20 total pts. enrolled in backfill cohorts at the RP2D or lower dose levels determined by the investigators to be potentially efficacious in order to better assess the drug's safety and efficacy. Accrual is ongoing. Specific dose levels and inclusion/exclusion criteria will be presented. Clinical trial information: NCT07027488. Research Sponsor: Asherbio Therapeutics.

TPS2688 **Poster Session**

A phase I/IIa study to evaluate the safety and tolerability, activity, and PK of a potential novel CNTN4-targeted checkpoint inhibitor, EP0089, in patients with advanced solid tumors.

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Background: Contactin 4 (CNTN4) has recently been identified as a novel cancer target which is overexpressed across a range of tumor types, including gastrointestinal, genitourinary, melanoma, breast and lung. Preclinical data shows that CNTN4 functions as an immune checkpoint through its binding to the T-cell transmembrane protein APP (Amyloid Precursor Protein). The interaction between CNTN4 on the surface of tumor cells and APP diminishes T cell receptor signaling cascades, inhibiting the activation and proliferation of CD4+ and CD8+ T cells. Tumor upregulation of CNTN4 may facilitate tumor immune evasion. Elevated CNTN4 levels have been associated with poorer outcomes for patients treated with anti-PD-1 checkpoint inhibitors. Therapeutic agents that block the interaction of CNTN4 with APP therefore have the potential to address significant unmet medical needs across a range of tumor types. EP0089 is a humanized IgG4 monoclonal antibody which specifically binds CNTN4 and inhibits the interaction between CNTN4 and APP, thereby enabling an immune response within the tumor microenvironment. *In vitro* and i*n vivo* studies demonstrated that EP0089 neutralized CNTN4-mediated suppression of T cell activation and promoted killing of CNTN4 over-expressing tumors. **Methods:** This is a first-in-human, open-label, phase I/IIa study (NCT07030478). Eligible patients will have a confirmed diagnosis of an advanced solid tumor with no available standard therapy or for whom standard therapy has failed, ECOG performance status of 0-1, life expectancy greater than 3 months, and measurable disease per RECIST v1.1 (or specified disease-specific guidelines). The population will be enriched for tumor types known to express CNTN4, including gastric, gastro-esophageal, esophageal adenocarcinoma, hepatocellular, bladder, gallbladder, endometrial, melanoma, and prostate. The primary objective is to determine the maximum tolerated dose and recommended phase II dose of EP0089. The secondary objectives are to characterize the PK and immunogenicity profile of EP0089 and assess preliminary antitumor activity. Exploratory objectives are to evaluate biomarkers of response, including the impact of CNTN4 expression and other PD biomarkers. Part A consists of dose-escalation, utilizing a 3+3 design, and dose expansion to further evaluate dose levels/regimens of interest. Part B will be determined based on review of Part A data and may include further dose optimization, and/or evaluation of specific populations of interest. Patients will initially receive EP0089 by IV infusion once every 2 weeks, subject to ongoing Safety Monitoring Committee review throughout dose escalation. The study is being conducted in the Republic of Korea, Australia and United States and later in Europe. Target recruitment is approximately 250 patients. Clinical trial information: NCT07030478. Research Sponsor: None.

TPS2689 Poster Session

TREGCHECK 102: A study of tagmokitug (CHS-114) in combination with toripalimab and/or other treatments in participants with advanced solid tumors.

Dani Ran Castillo, Li-Yuan Bai, Hsin-Chen Lin, Jonathan Mizrahi, Meredith Pelster, Narendiran Rajasekaran, Theresa LaVallee, Hong Tang, Varun N. Kapoor, Subaweerage Dias, Yelena Y. Janjigian; City of Hope, Duarte, CA; China Medical University Hospital, Taichung, Taiwan; Taichung Veterans General Hospital, Taichung, Taiwan; Ochsner Medical Center, New Orleans, LA; Sarah Cannon Research Institute, Nashville, TN; Coherus Oncology, Redwood City, CA; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: Advanced solid tumors frequently exhibit resistance to standard therapies, including immune checkpoint inhibition. Intratumoral Tregs have been associated with immune suppression, tumor progression and anticancer resistance. Intratumoral Tregs preferentially express CCR8 and are abundant in many solid tumors (Plitas 2020; Plitas 2016; Kidani 2022). Tagmokitug is a novel, selective cytolytic anti-CCR8 mAb designed to deplete CCR8+ Tregs and remodel the tumor microenvironment to promote antitumor immunity. Preclinical and phase 1 clinical studies show tagmokitug can significantly deplete CCR8+ intratumoral Tregs, increase immune activation and has antitumor activity in combination with a PD-1 inhibitor (Wang 2026; Worden 2025; Kapoor 2025). These findings warrant evaluation of tagmokitug in combination with toripalimab, a PD-1 inhibitor, and/or other anticancer therapies across multiple tumor types. **Methods:** This multicenter, open-label, phase 1b/2a study evaluates tagmokitug in combination with toripalimab and/or other therapies in adults with advanced solid tumors in 4 cohorts: gastric, gastroesophageal junction (GEJ), and esophageal adenocarcinoma; second-line esophageal squamous cell carcinoma (ESCC); first-line ESCC; and advanced MSS/pMMR colorectal cancer. Eligible participants have histologically or cytologically confirmed advanced or metastatic solid tumors not amenable to curative therapy, measurable disease per RECIST v1.1, ECOG 0–1, and adequate organ function. Key exclusions include active autoimmune disease requiring systemic therapy, uncontrolled cardiovascular conditions, or other factors interfering with study participation. Tagmokitug is administered IV Q3W at pharmacologically active doses following toripalimab 240 mg IV and/or other anticancer therapies where indicated per protocol. Imaging assessments are performed every 6 weeks through week 24, every 9 weeks through week 51 and every 12 weeks through week 99. Patients continue treatment until disease progression, unacceptable toxicity, or withdrawal of consent. The primary objective is to evaluate the safety and tolerability of tagmokitug in combination with toripalimab and/or other anti-cancer therapies as measured by adverse events and laboratory abnormalities. Secondary endpoints include ORR, DOR, DCR, and PFS per RECIST v1.1, and assessment of PK and ADA. Exploratory endpoints include OS and biomarker analyses including evaluation of CCR8+ Tregs in tumors. Enrollment is ongoing. Approximately 150 participants are planned across all cohorts. Additional cohorts may be added based on emerging data. Clinical trial information: NCT06657144. Research Sponsor: Coherus Oncology.

TPS2690 **Poster Session**

Cohort expansion of a phase I study of PLN-101095, a first-in-class dual $\alpha_v\beta_8/\alpha_v\beta_1$ integrin inhibitor, in combination with pembrolizumab in patients with advanced solid tumors refractory to immune checkpoint inhibitors (ICI).

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Background: Transforming growth factor-β (TGF-β) drives immunosuppression and T-cell exclusion in solid tumors and contributes to immune checkpoint inhibitor (ICI)-acquired resistance. The integrins $\alpha_v\beta_8$ and $\alpha_v\beta_1$ activate latent TGF-β in the tumor microenvironment, promoting immune escape. PLN-101095 is a first-in-class, oral dual $\alpha_v\beta_8/\alpha_v\beta_1$ inhibitor designed to block TGF-β activation and restore antitumor immunity in patients with advanced solid tumors refractory to prior ICI. Part 1 of our study (NCT06270706) employed a Bayesian optimal interval design for dose escalation. The Part 2 expansion cohorts were driven by Part 1 efficacy signals, including 4 responders with secondary resistance to ICI, most of whom had high tumor mutational burden (TMB-H) prior to baseline. **Methods:** This is an ongoing Phase 1 open-label multicenter study conducted in the United States. Part 1 (dose escalation) enrolled patients with advanced or metastatic solid tumors who had either primary or secondary resistance to prior ICI. Part 2 (dose expansion) will enroll only patients meeting Society for Immunotherapy of Cancer (SITC) criteria for secondary resistance to prior ICI therapy based on a Simon 2-stage design. The Part 2 expansion cohorts will be as follows: 1) non-small cell lung cancer; 2) head and neck squamous cell carcinoma; 3) clear cell renal cancer; and 4) TMB-H tumors (historical ≥10 mutations/megabase, as determined by local testing with a Clinical Laboratory Improvement Amendments–certified next-generation sequencing [NGS] assay). The target sample size for cohorts 1-3 is 19 patients each, and the target for cohort 4 is 36 patients. The primary endpoints are objective response rate (ORR) and disease control rate (DCR) per immune RECIST. The secondary endpoints are pharmacokinetics (PK), safety and tolerability, and duration of response (DOR). Planned exploratory biomarkers analyses include characterization of integrin expression, TGF-β and immune-related gene expression, and tumor microenvironment (TME) in tumor biopsies. Plasma cytokine profiling and circulating tumor DNA (ctDNA) will also be examined. Clinical trial information: NCT06270706. Research Sponsor: Pliant Therapeutics, Inc.

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TPS2691 Poster Session

Phase II open-label trial of neoadjuvant immunotherapy in combination with CAPOX for resectable non-metastatic proficient mismatch repair (pMMR) colon cancer: NICER study.

Atif Iqbal, Shalini Makawita, Hector Garcia-Chavez, Karen Riggins, Benjamin Leon Musher, Tannaz Armaghany, Yesenia Rojas-Khalil, Eric Jay Silberfein, Punam Amin, Cary Hsu, Ernest Ramsay Camp, Ashley Waldon, Megan Crawford; Baylor College of Medicine, Houston, TX; Dan L. Duncan Comprehensive Cancer Center at Baylor College of Medicine, Houston, TX; Baylor College of Medicine Division of Diabetes Endocrinology and Metabolism, Houston, TX

Background: Colorectal cancer (CRC) is the third most common malignancy worldwide. Immune checkpoint inhibition has transformed outcomes in deficient mismatch repair (dMMR/MSI-H) CRC but has demonstrated limited efficacy in metastatic proficient mismatch repair (pMMR) tumors, likely related to low tumor mutational burden and limited immune infiltration. Emerging neoadjuvant studies suggest that earlier exposure to immunotherapy may enhance antitumor immunity and induce pathologic responses in pMMR colon cancer. Neoadjuvant chemotherapy may further augment immunogenicity through tumor debulking, antigen release, and modulation of the tumor immune microenvironment. Combination chemo-immunotherapy has improved outcomes across multiple solid tumors and may overcome resistance to immune checkpoint blockade. Early neoadjuvant immunotherapy studies in pMMR colon cancer have demonstrated encouraging pathologic responses without compromising surgical outcomes. The NICER study evaluates the safety, feasibility, and biological activity of neoadjuvant atezolizumab plus CAPOX in resectable pMMR colon cancer. Correlative studies include longitudinal circulating tumor DNA (ctDNA) analysis and paired tissue assessment to characterize immune microenvironmental changes following treatment. **Methods:** This is a phase II, open-label study evaluating neoadjuvant atezolizumab in combination with capecitabine and oxaliplatin (CAPOX) in patients with resectable, non-metastatic pMMR colon adenocarcinoma. The planned accrual is 28 patients. Participants receive four 3-week cycles of neoadjuvant atezolizumab plus CAPOX, followed by standard-of-care surgical resection. Adjuvant chemotherapy is permitted per investigator discretion for high-risk patients. Key eligibility criteria include pMMR colon adenocarcinoma with tumor ≥12 cm from the anal verge and at least one high-risk feature (elevated CEA, low lymphocyte-to-monocyte ratio, poor differentiation, lymphovascular or perineural invasion, CT-defined T3–T4 disease ≥4 cm, or regional lymphadenopathy). Exclusion criteria include metastatic disease, autoimmune disorders, recent malignancy, or synchronous colorectal primaries. The primary endpoint is tumor regression grade (TRG) using the modified Ryan scoring system. The regimen will be considered promising if the post-therapy TRG 1 rate is ≥15%, compared with an expected rate of 0% with upfront surgery. Secondary endpoints include pathologic complete response, R0 resection rate, lymph node yield, safety, surgical timing, recurrence outcomes, and quality of life. As of January 2026, 7 of 28 planned patients have been enrolled since accrual began in July 2025. ClinicalTrials.gov ID NCT05870800. Clinical trial information: NCT05870800. Research Sponsor: Genentech, Inc. (subsidiary Roche - Switzerland).

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TPS2692 Poster Session

Induction adebrelimab combined with chemotherapy followed by response-adaptive concurrent chemoradiotherapy guided by PET-CT in locally advanced unresectable esophageal squamous cell carcinoma: A prospective, single-arm, phase II study.

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Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced unresectable esophageal cancer. Currently, data on PD-L1 inhibitors combined with chemoradiotherapy in this setting still remain limited. Furthermore, the efficacy of induction immunotherapy prior to CCRT, and the utility of PET-CT assessment to guide subsequent CCRT regimens, have not been explored. This study aims to evaluate the efficacy and safety of induction adebrelimab (an anti-PD-L1 antibody) combined with chemotherapy, followed by a PET-CT guided adaptive chemotherapy regimen during CCRT for locally advanced unresectable esophageal squamous cell carcinoma (ESCC). **Methods:** This single-arm, open-label, exploratory study will recruit 36 patients with locally advanced unresectable ESCC (clinical stage T1N+M0 or T2-4bNxM0) who have not received prior antitumor treatment. Patients will undergo 2 cycles of induction therapy with adebrelimab (1200 mg, d1, iv, q3w) plus the TP regimen (nab-paclitaxel 180 mg/m^2 or paclitaxel 135 mg/m^2, d1, iv; carboplatin AUC=5, d1, iv, q3w). Following induction, response will be assessed via PET-CT. Responders (defined as SUV reduction ≥35% or partial response) will continue with the TP regimen (nab-paclitaxel 60 mg/m^2 or paclitaxel 50 mg/m^2, d1, iv; carboplatin AUC=2, d1, iv, qw for 5 cycles) during concurrent radiation (50.4–60 Gy/28–33f). Non-responders will switch to the FP regimen (fluorouracil 750–1000 mg/m^2, civ 96h; cisplatin 75 mg/m^2, d1, iv, q4w for 2 cycles) during concurrent radiation. All patients will proceed to maintenance therapy with adebrelimab following CCRT until disease progression or unacceptable toxicity. The primary endpoint is the 1-year progression-free survival (PFS) rate. Secondary endpoints include the clinical complete response (cCR) rate, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS, overall survival (OS), and safety profile. Clinical trial information: NCT07112833. Research Sponsor: None.

TPS2693 Poster Session

ASCEND: A phase 1/2, dose-escalation, optimization, and dose-expansion study to evaluate the safety and antitumor activity of CR-001 in adults with locally advanced or metastatic solid tumors.

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Background: CR-001 is a tetravalent bispecific antibody targeting anti-programmed cell death-1 (PD-1) and vascular endothelial growth factor (VEGF), designed to enhance antitumor activity through combined immune modulation and antiangiogenic effects. Its proposed mechanism of action involves dual binding and blockade of both PD-1/programmed death ligand-1 (PD-L1) and VEGF/vascular endothelial growth factor receptor 2 (VEGFR2) signaling. The blockade of VEGF signaling is aimed at inhibiting tumor angiogenesis and reversing immunosuppressive effects in the tumor microenvironment, while PD-1 binding is aimed at preventing T-cell suppression, thereby promoting the immune recognition and elimination of tumor cells. The established benefit/risk profiles and regulatory precedents for PD-1-, VEGF-, and dual-pathway-directed antibodies support evaluation of CR-001 in solid tumors. **Methods:** ASCEND (NCT07335497) is a global, first-in-human, open-label, phase 1/2 study assessing CR-001 monotherapy in adults with advanced solid tumors. The purpose of this study is to determine the safety and tolerability of CR-001 and identify the maximum tolerated dose, and/or recommended phase 2 dose. The study will initially involve three parts: dose escalation, backfill, and dose optimization. Key eligibility criteria include: age ≥18 years; locally advanced (nonresectable) or metastatic hepatocellular carcinoma, biliary tract cancer, gastric or gastroesophageal junction cancer, colorectal cancer, endometrial cancer, cervical cancer, ovarian cancer, or non-small-cell lung cancer; and progression on, intolerance to, or ineligibility for local standard-of-care anticancer therapies. Additional criteria include ≥1 measurable lesion and ECOG performance status 0–1. As part of a standard 3+3 dose-escalation design, CR-001 is planned to be administered at 4 dose levels as an intravenous infusion every 2 or 3 weeks. Tumor-specific backfill cohorts will enroll concurrently with dose escalation. Earlier-line participants, including those untreated in the advanced or metastatic setting, may also be eligible to participate in backfill cohorts. The recommended phase 2 dose will be determined based on review of pharmacokinetics/pharmacodynamics, safety, tolerability, and preliminary signs of antitumor activity. Up to 290 patients are planned to be enrolled across the dose-escalation, tumor-specific backfill, and dose-optimization cohorts. This global trial is currently enrolling. Clinical trial information: NCT07335497. Research Sponsor: Crescent Biopharma.

TPS2694 Poster Session

Efficacy and safety of QL1706-based combination therapy in recurrent or metastatic endometrial carcinoma previously treated with chemotherapy and immune checkpoint inhibitors: A single-arm, prospective, phase II trial.

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Background: Patients with advanced endometrial cancer who have progressed after platinum-based chemotherapy and immune checkpoint inhibitors have limited subsequent treatment options and a very poor prognosis. Iparomlimab and tuvonralimab injection (QL1706) is a bifunctional combination antibody targeting both programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), developed using the MabPair biotechnology platform. This study aims to evaluate the efficacy and safety of QL1706 combined with chemotherapy ± bevacizumab in patients with recurrent or metastatic endometrial cancer previously treated with immune checkpoint inhibitors. **Methods:** In this prospective, single-arm, multicenter phase II clinical trial, up to 30 participants will be enrolled. Eligible patients must be aged ≥18 years, have an Eastern Cooperative Oncology Group Performance Status score of 0 to 1, be diagnosed with recurrent or metastatic endometrial carcinoma, have previously received PD-(L)1 therapy for over 6 months, and have experienced disease progression during or after prior chemotherapy and PD-(L)1 targeted therapy. Up to two prior lines of systemic therapy are permitted. Patients who previously received PD-(L)1 plus CTLA-4 targeted therapy or discontinued anti-PD-1/PD-L1 antibody therapy due to related toxicities are excluded. Enrolled patients will receive QL1706 (5 mg/kg every 3 weeks) combined with chemotherapy (investigator's choice, administered for 3–6 cycles) ± bevacizumab (15 mg/kg every 3 weeks) until disease progression, unacceptable toxicity, or other protocol-specified termination events. The primary endpoint is the objective response rate (ORR) as assessed by the investigator according to RECIST v1.1. Secondary endpoints include progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety. As of January 2026, 5 of the planned 30 patients have been enrolled. Clinical trial information: NCT06917092. Research Sponsor: None.

TPS2695 **Poster Session**

SYNERGY: A phase 1b/2 study of nenocorilant, a selective glucocorticoid receptor antagonist, plus nivolumab in patients with advanced solid malignancies.

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Background: Acting through the glucocorticoid receptor (GR), glucocorticoids (GCs) suppress the anticancer immune response by decreasing antigen presentation, exhausting CD8+ T-cell effector function, and increasing the immunosuppressive function of regulatory T cells and tumor-infiltrating myeloid cells. The use of GCs with anti-programmed death (ligand) 1 (anti-PD[L]1) therapy is associated with poor outcomes in several solid tumor types. Selective GR antagonists (SGRAs) inhibit the effects of GCs at the GR and show synergistic activity with cytotoxic chemotherapy, as demonstrated by the phase 3 ROSELLA study in patients with platinum-resistant ovarian cancer (Olawaiye *Lancet* 2025). SGRAs enhance tumor growth inhibition when combined with anti-PD1 therapy in syngeneic mouse tumor models that are refractory to immune checkpoint inhibition (Greenstein *Int Immunopharmacol* 2023). We hypothesize that GR antagonism with nenocorilant, an SGRA, may enhance or restore sensitivity to anti-PD(L)1 therapy and provide clinical benefit for patients with solid malignancies.
Methods: This phase 1b/2, open-label, multicenter study (NCT07276373) is evaluating nenocorilant + nivolumab in patients with advanced solid malignancies. Key eligibility criteria for phase 1b include having received standard-of-care therapies, no prior immune-related adverse events (AEs) grade $\geq$3 or leading to anti-PD(L)1 discontinuation, no ongoing requirement for GCs, and evaluable disease (per Response Evaluation Criteria in Solid Tumors version 1.1). Treatment will continue until disease progression or discontinuation criteria are met. Nenocorilant will be given orally once daily in escalating doses (starting at 200 mg) across 3 cohorts of 10 patients each. Nivolumab 240 mg will be given intravenously once every 2 weeks. If $\leq$3 patients in a cohort experience dose-limiting toxicities (DLTs) during the 28-day evaluation period, enrollment will proceed to the next cohort at a higher dose of nenocorilant. Primary objectives include characterizing safety/tolerability (DLTs, AEs, serious AEs, dose modifications, and treatment discontinuations due to AEs) and determining the maximum tolerated dose and/or optimal dose/schedule. Secondary objectives are to characterize the anticancer activity, pharmacokinetics, and corrected QT interval effects of this combination. Safety endpoints will be summarized using descriptive statistics and time-to-event endpoints will be estimated using Kaplan-Meier methods. Data from the currently enrolling phase 1b part of the study will inform the dosing regimen for phase 2, which will further characterize the anticancer activity and safety of nenocorilant + nivolumab in specific solid malignancies. Clinical trial information: NCT07276373. Research Sponsor: Corcept Therapeutics.

TPS2696 **Poster Session**

Phase I study of zeaxanthin alone or in combination with pembrolizumab in metastatic solid tumors.

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Background: Zeaxanthin is a carotinoid synthesized by plants that accumulates via dietary intake in the macula. Preclinical studies demonstrated anti-proliferative properties in cancer cell lines *in vitro.* In uveal melanoma cell lines SP6.5 and C918, zeaxanthin reduced cell viability in a dose dependent manner while not doing so in normal ocular melanocytes. Decreased cell viability associated with decreased expression of anti-apoptotic proteins bcl-2 and bcl-xL and increased expression of pro-apoptotic bak and bax (1). Anti-proliferative effects were demonstrated in nude mice inoculated in the choroid with uveal melanoma cells (2). Zeaxanthin enhances anti-tumor immunity. Screening a blood nutrient compound library found zeaxanthin to augment CD8+ T-cell activity through direct engagement with the T-cell receptor (3). Murine models showed zeaxanthin enhanced anti-cancer efficacy of anti-PD-1 immunotherapy (3). Pro-apoptotic and immunomodulatory properties of zeaxanthin suggest potential for efficacy in treating cancer patients warranting clinical investigation. The primary objectives of this phase I study are to determine safety and tolerability of escalating doses of zeaxanthin monotherapy or combination of zeaxanthin plus pembrolizumab in patients with metastatic solid tumor malignancies and to determine MTD and recommended phase 2 dose. Secondary objectives assess pharmacokinetics and efficacy. Exploratory endpoints assess blood based biomarkers, transcriptome changes, and immunologic effects. Pre- and on-treatment tumor biopsies assess tumor microenvironment change. **Methods:** This 2 cohort study treats standard therapy refractory metastatic solid tumor patients with zeaxanthin (monotherapy cohort) or zeaxanthin and pembrolizumab (combination cohort). Combination cohort inclusion requires prior progression on a PD-1/L1 inhibitor. Oral zeaxanthin is administered daily with escalating doses (2 mg/kg to 10 mg/kg). The combination cohort escalates doses of zeaxanthin with a fixed dose of pembrolizumab (400 mg) infused every 6 weeks. Dose escalation utilizes a 3+3 design. Combination cohort dose level enrollment occurs after a zeaxanthin dose demonstrates no monotherapy DLT. Pharmacokinetic assessments occur at specified time points, Required large volume blood draws for pharmacodynamic analysis and optional tumor biopsies are obtained within 15 days prior to treatment initiation and at 6 weeks on treatment. Cohort 1 of zeaxanthin monotherapy (2 mg/kg daily) completed without DLT. Enrollment to monotherapy cohort 2 (zeaxanthin 4 mg/kg daily) and combination cohort 1 (zeaxanthin 2 mg/kg plus pembrolizumab 400 mg IV every 6 weeks) began November 2025 and are actively accruing patients. Clinical trial registry number: NCT05232409. (1) Bi et al. Evid. Based Compl. Alt. Med. (2013)12; (2) Xu et al. J Opthal (2015)10; (3) Zhang et.al. Cell Rep. Med. (2025)6. Clinical trial information: NCT05232409. Research Sponsor: Dr. Richard Rosen Cancer Research Fund.

TPS2697 Poster Session

Organ preservation strategy using dostarlimab for dMMR/MSI-H resectable solid tumors with whole-genome–based MRD monitoring (D-CURE: EPOC2401).

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Background: Mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) solid tumors accumulate numerous genomic alterations that generate neoantigens, which are presented on MHC molecules and activate potent Th1 and cytotoxic T-cell responses. This heightened immunogenicity simultaneously induces adaptive immune resistance through PD-1/PD-L1 upregulation, providing a strong biological rationale for the effectiveness of immune-checkpoint inhibitors in dMMR/MSI-H tumors. Neoadjuvant immune-checkpoint inhibition is particularly effective in dMMR/MSI-H tumors because it leverages the intact tumor and lymphatic microenvironment to prime robust systemic antitumor immunity before surgical removal. Standard surgery for solid tumors varies widely depending on the cancer type, but it carries risks of functional impairment and postoperative morbidity. Therefore, nonoperative management (NOM) has emerged as a clinically meaningful strategy to preserve organ function and improve patients' quality of life. **Methods:** D-CURE is a multicenter phase II trial evaluating whether dostarlimab, an anti–PD-1 IgG4 humanized monoclonal antibody, can safely achieve clinical complete response (cCR) and enable NOM with organ preservation in patients with dMMR/MSI-H resectable solid tumors (excluding colorectal cancer). Patients will receive 9 cycles of dostarlimab (500 mg/body every 3 weeks). Observation with NOM will be offered to patients who achieve cCR or near-cCR. Patients undergoing NOM will be followed for up to 2 years from the date of enrollment. The primary endpoint is the 12-month cCR rate after dostarlimab. Key eligibility criteria are as follows: untreated malignancy (excluding colorectal cancer); dMMR/MSI-H confirmed in tissue or blood; age ≥18 years; ECOG PS 0–1; and clinical stage eligible for surgical resection, definitive radiotherapy, or definitive chemoradiotherapy according to the TNM 8th Edition. The target sample size of 80 was determined based on 90% power, a one-sided alpha of 5%, a threshold 12-month cCR rate of 38%, and an expected 12-month cCR rate of 56%. We also integrate personalized precise molecular residual disease (MRD) monitoring incorporating up to 1,000 tumor-specific alterations identified through whole-genome sequencing of tumor tissue, with serial ctDNA-based MRD assessment and parallel enrollment in the MONSTAR-SCREEN-3 study (UMIN000053975). Through this linkage, patients will also have access to the multi-omics platform, enabling spatial transcriptomics, bulk WES/WTS, plasma proteomics, and microbiome analyses to elucidate tumor-immune dynamics and comprehensively characterize treatment response and resistance. Enrollment of the D-CURE trial started in September 2025 and is ongoing at 12 facilities in Japan. Clinical trial information: jRCT2031250364. Research Sponsor: GlaxoSmithKline Research & Development Limited.

Visit meetings.asco.org and search by abstract for the full list of abstract authors and their disclosure information. Abstract data current as of May 12, 2026.

TPS2698 **Poster Session**

A phase II study of the DNA plasmid-based vaccine STEMVAC in patients with metastatic triple-negative breast cancer (mTNBC).

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Background: Adding immune checkpoint inhibitors for the treatment of mTNBC improves the efficacy of traditional chemotherapy in select populations. In populations who are not predicted to benefit from PD-1 checkpoint inhibitors, a vaccine may sensitize Th1 cells against cancer-associated antigens to facilitate immune-mediated tumor killing. STEMVAC is a safe, immunogenic plasmid DNA-based vaccine encoding T-helper 1 (Th1) selective epitopes from five antigens (MDM2, YB1, SOX2, CDH3, CD105) associated with breast cancer stem cells and the epithelial-mesenchymal transition. In addition to direct cytotoxic effects directed against cancer cells, we have demonstrated that vaccine-induced Th1 cells secrete IFN-γ, which upregulates suppressor of cytokine signaling 1 (SOCS1), leading to slowed tumor growth and increased vulnerability to cytotoxic agents. Combining STEMVAC with chemotherapy could thus have synergistic effects leading to enhanced cancer sensitivity to treatment and possible eradication. **Methods:** The study (NCT07078604) includes adults with PD-L1 negative mTNBC receiving standard therapies inclusive of chemotherapy, antibody-drug conjugates, and oral PARP inhibitors in the first and second line. Eligible patients will have histologically-confirmed mTNBC, radiographically measurable disease by RECIST v1.1, and a lesion amenable to biopsy. Key exclusion criteria include concomitant B-cell malignancies, ongoing systemic steroid use, and known hypersensitivity reaction to GM-CSF. Participants receive intradermal STEMVAC 300mcg with 100mcg of GM-CSF given during the nadir period of standard of care chemotherapy. Participants receive three priming vaccines given every 21-28 days concurrent with chemotherapy, followed by booster doses at 6 and 9 months then every six months thereafter. The primary endpoints are 1) observance of immunogenicity to one of the five vaccine antigens, measured by interferon-gamma enzyme-linked immunospot assay, and 2) safety. Secondary endpoints include objective response rate, real-world PFS2, overall survival, and magnitude of immunogenicity. Exploratory endpoints include quantitative levels of CD8+ infiltrating lymphocytes and expression of genes associated with epithelial-mesenchymal transition before and after vaccine priming. Current status: This trial is recruiting patients, with up to 20 patients expected to be recruited across multiple sites. Safety data and preliminary outcomes will be reported as they become available. This trial aims to evaluate whether STEMVAC would achieve clinically relevant immunogenicity when administered concurrently with chemotherapy for the treatment of mTNBC. The trial will evaluate the safety and preliminary efficacy of this novel combination and explore tumor-immune microenvironment biomarkers to gain mechanistic insight. Clinical trial information: NCT07078604. Research Sponsor: Kuni Foundation.

A clinical study of a prototype DAA/TAA vaccine targeting MUC1 for immune interception and prevention in ductal carcinoma in situ.

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Background: Hypoglycosylated tumor MUC1 is a transmembrane glycoprotein, recognized by human T-cells and antibodies as a tumor-associated antigen. It is overexpressed in premalignant precursor lesions, including ductal carcinoma in situ (DCIS), serving as a potential potent DCIS rejection target. Vaccine-induced immune response to MUC1 may halt DCIS recurrence or progression to invasive disease and offer a future strategy for disease prevention in high-risk individuals. The hypothesis is MUC1 peptide vaccine is safe and immunogenic in patients with DCIS and the elicited systemic immune response will affect changes in the microenvironment of the DCIS from pro- to anti-tumor. Eligibility: Female, 18 years or older with biopsy proven ER+ DCIS with surgery planned as part of definite local therapy. Design: This single institution, open label, randomized phase I clinical trial (NCT06218303) is seeking 50 women with untreated ER+ DCIS confirmed on core needle biopsy (CNB). Patients are randomized 2:1 to the vaccine group. The vaccine is composed of a 100aa long MUC1 peptide corresponding to 5 tandem repeats of 20 amino acids from the MUC1 variable number of tandem repeats region (VNTR), admixed with the poly-ICLC adjuvant Hiltonol. The vaccine group receives the MUC1 peptide vaccine series pre-op (at 0, 2, and 10 weeks) with optional tamoxifen or an aromatase inhibitor (AI). The control group receives only optional tamoxifen or AI. All have surgery at 12 weeks. Research blood is drawn in the vaccine group at baseline and 2 weeks after each vaccine, and in the control group at baseline and at week 12. Tissue from the pre-treatment CNB and the post-treatment surgery are collected. An optional booster is available to vaccine responders 6 months post-surgery. Aims: The primary objective is to assess the immunogenicity of the MUC1 vaccine in ER+ DCIS patients prior to surgery. The secondary objective is to assess the safety and feasibility of the MUC1 vaccine in ER+ DCIS patients prior to surgery. The exploratory objective is to characterize peripheral MUC1-specific effector T-cells, regulatory T-cells and myeloid-derived suppressor cells (MDSC) at baseline and after vaccination. Changes in features of the tumor microenvironment and peripheral immunity at baseline and after vaccination may also be explored. **Methods:** Sample size/power: Assuming a one-sided type I error $\alpha \leq 0.05$ and the rate of patients having a $\geq 2\times$ change in anti-MUC1 IgG 1 is 35% in the vaccine arm and 2% in the control arm, a sample sizes of n=32 and 18 respectively in each arm will yield 88% power. With a dropout of up to 3 patients in each arm, the remaining sample size will still yield power of 82%. Statistical analysis: Fisher's exact test will be performed at the one-sided α=0.05 for the primary immunogenicity endpoint for comparing the experimental arm to the control arm. Clinical trial information: NCT06218303. Research Sponsor: Breast Cancer Research Foundation.

TPS2700 **Poster Session**

A phase 1 trial of the oncolytic virus SVV-001 with nivolumab and ipilimumab in patients with high-grade neuroendocrine neoplasms.

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Background: Poorly differentiated neuroendocrine carcinomas (NECs), including small cell and large cell neuroendocrine tumors, and grade 3 neuroendocrine tumors (NETs) represent a highly aggressive disease collectively classified as high-grade neuroendocrine neoplasms (NENs). These tumors are marked by rapid tumor growth, early dissemination, genomic instability, and poor outcomes. Despite initial sensitivity to chemotherapy and radiotherapy, relapse rates remain high, and immune checkpoint inhibitors (ICIs) have demonstrated limited activity, highlighting a substantial unmet therapeutic need. Seneca Valley Virus (SVV-001) is a novel oncolytic picornavirus that has demonstrated synergistic antitumor activity with ICIs in preclinical models. Additionally, SVV-001 has shown a favorable safety profile and the ability to reverse ICI resistance in vivo, supporting its evaluation in combination with nivolumab + ipilimumab. **Methods:** This is an investigator-initiated, phase 1, dose-escalation and cohort-expansion study evaluating intratumoral SVV-001 in combination with nivolumab + ipilimumab in patients with histologically confirmed high-grade NENs who have progressed on at least one prior line of standard-of-care therapy. Eligible patients must have at least one lesion suitable to repeated intratumoral injections of SVV-001 (up to 6 injections every two weeks). The trial was activated in March 2025 at Sylvester Comprehensive Cancer Center, with enrollment currently ongoing and a planned accrual of up to 36 patients. Part 1 used a standard 3+3 dose-escalation design. Enrollment in the first three cohorts (Part 1A), evaluating single-dose SVV-001 in combination with nivolumab and ipilimumab, is complete with no dose-limiting toxicities observed. Enrollment into cohort 4 (Part 1B), which will evaluate multiple doses of SVV-001 (up to 6 injections) is planned to begin in February 2026 followed by Cohort 5. Part 2 consists of a cohort-expansion phase in which up to 6 additional patients will be treated at the optimal recommended phase 2 dose (RP2D) of SVV-001. The primary objective is to determine the maximum tolerated dose (MTD) and/or RP2D. Secondary objectives include radiographic progression-free survival (PFS), overall response rate (ORR), duration of response, clinical benefit rate (CBR), and safety. Correlative studies will assess viral kinetics, including viral release and viral load in plasma, as well as Tumor Endothelial Marker 8 (TEM8), a potential biomarker of SVV-001 sensitivity and its association with efficacy signals. Additional exploratory analyses will characterize the tumor immune microenvironment and gut microbiome markers in the dose-expansion cohort. ClinicalTrials.gov Identifier: NCT06889493. Clinical trial information: NCT06889493. Research Sponsor: None.