

Individualized neoantigen therapy intismeran autogene (intismeran) plus pembrolizumab (pembro) in resected melanoma: 5-year update of the KEYNOTE-942 study.

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Background: Intismeran is an mRNA-based individualized neoantigen therapy designed to increase endogenous neoantigen-specific antitumor T-cell responses. The phase 2b KEYNOTE-942 study of high-risk resected melanoma showed clinically meaningful improvements in recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) with intismeran + pembro vs pembro alone at primary analysis. Intismeran + pembro had a manageable safety profile without potentiation of immune-related AEs vs pembro alone. Clinical benefits of intismeran + pembro were sustained at 3 y, with a 49% risk reduction of RFS and 62% risk reduction of DMFS. Intismeran + pembro also induced greater novel T-cell clonal expansion vs pembro, which was positively associated with RFS for intismeran + pembro but not pembro alone. We report results from KEYNOTE-942 after 5 y of planned follow-up. **Methods:** Eligible participants (pts; aged ≥ 18 y) with resected stage IIIB–IV cutaneous melanoma were randomized 2:1 to receive 9 doses of intismeran 1 mg IM Q3W + 18 doses of pembro 200 mg IV Q3W or 18 doses of pembro 200 mg Q3W alone. Primary endpoint was RFS; secondary endpoints included DMFS and safety. Exploratory endpoints included OS. No alpha was assigned to this analysis. **Results:** From Jul 2019 to Sep 2021, 157 pts were randomized to intismeran + pembro (n=107) or pembro (n=50). With an additional 2 y of follow-up (data cutoff, Dec 15, 2025; median planned follow-up, 60.3 [range, 50.5–76.4] mo) after the 3-y analysis, minimal new events occurred. RFS risk reduction for intismeran + pembro vs pembro alone was 49% (HR, 0.51; 95% CI, 0.29–0.89), with landmark 5-y RFS rates of 68.8% (95% CI, 56.3%–78.3%) for intismeran + pembro vs 49.1% (95% CI, 33.3%–63.0%) for pembro alone. DMFS risk reduction was 59% (HR, 0.41; 95% CI, 0.20–0.84). In the intismeran + pembro arm, 7 pts (6.5%) died (disease progression, n=4) vs 7 pts (14.0%) in the pembro arm (disease progression, n=6). There was a trend for improved OS (HR, 0.47; 95% CI, 0.17–1.35); 5-y rate was 92.2% (95% CI, 84.2%–96.3%) for intismeran + pembro vs 71.3% (95% CI, 35.4%–89.6%) for pembro alone. The safety profile of intismeran was consistent with prior analyses. **Conclusions:** After a median 5 y of follow-up, intismeran + pembro continued to prolong RFS and DMFS, along with a trend for improved OS vs pembro alone in pts with high-risk resected melanoma. These long-term findings show that intismeran + pembro treatment benefits were sustained and durable over time, despite all pts having completed study treatment before primary analysis (2021). As reported previously, intismeran was well tolerated, with a manageable safety profile for intismeran + pembro. Intismeran + pembro is being evaluated in a phase 3 study of high-risk resected stage II–IV melanoma (INTerpath-001; NCT05933577) and in studies of pts with other malignancies. Clinical trial information: NCT03897881. Research Sponsor: This research was supported by Moderna, Inc., Cambridge, MA, USA, in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

A phase II study of neoadjuvant ipilimumab-nivolumab-relatlimab (INR) combination immunotherapy in high-risk resectable melanoma.

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Background: Advances in the neoadjuvant (neo) setting of locoregionally advanced melanoma have recently transformed practice. However, there continues to be a need to enhance efficacy while deescalating the duration of systemic therapy for those who achieve major pathologic (path) responses (MPR). Recent data support an important role for triplet INR checkpoint inhibitor therapy targeting CTLA4, PD1 and LAG3 in the treatment of advanced melanoma.

Methods: A phase II trial of INR in patients (pts) with resectable clinical AJCC8 stages IIIB-D. It planned to enroll 20 evaluable pts to neo ipilimumab 1 mg/kg x1 dose combined with nivolumab-relatlimab (NR) 480/160 mg every 4 weeks x2 doses, followed by definitive surgery. Primary endpoint was MPR consisting of complete path response (pCR; 0% viable tumor) and near-pCR (< 10%). Secondary endpoints included other path responses, recurrence free survival, overall survival, event-free survival [EFS: disease progression (PD), recurrence or death] and safety. Adjuvant therapy was given in the absence of MPR. Biospecimens for research from consenting pts were banked at baseline, during treatment, at surgery and in follow up. **Results:** The study enrolled 20 pts August 2024-January 2026, including 7 female, 13 male, 16 cutaneous (2 acral) and 4 unknown primary. Median age was 65 (63-80). Baseline clinical stages were 9 IIIB, 9 IIIC, 2 IIID, including 4 pts with in-transit metastases. Among 19 patients who completed the neoadjuvant phase, all received ipilimumab and the median number of neo NR doses was 2. Among 19 pts who initiated treatment, 5 pts (26%) experienced Gr3 related AEs including colitis (1), encephalitis (1), headache (1), hyperglycemia (1), rash (1), and one pt experienced an event of Gr5 myocarditis. Among 18 pts who completed radiologic tumor response assessment, there were 13 (72%) partial response (PR), 4 stable disease (SD) and 1 disease progression (PD) preoperatively. There was 1 event of death before surgery. One patient declined surgery following deep PR, 1 pt is pending surgery and 1 pt continues in the neo phase. Among 16 pts who had surgery, median time from enrollment to surgery was 73 days. Pathologic responses were 5 path non-response (pNR), 1 near-pCR (microscopic residual disease) and 10 pCR (63%; 95% CI, 38.64 – 81.52). MPR rate (pCR + near-pCR) was 11/16 (69%; 95% CI, 44.40 – 85.84) and none of these patients received adjuvant therapy. Median follow up time from enrollment was 9.8 months. Among all pts, no pt experienced recurrence after surgery to date. **Conclusions:** Neoadjuvant INR demonstrated encouraging clinical activity in pts with resectable clinical stages IIIB/IIIC/IIID melanoma, warranting further investigation. The toxicity profile was consistent with reported data of INR and other combinations in this setting. Mechanistic and biomarker studies related to response, resistance and toxicity are underway. Clinical trial information: NCT06295159. Research Sponsor: Bristol Myers Squibb; H. Lee Moffitt Cancer Center and Research Institute.

A phase 2 study of neoadjuvant nivolumab (nivo) + relatlimab (rela) in high-risk stage II cutaneous melanoma (NeoReNi).

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Background: Patients (pts) with stage II melanoma account for ~50% of those who develop metastatic disease. Checkpoint inhibitor neoadjuvant therapy (NAT) is standard for resectable stage III melanoma (NADINA & SWOG 1801) and pathological response correlates with recurrence. Other NAT benefits include personalised prognosis, tailored subsequent management, and collection of translational specimens to explore response and resistance mechanisms. The NeoReNi II trial aimed to determine feasibility, response and safety of NAT nivo+rela in resectable stage II melanoma. **Methods:** Eligible pts had biopsy (partial) confirmed AJCC (v8) clinical stage IIA (T2b, T3a), IIB (T3b, T4a), or IIC (T4b) cutaneous melanoma with residual macroscopic primary disease at enrolment. IIA pts had $\geq 20\%$ 5 yr recurrence risk according to Melanoma Institute Australia stage II risk calculator (melanomarisks.org.au). All pts underwent sentinel lymph node (SLN) mapping at baseline and peri-operatively, and resection (wide excision + SLN biopsy [RES]) at wk 6 following 2 doses of nivo (480 mg, IV) + rela (160 mg, IV). Pts without major pathological response (MPR) had 11 cycles (Q4W) of adjuvant nivo/rela. FDG PET/CT was performed at baseline; CT prior RES; dermoscopy and reflectance confocal microscopy (RCM) baseline, wk 3 and prior to RES. The primary endpoint was the path complete response (pCR) rate. Secondary endpoints included feasibility of NAT in stage II, RECIST response, RFS, OS, safety/tolerability, surgical outcomes, QOL. Exploratory; biomarker, dermoscopy and RCM analyses. **Results:** From 6 Oct 2023 to 21 Oct 2025, 20 pts were recruited and received NAT, demonstrating partial biopsy leaving residual macroscopic stage IIA–C primary melanoma was feasible. Median age 67 yrs (46–81yrs), 9 females, 8 IIA, 8 IIB and 4 IIC. 18 (90%) pts received both NAT doses. 12 (60%) pts had pCR in the primary melanoma, 1 near-pCR (MPR 65%), 1 pPR and 6 (30%) pNR. Drug treatment related adverse events (TRAE) $\text{gd} \leq 2$ occurred in all 20 pts (100%); 11 (55%) with fatigue, 8 rash (40%) and 5 arthralgia (25%). 3 (15%) pts had $\text{gd} 3$ (secondary adrenal insufficiency, nephritis, pneumonitis). There were no $\text{gd} 4$ or 5 TRAEs. 1 (5%) pt had a $\text{gd} 3$ AE related to surgery (cellulitis). 19 (95%) pts had no change in SLN mapping from pre to RES. 2 pts with pNR in primary melanoma had positive SLN and 1 pt with pCR had focal fibrosis within a negative SLN, suggestive of possible treatment effect. Dermoscopy showed regression in all 12 MPR (100%) pts; 11 also showed changes in RCM (collagen reorganization and inflammatory infiltrates) concordant with pathology. At datacut off (11 Dec 25) 2 pts recurred, 5 and 11 mo respectively (both pNR); 1 died due to melanoma (15 mo after 1st recurrence; 20 mo after enrolment. Positive SLNBx at pNR). **Conclusions:** NAT with nivo + rela in resectable stage II melanoma was feasible and induced a high rate of pCR and MPR in the primary melanoma. Clinical trial information: NCT05418972. Research Sponsor: None.

Darovasertib plus crizotinib vs investigator's choice as first-line treatment for patients with HLA-A2 negative metastatic uveal melanoma: Primary results from the OptimUM-02 trial.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in patients with Merkel cell carcinoma and lymph node metastases.

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Updated outcomes from STAMP: Surgically treated adjuvant Merkel cell carcinoma with pembrolizumab, a phase III trial—ECOG-ACRIN EA6174.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

A phase II, multicenter, single-arm clinical trial of response-adapted definitive radiotherapy and cemiplimab-rwlc immunotherapy for locally advanced, unresectable cutaneous squamous cell carcinoma: RAMPART.

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Background: Locally advanced (T3-4/N+/Mo) and unresectable cutaneous squamous cell carcinoma (LAUSCC) patients (pts) have been historically treated with definitive radiotherapy (RT) +/- chemotherapy, yielding poor outcomes (18m progression-free survival [PFS] rates of ~38%). More recently, anti-PD1 immunotherapy with cemiplimab (cemi) led to an 18m PFS rate of ~55% in locally advanced pts that were not candidates for RT or surgery. In this prospective, multicenter trial, we assessed definitive RT with neoadjuvant, concurrent, and adjuvant cemi for LAUSCC pts. **Methods:** Pts with T3-4/N+/Mo LAUSCC according to local multidisciplinary consensus, ECOG ≤ 2 , were enrolled and treated with 2 doses of cemi (350 mg IV q3w). Those with progressive disease (PD) after 2 doses received RT (70 Gy/35 fractions). Those without PD received 2 additional doses of cemi followed by response-adapted RT (50-70 Gy/25-35 fractions) with concurrent cemi followed by adjuvant cemi for a maximum of 1y. The primary endpoint was event free survival (EFS) at 18m after cemi start. Secondary endpoints included safety, response (by RECIST v1.1, see table), quality of life, overall survival (OS) and PFS (after RT start). To test the hypothesis that the 18m EFS was 60%, compared to a historic 18m PFS rate after RT of 38% with 80% power and 5% type 1 error rate, 34 pts were planned for enrollment (accounting for 40% attrition). **Results:** 34 pts (median age 77y, 82% men, ECOG 0/1/2 in 41/53/6%) were enrolled with stage III (41%) and IV/Mo (59%) LAUSCC (56% recurrent, 91% head/neck) between 2022-2024. 85% completed 4 doses of neoadjuvant cemi and 94% completed RT as planned. With median follow up of 18m (range 2-36m), 18m EFS is estimated to be 86% (1 sided 95% CI lower bound of 73%) among all pts. Adverse events were consistent with prior studies of cemi or RT. 18m PFS and OS are estimated to be 86% and 92%. Quality of life analyses are in progress. **Conclusions:** The study met its primary endpoint demonstrating the highest rate of EFS, PFS and OS after treatment of LAUSCC ever reported. As the largest prospective study of definitive RT for LAUSCC, the data suggest integrating cemi with RT may benefit appropriate pts. Future studies identifying pts who are best served with this approach are warranted. Clinical trial information: NCT05574101. Research Sponsor: Regeneron; National Cancer Institute (US).

Response over time.

	Complete response	Partial response	Stable disease	Progressive disease	Non-response/Non-progression ¹	NA ²
Time						
6w post cemi	1 (3%)	11 (32%)	15 (44%)	3 (9%)	4 (12%)	0
12w post cemi	4 (12%)	15 (44%)	6 (18%)	1 (3%)	4 (12%)	4 (12%)
12w post RT	10 (29%)	10 (29%)	4 (12%)	3 (9%)	4 (12%)	3 (9%)
18m post cemi	11 (32%)	6 (18%)	0	1 (3%)	4 (12%)	12 (35%)

¹Pts with non-target lesions only.

²Pts not assessed (response assessment pending or not performed because of PD at 6w post cemi, or withdrawal).

OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy with regulatable membrane-bound IL15 (mbIL15) in patients with advanced melanoma that has progressed on/after immune checkpoint inhibitors (ICI): Phase 2 results.

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Background: OBX-115 TIL are engineered to express mbIL15 under regulatory control of the small-molecule drug acetazolamide (ACZ); this engineering abrogates the need for toxic high-dose IL2 cytokine support after TIL infusion. Early data demonstrated differentiated safety and promising efficacy at the recommended phase 2 dose (RP2D; Chesney ASCO 2025). We report additional data evaluating OBX-115 in patients (pts) with advanced melanoma treated at the RP2D in the Agni-01 study. **Methods:** This single-arm, open-label, phase 1/2 study (NCT06060613) assesses safety, tolerability, and efficacy of the OBX-115 TIL cell therapy regimen in pts with advanced non-veal melanoma and NSCLC (Shoushtari AACR 2025); eligibility was not restricted by LDH, HLA, or melanoma subtype. Phase 1 established an RP2D of OBX-115 $1-100 \times 10^9$ cells, with ACZ 500 mg/d orally on Days 0–6 (Wk 1) and 14–20 (Wk 3). Phase 2 evaluates efficacy of the regimen at RP2D by RECIST v1.1 per investigator in pts with ≤ 2 prior lines of therapy. OBX-115 is manufactured from pt tumor tissue (core needle biopsy [CNB] or surgical excision) and infused after low-dose (Cy 750 mg/m²/d $\times$ 3; Flu 30 mg/m²/d $\times$ 4) lymphodepletion (LD). ACZ is redosed (7 d) after recovery from LD every 6 wks until Wk 24. Primary data cutoff is 19Dec2025; RECIST efficacy was updated on 22Jan2026. **Results:** OBX-115 was successfully manufactured (median dose 83.4×10^9 cells) and infused at RP2D schema for 15 pts with advanced melanoma progressing on/after ICI (doublet ICI in 93%); 6/8 pts (75%) with BRAF-mut disease had prior BRAF-/MEK-inhibitor exposure. 2 pts (13%) had tumor tissue procurement by CNB; 4 pts (27%) received outpatient LD. Confirmed ORR was 67% (1 CR, 9 PR, 4 SD; DCR 93%). At median study follow-up of 18.6 wks (range 10.1–73.4), median duration of response was not reached (range 4.6+ to 55.1+ wks). There was no dose-limiting toxicity, ICU transfer, or treatment-related mortality. Immune-related adverse events (AEs) included CRS (G3 n=1; G<3 n=4) and hypoxia (G3 n=1; G<3 n=2), which responded to short-course steroids; no ICANS was observed. 3 pts reported 4 OBX-115-related serious AEs. 13 pts were alive as of the datacut. **Conclusions:** OBX-115 TIL cell therapy at RP2D demonstrated encouraging efficacy in 2/3L advanced non-veal melanoma, an area of unmet medical need. Unique aspects of the OBX-115 regimen, such as low-dose LD, ACZ-inducible mbIL15 expression, and CNB-enabled manufacturing, were associated with manageable side effects and compare favorably with other adoptive TIL approaches. Data support continued investigation of OBX-115 in the ongoing phase 2 portion of Agni-01 and planned registrational study. Clinical trial information: NCT06060613. Research Sponsor: Obsidian Therapeutics, Inc.

Patient-level clinical response dynamics in advanced melanoma with anzutresgene autoleucel (anzu-cel), a PRAME-directed T-cell receptor (TCR) T-cell therapy.

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Background: Pts with advanced melanoma frequently experience progressive disease (PD) with limited long-term survival following available therapies; there is a need for novel systemic treatments that can induce deep and durable responses. PRAME is a cancer-associated antigen expressed in >50 cancers, including melanoma. Anzu-cel (IMA203) is an autologous PRAME-directed TCR T-cell therapy engineered to recognize intracellular PRAME-derived peptides presented by HLA-A*02:01 and mediates a potent and specific anti-tumor immune response (Wermke et al. ASCO, 2025). A registration-directed phase 3 trial (SUPRAME; NCT06743126) is underway. **Methods:** IMA203-101 is an ongoing, multicenter, phase 1/2 trial evaluating anzu-cel in pts with advanced PRAME-positive solid tumors. Pts underwent lymphodepleting (LD) chemotherapy followed by a single infusion of anzu-cel +/- low-dose SUBQ IL-2. This analysis focuses on melanoma pts in phase 1b treated at RP2D. Data cutoff was Sep 24, 2025. Exploratory analyses evaluated lesion-level patterns of progression among pts evaluable per RECIST1.1. **Results:** As of data cutoff, 33 pts with melanoma were evaluable, incl. cutaneous (n=14), uveal (n=16), and other subtypes (n=3). Most frequent AEs were LD-related cytopenias. AEs of special interest included cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and hemophagocytic lymphohistiocytosis (HLH). CRS was predominantly low grade (G1: 36%, G2: 46%, G3: 18%) and occurred early after infusion, with incidence and severity decreasing over time. ICANS (G1: 6%, G3: 6%) and HLH (G2: 3%, G3: 3%) were infrequent. Confirmed ORR was 56% (cCR=1, cPR=17) and DCR was 91%. mDOR was 14.6 mos (4.2-38.2+), mPFS was 6.1 mos (1.4-39.6+), and mOS was 16.2 mos (2.4-39.6+). Responses were observed in target and nontarget lesions, with most pts demonstrating initial lesion responses within the first 6 weeks of treatment; median time to BOR of cPR/cCR was 1.4 mo (1.2-2.8). 25 pts were evaluable for patterns of PD. At the time of PD, 68% (17/25) developed new lesions (NL); 1 pt developed new central nervous system (CNS) lesions. PD via growth of existing lesions was observed in 56% (14/25); 24% (6/25) experienced PD by both growth of existing lesions and NLs. No specific pattern of PD was identifiable in those who achieved cPR compared to those who did not. **Conclusions:** Anzu-cel demonstrated favorable tolerability and induced clinically meaningful and durable responses. Exploratory analyses suggest that the CNS was not a common site for relapse. Future analyses will characterize response dynamics and progression patterns to better define scenarios in which progression following cPR remains clinically manageable, potentially supporting individualized decision-making regarding timing and necessity of subsequent systemic therapy. Clinical trial information: NCT06743126. Research Sponsor: Immatics.

A multicenter, randomized, controlled, open-label, phase II trial of autologous tumor-infiltrating lymphocytes (GC101 TIL) in patients with advanced melanoma.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Real-world safety of adoptive cellular therapy with lifileucel in patients with advanced melanoma.

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Background: Although acute toxicities associated with adoptive cellular therapy using lifileucel are well described and largely occur within the first 2 weeks of treatment, adverse events beyond this early window remain incompletely characterized. We sought to characterize treatment-related adverse events (AEs) with emphasis on those starting or persisting ≥ 2 weeks after lifileucel infusion. **Methods:** We conducted a retrospective multicenter study across three centers (Moffitt Cancer Center, Massachusetts General Hospital, and Mayo Clinic). Patients with advanced melanoma treated with lifileucel were included. The primary endpoint was incidence and characterization of AEs occurring or persisting ≥ 2 weeks after standard of care lifileucel infusion. **Results:** Among 79 patients (median follow-up 11 months [95% CI, 9.6–15]), median age was 63 years (range 30–79), 59% were male ($n = 47$), 41% were female ($n = 32$), and ECOG PS was 0–1 in 98%. Patients received a median of 5 IL-2 doses (range 0–6). Of 79 patients, 78 experienced treatment-related adverse events that either persisted or occurred > 2 weeks after cell infusion. A total of 308 delayed treatment-related adverse events were identified; 96 were new events (31%) and 212 (69%) were continued toxicities that started < 2 weeks after cell infusion. Lymphopenia was the most common delayed or persistent toxicity, occurring in a majority of patients ($n = 68/79$, 86%). Treatment-associated anemia ($n = 59/79$, 75%), fatigue ($n = 56/79$, 71%) and thrombocytopenia ($n = 24/79$, 30%) were also common. Viral infections occurred in 9.0% ($n = 7$), including CMV/EBV viremia ($n = 1$) and respiratory or gastrointestinal viral infections (metapneumovirus, parainfluenza, SARS-CoV-2, and norovirus). Hemophagocytic lymphohistiocytosis (HLH) occurred in 2 patients ($n = 2/79$, 3%) and was fatal in both cases. No other toxicity related deaths were noted. Autoimmune toxicities directly attributable to TIL included vitiligo in 9% ($n = 7$; median onset 41 days), uveitis in 5% ($n = 4$; median onset 26 days), and sensorineural hearing loss in 1% ($n = 1$; onset 28 days). All patients underwent TIL infusion in the inpatient setting; a total of 14 of 79 patients (18%) were re-admitted after discharge due to treatment-related toxicity (median time from infusion 19 days). **Conclusions:** In this multicenter real-world cohort, toxicities persisting beyond two weeks were largely driven by lymphodepleting chemotherapy-associated immunosuppression and cytopenias. These findings highlight the importance of structured post-discharge monitoring and support ongoing efforts to de-intensify lymphodepleting chemotherapy to improve safety while maintaining clinical benefit. Research Sponsor: None.

Immunologic determinants in procured melanoma tissue as drivers of durable response to tumor-infiltrating lymphocyte therapy.

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Background: Predictive biomarkers that identify melanoma tumors capable of generating therapeutically effective tumor-infiltrating lymphocytes (TIL) remain inadequately defined. We conducted an integrated spatial and histopathologic evaluation of resected melanoma specimens to characterize tumor microenvironmental features associated with durable clinical benefit (≥ 12 months) and improved survival following TIL therapy. **Methods:** Data were extracted from early-phase clinical trials conducted at Moffitt Cancer Center enrolling patients with advanced melanoma treated with TIL. Tumor specimens from 45 of 50 patients undergoing TIL manufacturing were evaluable based on tissue availability. Histopathology, multiplex immunofluorescence, and NanoString GeoMx spatial transcriptomics were performed on procured tumors. Tertiary lymphoid structures (TLS) were defined as organized aggregates of CD3⁺ T cells and CD20⁺ B cells and classified as immature or mature based on CD21/CD23 expression. Associations with ex vivo TIL expansion, infused product composition, clinical response, progression-free survival (PFS), and overall survival (OS) were assessed. **Results:** Procurement sites included subcutaneous/soft tissue (78%), lymph node (18%), and lung (4%). Viable tumor content and necrosis were not associated with ex vivo TIL expansion or response. TLS were present in 56% (25/45) of tumors and were strongly associated with clinical response (18/45 responders overall; response rate 56% [14/25] in TLS-positive tumors vs 20% [4/20] in TLS-negative tumors; $p=0.014$), improved PFS after adjusting for procurement site (HR=0.32; $p=0.005$) and improved OS ($p<0.0001$). Evaluation of ex vivo TIL expansion demonstrated that TLS presence did not affect the total number of expanded TIL ($p=0.3$) but was significantly associated with a higher proportion of CD8⁺ T cells within the infusion product (83% vs 56%, $p=0.027$). Spatial transcriptomics of 132 immune-enriched regions of interest demonstrated that responders exhibited marked upregulation of antigen-presentation and interferon-response programs, including MHC I/II genes, *STAT1/2*, *IFI6*, and *CXCL9*. A patient-level immune activation score derived from the top 25 responder-associated transcripts correlated with improved PFS ($p<0.0001$). To independently validate the significance of this immune gene set score, we analyzed an external dataset from the Lauss et al., 2017 cohort. Consistent with our findings, the gene set score was significantly higher in TIL responders compared with non-responders ($p=0.048$). **Conclusions:** TLS and spatial immune activation signatures in procured melanoma tumors are strongly associated with response and survival following TIL therapy. These findings support the integration of tumor microenvironment biomarkers into patient selection and optimization strategies for TIL therapy. Research Sponsor: None.

Phase 1b study of a brain-penetrant MEK inhibitor, PF-07799544, plus next-generation BRAF dimer inhibitor, PF-07799933, in advanced *BRAF*-mutant melanoma.

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Background: Treatment of *BRAF*-mutant (mut) melanoma has been transformed by targeted inhibition of MEK and BRAF kinases. However, duration of clinical benefit has been limited by de novo and acquired resistance through RAF-kinases signaling as dimers, poor activity in brain metastases (BMs), and paradoxical activation adverse events (AEs) negatively impacting tolerability. PF-07799544 is an oral, brain-penetrant, reversible MEK inhibitor (MEKi). PF-07799933 is an oral, brain-penetrant, selective BRAF dimer inhibitor (BRAFi) with activity against *BRAF*^{V600} and non-V600 muts. We report initial results of this next-generation BRAFi/MEKi combination from ongoing phase 1 study. **Methods:** This platform study (NCT05538130) is evaluating PF-07799544 as monotherapy or combined with other targeted therapy for *BRAF*-mut melanoma and other solid tumors. Substudy B is an open-label, multicenter study assessing safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and clinical activity of PF-07799544 + PF-07799933. Dose escalation (DE) enrolled into 4 dose levels patients (pts) with *BRAF*-mut advanced melanoma who had progressed on standard therapy, including pts with BMs. Randomized dose optimization (DO) enrolled pts with *BRAF*^{V600}-mut advanced melanoma previously treated with 1-2 immunotherapy (IO) lines and ≤ 1 BRAFi $\pm$ MEKi line; pts with BMs were eligible if asymptomatic. We report pooled baseline characteristics and safety and separate efficacy. **Results:** As of Nov 12, 2025, 60 pts received ≥ 1 dose of study treatment. At baseline: median age, 54.5 years; female, 50%; White, 95%; ECOG PS of 0, 63%; adrenal insufficiency, 25%; BMs, 53%; and *BRAF*^{V600} mutation, 95%; 77% received ≥ 3 prior systemic anticancer therapies, 100% received prior IO, 100% of pts with *BRAF*^{V600} mutation received prior BRAFi $\pm$ MEKi, and 73% received BRAFi $\pm$ MEKi < 6 months before beginning study treatment. Any-grade treatment-emergent AEs (TEAEs) occurred in 95%; most common ($\geq 20\%$) were rash (40%), fatigue (37%), diarrhea (32%), and peripheral edema (22%). Grade ≥ 3 TEAEs occurred in 67%; most common ($\geq 5\%$) were rash (7%), disease progression (7%), anemia (5%), and fall (5%). Dose modifications due to TEAEs (any-causality, treatment-related) included reductions (13%, 13%), interruptions (53%, 33%), and discontinuations (10%, 3%). Objective response rate (ORR; including unconfirmed) by investigator was 27% in 41 DE pts and 32% in 19 DO pts. In pts with baseline BMs, intracranial (IC) ORR was 30% in 23 DE pts and 22% in 9 DO pts. PK showed BRAFi/MEKi exposures consistent with preclinical exposures which showed antitumor activity supporting selected DO doses. **Conclusions:** PF-07799544 + PF-07799933 showed manageable safety and promising systemic and IC antitumor activity in heavily pretreated *BRAF*-mut advanced melanoma. Evaluation of dose expansion cohorts is ongoing. Clinical trial information: NCT05538130. Research Sponsor: Pfizer.

Combination of vemurafenib with cobimetinib in *BRAF* V600E/K mutated melanoma patients to normalize LDH and optimize immunotherapy with nivolumab and ipilimumab (COWBOY): A randomized, open-label phase 2 clinical trial.

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Background: Elevated levels of serum lactate dehydrogenase (LDH) in patients (pts) with metastatic melanoma are associated with reduced response to immune checkpoint inhibitors (ICIs). In a phase 2 trial, we investigated whether upfront reduction of tumor burden and normalization of LDH through six weeks of BRAF/MEK inhibitor (BRAF/MEKi) induction, prior to the initiation of ICIs, could improve response rates compared to standard first-line dual ICI.

Methods: In this two-arm, multicenter, phase 2 trial, treatment naïve pts with unresectable stage III or stage IV BRAFV600E/K mutation-positive melanoma and elevated baseline LDH levels ($< 5\times$ upper limit of normal) were randomized 1:1 (stratified by LDH) to one of two treatment arms. Arm A received 6 weeks of induction with vemurafenib 960 mg bid + cobimetinib 60 mg QD on a 21/7-day schedule, directly followed by four courses of ipilimumab 3 mg/kg q3wk (ipi3) plus nivolumab 1 mg/kg q3wk (nivo1). Arm B directly started with four courses of ipi3 + nivo1. Both arms received response-adapted nivolumab maintenance. The primary endpoint was to compare the best overall response rate (BORR) within 18 weeks from the start of treatment between two treatment arms, as assessed by RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and the rate of grade 3/4 toxicity. Exploratory endpoints focused on circulating tumor DNA dynamics (ctDNA), blood transcriptome, and tumor immunoprofiling. ClinicalTrials.gov identifier: NCT02968303. **Results:** Between 2017–2021, 71 pts were randomly assigned, 36 to arm A and 35 to arm B. The study was prematurely terminated due to slow patient accrual (planned accrual: 200 pts). The median follow-up time was 27.9 months (IQR 16.8–57.8). In arm A, the BOR was partial response (PR) in 75% of the pts (36.1% had an ongoing response after treatment switch), stable disease (SD) in 22.2%, and progressive disease (PD) in 2.8%. In arm B, 54.3% had PR, 22.9% SD, and 20% PD (1 pt was not evaluable). BRAF/MEKi induction prior to ICI was associated with a significantly shorter median PFS as compared with upfront dual ICI (4.4 months vs 25.0 months, HR 0.52, 95% CI 0.30–0.91; $p=0.02$). Median OS was also shorter in arm A (13.5 months), whereas the median OS was not reached in arm B (HR 0.38, 95% CI 0.19–0.68; $p=0.002$). Treatment-related grade ≥ 3 adverse events occurred in 25 of 36 pts (69%) in arm A and 15 of 35 pts (43%) in arm B. When combining both arms, pts with undetected ctDNA at 6–12 weeks after ICI initiation had significantly longer PFS than those with detected ctDNA (HR 2.05, 95% CI 1.05–4.0; $p=0.03$). **Conclusions:** BRAF/MEKi induction prior to dual ICI did not improve response rates to ICI and was associated with worse PFS and OS in pts with BRAFV600E/K mutated melanoma and elevated LDH compared to upfront dual ICI. Clinical trial information: NCT02968303. Research Sponsor: Bristol-Myers Squibb; Roche; Paul Speth Fund; PAMgene.

MATRiX: A randomized phase II trial of tuvusertib (ATR inhibitor) with or without avelumab in advanced anti-PD(L)-1 refractory Merkel cell carcinoma.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

A phase II study of neoadjuvant cemiplimab in hedgehog inhibitor (HHI)–naïve basal cell carcinoma of the head and neck.

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Background: Surgical resection of locally advanced basal cell carcinoma of the head and neck (BCCHN) often carries significant morbidity. This phase II study seeks to investigate the response to neoadjuvant cemiplimab on surgical morbidity in BCCHN patients. **Methods:** In this prospective, nonrandomized, multicenter, phase II trial (NCT05929664), anti-PD1 and HHI-naïve patients with resectable BCCHN received 2 to 6 cycles of cemiplimab (350mg IV Q21 days), followed by surgical resection or biopsy. Surgical plan at enrollment required functional organ sacrifice (orbit, eyelid, ear, nose, lip, or facial nerve). RECISTv1.1 tumor measurements were performed every 2 cycles to determine primary endpoints of ORR and DCR. Patients with PD (>20% growth) or SD with 5 to 20% growth at any assessment were offered HHI or surgery. Patients with CR at any assessment proceeded to surgery or directed biopsy. Secondary endpoints included: surgical benefit rate (SBR, defined as rate of functional organ preservation, determined by the investigator, comparing surgical resection to surgical plan at time of enrollment), rate of pCR, safety (CTCAEv5.0), and quality of life (FHNSI, FACE-Q and VFQ-25). Correlative studies include examination of the tumor immune microenvironment related to functional changes in immune cell composition. **Results:** Between August 2023 and September 2025, 33 patients were enrolled: 40–89 yo; 22 M/11 F; sites of disease included eyelid (n=17), orbit (n=4), nose(n=5), lip (n=1), facial nerve (n=1), ear (n=1), and scalp or cheek (n=5). 30 were evaluable: 23 (76.7%) completed 6 cycles. Among the remaining 7 patients, 1 experienced CR after 4 cycles; 1 was taken off therapy for grade 3 myalgia; 1 had SD with 5–20% growth and 2 had PD, and were taken to surgery per protocol; 2 chose surgery due to stagnant response after initial PR. 12 patients (40%) experienced a grade 1–2 treatment-related AE. 1 patient (3.33%) experienced a grade 3 treatment-related AE as above. The ORR was 66.67%. The DCR was 90.0%. Based on RECISTv1.1 criteria, 3.33% (n=1) had CR, 63.33% (n=19) had PR, 23.33% (n=7) had SD, and 10.0% (n=3) had PD as best overall response 8 patients (26.67%) achieved pCR. The SBR was 43.3%, with functional preservation of the eyelid (n=7), nose (n=2), lip (n=1), ear (n=1), or orbit (n=1). **Conclusions:** Neoadjuvant cemiplimab had an acceptable safety profile and shows promising efficacy in the treatment of advanced, surgically-resectable BCCHN. This novel approach may alleviate the morbidity of subsequent surgical resection. (NCT05929664 supported by Regeneron Pharmaceuticals, Inc.). Clinical trial information: NCT05929664. Research Sponsor: None.

Cadonilimab or ivonescimab plus axitinib in metastatic mucosal melanoma: Results from a phase Ib trial.

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Background: Mucosal melanoma (MM) is a rare and aggressive cancer with a poor prognosis. Unlike its more common counterpart, cutaneous melanoma, MM responds poorly to standard single-agent immunotherapy, such as anti-PD-1 monoclonal antibodies (mAbs), limiting treatment options. This clinical challenge underscores the need for more effective strategies, making combination therapies a clear future direction. The aim is to overcome resistance by targeting multiple pathways simultaneously. The main objective of this study is to explore and compare two distinct immunotherapy backbones—targeting the PD-1/CTLA-4 and VEGF pathways—for their potential in future rational combinations against MM. **Methods:** This is a phase Ib, dose de-escalation and cohort-expansion, open-label trial. The combination dose of axitinib will utilize a "3+3" dose de-escalation design. The starting dose is 5 mg. If dose-limiting toxicity (DLT) is observed at this dose level, the dose for subsequent cohorts will be reduced to 3 mg. Patients with metastatic melanoma receive 10 mg/kg cadonilimab Q3W (cohort 1) or 20 mg/kg ivonescimab Q3W (cohort 2) in combination with 5 mg axitinib BID. Primary endpoints are rate of dose-limiting toxicities (DLTs) and safety. Secondary endpoints are objective response rate (ORR) by investigator assessment, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and overall safety. **Results:** As of December 25, 2025, a total of 28 patients have been enrolled in the study (14 cohort 1; 14 cohort 2). Median follow-up of 13 months. The distribution of primary tumor sites was as follows: oral cavity 14.3%, esophagus 17.9%, rectum 32.1%, and cervix 35.7%. 21% had elevated LDH. BRAF status, known for 71% of patients, was positive in 25%. No DLT or treatment related death was observed. Axitinib was selected as 5 mg BID. 71.4% patients experienced treatment related AE (TRAE) and 17.9% patients experienced Grade 3-4 TRAEs. In cohort 1, the most common TRAEs include hypothyroidism, hypertension, diarrhea, anorexia and rash. In cohort 2, the most common TRAEs include proteinuria, myalgia, hyperthyroidism, hypertension, abnormal transaminase levels, anorexia and hyperlipidemia. No patient discontinued treatment due to TRAE. ORR, DOR, DCR, and median PFS for all cohorts are shown in Table. **Conclusions:** The combination therapy involving cadonilimab or ivonescimab plus axitinib demonstrates a promising safety and efficacy profile. These findings suggest that such dual-antibody-based regimens could provide synergistic anti-tumor activity with an improved therapeutic index, warranting further clinical investigation. Clinical trial information: NCT06424626. Research Sponsor: None.

Secondary Endpoint	Cohort 1 (n=14)	Cohort 2 (n=14)
PR	5	5
SD	4	5
PD	5	4
ORR	35.7%	35.7%
DCR	64.3%	71.4%
DOR (mo)	6.7	6.4
mPFS (mo)	5.8	8.7
mOS (mo)	NA	NA

Neoadjuvant intralesional daromun (L19IL2/L19TNF) in resectable locally advanced melanoma: An update on the primary outcome and sensitivity analyses (EFS) from the PIVOTAL phase 3 trial.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

A 3-year landmark overall survival analysis of RP1 plus nivolumab in patients with anti-PD-1–failed melanoma from the IGYTE clinical trial.

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Background: Advanced melanoma has a high mortality rate; however, survival for patients (pts) treated with anti-PD-1–based therapy tends to plateau at 3–4 years, suggesting that pts alive at 3 years are likely to have prolonged benefit. This highlights the need for novel therapies that offer increased survival beyond 3–4 years. RP1 (vusolimogene oderparepvec) is an HSV-1–based oncolytic immunotherapy expressing GM-CSF and a fusogenic glycoprotein (GALV-GP-R⁻). In the IGYTE trial (data cutoff [DCO]: 15OCT2024), pts with advanced melanoma that had confirmed progression on anti-PD-1 therapy who received RP1 + nivolumab (nivo) had an objective response rate by RECIST 1.1 of 33.6% (16.4% complete response); median duration of response was 24.8 months. Here, we present a 3-year survival analysis of pts treated with RP1 + nivo from IGYTE (last pt in: 9MAR2023; DCO: 11JUN2025). **Methods:** Pts ≥18 years with advanced melanoma and confirmed progression while being treated for ≥8 weeks with anti-PD-1 ± anti-CTLA-4 as the last prior therapy were enrolled (NCT03767348). An initial dose of RP1 was administered intratumorally (1×10^6 PFU/mL), followed by up to 7 doses every 2 weeks (Q2W; 1×10^7 PFU/mL) in combination with intravenous nivo 240 mg Q2W/480 mg Q4W for up to 2 years; additional RP1 was allowed if protocol-specified criteria were met. This updated analysis evaluated overall survival (OS) using the Kaplan-Meier (KM) method. **Results:** Of 140 enrolled pts, 49.3% had stage IVM1b–d disease, 55.7% had PD-L1–negative tumors, 46.4% had prior anti-PD-1 + anti-CTLA-4 therapy, and 65.0% had primary resistance to prior anti-PD-1 (ie, progression within 6 months of starting the immediate prior course of anti-PD-1). The median (95% CI) OS was 32.2 (25.8, 39.2) months (the median OS follow-up was 3 years by reverse KM method). OS rates (95% CI) at 1, 2, and 3 years were 75.3% (66.9%, 81.9%), 61.6% (52.5%, 69.4%), and 45.5% (35.8%, 54.7%), respectively. Importantly, among responders (n=47), the 3-year OS rate (95% CI) was 81.8% (65.2%, 91.0%) vs 22.5% (12.6%, 34.2%) for non-responders (n=93). The 3-year OS rates were 41.8% in pts with stage IVM1b–d disease (n=69), 37.2% for those with PD-L1–negative tumors (n=78), 37.4% in pts with prior anti-PD-1 + anti-CTLA-4 therapy (n=65), and 44.8% in pts with primary resistance to anti-PD-1 (n=91). The safety profile for RP1 + nivo remained consistent with prior reports; no new safety signals were seen. **Conclusions:** The 3-year landmark OS rate of 45.5% in the overall population and 81.8% among responders provides further evidence that the deep and durable responses provided by RP1 + nivo translate into long term clinical benefit, including extended OS in pts with melanoma post-confirmed progression on prior anti-PD-1–based therapy. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

A phase 2 trial of IO102-IO103 and nivolumab-relatlimab in previously untreated, unresectable melanoma.

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Background: IO102-IO103 is an investigational cancer vaccine that targets both tumor and immune-suppressive cells in the tumor microenvironment. IO102-IO103 has demonstrated clinical activity in combination with anti-PD-1 monotherapy in advanced melanoma, with concordant clonal T cell expansion observed in the tumor and peripheral blood in patients with radiographic response. IO102-IO103 has not yet been assessed in combination with nivolumab-relatlimab (nivo-rela). **Methods:** In this multicenter, phase 2 trial (NCT05912244) patients with unresectable, previously untreated non-veal melanoma were treated with subcutaneous IO102-IO103 and intravenous nivo-rela for up to two years. IO102-IO103 was administered every two weeks for eight weeks, and every four weeks thereafter. PD-L1 protein expression was assessed using the 28-8 pharmDx assay on pre-treatment tissue. The primary endpoint was best overall response rate (BORR) by RECIST v1.1, with a plan to reject the null hypothesis based on the proportion of patients with $\geq 1\%$ membranous PD-L1 staining in the tumor compartment. Secondary endpoints included progression-free survival (PFS), safety assessed by Common Terminology Criteria for Adverse Events v 5.0, and duration of response (DOR). PFS and DOR were summarized using Kaplan-Meier methods. Bulk T cell receptor (TCR) sequencing was performed on peripheral blood mononuclear cells using an RNA-based assay at baseline, week 4 and week 8. **Results:** Among 43 evaluable patients, the BORR was 60% (95% confidence interval [CI]: 44-75%), including 19 patients with partial response and 7 patients with complete response. At database lock (Dec 1 2025), median follow up was 10.1 months (interquartile range 6.1-19.3). The median duration of response was not reached (95% CI: 14, NR) and median PFS was 8.2 months (95% CI 6.8, not reached [NR]). Among patients with PD-L1 negative tumors (n = 25), the BORR was 52% (95% CI 31-72%) and median PFS was 8.2 months (4.2, NR). Grade 3-4 treatment-related adverse events occurred in 9 patients (21%), including adrenal insufficiency (2 patients), acute kidney injury (2), aseptic meningitis (1), arthritis (1), maculopapular rash (1), myositis (1), neutropenia (1), and colitis (1). There were no treatment related deaths. T cell clonal expansion was observed at on-treatment time points compared to baseline in patients with and without radiographic response. **Conclusions:** IO102-IO103 in combination with nivo-rela was associated with a higher objective response rate compared to historical data for nivo-rela alone, meeting the trial's primary endpoint. No unexpected safety signals were observed. These findings support the further clinical investigation of IO102-IO103 with nivo-rela as an initial treatment for unresectable melanoma. Clinical trial information: NCT05912244. Research Sponsor: IO Biotech; NCCN Foundation; National Cancer Institute; P30 CA008748.

Response-focused analyses of the impact of circadian rhythm on efficacy of first-line immunotherapy in melanoma.

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Background: Several retrospective studies have associated better clinical outcomes with morning infusions of immune-checkpoint inhibitors (ICI), attributing the same to circadian differences in T-cell activity. However, these studies have largely focused on survival endpoints, which are susceptible to confounding by skewed cohort distributions, treatment heterogeneity or other unknown variables. In this study, we explore the impact of timing of ICI infusions by primarily focusing on objective response as a more direct and immediate measure of immunologic activity, and possibly less susceptible to confounding variables. **Methods:** We conducted a single center, retrospective study of patients with advanced melanoma with response-evaluable disease and treated with an ICI regimen in the first-line setting. We recorded baseline patient and tumor characteristics and the start time of the first ICI infusion. Based on the median start time (~1:00 PM) of all ICI infusions in our clinic, we classified patients into “Early” (before 1:00 PM) and “Late” cohorts (1:00 PM & after). We analyzed objective response rate (ORR) per RECIST v1.1, time-to-response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS), comparing endpoints between cohorts using logistic or Cox regression, with adjustments for variables including age, sex, ECOG score, and disease stage. **Results:** We identified 216 eligible patients treated between 2014 – 2025, including 78 in the Early cohort and 138 in the Late cohort. Median age was 64 years (range 19 – 95) and 69% were male. Median follow-up duration was 27 months (range 6 days – 12 years). There were no significant differences in baseline patient and tumor characteristics between the two cohorts. ORR for the Early cohort was 64.1% (50/78; complete response [CR] – 34.6%, partial response [PR] – 29.5%) and for the Late cohort was 61.6% (85/138; CR – 28.3%, PR – 33.3%) [p = 0.71]. There were no significant differences in TTR and DOR between the cohorts. The distribution of first ICI infusion start-time in the responders mirrored that of all ICI infusions in all patients with melanoma. Adjusted PFS and OS were also similar between the cohorts (see Table). **Conclusions:** Our response-focused analyses do not suggest an association of early timing of ICI infusion to better efficacy outcomes, in contrast to findings from other studies. Our findings are consistent with the known long terminal half-life of ICI agents, which should provide steady availability of ICI antibodies to immune cells throughout the day. Our results do not support implementing time-based ICI infusion strategies in the oncology clinics. Research Sponsor: None.

Endpoint	Early cohort	Late cohort	Hazard ratio (95% CI)	P-value
PFS, Median months (95% CI)	12 (9, NR)	16 (9, 28)	1.01 (0.68, 1.50)	0.97
OS, Median months (95% CI)	82 (66, NR)	88 (62, NR)	1.07 (0.61, 1.89)	0.82

CI = Confidence interval; NR = Not reached.

Metabolic signatures of response: 2-hydroxybutyric acid as a biomarker in melanoma patients receiving ipilimumab–nivolumab.

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Background: 2-Hydroxybutyric acid (α -HB) is an established biomarker in metabolic disease of insulin resistance and oxidative stress but its role in immuno-oncology remains unclear. This study conducted an exploratory analysis to evaluate whether α -HB could be used as a biomarker in advanced melanoma patients treated with ipilimumab–nivolumab, and its association with treatment response and toxicity. **Methods:** In this single-center retrospective study, 36 patients with unresectable/metastatic melanoma received ipilimumab–nivolumab. α -HB levels were measured by targeted mass spectrometry and measured relative metabolomic signal intensities. Descriptive statistics assessed α -HB across subgroups defined by age, sex and BRAF status. Associations between α -HB and grade ≥ 3 immune-related toxicity, treatment response, and survival at last contact were tested using univariable logistic regression with α -HB entered as a continuous predictor ($\log_2$ -transformed). Prespecified sensitivity analyses dichotomized α -HB at the median (1.13) and 75th percentile (1.55). For mortality, we additionally derived an exploratory ROC-based Youden threshold to define a “high α -HB” group and report diagnostic performance (specificity, PPV, NPV) and odds ratios. **Results:** Median age was 53.5; 63.9% were male; 80.6% had cutaneous melanoma; 33.3% were BRAF-mutant; 80.6% received first-line therapy. Baseline α -HB was lower in patients who developed grade ≥ 3 toxicity (mean 1.01 vs 1.54; $p=0.013$) and in responders (1.09 vs 1.60; $p=0.021$), while it was higher among those who died (1.49 vs 1.06; $p=0.045$). In logistic models using $\log_2$ -transformed α -HB, each doubling in α -HB was associated with reduced odds of grade ≥ 3 toxicity (OR 0.165, 95%CI 0.036–0.744; $p=0.019$) and response (OR 0.268; 95% CI 0.075–0.961; $p=0.043$; AUC = 0.79; HL $p=0.803$, where higher p indicates better fit), consistent with lower α -HB marking both toxicity and response. Higher α -HB trended toward increased death risk (OR 3.3 per doubling; $p=0.066$). Using a Youden-derived cutoff (α -HB ≥ 1.58), high α -HB defined a high-risk subgroup (OR 10.0; 95% CI 1.09–91.4; $p=0.041$) with high specificity for death (94%); PPV 89% and NPV 56%. **Conclusions:** Elevated α -HB was associated with reduced response, lower incidence of immune-related toxicity, and higher rates of death, suggesting a metabolically suppressed immune phenotype. Further validation is needed to determine whether metabolic interventions could improve immunotherapy outcomes in selected patients. Research Sponsor: None.

Final results and correlative analysis of entinostat (E) plus pembrolizumab (P) in patients (Pts) with metastatic melanoma (MM) previously treated with anti-PD-(L)1 therapy (Tx).

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Background: PD(L)1 inhibitors have transformed MM tx, yet several pts experience resistance. Preclinical data suggest that epigenetic modifications may overcome this. Here, we present the results of an expansion MM cohort treated with E+P following prior anti-PD(L)1 tx. **Methods:** Pts with unresectable stage III/IV melanoma, progression to anti-PD(L)1 and BRAF-targeted tx (if BRAF-mutant) were eligible. Pts were treated with E, 5 mg PO qwk, and P, 200 mg IV q3wks. The primary endpoint was to determine the objective response rate (ORR) per the irRECIST criteria. Secondary endpoints included assessment of the safety of E+P tx, progression-free (PFS), and overall survival (OS). Correlative analyses were performed on baseline and on-tx tissues. **Results:** 53 pts were treated (median [mdn] age, 61 years; 60% male; 55% with ECOG performance status of 0; 64% with visceral metastases; 23% with BRAFV600 mutation), including 43% with primary resistance to anti-PD(L)1 inhibitors, respectively. The mdn number of prior systemic tx was 3 (range 1-8), and 70% of pts had previous tx with CTLA4 inhibitors. 49% pts developed $\geq$ grade 3/4 toxicity, and 19% pts discontinued at least one drug due to adverse events. 10 pts had a partial (n=9) or complete (n=1) response, for an ORR of 19%. The mdn follow-up was 11.5 months (mon), and the mdn response duration was 23.7 mon (range 2.6-45.6+ mon); 9 pts had stable disease $>$ 6 mon. The mdn PFS and OS were 4.0 and 11.5 mon, respectively. Blood analysis showed that the tx significantly decreased Ki67-PD1+ T cells and T regs and significantly increased Ki67-HLA-DR+ and ICOS+ T cells. Analysis of baseline (n=30) and on-tx (n=10) tumor biopsies using NanoString and/or bulk RNAseq showed increased immune infiltration with tx and increased expression of key genes in antigen presentation (*B2M*), chemoattraction (*CXCL11* & *13*), and IFN γ . Hallmark gene set enrichment analysis suggests that pts bearing inflamed, non-proliferating baseline tumors had a more durable clinical benefit to tx (i.e., no disease progression for $>$ 6 mon). Exploratory analysis using quantitative multiplex immunohistochemistry showed that pts with more durable clinical benefit had baseline tumors with a higher lymphoid-to-myeloid (L/M) ratio, and higher numbers of tumor-infiltrating (TI) CD4+ and CD8+ cells, particularly CD8+PD1+ cells. With tx, pt tumors with clinical benefit maintained a higher L/M ratio, had lower TI CD8+PD1+ cells, and increased density of TI CD20+ cells. TI CD8+PD1+ cells increased in pt tumors without clinical benefit. **Conclusions:** E+P tx in anti-PD(L)1-resistant MM was associated with durable clinical benefit in a pt subset and was well tolerated. Correlative analysis revealed that tx increased inflammation across most analyzed pt tumors; the most significant benefit, however, was observed in pts with pre-existing inflamed tumors. Clinical trial information: NCT02437136. Research Sponsor: SYNDAX Pharmaceuticals.

Clinical characteristics, molecular features, and treatment of primary central nervous system melanoma.

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Background: Primary Central Nervous System (CNS) Melanoma is a rare and aggressive malignancy, comprising 1% of melanoma cases and 0.07% of brain tumors. Due to its rarity, its natural history, molecular features and optimal management remain poorly defined. **Methods:** We retrospectively reviewed patients at our institution between January 1998 and October 2025 with primary CNS melanoma or melanocytoma with melanoma transformation. Clinical characteristics, molecular profiling, treatments and survival outcomes were collected. Overall survival (OS) and progression free survival (PFS) were estimated using Kaplan-Meier curves. **Results:** Nineteen patients were identified, including eight (42%) with melanocytoma to melanoma transformation. Median time of transformation was 34.4 months. Thirteen (68%) patients were female with a median age at diagnosis of 59.3 years. Common presenting symptoms were sensory disturbances (58%), pain (53%), motor deficits (37%) and nausea or vomiting (32%). At diagnosis, location of disease was spinal (n=12), intracranial (n=6) and multifocal (n=1). Thirteen patients had leptomeningeal involvement. Molecular profiling was performed in 15 patients, revealing mutations in *GNAQ* (n=7), *GNA11* (n=3), *CKIT* (n=2), *BAP1* (n=1), *EIF1AX* (n=1), and *BRAF* v600 (n=1). Thirteen (68%) patients underwent subtotal resection (STR), five (26%) gross total resection (GTR) and one radiation only. Median resected tumor size was 1.7 cm. Seventeen (94%) patients had recurrence at a median of 9.1 months, and four patients underwent repeat surgery. Fourteen (74%) patients received adjuvant radiation and 14 (74%) received immunotherapy, most commonly ipilimumab with nivolumab (71%). Nine patients received chemotherapy: temozolomide (n=5), bevacizumab (n=2) and one each of intrathecal IL-2, tebentafusp, imatinib and encorafenib with binimetinib. Four patients received chemotherapy before immunotherapy. Median OS from diagnosis of CNS melanocytoma or melanoma was 50.9 months (13.4 – 80). Median OS from time of transformation to melanoma or CNS melanoma diagnosis was 24.0 months (11.9 – NA). One-, three- and five-year OS rates were 73%, 53% and 40% respectively. GTR was associated with increased median OS compared to STR (80.0 vs 19.7 months, $p=0.02$). Age at diagnosis, immunotherapy, chemotherapy, adjuvant radiation, STR with or without radiation, disease location, leptomeningeal involvement, tumor size >3cm and presence of *GNAQ* mutation were not associated with survival. Median PFS was 3 months with chemotherapy and 5.7 months with immunotherapy. **Conclusions:** To our knowledge, this is the largest single center study of primary CNS melanoma. Outcomes remain poor, with survival primarily associated with GTR. The predominance of *GNAQ* and *GNA11* alterations with rare *BRAF* v600 mutations highlight the distinct biology of primary CNS melanoma and need for novel targeted therapies. Research Sponsor: None.

A propensity score-matched analysis comparing first-line regional, systemic, and intralesional treatments for melanoma in-transit metastases in a contemporary patient population.

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Background: Unresectable melanoma in-transit metastases (ITM) can pose a significant clinical challenge. Our recently published data comparing first-line treatments for ITM, isolated limb infusion or perfusion (ILI/ILP), immune checkpoint inhibitors (ICI) and intralesional talimogene laherparepvec (TVEC), found superior outcomes with TVEC. However, TVEC was used more often in patients with lower disease burden and earlier stage (IIIB vs. IIIC/D). Therefore, we sought to better investigate these differences with a propensity score-matched (PSM) analysis. **Methods:** A multi-institutional, international IRB- approved retrospective analysis was conducted for unresectable melanoma ITM from 2016-2022. PSM analysis comparing first-line ILI/ILP, ICI, and TVEC for was performed. Patients were matched for stage, number of ITM, anatomical site, CLND status, gender and age. Kaplan-Meier curves (OS, PFS, DMFS) and Cumulative incidence function (MSS) were used to visualize time-to-event outcomes in the PSM cohort, though both methods do not account for the matched structure. **Results:** 274 patients were identified, 120 female/154 male; 96 treated with ILI/ILP, 111 with ICI, and 67 with TVEC. Median follow-up was 40 months (range, 1-80). PSM was performed and identified 36 TVEC-ICI pairs and 27 TVEC-ILI pairs. These were combined resulting in a final cohort of 108 observations (45 TVEC, 36 ICI and 27 ILI). The groups were well balanced. No statistical difference was found for metastasis-free survival (DMFS), progression-free survival (PFS), melanoma-specific survival (MSS), and overall survival (OS) between treatment modalities. TVEC was associated with significant improvement in local PFS (median was 2.2 years (y) for ILI/ILP, 1.5y for ICI and not reached for TVEC, $p=0.048$). While not statistically significant, a clinical benefit was seen in PFS being longer for TVEC (2.1y for TVEC vs. 1.2y for ILI/ILP and 1.1y for ICI; $p=0.2$) and OS (not reached vs 2.9y for ILI/ILP and 5.2y for ICI; $p=0.2$). On mixed effect Cox regression proportional hazard model using the matched data set, there were no significant differences in any of the survival and recurrence outcomes. **Conclusions:** When patients are propensity-matched, there were no significant differences in first-line treatment modalities for unresectable melanoma ITM. Treatment with TVEC did result in clinically meaningful improved overall and local PFS and OS. This supports that selection of ITM therapy should incorporate an individualized approach, incorporating disease distribution, stage, burden, treatment side effects and patient priorities. Research Sponsor: None.

A phase I/IIa, first-in-human, multicenter, monotherapy and combination therapy with nivolumab dose-finding study of [^{212}Pb]VMT01 melanocortin-1-receptor-targeted, image-guided, alpha-particle therapy in subjects with previously treated unresectable or metastatic melanoma.

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Background: Melanocortin-1 receptor (MC1R) is a novel target for radiopharmaceutical therapy and is highly expressed on melanoma tumor cells. VMT01 is an MC1R-targeted peptide. ^{203}Pb is used for patient selection via SPECT imaging. Peptide radiolabeling with ^{212}Pb delivers alpha-particle therapy. Here, we present data on the treatment of adult patients with MC1R-positive metastatic melanoma receiving [^{212}Pb]VMT01 either as a monotherapy or in combination with the programmed death-1 (PD-1) checkpoint inhibitor, nivolumab. **Methods:** This is an ongoing phase I/IIa, first-in-human, prospective, multicenter, open-label, radioactive dose-finding and dose-expansion trial. The objectives are to investigate safety, pharmacokinetics, dosimetry, and efficacy. Participants receive up to 3 treatment cycles with either [^{212}Pb]VMT01 3 mCi, 5 mCi, or 1.5 mCi monotherapy, or combination therapy with [^{212}Pb]VMT01 (1.5 mCi) + nivolumab (480 mg, Q4W) or [^{212}Pb]VMT01 (3 mCi) + nivolumab. Participants are evaluated for any DLTs for the first 6 weeks after cycle 1. Efficacy is assessed by RECIST v1.1 criteria by the investigator. **Results:** As of 24 December 2025, 26 participants (53.8% male; median age: 68 years [range: 27–81]) with MC1R-positive metastatic melanoma were enrolled. The median prior systemic therapies was 4. All 26 enrolled participants received ≥ 1 dose of [^{212}Pb]VMT01. No DLTs were reported. All SAEs (including one grade 5 SAE) were attributed to disease progression. Most TEAEs were grade 1 (19.2%) and grade 2 (34.6%). Grade 3 TEAEs occurred in 8 participants (30.8%), 5 on monotherapy and 3 on combination therapy (3 mCi + nivolumab). Of the 22 evaluable participants, 1 PR, 9 SD, and 12 PD were reported. Four participants had progression-free survival of ≥ 6 months. **Conclusions:** [^{212}Pb]VMT01 as a monotherapy and in combination with nivolumab was generally safe and well-tolerated in 26 enrolled participants, with antitumor activity observed at the 3 mCi dose level. These data may be supplemented with a more complete follow-up at the time of the meeting. Clinical trial information: NCT05655312. Research Sponsor: None.

Imneskibart + low-dose subcutaneous IL-2 ± nivolumab in patients with CPI-refractory cutaneous melanoma: Promising results from an ongoing phase 1/2 study.

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Background: Imneskibart (AU-007) is an AI designed monoclonal antibody binding to interleukin-2 (IL-2) preventing binding to CD25 in the trimeric IL-2 receptor (IL-2 R), while allowing engagement with the dimeric IL-2R, CD122/CD132. Imneskibart-bound IL-2 expands T effector (Teff) and NK cell populations (dimeric IL-2R) without expanding regulatory T cells (Tregs; trimeric IL-2R). **Methods:** Patients (pts) with locally advanced/metastatic cutaneous melanoma were evaluated in Phase 1 (Ph1) dose escalation and in 2 ongoing Ph2 expansion cohorts. Rigorous eligibility criteria were applied requiring pts to have objective progression after ≥ 2 cycles of prior doublet checkpoint inhibitors (CPI, anti-PD-1 + anti-CTLA-4 or anti-LAG-3) with confirmation of progression ≥ 4 weeks later. Ph2 Cohort 1 evaluated the recommended Ph2 dose (RP2D) of 9 mg/kg imneskibart IV Q2W. Ph 2 Cohort 2 evaluates the RP2D of imneskibart IV Q2W + nivolumab (nivo) 480 mg Q4W. Both cohorts receive subcutaneous (SC) 135K IU/kg aldesleukin dose on Day 1 of first cycle with additional doses of aldesleukin administered at the beginning of each cycle until at least a partial response (PR) is obtained. Tumor reassessment is performed at the end of each 8-week cycle. **Results:** Fifteen pts received imneskibart + aldesleukin: 2 in Ph1 and 13 in Ph2. Fourteen pts were efficacy evaluable. Nine pts had tumor reductions ranging from -1 to -100% including pts with -100% and -58% reductions (continue treatment at 24 and 18 M respectively), and a -48% reduction (14 M on treatment). The median PFS and duration on treatment were 7.6 and 9 M respectively (9.3 M median follow up); 6 pts continue treatment. Nine of 14 evaluable pts have received imneskibart + IL-2 for a longer duration than their prior CPI doublet therapy. Eight pts enrolled in Ph2 Cohort 2 and 2 of the 6 efficacy evaluable pts to date (33%) had PRs with -35% and -31% tumor reductions and continue treatment. Two of 6 had SD and continue treatment. Overall, 67% had disease control at 4 months. Six pts continue treatment. Imneskibart led to a decrease in peripheral Tregs and increase in CD8 cells leading to CD8/Treg ratio increases up to 2 – 3 fold over BL. CD8/Treg ratio increases > 2 fold over BL were associated with longer median duration on treatment, PFS, and OS. Imneskibart + IL-2 was well-tolerated with Grade 3/4 drug-related adverse events (AE) occurring in only 14% of pts and in 0 of the 8 pts who received this combination + nivo. No patient discontinued treatment due to a drug-related AE. **Conclusions:** Compelling anti-tumor activity is observed with imneskibart + IL-2, with a strong emerging signal of enhanced activity with the nivolumab combination in pts with melanoma refractory to doublet CPI therapy. Imneskibart + IL-2-associated Treg reduction likely drives the high disease control rate, supporting durable benefit with prolonged treatment exposure and PFS. Clinical trial information: NCT05267626. Research Sponsor: Aulos Bioscience.

Phase 1 evaluation of the PRAME-targeted ImmTAC brenetafusp in advanced melanoma (Mel).

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Background: Brenetafusp (brene) is an ImmTAC bispecific (PRAME × CD3) therapy that promotes T cell recruitment into tumors. Initial Phase (Ph) 1 data showed acceptable safety, robust T cell activation at target doses (TD) ≥ 20 mcg and promising clinical activity in multiple tumors including heavily pretreated cutaneous melanoma (CM) (Hamid 2022, 2024; NCT04262466)]. We present updated monotherapy (mono) and PD1 immune checkpoint inhibitor (ICI) combination (combo) safety and efficacy results supporting brene dose selection in Mel (CM, mucosal [Mu] or acral [Ac]). **Methods:** HLA-A*02:01+ Mel patients (pts) who exhausted standard treatments were eligible. Primary objectives: safety and recommended dose; additional objectives included efficacy, biomarkers and ctDNA response. Brene mono was administered intravenously weekly (QW) with 1–2 step-up doses to TD; TD 40 and 160 mcg were evaluated in expansion. Combo was 160 mcg brene QW + 400 mg pembrolizumab (pembro) Q6W. Molecular response: ≥ 0.5 log [68%] ctDNA reduction by week 9 (Hamid 2024). T cell fitness defined as 3-gene (TESPA1, CD28 and GPR183) signature in blood (Sacco 2024). Tumor PD-L1 measured by immunohistochemistry, beta2 microglobulin (B2m) by immunofluorescence. **Results:** As of Oct 2025, 66 pts with Mel (median 2.5 prior lines, 100% prior PD1, 30% PD1 refractory [progression <6 mo post start of first anti-PD1], 68% St IV-c/IV-d) received brene mono (TD 40, n=16; TD 160, n=24; other TD 10–320 mcg, n=26). The 40-mcg cohort had more favorable baseline prognostic factors (ECOG PS, tumor burden, ctDNA, prior treatment) and T cell fitness. Ten pts (median 2.5 prior lines, 90% prior PD1, 50% prior BRAF/MEKi, 70% St IV-c/IV-d) received brene + pembro. Safety was similar at TD 40 and 160 mcg with Gr1/2 CRS (56% vs 42%) and rash (44% vs 42%) initially. Gr3/4 events occurred in 25% vs 54%: mainly transient lymphocyte decrease, consistent with mechanism. Of 10 pts with prior ICI Gr3/4 irAE, none had recurrence. Combo profile resembled each agent alone. No new safety signals observed. Disease control, RECISTv1.1 response and ctDNA molecular response rates were numerically higher at 160 vs 40 mcg (Table), with similar rates across subgroups typically less responsive to anti-PD1. Overall survival was associated with baseline T cell fitness and tumor B2m, but not with PD-L1 status. **Conclusions:** Brene shows promising monotherapy activity in late-line Mel, including difficult to treat populations, without causing ICI-like irAEs, and can be safely combined with pembro. Ph1 results support 160 mcg as the selected dose in the Ph3 PRISM-MEL trial evaluating brene with nivolumab versus standard nivolumab regimens (NCT06112314). Clinical trial information: NCT04262466. Research Sponsor: Immunocore Ltd.

	N	DCR% (PR + SD)	ORR%	6mo OS%	ctDNA-evaluable N	ctDNA response%
Brene mono	66	52	12	83	50	38
40 mcg	16	56	6	81	10	20
160 mcg	24	67	17	79	15	33
PD1 refractory	20	55	10	70	15	53
Ac / Mu	7	57	14	86	5	40
Sum target lesions >10 cm	25	44	12	80	19	32
Brene + pembro	10	70	20	80	5	40
PD1 refractory	6	67	33	67	2	50

Comparison of baseline gut microbiome features between response subgroups of patients (pts) with advanced melanoma undergoing immune checkpoint inhibitor (ICI) therapy.

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Background: Gut microbiome composition has been implicated as a potential biomarker of response to ICIs in melanoma pts, but it is unclear whether baseline gut microbiome composition may predict emergence of specific ICI resistance subtypes (primary vs. acquired resistance) or immune-related adverse events (irAEs). We sought to define clinical characteristics and baseline gut microbiome features that correlate with ICI resistance subtypes and irAEs in melanoma pts. **Methods:** We identified 90 pts from our institution's fecal biorepository of advanced melanoma pts who received ICIs and who had ≥ 1 pre- or on-treatment fecal sample available for 16S rRNA amplicon sequencing. Pts were categorized into 3 responder subgroups: responder (R, no progression on ICI), primary resistance (pR, progression < 6 months from ICI start), or acquired resistance (aR, progression ≥ 6 months from ICI start). Associations between clinical covariates and survival were analyzed using Kaplan-Meier and Cox proportional hazards models. Microbial features were compared using alpha and beta diversity metrics and pairwise comparisons at each taxonomic level using Wilcoxon rank-sum tests. **Results:** Baseline demographic and clinical characteristics were similar between subgroups (R, n = 35; pR, n = 32; aR, n = 23). irAE occurrence rates significantly differed between responder subgroups ($p = 0.048$). Pts who developed irAEs had significantly longer progression-free survival (PFS) than those without irAEs (median PFS 1412 vs. 106 days, $p = 0.026$). Later treatment line and receipt of prior ICI were associated with significantly higher hazard ratios (HRs) for death and progression, while resectable disease and development of any-grade irAE were associated with lower HRs for death and progression. There was no significant difference in baseline alpha diversity between responder subgroups or irAE groups. A trend toward differences in baseline beta diversity between responder subgroups was observed ($p = 0.084$). Abundance of *Faecalibacterium prausnitzii*, a known butyrate producer, was significantly higher in R than pR ($p < 0.001$, $p_{adj} = 0.029$), aR than pR ($p < 0.001$, $p_{adj} = 0.071$), and in pts who did not develop irAEs ($p = 0.02$). Other operational taxonomic units more abundant in responders (aR vs. pR, R vs. aR/pR) and pts who did not develop irAEs include the short-chain fatty acid (SCFA) producers *Coprococcus comes*, *Dorea longicatena*, and *Blautia glucerasea* ($p < 0.001$, $p_{adj} = 0.071$). **Conclusions:** Although no significant differences in baseline alpha diversity were observed between responder subgroups or irAE groups, responders and those without irAEs had significantly higher levels of SCFA-producing taxa at baseline, suggesting a potential immunomodulatory role for SCFAs such as butyrate in mediating ICI response and protection from irAEs. Research Sponsor: Bristol-Myers Squibb; Bloomberg-Kimmel Institute for Cancer Immunotherapy; U.S. National Institutes of Health; K08CA263316; Damon Runyon; The Marilyn and Michael Glosserman Fund for Basal Cell Carcinoma and Melanoma Research; The Barney Family Foundation; The Laverna Hahn Charitable Trust; American Society for Clinical Oncology.

Prospective, non-interventional, multisite evaluations of TRAQinform Immuno algorithmic quantitative treatment response analysis on treatment intent decisions in metastatic melanoma.

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Background: Molecular imaging plays a critical role in assessing immunotherapy response in metastatic melanoma, but current assessment methods may not fully leverage imaging data to inform clinical decision-making. This study prospectively evaluated whether integrating TRAQinform Immuno quantitative analysis into clinical assessment would alter oncologists' treatment intent in metastatic melanoma patients receiving checkpoint inhibitor combinations. **Methods:** In this prospective, multisite, non-interventional study (NCT05819255), patients with metastatic melanoma receiving dual-agent immunotherapy were enrolled at the University of Wisconsin Carbone Cancer Center and Massachusetts General Hospital Cancer Center. FDG PET/CT scans were acquired at baseline, 3-4 weeks and 12 weeks. All scans were analyzed using a research version of the TRAQinform IQ (TRAQinform) algorithmic quantitative software. At each timepoint, treating oncology and nuclear medicine teams recorded treatment intent before and after review of the TRAQinform analysis report. A cross-site, blinded review was conducted to assess potential status quo bias. **Results:** Twenty-six patients were enrolled (12F, 14M, mean age 65 years), 25 of whom completed all study scans. At week 3-4, 27% of cases (7/26) showed an intent to change treatment after oncologists reviewed the TRAQinform report, ($p=1.0$). At the 12-week assessment, 56% of cases (14/25) demonstrated intent to change treatment ($p=0.0008$). Considering either timepoint, 65% of cases (17/26) exhibited a change in treatment intent compared to baseline ($p=0.000006$). Cross-site analysis indicated minimal influence of status quo bias on intent decisions. **Conclusions:** In this prospective study assessing intent to treat, TRAQinform analysis of standard-of-care FDG PET/CT images influenced oncologists treatment decision in the majority of metastatic melanoma patients, suggesting it provides clinically actionable information. For oncologists managing patients on dual-agent immunotherapy - where treatment decisions often involve uncertainty and clinical judgment, this study demonstrates that TRAQinform offers an additional data-driven tool to support optimal therapeutic decision-making. Research reported in this abstract was supported by the National Cancer Institute of the National Institutes of Health and under Award Number R44CA257253. The content is solely the responsibility of the authors and does not necessarily represent the official news of the National Institutes of Health. Clinical trial information: NCT05819255. Research Sponsor: NIH-NCI; R44CA257253.

Long-term efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: An updated indirect treatment comparison (ITC) with 5-year follow-up data.

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Background: An ITC comparing NIVO + RELA and NIVO + IPI, approved dual immunotherapy treatment options for patients (pts) with advanced melanoma, was previously conducted using pt-level data from the pivotal RELATIVITY-047 (RELA-047; NIVO + RELA vs NIVO) and CheckMate 067 (CM-067; NIVO + IPI or NIVO vs IPI) trials (Long JCO 2024). Here we present updated results using 5-year follow-up data from RELA-047. **Methods:** Inverse probability of treatment weighting was used to adjust for cross-trial imbalances in baseline characteristics. CM-067 follow-up was truncated to best align with the follow-up length in RELA-047. Progression-free survival (PFS) per investigator (INV), confirmed objective response rates (ORRs) per INV, overall survival (OS), and melanoma-specific survival (MSS) were analyzed. Outcomes were also evaluated across key subgroups. The weighted NIVO arms from each trial were compared for validation. **Results:** After weighting, key baseline characteristics were balanced for NIVO + RELA (n = 339) and NIVO + IPI (n = 297). Outcomes after weighting were similar between NIVO + RELA and NIVO + IPI (hazard ratio [HR] [95% CI]: PFS, 1.10 [0.90–1.34]; OS, 0.96 [0.77–1.20]; MSS, 0.88 [0.68–1.12]; table). Grade 3–4 treatment-related adverse event (TRAE) rates were numerically lower with NIVO + RELA than with NIVO + IPI (23% vs 62%, respectively). Across subgroups, efficacy appeared similar between treatments, although trends favoring NIVO + IPI were observed for ORRs among pts with BRAF mutant disease (59% vs 48%) or serum lactate dehydrogenase > 2× the upper limit of normal (33% vs 12%). Among pts progression-free at 3 years, both NIVO + RELA and NIVO + IPI were associated with sustained benefit, with 5-year OS of 96% and 94% and MSS of 100% and 98%, respectively. **Conclusions:** Consistent with earlier findings, this updated ITC with a 5-year minimum follow-up from RELA-047 suggests that 1L treatment with NIVO + RELA may have efficacy comparable to NIVO + IPI in pts with advanced melanoma, overall and across most, but not all, subgroups. Results should be interpreted with caution because of differences in study design and the evolving treatment landscape over time. Research Sponsor: Bristol Myers Squibb.

Efficacy outcomes after weighting.						
	NIVO + RELA (n = 339)	NIVO + IPI (n = 297)	HR/OR (95% CI) ^a	NIVO RELA-047 (n = 338)	NIVO CM-067 (n = 288)	HR/OR (95% CI) ^b
Median PFS per INV, mo (95% CI)	12.0 (8.2–17.1)	11.2 (8.5–18.1)	1.10 (0.90–1.34)	6.7 (4.6–10.2)	5.7 (3.9–9.1)	0.96 (0.79–1.16)
Confirmed ORR per INV, %	48	50	0.92 (0.73–1.15)	40	40	0.99 (0.78–1.26)
Median OS, mo (95% CI)	64.2 (38.6–NR)	61.4 (37.1–NR)	0.96 (0.77–1.20)	34.7 (27.3–47.3)	35.7 (26.4–52.7)	1.04 (0.85–1.28)
Median MSS, mo (95% CI)	NR (NR–NR)	NR (61.4–NR)	0.88 (0.68–1.12)	51.2 (34.7–NR)	44.8 (32.3–NR)	1.00 (0.80–1.25)

^aNIVO + RELA vs NIVO + IPI.
^bNIVO arms. NR, not reached; odds ratio, OR.

Transposable elements and homotypic niches as drivers of immune dynamics and resistance in melanoma epigenetic-based immunotherapy.

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Background: Melanoma plasticity facilitates immune evasion and therapy resistance through dynamic cell-state transitions. While epigenetic remodeling critically influences these processes, its role in reshaping the tumor ecosystem under therapeutic pressure remains unresolved. We investigated the molecular and spatial mechanisms underlying clinical response to epigenetic-based immunotherapy in the phase Ib NIBIT-M4 trial (NCT02608437), which evaluated the DNA methyltransferase inhibitor guadecitabine combined with the anti-CTLA4 antibody ipilimumab. **Methods:** We performed longitudinal single-cell multiome profiling (paired snRNA-seq and snATAC-seq) on tumor biopsies collected at baseline and during treatment (weeks 4 and 12) from five melanoma patients (two responders, three non-responders). To resolve the spatial architecture of cell states, we integrated these data with high-resolution spatial transcriptomics (Visium HD) across nine samples. Analyses focused on defining malignant meta-programs (MPs), tumor microenvironment (TME) remodeling, and the regulatory role of transposable elements (TEs). **Results:** Integrated analysis resolved seven malignant MPs. Responders exhibited progressive enrichment of an Antigen Presentation/Interferon program, coupled by coordinated TME remodeling with T- and B-cell expansion. Conversely, non-responders were enriched for a de-differentiated Neural crest-like state. Spatial modeling revealed that this resistant Neural crest-like program relies on homotypic clustering to form compact, centrally localized niches that stabilize its transcriptional identity. In contrast, Wnt/ β -catenin subpopulations displayed a bimodal architecture, existing as either cohesive clusters or dispersed plastic cells. Epigenetic therapy reactivated TEs, which provided regulatory signals priming innate immunity and generated tumor-associated antigens that drove immunoediting in responders. Mechanistically, NFATC2 emerged as a master regulator of the Neural crest-like phenotype, and its inhibition promoted re-differentiation toward immunogenic states. **Conclusions:** Epigenetic-based immunotherapy dynamically reshapes the melanoma ecosystem by modulating TE activity and cell-state plasticity. Clinical response links to TE-driven immune priming, whereas resistance is maintained by spatially consolidated Neural crest-like niches stabilized by NFATC2. These findings identify spatial clustering as a principle of resistance and highlight NFATC2 as a potential therapeutic target. Research Sponsor: NIBIT Foundation Onlus; Fondazione AIRC; National Cancer Institute Cancer Center Support Grant (CCSG).

Nivolumab + relatlimab (NIVO + RELA) in advanced melanoma: 5-year update of RELATIVITY-047.

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Background: NIVO + RELA improved progression-free survival (PFS) vs NIVO in patients (pts) with advanced melanoma in the randomized, double-blind, phase 3 RELATIVITY-047 trial (NCT03470922), leading to regulatory approval as a fixed-dose combination (FDC). The combination also improved clinically meaningful efficacy outcomes (objective response rate [ORR], overall survival [OS], melanoma-specific survival [MSS]) vs NIVO. Here, we report 5-year trial outcomes that characterize long-term response durability and landmark survival. **Methods:** 714 pts were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg intravenously every 4 weeks, as previously described. PFS per RECIST v1.1 (primary endpoint) was assessed by blinded independent central review (BICR); secondary endpoints included ORR per BICR and OS. MSS (censoring nonmelanoma-related deaths) was a post hoc analysis. **Results:** At data cutoff (25 Sept 2025), minimum potential follow-up was 57.3 months (mo; time from last pt randomization to clinical cutoff date). NIVO + RELA continued to show a clinically meaningful benefit vs NIVO for PFS, OS, MSS, and ORR (table). Improvements in absolute landmark survival rates were observed over 3, 4, and 5 years as follows: PFS, 4%, 7%, and 10%; OS, 7%, 9%, and 10%; MSS, 9%, 10%, and 13%. In addition, NIVO + RELA demonstrated consistent improvement in efficacy outcomes vs NIVO across the majority of key subgroups. Subsequent systemic therapy was received by 40% of pts treated with NIVO + RELA and 41% with NIVO. Secondary efficacy and biomarker analyses will be presented. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 23% of pts treated with NIVO + RELA and 12% with NIVO; TRAEs (any grade) led to treatment discontinuation in 17% and 10% of pts, respectively. No new treatment-related deaths were reported since the 2-year analysis. **Conclusions:** With a follow-up of 5 years, first-line NIVO + RELA continued to demonstrate durable, clinically meaningful long-term improvements in PFS, OS, ORR, and MSS vs NIVO, with median MSS not reached for the combination. Across landmark timepoints, absolute separations in PFS, OS, and MSS rates were maintained and increased at the 5-year follow-up. Safety remained consistent with prior reports, with no new or unexpected safety signals. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 355)	NIVO (n = 359)	HR/ORR difference (95% CI)
Median PFS, mo (95% CI)	10.2 (6.5–15.7)	4.6 (3.5–6.5)	0.77 (0.65–0.92)
60 mo PFS rate, % (95% CI)	29 (24–35)	19 (15–24)	—
Median OS, mo (95% CI)	54.8 (33.6–81.1)	33.2 (25.2–44.7)	0.78 (0.64–0.95)
60 mo OS rate, % (95% CI)	48 (43–53)	38 (33–43)	—
Median MSS, mo (95% CI)	NE (NE–NE)	47 (34–65)	0.71 (0.57–0.88)
60 mo MSS rate, % (95% CI)	58 (52–63)	45 (40–51)	—
ORR, % (95% CI)	44 (39–49)	34 (29–39)	10 (3–17)

Descriptive analyses; minimum follow-up: 57.3 mo.

HR, hazard ratio; NE, not estimable.

Circulating tumor DNA (ctDNA) clearance after immune checkpoint inhibition (ICI) with radiotherapy (RT) as a prognostic indicator for patients with advanced melanoma.

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Background: ctDNA is becoming a useful biomarker for ICI treatment response assessment in advanced melanoma. RT is capable of producing an abscopal effect, potentially enhancing ICI efficacy. The utility of ctDNA monitoring with concurrent ICI and RT remains incompletely explored. Here, we describe the clinical characteristics and survival outcomes of patients with advanced stage melanoma treated with ICI and palliative RT based on ctDNA dynamics. **Methods:** In this multicenter, retrospective study, patients with unresectable stage III/IV melanoma treated with ICI and palliative RT were identified. Patients had prospectively collected, tumor-informed, exome-based, ctDNA monitoring (Natera). Within 3 months prior to RT, patients had a baseline ctDNA level. Patients were separated into 3 cohorts based on nadir ctDNA dynamics within 3 months after RT. Those with undetectable ctDNA were categorized as “ctDNA cleared.” Patients with a positive fold ctDNA change were “increasing ctDNA” and negative fold change were “decreasing ctDNA.” Hazard ratios for overall survival (OS) probability were determined via log-rank tests and multivariate analysis (MVA) used cox proportional hazard models. **Results:** 50 patients treated with ICI and palliative RT were analyzed. Median follow up was 8.0 months from RT start. Median age was 65 (24-86) and median baseline ctDNA level was 8.9 MTM/mL (0-11390 MTM/mL). Melanoma primaries included: 82% (41) cutaneous, 10% (5) mucosal, 8% (4) unknown primary. ICI regimens included 70% (35) ipilimumab/nivolumab, 16% (8) nivolumab/relatlimab, 2% (1) anti-PD-1/investigational ICI, 12% (n=6) anti-PD-1 monotherapy. 20 patients had ctDNA clearance, 12 patients had decreasing ctDNA, and 18 patients had increasing ctDNA following RT with ICI. The most common RT sites were the CNS (50%, n=25) and skin/soft tissue (24%, n=12), followed by lymph nodes and bone (each 14%, n=7), and lung and liver (each 6%, n=3). Patients with ctDNA clearance had longer OS ($p=0.001$) compared to those with increasing or decreasing and detectable ctDNA following RT. One year OS was 85.9% with ctDNA clearance, 30.6% with decreasing ctDNA, 22.0% for increasing ctDNA. In a MVA adjusting for age, M substage, radiation site, and melanoma subtype, both decreasing and increasing ctDNA were associated with worse OS compared with ctDNA clearance (HR 5.08 [95% CI, 1.26–20.48, $p=0.022$] and HR 9.83 [95% CI, 2.69–35.94, $p<0.001$], respectively). **Conclusions:** Among patients with advanced melanoma treated with ICI and palliative RT, ctDNA clearance is associated with significantly improved OS compared to patients with detectable ctDNA within 3 months following RT. Ongoing prospective studies are needed to understand the long-term clinical impact of RT on ICI-treated patients with melanoma, and better define the role of ctDNA monitoring for this population. Research Sponsor: None.

Optimal timing of circulating tumor DNA (ctDNA) dynamics to prognosticate immune checkpoint inhibitors (ICI) efficacy in patients with advanced stage melanoma.

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Background: ctDNA predicts relapse in resected tumors, but its role in advanced disease is less defined. We previously reported that early ctDNA changes at 3–4 weeks after ICI initiation can inform treatment response and survival. In this study, we attempt to identify the optimal timing of ctDNA dynamics within 90 days at various windows to better associate with ORR, PFS, and OS outcomes in patients (pts) with advanced stage melanoma treated with ICI. **Methods:** We performed a multicenter retrospective analysis using a personalized tumor-informed ctDNA assay (Natera) on prospectively collected plasma from pts with unresectable stage III/IV melanoma treated with anti-PD-1-based therapy. ctDNA was assessed at baseline and within 90 days of ICI initiation, stratified by ≤ 30 , 31–60, and 61–90 days. Logistic regression evaluated associations between ctDNA change (decrease/stable vs increase) and ORR. Cox proportional hazards models assessed PFS and OS. Pearson (ORR) and Spearman (PFS, OS) correlations were used for continuous ctDNA analyses. **Results:** Among 182 pts, 80% had cutaneous, 11% mucosal, and 9% unknown primary melanoma; 23% had unresectable stage III and 77% stage IV disease. Treatments included ipilimumab/nivolumab (55%), nivolumab/relatlimab (24%), and anti-PD-1 monotherapy (20%). Median follow-up was 12.1 months. Decreasing/stable ctDNA at all timepoints was strongly associated with ORR ($p < 0.0001$), with the greatest effect at 31–60 days (OR 25.38, 95% CI 7.12–90.45). Similar patterns were observed for survival, with improved PFS across all windows and strongest separation at 61–90 days (HR 0.170, 0.101–0.288). OS was likewise improved, most notably at 61–90 days (HR 0.137, 0.058–0.321). Continuous ctDNA change correlated with ORR ($r = -0.51$ to -0.63) and PFS ($\rho = -0.35$ to -0.47); OS correlations were weaker but significant at 61–90 days ($\rho = -0.21$). See Table 1. **Conclusions:** While ctDNA dynamics within 30 days showed prognostic value, associations with ORR, PFS, and OS were strongest and most consistent at 31–60 and 61–90 days. Prospective studies are needed to validate ctDNA for ICI treatment monitoring. Research Sponsor: The Institute for Clinical and Translational Research KL2 Scholars Program at the University of Wisconsin; UL1TR002373 and KL2TR002374.

Association of ctDNA dynamics with outcomes by time interval.			
	≤ 30 days	31–60 days	61–90 days
ORR (OR, 95% CI)	15.28 (5.58–41.78), $p < 0.0001$	25.38 (7.12–90.45), $p < 0.0001$	17.82 (5.66–56.08), $p < 0.0001$
PFS (HR, 95% CI)	0.373 (0.224–0.621), $p < 0.0001$	0.233 (95% CI 0.139–0.388), $p < 0.0001$	0.170 (0.101–0.288), $p < 0.0001$
OS (HR, 95% CI)	0.477 (0.237–0.961), $p = 0.038$	0.392 (95% CI 0.185–0.831), $p < 0.015$	0.137 (0.058–0.321), $p < 0.0001$
ORR (Pearson, r)	-0.553, $p < 0.0001$	-0.628, $p < 0.0001$	-0.513, $p < 0.0001$
PFS (Spearman, ρ)	-0.352, $p < 0.0001$	-0.438, $p < 0.0001$	-0.473, $p < 0.0001$
OS (Spearman, ρ)	-0.128, $p = 0.168$	-0.104, $p = 0.240$	-0.210, $p = 0.0171$

Anti-PD-1 (PD-1) monotherapy versus combination with anti-CTLA-4 for metastatic uveal melanoma (MUM) patients (pts).

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Background: MUM carries a poor prognosis with few effective treatments, especially for HLA-A*02:01-negative pts. While a subset of MUM pts responds to immune checkpoint inhibitors, the comparative efficacy of IPI+PD1 versus PD1 monotherapy is unclear. This study compares objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety between these regimens in MUM. **Methods:** MUM pts treated with PD1 or IPI+PD1 at 15 major melanoma centres (from Australia, Europe, United States and Israel) were included. Demographics, patient and disease characteristics, and clinical outcomes were examined. Univariate and multivariate (MVA) analyses were performed to identify clinical predictors of response and survival. **Results:** Of 412 MUM pts treated, 150 (36%) had PD1 and 262 (64%) received PD1+IPI. Compared to the PD1 group, PD1+IPI-treated pts were younger (64 vs. 70 years; $p<0.001$), had higher rate of elevated LDH (44% vs. 31%; $p=0.037$), and more frequently had prior treatment with tebentafusp (6.5% vs. 1.3%; $p=0.031$). Median follow-up from commencement of PD1+/-IPI was 4.9 years (95% CI 4.7 – 6.1). ORR was higher in IPI+PD1 group (18%) vs. PD1 (9%) ($p=0.008$), particularly in males ($p=0.009$), patients with liver metastases ($p=0.018$) and with lung metastases ($p=0.011$), with elevated LDH ($p=0.047$) and with no prior treatment with tebentafusp ($p=0.007$). PFS and OS at 1 and 2 years were numerically higher with IPI+PD1 (1- and 2-year PFS: 23% and 15%; 1- and 2-year OS: 63% and 39%) vs. PD1 (1- and 2-year PFS: 17% and 11%; 1- and 2-year OS: 54% and 36%), but these differences were not statistically significant ($p>0.05$). On MVA, adjusting for predefined variables (age, gender, ECOG PS, LDH, presence/absence of liver/lung metastases, prior treatment with tebentafusp), IPI+PD1 was associated with higher ORR (OR 2.71, 1.30 – 6.05; $p=0.01$) but not with PFS or OS compared to PD1. Presence of liver metastases (ORR [OR 0.28; 95% CI 0.13 – 0.64], PFS [HR 1.61; 95% CI 1.11 – 2.34], OS [HR 2.02; 95% CI 1.32 – 3.10]), ECOG PS $\geq$ 2 (PFS [HR 1.82; 95% CI 1.07 – 3.10], OS [HR 2.24; 95% CI 1.25–4.01]), elevated LDH (PFS [HR 1.66; 95% CI 1.30 – 2.11], OS [HR 2.39; 95% CI 1.84–3.10]) and prior tebentafusp treatment (OS [HR 2.36; 95% CI 1.21–4.59]) were also independent predictors of response and/or survival. A higher percentage of pts experienced grade $\geq$ 3 immune-related adverse events (irAEs) in the IPI+PD1 group compared to the PD1 group (34% vs 13%, $p<0.0001$). Most pts ceased treatment due to progression (234, 57%), and more pts stopped due to toxicity in the IPI+PD1 vs. PD1 group (25% vs. 9%, $p<0.0001$). **Conclusions:** In pts with MUM, IPI+PD1 demonstrated a higher ORR but did not improve survival compared with PD1 alone. IPI+PD1 was more toxic, leading to early treatment discontinuation in one-quarter of pts. These findings may help guide treatment selection in MUM. Research Sponsor: None.

Real-world experience with lifileucel, tumor selection, and dead-in therapy from a single-institution series.

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Background: Lifileucel is the first approved cellular therapy for persons with metastatic melanoma after upfront treatment with immune checkpoint inhibitor(s) (ICIs) and BRAF-targeted therapy (if applicable). There is not an established consortium to centralize data surrounding procurement and outcomes. Until then we report a single institution series of lifileucel used in the real-world in patients (pts) with previously treated metastatic melanoma. We evaluate whether there are differences in outcomes based on tumor procurement sites, lead-in therapy, and presence of CNS metastases prior to being treated with lifileucel. In addition, for those with progressive disease (PD) will describe the pattern of progression after lifileucel. **Methods:** The University of Colorado and its affiliated hospital UCHHealth became an authorized treatment center for TIL in November 2024. Between November 2024 and January 2026, tumor tissue procurement was completed on 27 patients diagnosed with a variety of melanoma subtypes, stages and received bridging therapy. 24 pts have been treated with lifileucel. All pts received prior combination ICIs and, if BRAF-V600mut, most received prior treatment with BRAF/MEK inhibitors. **Results:** 41.7% of pts treated with lifileucel have had at least partial response (PR) as best overall response (BOR). 12% of pts have had a complete response (CR) as BOR. 16.7% had an initial PR but then had PD within 3 mos. 37.5% of pts had PD as BOR. In regard to tumor procurement site, tumor sites were subcutaneous/superficial soft tissue, lymph node, or visceral locations. The response rate from subcutaneous tumors was 16.7%, the response rate from lymph node was 33.3% and the response rate from visceral sites was 42.3%. The response rate from a single tumor used for procurement was 27%. The response rate from combining multiple tumors from different sites was 46%. The most recent therapy prior to lifileucel included: 1) ipilimumab+nivolumab, (5 pts) with 40% response rate, 2) relatlimab+nivolumab, (8 pts) with 75% response rate, 3) anti-PD-1 monotherapy, (3 pts) with 66% response rate, 4) BRAF/MEK inhibitor, (5 pts) with no response to lifileucel. 10 pts had CNS lesions treated prior to lifileucel, 6 pts had CNS lesions treated after lifileucel infusion, 5 were treated with BRAF/MEK prior to receiving lifileucel. 4 pts had PR and 2 had CR of metastatic sites present prior to lifileucel but had PD within 3 mos to new visceral sites. **Conclusions:** From our single-institution series, using lymph node and visceral tumors for lifileucel generation is associated with higher overall response rate. Combining more than one tumor for lifileucel generation is also associated with higher overall response rate. There were 6 patients that had CNS progression after lifileucel but the majority had used BRAF/MEK prior to receiving lifileucel which raises question of what effect this has on lifileucel efficacy. Research Sponsor: None.

Prognostic and therapeutic implications of HRR gene mutations in non-cutaneous melanoma: Association with anti-PD-1 efficacy.

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Background: Homologous recombination deficiency (HRD) describes a tumor cell state characterized by impaired DNA double-strand break repair via the homologous recombination repair (HRR) pathway. Deficiencies in this pathway may serve as predictive biomarkers. However, the relevance of HRR gene mutations remains inadequately characterized in non-cutaneous melanoma. In this study, we aimed to delineate the mutational landscape of HRR genes in this population and evaluate their predictive implications for clinical management. **Methods:** We conducted a retrospective analysis of 932 patients with non-cutaneous melanoma treated at Beijing Cancer Hospital from January 2008 to January 2026. Tumor genomic profiling was performed using targeted next-generation sequencing with either an 81- (n=852) or a 425-gene (n=80) panel. Associations between HRR mutation status and survival outcomes were assessed using Kaplan-Meier survival estimates and Cox proportional hazards regression models. **Results:** HRR mutations were identified in 92 patients (9.9%), with the most frequent alterations occurring in ATM (3.5%), ARID1A (3.4%), BRCA2 (2.7%), and BRCA1 (1.8%). Within this HRR-mutated cohort, the primary subtypes were mucosal (44.6%) and acral (29.3%) melanoma. And the disease stages were distributed as follows: stage I, 31 patients (33.7%); stage II, 15 (16.3%); stage III, 22 (23.9%) and stage IV, 24 (25.0%). After a median follow-up of 63.7 months, the median overall survival (OS) was 57.5 months (95% CI: 43.4–71.7), with 1-, 2-, 3-, and 5-year OS rates of 92.1%, 84.9%, 74.7%, and 56.8%, respectively. Multivariate analysis confirmed age ≥ 65 years as an independent predictor of poorer overall survival (HR 2.7, 95% CI 1.3–5.4, $P = 0.005$), whereas ATM mutation emerged as a significant protective factor associated with a 68% reduction in mortality risk (HR 0.32, 95% CI 0.1–0.7, $P = 0.007$). Among 59 HRR-mutated patients who received first-line systemic therapy, 41 were treated with anti-PD-1-based regimens and 18 with non-PD-1-based regimens. In the 54 evaluable patients, median progression-free survival (PFS) was 9.0 months (95% CI: 3.8–14.2) and median OS was 55.0 months (95% CI: 39.0–71.0). The objective response rate (ORR) was 11.1%, and the disease control rate (DCR) was 61.1%. The DCR was 77.8% (21/27) in the mucosal subgroup versus 37.5% (6/16) in the acral subgroup with a statistically significant difference ($P = 0.028$). In a subgroup analysis, although not statistically significant, anti-PD-1-treated patients trended toward a longer median PFS compared with those not receiving anti-PD-1 therapy (15.0 vs. 6.0 months, $P = 0.249$). **Conclusions:** HRR mutations define a distinct molecular subset in non-cutaneous melanoma. ATM mutation serves as an important prognostic biomarker, and patients with HRR-mutated melanoma may derive survival benefit from anti-PD-1 immunotherapy. Research Sponsor: None.

Novel adaptive versus continuous dosing of encorafenib and binimetinib in combination with nivolumab in advanced *BRAF V600E* mutant melanoma.

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Background: In *BRAF V600* mutant melanoma, continuous treatment with *BRAF/MEK* inhibitors invariably begets acquired resistance. Preclinical success of intermittent dosing to overcome resistance did not translate to clinical benefit in the randomized SWOG S1320 trial, possibly due to fixed schedule of intermittent dosing (5 wk on/3 wk off cycles). Leveraging intra-tumoral competition dynamics to slow expansion of resistant tumor subpopulations via patient-specific adaptive MAPK therapy may improve outcomes. We hypothesized that adaptive drug scheduling of *BRAF/MEKi* combined with anti-PD-1 would lead to non-inferior or improved outcomes with less toxicity compared to a continuous triplet regimen. **Methods:** In a pilot prospective trial, pts with advanced *BRAF V600E* mutant melanoma, naïve to systemic tx in this setting, with detectable plasma circulating tumor DNA (ctDNA) were eligible (using *BRAFV600E* ctDNA ddPCR). Ten pts were randomized 1:1 to continuous (Arm A) or patient-specific adaptively dosed (Arm B) ENCO plus BINI, with continuous biweekly NIVO in both arms. A mathematical model was calibrated for Arm B using pts' ctDNA values (baseline and biweekly sampling) and standard CT response imaging every 12 weeks. This model was a coupled system of differential equations to guide treatment decisions biweekly by simulating the future response on or off drugs (ENCO+BINI) based on that pt's known ctDNA levels and response data. Therefore, pts in Arm B all had differing lengths of time that they received ENCO+BINI. Primary endpoint was feasibility of the adaptive approach, by adherence to protocol from baseline to week 12. **Results:** Ten pts, median age 59, 70% male, 80% with stage IV melanoma, were randomized. In Arm B, NIVO alone was often effective enough to not trigger resuming ENCO+BINI; in Arm A, pts were on E+B for a median of 61 weeks (89% of time on tx, as drugs could be held for toxicity), while in adaptive Arm B, patients were on E+B for median 11 weeks (24% of time on tx). ORR was 100% in Arm A and 60% in Arm B, all partial responses, with 2 stable disease in Arm B. At median follow-up of 45.5 months, median PFS was 26.9 months (95% CI 5.5-NA) with 3 progressors in Arm A. Median PFS was not reached (17.8-NA) in Arm B and 2 progressed (log-rank $p=0.5$). Median OS was 32 months (8.8-NA) in Arm A (2-year OS 60%, 3 pts died). Median OS was not reached (17.8-NA) in Arm B (2-year OS 75%, 1 pt died), log-rank $p=0.18$. In Arm A, there were 16 treatment-related grade 3 adverse events, with only 6 grade 3 AEs in Arm B. **Conclusions:** In this innovative study, we demonstrated the feasibility of patient specific mathematical modeling incorporating ctDNA and imaging, to inform adaptive dosing of ENCO+BINI with concurrent NIVO. The adaptive arm did not compromise efficacy and had lower toxicity. Successful confirmation of this approach in larger trials may favorably impact patient QOL and reduce cost of therapy. Clinical trial information: NCT03543969. Research Sponsor: None.

Pretreatment spatial immune architecture and 1-year clinical benefit to first-line ICB in advanced melanoma.

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Background: Predictive biomarkers for immune checkpoint blockade (ICB) in advanced cutaneous melanoma (CM) remain limited. Imaging mass cytometry (IMC) enables spatially resolved profiling of the tumor microenvironment (TME) and can capture immune-tumor architecture beyond cell density. **Methods:** Patients with advanced CM treated with first-line ICB and available pretreatment FFPE tissue were analyzed using IMC (40-marker panel). The primary endpoint was durable 1-year clinical benefit (1y-CB: metabolic CR/PR or stable metabolic disease ≥ 12 months by PERCIST on FDG-PET/CT); the secondary endpoint was 1-year progression-free survival (1y-PFS). Cell densities, tumor marker expression, and spatial neighborhood metrics were evaluated. Reproducibility was assessed by re-analyzing an independent published IMC melanoma cohort (PMC8026677). **Results:** Twenty-nine patients (anti-PD-1 n=27; ipilimumab+nivolumab n=2); 15 achieved 1y-CB. 1y-CB was associated with higher leukocyte infiltration and increased densities of B cells, conventional CD4⁺ T cells (Tconv), CD8⁺ T cells, and plasma cells, whereas higher tumor density was associated with lack of benefit and inferior 1y-PFS (HR 10.57; $p < 0.001$). Higher CD8⁺ and B-cell densities were associated with improved 1y-PFS (HR 0.26, $p = 0.013$; and HR 0.26, $p = 0.047$). Tumor PD-L1 and HLA-DR expression correlated with 1y-CB ($p = 0.022$ and $p = 0.040$). Spatial metrics further stratified outcomes: increased tumor-tumor proximity was associated with poor 1y-CB ($p = 0.0016$), while increased B-Tconv proximity was associated with 1y-CB and longer 1y-PFS (HR 0.20; $p = 0.037$). The strongest spatial association was macrophage proximity to HLA-DR⁺ tumor cells ($p \leq 0.0001$). In the external cohort (n=60), responder enrichment for Tconv/CD8⁺ T cells and macrophage proximity to HLA-DR⁺ tumor cells were reproduced. **Conclusions:** Pretreatment IMC identifies both compositional and spatial TME features associated with durable benefit from first-line ICB in advanced CM. T-cell enrichment and macrophage proximity to HLA-DR⁺ tumor cells emerged as reproducible candidate spatial biomarkers warranting prospective validation. Research Sponsor: European Regional Development Fund (ERDF/FEDER); RU-000950; Pfizer; Novartis.

Main predictors of 1y-CB and 1y-PFS.

Parameters	1y-CB events/N	1y-CB p-value	1y-PFS HR (95% CI)	1y-PFS p-value
B cells ≥ 9.5	5/15 vs 9/14	0.026	0.26 (0.00–0.99)	0.047
CD8 ⁺ T cells ≥ 36	7/20 vs 7/9	0.023	0.26 (0.00–0.76)	0.013
Plasma cells ≥ 1	3/12 vs 11/17	0.017	0.28 (0.08–1.00)	0.050
Tumor density ≥ 4194	5/5 vs 9/24	0.006	10.57 (3.08–36.23)	< 0.001
B-Tconv proximity $\geq 13.3\%$	2/10 vs 10/16	0.018	0.20 (0.00–0.91)	0.037
HLA-DR $\geq 58.4\%$	1/7 vs 13/22	0.040	0.17 (0.02–1.28)	0.085
PD-L1 $\geq 3.3\%$	8/20 vs 6/9	0.022	0.48 (0.16–1.38)	0.171

A phase III randomized study comparing BCD-201, a pembrolizumab biosimilar candidate, and reference pembrolizumab in patients with advanced melanoma.

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Background: The development of clinically comparable biosimilars of key immuno-oncology agents is essential to improving global access to effective therapy. BCD-201 is a proposed pembrolizumab biosimilar that has shown high analytical similarity in preclinical studies, and pharmacokinetic equivalence to the reference pembrolizumab in phase I study (NCT05739006). This phase III trial evaluated the clinical equivalence of BCD-201 versus reference pembrolizumab in patients with advanced melanoma. **Methods:** This international, multicenter, randomized, double-blind phase III study enrolled adult patients with unresectable or metastatic cutaneous melanoma. Patients were randomized 1:1 to receive BCD-201 or reference pembrolizumab 200 mg IV every 3 weeks for 24 weeks. Randomization was stratified by ECOG (0 vs 1), PD-L1 expression ($<5\%$ vs $\geq 5\%$), and disease stage (AJCC 7th edition M0/M1a/M1b vs M1c). The primary endpoint was objective response rate (ORR) per RECIST v1.1 assessed by blinded independent central review (BICR) at week 24 in the ITT population. Equivalence was concluded if the 95% confidence interval (CI) for the ORR difference fell within prespecified margins of -15% to $+15\%$. Secondary efficacy endpoints included ORR per iRECIST, progression-free survival (PFS), overall survival (OS). **Results:** A total of 479 patients were included in the ITT population (BCD-201, $n=234$; reference pembrolizumab, $n=245$), with balanced baseline characteristics. At week 24, ORR was 33.3% in the BCD-201 group and 32.7% in the reference pembrolizumab group in ITT population. The unstratified ORR difference was 0.7% (95% CI -7.7 to 9.1), fully within the prespecified equivalence margins. Results were consistent across per-protocol and stratified sensitivity analyses. Secondary efficacy endpoints, including ORR per iRECIST, OS, and DOR, were comparable between groups. At 24 weeks, PFS rates were 51.9% for BCD-201 and 50.5% for reference pembrolizumab per RECIST 1.1. OS rate at 24 week was 90.2% in the BCD-201 group and 89.3% in the reference pembrolizumab group. Longer-term efficacy and safety data will be reported in future analyses. Safety profiles were similar between groups, with grade ≥ 3 AEs reported in 19.7% and 21.9% of patients for BCD-201 and reference pembrolizumab. Main PK parameters (AUC and C_{max}) met equivalence criteria. Immunogenicity was low and comparable between groups, with binding antibodies (Abs) detected in 7 (3.1%) and 6 (2.6%) patients in the BCD-201 and comparator groups, respectively. No neutralizing Abs were detected. **Conclusions:** BCD-201 demonstrated equivalent efficacy to reference pembrolizumab with comparable safety, pharmacokinetics, and immunogenicity in patients with advanced melanoma. These data support BCD-201 as a pembrolizumab biosimilar and highlight its potential to expand access to anti-PD-1 therapy. Clinical trial information: NCT05986331. Research Sponsor: None.

The prognostic and predictive role of FDG PET/CT in melanoma patients treated with immune checkpoint blockade: A meta-analysis.

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Background: Immune checkpoint blockade (ICB) is standard therapy for advanced melanoma, but many patients derive limited benefit. Biomarkers to guide treatment decisions are needed. FDG PET/CT (PET) shows promise for response assessment, but most studies are small or evaluate a single timepoint. Here, we conducted a meta-analysis to assess the prognostic value of metabolic response for overall survival (OS) and progression-free survival (PFS), and the diagnostic performance of PET-derived parameters. **Methods:** PubMed, Cochrane, and EMBASE were searched for studies including melanoma patients treated with ICB who underwent baseline and follow-up PET. Metabolic response was defined using PERCIST, PERCIST5, or EORTC criteria, dichotomizing patients as responders or non-responders. Random-effects meta-analyses estimated pooled hazard ratios (HRs) for OS and PFS, with subgroup analyses by PET timing (early ≤ 4 months vs late > 4 months). Univariate diagnostic meta-analyses evaluated the accuracy of changes in total lesion glycolysis (TLG) and metabolic tumor volume (MTV) for predicting death or OS, as well as the ability of PET-defined progressive metabolic disease (PMD) to identify clinical or RECIST-based disease progression. **Results:** Of the 15 studies included, 943 pts were included. Interval metabolic response was significantly associated with improved OS (HR 0.22; 95% CI 0.13–0.36; $p = 0.02$), with no significant difference according to the time of PET assessment early vs late (p for interaction = 0.75). Similarly, metabolic responders experienced significantly longer PFS (HR 0.21; 95% CI 0.11–0.39; $p = 0.03$). Although the association was statistically significant for late (HR 0.21; 95% CI 0.11–0.41), but not for early assessment (HR 0.13; 95% CI 0.01–1.91), no subgroup difference was observed (p for interaction = 0.73). In diagnostic analyses for OS prediction, changes in TLG demonstrated a pooled sensitivity of 0.70 (95% CI 0.54–0.82) and specificity of 0.79 (95% CI 0.52–0.93). Changes in MTV showed comparable performance, with a sensitivity of approximately 0.70 (95% CI 0.54–0.82) and a specificity of 0.83 (95% CI 0.42–0.97). PET-defined PMD showed good diagnostic accuracy for identifying clinical or RECIST-defined disease progression, with a pooled sensitivity of approximately 0.71 (95% CI 0.42–0.89) and specificity of 0.86 (95% CI 0.69–0.95). **Conclusions:** In our study, metabolic response by PET was associated with improved OS and PFS, irrespective of the timing of imaging. Quantitative changes in TLG and MTV provide moderate accuracy for predicting survival, while PET/CT-defined PMD reliably identified RECIST-based disease progression. These findings support future prospective studies investigating the role of PET dynamics as a minimally invasive prognostic and predictive biomarker for pts with advanced melanoma undergoing treatment with ICB. Research Sponsor: None.

Botensilimab (BOT) ± balstilimab (BAL) in patients (pts) with advanced cutaneous melanoma (cMEL) refractory/resistant (R/R) to anti-PD-(L)1 ± CTLA-4: A phase 2 trial.

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Background: Pts with advanced cMEL R/R to PD-(L)1-based therapy, including PD-(L)1+CTLA-4, have few treatment options. BOT (Fc-enhanced anti-CTLA-4) augments T-cell priming, depletes Tregs, and activates antigen-presenting cells to overcome immune checkpoint inhibitor (ICI) resistance. BOT ± BAL (anti-PD-1) has shown activity in ICI-R/R and cold tumors. **Methods:** The open-label, global phase 2 C-800-23 trial (NCT05529316) enrolled pts with cMEL (stage III unresectable or IV) R/R to prior anti-PD-(L)1 ± CTLA-4. Part 1: randomized 1:1 to BOT 50 mg or 150 mg every 3 weeks (Q3W; up to 4 doses). Part 2: BOT 75 mg Q3W (up to 4 doses) plus BAL 450 mg Q3W (up to 2 years). Endpoints included confirmed objective response rate (ORR; primary; RECIST 1.1), progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety. Clinical benefit rate (CBR) was complete or partial response or stable disease for ≥24 weeks. **Results:** As of Dec 13, 2025, 138 pts received BOT monotherapy (median follow-up, 12.3 mo; range, 0.2–35+) and 36 pts received BOT+BAL (median follow-up, 13.8 mo; range, 2–26+). Overall, 51% had stage M1c or M1d disease, 29% had BRAF mutant disease, and 39% had LDH >ULN. In pts R/R to anti-PD-(L)1, 72% (60/83 with pre-trial data available) had primary resistance (best overall response of progressive disease [PD] or PD ≤6 mo from most recent course of respective ICI type). In pts R/R to anti-PD-(L)1+CTLA-4, 69% (61/88) had primary PD-(L)1 resistance and 69% (60/87) had primary CTLA-4 resistance. With BOT+BAL, ORR was 22% (95% CI, 10–39), CBR was 33% (95% CI, 19–51), median DOR was not reached (NR; 95% CI, 4.17–NR), 12-mo PFS was 29% (95% CI, 15–44), and median OS was 16.6 mo (95% CI, 9.1–NR; 24-mo OS, 46%; 95% CI, 29–61). ORR with BOT+BAL was numerically higher in PD-(L)1+CTLA-4 R/R pts (29%, 4/14; 95% CI, 8–58; 3/4 responders had primary ICI resistance) vs PD-(L)1-only R/R pts (18%, 4/22; 95% CI, 5–40; all responders had primary ICI resistance). With BOT alone, ORR was 6% (95% CI, 3–11), CBR was 14% (95% CI, 9–21), 12-mo PFS was 7% (95% CI, 3–13), and median OS was 12.9 mo (95% CI, 9.7–16.2; 24-mo OS, 28%; 95% CI, 20–36). Responses were irrespective of Fcγ receptor genotype. Treatment-related adverse events occurred in 81% (grade ≥3, 30%) with BOT alone and 94% (grade ≥3, 36%) with BOT+BAL; most common was diarrhea (BOT 33%; BOT+BAL 42%). One possibly treatment-related death was reported with BOT monotherapy (immune-mediated enterocolitis). No new safety signals occurred. **Conclusions:** In this ICI-R/R cMEL population enriched with primary ICI-resistant pts, BOT+BAL showed durable responses, encouraging survival, and a stronger signal in pts who had prior conventional anti-CTLA-4. BOT monotherapy also showed activity. This supports a differentiated mechanism for BOT and continued development of BOT+BAL, including for pts with dual ICI-R/R cMEL. Clinical trial information: NCT05529316. Research Sponsor: Agenus Inc.

Final results of the phase III OCTAVA trial: Clinical benefit of low-dose anti-CTLA-4 plus anti-PD-1 combination vs anti-PD-1 monotherapy in unresectable or metastatic melanoma.

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Background: BCD-217-2/OCTAVA is an international, multi-center, randomized, double-blind, placebo-controlled phase III study conducted to assess the efficacy and safety of nurulimab +prolgolimab (nuru + prolgo) combination therapy with continued prolgolimab therapy compared to prolgolimab monotherapy at the 1st line treatment of patients (pts) with unresectable or metastatic melanoma (un/mM). BCD-217 is a fixed-dose combination of nurulimab (aCTLA-4, 5 mg/ml) and prolgolimab (aPD-1, 15 mg/ml) which was recently approved for this indication in Russia and Belarus. Here we present efficacy results based on 24 mos of therapy. **Methods:** Treatment-naïve pts with un/mM (stage IIIC–IV) were randomized 1:1 to two arms. The nuru+prolgo arm received a combo of nurulimab (1 mg/kg) and prolgolimab (3 mg/kg) at 0.2 ml/kg Q3W for the first four infusions. The prolgo arm received prolgolimab monotherapy (3 mg/kg Q3W) for the first four infusions. Both arms then received prolgolimab maintenance therapy for up to two years. The primary endpoint of the study was PFS. **Results:** 271 pts were randomized to nuru+prolgo (n=135) or prolgo monotherapy (n=136) arms. After a median follow-up of 24.7 mos the mPFS was 15.4 (95% CI 8.4; NA) mos in the nuru+prolgo arm and 8.3 (95% CI 4.2; 14.8) mos in the prolgo monotherapy arm (HR 0.696, 95% CI 0.502; 0.965), iRECIST, ITT population). The PFS benefit was consistent per RECIST 1.1 (HR 0.717, 95% CI 0.533; 0.964). ORR, DCR and TTR were also higher in nuru+prolgo arm. mOS was not reached in both groups (HR 0.836, 95% CI 0.495; 1.41). 24-mos OS was 76.1% in nuru+prolgo arm and 71.7% in prolgo arm respectively. The mDOR was also not reached in any arm, meaning that more than half of the pts who responded to therapy maintained their response until the end of the FU period. Grade ≥ 3 treatment-related AEs occurred in 17.8% of pts (nuru+prolgo) vs 13.2% (prolgo). Gr ≥ 3 irAEs were 14.1% vs 5.1%, respectively (p=0.0126). Any-grade irAEs were reported in 51.9% vs 33.8% of cases (p=0.0027). Treatment discontinuation due to AEs was 11.1% vs 5.1%. **Conclusions:** The OCTAVA trial results demonstrated a statistically significant and clinically meaningful improvement in PFS for the 1st line low-dose nuru + prolgo combination followed by prolgo maintenance, compared to prolgo monotherapy, in patients with unresectable or metastatic melanoma. This efficacy benefit was accompanied by manageable rate of immune-related AE, consistent with the known profile of CTLA-4/PD-1 combinations. These results support the use of the nuru + prolgo regimen as a valuable 1st line treatment option for this population. Clinical trial information: NCT05732805. Research Sponsor: JSC BIOCAD.

Twenty years of metastatic uveal melanoma management: Real-world experience from a comprehensive cancer center in a low- and middle-income country (LMIC).

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Background: Uveal melanoma (UM) is a rare malignancy arising from melanocytes of the uveal tract and accounts for 85% of primary ocular malignancies. Despite effective local control, 10–50% of patients develop metastatic disease, which is associated with poor prognosis and a median overall survival (OS) of approximately one year. Until recently, no effective standard systemic therapy existed for metastatic UM. Real-world data especially from LMICs remain lacking. This study evaluates the clinical characteristics, treatment patterns, and survival outcomes of patients with metastatic UM treated in a LMIC. **Methods:** This retrospective study included adult patients with metastatic UM treated and followed at King Hussein Cancer Center in Amman, Jordan between January 2006 and December 2025. Collected data included baseline demographic and clinical characteristics, metastatic and treatment patterns. Descriptive and survival analyses were conducted using JASP software (version 0.95.4). A two-sided P value <0.05 was considered statistically significant. **Results:** Among 125 patients with UM, 31 (24.8%) had metastatic disease, including two patients with metastasis at initial presentation. Median age at diagnosis was 51 years, and 61.3% were males. ECOG performance status was 0–2 in 81.5% of patients. Hepatic-only metastasis occurred in 51.6% of patients, combined hepatic and extrahepatic in 38.7%, and extrahepatic-only in 9.7%, with 58.6% classified as M1a disease. Median time to distant metastasis was 25 months. Median OS from initial UM diagnosis was 35 months, while median post-metastatic OS (PM-OS) was 10 months. First-line Immunotherapy was associated with significantly improved PM-OS compared to Dacarbazine (median 11 vs 5 months; P = 0.034), with 24-month PM-OS of 44.4% vs 0% respectively. Treatments included Immunotherapy, chemotherapy, Targeted therapy in one patient, local interventions, and best supportive care (Table). **Conclusions:** Metastatic UM remains associated with poor survival outcomes in this real-world cohort. First-line Immunotherapy was associated with longer survival compared to chemotherapy. This study highlights ongoing unmet outcomes needs and underscores disparities in access to emerging therapies, such as Tebentafusp, in LMICs. Broader availability of novel agents and inclusion of patients from LMICs in clinical trials are required. Research Sponsor: None.

First-line Treatments	Second-line Treatments	Third line Treatments	Additional Local interventions
Pembrolizumab (n=15)	Dacarbazine (n=7)	Carboplatin plus Paclitaxel (n=1)	Radiotherapy (n=9)
Nivolumab and Ipilimumab (n=4)	Nivolumab and Ipilimumab (n=1)	Single agent Paclitaxel (n=1)	Microwave ablation (n=1)
Dacarbazine (n=3)			Surgery (n=1)
Darovasertib and Crizotinib (n=1)			
Best supportive care only (n=8)			

Overall survival of patients with mucosal melanoma in the US before and after the advent of PD-1 based immune checkpoint inhibitor treatment.

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Background: Mucosal melanoma (MM) is a rare, aggressive melanoma subtype with poor survival. Prior to 2010, systemic therapy for MM was limited to chemotherapy, adjuvant interferon, and bolus interleukin-2; after 2015, immune checkpoint inhibitors (ICIs), specifically programmed cell death protein-1 (PD-1) based therapies, were widely adopted. The magnitude of overall survival (OS) benefit from ICIs in MM remains poorly defined. **Methods:** We conducted a retrospective cohort study of 8,125 patients with histologically confirmed MM from the National Cancer Database. Patients were stratified by diagnosis era (pre-ICI: diagnosed before 2010; post-ICI: diagnosed after 2015) and receipt of first-line systemic therapy (immunotherapy and/or chemotherapy versus none). Survival analysis was conducted using Kaplan-Meier methods and Cox proportional hazards models. Difference-in-differences (DID) models using Cox regression estimated survival improvements attributable to systemic therapy in the post-ICI era. Multivariable logistic regression was fitted to assess changes in the characteristics of patients receiving systemic therapy between eras. Subgroup analysis included metastatic patients and stratification by primary tumor site (genitourinary [GU], gastrointestinal [GI], head and neck [HN]). Covariates for multivariable models were selected a priori based on clinical relevance. **Results:** Median OS (mOS) significantly improved in the post-ICI era with covariate adjustment (36.2 vs. 25.0 months; HR: 0.63, 95% CI: 0.59-0.66). Adjusted DID analysis demonstrated survival benefits attributable to systemic therapy (HR: 0.86, 95% CI: 0.77-0.97). mOS of metastatic patients also improved in the post-ICI era (12.0 vs. 7.33 months; HR: 0.63, 95% CI: 0.54-0.73). All tumor sites demonstrated significantly longer mOS in the post-ICI era, with GU patients living the longest (49.5 months), followed by HN (34.5 months), and GI (24.4 months). Post-ICI systemic therapy recipients were more likely to be older and publicly insured, to have a high comorbidity burden (Charlson Deyo score), to be ineligible for surgery, and to receive immunotherapy alone compared to pre-ICI patients. **Conclusions:** Survival of MM patients has improved by 37% since the introduction of ICIs. While OS varies by tumor site, all sites showed relative improvement in the post-ICI era. DID analysis suggested that modern survival benefits are driven by ICIs despite an older and more clinically complex treatment population. Research Sponsor: National Cancer Institute of the National Institutes of Health; R25CA281789.

Health-related quality of life following tumor-infiltrating lymphocyte (TIL) therapy with commercial lifileucel in metastatic melanoma: Real-world longitudinal patient-reported outcomes.

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Background: Although the efficacy of lifileucel has been demonstrated in metastatic melanoma, real-world longitudinal patient-reported outcomes remain limited. We evaluated health-related quality of life (HRQoL) among patients treated with commercial lifileucel at Moffitt Cancer Center using the Functional Assessment of Cancer Therapy–Melanoma (FACT–M) instrument. **Methods:** FACT–M surveys were administered at Baseline, Day +7, Month +6, and End of Treatment (April–December 2025). Scores were calculated using validated procedures. Clinical benefit was defined as complete response/ no evidence of disease or partial response as the best response per RECIST v1.1. Minimally important differences (MID) were defined as 4–7 points for the FACT–G total score and 4–6 points for the FACT–M combined scores. Comparisons used Wilcoxon rank-sum tests. **Results:** Thirty-two patients were enrolled, with 97 surveys completed out of 105 requested (92% completion rate). Median age was 66 years (range 29–78); 56% were male (n=18) and 44% female (n=14). ECOG performance status was 0–1 in 93%. Patients received a median of 5 IL–2 doses (range 1–6), and 53% experienced clinical benefit (n=17). Baseline, Day +7, and Month +6 FACT–M subscale and total scores are presented in Table 1. Among all patients, FACT–M and FACT–G scores remained stable from baseline to Day +7 and demonstrated clinically meaningful improvement exceeding the minimally clinically important difference at Month +6. While baseline HRQoL scores did not differ by treatment outcome (median FACT–G, 87 in both groups; median FACT–M, 108 in patients without clinical benefit and 109 in those with benefit), scores were significantly higher across follow-up assessments among patients with clinical benefit compared with those without. Median FACT–G scores were 102 vs. 76 (p=0.012), and median FACT–M scores were 125 vs. 94 (p=0.017), respectively. **Conclusions:** HRQoL, as measured by FACT–G and FACT–M, was maintained following commercial lifileucel in a real-world metastatic melanoma cohort, supporting the tolerability of TIL therapy. HRQoL outcomes varied according to clinical benefit. Larger studies with extended follow-up are warranted to confirm these findings. Research Sponsor: None.

Median baseline, day+7, and month +6 FACT-M subscale and total scores.

Characteristic	Baseline N = 17 [†]	Day +7 N = 11 [†]	Month +6 N = 13 [†]	Baseline to Month+6 difference
Physical well Being (PWB)	25	20	26	+1
Social well Being (SWB)	25.67	25.20	26.00	+0.33
Emotional well Being (EWB)	22.2	22.2	23.3	+1.1
Functional well Being (FWB)	21	20	23	+2
Melanoma (MS)	22.3	20.6	24.5	+2.2
Melanoma Surgery (MSS)	24.5	24.5	27.1	+2.6
FACT-G (sum of PWB, SWB, EWB, + FWB)	90	89	97	+7
FACT-M (sum of FACT-G + MS)	111	111	124	+13

[†]Median.

Real-world outcomes of dual checkpoint inhibition (nivolumab + ipilimumab) versus anti-PD-1 monotherapy in metastatic uveal melanoma: Impact of local therapy and adjusted survival analysis—A multicenter retrospective study in Russia.

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Background: Metastatic uveal melanoma (mUM) remains a rare and aggressive malignancy. Immune checkpoint inhibitors (ICI) demonstrate modest activity, and real-world evidence comparing dual (nivolumab + ipilimumab) versus anti-PD-1 monotherapy, as well as the additive role of local therapy is limited. **Methods:** Multicenter retrospective observational study conducted in Russia (IRB-approved at participating centers). Outcomes assessed: median progression-free survival (mPFS), median overall survival (mOS), objective response rate (ORR), disease control rate (DCR), and grade ≥ 3 immune-related adverse events (irAEs). Stratified by treatment line, ICI type, and local therapy use. Univariable Cox proportional hazards regression was performed. **Results:** Patients with metastatic uveal melanoma treated between 2019 and 2025 were included (n=262). Of these, 25 patients (9.5%) who did not receive systemic treatment or received only palliative care were excluded. Among the full cohort: 158 (60.3%) were female, median age at primary diagnosis was 55.9 years, median time to metastatic disease was 2.42 years. Liver metastases were present in 90.8%. After exclusion, 237 patients were analyzed for survival. Results are presented in Table 1. Univariable Cox regression (after exclusion n=237): Dual ICI exposure (yes vs no): HR 0.60 (95% CI 0.44–0.84, p=0.003); Any ICI exposure (yes vs no): HR $\approx$ 0.72 (p=0.102) — non-significant trend. **Conclusions:** Dual ICI (nivolumab + ipilimumab) was associated with improved overall survival (HR 0.60, p=0.003), particularly with combination with local therapy (predominantly IHP, STRT, and TACE), which substantially enhanced ORR, DCR, PFS, and OS across ICI types. Patients who were unable to receive ICI in the first-line setting may be candidates for this option in the second-line; however, this requires further investigation through subgroup comparative analyses. Research Sponsor: None.

Results.								
Treatment Line	ICI Type	Local Therapy	n	mPFS, mo (95% CI)	mOS, mo (95% CI)	ORR (%)	DCR (%)	Gr ≥ 3 irAEs (%)
First-line	Dual (nivo+ipi)	Without	28	3.5 (3.0–6.6)	18.4 (13.4–33.5)	10.7	28.6	39.3
First-line	Dual (nivo+ipi)	IHP 60% STRT 35% TACE 5%	20	7.5 (6.2–18.2)	45.7 (23.4–NR)	45.0	80.0	45.0
First-line	Mono anti-PD-1	Without	47	3.1 (2.8–3.7)	18.8 (11.9–27.5)	2.1	14.9	2.1
First-line	Mono anti-PD-1	STRT 50% IHP 40% TACE 6.7% RFA 3.3%	30	7.53 (4.5–12.3)	27.9 (18.6–NR)	36.7	60.0	16.7
Second-line	Dual	Without	35	3.3 (2.5–5.5)	13.1 (9.3–18.8)	2.9	31.4	45.7
Second-line	Dual	STRT 100%	3	9.3 (8.7–NR)	39.1 (9.6–NR)	33.3	100.0	33.3
Second-line	Mono anti-PD-1	Without	15	9.0 (5.2–21.6)	21.3 (14.8–NR)	13.3	46.7	0
Second-line	Mono anti-PD-1	STRT 50% IHP 25% TACE 25%	8	8.6 (4.7–NR)	17.3 (13.3–NR)	0	75.0	0

The clinical significance of *TET2*-driven clonal hematopoiesis (*TET2*-CH) in ICI-treated melanoma patients.

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Background: Clonal hematopoiesis (CH) arises from age-related somatic mutations in hematopoietic stem cells and has been linked to altered immune function and clinical outcomes in solid tumors. While recent studies in colorectal and lung cancers suggest *TET2*-mutant CH may enhance immunotherapy responses, the impact of CH genotype on melanoma outcomes remains unclear and potentially context-dependent. **Methods:** We performed a retrospective cohort study of 361 patients with unresectable stage III/IV melanoma who underwent whole blood sequencing prior to anti-PD-1-based immunotherapy (2014-2024). CH was defined as somatic mutations in CH driver genes with variant allele fraction (VAF) > 2%. Progression-free survival (PFS) and overall survival (OS) were measured from ICI initiation; patients without events were censored at last follow-up. Kaplan-Meier curves and multivariable Cox models adjusted for age, sex, BRAF V600E status, stage, and prior therapy estimated hazard ratios (HRs) compared to patients without CH. Chi-squared analysis assessed CH prevalence among melanoma patients compared to a healthy control cohort (n = 12,346) matched for age and sex. **Results:** CH prevalence was significantly elevated in melanoma patients compared to age and sex-matched healthy controls (27.7% vs. 21.4% $\chi^2 = 7.94$, p = 0.004). Among 361 patients, 32 (8.9%) harbored *TET2*-driven CH, 48 (13.3%) had *DNMT3A*-CH, and 20 (5.5%) had other CH mutations. *TET2*-CH was associated with significantly worse OS compared to patients without CH (HR = 1.79, p = 0.014) and a trend toward inferior PFS (HR = 1.42, p = 0.119). In contrast, neither *DNMT3A*-CH (N = 48) nor other CH genotypes demonstrated significant associations with clinical outcomes (*DNMT3A*-CH: OS HR = 1.38, p = 0.11; PFS HR = 1.21, p = 0.32), establishing genotype-specific effects. **Conclusions:** In this cohort of patients with unresectable Stage III/IV melanoma receiving ICI therapy, *TET2*-CH was associated with inferior survival outcomes, while no significant survival differences were found among patients with *DNMT3A*-CH or other CH genotypes. Incorporating CH genotyping into pre-treatment risk stratification may identify high-risk melanoma patients who could benefit from alternative or intensified therapeutic strategies. Mechanistic studies are warranted to elucidate the biological basis for these genotype-specific effects and explore therapeutic interventions targeting CH-driven immune dysfunction. Research Sponsor: None.

Multivariable PFS and OS hazard ratios by clonal hematopoiesis genotype in ICI-treated melanoma patients.					
CH Group	Number (N)	PFS HR (95% CI)	PFS p-value	OS HR (95% CI)	OS p-value
No CH	261	1.00 (reference)	-	1.00 (reference)	-
CH	100	1.21 (0.92-1.60)	0.178	1.48 (1.10-1.99)	0.010
<i>TET2</i> -CH	32	1.42 (0.91-2.19)	0.119	1.79 (1.12-2.84)	0.014
Non- <i>TET2</i> CH	68	1.13 (0.82-1.56)	0.445	1.36 (0.97-1.92)	0.079
<i>DNMT3A</i> -CH	48	1.21 (0.83-1.74)	0.319	1.38 (0.93-2.03)	0.108

Survival outcomes of adding stereotactic radiosurgery to dual immune checkpoint blockade in melanoma brain metastases: A systematic review and meta-analysis.

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Background: Melanoma brain metastases (MBM) carry a poor prognosis and remain understudied in prospective trials. Dual immune checkpoint blockade (ICB) with nivolumab plus ipilimumab (N+I) achieves durable intracranial responses; stereotactic radiosurgery (SRS) is sometimes added but its survival benefit is unclear. Despite the increasing real-world use of SRS in combination with dual ICB, no prior meta-analysis has compared survival outcomes of N+I + SRS versus N+I alone. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. PubMed, Embase, Scopus, and Web of Science were searched for randomized controlled trials (RCTs) and observational/real-world (ORW) studies published from January 2015 to July 1, 2025. Primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary outcomes included radiologic responses rates assessed by RECIST 1.1 and prognostic biomarkers. Random-effects models were used to pool risk ratios (RRs) and hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed in RevMan and R. **Results:** From 2,972 records, a total of thirteen studies included (ten ORW studies and three RCTs) met our inclusion criteria, including 2,055 patients. Median age was 57.2 years and 64.28% were male. N+I + SRS significantly improved OS compared with N+I alone (HR = 0.56; 95% CI, 0.44–0.71; $p < 0.00001$). Two-year OS for N+I + SRS (RR = 1.35; 95% CI, 1.17–1.55; $p < 0.0001$). Among patients receiving N+I alone, two-year OS was 48% (95% CI, 35–60) and PFS was 52% (95% CI, 45–59). Radiologic response rate with N+I included a complete response rate of 29% (95% CI, 22–37) and a partial response rate of 44% (95% CI, 29–59). High lactate dehydrogenase (LDH $> 2 \times$ upper limit of normal) was observed in 37% of patients (95% CI, 20–58) and was associated with inferior survival outcomes. **Conclusions:** In patients with MBM, the addition of stereotactic radiosurgery with dual immune checkpoint blockade is associated with significant overall survival advantage compared with N+I alone. This first meta-analysis defines the incremental survival benefit of adding SRS to contemporary dual immunotherapy N+I integrating long-term survival outcomes, radiologic response, and prognostic biomarkers. These findings support N+I as the systemic backbone for MBM management and support SRS integration for appropriately selected patients. Prospective trials are warranted to optimize sequencing, timing, and patient selection. Research Sponsor: None.

CD4 T-cell reconstitution and CD4:CD8 inversion following lymphodepleting chemotherapy for tumor-infiltrating lymphocyte therapy in metastatic melanoma.

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Background: Lymphodepleting (LD) chemotherapy is required prior to tumor-infiltrating lymphocyte (TIL) therapy, yet the depth, kinetics, and completeness of peripheral T-cell recovery in practice remain poorly defined. Using a pooled, multi-institution cohort, we characterized longitudinal CD4 and CD8 T-cell reconstitution and the prevalence of CD4 lymphopenia following TIL therapy. **Methods:** We conducted a retrospective multicenter study across Mayo Clinic, Moffitt Cancer Center, and Massachusetts General Hospital of patients with metastatic melanoma treated with TIL (N = 41, median follow-up 7.6 months). Absolute CD4 and CD8 T-cell counts and CD4:CD8 ratios were assessed at baseline (pre-LD), week 4, month 3, and month 6 post-TIL. Clinically significant CD4 lymphopenia was defined as CD4 < 200 cells/ μ L. All patients received *Pneumocystis jirovecii* and antiviral prophylaxis, with antibacterial and antifungal prophylaxis administered per institutional protocols. Post-TIL infections were recorded. Paired changes from baseline were evaluated using Wilcoxon signed-rank testing. **Results:** Median age was 65 years (range 35–79), and 68% were male. At baseline, 16 patients (39%) had CD4 counts below the institutional lower limit of normal prior to LD. Eighteen patients (44%) received bridging therapy prior to TIL and had lower baseline CD4 and CD8 counts compared with those who did not ($p < 0.05$ for both); however, post-TIL CD4 and CD8 recovery trajectories did not differ between groups. CD4 counts declined sharply following LD and demonstrated incomplete and heterogeneous recovery. Median CD4 decreased from 490 cells/ μ L at baseline to 250 at week 4, 290 at month 3, and 220 at month 6, remaining significantly below baseline at all post-TIL timepoints ($p < 0.05$). Clinically significant CD4 lymphopenia was observed in 45% (10/22) of evaluable patients at month 3 and in 50% (44%, 7/16) at month 6. In contrast, CD8 counts increased early after TIL (median 240 to 590 cells/ μ L at week 4; $p = 0.004$) and remained higher than baseline at month 6. The CD4:CD8 ratio inverted from a median of 2.02 at baseline to 0.46 at week 4 and remained below 1.0 through month 6, reflecting sustained CD4 suppression despite CD8 recovery. Post-TIL infections occurred despite widespread prophylaxis, including bacterial (13%), viral (10%), and fungal (4.9%) infections. **Conclusions:** In a multi-institution cohort, LD chemotherapy preceding TIL is associated with profound and prolonged CD4 T-cell suppression, persistent CD4:CD8 inversion, and a high prevalence of CD4 < 200 cells/ μ L through 6 months. These findings identify delayed immune reconstitution as a common and clinically relevant consequence of TIL therapy and support prospective optimization of antimicrobial prophylaxis duration, vaccination timing, and immune monitoring strategies. Research Sponsor: Mayo Clinic Comprehensive Cancer Center Grant; CA015083.

Real-world outcomes of lifileucel in advanced melanoma: A single-institution experience.

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Background: Lifileucel (Amtagvi), an autologous tumor-infiltrating lymphocyte (TIL) therapy, was FDA approval for unresectable or metastatic melanoma after progression on systemic therapy based on clinical trial data. However, real-world data describing early outcomes with lifileucel remain limited. **Methods:** We retrospectively reviewed a prospectively maintained database of patients with unresectable/metastatic melanoma who progressed on immune checkpoint inhibitors (and BRAF ± MEK therapy if applicable) and received lifileucel per standard protocol at a single institution April 2024–January 2026. Eligible patients received an in-specification TIL product and had evaluable imaging ≥12 weeks post-infusion unless progression was detected sooner. Responses were assessed per RECIST v1.1. Endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and grade ≥3 treatment-related adverse events (TRAEs), excluding lymphodepletion-related cytopenias. Time-to-event endpoints were estimated using Kaplan–Meier methods. **Results:** Of 38 patients who underwent surgical TIL harvest, 32 (84%) received lifileucel, including 5 via the Expanded Access Program due to out-of-specification product. Among 27 patients receiving in-specification lifileucel, 20 had evaluable imaging and were included in the analysis. Patients received a mean of 2.2 prior therapies, and 35% had acral lentiginous or mucosal melanoma. All patients had Stage IV disease, including liver (40%) and brain (30%) metastases. 55% received bridging therapy after surgery prior to infusion. Median follow-up was 5.7 months (range, 0.9–16.9). ORR was 30% (3 CR, 3 PR), and DCR was 45%. Among responders, 67% (4/6) have ongoing response and median DoR was not reached. Median PFS was 3.5 months (95% CI, 2.1–5.3) and median OS was 6.1 months, with 6- and 12-month OS rates of 51% and 44%, respectively. Non-cytopenic grade ≥3 TRAEs occurred in 55%. **Conclusions:** In this early real-world experience, lifileucel demonstrated encouraging antitumor activity with ongoing responses in heavily pretreated patients despite high-risk features such as elevated LDH and liver and brain metastases. Additional studies and longer follow-up are warranted to optimize patient selection and define durability of benefit and survival outcomes. Research Sponsor: None.

Baseline patient characteristics and safety outcomes.	
Characteristic/Outcome	Overall (N=20)
Age, median (range), y	62 (38-80)
Male sex, n (%)	12 (60)
Acral lentiginous/mucosal subtype, n (%)	7 (35)
BRAF V600E mutation, n (%)	4 (20)
LDH level > ULN, No. (%)	5 (25)
Liver Metastases, No (%)	8 (40)
Brain Metastases, No (%)	6 (30)
Prior systemic therapies, mean (range)	2.2 (1-5)
Patients with grade ≥3 non-hematologic TRAEs, n (%)	11 (55)

A phase II trial of olaparib in combination with pembrolizumab in metastatic uveal melanoma.

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Background: Metastatic uveal melanoma (mUM) has a poor prognosis with modest response to immune checkpoint blockade (ICB). Inactivating mutations in BRCA-1 associated protein 1 (BAP1) are common in mUM leading to deficient homologous recombinant DNA repair and increasing reliance on alternate repair pathways, including poly[ADP-ribose] polymerase (PARP). We investigated if the PARP inhibitor olaparib could improve objective response to pembrolizumab (PEM) in mUM (NCT05524935). **Methods:** Key eligibility included mUM with measurable disease, ECOG 0-1, and adequate organ function. Prior liver directed therapy was allowed. Patients (pts) received PEM 200mg IV every 21 days plus oral olaparib 300mg BID till progression, toxicity, or completion of 2 years of treatment. In a Simon 2-stage optimal design, > 1 response by RECIST 1.1 in 12 evaluable patients would permit accrual to expand to 37 pts. **Results:** Twelve eligible mUM pts, 6 male and 6 female, median age 59 years (42, 84) were treated in stage 1 of this trial. Most pts (11/12; 92%) had both liver and extra-hepatic metastatic disease; 5 pts had elevated serum LDH at baseline. Seven pts (58%) were naïve to prior systemic therapy; 4 had prior liver directed therapy. There was no objective response observed; best response was stable disease (SD, n=5), remainder (n=7) with progression; disease-control rate was 42%. One patient continues treatment at 13 months with ongoing SD. Of 4 pts who received prior tebentafusp, three had SD lasting greater than 6 months. At median follow-up of 13 months, the median progression-free survival (PFS) was 3.6 months (95% CI: 2.2, 8.3), and median overall survival (OS) was 13.8 months (95% CI: 2.5, 24.3). Six-month PFS and OS were 0.42 (95% CI: 0.15, 0.67) and 0.83 (95% CI: 0.48, 0.96) respectively; one year OS was 0.73 (95% CI: 0.37, 0.91). Most common ($\geq 25\%$) all grade treatment related adverse events (AEs) were fatigue, arthralgia, diarrhea, nausea/vomiting, dyspnea, anemia, abdominal pain, bloating, anorexia, muscle weakness, pruritus, rash, vitiligo, cough, hypertension, muscle weakness, $\uparrow$ AST, $\uparrow$ alkaline phosphatase, $\downarrow$ lymphocyte count, $\uparrow$ glucose, $\uparrow$ potassium and $\downarrow$ albumin. Grade 3 AEs were infrequent; nausea, anorexia, dehydration, hypotension, and muscle weakness (all n=1); there was no treatment related death. 5/12 (42%) pts required a dose reduction for olaparib. **Conclusions:** The addition of olaparib to pembrolizumab was well tolerated but did not result in any objective response in molecularly unselected mUM. Landmark survival results appear clinically meaningful and likely related to disease control with stable metastatic burden. Ongoing biomarker studies of tumor tissue (BAP1, PD-L1, PARP1, TIL) and blood may help discern which patients could benefit from this combination regimen. Optimal sequencing of ICB with tebentafusp in HLA-A*02:01+ mUM should be explored further. Supported by Merck, Inc. Clinical trial information: NCT05524935. Research Sponsor: Merck, Inc.

Stage I results of a phase II study evaluating thymosin α 1 combined with toripalimab in elderly patients with advanced melanoma.

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Background: Anti-PD-1 monotherapy yields limited response rates in Chinese patients with melanoma, highlighting the need for effective combination strategies. Elderly patients frequently present with multiple comorbidities and immunosenescence which may compromise both the efficacy and safety of immunotherapy. Thymosin α 1 ($T\alpha$ -1) promotes T-cell activation and survival, potentially enhancing responsiveness to immunotherapy, while exerting immunomodulatory effects during excessive inflammation that may reduce the risk of immune-related adverse events (irAEs). This study aimed to evaluate whether combining $T\alpha$ -1 with toripalimab could improve efficacy while mitigating irAEs in elderly patients with advanced melanoma. **Methods:** This was a single-arm, open-label, Simon two-stage phase II study. Patients aged ≥ 60 years with pathologically confirmed unresectable stage III or IV melanoma and no prior immune checkpoint inhibitor exposure were enrolled. Treatment consisted of $T\alpha$ -1 (1.6 mg daily during week 1, then three times weekly during weeks 2–3) plus toripalimab 240 mg intravenously every 3 weeks for up to four cycles, followed by toripalimab maintenance until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Stage I required ≥ 3 responses among 19 evaluable patients to proceed to Stage II. **Results:** Between July 2023 and September 2025, 19 patients were enrolled (median age 72 years, range 60–81). Acral melanoma accounted for 78.9% (n=15). All patients had chronic comorbidities; 63.2% had ECOG ≥ 2 and 47.4% had metastases in ≥ 3 organs. At a median follow-up of 10.5 months, ORR was 47.3% (95% CI, 22.6–72.1). Median PFS was 8.0 months (95% CI, 4.4–11.6), and median OS was not reached. Median PFS was 8.1 vs. 4.5 months in acral versus non-acral cutaneous melanoma ($P=0.4$). Elevated LDH showed a trend toward shorter PFS (2.8 vs. 8.1 months, $P=0.076$). Six grade 1 irAEs were observed (vitiligo n=2, transaminase elevation n=2, thyroiditis n=2). Patients without progressive disease had lower neutrophil-to-lymphocyte ratios and higher lymphocyte percentages than those with PD. **Conclusions:** $T\alpha$ -1 combined with toripalimab demonstrated promising efficacy and excellent tolerability in elderly patients with advanced melanoma. The prespecified criteria for Stage II expansion were met, and enrollment of an additional 36 patients is ongoing. Research Sponsor: None.

Patient demographics.	
Characteristics	No. of Patients (N=19)
Age (median, range)	72 (60-81)
Male (%)	8 (42.1%)
Melanoma subtype	
Acral	15 (78.9%)
Cutaneous	4 (21.1%)
NRAS status	
Wild type	14 (73.7%)
Mutation	4 (21.1%)
unknown	1 (5.3%)
No. of organs with metastasis	
≥ 3	9 (47.4%)
Liver metastasis	
Yes	4 (21.1%)
No	15 (78.9%)
Brain metastasis	
Yes	2 (10.5%)
No	17 (89.5%)
ECOG PS	
1	7 (36.8%)
≥ 2	12 (63.2%)

Risk and protective factors for acral, mucosal, and uveal melanoma in a multi-institutional cohort of veterans and civilians.

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Background: Melanoma is the 4th most common cancer among US Veterans. Non-acral cutaneous melanoma has well-established risk factors including history of sunburn, ultraviolet (UV) exposure, fair skin and features. Risk factors for acral (AM), mucosal (MM), or uveal melanoma (UM), are less understood. **Methods:** We conducted a nested case-control study (2000–2024) identifying cases of acral (N=1,292, Veterans only), mucosal (N=520, combined Veteran and civilian cohort), and uveal (N=2,010, combined Veteran and civilian cohort) melanoma using the Veterans Affairs (VA) Cancer Registry, natural language processing applied to pathology reports, and Mass General Brigham Research Patient Data Repository. **Results:** For AM, current smoking was associated with reduced odds, while Agent Orange Exposure (AOE) was associated with increased odds compared to both control populations. Compared to non-melanoma controls, prior nevus, keratinocyte carcinoma (KC), and actinic keratosis (AK) were associated with increased odds of AM. For MM, prior KC was associated with higher odds of MM compared to non-melanoma controls, consistent across anogenital, sinonasal, and upper aerodigestive tract sites. Smoking status was associated with reduced MM odds in the sinonasal cohort. For UM, we conducted a case-control study using data from 3 academic medical centers and the VA. Prior cutaneous and systemic immune disease were protective of UM development compared to CM. Smoking status and prior nevi had higher odds of UM compared to CM and non-cancer controls. **Conclusions:** To our knowledge, this is the largest cohort of AM, MM, and UM cases to date. Our study identified unique factors associated with risk of, or protection from, AM, MM, or UM, compared to CM or non-cancer controls. These findings provide novel insights into potential risks for rare melanomas and can help guide future biologically driven studies. Research Sponsor: CDMRP Department of Defense; W81XWH2110819.

Risk and protective factor associations across rare melanomas.				
Melanoma type	Factor type	Both cohorts	CM only	Non-cancer only
Acral	High risk as-sociation factors	Younger age, female sex, Black race, Hispanic ethnicity, AOE	Asian race	Prior nevus, prior KC, prior AK
	Protective factors	Current smoking	≥2 comorbidities, AUDIT-C positive, prior KC, prior AK	Former smoking
	No associations	BMI		
Mucosal	High risk as-sociation factors	Younger age, female sex	Black race, Hispanic ethnicity	Prior KC
	Protective factors		Former smoking	Current smoking, ≥2 comorbidities
	No associations	Prior nevus, BMI		
Uveal	High risk as-sociation factors	Older age, former smoking, current smoking, prior nevus	Black race, American Indian/ Alaska Native race, obesity	
	Protective factors	≥1 comorbidities, prior photosensitizing medication use, prior cutaneous autoimmune disease, prior systemic autoimmune disease	Prior non-melanoma skin cancer	Hispanic ethnicity, normal or underweight BMI
	No associations	Sex		

Long term survival outcomes of immune checkpoint inhibitors in metastatic melanoma: Later relapse and long-term outcomes beyond 5 years.

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Background: Immune checkpoint inhibitors (ICI) have improved survival outcomes in patients with metastatic melanoma, with a subset achieving durable long term survival outcomes. However, the incidence of late relapse and outcomes among patients who are alive but not progression-free at 5 years remain unknown. **Methods:** This is a multi-institutional retrospective study of patients with metastatic melanoma treated with either single agent anti-PD1 therapy or a combination of anti-PD1/CTLA-4 who started treatment prior to January 1, 2016. We analyzed the following outcomes: progression free survival at 5 years, late relapses (defined as progression > 5 years after ICI initiation), sites of late relapse, and long-term overall survival. **Results:** 206 patients with metastatic melanoma were included; 65% (n = 135) were male. Most patients 86% (n = 177) had cutaneous melanoma and 29% (n = 59) had BRAF V600E/K mutations. In this cohort, 56% (n = 115) received a single agent anti-PD1, while the remaining 44% (n = 91) of patients received a combination of Ipilimumab (IPI) plus anti-PD1. The median follow-up from treatment initiation was 9.1 years. At 5 years, 68% (n = 140) of patients were progression-free. Late relapse, occurring > 5 years after ICI treatment initiation, was seen in 6% (n = 12) of patients, at a median of 8.2 years from ICI treatment initiation. Among 12 patients with melanoma relapses, site of relapses was most commonly at nodal metastases (50%), followed by visceral (17%), brain (17%), and bone/spine (17%), soft tissue (8%), and unspecified sites (8%). Overall, 50% of patients had oligo progression, 33% had metastasis at multiple sites, and 17% unspecified. Following late relapse, 83% (n = 10) were rechallenged with ICI; 50% were rechallenged with the same ICI, 17% switched from IPI plus anti-PD1 to single agent anti-PD1, 17% unspecified, and the other 17% were not rechallenged with ICI. The disease control rate was 75% among patients rechallenged with anti-PD1, 100% among those rechallenged with IPI plus anti-PD1, and 100% among patients who switched from IPI plus anti-PD1 to single agent anti-PD1. At last follow-up, 75% (n = 9) of patients with late relapse were alive. Additional analyses, including Kaplan Meier estimates of progression-free and overall survival and incidence of long term sequelae from immune related adverse events will be reported. **Conclusions:** In this multi-institutional cohort of long-term survivors with metastatic melanoma, late relapse occurred uncommonly. And the outcomes following late relapses were generally favorable, with many patients still experiencing ongoing survival. The findings in our study support continued long-term surveillance beyond 5 years and provide clear expectations in daily clinical practice regarding cure and survivorship following anti-PD1 based therapy in metastatic melanoma Research Sponsor: None.

Influence of peri-dose high-sensitivity troponin on clinically significant cardiac events and IL-2 interruption during post-TIL high-dose IL-2 therapy.

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Background: High-dose interleukin-2 (IL-2) is administered following tumor-infiltrating lymphocyte (TIL) therapy, yet cardiotoxicity frequently limits dose delivery. The clinical significance of peri-dose troponin elevations during IL-2 remains poorly defined. We evaluated troponin kinetics during IL-2 dosing and their association with significant cardiac events and IL-2 interruption. **Methods:** We retrospectively analyzed patients with metastatic melanoma treated with TIL therapy followed by inpatient high-dose IL-2 at Mayo Clinic Rochester (N = 24; 87 IL-2 doses). High-sensitivity troponin and ECGs were obtained before and after each IL-2 dose. Clinically significant cardiac events were defined as QTc prolongation > 480 ms, arrhythmias (excluding isolated sinus tachycardia), new ECG abnormalities, vasopressor requirement, or cardiology consultation. Dose-level outcomes included cardiac events and subsequent IL-2 dose interruption. Paired troponin changes were assessed using Wilcoxon signed-rank testing. Dose-level associations were evaluated using clustered logistic regression to account for repeated IL-2 doses within patients. **Results:** 24 patients received 87 IL-2 doses (median 3 [IQR 2 - 5]). Median age was 63 years (IQR 54 - 70), and 58% were male. Baseline troponin median was 11 ng/L (IQR 6 - 21); 38% had baseline troponin > 14 ng/L. Post-dose troponin exceeded 14 ng/L in 16/24 patients (67%) and 48/87 doses (52%). Median delta troponin was 0 ng/L (IQR -1 to 6; range -24 to 133), with post-dose levels higher than pre-dose values ($p = 0.02$). Clinically significant cardiac events occurred in 33% of patients; no post-IL-2 reductions in left ventricular ejection fraction were observed. At the dose level, cardiac events occurred only when post-dose troponin exceeded 14 ng/L (15/48 [31%] vs 0/39 doses; $p < 0.001$). In clustered logistic regression, post-dose troponin ≥ 15 ng/L was independently associated with cardiac events (OR 9.6, 95% CI 1.5 - 60.6; $p = 0.02$) and subsequent IL-2 dose interruption (OR 3.4, 95% CI 1.1 - 10.7; $p = 0.04$). When modeled continuously, each 1-unit increase in log-transformed post-dose troponin was associated with higher odds of cardiac events (OR 3.3, 95% CI 1.6 - 6.7; $p = 0.001$) and IL-2 interruption (OR 2.8, 95% CI 1.6 - 4.9; $p < 0.001$). Baseline troponin correlated with peak post-dose troponin ($\rho = 0.44$, $p = 0.04$). **Conclusions:** Peri-dose troponin elevations are common during post-TIL high-dose IL-2; however, higher post-dose troponin independently identifies clinically significant cardiac toxicity and predicts IL-2 interruption after accounting for repeated dosing within patients. Baseline troponin modestly predicts peak elevations, supporting standardized, risk-stratified troponin monitoring and prospective evaluation of toxicity-adaptive IL-2 delivery strategies in TIL therapy. Research Sponsor: Mayo Clinic Comprehensive Cancer Center Grant; CA015083.

Real-world comparison of ipilimumab–nivolumab dosing strategies in melanoma brain metastases.

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Background: Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg (Ipi3+Nivo1) is the standard immunotherapy regimen for metastatic melanoma with brain metastases (MBM) but is associated with significant immune-related toxicity, particularly neurologic toxicity. Ipilimumab 1 mg/kg plus nivolumab 3 mg/kg (Ipi1+Nivo3) has demonstrated improved tolerability in extracranial melanoma, though comparative data in MBM are limited. We compared efficacy and toxicity of these dosing strategies in a multisite real-world cohort. **Methods:** We retrospectively identified patients with MBM treated with ipilimumab plus nivolumab across three Mayo Clinic sites between 2016 and 2024. Patients were classified by induction dosing as Ipi1+Nivo3 or Ipi3+Nivo1. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared using log-rank tests. Best overall response (BOR) and toxicity outcomes were summarized descriptively. **Results:** Among 147 patients (Ipi1+Nivo3 n=32; Ipi3+Nivo1 n=115), 144 were evaluable for survival. Median age was higher in the Ipi1+Nivo3 group (69.5 vs 66.0 years); males predominated in both groups (71.9% vs 61.7%), and the cohort was predominantly White (>96%). Most patients had ECOG 0–1 in both groups (84.4% in Ipi1+Nivo3 and 90.4% in Ipi3+Nivo1). BRAF mutation status was balanced between regimens, with approximately half of patients harboring BRAF-mutant disease (51.6% vs 53.2%). Median OS was 18.5 months (95% CI, 5.7–54.7) with Ipi1+Nivo3 versus 10.6 months (95% CI, 6.5–19.1) with Ipi3+Nivo1 (log-rank p=0.25). Two-year OS was 45.9% and 35.0%, and five-year OS was 24.5% and 19.2%, respectively. Median PFS was 7.3 months (95% CI, 1.8–10.9) versus 2.8 months (95% CI, 2.1–4.4) (log-rank p=0.16). BOR was available for 138 patients; objective response rates were 35.5% and 31.8%, respectively. 3–5 adverse events occurred in 24.1% of Ipi1+Nivo3 versus 30.5% of Ipi3+Nivo1 patients. Hospitalizations were less frequent (16.7% vs 36.1%), and neurologic adverse events occurred only with Ipi3+Nivo1 (11.9% vs 0%). **Conclusions:** In this multisite real-world MBM cohort, Ipi1+Nivo3 demonstrated comparable efficacy, numerically longer survival, and a more favorable toxicity profile compared with standard Ipi3+Nivo1. Notably, no neurologic toxicity was observed with the Ipi1+Nivo3 regimen. These findings support further prospective evaluation of lower dose ipilimumab strategies. Research Sponsor: None.

Response and survival outcomes.		
Outcome	Ipi1 + Nivo3	Ipi3 + Nivo1
Complete response (CR)	2 / 31 (6.5%)	8 / 107 (7.5%)
Partial response (PR)	9 / 31 (29.0%)	26 / 107 (24.3%)
Objective response rate (ORR = CR+PR)	11 / 31 (35.5%)	34 / 107 (31.8%)
Disease control rate (DCR = CR+PR+SD)	18 / 31 (58.1%)	51 / 107 (47.7%)
Median PFS, months (95% CI)	7.3 (1.8–10.9)	2.8 (2.1–4.4)
2-year PFS	27.6%	22.3%
Median OS, months (95% CI)	18.5 (5.7–54.7)	10.6 (6.5–19.1)
2-year OS	45.9%	35.0%
5-year OS	24.5%	19.2%

Integrated AI-informed morphologic and spatial transcriptomics features from H&E slides to enable risk stratification of primary melanoma patients.

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Background: Tumor proliferative activity and the tumor-stroma microenvironment are key determinants of melanoma aggressiveness and prognosis, yet their assessment from routine histology remains limited and subjective. Mitotic activity and stromal composition are histologic markers of tumor aggressiveness associated with overall survival (OS). While spatial transcriptomics (ST) can capture tumor biology associated with prognosis, its cost and limited availability restrict clinical use. Recent advances in computational pathology enable inference of spatial gene expression directly from routine hematoxylin and eosin (H&E) whole slide images (WSIs). We evaluated whether integrating AI-informed histologic biomarkers with ST features derived from routine H&E slides improves OS prediction in primary melanoma.

Methods: Formalin-fixed paraffin-embedded H&E WSIs from TCGA-SKCM primary melanoma cases with available survival data were analyzed (N=291). Automated mitotic index (MI) in tumor region was quantified using a Detectron2-based mitosis detection model, and tumor-stroma ratio (TSR) was computed from automated tissue segmentation. Spatial gene expression for 18 melanoma relevant genes was inferred from WSIs using a pretrained DeepSpot model, and quantified for spatial heterogeneity and clustering. Three Cox regression models were created: i) $M_{\text{Path+Clinical}}$ (MI, TSR, age), ii) $M_{\text{AI-ST+Clinical}}$ (ST features, age), and iii) $M_{\text{Integrated}}$ (MI, TSR, ST features and age). Feature selection was performed on training cohort (N=174), and model performance for 10-year OS prediction was evaluated on holdout test cohort (N=117) using hazard ratio (HR) with 95% confidence interval, C-index, and log-rank tests. Independent contributions of various features were assessed by multivariable analysis.

Results: In hold-out test cohort, both $M_{\text{Path+Clinical}}$ model (C-index = 0.639, $p = 0.001$, HR = 2.71 [1.49-4.94]), and $M_{\text{AI-ST+Clinical}}$ model (C-index = 0.603, $p = 0.002$, HR = 2.51 [1.37-4.59]) were prognostic for 10 year OS. AI-ST signature consisted of spatial heterogeneity and clustering metrics of ARG1, TFAP2A, and KRT6B genes, along with global gene expression metrics. The integrated model $M_{\text{Integrated}}$ resulted in the best OS stratification (C-index = 0.644, $p = 0.007$, HR = 2.24 [1.23-4.07]). Multivariable analysis demonstrated independent association of MI, ST features and age with OS. **Conclusions:** AI-derived ST features contributed additional prognostic value beyond histologic and clinical features, yielding the strongest OS stratification when integrated into a unified model. By combining established histologic biomarkers with virtual spatial omics, this approach improves survival prediction without additional tissue or molecular assays, supporting its potential clinical utility for risk adapted management of melanoma patients. Research Sponsor: None.

Systematic evaluation of machine learning optimization strategies for uveal melanoma detection using ultra-widefield photography.

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Background: Early differentiation of uveal melanoma (UM) from benign intraocular lesions remains clinically challenging, particularly in regions with limited access to specialized ocular oncologists. Diagnostic uncertainty can delay referral and treatment, highlighting a gap between current practice and the desired goal of timely, accurate early UM detection. Machine learning (ML) offers a promising approach to improving diagnostic support with early detection of UM. This study developed, trained, and optimized eight ML classification models for early UM detection using ultrawidefield fundus (UWF) imaging to evaluate methods to increase clinical utility and readiness of current models. **Methods:** 1,592 UWF images from 784 patients were retrospectively collected and labeled into four classes: UM ($n = 364$), choroidal nevus ($n = 824$), congenital hypertrophy of the retinal pigment epithelium (CHRPE, $n = 102$), and healthy controls ($n = 302$). Images with multiple lesions, significant media opacity, or poor tumor visualization were excluded. All models used a ResNet-50 architecture, and a binary UM/nevus classifier was developed as the control. Optimization strategies included 1) class expansion with healthy control and CHRPE images, 2) training dataset augmentation with multiple images per patient and post-treatment images, and 3) a region of interest (ROI) dilation preprocessing pipeline. A 70/15/15 train/validation/test split was used with patient-level stratification to prevent data leakage. The test set was held constant across all models to ensure fair comparison. Performance was assessed using per-class F1 score and area under the curve (AUC) with 5-fold cross-validation. Grad-CAM images were generated to aid in model interpretability. **Results:** The control model achieved an AUC of 0.94 ± 0.01 and F1 scores of 0.90 ± 0.01 for nevus and 0.80 ± 0.03 for UM. ROI dilation achieved the greatest improvement (AUC 0.99 ± 0.001 ; nevus F1 0.98 ± 0.01 ; UM F1 0.95 ± 0.01). Other optimization strategies showed variable impact, with multi-optos yielding the second-best performance (AUC 0.95 ± 0.02 ; nevus F1 0.91 ± 0.02 ; UM F1 0.83 ± 0.04). A final model integrating the most effective strategies demonstrated robust performance (AUC 0.95 ± 0.01 ; nevus F1 0.91 ± 0.03 ; UM F1 0.82 ± 0.06). Grad-CAM confirmed an appropriate lesion-centered focus. **Conclusions:** Our findings show that targeted ML optimizations can meaningfully improve performance for early UM detection. While ROI dilation preprocessing had the most performance gain, results varied across optimization pathways, indicating room for refinement. Further evaluation on external datasets is needed to assess generalizability, paving the way for end-stage clinical rollout. Research Sponsor: National Eye Institute; VitreoRetinal Surgery Foundation; Research to Prevent Blindness; Illinois Society for the Prevention of Blindness.

Machine learning (ML) model integrating cell death pathways as a prognostic and predictive biomarker for patients with melanoma.

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Background: Established regulated non-apoptotic cell death mechanisms, including ferroptosis, necroptosis, and pyroptosis, can govern cancer cells' fate. Early reports suggest that these pathways can drive antitumor immune response, and may be associated with survival outcomes for pts treated with checkpoint blocker antibodies (ICB). We developed a ML model based on transcriptomic data (CDPS), integrating these 3 pathways, and interrogated its prognostic and predictive role in pts with melanoma. **Methods:** An ML score based on 148 non-redundant cell-death-related genes was developed and evaluated in patient-level data from TCGA-SKCM and validated in external cohorts of pts with melanoma (GSE65904, MEL-DFCI-2019, GSE98394, GSE54467). Prognostic performance was assessed using C-index, time-dependent ROC, Kaplan–Meier analysis, and univariable Cox models, with pts stratified by cohort-specific medians. Pathway activity was examined using gene set enrichment analysis (MSigDB Hallmark and Reactome gene sets; pathways were significant if $FDR < 0.05$). Immune infiltration was estimated with MCP-counter as per Cliff'delta (Mann–Whitney test $p < 0.05$). Predictive value was tested in pts treated with ICB (GSE78220, GSE91061, GSE168294), which also included on-treatment samples (GSE91061). **Results:** Across discovery and validation cohorts, a random survival forest model with ridge regression showed consistent prognostic performance (C-index range, 0.58–0.66). 7 genes emerged as dominant contributors during feature selection. The CDPS-high group showed a downregulation of *MLKL* and *GSDMD* (key mediators of necroptosis and pyroptosis, respectively), and an upregulation of *SLC3A2* (a negative regulator of ferroptosis), suggesting suppression of these regulated cell-death pathways. Across all 5 cohorts, CDPS-high pts exhibited significantly worse overall survival ($p < 0.05$), corroborated by time-dependent ROC analyses at 1 (0.61 – 0.72), 3 (0.84 – 0.75), and 5 years (0.58–0.76). Functional pathway analyses revealed statistically significant positive enrichment of proliferative, anabolic, and DNA-repair signalling in the CDPS-high group and negative enrichment of immune-related pathways ($FDR < 0.05$). Similarly, CDPS-high tumors demonstrated broadly reduced innate and adaptive immune cell infiltration, indicating a less favorable tumor immune microenvironment ($p < 0.05$). CDPS was significantly lower in responders (R) vs non-responders ([NR], $p = 0.04$) in GSE168294. Notably, a decrease in CDPS levels was observed during treatment for R, whereas remained stable in NR (GSE91061). **Conclusions:** CDPS exhibited robust and consistent performance by combining selected programmed death pathways (ferroptosis, necroptosis, and pyroptosis), especially in pts treated with ICB. Future efforts will aim to validate CDPS in a prospective cohort of pts with melanoma. Research Sponsor: None.

The efficacy and safety of neoadjuvant toripalimab combined with temozolomide in resectable stage III melanoma: A prospective, single-center, phase 2 trial.

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Background: Neoadjuvant immune checkpoint inhibitors (ICIs) have demonstrated efficacy in resectable cutaneous melanoma and are recommended by current guidelines. Nevertheless, the clinical benefit of combining ICIs with chemotherapy as neoadjuvant setting in Chinese patients remains to be established. This study is being conducted to explore the efficacy and safety of neoadjuvant toripalimab combined with temozolomide in resectable stage III melanoma. **Methods:** This is a prospective, single-center, single-arm clinical trial (ClinicalTrials.gov identifier: NCT05827770). Patients with resectable stage IIIB-IIID acral or cutaneous melanoma and an ECOG performance status of 0-1 were enrolled and received two cycles of neoadjuvant temozolomide 200 mg/m² plus toripalimab 240 mg every 3 weeks, followed by radical surgery. The primary endpoint was the pathologic response rate (pRR). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), recurrence-free survival (RFS), overall survival (OS) and safety. **Results:** As of December 2025, 20 eligible patients with resectable stage IIIB-IIID melanoma were enrolled, with 14 (70%) acral, 5 (25%) cutaneous and 1 (5%) of unknown primary. Of 20 patients underwent surgery, nine achieved pRR (45%), including 3 with near pathologic complete response (near pCR) and 6 with partial pathologic response (pPR). Radiological assessment showed partial response in 5 patients, stable disease in 12 patients, and progressive disease in 3 patients, yielding an objective response rate of 25% (5/20) and a disease control rate of 85% (17/20) according to RECIST criteria. With a median follow-up of 12 months, 8 recurrence-free survival events had been observed; the median RFS and OS had not yet been reached. Notably, one patient who attained near pCR remained relapse free for 27 months. No new safety signals were observed with the combination therapy. We further performed single-cell-resolution spatial transcriptomics and single-cell RNA sequencing in the current cohort. Integrative multi-omics analyses identified a T cell-excluded tumor microenvironment preferentially associated with non-response. Leveraging these features, we robustly distinguished immunotherapy responders from non-responders. **Conclusions:** This study demonstrates the preliminary efficacy and tolerability of toripalimab combined with temozolomide in the neoadjuvant treatment of patients with resectable stage IIIB-IIID acral and cutaneous melanoma. Given the fact that ICIs alone has limited response rate in acral melanoma, further studies are warranted. Clinical trial information: NCT05827770. Research Sponsor: None.

Treatment outcomes.			
Pathologic Response	Eligible patients (%) N=20	Radiological Response	Eligible patients (%) N=20
Near pCR	3 (15)	PR	5 (25)
pPR	6 (30)	SD	12 (60)
pNR	11 (55)	PD	3 (15)
pRR (pCR+Near pCR+pPR)	9 (45)	ORR (CR+PR)	5 (25)
		DCR (CR+PR+SD)	17 (85)

Survival outcomes of stage IIB/IIC cutaneous melanoma treated with wide local excision and adjuvant immunotherapy without sentinel lymph node biopsy.

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Background: The Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) reported no significant difference in 10-year overall survival (OS) in patients with thick melanomas who had only wide local excision (WLE) versus WLE and sentinel lymph node biopsy (SLNB). With expanded immunotherapy eligibility for stage IIB/C melanoma per KEYNOTE-716, does omission of sentinel node negatively impact nodal basin disease control? Thus, we studied patients with stage IIB/C cutaneous melanoma treated with WLE and adjuvant pembrolizumab.

Methods: We performed a single-institution retrospective review and included patients with stage IIB/C cutaneous melanoma treated with only WLE and adjuvant pembrolizumab with at least 6 months of follow-up. The primary endpoints were OS and cumulative incidence of nodal metastasis (CINM). Secondary endpoints were recurrence-free survival (RFS) and nodal metastasis-free survival (NMFS). Survival was estimated via Kaplan-Meier survival analysis and compared to the thick melanoma observation arm of MSLT-1. **Results:** Thirty-three patients met inclusion criteria between 2021-2025. Our sample was 58% male, 100% White, non-Hispanic, and median age at surgery was 59 ± 13 years. Twenty-six (79%) patients were clinical group stage IIB. Tumor subtypes included acral lentiginous (3%), desmoplastic (3%), nodular (45%), spindle cell (3%), and superficial spreading (24%). Median follow-up was 24.3 ± 12.3 months. Four deaths occurred at 11, 17, 32, and 42 months, and OS probability was 96.2% at 12 months and 84.0% at 36 months. We observed 11 recurrences (33.3%). Six occurred in regional lymph nodes at 3, 3, 7, 7, 20, and 34 months, and 5 were distant metastases at 6, 11, 19, 20, and 25 months. At 12 months, RFS probability was 80.4%, 65.9% at 24 months, and 47.9% at 36 months. The probability of NMFS was 87.5% at 12 months, 82.8% at 24 months, and 69.0% at 36 months. Our CINM, over a median follow-up duration of 24.3 ± 12.3 months, was 18.2%, of which 3 began nivolumab/relatlimab and had complete radiological response and no subsequent recurrence. Of the 5 distant metastases, 3 underwent radiation or surgery for brain lesions and 1 began nivolumab/relatlimab for a chest wall nodule, both groups had complete radiologic response with no recurrence. Per MSLT-1, melanoma-specific survival of thick melanomas was between $76.1 \pm 5.2\%$ and $53.8 \pm 7.6\%$ at 60 months, and CINM was $33.2 \pm 4.5\%$ at 36 months. **Conclusions:** In our cohort, OS and CINM were comparable or better to the thick melanoma observation arm of MSLT-1. Our data suggests that omission of SLNB is highly likely to not negatively impact outcomes and may be offered to patients with significant operative risk. A larger sample with longer follow-up is needed to substantiate this conclusion. Research Sponsor: None.

Intismeran autogene to induce de novo neoantigen-specific T cells as adjuvant therapy in melanoma.

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Background: Intismeran autogene (intismeran) is an individualized mRNA-based neoantigen (neoAg) therapy designed to enhance endogenous antitumor T-cell responses by targeting patient-specific tumor mutations. In the phase 2 KEYNOTE-942 trial of resected high-risk melanoma, intismeran combined with pembrolizumab (pembro) significantly improved recurrence-free survival (RFS) vs pembro alone. Previously, it was shown that the combination induced greater expansion of *de novo* T-cell clonotypes, which correlated with RFS in the intismeran arm. Here, we show that *de novo* T-cell clonotypes are reactive to intismeran-encoded neoAg. **Methods:** Peripheral leukapheresis samples longitudinally collected from a subset of intismeran plus pembro treated participants (pts) with melanoma from phase 1 and 2 studies (NCT3313778 and NCT03897881) were assessed at single-cell level to characterize neoAg-specific T cells. In 7 pts, functional assessment of neoAg-reactive CD8⁺ T cells was performed by intracellular cytokine staining and activation-induced marker assays. To define antigen specificity and phenotype of intismeran-induced T cells, we combined longitudinal bulk and single-cell T-cell receptor (TCR) sequencing with functional validation assays from 3 pts. *De novo* expanded TCRs were tested in Jurkat NFAT-luciferase reporter cells for reactivity against pt-specific intismeran mRNA cassettes and individual neoAg. For reactive TCRs, minimal epitopes were mapped and mutant vs wild-type peptide reactivity was quantified. **Results:** Using the combination of bulk and single-cell TCR sequencing and Jurkat NFAT-luciferase reporter assays in 3 pts, we identified 20 TCRs expanded following intismeran therapy across all pts mapping to 11 neoAg, providing direct evidence of intismeran-driven polyclonal T-cell expansion. These responses targeted multiple neoAg with persistence >100 days after last intismeran dose. Reactive TCRs showed stronger recognition of mutant vs wild-type peptides, confirming antigen specificity. Functional assessment of T cells from 7 pts showed that neoAg-reactive CD8⁺ T cells secreted IFN γ and TNF α and coexpressed markers for degranulation/activation upon peptide restimulation, demonstrating functional activity. Flow cytometry-based characterization of neoAg-reactive T cells *ex vivo* revealed that these cells predominantly exhibited an effector-memory phenotype. Upon stimulation, they were polyfunctional (IFN γ ⁺ TNF α ⁺), mobilized CD107a, and were granzyme B⁺, consistent with cytotoxic effector function relevant to tumor control. **Conclusions:** Complementary sequencing and functional analyses demonstrated that adjuvant therapy with intismeran plus pembro induced durable, polyclonal, neoAg-specific T-cell responses with effector-memory characteristics, providing mechanistic data consistent with the clinical benefit observed in pts with melanoma. Clinical trial information: NCT3313778 & NCT03897881. Research Sponsor: This research was supported by Moderna, Inc., Cambridge, MA, USA, in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Outcome of neoadjuvant immunotherapy for patients with resectable stage III/IV cutaneous melanoma: A Swedish nationwide population-based study (NEO-MEL).

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Background: Randomized trials have shown that neoadjuvant immune checkpoint inhibitor (ICI) improves outcomes compared with adjuvant therapy alone in patients with resectable stage III–IV cutaneous melanoma. Furthermore, pathological response was a strong predictor for relapse-free survival (RFS). The translationability to routine real-world patients is unknown. **Methods:** This population-based cohort study included all patients with macroscopic, resectable cutaneous melanoma treated with neoadjuvant immune checkpoint inhibitor(s) across all academic melanoma centers in Sweden between January 1, 2022 and December 30, 2025. Clinical and pathological data were extracted from medical records. **Results:** A total of 279 patients initiated neoadjuvant ICI and received a median of two treatment cycles, 94% received PD1-inhibitor monotherapy, 91% underwent surgery as planned and 251 had evaluable pathological assessment. Among all patients who started treatment, 37% had a complete pathological response (pCR), 6% near pCR, 15% a partial pathological response (pPR) and 32% no pathological response (pNR). At a median follow-up time of 20 months, the estimated 24-month event-free survival was 69% (95% CI, 62–76), distant metastasis-free survival (DMFS) 75% (95% CI, 69–82) and overall survival (OS) 87% (95% CI, 82–92). Among those who underwent surgery and had an evaluable pathological assessment, RFS, DMFS and OS stratified by pathological response are shown in the table. **Conclusions:** Early nationwide implementation of neoadjuvant ICI in patients with resectable cutaneous melanoma resulted in favourable outcomes that closely mirror those reported in randomized clinical trials. Research Sponsor: None.

Pathological response	N	RFS at 24 months % (95% CI)	DMFS at 24 months % (95% CI)	OS at 24 months % (95% CI)
pCR	103	92 (85-100)	93 (86-100)	94 (87-100)
near pCR	17	76 (56-100)	83 (64-100)	90 (73-100)
pPR	41	83 (71-97)	85 (74-98)	92 (81-100)
pNR	90	48 (36-63)	63 (52-78)	81 (70-92)

Adjuvant versus no adjuvant therapy after major pathological response to neo-adjuvant immunotherapy in resectable melanoma: A Swedish nationwide population-based study (NEO-MEL).

Axel Nelson, Ellen Krabbe, Karl Björkstöm, Anne Huibers, Christian U. Blank, Braslav Jovanovic, Måns Kadefors, Ana Carneiro, Karolin Isaksson, Sara Wirén, Mikael Wallander, Antonios Valachis, Gustav Jörgen Ullenhag, Hildur Helgadóttir, Lars Ny, Roger Olofsson Bagge, Neo-Mel; Sahlgrenska University Hospital, Gothenburg, Sweden; University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden; Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; Gothenburg University, Gothenburg, Sweden; The Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Skåne University Hospital and Lund University, Lund, Sweden; Department of Clinical Sciences, Surgery, Lund University, Lund and Department of Surgery, Skåne University Hospital, Kristianstad, Sweden; Department of diagnostics and intervention, Oncology, University Hospital of Umeå, Umeå, Sweden; Department of Oncology, Ryhov Hospital, Jönköping, Sweden; Department of Oncology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; Department of Immunology, Genetics, and Pathology, Section of Oncology, Uppsala University, Uppsala, Sweden; Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden

Background: Randomized trials have shown that neoadjuvant PD-1–based immunotherapy improves outcomes compared with adjuvant therapy alone in patients with resectable stage III–IV cutaneous melanoma. In trials, patients experiencing a major pathological response (MPR) rarely relapse, and in the NADINA trial, adjuvant therapy was omitted in this group. However, the need for continued adjuvant treatment after MPR has never been prospectively tested, and real-world evidence is limited. **Methods:** This population-based cohort study included all patients with macroscopic, resectable cutaneous melanoma treated with neo-adjuvant immune checkpoint inhibitor(s) across all academic melanoma centers in Sweden between January 1, 2022 and December 30, 2025. Clinical and pathological data were extracted from medical records. MPR was defined as pathological complete response (pCR) or near-pCR. Recurrence-free survival (RFS) was estimated using the Kaplan–Meier method and differences assessed with log-rank test. **Results:** A total of 279 patients initiated neoadjuvant treatment; 254 (91%) underwent surgery as planned, and 251 had evaluable pathological assessment. Overall, 103 patients (37%) experienced pCR and 17 (6%) near-pCR, yielding 120 patients (43%) with MPR. At a median follow-up of 19 months, the estimated 24-month RFS for patients with MPR was 92%. Among MPR patients, 52 (43%) received continued adjuvant immune checkpoint inhibitor therapy, while 68 (57%) received no adjuvant treatment. RFS differed significantly between groups, with estimated 24-month RFS of 96% in patients receiving adjuvant therapy versus 80% in those who did not ($P=0.048$). In the non-adjuvant group, there were five recurrences (three had pCR and two had near pCR), two were local recurrences and three were distant metastatic events, compared with no recurrence events in the adjuvant group. One unrelated death occurred in the non-adjuvant group and two unrelated deaths in adjuvant group. **Conclusions:** In this nationwide real-world cohort, patients experiencing MPR after neoadjuvant immunotherapy had excellent outcomes overall. However, a small but clinically relevant risk of relapse was observed among patients who did not receive continued adjuvant therapy after MPR. These findings emphasize the need for individualized assessment when considering adjuvant treatment in patients with MPR. Longer follow-up is needed to determine whether additional events emerge and, importantly, whether relapses can be effectively salvaged with immune checkpoint inhibitor rechallenge. Research Sponsor: None.

ADAPT-M: A tool to predict individualized benefit from adjuvant anti-PD-1 (PD-1) in resected high-risk melanoma.

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Background: Resected stage IIB/C and microscopic stage IIIA/B/C/D melanoma presents a significant risk of recurrence risk of 37 to 62% at 5 years (yrs). While 1 year of adjuvant PD1 therapy reduces this risk by approximately half, the individual patient's baseline risk without treatment and their specific benefit from adjuvant PD1 remain unknown. We aimed to generate two separate predictive models for recurrence – one for untreated and one for treated pts – to calculate the individualised benefit of adjuvant PD1. **Methods:** Pts with resected stage IIB/C or microscopic stage IIIA/B/C/D melanoma, either treated with adjuvant PD1 or untreated at 13 major melanoma centres, and with at least 2 years of follow-up from surgery were included. We analysed pts demographics, disease characteristics, blood parameters, pathological and imaging data at baseline, and clinical outcomes. Propensity scores were estimated using logistic regression with covariates associated with treatment in univariate screening ($p < 0.05$). Separate penalised multivariable logistic regression models were built to predict recurrence for treated and untreated pts. A tool based on these models was created to calculate the individual patient benefit from adjuvant PD1. **Results:** A total of 3560 pts was included, divided into untreated (discovery $n=2384$ and validation $n=597$) and treated (discovery $n=404$ and validation $n=175$) cohorts. The model for untreated pts included age, gender, primary site, histological subtype, Breslow thickness, ulceration, mitosis, number and site of regional lymph nodes (LN), mutation status and LDH (AUC 0.70 in discovery, 0.69 in validation). The model for treated pts included age, gender, Breslow thickness, site of regional LN, and mutation status (AUC 0.69 in discovery, 0.61 in validation). ADAPT-M (ADjuvant Anti-PD-1 Tool for Melanoma) calculates the individualized benefit of adjuvant PD1. For example, patient A, a woman ≤ 45 years old with a primary head & neck melanoma (superficial spreading, thickness $>1-2$ mm, no ulceration, 1 mitosis/mm²), 2 clinically occult LN metastases in the neck, NRAS mutant, and normal LDH, has a 12-month recurrence risk of 21.9% untreated vs 2.3% treated (benefit 19.6%), and a 24-month risk of 41.1% untreated vs 6.4% treated (benefit 34.7%). While, patient B, a man ≤ 45 years old with a primary melanoma in the lower limb (nodular, thickness $>1-2$ mm, no ulceration, 1 mitosis/mm²), 2 clinically occult LN metastases in the groin, BRAF V600 mutant, and normal LDH, has a 12-month recurrence risk of 14.2% untreated vs 11.8% treated (benefit 2.5%), and a 24-month risk of 28.0% untreated vs 30.1% treated (no benefit). **Conclusions:** ADAPT-M, a clinical tool that estimate individualized recurrence risks with and without adjuvant anti-PD1 therapy, quantifies the absolute benefit of treatment for pts with high-risk resected melanoma, facilitating personalized adjuvant therapy decisions. Research Sponsor: None.

Assessment of recurrence risk in stage IIB/C melanoma across time: Implications for stratification and surveillance.

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Background: Stage IIB/C cutaneous melanoma is associated with high recurrence risk, however stratification of risk in relation to time after surgery has not been comprehensively evaluated. We evaluated recurrence-free survival (RFS) at key time points, stratified by clinicopathologic factors, to identify patients (pts) at higher recurrence risk and personalize postoperative surveillance strategies. **Methods:** In this multi-institutional, international retrospective cohort study from the Sentinel Lymph Node Working Group database, we included pts with pathologic T3b/T4a/T4b and No disease who underwent surgical resection and sentinel node biopsy from 1994-2025. The type of first recurrence (local, regional, distant) was characterized based on time category (0-12, 12-24, 24-60, and 60+ months after surgery). Restricted mean survival time (RMST) analysis was used to measure the average survival time up to a specified time point (6-, 12-, 24-, and 60-months after surgery), and associations of clinicopathologic variables (age, sex, Breslow thickness, ulceration and lymphovascular invasion [LVI]) with RFS. **Results:** We included 2514 stage IIB/C pts from 19 sites in 4 countries, with a median follow-up of 53 (stage IIB) and 49 (stage IIC) months. 675 (27%) pts experienced a recurrence (92 [14%] local, 238 [35%] regional and 345 [51%] distant), and 400 (59%) recurrences occurred within 24 months. The proportion of distant recurrences as the first recurrence increased significantly with time, comprising 39%, 50%, 62%, and 59% of recurrences in the 0-12, 12-24, 24-60, and 60+ month time categories respectively (χ^2 $p < 0.001$). No significant differences were observed for the included clinicopathologic variables for 6-month RMST estimates. At 12 months, RMST estimates for thickness ≥ 4 mm (11.2 vs 11.6 months for thickness 2-3.99 mm, $p < 0.001$) and presence of LVI (10.7 vs 11.4 months, $p = 0.009$) were significantly different. 24-month RMST estimates differed for male sex (20.7 vs 21.5 months vs females, $p = 0.002$), thickness ≥ 4 mm (20.5 vs 21.9 months, $p < 0.001$), and presence of LVI (19.0 vs 21.1 months, $p < 0.001$). Lastly, 60-month RMST estimates differed for male sex (42.0 vs 45.2 months, $p = 0.001$), thickness ≥ 4 mm (41.5 vs 46.2 months, $p < 0.001$), LVI (36.0 vs 43.7 months, $p < 0.001$), and age > 65 years (41.5 vs 46.4 for age < 42 , $p = 0.022$). **Conclusions:** In this real-world, multi-center analysis of pathologic stage IIB/C melanoma pts, recurrence patterns varied based on time after surgery. Breslow thickness, LVI, male sex, and age were significantly associated with earlier recurrence at different time intervals on RMST analysis. Additionally, given that $> 50\%$ of first recurrences 12+ months after surgery were distant, active surveillance for distant relapses may be warranted. Research Sponsor: None.

Real world outcomes of neoadjuvant immune checkpoint blockade (ICB) for resectable stage III melanoma: Pathologic response and FDG PET/CT correlates.

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Background: Neoadjuvant (NA) ICB is standard of care for resectable stage III melanoma, with major pathological (p) response (R) (MPR, $\leq 10\%$ viable tumor) strongly predicting relapse free survival (RFS). Imaging biomarkers to predict MPR are lacking. We evaluated the outcomes of patients (pts) treated with NA pembrolizumab (Pem) or nivolumab (NIVO) + ipilimumab (IPI) therapy, focusing on pR and FDG PET/CT metabolic changes. **Methods:** We retrospectively analyzed pts with resectable stage IIIB-D melanoma treated with NA Pem or NIVO + IPI at Peter Mac from March 2022 to Dec 2025. Clinical characteristics, pR, RFS, and treatment-related adverse events (TRAEs) were analyzed. RFS was calculated from date of surgery until day of death, recurrence or last follow up. Maximum standardized uptake value (SUVmax) of the most avid lesion (lymph node (LN) or in-transit metastases (ITM)) at baseline and post NA ICB on FDG PET/CT scans were recorded. **Results:** Of the 130 pts, 100 had LN metastasis only, 19 ITM only and 11 LN + ITM. 77 (59.2%) received Pem and 53 (40.8%) received NIVO + IPI. 117 pts (90.0%) underwent surgery: LN dissection in 40, index LN (ILN) excision in 58, ITM excision in 18 and excision of ITM + ILN in 1. 13 pts did not have surgery, 10 due to progressive disease on FDG PET/CT, complete resolution of ITM in 2, and toxicity in 1. MPR was seen in 74 (63.2%), partial response (pPR) in 7 (6.0%) and pathological non-response (pNR) in 36 (30.8%) pts. A ΔSUVmax decline $\geq 50\%$ post NA ICB was strongly predictive of MPR, whereas pts without significant metabolic response were more likely to have pNR (sensitivity 93.2%, specificity 60.0%, positive predictive value 71.9%, negative predictive value 88.9% and accuracy 77.4% $p=0.005$). In ILN disease, 40/43 pts (93.0%) with $\geq 50\%$ drop in ΔSUVmax achieved MPR ($p<0.0001$). In ITMs, a decline in ΔSUVmax $\geq 50\%$ resulted in MPR in all 10 pts (table 1). At 12 months (m) median follow up, 14 pts recurred including 4 after MPR. The estimated 12m RFS was 89.0% for Pem and 79.3% for NIVO + IPI. 12m RFS in pts with ΔSUVmax decline $\geq 50\%$ for Pem was 97% and 82% for NIVO + IPI ($p=0.045$). Grade ≥ 3 TRAEs occurred in 12 pts (7.5%), more frequently with NIVO + IPI. **Conclusions:** NA ICB yields high MPR rates in stage III melanoma. Early metabolic response on FDG PET/CT, defined as a ΔSUVmax $\geq 50\%$ decline is a strong, readily implementable imaging biomarker for predicting MPR following NA ICB, enabling early treatment adaptation and personalized surgical decision-making. Research Sponsor: None.

	Pem (n=77)	NIVO + IPI (n=53)
Median age [range]	67 [41-92]	67 [20-82]
BRAF mutant, n (%)	23 (29.9)	27 (50.9)
Stage III B/C/D, n	26/50/1	20/33/0
Site of disease, neck/axilla/groin/ITM, n	23/28/13/13	18/20/12/6
MPR, n (%)	45 (65.2)	29 (60.4)
MPR ΔSUVmax decline $\geq 50\%$	33/35	13/14
MPR ΔSUVmax decline $< 50\%$	12/34	7/22
12m RFS ΔSUVmax decline $\geq 50\%$ (95% CI)	96% (89%-100%)	100%
12m RFS ΔSUVmax decline $< 50\%$ (95% CI)	82% (67%-100%)	80% (59%-100%)

5-year overall survival after adjuvant treatment for stage III melanoma: An English nationwide registry-based study.

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Background: Adjuvant treatments for stage III cutaneous melanoma were approved based on significant improvement in recurrence free survival (RFS) with both anti-PD-1 and BRAF+MEK inhibitors. However, registration trials have not demonstrated a significant overall survival (OS) benefit to date. Given the potential patient and financial toxicity associated with adjuvant therapy, the effect on OS remains an important consideration. **Methods:** A retrospective study linking national registry data for all patients diagnosed with stage III melanoma in England between 2016 and 2021 were included and divided into two cohorts based on date of initial melanoma diagnostic staging: pre- and post-May 2018, when adjuvant therapy was initially approved in England. Key data collected were: patient age, sex, date of stage III melanoma diagnosis, TNM stage, systemic therapy for melanoma, cause and date of death. Data cut-off for follow-up was 1st August 2025. Melanoma-specific survival (MSS) and OS were calculated using the Kaplan-Meier method and Cox regression analyses. **Results:** A total of 6,297 patients were analysed (pre-May 2018: n=2,089; post-May 2018: n=4,208). Survival outcomes improved significantly in the post-adjuvant cohort. The 5-year overall survival (OS) rose from 60.9% (95% CI: 58.8–63.0) to 64.2% (95% CI: 62.7–65.7), with a hazard ratio of 0.89 (95% CI: 0.82–0.96; p=0.004). Similarly, 5-year melanoma-specific survival (MSS) improved from 70.4% (95% CI: 68.4–72.5) to 72.8% (95% CI: 71.4–74.3), HR 0.89 (95% CI: 0.81–0.99; p=0.025). When stratifying by age, sex or melanoma TNM stage, no significant OS or MSS was observed. **Conclusions:** English national registry data demonstrates a statistically significant improvement in both OS and MSS for patients diagnosed with stage III melanoma after approval of adjuvant therapy for stage III melanoma. This is consistent with published real world data from France, but contrasts with findings in Sweden and the Netherlands. The reduced utilisation of subsequent therapy for metastatic disease likely reflects the established RFS benefit. The OS benefits are modest, so careful discussion of the potential risks and benefits of adjuvant therapy remains central to patient care. Research Sponsor: Melanoma Focus UK.

Cohort	Pre-May 2018	Post-May 2018	Hazard ratio (95% CI)
Number (N)	2,089	4,208	
Median duration of follow up (years)	8.38	6.23	
Median age (range)	66 (18,103)	67 (18,102)	
Stage (AJCC V8)	127 (6.1%)		
3A	161 (7.7%)	487 (11.6%)	
3B	1042 (49.9%)	698 (16.6%)	
3C	97 (4.6%)	2085 (49.5%)	
3D	662 (31.7%)	168 (4%)	
3 (unspecified)		770 (18.3%)	
Received adjuvant systemic therapy	148* (7%)	1772 (42%)	
Received systemic therapy for metastatic melanoma	676 (32%)	685 (16%)	
5-year OS (95% CI)	60.9 % (58.8 – 63.0)	64.2% (62.7 – 65.7)	0.89 (0.82 – 0.96) p = 0.004
5-year MSS (95% CI)	70.4% (68.4 – 72.5)	72.8% (71.4 – 74.3)	0.89 (0.81 – 0.99) p = 0.025

Neoadjuvant camrelizumab plus apatinib and temozolomide for resectable stage III acral melanoma: Updated CAP 03-NEO trial results and external control comparison.

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Background: SWOG1801 and NADINA trials suggested that neoadjuvant therapy may provide greater benefits than adjuvant therapy in melanoma. CAP 03-NEO explores the efficacy and safety of camrelizumab combined with apatinib and temozolomide triple-drug regimen as neoadjuvant therapy in patients (pts) with resectable stage II/III acral melanoma (AM). **Methods:** This two-stage trial (NCT05512481) aimed to enroll 60 pts with resectable stage II/III AM. Pts received two 4-week cycles of neoadjuvant camrelizumab (200 mg IV Q2W), apatinib (250 mg orally QD), and temozolomide (200 mg/m² IV daily D1–5), followed by surgery and 15 cycles of adjuvant camrelizumab (200 mg Q3W). A total of 30 pts were assessed in stage 1, demonstrating stage III AM benefiting more from neoadjuvant therapy (ASCO 2025, abstract 9512). Therefore, stage 2 exclusively enrolled stage III pts. Endpoints included pathological response, EFS, RFS and DMFS. To further evaluate the neoadjuvant benefit, an external contemporary cohort of stage III AM pts treated with upfront surgery and adjuvant PD-1 inhibitor alone was retrospectively collected for comparison. Propensity score matching (PSM 1:1 nearest neighbor method) and inverse probability of treatment weighting (IPTW) were used to minimize bias. Kaplan-Meier method and Cox regression were performed for survival analysis. Stage 2 results and this post-hoc comparison are reported here. **Results:** As of Jan. 26, 2026, thirty-one pts in stage 2 were enrolled, with a median follow-up of 13 months. The median age was 60 years (IQR: 49–68). Of 28 pts undergoing surgery, 18 (64.3%) achieved any pathological response, including 10 with major pathological response (7 with pCR, 3 with near pCR), and 8 with pPR. Surgery was canceled for 2 pts due to progressive disease. Neoadjuvant therapy was still ongoing for one patient. The 12-month rates of EFS, RFS and DMFS were 74.4%, 80.3% and 84.0%, respectively. All median values were not reached. As compared to external control cohort (adjuvant treatment alone), both unadjusted and adjusted analyses showed that pts treated with additional neoadjuvant therapy achieved significantly better EFS, RFS and DMFS (Table 1, all p values <0.05). The safety profile between stage 1 and stage 2 were similar and no new safety signal was identified. **Conclusions:** Stage 2 results and external control comparison of CAP 03-NEO further confirmed the significant benefit of neoadjuvant camrelizumab, apatinib and temozolomide in pts with resectable stage III AM. Clinical trial information: NCT05512481. Research Sponsor: None.

HR and 95% CI for EFS, RFS, and DMFS (sample size of stage 2 vs. external control).

Survival	Unadjusted (31 vs. 50)	PSM 1:1 (30 vs. 30)	IPTW (31 vs. 50)
EFS	0.309 (0.129-0.743)	0.246 (0.078-0.778)	0.317 (0.124-0.810)
RFS	0.244 (0.086-0.694)	0.241 (0.071-0.812)	0.242 (0.081-0.728)
DMFS	0.286 (0.099-0.822)	0.203 (0.051-0.807)	0.290 (0.094-0.893)

Ultrasensitive ctDNA detection for relapse and response prediction in melanoma patients treated with immunotherapy.

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Background: Immune checkpoint inhibitors (ICIs) have markedly improved outcomes in melanoma and are now standard of care in advanced and adjuvant settings. However, substantial toxicities remain, and up to 50% of patients derive no clinical benefit. Conventional clinicopathological factors lack sufficient precision for risk stratification, resulting in under- and overtreatment. Circulating tumor DNA (ctDNA) has emerged as a highly specific biomarker for molecular residual disease (MRD) detection, enabling real-time, minimally invasive monitoring to guide personalized ICI strategies. **Methods:** We analyzed 847 plasma timepoints from 98 melanoma patients treated with ICI in either the unresectable advanced (metastatic) setting (25 patients) or adjuvant setting following complete resection of the primary and/or loco-regional metastases (73 patients). Plasma samples were analyzed using NeXT Personal, a whole-genome-sequencing-based tumor-informed assay designed to track up to 1,800 patient-specific variants. This ultrasensitive liquid biopsy approach achieves detection limits of down to ~1 part per million (PPM) at high specificity (>99.9%), enabling identification of MRD and early molecular relapse that may inform timely therapeutic intervention. **Results:** Baseline ctDNA was detected in 100% of 25 patients with unresectable melanoma. Within this group, an early molecular response defined by a $\geq 30\%$ decrease in ctDNA by cycle 3 predicted an 80% reduction in the risk of progression or death (PFS HR 0.2, $P=0.01$; OS HR 0.2, $P=0.03$). In the adjuvant cohort, landmark ctDNA positivity at 3 months post-surgery prior to immunotherapy, was 35% and identified patients with significantly inferior outcomes, with a >3-fold increase for the risk of distant metastasis or death (DMFS HR 3.8, $P=4.95 \times 10^{-3}$; OS HR 4.1, $P=3.61 \times 10^{-3}$). Longitudinal monitoring further established that any $\geq 20\%$ increase in ctDNA during adjuvant treatment was highly prognostic of poor survival (DMFS HR 3.0, $P=0.01$; OS HR 3.5, $P=0.02$). These molecular increases identified recurrences a median of 212 days prior to radiographic detection. The clinical necessity of ultrasensitive assays was underscored by the fact that 71% of these early detections occurred at ultra-low levels below 100 PPM. Real-time variant tracking revealed mutations druggable mutations such as BRAF V600E. **Conclusions:** Detection of MRD with PPM sensitivity represents a major advance in treatment monitoring for both unresectable and completely resected melanoma. Early on-treatment ctDNA decreases identify responders in advanced disease, while postoperative ctDNA positivity identifies adjuvant patients at highest relapse risk. Early MRD-based detection of loco-regional or distant relapse enables timely adaptation of therapeutic strategies. Research Sponsor: Personalis.

Linking T-cell receptor dynamics to outcomes in neoadjuvant-treated melanoma.

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Background: Clinical Stage III (cSIII) melanoma patients are at high risk of recurrence following therapeutic lymph node dissection (TLND) and adjuvant therapy. Neoadjuvant immunotherapy based regimens have shown promising results in this setting, with pathological response being the best predictor of recurrence free survival (RFS) and distant metastases free survival (DMFS). T-cell Receptor (TCR) abundance and clonality are being explored as biomarkers. **Methods:** In the phase II NeoACTIVATE (NCT03554083) trial, patients were treated based on BRAF status with 12 weeks of neoadjuvant atezolizumab, vemurafenib and cobimetinib (Arm A, BRAF-mutated) or atezolizumab and cobimetinib (Arm B, BRAF wildtype), followed by TLND and 6 months adjuvant atezolizumab. TCR sequencing (n=23) was performed on the pretreatment involved lymph node (iLN) and on the same node, along with an adjacent uninvolved node (uiLN) after TLND. The fraction productive of T cells (fpTC) was defined as the percentage of in-frame TCR sequences (capable of encoding a functional expressed receptor protein) of all TCR sequences identified. Simpson Clonality Index (SCI) was used to measure relative abundance of specific clones, with a higher score indicating a more monoclonal repertoire. Comparisons were made using the Wilcoxon Rank Sum test. **Results:** 30 patients were enrolled, 15 in each arm. 2 patients were not operated on, and one did not receive adjuvant treatment, leaving 27 patients for outcome analysis. 3-year RFS was 55.6% (95% CI 9.5%–77.8%), median of 62.2 months (95% CI 19–NR); DMFS was 64.3% (95% CI 48%–86.3%), median 62.2 months (95% CI 33.9–NR). The fpTC was higher in the pretreatment iLN for those without an RFS event (p=0.04) with a trend in the uiLN as well (p=0.06). Patients without a DMFS event had a higher fpTC in the uiLN (p=0.03) but not in the iLN. The SCI was significantly higher only in the post treatment iLN for patients without an RFS event (p=0.03) and was not significantly different when compared based on DMFS status. When performing pairwise comparisons of nodes based on recurrence status, we found that patients who did not suffer an RFS event had a significantly higher SCI in the post treatment iLN compared to the uiLN (p=0.02). **Conclusions:** Neoadjuvant immunotherapy and targeted therapy for cSIII melanoma can lead to durable RFS. Higher pretreatment fpTC as well as higher post-treatment iLN TCR clonality were both associated with improved RFS. These data indicate that TCR repertoire characteristics within iLN and uiLN may reflect differential immune responses to neoadjuvant therapy and could inform future studies evaluating biomarkers to stratify risk of recurrence and allow personalization of therapy. Clinical trial information: NCT03554083. Research Sponsor: Stand Up to Cancer-Genentech Catalyst Research Grant; SU2C-AACR-CT1017; Mayo Clinic Center for Clinical and Translational Science (cCaTS).

	fpTC		Simpson Clonality Index	
	RFS event	DMFS event	RFS event	DMFS event
Pretreatment iLN	0.04	0.12	0.43	0.11
Posttreatment iLN	0.09	0.09	0.03	0.12
uiLN	0.06	0.03	0.79	0.48
Δ iLN (post-pre)	0.79	0.37	0.07	0.41
Δ posttreatment iLN – uiLN	0.21	0.21	0.02	0.08

Surgical de-escalation in high-risk resectable melanoma with major pathologic response (MPR) after neoadjuvant immune checkpoint inhibition (ICI).

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Background: Neoadjuvant ICI renders MPR in 50–60% of resectable Stage III/IV melanoma. Early data illustrated the ability to de-escalate surgery in cases of MPR in the index lymph node (ILN). However complete lymph node dissection (CLND), a procedure with considerably morbidity, remains the standard of care. Real-world data demonstrating the ability to de-escalate surgery while maintaining disease control, can inform optimal practice. **Methods:** In our retrospective study performed at two academic institutions (MGB/DFCI), patients with resectable, macroscopic Stage III/IV cutaneous melanoma treated with neoadjuvant ICI were identified. Pre-treatment fiducial placement was routinely performed in cases of macroscopic nodal disease to facilitate index node excision (INE). Data pertaining to treatment course, anti-tumor outcomes, and safety were collected. Signatera ctDNA was evaluated as a non-invasive biomarker of early response. **Results:** From 2020–2025, 126 patients received neoadjuvant ICI: 60 anti-PD-1 monotherapy, 62 ipilimumab/nivolumab (I/N) and 4 nivolumab/relatlimab (N/R). The majority had macroscopic stage III disease (95%) and completed the full neoadjuvant course (86%). Ten patients (8%) did not undergo surgery (clinical CR, n = 3; toxicity, n = 1; progression, n = 6). Of the 116 (92%) who underwent surgery; 43 (37%) had an upfront TLND; 52 (45%) had an INE and 21 (18%) excision of N1c or M1a disease. After INE (n = 52), reflex CLND was performed in 7 (13%) all due to non-MPR. The MPR of the total cohort was 54% (n = 63) with a pCR rate of 51% (n = 59). The MPR/pCR rate was similar between ICI regimens. In the MPR cohort, 35 underwent an INE only whereas 17 underwent CLND; the remainder had excision of N1c/M1a disease. Post-operatively, 15 required drain placement, of whom 2 had an INE. Adjuvant ICI was utilized in 23 patients, the majority receiving peri-operative pembrolizumab (n = 20). After a median follow-up of 15.5mths (3.2–68.7mths), in those who underwent surgery, 20% (23/116) have recurred; 3 with a MPR (INE, n = 1; excision, n = 2). Of these, 2 were distant metastases with no nodal recurrence. Notably, 33 patients had pre-operative ctDNA results (Signatera). At the time of surgery, ctDNA was undetectable in the majority of MPR patients (19/20), while the majority of non-MPR patients remained detectable (8/13). Pre-surgery ctDNA assessment prognosticated RFS for the 20 patients who were detectable at baseline (p = 0.035) with ctDNA clearance associated with both MPR and improved RFS. Updated clinical and ctDNA data will be presented at the meeting. **Conclusions:** Similar to published data, patients with a MPR had low rates of recurrence, with no difference between those who underwent INE compared to upfront CLND. Pre-operative ctDNA levels, particularly ctDNA clearance, correlate with clinical outcomes and may inform de-escalation strategies. Research Sponsor: None.

Microbiome-derived bile acids and association with dietary fiber intake to anti-tumor responses in patients with melanoma receiving immune checkpoint blockade (ICB).

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Background: Multiple studies have now linked high fiber diet (HFD) and outcomes with ICBs, however, the clinical actionability and mechanistic basis of this association remain incompletely defined. We investigated whether microbiome-derived metabolites may function as potentially actionable mediators of this interaction. **Methods:** Blood samples from two studies in patients (pts) with melanoma starting ICB were utilized: (1) longitudinal samples from the prospective Phase II DIET clinical trial (NCT04645680), in which pts with melanoma starting ICBs were randomized (2:1) to a HFD [up to 50 g fiber/day (d)] or a healthy control diet (HCD, 20 g/d) and (2) baseline samples from an observational prospective diet/microbiome ICB-treated melanoma cohort. Untargeted and targeted metabolome analysis of bile acids and tryptophan-metabolites were performed via liquid chromatography (LC)- and short-chain fatty acids (SCFAs) via gas chromatography (GC)-mass spectrometry. Circulating metabolite levels were compared between pre- and on-treatment samples in DIET trial by arm and between pts with response (R, assessed by RECIST 1.1) and no response (NR) in the observational cohort. **Results:** A total of 110 pts were included: 45 DIET study pts randomized to HFDI (n=30) vs HCD (n=15), and 65 pts in the observational cohort. As previously reported, response rates were numerically improved in HFD (77% vs 29% in HCD (p=0.06), in the DIET study. Untargeted metabolomics yielded 38 metabolites with statistically significant differences (nominal p<0.05) in change over time in the HFD arm vs in the HCD arm, with notable reductions in glycine conjugated bile acids with HFD. Bile acid biosynthesis metabolite sets were the most significantly differentially enriched (p<0.01, enrichment ratio >5.0). Targeted metabolomics showed that HFD reduced secondary-to-primary bile acid ratios (deoxycholic acid [DCA] to cholic acid [CA], p=0.02) as well as glycine- and taurine-conjugated to unconjugated bile acid ratios (glycocholic acid [GCA] to CA, taurocholic acid [TCA] to CA, both p=0.03). In the observational cohort, GCA/CA and TCA/CA ratios were significantly lower in R vs NR (p=0.03 and p=0.04, respectively) whereas no difference was seen in DCA/CA ratios. SCFAs and tryptophan metabolites showed neither temporal changes in DIET trial nor response associations in the observational cohort. **Conclusions:** We observed that bile acid deconjugation, a key microbiome-mediated step, was reduced by an HFD intervention and inversely associated with response to ICB in an observational cohort. Building on prior work demonstrating that additional HFD-mediated secondary bile acids can impair T cell function, microbial bile acid metabolism emerges as a potential determinant of anti-tumor response targetable through HFD. Clinical trial information: NCT04645680. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Outcome of adjuvant BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600K– compared to V600E-mutated melanoma.

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Background: Patients with resected stage III BRAF V600 mutated melanoma can be treated with combined dabrafenib and trametinib (D/T) with significant improvement of recurrence-free survival (RFS). The results of the pivotal Combi-AD study showed overall survival (OS) improvement only for patients with BRAF V600E mutations, while for V600K there was even an OS impairment as compared to placebo, although not statistically significant. **Methods:** We analysed EUMelaReg data for patients with adjuvant D/T therapy for resected stage III melanoma. Only patients with V600E and V600K mutations were selected, where n=93 from a total of 1,033 patients (9.0 %) harboured V600K. **Results:** Demographics of patients with V600K mutations differed significantly for age (67 vs. 58 years, $p < 0.001$) and a higher proportion of males (67.0% vs. 54.6%, $p=0.03$) at baseline. Other baseline variables, including substage, were not significantly different. One year of treatment was completed in 51.6% for V600K, and 62.8% for V600E, respectively, while with V600K mutations 22.6% of the patients stopped for toxicity (vs. 18.8% with V600E), and 10.8% for disease recurrence (vs. 6.9%), which was not statistically significant. After a median follow-up of 41.7 (V600K) and 41.2 (V600E) months, Kaplan-Meier analysis estimated 4-year overall survival of 75.7% for V600K compared to 77.8% for V600E. The 4-y-RFS estimates were 48.3% for V600K and 47.0% for V600E. These differences were not statistically significant. Cox regression analysis revealed no different results when adjusted for demographic co-variables, including age and sex, for RFS and OS, respectively. **Conclusions:** It appears that V600E and V600K mutations are not associated with a different outcome from adjuvant treatment with combined D/T. The findings offer no explanation for differences found in the Combi-AD trial, although part of these differences also resulted from a different natural course of V600K mutated melanomas the placebo group. A longer follow-up will help to further confirm these results and also analyse the possible role of further treatments in the metastatic setting. Research Sponsor: None.

Baseline characteristics and outcome.			
	V600E(N=940)	V600K(N=93)	P-value
SEX			0.035
Female	426 (45.3%)	31 (33.3%)	
Male	514 (54.7%)	62 (66.7%)	
AGE			<0.001
Mean (SD)	57.4 (13.8)	65.6 (11.9)	
Median [Min, Max]	58.0 [17.0, 90.0]	67.0 [28.0, 87.0]	
ECOG			0.1
0	846 (90.0%)	82 (88.2%)	
1	51 (5.4%)	8 (8.6%)	
2	5 (0.5%)	2 (2.2%)	
Baseline Stage			0.34
III	8 (0.9%)	1 (1.1%)	
IIIA	126 (13.4%)	7 (7.5%)	
IIIB	293 (31.2%)	29 (31.2%)	
IIIC	470 (50.0%)	54 (58.1%)	
IIID	43 (4.6%)	2 (2.2%)	
STAGE III DIAGNOSIS TYPE			0.96
Primary Diagnosis	679 (72.2%)	68 (73.1%)	
Relapse	260 (27.7%)	25 (26.9%)	
SUBTYPE			0.06
SSM	358 (38.1%)	26 (28.0%)	
NMM	315 (33.5%)	44 (47.3%)	
NOS	207 (22.0%)	18 (19.4%)	
MUP	49 (5.2%)	4 (4.3%)	
OUTCOME			
4-Year RFS (95%-CI)	0.47 (0.43; 0.51)	0.48 (0.38; 0.61)	0.94
4-Year OS (95%-CI)	0.78 (0.75; 0.81)	0.76 (0.65; 0.88)	0.94

Longitudinal monitoring for post-surgical molecular residual disease in patients with stage I–IIIB melanoma using a whole-genome sequencing–based ctDNA assay.

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Background: Circulating tumor DNA (ctDNA) is a novel biomarker for detecting molecular residual disease (MRD) and monitoring recurrence risk in melanoma. Personalized, tumor-informed ctDNA assays may enable highly sensitive and specific longitudinal detection of disease burden following curative-intent surgery. Here, we evaluate the prognostic value of whole-genome sequencing (WGS)-based ctDNA detection in patients with resected stage I–IIIB melanoma. **Methods:** This was a retrospective analysis of residual samples from a deidentified real-world dataset. Clinicopathologic information was collected from Natera's commercial database under an IRB-approved protocol (#20-049-ALL). Patients with stage I–IIIB melanoma who underwent surgery between March 2018 to May 2023 were included. Whole genome-based ctDNA assays (Signatera Genome, Natera, Inc.) were designed from the respective patients' matched tumor and normal WGS data. ctDNA was subsequently tracked in the patients' longitudinal blood samples, which were collected postoperatively until recurrence/end of follow-up. The correlation between ctDNA status post-definitive treatment and recurrence-free survival (RFS) was assessed using Cox regression analysis with a time-dependent covariate and the Kaplan-Meier method. **Results:** A total of 103 patients with stage I–IIIB melanoma and residual material available for testing were included with a median of 6 tests per patient (range: 1–23) and a median of 91 days between ctDNA tests. Median follow-up was 25.1 months (range: 8.5–73.4). Stage distribution was: 1.9% (2/103) IA, 3.9% (4/103) IB, 7.8% (8/103) IIA, 39.8% (41/103) IIB, 20.4% (21/103) IIC, 8.7% (9/103) IIIA, and 17.5% (18/103) IIIB, and 38 patients received adjuvant treatment, with the majority 87% (33/38) receiving immunotherapy only. ctDNA results during the post-operative treatment window were available for 95 patients. Among the 15 patients who experienced recurrence after completion of definitive treatment, 12 (80%) were ctDNA-positive prior to or within 2-weeks of clinical recurrence (range: 99 days pre - 12 days post-imaging). Among patients who did not experience recurrence, 97.5% (78/80) were serially ctDNA-negative. ctDNA positivity at any time during post-definitive treatment was associated with significantly shorter RFS compared with persistent ctDNA-negativity (HR 55.3; 95% CI 18.7–163.3; $p < 0.0001$). Analyses are ongoing to characterize ctDNA dynamics (including quantification) and clinical outcomes in an expanded cohort. **Conclusions:** This analysis demonstrates the prognostic value of longitudinal post-operative ctDNA monitoring for the detection of recurrence in patients with stage I–IIIB melanoma using a WGS-based, personalized, tumor-informed assay with implications for optimizing surveillance and improving clinical outcomes. Research Sponsor: None.

Clinical validation of an AI-based prognostic assay for stage I-II cutaneous melanoma.

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Background: In early-stage cutaneous melanoma (CM), AJCC staging demonstrates limited ability to identify patients at elevated recurrence risk who may benefit from adjuvant therapy or intensified surveillance. We evaluated DiaSurv, an AI-based prognostic assay analyzing standard H&E whole-slide images (WSI) to refine risk stratification in stage I-II melanoma. **Methods:** DiaSurv was validated on a retrospective cohort of 456 stage I-II primary CM patients with 5-year follow-up at Gustave Roussy. The algorithm assigns high- or low-risk scores based solely on primary tumor WSI analysis. Kaplan-Meier analysis estimated 5-year recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS). Log-rank tests compared survival between risk groups. Multivariable Cox regression assessed independent prognostic value after adjusting for clinicopathological factors (Breslow thickness, ulceration, age, sex, tumor location, histological subtype, mitotic count). **Results:** Among 456 stage I-II patients (109 recurrences, 67 distant metastases, 57 deaths), DiaSurv classified 285 (62.5%) as low-risk and 171 (37.5%) as high-risk. Low-risk patients had significantly better 5-year outcomes compared to high-risk patients: RFS 92% vs 38% (HR = 7.71, 95%CI 4.86-12.23, $p < 0.001$), DMFS 94% vs 55% (HR = 10.39, 95%CI 5.31-20.36, $p < 0.001$), and OS 96% vs 71% (HR = 8.12, 95%CI 4.10-16.07, $p < 0.001$). In multivariable analysis, DiaSurv was independently associated with all endpoints (RFS: HR = 2.43, $p = 0.006$; DMFS: HR = 3.71, $p = 0.002$; OS: HR = 3.78, $p = 0.003$). In the clinically relevant stage I-IIA subgroup ($n = 368$), DiaSurv identified 86 patients (23.4%) with high-risk profiles despite favorable AJCC staging. These patients had markedly inferior outcomes compared to the 282 low-risk patients: 5-year RFS 71% vs 92% (HR = 4.85, $p < 0.001$), DMFS 77% vs 96% (HR = 5.48, $p < 0.001$), and OS 84% vs 96% (HR = 4.39, $p < 0.001$). The NPV of low-risk classification at 5 years in stage I-IIA was 92.2% for RFS, 96.5% for DMFS, and 96.5% for OS which is in line or superior to some commercially available gene-expression profiling assays. **Conclusions:** In early-stage melanoma (I-IIA), where adjuvant therapy is not currently standard, DiaSurv identifies nearly one-quarter of patients with a high-risk profile and significantly elevated recurrence rates. This AI-based assay provides actionable prognostic information beyond AJCC staging to guide decisions regarding adjuvant therapy consideration, sentinel lymph node biopsy, and surveillance intensity. Research Sponsor: None.

Neoadjuvant anti-PD-1 prolgolimab monotherapy in resectable high-risk melanoma: Pathologic response and early event-free survival in a prospective single-arm phase II CRISTINA study.

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Background: In resectable high-risk melanoma, neoadjuvant anti-PD-1 aims to exceed the ~40% MPR benchmark; while combos may deepen response, they add tox, complexity, and cost. Recently reported data for prolgolimab+nurulumab (N = 205) showed pCR 38.5%, near-CR 4.4%, motivating evaluation of prolgolimab mono as a simpler potentially non-inferior approach. **Methods:** MelPRO-0322 (CRISTINA; NCT06299878) is a prospective single-arm study in resectable stage IIIB–IV melanoma: 3 neoadj doses of prolgolimab followed by radiologic assessment followed by surgery (regional lymphadenectomy or M1a-equivalent metastasectomy). Central pathology used INMC criteria. Interim analysis after full enrollment and pathology assessment. **Results:** Pt characteristics (N = 82): Median age 61.5 y (range 23.2–87.3); median BMI 28.2 kg/m² (21.0–46.5). Females 47 (57.3%); ECOG 0/1: 56 (68.3%)/26 (31.7%). Primary melanoma: cutaneous or UPO 73 (89.0%), acral 7 (8.5%), mucosal 2 (2.4%). Stage: IIIB 12 (15.8%), IIIC 54 (71.1%), IIID 3 (3.9%), IV 7 (9.2%); stage missing 6 (7.3%). BRAF V600 mut in 43/74 (58.1%). Median neoadj tx duration 28 d (0–108). Median time from start of neoadj tx to surgery 67 d (29–176). LND/resection performed in 66/82 (80.5%). RECIST 1.1 (ITT, N = 82): ORR 23 (28.0%); CR 5 (6.1%), PR 18 (22.0%), SD 27 (32.9%), PD 24 (29.3%); not evaluable 8 (9.8%). Pathologic response (ITT, N = 82): pCR 28 (34.1%), near-pCR 7 (8.5%), MPR 35 (42.7%); pathology not available in 16 (19.5%). Among evaluable (n = 66): pCR 42.4%, MPR 53.0%. Achieving MPR correlated with better radiologic response by RECIST (p < 0.001) and lower nodal tumor burden (fewer positive nodes; p = 0.012). With a median follow-up of 11.8 mo by reverse KM (95% CI 7.5–17.4), EFS in the ITT cohort (N = 82; events = relapse/progression/death) showed 20 events with median EFS 32.2 mo (95% CI not estimable) and RMST 29.8 mo (SE 4.71). In the pathology-evaluable set (n = 66), EFS was longer in pts achieving MPR vs non-MPR/PD (log-rank p = 0.002): median EFS 19.3 mo for non-MPR/PD (n = 31; 10 events) vs not reached for MPR (n = 35; 2 events); RMST 20.3 vs 30.1 mo. In exploratory multivariable Cox models, MPR remained strongly associated with improved EFS (HR 0.043, 95% CI 0.003–0.684; p = 0.026), while higher PLT/LYM ratio (HR 1.029, 95% CI 1.006–1.052; p = 0.015) and male sex (HR 8.74, 95% CI 1.12–68.21; p = 0.039) showed associations with inferior EFS, while time from neoadj start to surgery and receipt of adjuvant therapy were not associated with EFS. **Conclusions:** NST prolgolimab monotherapy achieved MPR rates above the historical benchmark with encouraging early EFS. MPR—especially pCR—was strongly associated with improved EFS, with no progressions observed among pCR pts. In exploratory analyses, neither time from neoadj start to surgery nor receipt of adjuvant therapy appeared to materially affect EFS. Clinical trial information: NCT06299878. Research Sponsor: None.

Non-melanoma skin cancer–related mortality in the United States: A 25-year CDC WONDER analysis.

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Background: Non-melanoma skin cancer (NMSC), including basal cell and squamous cell carcinoma, is the most common malignancy worldwide, with rising incidence due to ultraviolet exposure and aging populations. Analyzing two decades of CDC WONDER data provides insights into mortality disparities and geographic variation. **Methods:** Using the CDC WONDER database for adults aged ≥ 25 , we analyzed age-adjusted and crude mortality rates (AAMRs and CMRs) per 100,000 for NMSC (ICD-10 C44.0 to C44.9) by year, sex, race/ethnicity, and geography. Joinpoint regression (version 5.4) estimated average annual percentage change (AAPC) and annual percentage change (APC) with 95% confidence interval (CIs). **Results:** From 1999–2023, NMSC caused 118,792 deaths (female: 36,921; male: 81,871), most occurring at the Decedent's home (37.7%). The AAMR rose 41% from 1.92 in 1999 to 2.72 in 2023 (AAPC: 1.55%; $p < 0.001$), with significant increases in 2005–2019 (APC: 1.88, 95% CI: 1.45 to 2.30) and 2019–2023 (APC: 4.92, 95% CI: 2.78 to 7.09). Adults ≥ 65 had the highest CMR (8.59), rising 1.57% annually ($p < 0.001$). Men consistently had higher AAMR about three times that of women in 1999 (3.24 vs. 1.03), and the gap remained in 2023 (4.35 vs. 1.50). Non-Hispanic (NH) Whites had the highest AAMR, rising 2.06% annually ($p < 0.001$), while NH Asians or Pacific islanders had the lowest with a slight decline (-0.19%; $p = 0.81$). Regionally, the West had the fastest rise in AAMR at 1.68% annually ($p < 0.001$), while the Midwest had the slowest at 1.24% ($p < 0.001$). Mortality in rural areas (AAMR: 2.35) rose faster (1.41%; $p < 0.001$) than in urban populations (AAMR: 1.93; 0.80%). Oklahoma and West Virginia ranked highest in the top 90th percentile. **Conclusions:** Mortality from NMSC has risen in the United States over the past two decades. However, significant demographic and geographic disparities in mortality continue, emphasizing the need for equitable healthcare access and targeted interventions, particularly among males, NH Whites, and high-burden states and regions. Research Sponsor: None.

Deaths and AAPC for trends related to non-melanoma skin cancer from 1999 to 2023.

Variable	Deaths	AAPC (1999-2023) with CI
Overall	118,792	1.55 (1.01 to 2.09)
Male	81,871	1.29 (0.71 to 1.87)
Female	36,921	1.54 (1.10 to 1.99)
NH White	108,523	2.06 (1.54 to 2.60)
NH Black	4,797	-0.67 (-1.74 to 0.40)
Hispanic	3982	0.76 (0.48 to 2.02)
NH Asians	1,105	-0.20 (-1.87 to 1.51)
Midwest	25,260	1.25 (0.66 to 1.83)
West	27,192	1.54 (1.03 to 2.05)
South	46,442	1.64 (1.12 to 2.17)
Northeast	19,898	1.69 (0.90 to 2.49)

Anti-tumor activity of FF-10850 (liposomal topotecan) in patients with advanced Merkel cell carcinoma.

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Background: FF-10850 is a novel liposomal topotecan with increased intratumoral accumulation and robust pre-clinical activity. The prolonged $t_{1/2}$ (27 hours) supported a twice-monthly dosing schedule in the first in human dose finding trial (NCT04047251), with anti-tumor activity demonstrated in heavily pre-treated patients (pts) with solid tumors; pts remained on study up to 20 months. Common AEs were nausea and fatigue, with manageable hematologic toxicity. A Merkel cell carcinoma (MCC) pt maintained a PR for 33 weeks after progression on prior topotecan and PD-1-directed therapy. Because MCC pts who have progressed or are ineligible for anti-PD-1 therapy have few effective systemic treatment options, we evaluated FF-10850 in an MCC expansion cohort. Results are reported for all MCC pts on study. **Methods:** Pts ≥ 18 years with advanced MCC were treated with FF-10850 2 mg/m² IV on Days 1 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. Pts must have progressed on or have been ineligible for all standard therapy and treated with or ineligible for PD-1 based therapy. In expansion, pts who progressed on camptothecin therapy within 6 months were excluded; prior etoposide was allowed. Response was assessed by RECIST 1.1. **Results:** 12 pts [8M/4F; median age 70 (58–84), ECOG PS 0 (5)/PS 1 (7)] were treated. Baseline disease (n): unresectable stage IIIA (1), IV (10)/IVB (1). The median # of prior therapies was 1 (0–5), 1 had prior topotecan; 2 pts had no prior therapy, one due to rheumatoid arthritis (RA) and another due to solid organ transplant. Common drug-related AEs were anemia (50%), nausea (50%), fatigue (42%), and thrombocytopenia (25%). One pt each had related Gr 3 anemia and neutropenia; no related Gr 4 toxicity was observed. Three pts had infusion-related reactions; one that did not restart treatment. Two pts left study before RECIST evaluation: one withdrew to hospice care, and one died of an unrelated MI after the first dose of FF-10850 following a clinically significant anti-tumor response 2 weeks after the single dose. Best overall response in 10 RECIST evaluable pts was: 1CR, 1 PR, 4 SD and 4 PD; disease control rate (CR+PR+2 consecutive SD) was 50%. Three pts remain on study: one that achieved a CR after 2 cycles maintains CR after 14 cycles, and 2 pts maintain durable SD after 6–12 cycles. The median (range) time on study was 9.4 (3.1–50.9) weeks; median PFS and OS were 7.5 (95% CI:1.2–NR) and 10.7 (95% CI:2.1–NR) months, respectively. **Conclusions:** FF-10850 has demonstrated encouraging preliminary activity in both pre-treated and treatment naïve MCC. The regimen of 2 mg/m² every 2 weeks is tolerable with manageable hematologic side effects. PFS and OS in this small study compare favorably with that reported for cytotoxic agents in 2nd line pts of 3 and 10 months, respectively. Further exploration of FF-10850 in MCC may offer a novel treatment option for this rare disease. Clinical trial information: NCT04047251. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

Incidence of new keratinocyte cancers during pembrolizumab in resectable cutaneous squamous cell carcinoma: The De-Squamate study.

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Background: Patients with advanced cutaneous squamous cell carcinoma (cSCC) or basal cell carcinoma (BCC) frequently develop new primary keratinocyte cancers (KCs) due to field cancerisation. Emerging data suggest immune checkpoint inhibitors (ICIs) may reduce this burden. We evaluated the incidence of new KCs in a prospective immunotherapy cohort. **Methods:** De-Squamate was a prospective phase II trial evaluating neoadjuvant pembrolizumab using a response-adapted management strategy in resectable cSCC. As part of protocol-mandated safety monitoring, all new primary KCs were prospectively recorded as adverse events. Events included histologically confirmed new cSCCs, BCCs, or other keratinocyte malignancies diagnosed and resected during or after treatment. Person-time was calculated for periods on pembrolizumab and off treatment. Incidence rates were calculated per person-year. Rate ratios were estimated using crude analyses and adjusted models accounting for within-patient clustering. **Results:** Among the 27 patients, 54 new KCs were recorded. Patients contributed 14.9 person-years on pembrolizumab and 33.4 person-years off treatment. KC incidence was lower during active therapy than after discontinuation (73.7 vs 143.6 per 100 person-years). The unadjusted rate ratio for new KC development off treatment versus on treatment was 1.95 (95% CI, 1.01–3.75). Adjusted analyses using negative-binomial modelling produced similar estimates (adjusted rate ratio 1.94; 95% CI, 0.64–5.89). Reductions were most pronounced for BCCs, with more modest effects observed for new primary cSCCs (table 1). **Conclusions:** In this prospective cohort, new KCs occurred at approximately twice the rate after discontinuation of pembrolizumab compared with during active therapy. These findings support the hypothesis that ICIs may suppress carcinogenesis within chronically damaged skin fields. Larger studies are needed to clarify the potential immunopreventative effect of ICIs in patients with field-driven KCs. Clinical trial information: NCT05025813. Research Sponsor: MSD.

Incidence of new keratinocyte cancers by treatment exposure.				
Outcome	On Pembrolizumab	Off Pembrolizumab (Follow-up)	Unadjusted Rate Ratio† (95% CI)	Adjusted Rate Ratio‡ (95% CI)
Person-years	14.9	33.4	–	–
All keratinocyte cancers	11 events0.74 / PY	43 events1.29 / PY	1.95 (1.01–3.75)	1.94 (0.64–5.89)
Cutaneous SCC (new primaries)	6 events0.40 / PY	10 events0.30 / PY	0.75*	–
Basal cell carcinoma	5 events0.34 / PY	38 events1.14 / PY	3.35*	–

†Off-treatment vs on-treatment.

‡Adjusted for patient-level clustering using negative-binomial model.

*Crude comparison shown; formal adjusted estimates limited by small event numbers.

Early burden reduction after two doses of cemiplimab in advanced non-melanoma skin cancer.

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Background: Advanced non-melanoma skin cancers (NMSC) frequently impose a high disease-related burden—severe pain, ulceration, intensive wound care—particularly in older and frail patients (pts). While cemiplimab has established antitumor activity, early pts-centered clinical benefit prior to first radiologic evaluation is under-described in routine practice. We quantified early changes in key burden domains after 2 infusions. **Methods:** A retrospective analysis was performed in a real-world cohort of pts with locally advanced/metastatic NMSC treated with cemiplimab. Assessments at T0 (≤ 7 days pre-treatment) and T1 (day 35–49; after 2 infusions). Pain intensity (0–10 Numeric Rating Scale, NRS), wound-care frequency (dressing changes/week), and analgesic exposure were extracted from structured clinical/nursing documentation; opioid exposure was quantified as daily morphine milligram equivalents (MME) using standard conversion. Primary endpoint: meaningful early pain benefit at T1 (≥ 2 -point NRS decrease without analgesic escalation). Other endpoints: opioid de-escalation, wound-care reduction (≥ 2 fewer dressing changes/week), and a pragmatic early-burden composite (improvement in ≥ 2 of: primary pain benefit; opioid de-escalation; wound-care reduction). Paired Wilcoxon signed-rank and McNemar tests were used. Infection status summarized. Confounding-restricted sensitivity analyses excluded pts receiving RT/surgery within 8 weeks of treatment initiation. **Results:** 53 pts included; median age 80yr (IQR 71–88); 81% locally advanced disease; ECOG 0–1 56%. Baseline burden: median pain NRS 7 (IQR 6–8); baseline opioid use 60%; wound-care frequency median 4/week; ulceration ≥ 2 64.2%. At T1 median pain NRS improved to 3 (IQR 2–4) (median $\Delta -3$; $p < 0.001$). The primary endpoint was achieved in 83% (44/53; 95% CI 70.8–90.8). The proportion of pts receiving opioids decreased from 60% (32/53) at T0 to 22.6% (12/53) at T1 ($p = 0.00024$). Median daily MME decreased from 20 mg (IQR 0–33) to 0 mg (IQR 0–14) ($p < 0.001$). Among baseline opioid users ($n = 32$), 100% reduced dose and/or discontinued opioids by T1 (32/32; 95% CI 88.6–100). Wound-care frequency decreased from median 4/week to 1/week ($p < 0.001$), with wound-care reduction ≥ 2 /week in 67.9% (36/53). The pragmatic early-burden composite was met in 79.2% (42/53). At first radiologic evaluation (median 91 days), RECIST evaluable in 51 pts; ORR was 76.4% (39/51) and disease control was 96.2% (50/52). Any immune-related AE occurred in 34% (18/53), with ≥ 3 in 1.9% (1/53). Infection decreased from 43% to 3.8% at T1. **Conclusions:** In an elderly, frail real-world population with NMSC and high supportive-care needs, cemiplimab was associated with rapid, meaningful early clinical benefit after two doses. Early burden endpoints may complement radiologic response to better capture patient-centered benefit and inform supportive-care planning in routine pathways. Research Sponsor: None.

Using stage-matched genomic analysis to support molecular similarity of unknown-primary Merkel cell carcinoma and identify ARID1B as a prognostic marker.

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Background: Merkel cell carcinoma (MCC) can present as nodal disease without an identifiable cutaneous primary, termed unknown-primary MCC (UP-MCC). UP-MCC has been reported to have distinct clinical outcomes compared with stage-matched known-primary MCC (KP-MCC), but its underlying biology is poorly understood. We compared the genomic landscapes of UP-MCC and stage IIIB KP-MCC and evaluated whether specific alterations are associated with survival in UP-MCC. **Methods:** A retrospective analysis was performed using the Dana-Farber Cancer Institute MCC repository (2012–2023). UP-MCC was defined as pathologically confirmed MCC without a detectable cutaneous primary; the comparator cohort comprised stage IIIB KP-MCC. Tumors underwent targeted next-generation sequencing (OncoPanel; 447 genes), and tumor mutational burden (TMB) and Merkel cell polyomavirus (MCPyV) status were recorded. Gene-level alteration frequencies were compared using Fisher's exact test, and MCC-specific survival (MCCSS) and overall survival (OS) were assessed using Kaplan-Meier and Cox proportional hazards models. **Results:** Fifty-two patients were included (20 UP-MCC, 32 KP-MCC). UP-MCC and KP-MCC showed highly overlapping genomic landscapes, including similar distributions of MCPyV status, TMB, and recurrent driver alterations, with no gene-level differences detected. Within UP-MCC, *SETBP1* alterations were associated with worse MCCSS (HR 6.74; 95% CI, 1.33–34.07; $p=0.030$), while *ARID1B* alterations identified a markedly high-risk UP-MCC subgroup with inferior MCCSS (HR 27.1; 95% CI, 3.02–243.11; $p<0.001$) and OS (HR 16.9; 95% CI, 1.9–152.9; $p=0.004$). All five *ARID1B*-altered UP-MCC patients died of MCC, compared with 4 of 15 *ARID1B*-wild-type; in multivariable analysis, *ARID1B* remained an independent predictor of worse MCCSS ($p=0.003$), whereas *SETBP1* did not ($p=0.313$). In KP-MCC cohort, *ARID1B* was not significantly associated with MCCSS ($p=0.1883$). **Conclusions:** Stage-matched genomic profiling demonstrates molecular similarity between UP-MCC and KP-MCC, supporting the hypothesis that UP-MCC often represents regressed primary cutaneous tumors. Within UP-MCC, *ARID1B* alterations identify a high-risk subgroup with markedly inferior MCCSS, suggesting that targeted genomic profiling may refine risk stratification, surveillance strategies, and clinical trial design for patients with UP-MCC and these findings warrant validation in larger, multi-institutional cohorts. Research Sponsor: None.

Baseline characteristics of UP-MCC and stage IIIB KP-MCC cohorts.

Parameter	UP-MCC (n=20)	KP-MCC stage IIIB (n=32)	p-value
Age, mean (SD), years	68.2 (12.9)	74.2 (12.1)	0.204
Male sex, n (%)	13 (65.0)	26 (81.3)	0.323
MCPyV positive, n (%)	11 (55.0)	15 (46.9)	0.776
High TMB, n (%)	8 (40.0)	11 (34.4)	0.909
TMB, mean (SD), mut/Mb	14.1 (13.9)	18.7 (24.6)	0.572

SD= Standard Deviation.

Efficacy and safety of cosibelimab 800 mg every 2 weeks for locally advanced cutaneous squamous cell carcinoma: Updated follow-up from a pivotal study.

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Background: Cosibelimab, a high-affinity programmed death ligand-1 (PD-L1)-blocking antibody, is approved by the US Food and Drug Administration (FDA) at a recommended dose of 1200 mg every 3 weeks (Q3W) for the treatment of adults with locally advanced or metastatic cutaneous squamous cell carcinoma (laCSCC or mCSCC) who are not candidates for curative radiation or surgery. The CSCC expansion cohort of the pivotal open-label Phase 1 study (NCT03212404) evaluated cosibelimab 800 mg every 2 weeks (Q2W) in patients with laCSCC or mCSCC and 1200 mg Q3W in patients with mCSCC. Results through March 2023 demonstrated robust and sustained responses with cosibelimab 800 mg Q2W. The 800-mg Q2W and 1200-mg Q3W regimens are considered similar based on pharmacokinetic criteria outlined by the FDA for alternative PD-L1-blocking antibody dosing regimens. We present new follow-up data for the 800-mg Q2W laCSCC cohort. **Methods:** Eligible patients were ≥ 18 years old and had an Eastern Cooperative Oncology Group performance status of 0 or 1 and unresectable laCSCC not amenable to local therapy. Cosibelimab 800 mg was administered intravenously on Day 1 of each 14-day cycle until complete response, worsening disease progression, toxicity, or clinical deterioration. The primary endpoint was objective response rate (ORR; best overall response: complete or partial) by independent central review per RECIST V1.1; duration of response (DOR) was the key secondary endpoint. Follow-up data presented are from investigator assessment. Other secondary endpoints included safety. **Results:** By the January 31, 2025, data cutoff, 64 patients with laCSCC received ≥ 1 dose of cosibelimab 800 mg Q2W; their median (range) age was 77 (51–95) years, and 66% were male. Patients received a median of 29 (2–89) doses over a median duration of 60 (4–184) weeks. The ORR (95% confidence interval) was 50% (37%, 63%), including 17 complete and 15 partial responses; over a median follow-up duration of 31 (1–59) months the median DOR was not reached. Treatment-emergent adverse events (TEAEs) were reported in 61 (95%) patients and considered treatment-related in 50 (78%) patients; none were fatal. The most common AEs were anemia and diarrhea, recorded in 17 (27%) patients each. Grade ≥ 3 TEAEs were reported in 26 (41%) patients and considered treatment-related in 7 (11%). Hypertransaminasemia, in 2 (3%) patients, was the only serious treatment-related TEAE reported. Immune-related AEs (irAEs) were recorded in 22 (34%) patients; Grade ≥ 3 irAEs occurred in 1 (2%) patient and were dermatologic in nature (maculopapular and pruritic rashes) and considered treatment-related. **Conclusions:** Responses to treatment with cosibelimab 800 mg Q2W remained robust and durable with stable ORR after continued follow-up in a larger cohort of patients with laCSCC, with no new safety signals identified. Clinical trial information: NCT03212404. Research Sponsor: Sun Pharma.

Final analysis of the efficacy and safety of oral S-1 for locally advanced or recurrent/metastatic cutaneous squamous cell carcinoma: A multicenter retrospective study.

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Background: Anti-PD-1 antibodies are the standard systemic therapy for advanced cutaneous squamous cell carcinoma (cSCC). Recent clinical trials have reported objective response rates (ORRs) of 44–58.3% in locally advanced (LA) disease and 35.2–45.2% in recurrent or metastatic (R/M) disease, with grade ≥ 3 adverse events occurring in 31.1–34.5% of patients. S-1, an oral fluoropyrimidine, has been suggested as an alternative option with potential advantages, including favorable clinical response, lower toxicity, feasibility of outpatient initiation, and substantially lower cost; however, evidence remains limited to small case series. We therefore conducted a large multicenter retrospective study to evaluate the real-world efficacy and safety of S-1 in patients with advanced cSCC. **Methods:** This multicenter retrospective study included patients with LA or R/M cSCC who received oral S-1 between 2007 and 2024. S-1 was administered for 28 consecutive days, followed by 14 days off (one cycle). The primary endpoint was ORR assessed according to RECIST criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and toxicity. Exploratory subgroup analyses were performed based on concomitant radiotherapy use and primary tumor site. **Results:** A total of 150 patients were analyzed (LA, $n = 44$; R/M, $n = 106$). The median age was 76 years (interquartile range, 67–83), and ECOG performance status was 0–1 in 127 patients (85%). Fifty-four patients (36%) had received prior systemic treatment. Among the R/M cohort, 59 patients had nodal metastasis and 47 had distant metastasis. The median follow-up was 13.4 months (LA, 15.0 months; R/M, 12.7 months). ORR was 55% (95% confidence interval [CI], 39–70) in the LA cohort and 40% (95% CI, 30–50) in the R/M cohort. The 12-month PFS and OS rates were 80% and 92% (95% CI, 63–90 and 76–97) in the LA cohort, and 41% and 62% (95% CI, 30–50 and 51–71) in the R/M cohort. Grade ≥ 3 adverse events occurred in 14% of patients, most commonly anemia ($n = 4$), thrombocytopenia ($n = 3$), neutropenia ($n = 3$), decreased appetite ($n = 3$), and oral mucositis ($n = 3$); no grade 5 events were observed. In exploratory analyses, patients receiving concomitant radiotherapy demonstrated higher ORR and PFS compared with those without radiotherapy, while OS was comparable between the groups. Tumors originating in the head and neck region were associated with superior ORR, PFS, and OS compared with other primary sites. **Conclusions:** Oral S-1 demonstrated antitumor activity comparable to that reported for anti-PD-1 antibodies, albeit without direct comparison, with a lower incidence of severe adverse events, suggesting its potential role in selected patients with advanced cSCC. Research Sponsor: None.

Circulating tumor DNA (ctDNA) as a biomarker for pathologic response and clinical outcomes in patients with cutaneous squamous cell carcinoma (CSCC) receiving neoadjuvant anti-PD-1 therapy.

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Background: ctDNA is a novel biomarker that can be used to evaluate recurrence and treatment response in multiple cancers. The utility of ctDNA in patients with CSCC receiving neoadjuvant immunotherapy (nIT) is unknown. **Methods:** In this retrospective study, we examined patients with CSCC who received nIT and had ctDNA assay available pre- and post- operatively. Positive ctDNA was defined as a value >0, and ctDNA sensitivity pre-operatively (pre-op) was reported in all patients. Patients with at least two ctDNA measurements pre-op were classified into two cohorts: cohort-A included patients whose ctDNA decreased; Cohort-B included patients whose ctDNA increased. Pathologic response (PR) was defined as complete (pCR) if 0% viable tumor [vt], major (mPR) if vt < or equal to 10%, and no-response (nPR) if vt >10%. The association between ctDNA kinetics during the pre-op period nIT and PR was analyzed using Fisher's exact test. During the post-op period, we used minimal residual disease (MRD) status defined by positive ctDNA measurement within 3 months post-op. Recurrence-free survival (RFS) (landmark analysis with time starting at post-MRD timepoint until recurrence, death or loss-to follow-up) was compared between patients who had detectable MRD (positive ctDNA within 3 months post-op) versus those who had undetectable MRD. **Results:** Forty nine patients were included of which 42 (85.7%) were male, 11 (22.4%) were immunosuppressed, and 31 (63.3%) had AJCC stage IV CSCC. The median follow-up time since starting nIT was 12.9 months. The ctDNA sensitivity at baseline (prior to starting nIT) was 79.6%. The median number of ctDNA collections per patient was 6 (range: 1, 21). Of the 49 patients who underwent surgery, 38 were eligible who had at least 2 ctDNA measurements pre-op. Cohort-A (35 patients) had higher cPR and mPR compared to cohort-B (3 patients) (p=0.05). When excluding 3 patients who did not have kinetic ctDNA changes (ctDNA value was 0 at all pre-op time points), ctDNA decrease was significantly associated with cPR and mPR (p= 0.03). For post-op period, patients with detectable MRD (n=5) had significantly lower RFS compared to those with undetectable MRD (median RFS 11.3 months vs. not reached, HR: 11.9; 95% CI: 2.2-65.8; p< 0.01)(Table). **Conclusions:** ctDNA changes and detectable MRD may be suitable biomarkers for pathologic response assessment and post-op period in patients with CSCC receiving nIT. Further research is essential to confirm these findings. Research Sponsor: None.

Recurrence-free survival according to MRD status.

MRD status	N	Median after 3-month post-op (95% CI) month	6-month RFS after 3-month post-op (95% CI) months	12-month RFS after 3-month post-op (95% CI) months	Hazard ratio (95% CI)
Negative	31	NA (NA, NA)	0.96 (0.89, 1)	0.89 (0.74, 1)	ref
Positive	5	11.3 (2.22, NA)	0.6 (0.29, 1)	0.3 (0.06, 1)	11.9 (2.2, 65.8)

Survival outcomes following resistance to immune checkpoint inhibition in advanced cutaneous squamous cell carcinoma.

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Background: Immune checkpoint inhibitors (ICI) are standard first-line therapy for advanced cutaneous squamous cell carcinoma (cSCC); however, 35% of patients experience disease progression. Evidence guiding optimal second-line management remains limited. We evaluated real-world outcomes of second-line treatment strategies in patients with cSCC resistant to ICI. **Methods:** A retrospective analysis of patients with unresectable locally advanced or metastatic cSCC treated with ICI monotherapy at two tertiary centres in Brisbane, Australia, was conducted. Patients with progressive disease (PD) were identified and classified as having primary resistance (PD < 4 months) or acquired resistance (PD ≥ 4 months). Second-line strategies included local therapy (LT - surgery and/or radiotherapy), systemic therapy +/- LT or best supportive care (BSC). Outcomes included progression-free survival from second-line initiation (PFS2), and overall survival (OS) using Kaplan–Meier estimates. **Results:** Seventy-four patients were identified. Median age was 74 years. Most patients had locoregionally advanced disease (77%), head and neck primary tumours (70%), ECOG performance status 0–1 (76%), and were immunocompetent (70%). Primary resistance occurred in 54% and acquired resistance in 46%, of which 21% progressed after ICI cessation. Locoregional progression was observed in 70% of patients, while 30% progressed with distant disease. Management of ICI resistance included LT (N = 32), systemic therapy +/- LT (N = 16), and BSC (N = 26). An objective response rate of 65% was observed in patients undergoing systemic therapy +/- LT with responses to both ICI rechallenge and/or EGFR targeted therapy (7 of 11 patients). With a median follow up of 46.6m the Median PFS2 was 10.7m. PFS2 was numerically higher in patients undergoing systemic therapy vs LT alone (11.9m vs 8.4m). Of those that underwent LT alone, further PD was seen in 16 patients (50%), with half requiring systemic therapy. Median OS for the overall cohort was 19.0m. OS was numerically reduced in immunocompromised patients (11.6m) and in those with primary ICI resistance (6.9m) vs those who had acquired resistance (22.5m) and progression after ICI cessation (47.1m). **Conclusions:** Selected patients with advanced cSCC, particularly those with acquired resistance, derive meaningful benefit from second-line therapy following ICI progression. Outcomes remain poor for immunosuppressed patients or those with primary resistance, highlighting a major unmet clinical need and the importance of prospective studies in the post-immunotherapy setting. Research Sponsor: None.

Outcomes of neoadjuvant immunotherapy (NeoIO) in Merkel cell carcinoma.

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Background: Merkel cell carcinoma (MCC) is an aggressive malignancy with high rate of nodal and distant metastasis, leading to poor overall survival. For clinically detected regional lymph nodes, treatment typically involves node dissection with adjuvant radiotherapy. Evaluation of NeoIO in resectable MCC resulted in a pathological complete response (pCR) rate of 47%; pCR correlated with relapse-free survival (RFS). However, there is no standardized NeoIO regimen. We report our single institutional NeoIO experience in resectable MCC and correlate regimen with clinicopathological response. **Methods:** We retrospectively reviewed pts with resectable MCC who received NeoIO with intent to offer surgery (SX) or radiation (RT), from 2015 to present. Demographic and clinicopathological characteristics were evaluated. Overall Response Rate (ORR), pCR, and Relapse Free Survival (RFS) were computed. Overall survival (OS) was evaluated via a 90-day landmark Kaplan-Meier plot to assess if time to definitive regional treatment impacted OS. **Results:** We identified 25 patients; median age was 77 years old; 75% were male. Majority were clinical stage III (IIIA 20%; IIIB 68%); 12% were stage IIA. 32% had immunosuppression at the time of treatment. 36% had primary MCC on extremity, 36% on head and neck, 8% on trunk, and 20% were of unknown primary origin. 80% of patients received neoadjuvant Pembrolizumab, 16% Avelumab and 4% ipilimumab plus nivolumab. The median number of IO cycles was 3 (1-18); those who completed 1-2 cycles were more likely to receive SX/RT compared to those who received 3 or more cycles (p-value = 0.024). 64% of patients had an adverse effect during therapy; majority (87.5%) had G1/G2 events. 24 patients had post NeoIO imaging to which ORR was 75%. Post NeoIO, 15 underwent SX, 4 had definitive RT, 2 had progression of disease and received systemic therapy, 3 had comorbidities precluding treatment, and 1 was lost to follow up. The median time from beginning of NeoIO to SX or RT was 3 months (1-19mo). Of those who underwent SX, 40% had a complete pathologic response, 20% had a major pathologic response, 33% had a partial response, and 6% had non-response. With a median 23.4 months of follow-up, 8 of the 25 patients (32%) have experienced an event and the median EFS has not been reached. 7 of the 25 (28%) patients have died, 4 due to MCC; median overall survival not reached. Median follow up was 23.4 months. Time to event analysis indicated six patients who received NeoIO, followed with SX or RT within 90 days, had fewer deaths compared with those who received SX/RT after 90 days. Survival was approximately 3.5 years for those who did not receive SX/RT within 90 days and no deaths for those who received SX/RT within 90 days. **Conclusions:** NeoIO for MCC at our single institution achieved an ORR of 75% and a mPR/pCR of 60%. Earlier incorporation of regional therapy post NeoIO appears to improve outcomes, suggesting importance of multimodal management for resectable MCC. Research Sponsor: None.

Characterization of germline pathogenic variants in melanoma patients.

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Background: Approximately 10% of melanomas arise from hereditary predisposition. NCCN guidelines recommend genetic counseling for patients with ≥ 3 invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma in an individual or family. However, predictors of germline pathogenic/likely pathogenic variants (P/LPV) in patients undergoing germline testing remain poorly characterized. **Methods:** A retrospective study of all melanoma patients referred for any indication to the University of Michigan Cancer Genetics Clinic from 2015–2024 was performed. Patients who declined testing or had known hereditary cancer syndromes (personal or familial) were excluded. Baseline demographics, referral reasons, melanoma characteristics, and genetic testing results were collected. Chi-square and Fisher's exact tests were used to evaluate associations with P/LPV ($p < 0.05$). **Results:** Among 624 patients, median age at melanoma diagnosis was 52 (IQR 38–63); 60.1% were female. The most common referral reasons were new melanoma diagnosis (64.4%), family history of non-melanoma cancers (57.1%), or family history of melanoma (39.4%). Overall, 88 (14.1%) harbored P/LPV (92 variants across 26 genes). P/LPV in established melanoma-risk genes were identified in 42 patients (6.7%): *CDKN2A* (n=16), *MITF* (n=8), *POT1* (n=5), *BRCA1/2* (n=6), *BAP1* (n=3), *TP53* (n=3), and *PTEN* (n=1). The strongest associations with any P/LPV were personal history of ≥ 2 additional non-skin primary cancers (OR 2.35; $p = 0.014$) and ≥ 2 primary melanomas (OR 1.80; $p = 0.017$). Diagnostic category (in situ, invasive, metastatic) and subtype (cutaneous, uveal, mucosal, acral, unknown primary) showed statistical significance with P/LPV ($p < 0.001$), though effect sizes were modest. Age at diagnosis (< 45 , < 55 , < 65), sex, and family history of melanoma or pancreatic cancer in 1° or 2° relatives were not associated with P/LPV. In a secondary analysis restricted to established melanoma-risk genes (n=42), ≥ 2 primary melanomas remained strongly predictive (OR 4.11; $p < 0.001$) and 1° family history of melanoma became significant (OR 2.01; $p = 0.03$), while ≥ 2 additional non-skin primary cancers was not associated ($p = 0.40$). **Conclusions:** In this melanoma cohort excluding patients with known hereditary syndromes, 14.1% had a P/LPV. Personal tumor burden, not family history, was the strongest predictor of a positive test, suggesting current NCCN criteria may miss high-risk individuals by emphasizing family history. For established melanoma-risk genes specifically, both personal history of multiple melanomas and 1° family history of melanoma were predictive, supporting a gene-specific approach to risk assessment. These findings support expanding referral criteria to include patients with ≥ 2 primary melanomas or ≥ 2 additional non-skin primary cancers, agnostic of family history, to better identify individuals most likely to benefit from germline testing. Research Sponsor: None.

ctDNA clearance durability and progression-free survival in unresectable or metastatic cutaneous malignancies.

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Background: Circulating tumor DNA (ctDNA) has emerged as a sensitive biomarker for disease monitoring and prognostication across malignancies. Yet, the clinical relevance of sustained ctDNA negativity (“clearance”) as a guide for immunotherapy duration in advanced cutaneous cancers remains poorly defined. This study evaluated the prognostic impact of durable ctDNA clearance in patients with unresectable or metastatic skin cancers treated with immune check-point inhibitors (ICIs). **Methods:** A single-institution retrospective study was performed using a personalized ctDNA assay (Signatera, Natera Inc.) on prospectively collected plasma from patients with stage III–IV unresectable cutaneous malignancies receiving ICIs every 3–6 weeks. ctDNA clearance was defined as a change from ctDNA-positive to ctDNA-negative on at least two consecutive samples obtained ≥ 4 weeks apart during ICI therapy and categorized as transient (< 12 months) or sustained (≥ 12 months). Demographics and clinical characteristics were summarized with descriptive statistics; progression-free survival (PFS) was estimated using the Kaplan–Meier method, and hazard ratios (HRs) were calculated with Cox proportional hazards models. **Results:** Among 75 patients (stage III: 23%, stage IV: 77%), most were male (72%) and had melanoma (87%), with a median age of 72 years and median follow-up of 20.4 months. Median ICI treatment duration was 6.9 months; all patients received ICIs, most commonly relatlimab/nivolumab (49%) or pembrolizumab (40%). Median ctDNA clearance duration was 8.2 months. Patients with sustained ctDNA clearance ($n=25$) experienced markedly improved 12-month PFS compared with those with transient clearance ($n=50$) (92.0% [95% CI, 71.6–97.9] vs 58.1% [95% CI, 42.6–70.8]). In a multivariable model adjusting for age, malignancy type, and treatment regimen, transient ctDNA clearance was associated with significantly worse PFS than sustained clearance (HR 12.1; 95% CI, 2.7–53.4). **Conclusions:** Sustained ctDNA clearance (≥ 12 months) is strongly associated with superior PFS in advanced cutaneous malignancies treated with ICIs, underscoring its potential as a dynamic biomarker to inform the treatment duration. Validation in larger, multi-institutional cohorts is warranted to confirm these findings and refine ctDNA-guided immunotherapy strategies. Research Sponsor: None.

Long-term survivorship rates among previously treated advanced melanoma patients achieving objective response (OR) with lifileucel.

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Background: Durability of response and associated long-term survival benefits of modern cancer therapies are often manifested as plateaus in duration of response (DoR) and overall survival (OS) curves for responders. In the single-arm, Phase 2 C-144-01 trial, unresectable/metastatic melanoma patients who progressed on immune checkpoint inhibitors (ICIs) showed durable clinical responses to lifileucel—an FDA-approved autologous T-cell therapy. This analysis evaluated the association between achieving an OR with lifileucel and possibility of being a long-term survivor (LTS) in the C-144-01 study. **Methods:** Mixture cure models (MCMs) were applied to analyze OS and DoR outcomes for patients who achieved confirmed OR by committee review among those receiving lifileucel within commercial specifications in Cohorts 2 and 4 (overall cohort; n=106, median follow-up: 47.4 months, OR rate 35.8%). In both analyses, LTS were subject to only non-melanoma-related mortality whereas non-LTS were subject to both melanoma- and non-melanoma-related mortality. In the DoR analysis, LTS were also assumed to remain in response until death. For LTS, OS/DoR outcomes were assumed to follow the survival trend of age- and sex-adjusted US general population, and derived from published lifetables whereas for non-LTS, they are modeled by parametric distributions. Fraction of LTS and OS/DoR distributions for non-LTS were estimated simultaneously via maximum likelihood methods. Candidate MCMs were evaluated based on statistical fit criteria, visual agreement with observed OS/DoR data, and underlying hazards. **Results:** Exponential MCM and gamma MCM provided best fits to the observed DoR and OS data, respectively, and estimated the fractions of LTS (95% CI) among responders as 52% (34.0%–69.4%) and 50.4% (31.3%–66.7%) from the OS and DoR data, respectively. Estimated fractions of LTS across clinically plausible models ranged between 48.4%–52.9% in the OS analysis and 50.4%–51.1% in the DoR analysis. Best-fitting MCMs projected 10-year mean OS and DoR as 70.7 and 62.2 months, respectively, and 10-year OS and DoR rates as 46.7% and 45.3%, respectively. Smoothed OS and DoR hazards derived from the observed data displayed convergence to general population mortality rates by the end of follow-up indicating maturity and suitability of data for modeling with MCMs. **Conclusions:** Responders had significantly higher fraction of LTS than the overall cohort, underscoring the importance of achieving OR to lifileucel for its long-term survival benefit. Estimated fractions of LTS from OS and DoR were robust to model choice, consistent with each other, and when scaled by OR rate, aligned with previously reported fractions of LTS from progression-free survival and OS for the overall cohort. Results support clinical potential of lifileucel for addressing unmet need in post-ICI advanced melanoma. Research Sponsor: Iovance Biotherapeutics, Inc.

Incidence and survival rates in pediatric and adolescent melanoma in the United States, 2001-2022.

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Background: Melanoma represents a significant malignancy in children, adolescents, and young adults. Recent trends in incidence and outcomes in this population have not been comprehensively characterized. We analyzed population-based data to evaluate temporal trends in melanoma incidence and survival among patients aged <40 years. **Methods:** Data from the North American Association of Central Cancer Registries (NAACR) and SEER registries (representing up to 76% of U.S. children, adolescents, and young adults) were analyzed for patients aged <40 years diagnosed between 2001-2022. Age-adjusted incidence rates per 1,000,000 were calculated and standardized to the 2000 U.S. population. Five-year relative survival rates were assessed for diagnoses from 2001-2020. Annual Percent Change (APC) and Average Annual Percent Change (AAPC) were calculated using Joinpoint Trend Analysis Software. **Results:** Melanoma incidence in patients aged <40 years demonstrated a consistent declining trend from 2001 to 2022. Incidence rates decreased from approximately 47-50 per 1,000,000 in the early 2000s to approximately 38 per 1,000,000 by 2022, representing approximately a 20% reduction over the study period. The decline was particularly notable after 2005, with a steady downward trajectory through 2022. Despite this declining incidence, 5-year relative survival rates remained consistently excellent throughout the entire study period at 95-97%, with a slight upward trend from approximately 95% in 2001 to approximately 97% in 2017-2020. Survival outcomes showed no statistically significant variation over time, remaining stable in the 95-97% range. **Conclusions:** This analysis reveals an encouraging 20% decline in melanoma incidence among children, adolescents, and young adults over two decades, likely reflecting the success of public health initiatives promoting sun protection, sunscreen use, and reduced indoor tanning. The sustained decrease in incidence, particularly among younger populations, suggests that prevention efforts have had measurable impact. Simultaneously, the consistently excellent 5-year relative survival rates exceeding 95% demonstrate the effectiveness of current diagnostic and therapeutic approaches for melanoma in this age group. The stable survival coupled with declining incidence represents a dual public health success, with both primary prevention reducing disease burden and clinical management maintaining excellent outcomes. These findings underscore the importance of continued emphasis on melanoma prevention strategies while supporting ongoing efforts to optimize early detection and treatment protocols in pediatric and young adult populations. Research Sponsor: None.

A propensity score–matched real-world analysis of immune checkpoint inhibitors in melanoma patients with autoimmune disease.

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Background: Immune checkpoint inhibitors (ICIs) are foundational in the treatment of melanoma. However, patients with pre-existing autoimmune diseases (AD) have been excluded from pivotal ICI clinical trials and remain underrepresented in real-world outcome data. We conducted a propensity score–matched cohort study to evaluate the impact of pre-existing AD on clinical outcomes among melanoma patients treated with ICIs. **Methods:** A retrospective cohort study was performed using the TriNetX Research Network, including adult patients with melanoma treated with ICIs. ICI regimens included PD-1, PD-L1, and CTLA-4–based therapies. Patients with documented pre-existing AD were compared with patients without AD using 1:1 propensity score matching (PSM) for demographics, baseline corticosteroid use, laboratory values, and comorbidities. Outcomes included overall survival (OS) at 1 and 3 years; infections, corticosteroid exposure, and non-steroidal immunosuppressant exposure within 90 days of ICI initiation; and immune-related adverse events (irAEs), analyzed as a composite outcome and stratified by organ system (cardiac, pulmonary, endocrine, and dermatologic) within 180 days. Outcomes were assessed using hazard ratios (HRs), risk ratios (RRs), and 95% confidence intervals (CIs). **Results:** A total of 21,236 patients met inclusion criteria, including 3,372 with pre-existing AD and 17,863 without. After PSM, 3,372 patients were included in each cohort. Patients with AD demonstrated improved overall survival at both 1 and 3 years compared with those without AD (1-year HR 0.70, 95% CI 0.62–0.79; 3-year HR 0.76, 95% CI 0.70–0.84). Patients with AD were at increased risk for composite irAEs (RR 1.66, 95% CI 1.47–1.87). Organ-specific analyses demonstrated higher risks of cardiac (RR 3.29, 95% CI 2.02–5.34), endocrine (RR 1.48, 95% CI 1.22–1.81), and dermatologic irAEs (RR 1.46, 95% CI 1.22–1.73) among patients with AD. Patients with AD also had higher rates of corticosteroid (RR 1.23, 95% CI 1.18–1.28) and non-steroidal immunosuppressant exposure (RR 4.96, 95% CI 3.73–6.61), as well as increased risk of infection (RR 1.28, 95% CI 1.13–1.44). **Conclusions:** In this large real-world analysis, melanoma patients with pre-existing AD treated with ICIs demonstrated improved overall survival despite increased irAEs, immunosuppressant exposure, and infection. These findings challenge excluding patients with AD from receiving ICI therapy and support inclusion in future clinical trials. Research Sponsor: None.

Outcome	AD [n= 3,372]	No-AD [n= 3,372]	HR/RR [95% CI]
1-year OS	85.2%	79.8%	0.70 [0.62-0.79]
3-year OS	71.1%	65.2%	0.76 [0.70-0.84]
Any irAE (180 days)	19.6%	11.8%	1.66 [1.47-1.87]
Cardiac irAE	2.1%	0.6%	3.29 [2.02-5.34]
Pulmonary irAE	0.8%	0.6%	1.34 [0.76-2.35]
Endocrine irAE	7.0%	4.7%	1.48 [1.22-1.81]
Dermatologic irAE	9.2%	6.3%	1.46 [1.22-1.73]
Infection (90 days)	15.9%	12.6%	1.28 [1.13-1.44]

First 1000 patients report of global practice patterns and clinical outcomes in the Collaborative Ocular Melanoma Natural History (OMNi) real-world database (NCT04588662).

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Background: OMNi (NCT04588662) is an ambispective natural history database developed to provide contemporary real-world data of UM. The overall objectives of OMNi are to characterize regional/international UM management practice patterns and associated clinical outcomes in an effort to inform best practice recommendations and provide real world evidence. Here we present characteristics, demographics and practice patterns in the first 1000 patients enrolled globally. **Methods:** OMNi utilizes the Pulse Infolife Healthie platform, enabling the longitudinal structured collection of data mapped to Observational Medical Outcomes Partnership. **Results:** Median age at diagnosis was 60 (15-94), with 47% of patients were female. Enrolment was from Australia (309), UK (93), USA (121) and Canada (477). When known, family history of UM was present in 2% (15/733). Recorded primary treatment modalities included plaque brachytherapy 44%, Enucleation 18%, Stereotactic radiotherapy 9%, Proton beam 3%, other radiotherapy 1%, other/ unknown 23%. Within the cohort, 30 patients were diagnosed with de novo metastatic disease and 343 patients had metastatic disease at any time. Of those, metastatic location was 166 extrahepatic and hepatic, 154 hepatic only, 18 extrahepatic only. HLA-A2 status was *0201 in 172/ 297(58%). Systemic treatments were administered to 176 patients first line- Tebentafusp (71 first line); Ipi/Nivo (58); Ipi (7); PD-1 inh (15). The total number of patients receiving systemic treatments were Tebentafusp 108; Ipi/Nivo 90; Ipi 22; PD-1 (82). In total, 133 patients received liver directed therapy. At last follow up, where available 29% of patients had died from UM (179/611). Data to be presented will include genetic profiling summaries. **Conclusions:** The OMNi dataset can serve and aid in interpretation of clinical trial outcomes in the real-world, and accelerate the development of diagnostics and therapeutics to provide comparative data. Research Sponsor: None.

Clinical trial in progress: Phase I/II study of tebentafusp in combination with liver-directed therapies for the treatment of metastatic uveal melanoma.

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Background: Uveal melanoma (UM) has a high rate of metastasis, most commonly to the liver. Tebentafusp-tebn (Tebe) is a first-in class immune-mobilizing monoclonal T cell receptor against cancer (ImmTAC) that gained regulatory approval after it showed significantly improved overall survival (OS) compared to single-agent investigator's choice in a pivotal randomized phase III trial. For patients with oligometastatic liver disease, liver-directed therapies (LDT) such as hepatic immunoembolization (IE) and chemoembolization (CE) have been used with success. LDT and Tebe may have therapeutic limitations when administered independently, but combining the two approaches is a potentially beneficial strategy that could provide both short-term hepatic disease control and long-term systemic disease control. **Methods:** This is an investigator-initiated, multicenter, open-label phase I/randomized phase II trial to assess the safety and clinical efficacy of Tebe in combination with LDT in HLA-A*02:01 positive patients with metastatic UM [NCT06626516]. In Part 1 of the study, we will investigate the safety and efficacy of Tebe + IE in patients with low to moderate hepatic disease burden (M1a or M1b disease with largest tumor ≤ 5 cm, AND $< 50\%$ liver involvement). In Part 2, we will investigate the safety and efficacy of Tebe + CE in patients with bulky hepatic disease (M1b disease with largest tumor > 5 cm, M1c disease, or $> 50\%$ liver involvement). Patients must be 18 years or older, HLA-A*02:01 with metastatic UM in the liver. Extra-hepatic disease is allowed. Patients must be treatment naïve in the metastatic setting for Part 1 and must have no more than two prior lines of treatment (systemic or liver directed) for Part 2. Patients will receive Tebe at the approved step-up dosing regimen (20 mcg IV on C1D1, 30 mcg IV on C1D8, then 68 mcg on C1D15 and weekly thereafter). Patients in Part 1 will receive IE with GM-CSF 1500mcg every 4 weeks (starting at week 5) for the first four treatments and then 4 weeks as maintenance if clinically indicated. Part 1 has a phase I safety lead-in (Part 1A), followed by a phase II trial (Part 1B) where patients are randomized 2:1 to receive Tebe + IE or Tebe alone. Patients in Part 2 will receive CE with BCNU 300mg every 4 weeks for a total of 2 (unilobar disease) or 4 (bilobar disease) treatments followed by weekly Tebe. Eighteen patients, 52 patients, and 39 patients will be enrolled in Part 1A, Part 1B, and Part 2, respectively (total 109 patients). Primary endpoints for Part 1A is safety lead-in and 6-month progression-free survival (PFS), 6-month PFS for Part 1B, and 6-month PFS for Part 2. Secondary endpoints include overall response rate, liver-specific PFS, OS, and toxicity. Enrollment for Part 1A began in October 2025 at Thomas Jefferson University Hospital. Clinical trial information: NCT06626516. Research Sponsor: Immunocore, Ltd.

A randomized, controlled, multicenter, phase 3 study of RP1 (vusolimogene oderparepvec) combined with nivolumab vs physician's choice of therapy in patients with advanced melanoma that has progressed on anti-PD-1 and anti-CTLA-4 therapy (IGNYTE-3).

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Background: Melanoma is the fifth most common cancer, with over 100,000 new cases and 8000 related deaths projected in the US for 2025. First-line systemic treatment with immune checkpoint inhibitors (ICIs) improves the objective response rate (ORR) and extends progression-free survival (PFS) and overall survival (OS) for patients with advanced disease. Among available treatments, combination anti-PD-1 (nivolumab) + anti-CTLA-4 (ipilimumab) therapy is associated with the highest ORR and best PFS and OS. However, only around half of patients respond to treatment, and limited options exist for patients whose melanoma then progresses following anti-PD-(L)1 ± anti-CTLA-4. RP1 (vusolimogene oderparepvec) is a herpes simplex virus type 1-based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R⁻). IGNYTE-3 will evaluate the OS and clinical benefit of RP1 + nivolumab for patients with advanced cutaneous melanoma whose disease has progressed after anti-PD-1 and anti-CTLA-4 therapy (or who are ineligible for anti-CTLA-4 therapy) vs physician's choice. RP1 + nivolumab has demonstrated durable, clinically meaningful anti-tumor activity (ORR, 33.% per independent central review), with minimal toxicity (NCT03767348). Repetitive intralesional and intravisceral injections were well tolerated in advanced ICI-refractory melanoma. All patients had confirmed progression on prior anti-PD-1 therapy. **Methods:** IGNYTE-3 (NCT06264180) is a global, randomized, controlled, phase 3 trial. Key eligibility criteria include age ≥12 years, stage IIIB–IVM1a–M1d cutaneous melanoma, disease progression on ≥12 weeks of an anti-PD-1 and anti-CTLA-4 treatment (administered in combination or in sequence, with anti-PD-1 last), ≥1 measurable and injectable tumor, and adequate hematologic, hepatic, and renal function. Patients who are not candidates for anti-CTLA-4 therapy may enroll following progression on anti-PD-1 therapy alone. Patients with BRAF V600-mutant melanoma should have received anti-BRAF ± anti-MEK-targeted therapy prior to enrollment, where appropriate. Patients (N ≈ 400) will receive RP1 + nivolumab or physician's choice (nivolumab + relatlimab, anti-PD-1 monotherapy rechallenge [nivolumab or pembrolizumab], or single-agent chemotherapy [dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel]). The primary endpoint of the study is OS; the key secondary endpoints are PFS and ORR per RECIST 1.1. Clinical trial information: NCT06264180. Research Sponsor: Replimune, Inc.

A randomized, phase 2/3 clinical trial investigating RP2 plus nivolumab vs ipilimumab plus nivolumab in immune checkpoint inhibitor-naïve patients with metastatic uveal melanoma.

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Background: Uveal melanoma (UM) is the most common primary intraocular malignancy, accounting for ~90% of ocular melanomas and 5% of all melanomas. Half of patients with UM develop metastases, most commonly in the liver (~90%). The prognosis for patients with metastatic UM (mUM) is poor, with a median overall survival (OS) of ~1 year. Effective treatment options for mUM are limited, as it responds poorly to single-agent immune checkpoint inhibitors (ICIs; <10% response rate). Response rates are slightly higher with combination therapies (12%–18%), but these often have increased toxicity. Tebentafusp is FDA-approved for mUM based on survival benefit but is restricted to patients who are HLA-A*02:01 positive, and only ~10% of patients achieve an objective response. RP2 is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy expressing GM-CSF, a fusogenic glycoprotein (GALV-GP-R⁻), and an anti-CTLA-4 antibody-like molecule. Prior preliminary clinical data of intratumoral RP2 as monotherapy or in combination with nivolumab demonstrated a promising safety profile and anti-tumor activity with an overall response rate (ORR) of 29.4% and disease control rate of 58.8% in 17 patients with mUM, most of whom had received prior ICIs. This study will assess the efficacy and safety of RP2 + nivolumab vs ipilimumab + nivolumab in patients with ICI-naïve mUM. **Methods:** This is a multicenter, randomized, controlled, phase 2/3 study (NCT06581406; RP2-202). Key eligibility criteria include age ≥18 years and confirmed unresectable mUM with at least 1 lesion amenable to injection; up to 1 prior line of therapy in the metastatic setting is allowed. Patients with prior exposure to ICIs since the time of mUM diagnosis, >50% liver involvement, or previous selected liver-directed therapies are not eligible. Enrolled patients (N = ~280) will be randomized 1:1 to receive either RP2 + nivolumab or ipilimumab + nivolumab. In the RP2 + nivolumab arm, RP2 will be given intratumorally initially at 1×10^6 plaque-forming units (PFU)/mL, then every 2 weeks (Q2W) at 1×10^7 PFU/mL for 7 doses in combination with intravenous (IV) nivolumab (240 mg). In the ipilimumab + nivolumab arm, patients will receive IV ipilimumab (3 mg/kg) and IV nivolumab (1 mg/kg) Q3W for 4 doses. Patients in both arms may then receive IV nivolumab at 240 mg Q2W or 480 mg Q4W for up to 2 years. The co-primary endpoints are OS and progression-free survival by independent central review using RECIST 1.1. Secondary endpoints are ORR, duration of response, disease control rate, clinical benefit rate, duration of clinical benefit, and safety, including incidence of treatment-emergent adverse events (AEs), serious AEs, and immune-mediated AEs. Clinical trial information: NCT06581406. Research Sponsor: Replimune, Inc.

Phase 2 study of metronomic cyclophosphamide with pembrolizumab in checkpoint inhibitor–refractory melanoma.

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Background: Immune checkpoint inhibitors (ICI) are standard of care treatment in advanced, metastatic melanoma as well as adjuvant treatment of resected high-risk disease. However, approximately 50% of patients do not respond to primary anti-programmed death ligand-1 (anti-PD1) treatment (primary resistance) or progress after initial response (secondary resistance). Second line treatments in this setting include addition of the anti-cytotoxic T-lymphocyte associated protein 4 (anti-CTLA-4) drug ipilimumab or targeted treatment in BRAF mutant melanomas. However, CTLA-4 blockade can confer significant immune-mediated toxicity in a low performance status (PS) population, and not all patients are eligible for BRAF/MEK inhibition. There remains an unmet clinical need to optimize ICI efficacy and overcome resistance. It is hypothesized that suppressive regulatory T-cells (T_{reg}) may inhibit the anti-tumor effect of ICI. Cyclophosphamide (CTX) is an alkylating anticancer agent. Prior studies in patients with recurrent ovarian cancer and soft tissue sarcoma have demonstrated that the combination of anti-PD1 agents with metronomic, or low dose, frequent, CTX was effective with no new safety signals. **Methods:** This phase 2, single-center, single-arm study explores the efficacy of adding oral metronomic CTX to intravenous pembrolizumab in patients with ICI–refractory locally advanced or metastatic melanoma. Key inclusion criteria are measurable disease by RECIST v.1.1 and receipt of investigational treatment within 9 weeks of last ICI treatment. Patients may have previously received single agent pembrolizumab or dual ICI with anti-LAG3 and anti-PD1 (relatlimab/nivolumab). Key exclusion criteria are symptomatic, untreated brain metastases, BRAF V600 mutation without prior receipt of BRAF/MEK inhibition, or prior grade 3 or greater immune-related adverse event (irAE). The primary endpoint is objective response rate (RR) as defined by complete response (CR) + partial response (PR) by RECIST v 1.1. A Simon's minimax two-stage design will be used, with the null hypothesis that the true response rate is .05 and the alternative hypothesis that true response rate is 0.3. In Stage I, a total number of 7 patients will be accrued. If there are 0 responses among 7 patients, the study will be stopped; otherwise, an additional 7 patients will be accrued to Stage II. 3 of 14 planned patients have been enrolled. This trial was approved by the UC Irvine Institutional Review Board; approval number is 6168. Trial registration NCT06771544. Clinical trial information: NCT06771544. Research Sponsor: University of California, Irvine; University of California, Irvine; UCI Melanoma Program.

Phase 1b/2 trial of melphalan-percutaneous hepatic perfusion (PHP) therapy and nivolumab/relatlimab in patients with metastatic melanoma and liver metastasis.

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Background: Despite advances with immune checkpoint inhibitors (ICIs), patients with metastatic melanoma and liver metastases (LM) experience poorer outcomes. In the CheckMate-067 subanalysis, patients with LM treated with nivolumab/ipilimumab had shorter median PFS (4.4 vs 18.1 months) and OS (28.2 months vs not reached) than those without LM, confirming its negative prognostic role. Nivolumab/ipilimumab and nivolumab/relatlimab show comparable efficacy; however, the latter is increasingly used for its improved safety profile (grade ≥ 3 adverse events: 59% vs 21%). Melphalan-PHP (Hepzato), a liver-directed therapy delivering high-dose melphalan through a closed filtration circuit, concentrates treatment in the liver while minimizing systemic exposure. Research by Yu et al. demonstrated that LM reduces peripheral and tumoral CD8⁺ T cells, creating an immune desert, while combining liver-directed therapy with ICIs can reactivate systemic immune responses. Based on these insights and the CHOPIN trial's safety data, the proposed Phase 1b/2 study will assess the safety, tolerability, and preliminary efficacy of melphalan-PHP plus nivolumab/relatlimab for first line treatment of metastatic non-veal melanoma patients with LM. **Methods:** Phase 1b/2, single-center, single-arm study will use a Simon two-stage (5+10) design (n=15). Patients will receive nivolumab/relatlimab on Day 1 of each 28-day cycle for up to 2 years and receive melphalan-PHP on Day 15 of Cycle 1 and Cycle 3. Eligible participants must have histologically or cytologically confirmed metastatic melanoma involving the liver and be systemic treatment-naïve in the metastatic setting. Prior adjuvant ICI is permitted provided it was completed >6 months prior to study enrollment. Key exclusions include metastatic uveal melanoma, prior treatment with melphalan-PHP or ICI combinations, uncontrolled or symptomatic brain metastases, prior grade 3+ adverse events from ICI requiring treatment discontinuation, ongoing immunosuppressive therapy, contraindications to anesthesia, and significant cardiac, hepatic (Child-Pugh B/C), or pulmonary disease. The co-primary objectives/endpoints in stage 1 are to assess the safety and tolerability as measured by 2 or less DLTs (any treatment-related grade 4+ non-hematologic event lasting >3 days); and preliminary efficacy as measured by 2 or more objective responses in hepatic and non-hepatic lesions. Secondary objectives include: disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and any tumor reduction. Open for enrollment in January 2026. Clinical trial registry number: NCT07281924. Clinical trial information: NCT07281924. Research Sponsor: Delcath.

Adaptive phase 2/3 study of EIK1001, a TLR7/8 dual agonist, in combination with pembrolizumab, as first-line therapy in participants with advanced melanoma (TeLuRide-006).

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Background: Immune checkpoint inhibitors (ICIs), including anti-PD-1 antibodies, reverse tumor induced immune suppression and promote effective anti-tumor T-cell responses. They have drastically improved outcome in advanced melanoma therapy, yielding durable improvements in progression-free survival (PFS) and overall survival (OS). Although adding anti-CTLA-4 or anti-LAG-3 enhances efficacy beyond anti-PD-1 alone, these approaches do not directly target dominant myeloid-mediated resistance mechanisms within the tumor micro-environment, and new agents targeting this axis are needed. EIK1001, a TLR7/8 dual-agonist, activates myeloid and plasmacytoid dendritic cells to stimulate innate inflammation and adaptive immunity. Across multiple studies, EIK1001 has been well tolerated and has demonstrated clinical activity both as monotherapy and in combination with ICIs. **Methods:** TeLuRide-006 (NCT#06697301) is a global, multicenter, randomized, double-blind, adaptive Phase 2/3 trial of EIK1001 or placebo, in combination with pembrolizumab (pembro), as first-line therapy for participants (pts) with advanced cutaneous melanoma. Approximately 740 pts will be randomized, including a dose-optimization (DO) stage in which pts are randomized 1:1:1 to two EIK1001 dose levels or placebo, each administered with pembro, followed by Phase 2/3 expansion evaluating the selected EIK1001 dose versus placebo, with pembro. Interim analyses will guide progression from DO to Phase 2 and subsequently to Phase 3. EIK1001 or placebo is administered IV QW until the end of Week 27 then Q3W; while pembro is administered IV Q3W. Pts are stratified by prior anti-PD-1 adjuvant therapy, LDH level, and BRAF mutational status. Key eligibility criteria include patients ≥ 12 years (with country-specific variations), life expectancy ≥ 3 months, unresectable Stage III or Stage IV melanoma, known BRAF V600 status, at least one RECIST v1.1-measurable lesion, and no prior or current pneumonitis/interstitial lung disease. Primary objectives are to assess the efficacy and safety of two EIK1001 doses with pembro in DO, and to compare PFS (RECIST v1.1 by blinded independent central review [BICR]) and OS between the selected EIK1001 dose and placebo in combination with pembro. Secondary objectives include safety and tolerability of either EIK1001 dose with pembro, objective response rate and duration of response per RECIST v1.1 by BICR. Exploratory objectives include time to response, EIK1001 exposure-response relationships, and health-related quality of life. This study enrolled (randomized) its first participant on 5/21/2025 and is activated at 91 sites in 22 countries at the time of abstract submission. Research Sponsor: None.

A phase I/II clinical study of DOC1021 (dubodencel) dendritic cell immunotherapy for refractory melanoma.

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Background: DOC1021 is an autologous dendritic cell (DC)-based immunotherapy. Loading of DC in tandem with both patient autologous tumor protein and amplified mRNA induces p38MAPK and mTORC1 signaling cascades that initiate cDC1-like skewing of monocyte-derived DC, generating downstream development of highly cytolytic memory effectors. This approach targets the multitude of antigens in a patient's own tumor, does not require myeloablative chemotherapy and has demonstrated a favorable safety profile in Phase I glioblastoma (NCT04552886) and pancreatic cancer trials (NCT04157127). Pre-clinical studies in a variety of animal models, including melanoma (subcutaneous B16F0-OVA tumors), have also shown improved tumor responses and evidence of antigen-specific immunity. While immune checkpoint inhibitors (ICI) have improved clinical outcomes in melanoma, many patients ultimately develop resistance, resulting in refractory disease. We hypothesize that DOC1021 may overcome ICI resistance in refractory melanoma through the generation of durable T cell responses with novel specificities, promoting long-term anti-tumor T cell surveillance and improved survival. **Methods:** This is a prospective, multi-center, open-label Phase I/II study in patients with refractory cutaneous melanoma, unresectable or metastatic, with progression following ≥ 1 prior systemic therapies including anti-PD-1. The study consists of two components: an initial Phase I study to confirm safety/tolerability of DOC1021 in refractory melanoma, and subsequently, a single-arm Phase II cohort to assess efficacy. Up to 12 patients will be enrolled in Phase I, and up to 35 evaluable patients will be enrolled in Phase II using a Simon's optimal two-stage design. DOC1021 will be prepared from mobilized peripheral blood mononuclear cells (PBMC), loaded with autologous tumor lysate and amplified tumor mRNA. All patients will receive 2 courses of DOC1021 (12×10^6 cells per administration) 2 weeks apart via perinodal injections near active disease sites, plus peg-interferon (pIFN) adjuvant on the day of each DOC1021 administration and 1 week after for 4 total doses. An optional DOC1021 booster course may also be given approximately 6 months after the first DOC1021 administration. The primary endpoint of the Phase I study is dose-limiting toxicities of DOC1021, while the primary endpoint of the Phase II study is the overall response rate per RECIST 1.1 criteria. This study will also evaluate survival, tumor responses, changes in circulating tumor DNA, as well as further investigate DOC1021's mechanism of action through biomarker-rich analyses of serial tumor biopsies and blood sampling. The first patient to enroll in the Phase I safety study is planned for early 2026. Clinical trial information: NCT07288112. Research Sponsor: Diakonon Oncology; Cancer Prevention and Research Institute of Texas (CPRIT).

Phase I/IIa dose finding study of triplet regimen of relatlimab (RELA) ipilimumab (IPI), and nivolumab (NIVO) in first-line therapy of metastatic melanoma (MM) (TRINITY).

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Background: Approved immune checkpoint blockade (ICB) agents for the treatment (tx) advanced, unresectable metastatic melanoma (MM) include NIVO (anti-PD1) alone or in combination with IPI (anti-CTLA-4) or RELA (anti-LAG3) and have transformed outcomes for patients with this disease. While doublet combinations induce higher rates of durable disease control and modestly improved survival vs single agent, higher doses of IPI induce higher objective response rates (ORR) also increase grade ≥ 3 immune-related adverse events. Notably, there is no established dose-response relationship for NIVO or RELA. IPI has a demonstrated role in expanding the T-cell receptor (TCR) repertoire, modulating suppressive T cell populations. NIVO+RELA regulates exhaustion of activated T cells, improving effector function. Together, these suggest potential synergy with triplet ICB. Results reported in RELATIVITY-048 (NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W) demonstrated impressive efficacy (ORR 59%) and seemingly improved progression free and overall survival (PFS, OS) over previously reported doublet tx. The RELATIVITY-048 study design did not include dose escalation (DE) of IPI. Our team seeks to identify the optimal dose and schedule of IPI to combine with NIVO+RELA, identify the recommended phase II dose (RP2D) for this triplet ICB treatment and, ultimately, seeking to maximize the clinical benefit while maintaining a toxicity profile comparable to approved doublet regimens. **Methods:** In this single center, investigator initiated, PhI/IIa study, our team is evaluating triplet ICB (NCT06683755) in untreated, unresectable MM pts. Pts will receive NIVO 480mg + RELA 160mg IV Q4W (FDA approved dose). IPI DE will begin at 0.5mg/kg Q4W, escalating to 2mg/kg Q4W x4 induction doses. Pts will receive maintenance tx with NIVO+RELA Q4W at the approved dose. The maximum tolerated dose and the RP2D will be determined using a Bayesian optimal interval design, accruing 12-18 pts in DE. An additional 12-18 pts will be enrolled at RP2D to determine the ORR (primary objective) by RECIST 1.1. Secondary objectives include PFS, OS, and correlative analysis. Non IPI containing prior adjuvant or neoadjuvant tx is allowed if the last dose has been >6 months. Pts with asymptomatic brain metastasis on ≤ 10 mg corticosteroids are allowed. Safely biopsiable lesions are required for pts enrolled in the PhII portion. By optimizing the dose and schedule of IPI in combination with NIVO+RELA, we seek to maximize clinical benefit while maintaining a toxicity profile comparable to approved regimens. This study is currently accruing at MD Anderson Cancer Center. Clinical trial information: NCT06683755. Research Sponsor: BMS.

TrioMBM: A multicenter, phase II trial of relatlimab, nivolumab, and ipilimumab in patients with asymptomatic and symptomatic melanoma brain metastases.

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Background: Melanoma brain metastases (MBM) are a leading cause of morbidity and mortality for patients (pts) with advanced melanoma. Modern systemic therapies including immune checkpoint blockade (ICB) are insufficient at controlling MBM, particularly in patients with who are symptomatic and/or require corticosteroids. The CheckMate 204 study established nivolumab (NIVO) 1 mg/kg + ipilimumab (IPI) 3mg/kg followed by maintenance NIVO as the standard treatment (tx) for pts with MBM based on intracranial (IC) objective response rate (ORR) of 55% and 6-month progression-free survival (PFS) of 64% in the asymptomatic cohort (Tawbi *et al. NEJM* 2018). In symptomatic pts, intracranial benefit rate (iCBR) was only 22% and median PFS was 1.2 mos (Tawbi *et al. Neuro Oncol* 2021). Triplet tx with the addition of LAG-3 inhibition with relatlimab (RELA) is now being explored as a mechanistically-driven means to improve efficacy of ICB. Arm 2B of RELATIVITY-048 (NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W) reported promising efficacy (ORR 59%, 3y PFS 52%) and 2 of 3 (67%) pts with MBM had confirmed responses (Ascierto *et al. ASCO* 2024) further justifying the need to explore this combination in this population. We hypothesize that triplet ICB will be more effective than NIVO+IPI for the tx of symptomatic and asymptomatic MBM. **Methods:** In this multicenter, investigator initiated, phase II study evaluating triplet ICB (NCT06712927) pts with MBM will be assigned to one of two cohorts: Cohort A (asymptomatic, n=40) and Cohort B (symptomatic, n=20) defined as having symptoms attributable to brain metastases and/or requiring steroids >10 mg prednisone/day or equivalent. All pts will receive NIVO 480mg + RELA 160mg IV Q4W (FDA approved dose) plus IPI 1mg/kg IV Q8W. Pts must have ≥ 1 untreated intracranial lesion (5–40mm) and no prior ICB for unresectable stage III/IV melanoma (>6 mo since neoadjuvant or adjuvant ICB). Primary endpoint is iCBR (CR+PR+SD ≥ 6 mo) determined by modified RECIST 1.1; secondary endpoints include safety, ORR, duration of response, and PFS. Extensive correlative analyses of peripheral blood mononuclear cells, plasma, tumors, and cerebrospinal fluid are planned. The study is currently enrolling at Stanford Cancer Center with multisite expansion underway. Clinical trial information: NCT06712927. Research Sponsor: Bristol-Myers Squibb; National Cancer Institute; P30CA124435.

Phase 2 sequential treatment of percutaneous hepatic perfusion with melphalan/hepatic delivery system followed by tebentafusp in the treatment of metastatic uveal melanoma.

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Background: Metastatic uveal melanoma (mUM) typically has a poor prognosis with limited treatment options. Tebentafusp (TEBE) is the only approved systemic agent for HLA-A*02:01 positive mUM, and percutaneous hepatic perfusion (PHP) is FDA approved for patients with mUM in the liver (solely or predominantly). Combining PHP with nivolumab plus ipilimumab in the randomized phase 2 CHOPIN trial significantly improved overall response (ORR), progression-free survival (PFS) and overall survival (OS) compared to PHP alone, but with significantly higher grade 3 or greater adverse events. In the phase 3 TEBE clinical trial there was a modest ORR of 11%, and improved OS compared to investigator choice therapy. We hypothesize that PHP causes antigen release and changes in the hepatic tumor microenvironment that may enhance response to TEBE. In this investigator-initiated trial, we aim to explore the combination of sequential regional and systemic therapy in HLA-A*02:01 positive mUM patients. **Methods:** This is a single institution phase 2 clinical trial combining PHP using the melphalan hepatic delivery system for 2 cycles followed sequentially by intravenous TEBE at approved dosage for up to 1 year of therapy. For patients with unequivocal progression on TEBE, up to 4 additional cycles of PHP will be considered if they continue to meet standard eligibility for PHP. The primary objective is to assess the PFS in uveal melanoma patients who have isolated or liver dominant metastases with landmark analyses at 6 months, 12 months and 24 months. Secondary objectives include (1) toxicity, (2) objective response and duration of response, (3) hepatic and extra-hepatic PFS, (4) OS, (5) biomarker discovery, RNA sequencing and spatial immunofluorescence analysis of the tumor microenvironment through core biopsies performed pre-PHP, after PHP number 2, and post-TEBE treatment. Blood samples for immune panel analysis will be collected at these timepoints. Response assessments are undertaken with standard cross-sectional imaging every 12 weeks for 36 months. Planned accrual is 18 patients with an interim futility analysis after 10 patients are treated to assess the 6-month PFS for the cohort. Primary analysis will be performed using the Kaplan-Meier method. Salient eligibility criteria include: (1) age ≥ 18 years, (2) histologically confirmed metastatic UM, HLA-A*02:01 positive, (3) measurable disease per RECIST v1.1, (4) ECOG performance status of ≤ 1 , (5) adequate marrow, renal and hepatic function; (6) no more than 50% of liver involvement by tumor. Limited extrahepatic disease is allowed. This study opened for enrollment in November 2025, and two patients have been treated to date (NCT07276386). This study is supported by Delcath Systems, Inc. Clinical trial information: NCT07276386. Research Sponsor: Delcath Systems.

SILVER (supplementing tebentafusp with subcutaneous IL-2 to verifiably eradicate radiological progression): A phase 1/2 trial of IL-2 with tebentafusp upon first radiological progression on first-line tebentafusp alone.

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Background: Metastatic uveal melanoma (mUM) remains a disease with a profound unmet clinical need. Tebentafusp, a bispecific T-cell receptor–anti-CD3 ImmTAC targeting gp100 is the first systemic therapy to demonstrate a reproducible overall survival benefit and is now the standard of care in eligible patients. Despite this advance, most patients ultimately develop radiological progression on tebentafusp, highlighting the need for rational combination strategies that can augment or restore antitumour immune activity. Interleukin-2 (IL-2) has long been recognised as a potent T-cell growth and activation factor. Pre-clinical data demonstrate that IL-2 enhances tebentafusp-mediated tumour cell killing by expanding and priming effector T-cell populations. These effects are mechanistically linked to increased cytotoxic function and improved immune synapse formation (Guc et al., 2025). Importantly, low-dose IL-2 administered subcutaneously has been shown in prior clinical studies to achieve biologically relevant serum concentrations with a substantially improved safety profile compared with historical high-dose intravenous regimens. Collectively, these data provide a strong biological and clinical rationale for combining tebentafusp with low-dose subcutaneous IL-2 in patients with mUM progressing on tebentafusp monotherapy. **Methods:** SILVER is an investigator-initiated, single-arm phase Ib study evaluating the safety, tolerability and preliminary efficacy of tebentafusp in combination with low-dose subcutaneous IL-2 in HLA-A*02:01–positive patients with metastatic or unresectable uveal melanoma who have RECIST-defined progression on tebentafusp alone. Patients receive IL-2 at 125,000 IU/kg subcutaneously, administered for three consecutive days prior to the initial tebentafusp dose, and then weekly 24 hours before each subsequent tebentafusp infusion. Tebentafusp is administered intravenously with step-up dosing in cycle 1, followed by standard weekly dosing thereafter. The primary endpoint is best overall response by iRECIST. Secondary endpoints include RECIST 1.1 response rate, clinical benefit rate, progression-free survival, overall survival, safety and tolerability (CTCAE v5.0), and quality of life. Extensive translational endpoints include serial diffusion-weighted MRI, ctDNA kinetics, and deep immune profiling from blood and tumour biopsies. Early treatment cycles incorporate inpatient monitoring to manage cytokine-mediated toxicities. **Conclusion:** By integrating robust pre-clinical rationale, an established and pragmatic IL-2 dosing strategy, and comprehensive translational analyses, this study aims to enhance tebentafusp activity and improving outcomes for patients with progressive mUM. Clinical trial information: NCT07063875. Research Sponsor: Immunocore; Department of Defence; ME230190 HT9425-24-1-0996.

Clinical trial in progress: Phase II trial of neoadjuvant tebentafusp in patients with locally advanced primary uveal melanoma.

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Background: Uveal melanoma (UM) is the most common intraocular malignant tumor in adults. Primary UM are effectively treated by plaque radiotherapy or enucleation; however, up to 50% of UM patients ultimately succumb to advanced disease. Tebentafusp-tebn is a bispecific gp100 peptide human leukocyte antigen (HLA)-directed cluster of differentiation 3 (CD3) T-cell engager that became the first FDA approved treatment for unresectable or metastatic UM. Among the metastatic UM patients who received tebentafusp on clinical trial (IMCgp100-01 (n=19), IMCgp100-102 (n=146), and IMCgp100-202 (n=245)), 12 patients had recurrent orbital tumors. All orbital lesions were stable or had achieved shrinkage with tebentafusp. The best percentage changes from baseline were reported as -3 to -40% reduction in intra-ocular target lesions. All intra-ocular non-target lesions were stable or achieved a complete response after tebentafusp treatments. These preliminary data indicate that tebentafusp may have potential for treating surgically unresectable primary UM. **Methods:** This is an investigator-initiated, prospective, single arm phase II trial evaluating neoadjuvant tebentafusp in patients with locally advanced primary UM [NCT06414590]. Patients must be 18 years or older, HLA-A*02:01 with a primary UM with T3 or T4 category tumor size. Patients cannot have a symptomatic UM that requires immediate ophthalmological intervention such as enucleation. Patients will be treated with up to 8 weeks of neoadjuvant tebentafusp, followed by radioactive plaque or enucleation. Tebentafusp will be administered as follows: 20mcg on Day 1, 30mcg on Day 8, 68 mcg on Day 15, and weekly doses of 68 mcg thereafter. The first three treatments will require inpatient hospitalization for overnight observation. The primary endpoint of the study is regression (defined as $\geq 20\%$ reduction in tumor volume) of primary UM after tebentafusp treatment in 20% of treated patients. Secondary endpoints include toxicity assessment and ctDNA analysis in both blood and aqueous humor. Exploratory endpoints include changes to visual acuity, radiation dose to the fovea, and treatment (enucleation to plaque brachytherapy). The efficacy of this combination treatment will be assessed using the Simon's two stage design. In stage I, a total number of 8 patients are accrued and if there are 0 responses among these 8 patients, further enrollment of patients may be stopped. Otherwise, an additional 11 patients will be accrued in stage II, resulting in a total sample size of 19 patients. Enrollment began in September 2025 at Thomas Jefferson University Hospital, in conjunction with Wills Eye Hospital. Clinical trial information: NCT06414590. Research Sponsor: Immunocore, Ltd.

Neoadjuvant darovasertib in uveal melanoma patients undergoing primary local therapy (OptimUM-10): Phase 3 trial.

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Background: Uveal melanoma (UM) is the most common intraocular malignancy and has high risk of metastatic progression and poor long-term survival. Standard treatment of the primary tumor includes enucleation (eye-removal), and radiation therapy including plaque brachytherapy (PB) and proton beam therapy, which can result in vision loss or removal of the eye. No approved neoadjuvant therapies exist that shrink the tumor or improve visual outcomes. Almost all UM tumors harbor *GNAQ/GNA11* initiating mutations with downstream constitutive activation of protein kinase C (PKC). Darovasertib, a first-in-class oral PKC inhibitor tested in study OptimUM-09, has demonstrated the ability to reduce UM tumor size resulting in enucleation sparing in patients with large tumors, and radiation reduction in patients with medium sized tumors requiring PB. In addition, visual improvements have been observed not only during neoadjuvant therapy but also in the predicted risk of legal blindness post PB using a vision prognostication tool. **Methods:** OptimUM-10 is an ongoing phase 3, randomized, multicenter, open-label trial enrolling patients with primary non-metastatic UM. Eligible patients must have high metastatic risk (class 2 gene-expression profile, monosomy 3, or AJCC stage 3). Additionally, for the PB cohort, moderate to high risk of vision loss (> 30Gy predicted radiation dose to key visual structures) is required for eligibility. Major exclusion criteria include metastatic disease or extraocular tumor extension, prior UM primary treatment, attributes necessitating immediate enucleation, and relevant ocular comorbidities. The trial has two cohorts: Cohort 1 (n=330) includes patients with medium UM tumors where PB is the standard treatment. Cohort 2 (n=120) includes patients with large UM tumors where enucleation is the standard treatment. In each cohort, eligible patients are randomized 2:1 to receive neoadjuvant darovasertib (300 mg twice daily for up to six 28-day cycles) or standard-of-care treatment with PB (cohort 1) or enucleation (cohort 2). The primary endpoint for cohort 1 is the proportion of patients with loss of Early Treatment Diabetic Retinopathy Study Best-Corrected Visual Acuity of ≥ 15 letters (%VL15) from randomization, while in cohort 2 it is eye preservation rate. Across cohorts, the key secondary objective is to evaluate response rate with neoadjuvant darovasertib. Additional secondary endpoints include event-free survival and safety, as assessed by treatment-emergent adverse events and serious adverse events. Enrollment is ongoing, and results will determine whether OptimUM-10 may establish darovasertib prior to definitive PB as the first neoadjuvant treatment for primary UM to meaningfully reduce tumor burden and expand vision- and eye-preserving treatment options for patients. Clinical trial information: NCT07015190. Research Sponsor: IDEAYA Biosciences, South San Francisco, CA USA.

A phase 3, international, multicenter, randomized, controlled trial of selective index lymph node resection versus therapeutic lymph node dissection after neoadjuvant immunotherapy for stage IIIB-D melanoma (MSLT-3/S2601/EORTC2519).

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Background: Neoadjuvant immunotherapy (NAT) with immune checkpoint inhibitors (ICI) is a standard therapy for resectable stage III melanoma, with randomized trials demonstrating superior outcomes compared to adjuvant therapy alone. The phase 2 SWOG-1801 trial showed 72% EFS at 2 yrs for NAT & 49% for adjuvant PEMBRO ($P=0.004$), while the phase 3 NADINA trial confirmed superiority of NAT IPI/NIVO over adjuvant NIVO (2-year RFS 83.7% vs 57.2%, HR 0.32). Pathological response, particularly major pathological response (MPR; $\leq 10\%$ viable tumor), strongly correlates with improved outcomes, with the International Neoadjuvant Melanoma Consortium (INMC) pooled analysis ($N=610$ ICI patients) demonstrating 3-yr RFS of 93% for MPR patients (pts) vs 41% for those with no pathological response. The PRADO trial demonstrated that selective index lymph node (ILN) resection (RES) can safely de-escalate surgery in MPR pts, with only 4/60 (6.7%) MPR pts recurring after median follow-up of 28.1 months, all locoregionally. ILN RES significantly reduced surgical morbidity & improved quality of life compared to therapeutic lymph node dissection (TLND). However, PRADO was a single-arm proof-of-concept study. An international survey of 117 melanoma experts showed 71% believe a phase 3 randomized controlled trial is needed to change practice. The MSLT-3 trial will definitively establish whether ILN RES is non-inferior to standard TLND for MPR pts.

Methods: This phase 3, international, multicenter, randomized, non-inferiority trial will enroll approximately 1,574 pts with resectable stage IIIB-D cutaneous melanoma to identify 496 with MPR following NAT. Eligible pts must have cytologically/histologically confirmed resectable stage IIIB-D melanoma with at least one macroscopic lymph node in groin, axilla or neck basins. All pts are randomized 1:1 to ILN RES or TLND, stratified by continent/region, AJCC stage, & NAT regimen. Prior to NAT, all pts undergo radiological placement of a marker in the largest metastatic lymph node. Pts receive NAT per institutional standard of care (minimum one PD-(L)-1 checkpoint inhibitor, maximum 6 weeks duration) followed by surgery at weeks 6-9 according to randomized arm. Pathological response is assessed per INMC criteria. Pts with MPR in the ILN arm undergo surveillance only; non-MPR pts in the ILN arm proceed to TLND within 3 weeks. Primary endpoint is 2-year recurrence-free survival in MPR pts (non-inferiority margin -5%). Secondary endpoints include escalation to TLND for isolated nodal recurrence, salvage therapy rates, distant metastasis-free survival, event-free survival, overall survival, surgery-related AEs, quality of life (QLQ-C30, EQ-5D-5L, FACT-M), concordance of imaging/ctDNA with pathology & health economics. Clinical trial information: NCT07049276. Research Sponsor: Australian Commonwealth Government.

NeoIRENIE: A phase 2 randomized trial of intensified neoadjuvant therapy for melanoma patients with multi-omic biomarker or clinically predicted poor response to standard immune checkpoint inhibitor (ICI) therapy.

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Background: Neoadjuvant immunotherapy (NAT) with immune checkpoint inhibitors (ICI) has emerged as superior treatment for stage III melanoma, demonstrating improved outcomes compared to adjuvant therapy. The SWOG-1801 trial showed 23% EFS benefit at 2 years for NAT versus adjuvant PEMBRO (72% vs 49%, $P=0.004$), while the NADINA trial confirmed superiority of NAT IPI/NIVO over adjuvant NIVO (2-year RFS 83.7% vs 57.2%, HR 0.32). Pathological response, particularly major pathological response (MPR; $\leq 10\%$ viable tumor), strongly correlates with improved outcomes, with the International Neoadjuvant Melanoma Consortium pooled analysis ($N=610$ ICI patients) demonstrating 3-year RFS of 93% for MPR patients versus 41% for those with no pathological response. However, standard NAT with IPI (1mg/kg) and NIVO (3mg/kg) achieves MPR in only ~60% of patients. Multi-omic biomarkers can predict poor response to anti-PD-1 therapy, identifying patients who may benefit from intensified ICI therapy. The NeoIRENIE trial evaluates whether intensified ICI regimens improve pathological response in poor prognosis patients identified by biomarker prediction, treatment failure, or mucosal histology. **Methods:** Phase 2, non-comparative, multicenter, randomized trial with 3 cohorts ($N=493$, Table 1). All pts undergo therapeutic lymph node dissection/completion surgery at week 6 with path response evaluation per INMC criteria. Cohorts 1a, 2 and 3 pts without MPR receive adjuvant NIVO 480mg Q4W for 11 doses. CT, MRI brain and FDG PET/CT performed at baseline, pre-surgery and during 10-year follow-up. Tumor, blood and stool samples collected at baseline, wk 3, surgery and recurrence. Primary endpoint: path response rate in each INMC response category. Secondary endpoints: event-free survival, RECIST response rate, metabolic response rate, overall survival, safety/tolerability, surgical outcomes and quality of life. Exploratory endpoints: biomarker analyses and validation of multi-omic predictive model. Clinical trial information: NCT06999980. Research Sponsor: None.

Cohort	N	Resectable Melanoma Patient Population	*Arms (Randomization)
1a	168	Stage IIIB/C/D cutaneous; biomarker-predicted poor responders; treatment-naïve	A-D (1:1:1:1)
1b	154	Stage IIIB/C/D cutaneous; biomarker-predicted high responders; treatment-naïve	E-F (1:1)
2	111	Stage IIIB/C/D cutaneous; recurrence within 6 months of adjuvant or NAT ICI therapy	A-C (1:1:1)
3	60	Any stage mucosal melanoma; treatment-naïve	A-B (1:1)

*Arms:

A=IPI 3mg/kg + NIVO 1mg/kg Q3W x2.

B=NIVO 480mg + RELA 160mg + IPI 1mg/kg Q4W x2.

C=NIVO 480mg + RELA 160mg Q4W x2.

D=IPI 1mg/kg + NIVO 3mg/kg Q3W x2.

E=IPI 1mg/kg + NIVO 3mg/kg Q3W x2.

F=PEMBRO 200mg Q3W x2.

EA6232: A phase II double-blind trial of sulforaphane for therapeutic prevention of melanoma in patients with multiple atypical nevi and a prior history of melanoma.

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Background: A significant risk factor for melanoma is presence of atypical/dysplastic nevi (A/DN), and evidence suggests a 10-fold increased risk of new primary melanoma with A/DN.¹ Patients with prior melanoma and multiple A/DN are thus reasonable targets for therapeutic prevention due to high risk of additional melanoma. Currently, no preventative systemic agent for melanoma is approved. Sulforaphane, an isothiocyanate of cruciferous vegetables, demonstrates therapeutic prevention potential in multiple clinical trials.²⁻³ Topical sulforaphane mitigates effects of UV radiation, a primary driver of melanoma development, in mouse and human skin.⁴ The proposed mechanism involves alterations of transcription factor Nrf2, an antioxidant modulator, and IL-6/STAT-3 pathways in A/DN and melanoma.⁵⁻⁷ Our team conducted a phase I trial of oral sulforaphane for 28 days in 17 patients with prior melanoma and ≥ 2 A/DN.⁸ Statistically significant decreases in several serum pro-inflammatory cytokines were reported with no dose-limiting toxicities. This phase II trial aims to elucidate effects of daily sulforaphane on A/DN lesions and compare pigmentation change to placebo over one year. We hypothesize sulforaphane will demonstrate a greater decrease in total area of pigmented nevocellular nevi (both A/DN and banal nevi) vs. placebo as documented by serial digital photography. **Methods:** This phase II trial (NCT07040280) will assess impact of daily sulforaphane for 12 months vs. placebo on total area, quantity, and features of A/DN. Patients with ≥ 3 clinical A/DN (≥ 5 mm diameter with macular component, and ≥ 2 features of ill-defined borders, color variegation, uneven contour, or erythema) and a history of early stage-melanoma are eligible. Enrolled patients will undergo a baseline clinical skin exam and scheduled follow-up exams every 3 months. Photography of index A/DN and a standardized area of the posterior trunk, excisional biopsy of an A/DN, and peripheral blood sampling will be performed at baseline, 3 months, and 12 months. The primary endpoint is effect of sulforaphane vs. placebo on change in total area of pigmented nevocellular nevi on the posterior trunk at 12 months, calculated by Derma-AI image analysis software.⁹ Secondary endpoints are number of posterior truncal nevi with moderate to significant changes in area, changes in A/DN features/area, and assessment of the safety/tolerability of sulforaphane. Exploratory endpoints include effects on circulating cytokine and chemokine levels assessed by multiplex technology, impact on A/DN immune cell infiltration by histopathology and immunochemistry, and evaluation of prespecified A/DN features at each timepoint. Outcome measures will be compared between arms over serial timepoints by Wilcoxon rank sum test. The study is open for enrollment with accrual goal of 120 patients. Research Sponsor: None.

A multicenter, randomized phase Ib trial to evaluate neoadjuvant immunotherapy combination of nivolumab alone or plus ipilimumab with the IL-2 superkine MDNA11 alone or with tocilizumab in patients with high-risk, surgically resectable melanoma: The NEO-CYT trial.

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Background: Neoadjuvant immunotherapy, administered upfront of surgery in patients with resectable stage III melanoma, has shown superior efficacy in recent trials compared to post-surgical adjuvant treatment, due to enhanced anti-tumor immunity when the tumor micro-environment is intact. A pre-operative regimen of 2 cycles of ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy (as per NADINA trial) results in substantially improved event-free survival. However, even with this regimen 41% of patients did not achieve a Major Pathologic Response (MPR), with 8% having a partial pathological response and 26.4% showing pathological non-response. Previous analyses have shown a 'cold' CD4-IL-2 signature being associated with no-response, which could be overcome by the addition of IL-2. MDNA11 is a long-acting engineered interleukin (IL)-2 albumin fusion protein, with enhanced affinity for IL-2 receptor β (IL-2R β /CD122) and no binding to IL-2R α (CD25). This design enhances the stimulation of IL-2R β -expressing CD8+ T cells and NK cells whilst diminishing the activation of Tregs constitutively expressing the heterotrimeric receptor containing IL-2R α . Thus, we hypothesize that MDNA11 combination with nivolumab +/- ipilimumab may further enhance clinical outcomes of neoadjuvant standard therapy. **Methods:** This is a phase Ib, prospective, open-label, randomised study where a 6-week neoadjuvant phase is followed by a 7-week surgery/post-surgery phase and a 49-week adjuvant phase as per clinical practice. The study population will include adult patients of either sex aged ≥ 18 years with surgically resectable stage IIIB/C/D cutaneous melanoma. Twenty patients will be enrolled in each arm for a total of up to 80 patients. The ARM A is the control one with Ipilimumab 80 mg plus Nivolumab 240 mg administered every 3 weeks for 2 cycles as for NADINA trial; the ARM B includes Nivolumab 240 mg every 3 weeks for 2 cycles plus MDNA11 at 30 μ g/kg on week 0 followed by MDNA11 at 60 μ g/kg on week 2 and week 4; the ARM C includes Ipilimumab 80 mg plus Nivolumab 240 mg administered every 3 weeks for 2 cycles plus MDNA11 at 30 μ g/kg on week 0 followed by MDNA11 at 60 μ g/kg on week 2 and week 4; the ARM D adds tocilizumab 4 mg/Kg on week 0 at the same schedule of the ARM C. The study's primary endpoint is the Major Pathologic Response (MPR) rate at surgery, defined as $\leq 10\%$ viable tumor in the treated tumor bed. Co-primary endpoints include the incidence, severity, and duration of treatment-related adverse events, particularly immune-related, as per CTCAE v5.0. Health-related quality of life will be analyzed using longitudinal models. Exploratory analyses will investigate biomarker associations with outcomes to generate hypotheses. Clinical trial information: 2024-519010-31-00. Research Sponsor: None.

A phase 2 study of neoadjuvant nivolumab + relatlimab versus nivolumab in patients with resectable high-risk basal cell carcinoma.

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Background: The high response rate of neoadjuvant anti-PD-1 has changed the management of locally advanced cutaneous squamous cell carcinoma. However, little is known about the benefit of neoadjuvant immunotherapy for basal cell carcinoma (BCC). Anti-PD-1 is approved second line for advanced BCC where it has modest response rates compared to the first line setting. High LAG-3 expression within the BCC tumor microenvironment may function as a subdominant checkpoint to synergize with anti-PD-1. The current randomized prospective multicenter phase 2 trial evaluates the safety and efficacy of neoadjuvant nivolumab (anti-PD-1) + relatlimab (anti-LAG-3) versus nivolumab alone in resectable high-risk BCC. **Methods:** This multicenter study conducted across the University of California Melanoma and Skin Cancer Consortium will enroll up to 30 patients with resectable high-risk BCC. High-risk BCC is defined by size 2.0 cm or greater in the head and neck region or 4.0 cm or greater for the trunk and extremities. All patients must have surgically resectable disease that is at increased risk for cosmetic disfigurement, functional defects, poor oncologic control, or anticipated to require skin grafting or free flap reconstruction. Patients must also be checkpoint and hedgehog inhibitor naïve with ECOG performance status of ≤ 2 . Key exclusion criteria include recent radiation therapy and any prior history of myocarditis. Patients will be randomized in 2:1 fashion to receive nivolumab 480 mg + relatlimab 160 mg or nivolumab 480 mg IV every 4 weeks for up to 4 doses. Patients may forgo surgery and continue beyond 4 doses for up to 1 year in cases of ongoing clinical benefit. Tumor tissue and peripheral blood will be interrogated for immune cell subsets and checkpoint expression before and after neoadjuvant treatment. The trial's primary endpoint is the combined rate of pathological complete response, major pathologic response, and clinical response following neoadjuvant therapy with secondary endpoints including surgical de-escalation, safety, duration of response, and recurrence-free survival. This trial uses a Simon's minimax two-stage design for the nivolumab + relatlimab cohort. Eleven patients will be enrolled in the first stage. If ≥ 2 patients respond to nivolumab + relatlimab, the study will continue enrollment for a total of 20 patients. This design yields a type I error rate of 0.1 and power of 0.8. This study was approved by UC San Diego's Institutional Review Board; approval number is 810617. Trial Registration NCT06624475. Clinical trial information: NCT06624475. Research Sponsor: Bristol Myers Squibb.

Spino-RT: A multicenter, randomized controlled phase III study of adjuvant radiotherapy versus surveillance in patients with cutaneous squamous cell carcinoma (cSCC) at high risk of recurrence.

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Background: cSCC is the second most common skin cancer, predominantly affecting elderly individuals. Most cSCCs are diagnosed at an early stage and cured with surgery. Recurrences are usually detected during routine clinical examinations or imaging (lymph-node ultrasound, cervicothoracic CT scan). In patients considered at high-risk, local recurrence rates may reach up to 30%. To date, no randomized trial has established the optimal management of cSCCs at high risk of recurrence after complete resection, and indications for adjuvant radiotherapy are only based on local practices or retrospective studies showing variable and contradictory results. **Methods:** This ongoing randomized phase III trial (NCT06692556) compares the efficacy and safety of two commonly used strategies (adjuvant radiotherapy versus surveillance) in patients with cSCC at high risk of recurrence. Key eligibility criteria include age ≥ 18 years, histologically confirmed localized cSCC, complete surgical resection and high-risk of recurrence, defined as: 1) microscopic peri nerval involvement (PNI) with or without one additional risk factor, or 2) the presence of two or three risk factors (excluding microscopic PNI): immunosuppression, tumor diameter > 20 mm, specific location (lip/ear/temple), deep invasion (thickness > 6 mm or invasion beyond the subcutaneous fat), poor differentiation or desmoplasia. The primary endpoint is recurrence free-survival, defined as the time from the date of randomization to the date of first documented relapse (local, regional or metastatic) or the date of death. Secondary endpoints include local and metastatic recurrence-free survival, overall survival, safety and quality of life (EORTC QLQ-C30 and QLQ-ELD14). Exploratory objectives include progression-free survival after treatment for local recurrence in the surveillance arm. A total of 120 events will provide 80% power to detect a significant improvement of the recurrence-free survival in favor of the radiotherapy arm (HR=0.6) at a 2-sided alpha risk of 5%. Considering a two-years recurrence-free survival rate of 60% in the control arm, an accrual period of 18 months, 36 months follow-up for the last patient, and 10% of non-evaluable patients, a total of 266 patients is required (133 par arm). Since the start of recruitment (February 2025), 38 patients have been randomized. 35 French health institutions will contribute to recruitment. Clinical trial information: NCT06692556. Research Sponsor: Ligue Nationale contre le Cancer; 2023.

Phase 2 study of ivonescimab in patients with cutaneous squamous cell carcinoma.

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Background: Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer. In the setting of unresectable locally advanced or metastatic disease, checkpoint inhibitors are standard of care and are associated with robust response rates and durable disease control. However, in those who do not respond or progress on immunotherapy, there are limited available standard therapies. Ivonescimab is a tetravalent bispecific antibody targeting programmed cell death protein 1 (PD-1) and vascular endothelial growth factor A (VEGF-A) that has shown promising activity in multiple tumor types. VEGF-mediated activities include driving angiogenesis creating a tortuous tumor vasculature and decreasing effector T-cells within the tumor microenvironment. Herein, we hypothesize that dual targeting of PD-1 and VEGF-A may overcome resistance to checkpoint inhibitors and extend the benefit of immunotherapy in CSCC. **Methods:** This phase 2, single-arm study will enroll up to 24 patients and will be conducted using a Bayesian optimal phase 2 (BOP2) design. Prespecified activity goal for the first stage of accrual was met; second stage accrual began in January 2026. Patients will receive Ivonescimab 20mg/kg intravenously every 3 weeks until progression, death, or intolerance. The main inclusion criteria include unresectable locally advanced or metastatic CSCC that is refractory to prior checkpoint inhibitors, Eastern Cooperative Oncology group performance score of 0-1, and measurable disease by RECIST version 1.1. Primary exclusion criteria comprise prior severe immunotherapy-associated toxicities, prior organ transplant, or major blood vessel invasion. There are no limits on lines of therapy. Primary objective and endpoint is objective response rate in CSCC. Key secondary endpoints include duration of response, disease control rate, progression free survival, and safety. Additional exploratory objectives include evaluating predictive biomarkers of treatment response or resistance utilizing a mandatory biopsy performed both pre-and on-treatment, with correlatives including whole exome sequencing, RNA sequencing, multiplex IHC. Active recruitment and enrollment are ongoing at The University of Texas MD Anderson Cancer Center, Houston, Texas. Copyright © 2026 AACR. Originally presented at AACR 2026. Reprinted with permission. Clinical trial information: NCT06567314. Research Sponsor: Summit Therapeutics.

A feasibility study of tumor-infiltrating lymphocytes (TIL) in patients with cutaneous squamous cell carcinoma and Merkel cell carcinoma after anti-PD-1 therapy.

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Background: Tumor infiltrating lymphocyte (TIL) therapy is an autologous cellular therapy isolated from a patient's tumor. Clinical data demonstrated that TIL therapy in heavily pre-treated melanoma patients yielded an objective response rate (ORR) in 30% of patients with 5-year overall survival (OS) of approximately 20%. TILs were approved by the FDA in February 2024 for the treatment of metastatic or unresectable melanoma that have progressed on anti-PD-1 therapy and BRAF+MEK inhibitors (in patients with *BRAFV600* mutation). Non-melanoma skin cancers, including cutaneous squamous cell cancer (CSCC) and Merkel cell cancer (MCC), share biologic features with melanoma, including an "inflamed" tumor micro-environment and high responsiveness to anti-PD-1 therapy. However, approximately, a third of patients will experience disease progression after anti-PD-1 therapy or will discontinue treatment due to toxicity and subsequently experience disease progression. Given the overlap between melanoma and CSCC/MCC, we hypothesize that TIL therapy may induce immune response against non-melanoma skin cancers. Because some of these tumors are superficial and are often ulcerated and can contain polymicrobial contamination, this trial will also assess the feasibility of TIL production in this unique patient population, alongside its safety and efficacy. **Methods:** Ten patients with CSCC (Cohort A) and 4 patients with MCC (Cohort B) adults will be eligible for TIL if they have disease progression after anti-PD-1 therapy. Eligible patients should have adequate organ function and be able to receive dose-reduced non-myeloablative lymphodepletion (NMA-LD) and interleukin-2 (IL-2). Following tumor harvest and TIL manufacturing, patients will receive NMA-LD including cyclophosphamide (30 mg/kg on days -5 and -4), and fludarabine (25 mg/m² on days -5 to -1). Subsequently, patients will receive TIL on day 0 followed by IL-2 (600,000 IU/kg) for up to 6 doses. The primary objective is to evaluate feasibility and safety of TIL production and administration in cohorts A and B (defined by successful tumor harvest that leads to a TIL product that contains $\geq 1 \times 10^9$ cells, administration of NMA-LD, infusion of TIL therapy and complete at least 1 dose administered of IL-2). Secondary objectives include ORR, progression-free survival, duration of response, OS and correlative studies. Within Cohort A, efforts will be made to achieve an approximately equal distribution of ulcerated and non-ulcerated lesions. To maintain this balance, ulceration status will be monitored throughout the enrollment process, and eligibility criteria may be modified as necessary to ensure proportional representation of each subtype. Clinical trial information: NCT07288073. Research Sponsor: Iovance.