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MELANOMA AND OTHER SKIN TUMOURS

1076O Primary analysis of the EORTC 1208 Minitub trial: Prospective registry of sentinel node (SN) positive melanoma patients with minimal SN tumor burden

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Background: Retrospective studies have shown the prognostic value of SN tumor burden (van der Ploeg et al. JCO 2011). There are different ways to assess SN tumor burden, e.g. as the microanatomic location (Dewar et al. JCO 2004) or the diameter of the largest deposit (van Akkooi et al. Ann Oncol 2006). The aim of this study was to determine outcomes of patients (pts) with minimal SN tumor burden, managed without complete lymph node dissection (CLND).

Methods: Melanoma pts with minimal SN tumor burden were prospectively followed. Pts were seen every 4 months (yr 1-2), 6 months (yr 3-5) and annually (yr 6-10). They had baseline imaging. An ultrasound of the lymph nodes at every visit was advised. The hypothesis was that the cumulative incidence of distant metastasis at 5 years was lower than 20% in pT2-3 pts.

Results: Between 2015 and 2021, 296 pts were recruited from 21 centers in 9 countries; 17 CLND and 279 observation (OBS), incl. 201 with pT2-3; 149 were eligible (main group). Central pathology review demonstrated 33 pts (11%) did not harbor metastases (macrophages/benign capsule nevi) and 36 (12%) no minimal SN tumor burden. Median follow-up was 4.5 yrs (IQR 3.0 — 5.5 yrs). The cumulative incidence of distant metastasis and death due to melanoma at 5 yrs were 15% (90% CI 10-21%, one-sided p=0.096) and 8% in the main group and 8% & 6% among all patients from OBS group with AJCC8 stage IIIA. SN tumor burden (> 0.1 vs < 0.1 mm)[HR 2.35, P=0.022] and AJCC stage [HR 3.09 for IIIB vs IIIA and 5.01 for IIIC vs. IIIA, P<0.001] were independent prognostic factors.

Conclusions: Central review revealed overdiagnosis in 11%. This first and only prospective study of melanoma pts with minimal SN tumor burden demonstrated low rates of distant metastases or death. SN tumor burden was an independent prognostic factor, and it should be considered to be added to future staging systems for improved prognostication, allowing to spare low-risk stage III pts the potential toxicity of adjuvant therapy.

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Table: 1076O

	Main group (N=149) N (%)	OBS group (N=279) N (%)
Age >65 yrs	34 (23)	71 (25)
Male	66 (44)	127 (46)
AJCC8 stage		
I-II	0 (0)	19 (7)
IIIA	87 (58)	152 (54)
IIIB	41 (28)	56 (20)
IIIC	16 (11)	45 (16)
Missing	5 (3)	7 (3)
Breslow		
pT1 (<1.00mm)	0 (0)	52 (19)
pT2 (1.01 — 2.00mm)	99 (66)	130 (47)
pT3 (2.01 — 4.00 mm)	50 (34)	71 (25) _
pT4 (>4.00mm)	0 (0)	26 (9)
Ulceration		
Absent	122 (82)	227 (81)
Present	22 (15)	42 (15)
Unknown	5 (3)	10 (4)
Number of SN+		
0	0 (0)	19 (7)
1	138 (93)	242 (87)
>1	11 (7)	18 (6)
Systemic therapy	24 (16)	42 (15)

1082O KEYMAKER-U02 substudy 02C: Neoadjuvant pembrolizumab (pembro) and investigational agents followed by adjuvant pembro for stage IIIB-D melanoma

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Background: Substudy 02C of the phase 1/2 KEYMAKER-U02 trial (NCT04303169) is evaluating neoadjuvant pembro with or without investigational agents followed by adjuvant pembro for stage IIIB-D melanoma. We present initial results from arm 4 (pembro + MK-4830 [anti-ILT4]) and arm 5 (favezelimab [anti-LAG-3] coformulated with pembro [fave/pembro]) and updated results from arm 1 (pembro + vibostolimab [vibo; anti-TIGIT]), arm 2 (pembro + gebasaxturev [geba; coxsackievirus A21]), and arm 3 (pembro alone).

Methods: Adults with resectable stage IIIB-D melanoma were randomly assigned to open arms. Patients (pts) received 2 doses of pembro 200 mg Q3W + vibo 200 mg

Table: 1082O

	Arm 1 pembro + vibo n = 26	Arm 2 pembro + geba n = 25	Arm 3 pembro alone n = 15	Arm 4 pembro + MK-4830 n = 25	Arm 5 fave/pembro n = 26
Major pathologic response (pCR + near pCR), % (95% CI)	50 (30-70)	40 (21-61)	47 (21-73)	32 (15-54)	58 (37-77)
pCR, % (95% CI)	38 (20-59)	28 (12-49)	40 (16-68)	28 (12-49)	38 (20-59)
Near pCR, % (95% CI)	12 (2-30)	12 (3-31)	7 (<1-32)	4 (<1-20)	19 (7-39)
pPR, % (95% CI)	31 (14-52)	12 (3-31)	27 (8-55)	8 (1-26)	19 (7-39)
Objective response rate per RECIST v1.1, % (95% CI)	50 (30-71)	32 (15-54)	27 (8-55)	44 (24-65)	35 (17-56)
RFS rate, %					
6 mo	95	95	100	94	93
18 mo	90	90	82	-	-
EFS rate, %					
6 mo	86	76	87	88	92
18 mo	81	72	80	78	-

Q3W in arm 1, 1 dose of pembro 400 mg + 5 doses of geba 3 × 10^8 TCID50 in arm 2, 1 dose of pembro 400 mg in arm 3, 2 doses of pembro 200 mg + MK-4830 800 mg Q3W in arm 4, and 2 doses of fave 800 mg/pembro 200 mg Q3W in arm 5. Resection occurred at week 6. At week 12, pts began adjuvant pembro 400 mg Q6W for ≤8 cycles. Primary end points were safety and pathologic complete response (pCR). Secondary end points included near pCR, partial pathologic response (pPR), and RFS. EFS was exploratory.

Results: 117 pts were assigned to arm 1 (n = 26), arm 2 (n = 25), arm 3 (n = 15), arm 4 (n = 25), and arm 5 (n = 26). Median (range) follow-up was 29.9 (25.9-42.5) mo in arm 1, 29.7 (24.5-40.1) mo in arm 2, 34.3 (29.6-41.5) mo in arm 3, 15.2 (9.6-18.5) mo in arm 4, and 9.4 (4.1-12.6) mo in arm 5. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 8% of pts in arm 1, 28% in arm 2, 7% in arm 3, 16% in arm 4, and 15% in arm 5. No grade 5 TRAEs occurred. Efficacy is reported in the table. Median RFS and EFS were not reached in any arm.

Conclusions: All arms had manageable safety in stage IIIB-D melanoma. With the promising antitumor activity observed in this study, further investigation of pembro + vibo and fave/pembro in this setting is warranted. RFS by major pathologic response will be presented.

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1077MO Adjuvant nivolumab v placebo in stage IIB/C melanoma: 3-year results from CheckMate 76K

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Background: Patients (pts) with resected stage IIB/C melanoma are at high risk of recurrence, similar to resected stage IIIB disease pts. CheckMate 76K (NCT04099251) demonstrated a significant reduction in the risk of recurrence or death with nivolumab (NIVO) vs placebo (PBO) in pts with completely resected stage IIB/C melanoma, leading to widespread regulatory approval. Updated data with 3-y follow-up are presented here.

Methods: Pts aged ≥ 12 y without evidence of residual disease following resection were stratified by tumor (T) category and randomized 2:1 to receive IV NIVO 480 mg or PBO Q4W for 12 mo. The primary endpoint (EP) was recurrence-free survival (RFS); other EPs were distant-metastasis free survival (DMFS), safety, and progression-free survival 2 (PFS2). Baseline tissue was analyzed for emergent biomarkers.

Results: A total of 790 pts were randomized 2:1 to NIVO or PBO. At the 3-y follow-up (median 34.2 mo [NIVO] and 33.9 mo [PBO]), recurrence events occurred in 22% *v* 34% of pts, respectively, including distant recurrence in 11% *v* 17%; distant recurrence sites included lung (8% *v* 12%), lymph node (4% *v* 8%), liver (3% *v* 3%), and brain (2% *v* 4%). NIVO continued to demonstrate improved RFS and DMFS *v* PBO (Table). RFS benefit was also observed across predefined subgroups, including T category (HR [95% CI]: T3b, 0.59 [0.37—0.94]; T4a, 0.57 [0.31—1.01]; T4b, 0.65 [0.44—0.96]). Fewer NIVO pts received subsequent systemic therapy (12%) *v* PBO (27%), and pts receiving adjuvant NIVO had sustained benefit *v* PBO beyond first progression (PFS2; Table). There were no new safety signals. At 24 mos, number needed to treat with NIVO to avoid 1 recurrence was 8 (95% CI, 6—18), and number needed for 1 additional grade 3-4 TRAE was 8 (95% CI, 6—12).

Table: 1077MO

	NIVO (n = 526)	PBO (n = 264)
	3-y rates, % (95% CI)	
	HR[a] (95% CI)	
RFS	71 (66—75)	61 (54—67)
	0.62 (0.47—0.80)	
DMFS	79 (74—82)	74 (68—80)
	0.72 (0.52—1.00)	
PFS2	87 (83—90)	85 (80—89)
	0.71 (0.48—1.06)	

[a] NIVO vs PBO (stratified Cox proportional hazards model).

Conclusions: 3-y follow-up results support the positive benefit—risk profile of adjuvant NIVO as a treatment option for pts with resected stage IIB/C melanoma. The benefit was observed across all subgroups and confirms NIVO as an effective adjuvant treatment. Biomarker data to be presented.

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1078MO Pembrolizumab (pembro) vs placebo as adjuvant therapy for high-risk stage II melanoma: Long-term follow-up, rechallenge, and crossover in KEYNOTE-716

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Background: Adjuvant pembro significantly prolonged RFS and DMFS vs placebo in patients (pts) with resected stage IIB or IIC melanoma in the phase III KEYNOTE-716 study (NCT03553836). We present updated data, including rechallenge and crossover to pembro.

Methods: Pts aged ≥12 y with resected stage IIB or IIC melanoma were randomly assigned 1:1 to pembro 200 mg (2 mg/kg up to 200 mg for pts <18 y) or placebo Q3W for ≤17 cycles (~1 y). The primary end point was RFS. Secondary end points were DMFS and safety. PRFS2 was exploratory. Pts with recurrence >6 mo after 17 cycles of pembro or at any time following placebo in part 1 were eligible to be rechallenged with or crossover to pembro in part 2 (≤17 cycles for resectable disease; ≤35 cycles for unresectable). Part 2 assessed RFS (resectable disease), progression-free survival (PFS; unresectable disease), and safety.

Results: Of 976 pts, 487 were assigned to pembro and 489 to placebo. With a median follow-up of 52.8 mo, pembro prolonged RFS (HR, 0.62 [95% CI, 0.50-0.78]; 48 mo, 71% vs 58%) and DMFS (HR, 0.59 [95% CI, 0.45-0.77]; 48 mo, 81% vs 70%) vs placebo. Median PRFS2 was not reached (NR) in either arm (HR, 0.75 [95% CI, 0.56-1.01]). Of all pts, 9 of 487 (2%) in the pembro group were rechallenged and 71 of 489 (15%) in the placebo group crossed over to pembro. Median follow-up for part 2 was 35.2 mo. Of pts with resectable disease, 0% (0/6) of rechallenged pts and 41% (17/41) of crossover pts had an RFS event (medians, NR). Among pts with unresectable disease, ORR was 0% (0/3; 95% CI, 0-71) in the rechallenge group and 43% (13/30; 95% CI, 26-63) in the crossover group; 33% (1/3) of rechallenge pts and 47% (14/30) of crossover pts had a PFS event (medians, NR and 22 mo). The part 1 safety profile was consistent with prior reports. In part 2, 67% of rechallenged pts and 61% of crossover pts had treatment-related AEs (grade 3/4, 11% and 10%; no grade 5). Immune-mediated AEs or infusion reactions occurred in 0% of rechallenged pts and 30% of crossover pts (grade 3/4, 0% and 6%; no grade 5).

Conclusions: With >4 y of follow-up, pembro continued to show prolonged RFS and DMFS and had promising PRFS2. OS data were immature and will be reported in the future.

Clinical trial identification: NCT03553836; June 12, 2018.

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1079MO Survival before and after the introduction of adjuvant treatment in stage III melanoma: A nationwide registry-based study

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Background: Based on recurrence-free survival outcomes, adjuvant treatments (Adj Tx) with PD-1 and BRAF + MEK inhibitors were approved in stage III cutaneous malignant melanoma (CMM) and have since been widely implemented. However, there are significant side effects and costs of the treatments, and the overall survival (OS)

effect is still uncertain. We previously reported that no OS benefit has been noted in stage III CMM patients after the introduction of Adj Tx in Sweden in 2018 (JNCI 2023). Here we present OS with one more year of follow-up in sentinel lymph node positive (SLN+) patients, together with data on received Adj Tx and OS in different subgroups.

Methods: The population based Swedish Melanoma Registry (SweMR), the Cause of Death Registry and medical records were used to gather data on patient and tumor parameters, received Adj Tx and survival. Patients diagnosed with SLN+ CMM, between 2016 and 2020 were included and divided depending on if they were diagnosed with SLN+ CMM January 2016 to August 2018 (pre cohort) or September 2018 to December 2020 (post cohort), based on the timepoint when Adj Tx was implemented in Sweden. Patients were followed until the end of 2022.

Results: There were 1117 patients registered with a SLN+ CMM in SweMR in 2016-2020. In the pre (n=506) and post (n=611) cohorts, 0.4% and 64% received Adj Tx, respectively (81% anti-PD1 and 19% BRAFi + MEKi). In the post-cohort, the most common reasons for not giving Adj Tx were, favorable tumor characteristics (64%) or comorbidity and/or high age (20%). The 3-year OS rates, in the post vs. the pre cohorts, were 80.9% (95% CI 77.6-84.4) and 80.1% (95% CI 76.6-83.8), respectively, HR 0.92 (95% CI 0.71-1.18 P=0.514). Among patients <75 years old (n=867), in stage IIIB-D (n=850), or with ulcerated tumors (n=505), the HR for OS in the post vs. the pre cohort was 1.13 (95% CI 0.80-1.60), 0.96 (95% CI 0.72-1.28), and 1.21 (95% CI 0.85-1.74), respectively, where 68%, 77% and 78% in the post cohort had received Adj Tx, respectively.

Conclusions: This population-based study is the first to assess the impact on OS following a national introduction of Adj Tx in stage III CMM. At a median follow-up of 3 years in the cohort diagnosed after the implementation of Adj Tx, there is still no evidence for an OS benefit.

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1080MO Sitravatinib plus tislelizumab for metastatic uveal melanoma with liver metastasis: The open-label, multicenter, phase II GEM-2101 trial

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Background: Immune checkpoint inhibitors have limited activity in metastatic uveal melanoma (MUM). Modulation of the tumor vasculature and immune microenvironment could increase patient survival, especially in patients with liver metastasis (LM). This study aims to assess the efficacy of the combination of sitravatinib (sitra), a pan-TKI inhibitor (targeting RET, the TAM family (TYRO3, AXL and MER-TK), VEGFR2, and KIT), and tislelizumab (tisle), an anti-PD1 antibody designed to minimize the binding to Fcγ receptors, in patients with MUM and LM.

Methods: This was a single-arm, phase II trial testing sitra and tisle (sitra+tisle) for systemic treatment-naïve patients or after failure to 1st line tebentafusp if HLA-A02:01. Eligible patients had confirmed diagnosis of LM for MUM that is considered adequate for correlative biopsies. Sitra (100 mg p.o. q.d.) and tisle (200 mg q.3-w) were administered until progressive disease (PD), toxicity, or withdrawal. The primary endpoint was ORR according to RECIST 1.1. Image evaluations were performed q.6-w.

Results: From Nov 2022 to Jul 2023, 16 patients were enrolled. Median age was 63 years (range: 49-86). Extrahepatic disease was present in 43.8%, high LDH in 56.2% and high ALP in 31.2%. Median duration of treatment was 6.6 months (95% CI: 3.5-12.2). ORR was 18.8%, with 3 confirmed partial responses. Stable disease was the most common outcome (81.2%), achieving a disease control rate of 100% with a median follow-up of 6.9 months (range: 2.8-13.4). Median PFS was 8.3 months (95% CI: 7.2-NR). The projected 1-year OS rate was 79.6% (95% CI: 61.1-100). Grade 3-4 treatment-related adverse events were reported in 8 (50%) patients, the most common being hypertension (25%) and diarrhea (18.5%). Treatment was discontinued due to toxicity in 3 (18.8%) patients.

Conclusions: Sitra+tisle showed promising activity with a manageable toxicity profile in patients with MUM and LM. The PFS observed is the longest PFS ever reported for systemic treatment in MUM. An update on translational research to understand synergy between both drugs using correlative liver biopsies is underway.

Clinical trial identification: EudraCT: 2021-002474-99; NCT05542342.

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1081MO Phase I study of WNT974 in combination with spartalizumab in patients with cutaneous melanoma

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Background: Wnt/β-catenin signaling has been linked to T-cell exclusion in melanoma, a feature that is associated with primary resistance to immunotherapy. WNT974, a porcupine inhibitor, has shown evidence of Wnt pathway inhibition in patients (pts) and is well tolerated when combined with spartalizumab, an anti-PD-1 mAb. We therefore hypothesized that WNT974 + spartalizumab may lead to clinical benefit in pts with advanced melanoma resistant to anti-PD-1-based therapy.

Methods: In the combination dose expansion (CDE) part of the Phase I study (NCT01351103), pts with advanced cutaneous melanoma received the recommended dose for expansion (RDE) of WNT974 (10 mg orally QD, d1-8 Q4W) for the first 4 cycles + spartalizumab IV Q4W. Eligible pts had disease that was either 1) primary refractory (PrR) to prior anti-PD-1-based therapy (best response of progressive disease [PD] or stable disease [SD] for ≤ 4 months (mo), or disease recurrence within the first 6 mo of adjuvant anti-PD-1 therapy) or 2) developed acquired resistance (AR) to prior anti-PD-1 based therapy (PD following response or SD for > 4 mo). Here, we present secondary objectives examined during the dose expansion part which include safety, pharmacokinetics, pharmacodynamics, and antitumor activity. We report on pts treated in the CDE, plus 4 pts with PrR cutaneous melanoma treated at RDE in the dose escalation part.

Results: Among 42 treated pts, 28 had PrR disease and 14 had AR. As of Jan 1, 2024, 39 pts had discontinued (81%; 34 due to PD) and 3 were ongoing. Treatment-related adverse events (TRAEs) were reported in 31 pts. The 2 most common TRAEs of any grade were nausea (23.8%) and alopecia (19%); 6 pts had Grade 3/4 TRAEs (increased

lipase, n=4, increased amylase, n = 2, increased blood bilirubin, n = 1 and immune-mediated gastritis, n = 1); no TRAE was fatal. In the PrR group, the overall response rate per RECIST v1.1 was 17.9% (4 partial responses, 1 complete response); 80% of responses were ongoing at 9 mo. Five pts (17.9%) had a best response of SD. Best response observed in the AR group was SD (n = 6, 42.9%). Biomarker analyses are ongoing.

Conclusions: WNT974 + spartalizumab was well-tolerated and demonstrated preliminary antitumor activity in pts with advanced melanoma who progressed on prior anti-PD-1-based therapy.

Clinical trial identification: NCT01351103.

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1083P KEYMAKER 02B: A randomized trial of pembrolizumab (pembro) alone or with investigational agents as first-line treatment for advanced melanoma

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Background: Substudy 02B of the phase 1/2 KEYMAKER umbrella trial (NCT04305054) is evaluating first-line pembro (anti—PD-1) alone or with investigational agents for advanced melanoma. We present results from patients (pts) treated with pembro + vibostolimab (vibo; anti-TIGIT; arm 1), pembro alone (arm 2), quavonlimab (qmab; anti—CTLA-4) coformulated with pembro (qmab/pembro; arm 3), and qmab/pembro + lenvatinib (len; multitargeted TKI; arm 4).

Methods: Pts were aged ≥18 y with previously untreated unresectable stage III or IV cutaneous melanoma who had measurable disease per RECIST v1.1 and an ECOG PS of 0 or 1, but no active brain metastases. Pts were randomly assigned to open arms: pembro 200 mg IV Q3W + vibo 200 mg IV Q3W for ≤35 cycles (arm 1), pembro 400 mg IV Q6W for ≤18 cycles (arm 2), qmab 25 mg/pembro 400 mg IV Q6W for ≤18 cycles (arm 3), or qmab 25 mg/pembro 400 mg IV Q6W for ≤18 cycles + len 20 mg PO QD (arm 4). Primary end points were safety and ORR. DOR was secondary and PFS was exploratory.

Results: Overall, 232 pts were assigned to arm 1 (n = 90), arm 2 (n = 24), arm 3 (n = 31), or arm 4 (n = 87). Median (range) follow-up was 20.3 mo (10.7-42.4) for arm 1, 35.5 mo (18.3-43.1) for arm 2, 27.2 mo (18.2-33.6) for arm 3, and 14.9 mo (7.1-35.9) for arm 4. Efficacy data are reported in the table. Treatment-related AEs (TRAEs) occurred in 88% of pts in arm 1, 79% in arm 2, 97% in arm 3, and 97% in arm 4. Grade 3-5 TRAEs occurred in 31%, 29%, 42%, and 63% of pts, respectively. Three pts (3%) in arm 1 died due to immune-mediated AEs (myasthenic syndrome, myositis, and encephalitis).

Conclusions: Preliminary results from KEYMAKER-U02B showed promising antitumor activity for first-line pembro + vibo and qmab/pembro. Safety was generally manageable. Additional treatment arms will be reported when available. Adjuvant vibo/pembro is being explored in high-risk stage IIB-IV melanoma in the KEYVIBE-010 study.

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Table: 1083P

	Arm 1 Pembro + vibo n = 90	Arm 2 Pembro alone n = 24	Arm 3 Qmab/pembro n = 31	Arm 4 Qmab/pembro + len n = 87
ORR per RECIST v1.1, % (95% CI)	46 (35-56)	38 (19-59)	68 (49-83)	47 (36-58)
DOR, median (range), mo	NR (2.1+ to 36.4+)	NR (2.0+ to 36.1+)	NR (2.1+ to 30.3+)	NR (2.0+ to 30.4+)
≥12 mo, %	84	86	89	80
PFS[a], median (95% CI), mo	13.1 (7.4-24.0)	10.4 (2.2-NR)	NR (16.2-NR)	NR (7.4-NR)
HR (95% CI)	vs arm 2 0.90 (0.49-1.64)	NA	vs arm 2 0.51 (0.23-1.14)	vs arm 3 1.52 (0.76-3.05)
12-mo PFS, %	52	47	73	53
24-mo PFS, %	36	42	57	53

'+' indicates no PD by time of last disease assessment. NA, not applicable; NR, not reached.
[a] PFS data are not yet mature.

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1084P Phase II study of AI-designed personalized neoantigen cancer vaccine, EVX-01, in combination with pembrolizumab in advanced melanoma

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Background: Despite the recent progress in CPI therapy, there remains an unmet need to further improve the outcomes of patients with advanced melanoma. Here, we report 1-year data from a phase II study, assessing safety, efficacy and immunogenicity of the personalized neoantigen (neoAg) peptide vaccine, EVX-01, combined with pembrolizumab in advanced melanoma (NCT05309421).

Methods: Patients (pts) with treatment naïve unresectable or advanced melanoma were enrolled. Pembrolizumab (400mg IV Q6W) was given for 12 wks prior to the first dose of EVX-01. EVX-01 was administered (2mg IM Q2W) for six priming and four booster doses. Investigator response was measured using RECIST 1.1. with scans at baseline and 12 wk intervals thereafter. Primary endpoint, SD to PR/CR or PR to CR conversion rate post EVX-01. Vaccine neoAgs were identified by Evaxion's target discovery AI-Immunology™ platform using tumor DNA- and RNA-sequencing data. T-cell responses were assessed by IFN-γ ELISpot assay and intracellular cytokine staining.

Results: 17 pts were enrolled; response data evaluable for 16. Data cut-off date 07-May-2024 with a med f/u 12.6 mo. PFS was 11.3 mo. At wk 12 post-pembrolizumab only, 8 (50%) PR, 6 (37.5%) SD and 2 (12.5%) PD. 12 pts were evaluable for response at wk 48. 3/12 (25%) had improvement in their response at wk 48 compared to their wk 12 scans; 2 SD pts achieved PR and 1 PR pt achieved CR. 1 PD pt showed 50% tumor RED from wk 12 to wk 72, 21.4% RED from wk 0 and metabolic CR on PET wk 52. EVX-01 induced neoAg-specific T-cell responses in all pts receiving all priming doses, with an observed T-cell reactivity against the majority of the EVX-01 neoAgs. This demonstrates the ability of the AI-Immunology™ platform to precisely predict effective vaccine targets. Treatment emergent adverse events (TEAEs) with EVX-01 were primarily G1/2 and included inj. site reaction (4.8%), diarrhea (4.0%), rash (2.4%), fatigue (1.6%), and one G3 TEAE, hepatitis. No additional toxicity was observed with the combination.

Conclusions: The AI-Immunology™ platform predicted tumor-specific neoAgs with a high success rate. Our results indicate that EVX-01 holds promise as a safe and effective therapeutic approach when used in combination with anti-PD1 therapy.

Clinical trial identification: NCT05309421; 09-Feb-2023.

Legal entity responsible for the study: Evaxion Biotech A/S.

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Disclosure: M.A.A. Khattak: Financial Interests, Personal and Institutional, Local PI, Presenting author of this abstract and previous. I could not retreive information through DOI. But Dr. Khattak has filled out via system: ID 48839: Evaxion Biotech A/S. P.A. Ascierto: Financial Interests, Personal, Other, Consultant and Advisory Role: BMS, Roche Genentech, Novartis, Merck Serono, Sun Pharma, Sanofi, Sandoz, Immunocore, Boehringer Ingelheim Ingelheim, Regeneron; Financial Interests, Personal, Other, Consultant, Advisory Role and Travel support: MSD, Pierre Fabre; Financial Interests, Personal, Other, Consultant and Advisory Role.Travel support: Pfizer/Array; Financial Interests, Personal, Other, Consultant Role: Italfarmaco; Financial Interests, Personal, Other, Consultant Role: Pfizer, Nouscom, Lunaphore; Financial Interests, Personal, Other, Consultant role: Medicenna; Financial Interests, Personal, Other, Consultant role and travel support: Bio-AI Health; Financial Interests, Personal, Advisory Board, Consultant and Advisory role: ValoTx; Financial Interests, Personal, Advisory Board, Consultant and Advisor role.Travel support: Replimmune; Financial Interests, Personal, Advisory Board, Advisor role: Bayer; Financial Interests, Personal, Other, Consultant and Advisory: Erasca; Financial Interests, Personal, Other, Consultant: Philogen; Financial Interests, Personal, Advisory Board: BionTech, Anaveon; Financial Interests, Institutional, Funding, Clinical trial and translational research: BMS; Financial Interests, Institutional, Funding, Clinical Trial: Roche Genentech, Pfizer/Array, Sanofi; Non-Financial Interests, Leadership Role, President since 2010: Fondazione Melanoma Onlus Italy; Non-Financial Interests, Leadership Role, President since 2014: Campania Society of ImmunoTherapy of Cancer (SCITO) Italy; Non-Financial Interests, Other,

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1085P Adoptive cell therapy with TCR gene-engineered T cells directed against MAGE-C2-positive melanoma: An ongoing phase I trial

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Background: MAGE-C2 (MC2) is an immunogenic cancer germline antigen that is highly expressed in melanoma, but not in normal tissues. For adoptive T cell therapy, we selected a highly specific T cell receptor (TCR) and developed a method to generate young MC2 TCR T cells. The primary objective of this first-in-human phase I trial is to determine the recommended phase II dose and demonstrate the safety and feasibility of treatment with autologous MC2 TCR T cells. Secondary objectives include treatment efficacy and measurements of MC2 TCR T cells as well as immune parameters in blood and tumor tissue.

Methods: This is an investigator-initiated single center clinical trial with accelerated titration of five dose levels up to $5.0x10^{10}$ MC2 TCR T cells. Patients with advanced melanoma are eligible if they have progressive disease after standard treatment, an HLA-A2 genotype and MC2-positive tumors. Prior to infusion of T cells, obtained by leukapheresis and processed into advanced therapeutic medicinal products (ATMPs), patients are treated with the epigenetic drugs valproic acid and 5-azacitine. Infusion of MC2 TCR T cells is supported by administration of low dose IL-2. Adverse events (AEs) are documented according to CTCAE v5.0, and tumor response is evaluated according to RECIST v1.1.

Results: So far, six eligible patients with uveal (n=3) and mucosal (n=3) melanoma have been treated. T cell ATMPs were successfully produced for the first four doses ($5x10^7$, $5x10^8$, $5x10^9$ and $1x10^{10}$ MC2 TCR T cells), and two T cell ATMPs were exceptionally released for a lower dose, enabling optimization of the production protocol. Up to the highest administered dose, no irreversible grade 3 or 4 AEs were observed. A mixed tumor response was observed at the second dose level. For higher dose levels, response evaluation is awaited. MC2 TCR T cells could be detected in blood up to six months post infusion.

Conclusions: Production of MC2 TCR T cell ATMPs is feasible. Treatment with MC2 TCR T cells, combined with epigenetic drugs and low dose IL-2, did not result in dose limiting AEs and is well tolerated. The recommended dose for phase II is expected to be at least $1x10^{10}$ TCR T cells, which is scheduled as an international, multicenter study with centralized production of T cell ATMPs.

Clinical trial identification: NCT04729543.

Legal entity responsible for the study: Erasmus MC.

Funding: Dutch Cancer Society (EMCR 2015-7741).

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1086P Intratumoral (IT) administration of autologous CD1c(BDCA-1)+/CD141(BDCA-3)+myeloid dendritic cells (myDC) with the immunologic adjuvant AS01B plus ipilimumab (IPI) and IV nivolumab (NIVO) in patients with refractory advanced melanoma: A phase Ib clinical trial

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Background: Advanced melanoma patients (pts), who progress on immune checkpoint blockade (ICB) or targeted therapy (for $BRAF^{mut}$) have a poor outcome. Conventional CD1c (BDCA-1)$^+$ and CD141 (BDCA-3)$^+$ myDC in the tumor microenvironment are crucial for eliciting antitumor immune responses and the effectiveness of PD-1/CTLA-4 ICB. Following a single IT injection of autologous myDC with (repeated Q2w thereafter) the synthetic saponin-based immune adjuvant $AS01_B$ and IPI plus IV NIVO, 3 responses were obtained in 8 refractory melanoma pts (*ClinicalTrials.gov Identifier: NCT03707808; J. Tijtgat et al. JITC 2024*).

Methods: In a second cohort of this phase Ib trial the safety of a weekly dose-intensified regimen of IT 10 mg IPI and 50 µg $AS01_B$, plus 10 mg NIVO IV Q2w was investigated. As previously, autologous blood myDC isolated by leukapheresis, were injected into the same lesion (day 2). Baseline and on-treatment biopsies were collected.

Results: Six pts (3 M, med age 55y [35-60]) with unresectable stage IIIC (n=2), stage IV-M1a (n=3), and -M1c (n=1) received the planned study treatment with a median of 5 IT and 6 IV injections. Two pts obtained a complete response (CR), and 1 pt a stable disease (disease control rate 50%). A pathological CR was documented in 3 out of 10 injected lesions (in 2 pts with "overall" 1 CR, and 1 SD). mPFS was 35w, mOS was not reached. Treatment related adverse events (TRAE) included transient grade 1/2 injection site reactions and constitutional symptoms. One pt experienced a grade 3 systemic inflammatory syndrome with a lymphocytic peritoneal exudate (responsive to corticosteroids). There were no grade 4-5 TRAE. Multiplex IHC analysis of tumor biopsies is ongoing.

Conclusions: The combination of IT CD1c (BDCA-1)$^+$/CD141 (BDCA-3)$^+$ DC-injection, with weekly IT IPI and $AS01_B$, plus low-dose IV NIVO is tolerable and demonstrated clinically meaningful anti-tumor activity in refractory advanced melanoma. The weekly administration regimen is considered the maximum tolerated treatment intensity. The trial continues as a randomized phase II trial.

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Legal entity responsible for the study: B. Neyns.

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Disclosure: All authors have declared no conflicts of interest.

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1087P Phase II study of niraparib in patients with advanced melanoma with homologous recombination pathway gene mutations

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Background: There are a limited number of therapeutic options available for metastatic melanoma patients progressing on the checkpoint inhibitor(s) and BRAF-targeting drugs. Approximately 21-34% of metastatic melanomas harbor at least 1 molecular aberration in the HR pathway, considered pathogenic leading to HR deficiency. We conducted a phase II study of niraparib in this patient population to evaluate clinical activity.

Methods: In this single-arm, open-label trial, we assessed the overall response rate to niraparib in patients with HR-deficient, unresectable, metastatic melanoma. Eligibility required mutation in *ARID1A/B, ARID2, ATM, ATR, ATRX, BARD1, BRCA1/2, BAP1, BRIP1, CHEK2, FANCD2, MRN11A, RAD50, RAD51, RAD54B or PALB2* gene;, and progression after PD1-antibody or BRAF/MEK inhibitors if BRAF mutant. Niraparib was administered orally once daily at 300 mg or 200 mg, based on body weight and platelet count.

Results: Due to a slow accrual, the enrollment was discontinued after 14 patients were enrolled and treated. Nine patients were female, a median age was 71. Nine patients had ECOG performance status of 1. The subtypes of melanoma were desmoplastic (3), acral lentiginous (2), mucosal (4), uveal (4), unspecified (1). Stages of the disease were III (3 pts) and IV (11 pts). Among the 14 treated patients, 2 (14%)

patients had a partial response, and 7 (50%) had a stable disease. The median PFS was 16 weeks (range, 0-96 weeks). Among 10 patients with non-uveal melanoma, 2 (20%) patients had a partial response with a time to progression of 24 weeks, each. Five (50%) patients had a stable disease lasting 16-98 weeks. None of 4 uveal melanoma patients had a response. There were no unexpected adverse events associated with niraparibe treatment. One responder with ARID1A mutation had detectable circulating tumor DNA at baseline, but it became undetectable during the treatment.

Conclusions: Despite the relatively small number of patients, niraparib showed potential benefits in metastatic melanoma with HR gene mutations, particularly in non-uveal melanoma. Further investigation of PARPi in combination with immunotherapy or other targeted therapy is warranted.

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Legal entity responsible for the study: K. B. Kim.

Funding: GSK.

Disclosure: All authors have declared no conflicts of interest.

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1088P Molecular profiling and matched targeted therapy for patients with advanced melanoma: Results from part I of the MatchMEL study

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Background: While the molecular landscape of melanoma (Mel) has been defined, the clinicopathological associations of pts with BRAF/NRAS wild-type (WT) Mel and immune-checkpoint inhibitors (ICIs) treatment outcomes are less well understood. The MatchMEL study investigated the mutational profile of WT Mel and examined whether targeted treatments could be matched to specific molecular alterations with clinical efficacy.

Methods: In Part 1, consecutive pts with newly diagnosed advanced Mel presenting to two centres in Australia were enrolled. WT pts underwent FoundationOneCDx® (CDx) sequencing. Clinicopathologic features and ICI outcomes were examined. A molecular tumor board analysed CDx results to match targeted therapy to molecular alterations. Part 2 assessed outcomes for patients treated with targeted therapies.

Results: 167 pts were enrolled from Nov '21 to Nov '23, 119 pts were treatment-naïve and 36 received prior neo/adjuvant treatment. A total of 51 (33%) pts had BRAFV600 and 36 (23%) NRAS mutations. Among 68 (44%) WT pts (Table), TMB was possible in 61, with a median 27 Muts/Mb. Pts with mucosal Mel had the lowest TMB (3.5), while the highest TMB was observed in pts with primary Mel of sun-exposed skin (53) and in pts with an NF1 mutation (55). The main mutations were identified in NF1 (37%), BRAF (non-V600; 19%), MEK1 (8%), KIT or PDGFRa (12%), CDKN2a or CDK4 (48%). In 16%, NF1 and CDKN2a/CDK4 mutations overlapped. Aftrer a median 11.6 (2.5-29) months follow-up, the ORR to first-line ICI in treatment-naïve pts was numerically higher in the NF1 population followed by the NRAS and BRAFV600 (75%, 64% and 51%, respectively, $p>0.05$); among WT pts, lower TMB was seen in neo/adjuvant ICIs progressors compared to treatment-naïve pts (11 vs. 37, $p=0.016$).

Table: 1088P BRAF/NRAS wild-type population (n=68)

Primary melanoma type		
Cutaneous, No. (%)	48 (71)	
Sun-exposed, No. (%)	27 (56)	
Non sun-exposed, No. (%)	21 (44)	
Acral, No. (%)	4 (6)	
Mucosal, No. (%)	4 (6)	
Unknown, No. (%)	12 (17)	
CDx results	n=63	**TMB, median**
NF1, No. (%)	23 (37)*	55 (10-264)
BRAF non-V600, No. (%)	12 (19), class 2 (n=8), class 3 (n=3)	21.5 (4-135)
KIT or PDGFRa, No. (%)	8 (12)	62 (0-140)
CDKN2A/B or CDK4, No. (%)	30 (48)*	24 (0-140)
MEK1, No. (%)	5 (8)	33 (5-72)
NRAS	1	8

* n=10 overlapping NF1 and CDKN2A/B or CDK4

Conclusions: Preliminary results of the MatchMel study revealed a variety of molecular mutations in WT melanoma pts. NF1 alterations appeared to be linked with Hi-TMB, which was associated with response to immunotherapy.

Clinical trial identification: NCT02645149.

Legal entity responsible for the study: Melanoma Institute Australia.

Funding: Roche, Novartis.

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1089P Longitudinal biomarker analysis and outcomes for patients (pts) treated with neoadjuvant nivolumab (nivo) and relatlimab (rela) in surgically resectable melanoma

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Background: The neoadjuvant systemic treatment (NST) platform has demonstrated improved clinical outcomes for pts with stage III, surgically resectable melanoma, and provided a unique opportunity for translational analysis into mechanistic insights and treatment (tx) personalization approaches. Our team previously reported NST outcomes with nivo (anti-PD1) + rela (anti-LAG3), which achieved a major pathologic response (MPR; $\leq$10% viable tumor) rate of 63% in a Ph II study (NCT02519322). Here we report the gene expression signature on the samples obtained from this study.

Methods: Baseline (BL), early on tx, and post dose 2/surgical samples were analyzed using the NanoString PanCancer IO360 panel. Differential expression was fit per signature using linear model for analysis (nSolver Advanced Analysis software). Pts were categorized into MPR vs non MPR. Event-free survival (EFS) was assessed using Kaplan-Meier estimation and differences were evaluated using log-rank test.

Results: The analysis included 53 RNA samples from 26 (17 MPR; 9 non MPR) of the 30 pts treated. The median follow up was 44 months (mos) for all pts. Among 14 BL samples, IFN- γ and tumor inflammation signatures (TIS) were significantly higher in pts with MPR vs non MPR. Conversely, BL B7-H3 was significantly lower in MPR pts vs non MPR pts. None of the 7 pts with high IFN- γ nor TIS, nor low B7-H3 have recurred, regardless of path response, with median EFS not being reached. Conversely, the median EFS for the 7 pts with low IFN- γ, TIS and high B7-H3 was 14.5 mos, $p = 0.0065$. At post dose 2/surgery, macrophages and mast cell populations were significantly higher in MPR vs non MPR pts.

Conclusions: The neoadjuvant platform offers unique insights into the tumor microenvironment and dynamics of the immune response over time. Our analysis reveals consistencies with previously published biomarkers associated with response to immune checkpoint inhibitors (IFN- γ) and provides insights into new biomarkers associated with response to nivo + rela, specifically B7-H3. Taken together, this work expands our insights into who may benefit from nivo + rela and provides insights into potentially actionable strategies to personalize tx approaches.

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Legal entity responsible for the study: The University of Texas MD Anderson Cancer Center.

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1090P High concurrent interferon gamma signature expression in the primary tumor and lymph node metastasis is associated with superior outcome upon neoadjuvant ipilimumab + nivolumab in stage III melanoma

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Background: The interferon gamma gene signature (IFNg) has been shown to be predictive and prognostic in patients (pts) with macroscopic stage III or IV melanoma. In macroscopic stage III melanoma, IFNg from lymph node biopsies (LN-IFNg) might be used in the future for neoadjuvant treatment decisions (combination vs monotherapy). To address the question of whether the IFNg can be analyzed using primary tumor material (P-IFNg) instead of LN-IFNg or, in the case of incongruencies, has a higher predictive value when combined with LN-IFNg, we analyzed the IFNg signature in paired samples (P and LN) from stage III melanoma pts.

Methods: Paraffin primary tumor tissue from pts with stage III melanoma, treated in the OpACIN-neo, PRADO and DONIMI trials (neoadjuvant anti-PD1 +/- anti-CTLA4 +/- domatinostat), was retrospectively analyzed with the nanostring nCounter PanCancer immune profiling panel and compared to fresh frozen LN biopsies. The cut-off was calculated based on event-free survival (EFS) using maximally selected rank statistics.

Results: Forty-four pts were included: the majority had a superficial spreading melanoma (68%), with a median Breslow thickness of 1.9mm (IQR: 1.1—2.9), ulceration of 23% and 57% had a BRAF mutation. The median time from primary tumor to trial registration was 21.8 months (IQR: 8.1-48.0). P-IFNg had a low correlation with LN-IFNg (r=0.33, p=0.03). High P-IFNg showed significantly prolonged DMFS and the same trend for EFS, RFS and OS **(Table)**. Pts with concurrent high P- and LN-IFNg had 3 year-EFS of 95% as compared to 88% for pts with LN-IFNg high only, suggesting that addition of P-IFNg could improve selection of pts with better outcomes.

Conclusions: Our results suggest that pts with concurrently high IFNg-signature expressions (high IFNg in P and LN) have a better outcome than LN-IFNg high pts only. If confirmed, these findings could inform treatment selection and prognosis.

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Legal entity responsible for the study: Netherlands Cancer Institute.

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Table: 1090P

	Low P-IFNg (n=14)	High P-IFNg (n=28)	Log rank p-value	Low LN-IFNg (n=15)	High LN-IFNg (n=27)	Log rank p-value	Low LN-IFNg &/or low P-IFNg (n=22)	High LN-IFNg & P-IFNg (n=20)	Log rank p-value
36 month(m) EFS	48%	79%	0.084	33%	88%	<0.0001	45%	95%	0.0052
36m relapse free survival (RFS)	52%	84%	0.056	42%	88%	0.00058	52%	95%	0.0033
36m distant metastasis free survival (DMFS)	53%	88%	0.046	42%	95%	<0.0001	54%	100%	0.00089
36m overall survival (OS)	76%	89%	0.3	59%	100%	0.00029	72%	100%	0.011

Co-Medical Director fee: Melanoma Institute Australia; Financial Interests, Personal, Officer: Bridport Pathology Pty Ltd; Financial Interests, Personal and Institutional, Coordinating PI, Investigator Grant (2022/GNT2018514): National Health and Medical Research Council of Australi. R.P.M. Saw: Financial Interests, Personal, Invited Speaker: Bristol Myers Squib, Novartis; Financial Interests, Personal, Advisory Board: MSD, Novartis, Qbiotics; Financial Interests, Personal, Advisory Board, for MelaSeq-38: Australian Clinical Labs; Financial Interests, Personal, Other, On Faculty, support of University of Sydney salary: Melanoma Institute Australia. A.J. Spillane: Financial Interests, Personal, Invited Speaker, Fee for preparation and delivery of online talk in Oct 2021: Eli Lily Australia. G. Hospers: Financial Interests, Institutional, Advisory Board: BMS, MSD; Financial Interests, Institutional, Research Grant: BMS, Seerave Foundation. A.M. Menzies: Financial Interests, Personal, Advisory Board, advisory board: BMS, MSD, Novartis, Roche, Pierre Fabre, QBiotics. A.C.J. van Akkooi: Financial Interests, Institutional, Advisory Board: Amgen, Bristol Myers Squibb, Novartis, MSD, Merck, Merck - Pfizer, Pierre Fabre, Sanofi, Sirius Medical, 4SC, Provectus; Financial Interests, Personal, Advisory Board: Neracare, SkylineDx; Financial Interests, Institutional, Research Grant, NIVEC study: Amgen; Financial Interests, Institutional, Research Grant: Merck - Pfizer. W. Van Houdt: Financial Interests, Institutional, Invited Speaker: Amgen, Boehringer Ingelheim Ingelheim; Financial Interests, Institutional, Advisory Board: Belpharma, Sanofi, MSD; Financial Interests, Personal, Other, travel grant: Novartis; Financial Interests, Institutional, Local PI: BMS; Financial Interests, Institutional, Research Grant: Amgen; Financial Interests, Institutional, Funding: Sirius. G.V. Long: Financial Interests, Personal, Other, Consultant Advisor: Agenus Inc, Amgen Inc, Array Biopharma Inc, AstraZeneca UK Limited, Bayer Healthcare Pharmaceuticals, BioNTech SE, Boehringer Ingelheim Ingelheim International GmbH, Bristol Myers Squibb, Evaxion Biotech A/S, Hexal AG, Highlight Therapeutics S.L, IOBiotech, Immunocore Ireland Limited, Innovent Bioilogics USA Inc, Merck Sharp & Dohme, Novartis Pharma AG, PHMR Limited, Pierre Fabre, Regeneron Pharmaceuticals Inc, Scancell Limited, SkylineDX B.V; Non-Financial Interests, Principal Investigator, GL is PI on over 30 clinical trials: GL is PI on over 30 clinical trials. C.U. Blank: Financial Interests, Institutional, Advisory Board: BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre; Financial Interests, Personal, Advisory Board: Third Rock Ventures; Financial Interests, Personal, Stocks/Shares: Immagene; Financial Interests, Personal, Stocks/Shares, intention to develop IFN signature algorithm: Signature Oncology; Financial Interests, Institutional, Coordinating PI: NanoString, BMS, Novartis, 4SC; Other, Other, pending patent: WO 2021/177822 A1. All other authors have declared no conflicts of interest.

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1091P Neoadjuvant cemiplimab for stage II–IV cutaneous squamous cell carcinoma (CSCC): 2-year follow-up and biomarker analyses

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Background: Neoadjuvant (neoadj) cemiplimab (cemi) led to high pathologic complete response (pCR) and major pathologic response (MPR) rates in advanced, resectable CSCC. We present 2-year event-free, disease-free and overall survival (EFS, DFS, OS), and new biomarker analyses.

Methods: This non-randomised multicentre phase 2 study (NCT04154943) included 79 patients (pts) with stage II–IV (M0) CSCC treated with $\leq$4 doses of neoadj cemi followed by curative-intent surgery. Adjuvant cemi, radiotherapy (RT) or observation alone were per investigator discretion. EFS, DFS and OS were estimated using the Kaplan-Meier method. Tumour tissue collected pretreatment and at day (D) 22 $\pm$ 3 (after the first cycle of cemi) was analyzed via flow cytometry and bulk RNA/TCR sequencing.

Results: As of 1 Dec 2023, median follow-up was 29.4 months (range: 1.3–41.4) for all 79 pts. Among 70 pts who underwent surgery, adjuvant care was observation alone (n=32), RT (n=17), cemi (n=16), or not available (n=5). 0/40 and 1/10 pts with pCR and MPR, respectively, experienced recurrence. 24-month EFS was 86% (95% CI: 75–92) for all pts: 92% (78–97) for pts with pCR; 89% (43-98) for pts with MPR; 64% (35-83) for non-responders/not evaluable. DFS was 90% (80–96) for pts who underwent surgery. OS was 86% (76–92) for all pts. For pts who received adjuvant cemi (n=16), 25% had $\geq$1 grade 3 or 4 treatment-emergent adverse event (TEAE); no additional serious TEAEs were observed since the last report. Neoadj cemi increased the % of Ki67+ PD1+ CD8 and CD4 T cells in circulation at D22 (n=69; paired t-test p<0.001). Bulk RNA sequencing from paired tumours collected at baseline and D22 (n=25) demonstrated increased expression of effector T-cell-related genes and significant enrichment of T cell activation, interferon-γ/α response, and TCR signalling pathways. Pts with pCR appeared to have significantly increased clonal abundance at D22 vs pts not experiencing pCR (Gini coefficient; paired Wilcoxon p=0.01).

Conclusions: In resectable stage II–IV CSCC, neoadj cemiplimab demonstrates favourable oncologic outcomes with 2 years of follow-up. Results from biomarker analyses indicate that neoadj cemiplimab enhances T cell responses, with increased clonal abundance in responders.

Clinical trial identification: NCT04154943.

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1092P Nivolumab plus relatlimab vs nivolumab in previously untreated metastatic or unresectable melanoma: 3-year subgroup analyses from RELATIVITY-047

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Background: RELATIVITY-047 demonstrated a statistically significant improvement with nivolumab (NIVO) + relatlimab (RELA) vs NIVO for the primary endpoint of PFS per BICR. At the 3-y follow-up, NIVO + RELA continued to show clinically meaningful benefit vs NIVO for PFS, OS, and ORR per BICR in patients (pts) with previously untreated metastatic or unresectable melanoma. Here we report post hoc subgroup analyses with ∼3 y follow-up.

Methods: Pts were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg as a fixed-dose combination or NIVO 480 mg intravenously Q4W. Descriptive post hoc analyses were performed according to baseline (BL) location of metastases (mets; pts could be counted in ≥ 1 category) and no. of mets sites, and by the presence of liver/lung mets (n = 581; mucosal and acral pts were excluded). Efficacy based on BL LDH level and *BRAF* mutation status was examined in all pts (n = 714).

Results: Median follow-up was 33.8 mo. Efficacy according to BL location/no. of mets sites favored NIVO + RELA vs NIVO in most subgroups (**Table**). In pts with BL liver mets, PFS and OS were longer with NIVO + RELA vs NIVO (HR [95% CI]: PFS 0.80 [0.53−1.22]; OS 0.59 [0.36−0.97]); ORR was higher (9.4% ORR difference; 95% CI, −7.7 to 25.6). The benefit of NIVO + RELA was similar for pts with BL lung mets. In pts with BL LDH > ULN, PFS and OS were longer with NIVO + RELA vs NIVO (HR [95% CI]: PFS 0.79 [0.59−1.05]; OS 0.78 [0.58−1.05]). PFS and OS also favored NIVO + RELA vs NIVO in *BRAF* mutant pts (HR [95% CI]: PFS 0.72 [0.54−0.96]; OS 0.75 [0.53−1.07]) and *BRAF* wild-type pts (HR [95% CI]: PFS 0.84 [0.67−1.06]; OS 0.84 [0.65−1.08]). No new or unexpected safety signals were identified.

Conclusions: With ∼3 y follow-up, efficacy outcomes continued to favor NIVO + RELA vs NIVO in pts with cutaneous nonacral melanoma regardless of BL location/no. of mets sites and in pts with BL liver/lung mets. NIVO + RELA was also favored in pts with LDH > ULN and regardless of *BRAF* mutation status. Additional analyses will be presented.

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Table: 1092P

	n	PFS per BICR HR (95% CI)	OS HR (95% CI)	ORR per BICR ORR difference, % (95% CI)
Location of mets				
Skin	22	0.53 (0.19−1.47)	0.55 (0.17−1.84)	18.3 (−20.7 to 50.5)
Soft tissue	65	0.82 (0.44−1.50)	0.71 (0.39−1.31)	7.4 (−14.9 to 29.4)
Liver	122	0.80 (0.53−1.22)	0.59 (0.36−0.97)	9.4 (−7.7 to 25.6)
Adrenal gland	36	0.89 (0.42−1.88)	1.47 (0.61−3.59)	7.4 (−23.6 to 32.6)
Lung	252	0.75 (0.55−1.01)	0.74 (0.52−1.06)	13.1 (0.9−24.7)
No. of met sites				
1	223	0.73 (0.51−1.04)	0.89 (0.59−1.35)	8.1 (−5.1 to 20.9)
2−3	284	0.82 (0.62−1.10)	0.69 (0.49−0.96)	10.4 (−1.1 to 21.4)
≥ 4	61	0.45 (0.24−0.84)	0.55 (0.29−1.02)	23.6 (−0.2 to 43.1)

Unstratified HR; NIVO + RELA vs NIVO. N = 581/714 (mucosal and acral patients excluded).

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1093P Preliminary biomarker analysis in the phase III PIVOTAL study: Evidence for the mechanism of action of daromun in melanoma

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Background: PIVOTAL (NCT02938299) is a randomized phase III trial studying the neoadjuvant use of intralesional Daromun, a combination of two antibody-cytokine fusions, in fully resectable locally advanced melanoma. The study completed the accrual of 256 patients (pts) in the EU and was recently reported to have met the primary endpoint of recurrence-free survival (RFS). Daromun treatment followed by surgery significantly improved RFS (HR=0.59; p=0.005) and distant metastasis-free survival (DMFS) (HR=0.60; p=0.029) compared to the surgery-only control arm. Preliminary translational studies were undertaken to explore Daromun's mechanism of action in the tumor microenvironment (TME) and in blood.

Methods: In a cohort of 32 pts (15 in the Daromun arm; 17 in the control arm), H&E and IHC staining for CD4+, CD8+, NK and Treg cells was performed on surgical specimens. Total tumor infiltrating lymphocytes (TILs) and lymphocyte subpopulations were analyzed both manually and using a digitally-assisted method. In another subset of 33 pts (16 in the Daromun arm; 17 in the control arm), PBMCs were collected at 3 different time points in both study arms and changes in lymphocyte subpopulations were assessed by FACS analysis.

Results: The H&E/IHC results showed a greater amount of TILs and a statistically significant higher influx in tumors of CD8+ T cells in Daromun-treated pts as compared to controls (unpaired t-test $p<0.0001$). To a lesser extent, also CD4+ T cells were increased ($p<0.015$). FACS analysis of PBMCs revealed a transient modest increase of Tregs and a trend to a decrease of MDSCs over time in Daromun treated pts. No differences were observed for CD4+, NK and CD8+ T cell but, for these last, an upregulation of CD25 (a marker of cytotoxic T cell activation) in Daromun-treated pts and significant downregulation in controls could be observed.

Conclusions: An increase in absolute amount and changes in the abundance of TILs and PBMCs subpopulations provide a rationale for the systemic anti-tumor immune response, indicated by a 40% reduction of the risk of distant relapse in the Daromun arm. These results will be discussed, also in relationship to prior treatment with systemic therapies or to post-surgery treatment with adjuvant therapy.

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1094P NeoRisk: Neoadjuvant immunotherapy (NeoIT) recurrence risk assessment tool

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Background: NeoIT with anti-PD-1 (PD1) is now a standard of care for patients (pts) with resectable stage IIIB–D melanoma. Although pathological response is predictive of recurrence, this variable alone cannot accurately identify those pts who will recur, particularly non-responders. We sought to build a recurrence risk assessment tool based on pts demographics, disease characteristics, pathological and imaging data.

Methods: Pts with resectable stage IIIB–D melanoma treated with PD1-based neoIT were included. Pts demographics, disease characteristics, blood parameters, pathological and imaging data at baseline (BL) and post-treatment (post-Tx), and clinical outcomes were analysed. A penalised multivariable logistic regression model was built to predict recurrence and a tool (*NeoRisk*) predicting the likelihood of recurrence for individual patients was generated.

Results: 164 pts who underwent surgery post PD1-based NeoIT and had at least 6 months of follow-up were included; training cohort (n=114; 16 recurrences, 14%) and validation cohort (n=50; 7 recurrences, 14%). After the analysis of >50 variables, the combination of 4 variables accurately predicted recurrence (training cohort, AUC=0.91; validation cohort, AUC=0.93): 1) % of viable tumour cells in the tumour bed post-Tx (AOR=2.55, p=0.0016); 2) density of tumour-infiltrating lymphocytes (TILs) post-Tx (absence, mild, moderate, marked; e.g. marked vs absence, OR=0.39, p=0.0115); 3) difference in the % of fibrosis from BL to post-Tx (OR=0.69, p=0.0531); and 4) % tumour change from BL by RECIST (OR=2.06, p=0.0043). *NeoRisk* can be used to predict recurrence for individual patients; for example, *Patient A* with 55% of viable tumour cells and mild TILs post-Tx, 0% and 2% of fibrosis at BL and post-Tx, respectively, and 13% increase of tumour size from BL, has a risk of recurrence of 82%; while *Patient B*, with the same % of viable tumour cells, but moderate TILs post-Tx, 0% and 35% of fibrosis at BL and post-Tx, respectively, and 12% decrease of tumour size from BL, has a lower risk of recurrence of 20%.

Conclusions: *NeoRisk* can accurately predict recurrence after NeoIT, which may help tailor adjuvant treatment and radiological surveillance interval based on the predicted risk of recurrence for individual patients.

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1095P Pembrolizumab versus placebo after a complete resection of high-risk stage III melanoma: 7-year results of the EORTC 1325-MG/Keynote-054 double-blind phase III trial

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Background: Based on earlier results from our trial, pembrolizumab became a standard adjuvant treatment following a resection of high-risk stage III melanoma. Since late recurrences may occur, long-term data is of key importance.

Methods: Adults with AJCC-7 stage IIIA and a lymph node metastasis >1 mm or IIIB/C without in-transit metastases were randomized 1:1 to receive pembrolizumab 200 mg every 3 weeks or placebo. Treatment continued until a patient received 18 doses or experienced a recurrence or unacceptable toxicity. The co-primary endpoints were recurrence-free survival (RFS) in the overall intention-to-treat (ITT) population and in patients with PD-L1-positive tumors. Distant metastasis-free survival (DMFS) was a secondary and progression/recurrence-free survival 2 (PRFS2, time from randomization until the 2nd recurrence, a progression of the 1st recurrence, or death) an exploratory endpoint. The clinical cut-off date for this analysis was January 3, 2024. The overall survival analysis is planned after 380 deaths or 10 years from the randomization of the last patient, whichever occurs first.

Results: Between Aug-2015 and Nov-2016, 1019 patients were randomized. Overall, 15%, 46% and 39% of patients had stage IIIA, IIIB and IIIC, respectively. The median follow-up was approximately 7 years. Pembrolizumab prolonged RFS, DMFS and PRFS2 compared with placebo. Consistent improvements were observed by BRAF-mutation and PD-L1 status. Overall, 286 patients had died.

Table: 1095P

Endpoint (population)	Pembrolizumab, % at 7 years (95% CI)	Placebo, % at 7 years (95% CI)	HR stratified by stage (95% CI)
RFS (ITT)	50 (46-55)	36 (32-41)	0.63 (0.53-0.74)
RFS (PD-L1+)	51 (46-56)	38 (33-42)	0.64 (0.53-0.76)
DMFS (ITT)	54 (50-59)	42 (37-46)	0.64 (0.54-0.76)
DMFS (PD-L1+)	55 (50-60)	43 (38-48)	0.64 (0.53-0.78)
PRFS2 (ITT)	61 (57-66)	53 (49-57)	0.69 (0.57-0.84)
PRFS2 (PD-L1+)	62 (57-67)	56 (51-60)	0.71 (0.58-0.88)

CI: confidence interval; HR: hazard ratio.

Conclusions: This long-term follow-up data shows that treatment with pembrolizumab following a resection of high-risk stage III melanoma results in a clinically meaningful improvement of RFS, DMFS and PRFS2 as compared with placebo.

Clinical trial identification: EudraCT: 2014-004944-37; NCT02362594.

Legal entity responsible for the study: Merck.

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1096P Camrelizumab plus apatinib in patients with advanced mucosal melanoma: A 3-year survival update with biomarker analysis

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Background: Mucosal melanoma (MM) is an aggressive melanoma subtype with poor response to programmed death receptor 1 (PD-1) inhibitors monotherapy. Our previous single-arm, phase 2 trial (ChiCTR1900023277) reported that camrelizumab plus apatinib had promising antitumor activity in advanced mucosal MM. Here, we reported the 3-year follow-up results from this trial.

Methods: Patients with inoperable stage III-IV or recurrent/metastatic MM received camrelizumab (200 mg biweekly) and apatinib (500 mg daily) until disease progression or intolerable toxicity. In this report, we updated the secondary endpoints of progression-free survival (PFS) and overall survival (OS) with an extended follow-up of 3 years. Peripheral blood samples, collected at baseline and after 2 cycles of treatment, were analyzed for lymphocyte phenotypic profiling and cytokine levels to assess their prognostic value.

Results: Thirty-two patients were enrolled between April 2019 and June 2022. At the cut-off date of 15 April 2024, the median follow-up was 36.21 months (IQR: 3.75-39.59). The median PFS was 8.05 months (95% CI, 6.77-11.89), and the median OS was 14.26 months (95% CI, 11.56-24.54). The OS rates at 1, 2, and 3years were 64.29%, 30.25%, and 20.74%, respectively. Notably, after 2 cycles of treatment, we observed a significant decrease in the proportion of PD-1 positive T lymphocytes (CD3+CD8+CD279+ cells). In addition, the change from baseline in the proportion of NK cells (CD3-CD16+CD56+ cells) was significantly higher in patients who responded to treatment (complete or partial response) than in those who did not respond (stable disease or disease progression). Higher IFN-γ levels at baseline correlated with improved OS (HR = 0.28) and a trend toward better PFS. Patients with lower IFN-γ at baseline had a median OS of 10.81 months, whereas those with higher levels did not reach the median OS.

Conclusions: The 3-year survival update demonstrated that camrelizumab plus apatinib provided long-term survival benefits in advanced MM patients. Peripheral blood levels of PD-1-positive T lymphocytes, NK cells and IFN-γ hold promise as prognostic biomarkers.

Clinical trial identification: ChiCTR1900023277.

Legal entity responsible for the study: Z. Zou.

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1097P Long-term follow-up of advanced melanoma (unresectable/metastatic - aMel) patients (pts) treated with fianlimab (FIAN) + cemiplimab (CEMI): Results from blinded independent central review (BICR) efficacy assessment

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Background: Treatment (Tx) with FIAN (anti-lymphocyte activation gene-3 [LAG-3]) + CEMI (anti-programmed cell death protein 1 [PD-1]) had a 61% ORR in pts with aMel by investigator assessment with an acceptable risk—benefit profile. Here, we present an efficacy analysis by BICR with 12-months (mos) additional follow-up and safety data on pts with aMel.

Methods: This study (NCT03005782) enrolled 3 independent expansion cohorts of pts who were anti—PD-(L)1 Tx-naïve for aMel. Pts received FIAN 1600 mg + CEMI 350 mg IV every 3 weeks (wk) up to 24 mos.

Table: 1097P Efficacy per BICR

	MM1 Initial cohort (n = 40)	MM2 Confirmatory cohort (n = 40)	MM3 neo/adjuvant experienced cohort (n = 18)	MM1+MM2+MM3 (N = 98)	Prior anti-PD-1 treatment in adjuvant/ neoadjuvant setting (n = 13)	Liver metastasis (n = 20)	LDH > ULN (n = 31)
Objective Response Rate (ORR) (95% CI)	60% (43—75)	63% (46—77)	39% (17—64)	57% (47—67)	46% (19—75)	35% (15—59)	55% (36—73)
Complete Response (CR)	23%	25%	28%	25%	31%	0	13%
Progression-Free Survival (PFS), median (95% CI), months	NR (8—NE)	19 (8—NE)	12 (1—NE)	24 (12—NE)	NR (1—NE)	7 (1—NE)	14 (4—NE)

CI, confidence interval; LDH, lactate dehydrogenase; NR: Not reached; NE: not estimated; MM: metastatic melanoma; ULN, upper limit of normal.

Results: 98 pts [median (med) age: 68 years (y)] were enrolled. As of data cutoff (31 October 2023), med follow-up was 23 mos, and med Tx duration was 36 wk. Grade ≥3 treatment-emergent adverse events (TEAEs), serious TEAEs, and immune-mediated adverse event (imAEs) occurred in 47%, 39% and 39% of pts, respectively; 21% of pts discontinued Tx due to a TEAE. Rates of imAEs were similar to PD-1 monotherapy, except for adrenal insufficiency (12% [all grades] and 5% [grade ≥3]). BICR-assessed efficacy data for cohorts MM1, MM2, and MM3 are shown in the Table. Per BICR, overall (N=98) CR, ORR, and med PFS was 25%, 57% (95% CI: 47—67), and 24 mos (95% CI: 12—NE), respectively; med time to response and CR was 1.5 and 4.1 mos, respectively. Disease control rate was 78% (95% CI: 68—85), with med overall survival NR (95% CI: 42—NE). 31% and 4% of pts completed 1-y and 2-y Tx; med duration of response was NR (95% CI: 23—NE). ORR was 50% and 71% in pts with PD-L1 <1% and ≥1%; and 50% and 61% in pts with LAG-3 <1% and ≥1%, respectively. Circulating tumour DNA was cleared by Cycle 4 Day 1 in 15/31 pts.

Conclusions: With longer follow up, FIAN + CEMI in aMel pts showed persistent high clinical activity by BICR regardless of PD-L1 or LAG-3 status and across high-risk subgroups with an acceptable safety profile. The prevalence of CRs increased over time.

Clinical trial identification: NCT03005782.

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1098P Mechanisms of recurrence following mRNA-4157 (V940) plus pembrolizumab or pembrolizumab alone in resected melanoma from the mRNA-4157-P201 (KEYNOTE-942) trial

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Background: mRNA-4157 is a novel mRNA-based individualized neoantigen therapy (INT) designed to enhance endogenous antitumor T-cell responses by targeting unique patient-specific tumor mutations. In the phase 2 mRNA-4157-P201 (KEYNOTE-942) trial, patients with completely resected high-risk stage IIIB—IV melanoma receiving mRNA-4157 + pembrolizumab (pembro) showed prolonged recurrence-free survival and distant metastasis—free survival versus those receiving pembro alone (Weber JS, et al. *Lancet* 2024). A subset of patients, however, had disease recurrence. Here, we examine potential mechanisms of recurrence.

Methods: Patients were randomized 2:1 to receive mRNA-4157 + pembro or pembro alone. A subset of paired baseline and recurrence tumor tissue samples were subject to whole exome and transcriptome sequencing to evaluate tumor mutation and gene expression profiles, respectively. Inflammatory signatures containing known tumor infiltrating lymphocyte and MHC I genes were included in the gene expression score (Ayers M, et al. *J Clin Invest* 2017).

Results: As of Nov 2023 data cut (median planned follow-up, 34.9 months), 16 patients (combination: 11; pembro alone: 5) had paired baseline and recurrent tumor samples available. Baseline characteristics of these patients showed lower inflammatory signatures and tumor mutational burden compared with the overall

population, consistent with prognostic characteristics of these biomarkers observed in the overall study population (Sullivan R, et al. AACR 2023, CT224). Decreased inflammatory signatures at recurrence were identified in 5 of 16 patients; the remaining 11 patients exhibited increased inflammatory signatures at recurrence. Tumors from patients with recurrence underwent evolution, evidenced by changes in tumor mutations and their allelic frequencies. 91% (median [95% CI: 65—100%]) of INT-encoded mutations were present at recurrence.

Conclusions: Multiple potential mechanisms of recurrence can be hypothesized from these observations, including primary resistance to therapy, changes in tumor inflammatory status, and tumor evolution. Further data will be available as the trial matures.

Clinical trial identification: NCT03897881.

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1099P COMBI-EU: Adverse event management of adjuvant dabrafenib plus trametinib (D+T) in patients with BRAF V600-mutant melanoma

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Background: The COMBI-AD study showed that adjuvant therapy with D+T significantly reduces recurrence risk in resected stage III *BRAF* V600—mutant melanoma patients (pts), leading to its EMA approval in 2018. In the study, 26.2% pts discontinued treatment (tx) due to adverse events (AE). The COMBI-APlus trial hypothesised that better AE management could improve tx adherence. The COMBI-EU is a prospective, non-interventional study which aims to assess the usage of adjuvant D+T in clinical practice, and the impact of AE management and usage of app-based documentation on tx adherence.

Methods: This study included adults with complete surgical resection of stage III *BRAF* V600-mutant cutaneous melanoma. AE management was classified as either high or low level of management based on published guidelines. Impact of AE management on time on tx was analysed by a self-developed algorithm and an adapted algorithm from COMBI-APlus. Usage of an app-based documentation of medication intake (Cankado PRO-React) was offered to pts and health-related quality of life was evaluated via the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Results: Of 225 pts, 138 (61.3%) completed tx and 37 (16.4%) discontinued due to tx-related AEs. At least 1 tx-related AE occurred in 181 pts (80.4%), pyrexia being the most common (38.2%). High-level AE management improved tx adherence (high level vs. low level: hazard ratio [HR]: 0.74 (95% confidence interval [CI] 0.49-1.14), this improvement was particularly notable with pyrexia management (HR: 0.52 [95% CI 0.29-0.93]). Only 79 of 225 pts intended to use the electronic app during the study. Age was a significant factor discriminating app users from app non-users (53.4 (14.0) vs. 59.0 (13.9) years). A similar proportion of pts remained on tx for 12 months with or without app usage (39.4% vs 36.5%).

Conclusions: High level AE management, particularly for pyrexia, correlated with improved tx adherence in resected *BRAF* V600-mutant melanoma pts treated with adjuvant D+T. The optional use of an app did not impact tx adherence. Further research is important to understand the impact of tx adherence for the effectiveness of adjuvant tx.

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1100P Anti-PD1 + low-dose anti-CTLA4 immunotherapy pathological response rate in patients with stage III resectable melanoma: Phase III NEOMIMAJOR trial interim analysis

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Background: In a phase III multi-center randomized open-label study BCD-217-3/NEO-MIMAJOR (NCT05751928) a treatment option without lymphadenectomy was investigated. The study drug BCD-217 is a fixed-dose combination of nurulimab (aCTLA-4, 5 mg/ml) and prolgolimab (aPD-1, 15 mg/ml) was recently approved as the 1st line treatment for metastatic melanoma. Here we present the primary interim analysis of the pathological response rate and safety of BCD-217 in neoadjuvant systemic therapy (NAST) arm.

Methods: Pts with respectable stage III melanoma were randomized in 2 treatment arms: BCD-217 arm and CLND + adjuvant pembrolizumab arm. In NAST arm pts received 2 infusions Q3W of 0.2 ml/kg BCD-217. Pts with complete or near complete pathological response (pCR or pnCR) continued with adjuvant aPD1 prolgolimab 250 mg Q3W up to 12 mos, pts not responded to NAST underwent CLND and continued the same adjuvant therapy. pCR was assessed using samples from the index lymph node resection according to International Neoadjuvant Melanoma Consortium (INMC) guidelines.

Results: At the cut-off 15th of Apr'24 108 pts with resectable stage III melanoma (III C/D-71.3% pts) were randomized in 2 treatment arms: NAST arm (n=57) and AT (n=51). For a median follow-up of 2.8 mos 43/57 (75.4%) pts of NAST arm undergo index lymph node resection for pCR assessment. 22/57 (38.6%) pts met pCR/pnCR criteria (ITT). Only 4/57 (7%) pts in the BCD-217 arm had radiological disease progression, 2/57 (3.5%) pts died (one before and one after 1st infusion). 35/55 (63.6%) pts in the BCD-217 arm had any grade (Gr) AEs, 4/55 (7.3%) had severe (3-5 Gr) AEs, 21/55 (38.2%) pts had irAEs (3 Gr - 1/55 (1.8%)) from the pts who received at least one administration or surgery. Surgery-related AEs (all Gr 1-2) were observed in 8/55 (14.5%) pts. No pts required therapy discontinuation due to AEs.

Conclusions: The presented data shows that 2 cycles of BCD-217 are enough to achieve pCR and potentially avoid CLND in ~40% pts. pCR/pnCR can be recognized as a hallmark of OS/DFS improvement according to INMC. There were no severe irAEs or treatment-related AEs. The study population in BCD-217-3/NEO-MIMAJOR initially had a worse prognosis compared to the similar trials.

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1101P Efficacy of anti PD-1 therapy in children and adolescent melanoma patients (MELCAYA study)

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Background: The incidence of melanoma in children and adolescents (CA) is reported to be about 5 per million. In these patients (pts), data on the efficacy and safety of anti PD-1 antibodies are lacking. The aim of this study was to determine outcomes of CA melanoma pts receiving anti PD-1 antibodies.

Methods: Melanoma pts ≤ 18 years treated with anti PD-1 based therapy were retrospectively retrieved from 11 academic centers. Information on histopathological diagnosis, surgical treatment, systemic therapy, objective response rate (ORR), safety profile was collected. A central pathology review was carried out in selected cases. Progression-free survival (PFS) and melanoma-specific overall survival (OS) were assessed by Kaplan-Meier method. The study was funded by an EU Horizon Grant (101096667).

Results: Between April 2016 and March 2024, 83 pts treated with systemic therapy were identified and data analysed. Median age was 14 yrs (range 2-18 yrs), 21 pts were ≤ 12 yrs. Overall, 27 CA pts with stage III disease received anti PD-1 antibodies in adjuvant setting, while 48 received anti PD-1-based therapy for advanced disease, and among them 32, 13 and 3 received treatment in 1st, 2nd and 3rd line, respectively. Finally, 2 pts received anti-PD-1 based neoadjuvant treatment. Median follow-up was 5 yrs (IQR 3 – 11 yrs). In CA pts with advanced disease, among the 32 CA pts who received a 1st line therapy with anti PD-1 the ORR was 37.5%, median PFS and OS

were 4.2 months (95%CI: 1.0-7.4) and 27.2 months (95% CI: 6.7-47.7), respectively. Median age of responders vs non responders was 13.5 (3-18) vs 12.0 (0-18), respectively. At 3 years the landmark OS was 41.5%. The ORR was lower in the 2nd (13.3%) and 3rd (16.7%) line settings. In CA pts treated with adjuvant anti PD-1 therapy, 3 yrs PFS and 3 yrs OS were 62.1% and 74.2%, respectively. Two pts treated with neoadjuvant PD-1 based therapy achieved pathologic complete response and are still disease free after 36 and 18 months of follow-up, respectively. Toxicities were consistent with previous studies in adult melanoma pts.

Conclusions: Our study provides the first evidence of efficacy of anti PD-1 antibodies in CA melanoma pts, particularly in the first-line setting. Our study supports the use of anti PD-1 therapy in pts < 18 yrs, included those < 12 yrs.

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1102P Immune checkpoint inhibitor rechallenge after treatment with tumor-infiltrating lymphocytes in unresectable melanoma

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Background: Adoptive cell therapy with tumor infiltrating lymphocytes (TIL) is a newly approved therapeutic strategy in melanoma refractory to immune checkpoint inhibitors (ICIs), but data to guide subsequent therapy decisions after TIL are limited. Specifically, the safety and efficacy of ICI rechallenge (often necessary due to limited alternatives) is unknown and may be affected by the infusion of large numbers of effector T cells with varying antigen specificity.

Methods: Patients with unresectable melanoma treated with sequential ICI therapy, TIL, and ICI rechallenge were identified at 10 international centers. Investigator-assessed response to ICI rechallenge was determined through radiographic and clinical review, and the response rate was calculated as the proportion of patients having a complete (CR) or partial (PR) response. Overall survival (OS) was calculated from post-TIL ICI treatment start to death or last follow up; duration of response (DOR) was calculated from date of response to progression, death, or last follow up.

Results: 102 patients rechallenged with ICIs after melanoma progression on TIL therapy were identified. The most common M stage was M1c (59%) and LDH was elevated in 46% of patients; 80% of patients had received anti-PD-1 monotherapy prior to TIL and 50% had received prior nivolumab-ipilimumab (nivo-ipi). Toxicity and response data were available for 93 and 97 patients respectively. ICI-related toxicity was identified in 22 patients (24%), and among those 6 patients (27%) had a recurrence of a toxicity seen with pre-TIL ICI. Among 97 patients with available response data to ICI rechallenge, the response rate was 7.2% (2 CR; 5 PR; 95% CI 3.0-14%). Reponses were observed with nivo-ipi (n=5) nivolumab-relatlimab (n=1), and ipilimumab monotherapy (n=1); 6 of 7 responders were exposed to a new ICI after TIL. Median OS from ICI rechallenge was 7.7 months (95% CI 6.2-12 months); median DOR was not reached.

Conclusions: ICI rechallenge has limited clinical activity in patients with melanoma that has progressed following initial ICI treatment and TIL therapy, with most responses occurring after the introduction of a new agent. No unexpected safety signals were observed.

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1103P Real-world efficacy of relatlimab and nivolumab in advanced or resectable melanoma

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Background: Fixed-dose combination NIV-RELA improves progression-free survival (PFS) compared to NIV in patients (pts) with therapy-naive advanced melanoma (MEL) (10.1m vs. 4.6m) but has limited activity after prior immunotherapy. The pathologic response rate (pathRR) to neoadjuvant NIV-RELA is 70%. Real-world data on safety & efficacy of NIV-RELA is lacking. We report the largest single center experience of NIV-RELA in advanced MEL & as neoadjuvant therapy in resectable MEL.

Methods: All MEL pts treated with NIV-RELA from FDA approval until 3/2024 were grouped in 3 cohorts (C): 1st line (C1, n=68) or subsequent line (C2, n=120) advanced MEL & neoadjuvant (C3, n=17). Safety, PFS, overall survival (OS) & pathRR in relation to MEL characteristics were evaluated.

Results: The table shows demographic and efficacy data. In C1, pts with ≥3 *vs.* <3 organs involved had worse PFS (p= 0.007); normal LDH *vs.* > upper level of normal (ULN) LDH pts had improved PFS (p=0.04). For C2 pts, ≥3 *vs.* <3 organs involved had worse OS (p=0.02); normal LDH *vs.* >ULN LDH and ECOG 0 *vs.* ECOG ≥1 had improved OS (p<0.001). In pts with prior anti-PD1 only (22%), the mPFS & mOS were 5.8m (3.4-NR) & 17m (12-NR) respectively. Adverse events (AEs) occurring in ≥5% C1 pts were dermatologic (40%), arthralgia (19%), colitis (10%), adrenal insufficiency (AI, 9%) & transaminitis (9%). In C2, AEs in ≥5% pts were dermatologic (18%), arthralgia (7.5%), colitis (5%) & transaminitis (5%). In 16 evaluable C3 pts, 3 had clinical progression, 2 partial & 6 pathologic non-response. PathRR was 44%, all in *BRAF* WT MEL. No pathologic responder has recurred. AEs in ≥10% of C3 pts were dermatologic (35%), AI (12%), myocarditis (12%) & transaminitis (12%).

Table: 1103P

	Cohort 1 (n=68)	Cohort 2 (n=120)	Cohort 3 (n=17)
Median follow-up	9.1m	11m	8.4m
Median age	70y	68y	65y
Female %	32	33	47
BRAF WT	34/57	72/117	12/17
Normal LDH	51/62	79/113	15/16
Liver mets %	10	28	0
≥3 organs involved %	13	34	0
mPFS	19m (7.3-NR)	3m (2.7-3.9)	NA
6m PFS/OS %	64/ 92	30 / 71	NA/100
mOS	NR	14m (9.7-19)	NR
12m PFS/OS %	57 / 83	14 / 56	NA/100
Major Pathologic Response Rate %	NA	NA	31
Pathologic Complete/Near-Complete response	NA	NA	3/2
TRAEs-requiring steroid therapy %	56	38	41

Conclusions: Combination Our cohort confirms 1st-line efficacy of NIV-RELA in advanced MEL but with high rate of steroid-requiring AEs. For subsequent lines, pts with prior anti-PD1 only may derive greater benefit. In resectable MEL, the pathRR appears lower than previously reported.

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1104P Early time-point ^{18}F-FDG-PET/CT at week four (W4) as a prognostic biomarker of survival in metastatic melanoma (mM) patients (pts) on immunotherapy

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Background: A considerable proportion of mM pts do not respond to immunotherapy with immune check-point inhibitors (ICI). There is a great need to develop non-invasive imaging biomarkers (IBM) to detect pts not responding to ICI. The aim of this

study was to evaluate the role of an early time-point ^{18}F-FDG-PET/CT at W4 as a prognostic biomarker of overall survival (OS) in mM pts on ICI.

Methods: In this prospective non-interventional, one-centre clinical study mM pts, receiving ICI, were regularly followed by ^{18}F-FDG PET/CT. Pts were scanned at baseline, at W4 after ICI initiation, week sixteen (W16) and week 32 (W32). Tumour response to ICI at W4 was assessed using a modified EORTC criteria. Pts were first classified into 6 categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), mixed response (MR), possible pseudoprogression (PP). The pts with PD were then classified into no clinical benefit group (no-CB), all others into clinical benefit group (CB). The primary end point was analysis of OS based on W4 ^{18}F-FDG PET/CT response. Kaplan-Meier analysis was done to compare different categories and Pearson correlation was used to correlate prognostic value of W4 scan and level of serum LDH at the beginning of ICI treatment.

Results: Altogether, 71 pts were included. Median follow-up of pts was 30 months (95% CI = [23.1-34.1]). Three (4%) pts had only baseline scan due to rapid disease progression and death prior to W4 ^{18}F-FDG-PET/CT. Fifty- one (72%) pts were classified into CB group and 17 (24%) into no-CB group. Twenty-three (32%) pts had elevated serum LDH. There was a statistically significant difference in median OS between CB group (mOS not reached; 95% CI = [18 - NA]) and no-CB group (mOS 6.3 months; 95% CI = [4.6-NA]), (p =. 001), and also in mOS between pts with normal level of LDH (mOS not reached, 95% CI = [18 - NA]) and elevated level of LDH (mOS 6.3 months; 95% CI = [3.8-NA]), (p =. 001). There was no correlation between tumour response at W4 and LDH level (r = -.34).

Conclusions: Evaluation of mM pts with early ^{18}F-FDG-PET/CT at W4, treated with ICI, can serve as a prognostic IBM. It is independent from serum LDH level.

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1105P Predicting the outcomes of advanced cutaneous melanoma cases following discontinuation of immune checkpoint inhibition

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Background: Cutaneous melanoma (CM) is among the most aggressive skin cancers. Immune checkpoint inhibition (ICI) has transformed the treatment of advanced melanoma, notably improving overall and progression-free survival rates. However, biomarkers to identify patients that can safely stop ICI are still lacking.

Methods: This multicentre study involved 83 patients diagnosed with unresectable or metastatic CM who electively stopped treatment with anti-PD-1 monotherapy or combination with anti-CTLA-4 in the absence of disease progression (Relapse vs relapse-free: N=27 vs 56). Patients with a minimum of 2 years of follow-up data were included in the study. Subsequent analysis utilized targeted-transcriptome profiling and image analysis. A total of 770 genes related to cancer-immune pathways were assessed and 5 image parameters were measured on tumor tissues using H&E images: tumor cell, lymphocyte, neutrophil, plasma cell, and eosinophil densities.

Results: Out of the five parameters assessed through image analysis, tumor cell density, plasma cell density, and eosinophilic granulocyte density significantly stratified CM patients based on their progression-free survival (PFS) after discontinuation of ICI (p = 0.04, 0.04, 0.017, respectively). To enhance stratification, a cumulative score combining lymphocyte, plasma cell, and tumor cell density parameters was generated, effectively stratifying patients based on PFS ($p < 0.0001$). Cox regression analysis indicated significant associations between 8 genes and PFS in our cohort. Multivariate Cox regression analysis revealed an interaction between TGFBR1, LOXL2, and the image parameter, where high expression of TGFBR1 and a higher score in the image parameter were significantly associated with relapse after discontinuation of ICI. Using these parameters, a model was trained and achieved 84.6% accuracy in predicting outcomes in the test cohort.

Conclusions: Through our study, we propose a novel approach to patient risk stratification for tumor progression after ICI treatment. Our investigation into predictive biomarkers for relapse post-ICI cessation aims to aid patients and physicians in informed decision-making.

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1106P NivoLag-when: International real-world study of combination immunotherapy sequences in melanoma

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Background: Three immune checkpoint inhibitor (ICI) regimens are standard of care in metastatic melanoma (MM): anti-PD1 combined with anti-CTLA4 (ipi/nivo), with anti-LAG3 (rela/nivo) or as monotherapy. Data describing the efficacy of sequential regimens are limited.

Methods: This multicenter retrospective and prospective study assessed patients (pts) who received rela/nivo followed by ipi/nivo (A); ipi/nivo followed by rela/nivo (B); or anti-PD1 followed by rela/nivo (C). Primary endpoint was objective response rate (ORR) to second treatment (Tx). Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety.

Results: With a median follow-up of 62.5 months (mo), 130 pts (A=26; B=43; C=61) from Europe, USA and Australia were included. Favorable baseline characteristics were observed in C, with lower prevalence of stage M1c-d (26.3%) compared with A (88.4%) and B (67.5%) and fewer pts with high LDH (14.8%) compared with A (46.2%) and B (32.6%). In C, 12 pts had received anti-PD1 as adjuvant Tx, of which 8 were primary resistant (PRes), as defined by the SITC (Kluger JITC 2020). B had more pretreated pts with ≥2 lines in 44.2%, vs 7.7% in A and 8.2% in C. ORR were 15.4%, 19% and 26.8% in A, B and C respectively. ORR were numerically lower in PRes to prior Tx than for secondary resistance (SRes) in A and B. In C, ORR was 33.4% (95% CI 9.9-65.1) for pts who received prior adjuvant anti-PD1 vs 23% (95% CI 11.8-38.6) in the metastatic setting. Disease control rates (DCR) were comparable in A and B. Six-mo DCR were 11.5% in A, 23.3% in B and 29.5% in C. No unexpected toxicity was observed and recurrent adverse events occurred in 7.7% in A, 11.6% in B and 13.1% in C. Discontinuation due to toxicity was 31% in A, 4.6% in B and 4.9% in C.

Table: 1106P

	A rela/nivo ->ipi/nivo			B ipi/nivo -> rela/nivo			C anti-PD1 -> rela/nivo		
	N=26	PRes N=15	SRes N=6	N=43	PRes N=21	SRes N=12	N=61	PRes N=34	SRes N=19
ORR% (95%CI)	15.4 (4.4-34.9)	6.7 (0.0-3.2)	33.3 (4.3-77.7)	19 (8.6-34.1)	14.3 (0.0-36.3)	33.3 (9.9-65.1)	26.8 (15.8-40.3)	23.3 (9.9-42.3)	26.3 (9.1-51.2)
DCR% (95%CI)	30.8 (14.3-51.8)	20 (4.3-38.1)	50 (11.8-88.2)	31.0 (17.6-47.1)	23.8 (8.2-47.2)	41.7 (15.2-72.3)	46.4 (33.0-60.3)	36.7 (19.9-56.1)	52.6 (28.9-75.6)
PFS, median (95%CI)	2.6 mo (2.1-3.1)			2.8 mo (2.4-3.2)			1.9 mo (1.4-2.5)		
OS, median (95%CI)	21.77 mo (6.6-36.9)			33.27 mo (20.2-46.4)			36.83 mo (25.5-48.2)		
Toxicity grade ≥2%	26.9			18.6			27.9		

Conclusions: Despite the limitation of a retrospective study, our results suggest that pts with MM respond more frequently to sequential ICI combination when they have previously responded to ICI (SRres), whereas PRes does not impair ORR in pts treated with adjuvant anti-PD1.

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1107P Characteristics and quality of life of nine-year survivors from 312 patients with metastatic melanoma treated with pembrolizumab

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Background: Immune checkpoint blockers (ICB) have improved overall survival of metastatic melanoma patients. Therefore, quality of life and long-term sequelae from ICB induced immune-related adverse events (irAE) are of importance.

Methods: 13 German skin cancer centers evaluated survival of melanoma patients that started pembrolizumab before 07/2015 after progression with at that time standard of care agents (ipilimumab, BRAF/MEK inhibition, chemotherapy). The number of melanoma survivors, deaths and patients lost to follow-up was assessed. For surviving patients baseline characteristics, efficacy and irAE under therapy were collected. Patients were interviewed about current symptoms and quality of life.

Results: From 312 treated patients 231 (74%) have died, 28 (9%) were lost to follow-up and 53 (17%) are still alive after a median follow-up of 9.1 years from treatment start. In this surviving cohort (n=53), baseline characteristics were: 31 (58%) male, median age 60 (range 27-76), 35 (66%) ECOG 0, 21 (40%) BRAFV600E/K mutated, 35 (66%) M1c/d stage, 23 (43%) with elevated LDH and a median number of 2 pretreatments (range 1-6). Survivors showed an overall response rate of 91% with 37 complete responses (CR, 70%). 21 (40%) patients eventually progressed with subsequent treatments being mainly ICB (18) and local therapies (10). As of January 2024, 45 (85%) patients are without evidence of disease and 6 (11%) with controlled disease. Concerning toxicity, 38 (72%) experienced irAE under therapy, 15 (28%) of grade 3/4. After now almost 10 years, 18 (34%) patients state persisting symptoms, mainly vitiligo (4), hypothyroidism (4), pituitary/adrenal gland insufficiency (3) and fatigue (3). Of 23 patients still in working age, 8 (35%) were not able to work anymore. However, quality of life as measured by median WHO-5 score was 19 (76%) which is above the mean scores for the general population in Germany.

Conclusions: Pembrolizumab induced long-term survival in 17% of patients with pretreated metastatic melanoma in a real-world setting, most of them responded to pembrolizumab with a CR. Permanent sequela from immunotherapy were noted, however, quality of life was good in most patients.

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1108P Impact of quantitative imaging of all disease on the prognostic value of ^{18}F-FDG PET/CT in patients treated with immunotherapy for metastatic melanoma

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Background: ^{18}F-FDG PET/CT is crucial in guiding immunotherapy for patients with metastatic melanoma (MM). Quantitative imaging offers a comprehensive view of disease burden, however optimal use of this information is undetermined. This study aimed to investigate the prognostic value of quantitative imaging information derived from FDG PET/CT for survival analysis.

Methods: 103 MM patients received immunotherapy: pembrolizumab (n=60), ipilimumab (n=7), nivolumab (n=12), or ipilimumab + nivolumab (n=24). TRAQinform IQ software (AIQ Solutions) tracked lesion-ROI on FDG PET/CT scans retrospectively collected from baseline (BL) and first on-treatment follow-up (FU) images. Imaging features, including size, intensity, percent change, and heterogeneity, were extracted. Cox Proportional Hazards CoxPH models assessed Overall Survival (OS) and Progression Free Survival (PFS) with varied input features and lesion-ROI subsampling. Model performance, evaluated using the C-index (C) of 1000 bootstrap iterations, was compared with paired t-tests.

Results: Model outcomes are summarized in the table. For OS: three CoxPH models with all lesion-ROI and subset of features reached max C=0.81; four models with all features and subset of lesion-ROI achieved max C=0.85. Top model, C=0.87, included all features and lesion-ROI. For PFS: three models with all lesion-ROI and subset of features reached max C=0.58; four models with all features and subset of lesion-ROI achieved max C=0.73. Best model, C=0.77, included all features and lesion-ROI. Paired t-tests among bootstrap samples reveal significant p-values (<0.001) across diverse inputs.

Table: 1108P

Input		C (median of 1000 bootstrap samples) ± std	
Lesion-ROI	Features	OS	PFS
All	BL	0.66±0.05	0.55±0.06
All	BL + FU	0.79±0.04	0.57±0.05
All	BL + FU + % change	0.81±0.04	0.58±0.05
1 Hottest	All (BL + FU + % change + heterogeneity of change)	0.80±0.04	0.64±0.05
5 Hottest	All	0.85±0.04	0.68±0.05
1 Largest	All	0.82±0.04	0.65±0.05
5 Largest	All	0.84±0.04	0.73±0.05
All	**All**	**0.87±0.03**	**0.77±0.05**

Conclusions: FDG PET/CT image analysis enabled the extraction of image features including characterizing lesion heterogeneity of change. The inclusion of all lesion-ROI and all features including lesion heterogeneity information helped improve the prognostic value of multivariable models for both OS and PFS.

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1109P Association of clinical features with long-term survival in patients with melanoma who responded to distinct checkpoint inhibitors

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Background: In metastatic melanoma, patients responding to checkpoint inhibitors (CPIs) may develop acquired resistance. This study explores clinical characteristics associated with favorable long-term outcomes among CPI responders.

Methods: We utilized the Danish Metastatic Melanoma Database (DAMMED), a national registry collecting prospective data on all patients undergoing systemic treatments. We retrospectively collected baseline, treatment, and clinical outcome information for patients treated with CPIs up to 4th line (ocular melanoma, reinductions and clinical trials excluded).

Results: A total of 3,120 patients were analyzed, receiving treatments with ipilimumab (ipi, n=821, ORR 19%), anti-PD-1 (PD-1, n=1557, ORR 47%), or ipilimumab+nivolumab (ipi+nivo, n=742, ORR 48%). Of these, 1,253 patients achieved partial response (PR) or complete response (CR). Median follow-up was 4.6 years. Estimated 5-year outcomes demonstrated excellent long term survival rates for unselected patients achieving CR (Table).

Table: 1109P

Estimated 5-year outcomes (all pts)	PR (n=669)			CR (n=584)		
	Ipi (n=95)	PD-1 (n=375)	Ipi+Nivo (n=199)	Ipi (n=62)	PD-1 (n=363)	Ipi+Nivo (n=159)
PFS	7%	12%	32%	73%	79%	79%
OS	46%	39%	55%	93%	86%	86%
MSS	49%	49%	61%	97%	93%	93%

In multivariable analyses on patients receiving PD1 ± ipi, factors such as no previous adjuvant therapy (point HR between 0.50 and 0.55) and CR (point HR between 0.11 and 0.16) but not other baseline characteristics such as treatment line, disease stage,

elevated LDH, performance status or presence of brain metastases were independently associated to improved PFS, OS and melanoma-specific survival (MSS). Propensity-score matched analysis showed superimposable long-term survival curves for responders to ipi+nivo or PD-1.

Conclusions: Unselected patients achieving CR to any CPI regimen exhibit excellent 5-year MSS, exceeding 93%. Among responders to PD1 ± ipi, key baseline features such as elevated LDH or presence of brain metastases do not predict outcomes; long-term outcomes are comparable across CPI regimens. These findings can guide follow up strategies for responders to CPI.

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1110P Follow-up brain imaging in patients with melanoma brain metastasis and immune checkpoint inhibitors

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Background: More than 50% of patients with advanced melanoma are eventually diagnosed with brain metastasis (BM). Immune checkpoint inhibitors (ICI) can induce durable responses in BMs and have improved survival of patients with BM. For monitoring BM, magnetic resonance imaging (MRI) is performed in long-term survivors of BM, while this may be redundant and cause unnecessary clinical dilemmas. The objective of this study was to assess the clinical impact of follow-up (FU) MRI in patients who are treated with ICI for melanoma BM and are without intracranial progressive disease (PD) >1 year after start of ICI.

Methods: A single-center, retrospective, cohort study was performed at the Erasmus MC, Rotterdam, the Netherlands, which is a large tertiary referral center for patients with melanoma. Consecutive patients with melanoma who started with first-line ICI (2012 - 2022) for the treatment of BM were included. Patients without FU MRI were excluded. We selected patients without intracranial PD at 1 year after start of ICIs, according to RANO-BM criteria. In this subgroup, we assessed intra- and extracranial disease status according to RANO-BM and RECISTv1.1 respectively, and the number of FU MRIs with clinical impact, defined as change in treatment strategy.

Results: 70 patients were identified who had a total of 172 BMs and, one year after start of ICI, 34 (49%) patients were without intracranial progression. In these 34 patients, best intracranial response was complete response, partial response and stable disease in 29%, 44% and 27% respectively. During a median imaging FU of 35.1 months (IQR 22.2 — 43.4), 10 (29%) of 34 patients had PD: intracranially (9%), extracranially (17%), or both intra- and extracranially (3%). During this FU period, starting at 1-year after the start of ICIs, 34 patients underwent a total of 254 MRI scans and 3% of these scans had clinical impact, leading to local treatment, other systemic treatment or supportive care.

Conclusions: The clinical impact of FU MRI seems limited in patients with melanoma who are without progressive BMs >1 year after start of ICIs. Therefore, use of MRI could be reconsidered for long-term FU of BMs with a favorable response after ICI.

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1111P Genomic and transcriptomic analysis of Japanese melanoma reveals candidate biomarkers for immune checkpoint inhibitor responders

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Background: Immune checkpoint inhibitor (ICI) has greatly improved the prognosis of advanced melanoma. However, the efficacy of ICI in Japanese patients has been found to be lower than Caucasian. It is thought that one of the causes is that acral and mucosal melanoma have a low tumour mutation burden and driver mutations such as BRAF. However, there is no report performing the genomic and transcriptomic analysis in Japanese patients. By analysing the Japanese patients with melanoma, we aimed to clarify how they differ from Caucasians. Furthermore, we challenged to explore biomarkers for the efficacy of ICI.

Methods: The blood and tumor samples were collected from the patients before and after ICI therapy at multiple facilities. Based on the clinical information, the genomic and transcriptomic analysis were performed. In particular, ICI responder and non-responder genomes were analyzed separately.

Results: In this analysis, 129 tumor samples from 78 cases were collected, and 112 tumors and 65 cases were analyzed. Somatic mutations in Japanese patients are significantly different from those in Caucasians. That is, there were few mutations such as single nucleotide variant and single base substitution, and the majority were triple wild type tumours without driver mutations such as BRAF. While the presence of these mutations is associated with treatment response in the Caucasian patients, the involvement of these mutations was found to be less significant in Japanese patients. In this context, we compared the gene expressions of responder and non-responder tumours and found differences in genes such as HLA-A24, follicular helper T cells, and MARCO. We considered that these genes might be potential biomarkers in Japanese melanoma.

Conclusions: This is the first and largest study in Japan in which tumour samples were prospectively analysed before and after ICI treatment for melanoma. Further studies focusing on these biomarkers are desirable.

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1112P Immunotherapy after progression to double immunotherapy: Pembrolizumab and Lenvatinib versus conventional chemotherapy for patients with metastatic melanoma after failure of PD-1/CTLA-4 inhibition

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Background: PD-1 inhibition as monotherapy following by CTLA-4 inhibition in progressive disease or as upfront co-inhibition have drastically improved the prognosis of metastatic melanoma. Still many patients develop primary/acquired resistance to both agents, relapse soon and survive less. For many years, conventional chemotherapy (CC)was the standard of care for these patients. Recently the phase II LEAP004 trial supported that pembrolizumab/lenvatinib could overcome anti-PD-1/anti-CTLA-4 refractoriness.

Methods: In absence of any prospective comparison in this frail population, we retrospectively debate here the LEAP004 proposed combination (pembrolizumab 200mg with lenvatinib, at a dose of 10mg, due to its known toxicity) with CC (carboplatin 4AUC and dacarbazine 850mg/m^2 Q3W) in real-world melanoma patients who relapsed to both ICIs, either in combinatorial or sequential setting, between July 2022 and January 2024. Patient and disease characteristics as well as treatment and safety outcomes were recorded. Survival analyses were performed using the Kaplan-Meier method.

Results: 84 patients were included in the final analysis (pembro/lenva, n=39 vs CC, n=45; males: 33.3% vs 46.7%, respectively). Median age was 67(45-87) and 64(34-87) years. The distribution of their metastatic sites was comparable, including 12.8% and 20% with brain involvement. Most patients had a PS<2 (69.9% vs 56.5%), increased LDH (71.8% vs 84.4%), BRAF-wild status (82.1% vs 84.8%) and received>=2 previous therapies (61.5% vs 53.3%). Median follow-up was 18 months. ORR was 23.1% and 11.1% in pembro/lenva and CC groups (P<0.0001). mPFS was 4.8 and 3.8 months (HR [95%CI]: 0.57 [0.36-0.92]; P=0.017) and mOS was 14.2 and 7.8 months(HR[95% CI]:0.39 [0.22-0.69]; P=0.0009), for pembro/lenva and CC arms, respectively. Grade 3-5 TRAEs were documented in 48.7% and 75.6% of patients (P=0.034), leading to discontinuation in 10.3% and 17.8% of cases, respectively.

Conclusions: This is the first comparative study in patients with metastatic melanoma refractory to PD-1/CTLA-4 inhibition and showed significantly longer outcomes in cases treated with pembro/lenva versus CC.

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1113P A machine learning model based on computed tomography radiomics to predict prognosis in subjects with stage IV melanoma

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Background: Biomarkers and clinical features don't currently enable the identification of standardized risk categories for optimal treatment strategies in metastatic melanoma. This issue underlines the need of a more sophisticated and comprehensive prognostic evaluation. The aim of this retrospective observational study is to develop a machine learning model based on pre-therapy Computed Tomography (CT) images to stratify the single-subject prognosis in melanoma patients.

Methods: Images from 60 metastatic lesions were collected, 32 (53.3%) belonged to "favorable prognosis" class and 28 (46.7%) to "unfavorable prognosis" class, according to patients' prognosis intended as Progression Free Survival (PFS) </> treatment median PFS. This image-set was used for the training and cross-validation of different radiomic-machine learning models through the Trace4Research software (DeepTrace Technologies srl, Italy). A radiomic approach was applied, under the hypothesis that radiomic feature could capture the disease heterogeneity among the two groups. Three models consisting of 4 ensembles of machine learning classifiers (random forests, support vector machines and k-nearest neighbor classifiers) were developed for the binary classification task of interest (favorable vs unfavorable), based on supervised learning, using prognosis as reference standard.

Results: The best model showed ROC-AUC (%) of 82 (majority vote), 81.6** (mean) [77.9-85.4], Accuracy (%) of 77, 75.4** [74.1-76.7], Sensitivity (%) of 84, 80.5** [78-83], Specificity (%) of 68, 69.6** [66.4-72.9], PPV (%) of 75, 75.2** [73.5-76.9], and NPV (%) of 79, 75.7** [73.8-77.7] (*p<0.05, **p<0.0001).

The model was external tested on 20 new patients (N=70 lesions) and the classification of each patient's prognosis was obtained using the one most frequently assigned by the classifier to the metastatic lesions of the same patient. The results show that the classifier can predict subjects with a favorable prognosis with good accuracy (85%). A third of patients (35%) with unfavorable prognosis were predicted.

Conclusions: These preliminary data underscore the potential of radiomics-based machine learning models in predicting prognosis in patients with metastatic melanoma.

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1114P Deciphering unresectable in-transit metastasis in melanoma: Multi-modal and longitudinal insights

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Background: In-transit metastases (ITM) in melanoma occur between the primary tumor and the draining lymph node, indicating worse survival and poor systemic therapy response. However, some patients exhibit locoregional recurrences with durable distant progression-free survival, and the mechanisms underlying these heterogeneous outcomes are not understood.

Methods: We investigated melanoma patients with unresectable ITM using whole-exome sequencing (WES) and bulk RNA sequencing (RNAseq) to compare those who progressed to distant metastasis (n=21) against those who did not (n=19). We also characterized the tumor-immune dynamics from longitudinal samples of two patients (pt1: 28 samples; pt2: 24 samples) using WES, RNAseq, snRNAseq, and high-plex CyCIF imaging.

Results: ITM patients exhibited high genomic heterogeneity, partly due to Acral samples. We observed enrichment of aging signatures correlated with genomic heterogeneity and copy number signature 9 (diploid with chromosomal instability). Patients who progressed to distant metastasis tended to have higher genomic heterogeneity and lower tumor mutational burden (TMB). Bulk deconvolution showed low immune infiltrate with CD4 memory resting T cells and M2 macrophages. Pt1 (Acral) experienced progressive disease after treatment with CDK4/6 and MEK inhibitors, and ICB, exhibiting aggressive features, low TMB, and an NRAS mutation. Distant metastases arose from a lineage with high aneuploidy and a TET2 mutation. Brain metastasis diverged early but emerged late, with the highest TMB and aneuploidy. CyCIF analysis revealed NGFR+/AXL+ tumor cells, low and heterogeneous immune composition. Pt2 cutaneous melanoma with a BRAF V600E mutation had abundant immune infiltrates. After DTIC chemo and limb perfusion, Pt2 achieved complete response without systemic therapy. Increased TMB and TCR diversity post-DTIC and regression features with abundant CD8+ T cells led to complete remission.

Conclusions: This study maps evolutionary dynamics from primary to ITM and distant metastasis, highlighting features leading to progression and differences in tumor-immune interactions. Pt2's autonomous response post-chemo suggests potential for combined chemo+ICB therapy in ITM patients.

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1115P Multiomics clustering of patients with cutaneous melanoma to reveal survival trends based on tumor immune evasion features

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Background: Immunotherapy resistance due to complex tumor-immune interactions leading to immune evasion is a major hurdle in treating melanoma. To better understand this complexity, we combined genomic and transcriptomic data linked to immune escape in a multiomics approach to discern patients with distinct tumor-immune microenvironment (TiME) types that define their survival.

Methods: Cutaneous melanoma samples from TCGA (discovery cohort, standard of care, n=442) were clustered using a non-negative matrix factorization model based

on transcriptomic (functional gene expression signature (FGES) scores and signaling pathway scores calculated by ssGSEA and PROGENy) and genomic (mutational signatures, copy number alterations, and pathogenic mutations) features. The best model parameters were defined by analyzing the clusters' Kassandra deconvolution, H&E TilMaps, and TCR/BCR repertoires. The CatBoost classifier was then trained to assign TiME types to a validation cohort treated with aPD-1 drugs (n=250). Overall survival (OS) was compared using log-rank test and multivariate Cox regression.

Results: Our analysis defined five TiME clusters. The Checkpoint-high TiME with high tertiary lymphoid structure score, diverse TCR/BCR repertoires, and alterations in melanogenesis pathway genes, showed the best OS in both the TCGA and aPD-1 cohorts. Next was the Immune-depleted TiME, low in all features except lymphoid checkpoints and DNA-repair gene deletions. The Interferon-deleted TiME, immune-rich with high myeloid component and altered interferon genes, showed poor OS in both cohorts. The Proliferative-metastatic TiME showed high tumor proliferation and hypoxia-associated features and the worst OS in the aPD-1 cohort. The Fibrotic/Exclusionary TiME with upregulated WNT signaling, matrix remodeling, and T cell exclusion had the worst OS in the TCGA cohort.

Conclusions: Our analysis of tumor genomics, signaling pathways, and FGES revealed specific TiME patterns affecting patient survival and expanded the transcriptome-only clusterization concept published in Bagaev et al, 2021, highlighting the potential utility of a multiomics approach for development of new therapeutic strategies in precision oncology.

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1116P Application of the Scottish inflammatory prognostic score to the south-east Scotland cancer network real-world melanoma cohort

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Background: The Scottish Inflammatory Prognostic Score (SIPS) has been shown to predict survival in patients with advanced/metastatic non-small cell lung cancer (NSCLC) receiving first-line pembrolizumab monotherapy. SIPS uses serum albumin and neutrophil measurements, routinely collected prior to treatment commencement, to generate a score of 0-2 (Table). We aimed to assess the prognostic utility of SIPS in patients with unresectable/metastatic melanoma treated with first-line pembrolizumab.

Methods: All patients treated with first line pembrolizumab for unresectable/metastatic cutaneous melanoma at a Scottish Regional Cancer Centre between 2013-2020 were included. Data extracted comprised patient demographics, oncological diagnosis and staging, first-line metastatic treatment details, radiological responses, and mortality status. Patients were stratified by SIPS. Progression-Free Survival (PFS) and Overall Survival (OS) were defined as the time from cycle 1, day 1 pembrolizumab monotherapy to progression or death (from any cause) respectively, or censorship. The relationship between SIPS and survival outcomes was evaluated.

Results: 145 patients were included. Median age was 71 (range 32-90) years and 58% were male. The minimum follow-up time of censored patients was 14.7 months. 92 (63%), 37 (26%) and 16 (11%) of patients were SIPS 0, 1 or 2 respectively. SIPS stratified both PFS and OS (both $p<0.001$) (Table).

Table: 1116P

	SIPS 0 (Albumin ≥35 g/l and Neutrophils ≤7.5 x10^9/L)	SIPS 1 (Albumin ≥35 g/l and Neutrophils >7.5 x10^9/L OR Albumin <35 g/l and Neutrophils ≤7.5 x10^9/L)	SIPS 2 (Albumin <35 g/l and Neutrophils >7.5 x10^9/L)
Progression-Free Survival	23.7 Months	5.0 Months	1.8 Months
Overall Survival	34.4 Months	7.0 Months	3.3 Months

Conclusions: As in NSCLC, SIPS may predict survival outcomes in patients with cutaneous melanoma, treated with pembrolizumab. In those with SIPS 2 we suggest careful consideration as to the merits of pembrolizumab therapy when discussing this option with patients. SIPS warrants further investigation, both through external validation in melanoma patients receiving pembrolizumab, and applicability to other treatment options, such as ipilimumab/nivolumab.

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1117P Intratumoral microbiota is associated with prognosis in Chinese patients with skin melanoma

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Background: Skin melanoma, particularly acral melanoma, is known for its poor prognosis, often exacerbated by infections and chronic ulcers. Recent research has highlighted the significant role of intratumoral microbiota in various cancers, but its impact remains less understood in Chinese patients with skin melanoma. This study aims to investigate the intratumoral microbiota in melanoma among this group and explore its potential influence on disease progression.

Methods: One hundred melanoma tissue samples from stage III/IV skin or acral melanoma patients at Sun Yat-sen University Cancer Center, collected between 2015 and 2021, were retrospectively collected and underwent LPS immunohistochemistry (IHC). Kaplan-Meier analysis was used to assess the relation of LPS expression and patients overall survival. Microbial diversity was analyzed through 16S rRNA sequencing. Spatial transcriptomics was applied to map LPS-positive and LPS-negative regions, enabling the exploration of transcriptional differences and cell distributions.

Results: Patients with high LPS levels exhibited a median overall survival (mOS) of 13.7 months (95% CI, 10.6—16.9), which was shorter compared to those with low LPS levels, who had not yet reached median survival. Analysis of tumor microbiota revealed significant diversity, with high proportions of *Bifidobacterium*, *Vibrio*, *Bacillus*, *Clostridium sensu stricto*, and *Pseudomonas*, among which *Pseudomonas* was the dominant genus. Spatial transcriptomic analysis of LPS-positive melanoma tissues showed an increased proportion of M2 macrophages and a decreased proportion of effector T cells. Gene set enrichment analysis (GSEA) further indicated the activation of epithelial-mesenchymal transition (EMT) pathways.

Conclusions: High levels of microbiota within melanoma tissues are correlated with poor overall survival and may facilitate tumor immune evasion and metastasis.

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1118P Immunological alterations during neoadjuvant BRAF/MEK inhibition in patients with prior unresectable regionally advanced melanoma: Translational analysis from the REDUCTOR trial

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Background: The REDUCTOR trial showed that neoadjuvant dabrafenib (D) plus trametinib (T) effectively reduced tumor size, enabling radical resection in 81% of patients (pts) with prior unresectable locally advanced melanoma. However, understanding of the immunological changes during BRAF/MEK inhibition and their correlation with responses remains limited. Here, we report translational research findings from the REDUCTOR trial, focusing on tumor immune infiltration changes.

Methods: In the REDUCTOR trial, 21 pts with unresectable, BRAF-mutated, locally advanced stage IIIC/oligometastatic stage IV melanoma received neoadjuvant D+T for 8 weeks, followed by surgery if sufficient downsizing was achieved. Pathologic responses were evaluated based on viable tumor cell percentage in the tumor bed.

Tumor biopsies were collected at baseline, week 2, and surgery. Multiplex immunofluorescence staining was done on formalin-fixed, paraffin-embedded tumor samples to analyze SOX10 expression and the infiltration of CD3, CD8, CD20, CD68, and FOXP3 immune cells.

Results: All 21 pts were included in the analysis. Pathologic responses were evaluated in 18 pts, with 13 showing a pathologic response (PR) (4 partial, 3 near-complete, 6 complete) and 5 a non-response (pNR). Already from week 2 of treatment, an increase in overall immune infiltration compared to SOX10+ melanoma cells was observed. Immune infiltration at week 2 and at surgery was higher in pts with a PR compared to pts with a pNR (99.8% vs 55.4% [p=0.018], and 97.3% vs 48.0% [p=0.036] cells per mm2, respectively). A significant increase in CD20+ B cells was observed at surgery compared to baseline and 2 weeks (320 vs 36 [p=0.015], and vs 35 [p=0.046] cells per mm2, respectively). Pts with a PR had a significantly higher abundance of CD20+ B cells at surgery compared to pts with a pNR (614 vs 87 cells per mm2 [p=0.046]). No significant changes during treatment or associations with response were found in other immune cell subsets.

Conclusions: Our results demonstrate an increase in CD20+ B cells during neoadjuvant BRAF/MEK inhibition in prior unresectable locally advanced melanoma pts, especially in responders.

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1119P Genomic and transcriptomic predictors of resistance to anti-PD1 monotherapy in patients with advanced melanoma

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Background: Anti-PD1 therapy has improved survival of patients with advanced melanoma. However, a substantial number of patients does not benefit due to tumor resistance. To understand failure of anti-PD1 therapy in advanced melanoma, the primary objective of this study was to identify genomic and transcriptomic characteristics associated with resistance to anti-PD1.

Methods: In this prospective multicenter study (NCT01855477), tumor biopsies and matched whole-blood samples were collected from 279 patients with advanced melanoma prior to the start of first-line systemic therapy. Whole genome sequencing (WGS) and high-quality RNA sequencing (RNA-Seq) were performed. To identify immune-predictive biomarkers, the cohort was split into two independent cohorts, a training cohort with in-depth clinical data (N=76) and a testing cohort (N=203). After tumor biopsy, 114 previously untreated patients were treated with anti-PD1 monotherapy. Based on their tumor response after anti-PD1 therapy, patients were categorized as good or poor responders.

Results: Overall, the two cohorts were similar based on clinical, genomic, and transcriptomic features. Unsupervised hierarchical clustering of the RNA-seq data revealed two distinct immunogenic gene expression patterns in the advanced melanoma transcriptome, reflecting low and high expression of immune cell-related genes. Patients with a poor tumor response after anti-PD1 generally had a lower number of specific immunogenic signatures and were categorized into a cluster with low expression of different immune cell-related genes, including signatures of IFN-gamma, effector T-cells and antigen presentation pathways. The cluster of patients with the low immunogenic gene expression score was also associated with a poor overall survival compared to the cluster with high immunogenic gene expression scores.

Conclusions: Based on different immune signatures, a cluster with low immune-related expression patterns was found in patients with a poor response after anti-PD1 monotherapy. This specific cluster may contribute to better understand resistance to anti-PD1 and identify patients with melanoma who need alternative treatment strategies.

Clinical trial identification: NCT01855477.

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1120P Tumoral and peripheral immunophenotype of patients with stage II/III melanoma undergoing adjuvant immunotherapy following tumor resection

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Background: Post-operative treatment with PD1 blocking agents has been shown to prolong recurrence-free survival in resected stage II/III melanoma (MEL). Nevertheless, there is a critical need to identify tissue and blood-based biomarkers to better identify patients who will recur. In the current study, we undertook in-depth translational evaluations to elucidate the biology associated with recurrence (REC) versus no REC (NED) in 44 patients with stage II/III MEL undergoing post-excision adjuvant immunotherapy.

Methods: Screening and longitudinal whole blood was assessed for circulating numbers of T, B NK and NKT cells, memory T cell subsets and immune checkpoint expression using spectral cytometry immunophenotyping assays. Selected Immuno-Oncology transcripts (n=1000) and proteins (n=100) were evaluated at single cell resolution using Nanostring CosMx technologies. Exploratory analyses of translational endpoints according to disease status following PD1 blockade were conducted by Wilcoxon rank-sum test.

Results: In the periphery, an increased number of total CD8+ cells and CD8+ effector memory (CD8+, CCR7- CD45RA-) was observed at baseline in patients NED for $>$ 14 months after anti-PD-1 treatment initiation. Conversely, an increased number of total CD4+ cells, CD4+ naïve ((CD4$^+$, CCR7$^+$, CD45RA$^+$), and a CD56-bright (CD56+, CD16-) NK cell subset expressing TIGIT and PD-1 was observed at baseline in patients with REC within 12 months of anti-PD-1 initiation. In the tumor microenvironment, significantly increased expression (fold change $>$ 2; $p < 0.001$) of markers associated acute inflammation (i.e Interferon Regulated Genes) and B cell maturation and recruitment (i.e. CD19, MS4A1) was found in lymph node and primary tumors from NED vs. REC patients.

Conclusions: The limited benefit of adjuvant immunotherapy in MEL patients is associated with a compromised peripheral and intra-tumoral antitumor effectors. The data reported here may guide patient selection strategies to identify MEL patients likely to recur following adjuvant PD-1 blockade who require new approaches to improve immunotherapy outcomes.

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1121P Artificial Intelligence to predict BRAF mutational status from whole slide images in melanoma

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Background: Improving the prognostication of melanoma is crucial for selecting patients for effective adjuvant therapies. Given that tumor tissue contains a large amount of clinically relevant hidden information that is not fully exploited, we applied a weakly-supervised deep learning approach to H&E-stained whole slide images (WSIs) to directly predict BRAF mutational status.

Methods: We designed an artificial intelligence algorithm that extracts features from no-padding patches of WSIs using a pre-trained deep neural network. These features are then fed into a classifier that assigns a BRAF mutational status probability to each WSI. The model was trained and validated using a cross-validation approach on 220 WSIs from the IHP Group (IHP-MEL-BRAF) with patients included from April 2014 to January 2023. The model was tested on the publicly available TCGA cohort. We used the area under the curve (AUC) as the metric to assess the performance of the model.

Results: The model yielded an AUC of 78.3% on the cross-validation folds and 75.7% on the testing folds. We show that the performance of the model is impacted by the amount of tumoral tissue present in the WSI, and that thin melanomas are highly subject to false predictions. In the external data, the model achieves an AUC of 68.3%. As the model learns to assign a weight to the tiles contributing to the mutational status characterization, we explore the main phenotypes that are more likely to explain the BRAF mutational status.

Conclusions: This pilot study in melanoma demonstrates that this novel deep-learning approach to H&E image analysis is capable of discovering new digital predictive and prognostic biomarkers. It has the advantage of leaving the exploration of the WSI and the selection of regions of interest entirely to the AI, thus reducing the bias introduced by annotations. Furthermore, these findings could potentially accelerate and improve the clinical decision-making process in the field of melanoma in the near future.

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1122P The role of imaging during follow-up after radical surgery of stage IIb-c and III cutaneous malignant melanoma: Survival results from an interim analysis of a randomized prospective multicenter study (TRIM)

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Background: In several countries, whole-body imaging has been introduced in the routine follow-up of high-risk cutaneous malignant melanoma (CMM) after surgery. However, evidence is lacking that earlier detection of recurrent disease by regular scans improves survival and recommendations vary considerably between countries. In Sweden, these patients have a physical examination every 6 to 12 months for 3 years and ultrasound of regional lymph node basins every 6thmonths in the case of a positive sentinel node status. The main aim of the TRIM study is to investigate whether imaging in the follow-up program for high-risk CMM improves survival by earlier detection of recurrence.

Methods: TRIM is a nationwide prospective randomized Swedish phase III study. After radical surgery of stage IIB-C and III CMM patients are randomly assigned 1:1 (stratified for tumor stage) to follow-up by physical examinations for 3 years +/- whole-body imaging with CT or FDG-PET/CT and blood test (including S100B protein and LDH) at baseline, 6, 12, 24 and 36 months. The goal is to include 1300 patients. The first patient was enrolled in June 2017. Cut-off date for the interim analysis was August 2023 at 1000 included patients. Primary endpoint is overall survival (OS) at 5 years.

Results: There were no statistically significant differences in relapse free survival (RFS) (p=0.26), distant metastases free survival (DMFS) (p=0.22), or OS (p=0.83) between the groups at a median follow-up time of 31 months. Three-year rates for RFS were 68.7% (95% CI 64.2 -73.5%) and 65.5% (95% CI 60.9-70.5%), for DMFS 81.4% (95% CI 77.5-85.4%) versus 79.2% (95% CI 75.2-83.4%) and for OS 88% (95% CI 84.8-91.4%) versus 87.6% (95% CI 84.1-91.2%) in the standard and imaging groups respectively. There was an even stage-distribution and similar frequency of patients receiving adjuvant treatment in the two groups.

Conclusions: The interim analysis indicates that there is no benefit from imaging in the follow-up program for high-risk CMM patients. However, so far only a few patients have completed the follow up time of 5 years.

Clinical trial identification: NCT 03116412; 2023-05-26:.

Legal entity responsible for the study: Uppsala University hospital.

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1123P Melanoma incidence and mortality decline in younger adults in Sweden: Start of a shift in the upgoing trend?

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Background: Over the past decades, many regions have experienced a steady increase in the incidence of cutaneous melanoma. In recent years a downward trend has been observed in younger age groups in Australia and USA. Yet, in none of the European countries a significant decline in the melanoma incidence has been reported, in any age group. Here we explore melanoma incidence and mortality trends in Sweden, focusing on individuals younger than the average age of onset for melanoma.

Methods: This study is based on the national population based Swedish Melanoma Registry, covering >99% of all invasive melanomas diagnosed in the country, including 87 930 registered cases. Incidence and mortality rates per 100,000 inhabitants were calculated, in 1990-2022. Joinpoint regression models were used to evaluate statistical significance of temporal trends and points of change.

Results: In the years 1990-2022, 33 415 cases of invasive melanoma were diagnosed among patients under the age of 60 years (ys), with the following numbers of cases in each age group, 0-12ys (n=13), 13-19ys (n=243), 20-29ys (n=2 292), 30-39ys (n=5 709), 40-49ys (n=10 498) and 50-59ys (n=14 660). Throughout the study period, a constant melanoma incidence rise was observed in those ≥50ys. In the age groups 20-29, 30-39 and 40-49ys, there was a consistent incidence peak in the years 2014-2015 in both males and females, with a significant decline or leveling off in the period until 2022. In those <20ys the melanoma incidence remained low with no significant trends. During the study period, there was also a significant decline in the melanoma mortality in those aged 20-59ys but not in those ≥60ys.

Conclusions: This is the first report from a European country demonstrating a significant downward trend in the melanoma incidence and mortality among young adults. National campaigns that were initiated in the 1990s, promoting skin-cancer awareness and UV protection, emphasizing the importance of protecting children are likely contributory. Other factors may be a reduced usage of tanning devices, more hours spent indoor, together with an immigration of populations with darker skin. More effective oncological treatments are also likely promoting a decline in the population mortality of melanoma among young people.

Legal entity responsible for the study: Karolinska Comprehensive Cancer Center.

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1124P Adjuvant treatment of patients with stage III melanoma: 4-year follow-up time of multicenter real-world study

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Background: Adjuvant treatment with immune checkpoint inhibition (PD1) and targeted therapy (TT) with BRAF+MEK inhibitors has significantly improved recurrence-free survival (RFS) of stage III melanoma patients in clinical trials. We investigated adjuvant therapy in melanoma patients under real-world conditions.

Methods: In a prior analysis of this multicenter cohort study, we reported the treatment course, recurrence characteristics, subsequent management and outcomes of stage III melanoma patients receiving adjuvant therapy at 2 years of follow-up (FU) (Lodde et al, EJC 2023). Updated data at 4 years of FU are now presented with a focus on patients with *BRAF*-mutated melanoma.

Results: FU data of 589 stage III melanoma patients was available (41 stage IIIA, 218 IIIB, 309 IIIC, 21 IIID; 232 *BRAF*-mutated). 479 patients had received PD1 (81%), and 110 TT (19%; 47% of all *BRAF*-mutated patients). At a median FU of 48.1 months, 55% of PD1-treated patients (265/479; 53% of BRAF-mutated patients [65/122]) and 45% of TT-treated patients (49/110) had disease recurrence. Median RFS was 24.7 months for all PD1 patients (95% confidence interval [95% CI] 18.4−41.1) and was not reached for TT patients (95% CI 34.8-NR). 4-year RFS was 43% (95% CI 38.5-47.8) for PD1 patients and 53% (95% CI 43.6-63.3) for TT patients. Death from melanoma occurred in 21% (100/479) of PD1 patients and 13% (14/110) of TT patients. Among the *BRAF*-mutated patient cohort, risk of recurrence was greater for PD1 than TT (hazard ratio HR crude 1.57, 95% CI 1.09-2.26; HR adjusted for age, sex, and tumor stage, 1.73, 95% CI 1.20−2.50). No clinically meaningful difference was detected for melanoma-specific survival (HR crude 1.36, 95% CI 0.69-2.68; HR adjusted for age, sex, and tumor stage 1.49, 95% CI 0.75−2.95). Second recurrence-/progression-free survival (RPFS2) from start of first adjuvant treatment to second relapse/death was 27.6 months for *BRAF*-mutated PD1-treated patients (95% CI 16.5-not reached) and 31.7 months for TT patients (95% CI 24.0-NR).

Conclusions: RFS at 4 years was clearly better in TT-treated patients compared to all PD1-treated patients. Patients with *BRAF*-mutated melanoma had a significantly higher risk of relapse when treated with adjuvant PD1 than when treated with TT.

Legal entity responsible for the study: E. Livingstone, G. Lodde.

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Lodde: Financial Interests, Advisory Board: Sun Pharma; Financial Interests, Sponsor/Funding: Pierre Fabre, Novartis, BMS; Financial Interests, Local PI: German Research Foundation. All other authors have declared no conflicts of interest.

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1125P Accuracy of PET-CT to assess extent of nodal disease in clinical stage III melanoma

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Background: With effective systemic therapies for melanoma, patients (pts) with clinical stage III (cS3) disease, previously first treated with operation, are now increasingly offered neoadjuvant therapy (NST). Excellent pathologic response rates (pRR) and improved event-free survival with NST have now raised questions about the extent of operation required for those with a favorable pRR, particularly pts with limited disease at baseline. PET-CT, for baseline and post-NST staging, is used primarily to exclude distant disease. While data exist showing nodal metabolic response is unreliable for predicting a pathologic complete response (pCR), data specifically

evaluating nodal imaging to nodal pathology correlation are scarce. We evaluated correlation between PET-CT nodal findings and operative pathology.

Methods: With IRB approval, we identified cS3 melanoma pts treated with NST 2011-2024 and operated on at our institution. We included pts with both pre- and post-NST PET-CT imaging. Imaging response was reported per RECIST v1.1 and EORTC PET response criteria. Pathology assessment was per IMNC guidelines.

Results: Of 60 pts, median age was 61 years, 50% were female. NST was immunotherapy (IO) + targeted therapy (IO+TT) in 48% and IO in 42%. Median NST duration was 12 weeks. Imaging response rate (iRR) overall was 60% per RECIST and 57% per EORTC PET and was higher for IO+TT (72%) than IO (48%). Pathology evaluation of a median 15 nodes (LNs)/pt showed pCR or near-pCR ($\leq$10% viable tumor) in 28/60 (47%) with 65% having a pRR with $<$50% viable tumor. Among pts with residual disease, the median number of positive LNs at operation was 2 (IQR 1-4). At baseline, 42% of pts had 1 positive LN, with a 56% iRR and 48% pRR with a 44% pCR/near-pCR rate, while 58% of pts had $\geq$2 positive LN with a 63% iRR and 66% pRR with 46% having a pCR/near-pCR. Enumerating the number of LN+ on PET-CT underestimated extent of disease: 27% had a greater number of involved LNs on pathology assessment than on preoperative imaging (32% for pts with 1 LN+, 23% for pts with $\geq$2 LN+ nodes on baseline imaging).

Conclusions: PET-CT nodal imaging should be interpreted cautiously as it may underestimate the number of affected LNs. Over-reliance on imaging to guide surgical management following NST may lead to suboptimal treatment.

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1126P A phase II study of nivolumab/relatlimab in metastatic uveal melanoma

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Background: Metastatic uveal melanoma (UM) is a difficult to treat rare malignancy. Lymphocyte activation gene 3(LAG-3) is an immune checkpoint receptor associated with T cell exhaustion highly expressed in uveal melanoma CD8+ T cells (Durante et al.). Relatlimab is a human LAG-3 specific blocking antibody currently approved in combination with PD-1 blocking antibody nivolumab in metastatic cutaneous melanoma. Here we report the results of a phase 2 study in patients with metastatic uveal melanoma (MUM).

Methods: A Simon two-stage minimax design was used. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), median duration of response (mDOR), and safety (AEs). The null hypothesis (ORR=5%) is rejected if 4 or more responses are observed in 27 patients.

Results: As of 1/31/2024, 27 patients were enrolled and treated. No prior PD-1, CTLA-4 and/or LAG-3 blocking antibody treatment was allowed. Patients were treated with nivolumab 480 mg/relatlimab 160 mg IV q4wks to progression or intolerable toxicity. At a median follow -up of 11.2 months, the ORR in the 26 evaluable patients was 7.7% (2/26).) SD and PD were 42.3% (6/18) and 50% (10/18) respectively. 92.6% of patients experienced treatment related adverse events (TRAE). Of 173 TRAE, 88.9%,66.7% and 25.9% were grade 1, 2 and 3, respectively. There were no grade 4/5 AEs. The most common TRAEs were fatigue (55.6%), ALT elevation (40.7%), AST elevation (29.6%) arthralgias (25.9%) and hypothyroidism (25.9%). There were 10 grade 3 TRAE in 7 patients. Six serious adverse reactions (SAE) were seen in 3 patients; one was considered treatment related and 5 were due to PD. Additional results of secondary outcomes will be presented. Results of extensive correlative studies will be submitted as a separate abstract.

Conclusions: Nivolumab + relatlimab is safe but is associated with a low response rate in MUM.

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Legal entity responsible for the study: University of Miami.

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1127P Subgroup analysis of FOCUS phase III trial efficacy results

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Background: The majority of metastatic uveal melanoma (mUM) patients require liver-directed therapy at some point in the course of their disease. Melphalan/Hepatic Delivery System (melphalan/HDS) is a drug/medical device combination that was recently approved by FDA for liver-directed treatment of unresectable mUM patients. The phase III FOCUS study demonstrated efficacy and safety of melphalan/HDS in a heterogenous patient population with unresectable mUM. Here we present efficacy analyses in clinically important subgroups.

Methods: Eligible patients with unresectable liver metastases from mUM, with or without extrahepatic disease, received treatment with percutaneous hepatic perfusion (PHP) of melphalan (3.0 mg/kg ideal body weight) once every 6-8 weeks for a maximum of 6 cycles. Efficacy endpoints including objective response rate (ORR), progression-free survival (PFS), overall survival (OS), were assessed among subgroups of patients with and without extrahepatic disease, previously treated and treatment-naive patients, and those with low (1-25%) and high (26-50%) liver tumor burden. Onset of ORR, serious adverse events (SAEs) and Grade 3/4 adverse events (AE) were assessed by treatment cycle.

Results: 102 patients with mUM were enrolled; treatment was attempted in 95 patients, and 91 patients received treatment. Across the 6 subgroups, ORR ranged from 31.6% to 37.5%, median PFS ranged from 6.2 to 9.3 months, and median OS ranged from 16.9 to 22.4 months. 57.6% of tumor responses were observed in the first two treatment cycles. The percentages of patients who experienced SAEs in treatment cycles 1-6 were 22%, 15.5%, 13.6%, 5.5%, 7.5% and 17.6%, respectively, of the patients treated in each cycle; by-cycle percentages for Grade 3/4 AEs were 53.8%, 57.1%, 53%, 45.5%, 50% and 47.1%, respectively.

Conclusions: Treatment with melphalan/HDS provides clinically meaningful efficacy across the evaluated subgroups. Objective tumor responses occurred throughout all 6 treatment cycles, without evidence of cumulative toxicity.

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Bristol Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, MaviVAX SA, T3 Pharma, Pfizer, Simcere. A.M. Arance: Financial Interests, Personal, Speaker, Consultant, Advisor: Pierre Fabre, Novartis, Roche, BMS, MSD, Biontech; Financial Interests, Personal, Other, Travel, accommodations, expenses: BMS, MSD. J. John: Financial Interests, Personal, Full or part-time Employment: Delcath Systems. J.S. Zager: Financial Interests, Personal, Advisory Board: Delcath Systems; Financial Interests, Personal and Institutional, Principal Investigator: Delcath Systems; Financial Interests, Institutional, Research Grant: Delcath Systems. All other authors have declared no conflicts of interest.

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1128P Preliminary results of first-in-human study of 225-Actinium MTI-201 (225Ac-MTI-201) in metastatic uveal melanoma

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Background: Metastatic UM (mUM) has a poor prognosis with limited therapy options. The melanocortin-1 receptor (MC1R) receptor is highly expressed in UM. Actinium-225 (^{225}Ac) is an alpha particle emitting radionuclide with high linear energy transfer & limited free path in tissue. We developed a novel MC1R targeted radiopharmaceutical, ^{225}Ac-MTI-201 with high biostability, affinity, MC1R-specific cytotoxicity & defined dosimetry/pharmacokinetics (PK) in preclinical studies. Murine studies in UM showed significant tumor growth delay & improved survival with ^{225}Ac-MTI-201. NCT05496686 is a first-in-human trial of ^{225}Ac-MTI-201 in mUM.

Methods: Eligibility includes mUM patients (pts) with progressive disease after at least 1 prior systemic or liver-directed therapy. Pts receive 1 dose of intravenous ^{225}Ac-MTI-201 with PK sampling. The one-compartment model was used to calculate blood and urine PK. There are 12 escalating dose levels (DL) from 4.7 µCi (0.17 MBq) to 1327 µCi (49.1 MBq). This follows a modified continual re-assessment method with cohort size of 1-2 based on dose limiting toxicity (DLT). Primary endpoint (EP) is safety with secondary EPs of PK, response rate & survival.

Results: Seven pts (3 female), median age 65 years (46-83), with median 2 (0-3) prior lines of systemic therapy, & three with prior liver directed therapy have been enrolled; six pts have received ^{225}Ac-MTI-201 up to dose level 5 (76µCi). There has been no DLT or G4 toxicity so far. Toxicities include leucopenia (1 G3; 1 G2), lymphopenia (1 G3, 1G2), neutropenia (1 G3), ↓ platelets (1 G2), anemia (1 G1) & high AST (1 G1). Best response has been stable disease (n=2), both at DL 4 and 5; one response is ongoing at 16 weeks post-dose. Blood half-life ranged from 28 to 99 minutes with an elimination rate constant (k_1) of 0.007 to 0.025 min^{-1}, and a urinary excretion rate constant (k_e) of 1.1 to 4.2 min^{-1}.

Conclusions: In early assessment, ^{225}Ac-MTI-201 single dose administration appears safe up to 76µCi with PK parameters as anticipated. The observation of disease stability is encouraging. Accrual & dose-escalation is ongoing & a multi-dose study of ^{225}Ac-MTI-201 in mUM is planned. Supported by NIH/NCI SBIR Phase II Contract HHSN261201700035C & Modulation Therapeutics.

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1129P Clinical outcomes from a tebentafusp UK expanded access program in patients with metastatic uveal melanoma (mUM)

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Background: Tebentafusp (T), a T Cell Receptor (TCR) bispecific therapeutic (gp100 x CD3) is licensed for the treatment of mUM in HLA A2.01 patients. Between July 2021 and June 2023, T was made available to HLA A2.01 positive patients with mUM in 17 treating centres in the UK.

Methods: Treating centres were asked to complete an audit database of anonymised outcomes. Submitting centres ensured local data transfer regulations were satisfied. At the time of abstract submission, survival data had been received on 92 patients and additional clinical data on 75.

Results: The audited population (n=75) had a median age of 62 years (range 18-82), 47% female, 53% male. 58% were ECOG PS 0, 39% PS1, 3% PS2. 66% had no previous systemic treatment. 25% had previous hepatic local treatment. 47% had hepatic only disease, 47% both hepatic + extra-hepatic, 6% extra-hepatic only. LDH was normal in 47%, 33% > 1x ULN, 20% > 2x ULNi.v. fluid support was required in 43% patients on wk 1, 37% wk 2, 29% wk 3, 13% wk 4, 4% week 5. G3-4 rash was seen in 17% of patients on wk 1, 16% wk 2, 14% wk 3, 4% wk 4. Corticosteroids were administered to 24% of patients wk1, 20% wk 2, 9% wk 3, 1% wk 4. Response data is currently available for 66 patients. Responses were investigator assessed: CR 3%, PR 12%, SD 51.5%, PD 33.5%. ORR 15%. Median PFS was 2.53 months (95% CI 2.3-2.76) (n=66) Median OS was 19 months (n=92).

Conclusions: This real-world dataset of patients with mUM receiving tebentafusp demonstrates clinically meaningful survival benefit compared with historical datasets. The proportion of patients requiring fluid or corticosteroid is of interest for resource planning. Updated data and additional clinical outcomes will be presented.

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1130P Phase II trial on nivolumab plus radiotherapy in patients with metastatic mucosal melanoma: PORTER-M3 trial

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Background: The response rate for nivolumab alone in mucosal melanoma is limited to about 20%. Combined radiotherapy has been reported to increase the effectiveness of immune checkpoint inhibitors. The objective of this phase II trial was to evaluate the efficacy and safety of nivolumab in combination with radiotherapy for metastatic mucosal melanoma.

Methods: Eligibility criteria were as follows: histological diagnosis of metastatic mucosal melanoma; age ≧ 20 years; ECOG performance status 0 or 1; and with measurable lesions. Patients received nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks with concurrent radiotherapy to measurable lesions for a total dose of 25 Gy/5 fractions/week. The primary endpoint was the response rate (RR) according to Response Evaluation Criteria in Solid Tumors version 1.1. The study was considered to have met its primary endpoint if 6 or more of the 16 patients had a response (RR, 37.5%≦). The secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and toxicity.

Results: Eighteen patients were enrolled between July 2018 and March 2022. Two patients were excluded from the efficacy analysis because they were not assessed for efficacy. The RR was 43.8%. Two patients achieved a complete response, 5 did partial response, and 4 did stable disease as their best response. The median PFS was 4.9 months (95% confidence interval, 2.2 to 15.1). The median OS was 20.1 months (95% CI, 7.5 to 31.5). Treatment-related adverse events of grades 3 or 4 occurred in 35.2% (6/17) of the patients. Radiation-related adverse events were grade 3 radiation dermatitis in one patient and grade 3 radiation pneumonitis in one patient.

Conclusions: Concurrent immune-radiotherapy consisting of nivolumab and radiotherapy showed promising efficacy with a manageable safety profile for patients with metastatic mucosal melanoma, and warrants further evaluation in large studies.

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1131P A phase II study of pembrolizumab combination with temozolomide as 1L treatment for Chinese metastatic acral melanoma patients

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Background: Acral melanomas are rare melanoma subtypes with poor prognosis and show limited response to the standard of care for the first line treatment of advanced melanoma (Dacarbazine). In this study, we evaluate the efficacy of the novel combination of pembrolizumab and temozolomide as the first line treatment in Chinese treatment-naïve metastatic acral melanoma patients.

Methods: This was a single arm, open-label, phase II study (ChiCTR2100050073). Eligible patients aged ≥18 years with histopathologically confirmed metastatic acral melanoma (stage III/IV) were enrolled. Patients received pembrolizumab 200 mg Q3W up to 35 cycles (approximately 2 years), and temozolomide 150mg/m^2/d on days 1-5 every 4 weeks. For patients who have completed the first treatment cycle without developing dose-limiting toxicity (DLT), Temozolomide would then be administered as 200mg/m^2/d on days 1-5, for up to 8 cycles. The primary endpoint was objective response rate (ORR) per RECIST 1.1 by investigator review. Secondary end points were duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety.

Results: A total of 38 patients were enrolled. The median age was 58 years (27-71 years), and 23 patients (60.5%) were male. At the data cut-off Apr 10, 2024, 35 patients have received at least one post-treatment radiological evaluation. The ORR was 37.1% (1 CR; 12 PR [95% CI: 21.5% - 55.1%]), 3 unconfirmed PR was included. The median DOR was 7.7 months (95% CI: 5.0-Not reached [NR]). The DCR was 80.0% (1 CR; 12 PR;15 SD [95% CI: 63.1-91.6%]). The median PFS was 7.7 months (95% CI: 4.9-13.2 months). The median OS was NR. No unexpected treatment-related adverse event was reported.

Conclusions: Pembrolizumab combined with Temozolomide is an effective and well-tolerated 1L regimen for Chinese patients with metastatic acral melanoma.

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Legal entity responsible for the study: Y. Ding.

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1132P Regorafenib in Caucasian patients with pretreated advanced KIT-mutant melanoma: A dual center case series

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Background: Oncogenic *KIT*-mutations (*KIT*^{mut}) are found in +/- 3% of melanoma patients (pts), most frequently in mucosal (15-21%), acro-lentiginous (11-23%), and melanoma arising on sun-damaged skin (CSDS; 16-27%). Only a minority of pts (20-30%) responds to treatment with small molecule *KIT*-inhibitors (e.g, imatinib, sunitinib, nilotinib, dasatinib). The activity of regorafenib (REGO, a multi-targeted small molecule inhibitor of KIT, TIE2, VEGFR, PDGFR, RET, RAF, and CSF-1R kinases) has never been studied in a Caucasian population with *KIT*-mutant melanoma.

Methods: The outcome of a prospectively identified cohort of advanced *KIT*^{mut} melanoma pts treated with REGO at two medical centers in the EU was investigated (database lock (DBL): 25APR2024).

Results: Eight patients were included: median age 60.7 years [range 41-76]; Caucasian (100%); AJCC stage IV-M1c: 7 pts, and -M1d: 1 pt; elevated baseline LDH: 3 pts; ECOG performance status 0 and 1: resp. 6- and 2 pts); primary mucosal 2-, acro-lentiginous 3-, and CSDS 3 pts. Oncogenic *KIT*^{mut} were documented in exon 11 (n=5), -13 (n=2), and -17 (n=1). Three pts participated in the prospective REGOMEL phase II clinical trial and 4 pts were treated on a compassionate use basis. All pts were pretreated and had previously progressed on anti-PD-1 and -CTLA-4 based therapy, 3 pts on imatinib. REGO was administered orally, once daily (QD), continuously, at a dose of 40 to 120 mg (n=7), or on a 21/28d regimen of 120 mg QD (n=1). In 7 response evaluable pts, the best overall responses (RECIST v. 1.1) were 1 complete response and 6 partial responses (overall response rate 100%, all responses were confirmed). After a median follow-up of 43w [range 3-65w], treatment and responses were ongoing in respectively 6 and 4 pts. Median duration of response was not reached [range 6-59w]. Median progression free survival was not reached and all pts were alive at DBL. All pts had at least 1 TRAE. Grade 3 TRAE included arterial hypertension, and digestive bleeding (n=1, each).

Conclusions: REGO demonstrated a manageable safety profile and high anti-tumor activity in this Caucasian population of pretreated advanced *KIT*^{mut} melanoma pts deserving further evaluation in a prospective clinical trial.

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1133P Only early adjuvant radiotherapy, particularly of the tumor bed rather than the lymph node region, improves prognosis in Merkel cell carcinoma: Results from the prospective German MCC registry

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Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer with neuroendocrine differentiation. Locoregional metastases are already present in ~30% of patients at initial diagnosis and recurrences occur in ~40% of cases during the first 2 years, even after initial complete resection. We evaluated the impact of locoregional treatment management on the course of the disease under real-world conditions before the widespread introduction of immune checkpoint inhibitors.

Methods: Between 1998 and 2017, 1049 patients with a pathologically confirmed MCC diagnosis were included in the prospective German MCC registry of the DeCOG. Patient and tumour characteristics of MCC were assessed and the locoregional treatment management analysed.

Results: Median age of MCC patients at first diagnosis was 74.0 years, 50.4% of the patients were male (n= 529). The primary tumour was located most frequently located in the head/neck region (32.2%, n=338) and the upper extremities (29.1%, n=305). At initial diagnosis, the majority of patients had localized disease without lymph node involvement or distant metastasis (AJCC < stage III disease 68.6%, n=720). At a median follow up of 10 years, progression-free (PFS) at 36 and 72 months was 68.5% (95% CI 65.3-71.7) and 61.2% (95% CI 57.7-64.9); overall survival (OS) 78.4% (95% CI 75.6-81.3) and 67.3% (95% 63.8-71.0), respectively. Safety margins of more than 1 cm improved the PFS (HR 0.62, 95% CI 0.42-0.91) and OS (HR 0.64, 95% CI 0.64-0.96), but an increase to more than 2 cm did not result in any additional benefit (PFS HR 0.89, 95% CI 0.61-1.31; OS HR 0.82, 95% CI 0.57-1.17). Delay of adjuvant radiotherapy of the tumor bed for more than 8 weeks after surgery resulted in a significant inferior PFS (HR 2.32, 95% CI 1.20-4.50) and reduced OS (HR 1.49, 95% CI 0.78-2.86). Additional irradiation of the lymph node region gave no additional benefit (PFS HR 1.46, 95% CI 0.79-2.70; OS HR 0.74, 95% CI 0.40-1.38).

Conclusions: MCC patients benefit most from safety margins of 1 cm and early adjuvant radiotherapy of the tumor bed within 8 weeks after surgery. No survival benefit was observed for larger margins or additional radiotherapy of locoregional lymph nodes.

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1134P Avelumab in metastatic Merkel cell carcinoma (mMCC): Conditional survival and long-term safety in patients treated for ≥1 or ≥2 years in JAVELIN Merkel 200

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Background: Avelumab, an anti—PD-L1 antibody, was approved worldwide for the treatment of mMCC based on results from the JAVELIN Merkel 200 phase 2 trial (NCT02155647). In patients treated with first-line (1L) avelumab, 1-, 2- and 4-year overall survival (OS) rates were 60%, 49%, and 38%, respectively. In patients treated with second-line or later (2L+) avelumab, 1-, 2- and 5-year OS rates were 50%, 36%, and 26%, respectively. We report the probability of additional OS and safety in patients treated with avelumab for ≥1 or ≥2 years.

Methods: Eligible patients had histologically confirmed stage IV MCC and no prior systemic therapy for metastatic disease (1L cohort; part B) or disease progression following ≥1 prior line of chemotherapy (2L+ cohort; part A). Patients received avelumab every 2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal of consent.

Results: In 116 and 88 patients who received 1L or 2L+ avelumab, treatment duration was ≥1 year in 40 (34.5%) and 23 (26.1%), and ≥2 years in 22 (19.0%) and 13 (14.8%), respectively. Compared with the overall population, a higher proportion of patients with ≥2 years of treatment had an ECOG performance status of 0 (1L, 72.7% vs 62.1%; 2L+, 69.2% vs 55.7%) or PD-L1+ tumors (1L, 27.3 % vs 18.1%; 2L+, 76.9% vs 64.8%). In patients who received ≥1 year of treatment, the probability of surviving for an additional 1, 2, or 3 years, respectively, was 97.4%, 89.5%, and 75.2% in the 1L cohort, and 87.0%, 78.3%, and 69.6% in the 2L+ cohort. In patients who received ≥2 years of treatment, the probability of surviving for an additional 1 or 2 years, respectively, was 100% and 81.0% in the 1L cohort, and 92.3% and 84.6% in the 2L+ cohort. Among patients in both cohorts who were still receiving treatment, treatment-related adverse events of any grade or grade ≥3 occurred after 1 year in 74.6% and 19.0%, and after 2 years in 45.7% and 5.7%, respectively.

Conclusions: Patients with mMCC who received ≥1 or ≥2 years of avelumab treatment had a high probability of surviving for an additional ≥2 years. Long-term safety was consistent with previous analyses. These results further support avelumab as a standard of care for patients with mMCC.

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1135P Multi-modal and longitudinal characterization of the tumor and immune microenvironment of Merkel cell carcinoma

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Background: Merkel cell carcinoma (MCC) is an aggressive neuroendocrine cancer of the skin, characterized by a high propensity for metastasis and a dismal prognosis particularly for advanced tumor stages. Immune-checkpoint blockade (ICB) is effective in MCC, but 60% of patients show primary or acquired resistance. Predictive biomarkers for the risk of metastasis and response to ICB are lacking. We studied the tumor microenvironment (TME) of 60 MCC patients to identify molecular mechanisms associated with response to ICB and profile the temporal dynamics occurring during tumor progression.

Methods: We collected 115 tissue biopsies from this MCC cohort with detailed clinical documentation and longitudinal follow-up and profiled the TME with high-plex imaging and matched bulk RNAseq that was collected from consecutive sections using laser-capture microdissection. We integrated clinical and molecular data and explored biomarkers using a lasso regressed CoxPH model.

Results: Our multi-modal data integration framework identified Merkel cell polyomavirus positivity, the abundance of CD8+ T cells and PD-L1+ macrophages as independent determinants of metastasis-free survival (DMFS), while the enrichment of cancer-associated fibroblasts at the tumor boundary correlated with distant metastasis. Response to ICB was correlated with the presence of central memory T cells (TCM), and Follicle-like cellular neighborhoods as well as a PD-L1+ tumor phenotype, that associated with an inflammatory macrophage signature (*CXCL9, CXCL10, CXCL13*) specifically at the tumor invasive front. By contrast, ICB failure associated with a cancer-stem phenotype (*SOX2, NELL*) and the downregulation of type-II interferon signaling (*STAT1, JAK1*). Last, we identified that exacerbation of T cell exhaustion, loss of TCM and inflammatory macrophages are critical elements of MCC evolutionary progression.

Conclusions: We demonstrate that high dimensional imaging of the MCC TME provides a framework to interrogate cellular interactions and tissue architecture *in-situ* at single-cell resolution. This framework enabled to identify genomic and phenotypic correlates for distant metastasis and response to ICB and map evolutionary changes during tumor progression.

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1136P Cosibelimab in advanced cutaneous squamous cell carcinoma (CSCC): Longer-term efficacy and safety results from pivotal study

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Background: Cosibelimab is a high-affinity, fully human monoclonal antibody that directly binds to programmed death ligand-1 (PD-L1) and blocks its interaction with the programmed death receptor-1 (PD-1) and B7.1 receptors to restore an anti-tumor immune response. Cosibelimab also has a functional Fc domain capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC) as an additional mechanism of anti-tumor immunity. Efficacy and safety data from a pivotal study (NCT03212404) supported a biologics license application for cosibelimab for the treatment of patients (pts) with advanced CSCC (metastatic [mCSCC] or locally advanced [laCSCC]) who are not candidates for curative surgery or radiation. Here, we present new longer-term follow-up data from the pivotal study.

Methods: Pts with mCSCC (Group [Gp] 1) and laCSCC (Gp 2) were treated with cosibelimab 800 mg Q2W. The primary endpoint was objective response rate (ORR; complete response + partial response) by independent central review (ICR) assessed by Gp. The safety analysis included all CSCC pts treated with at least one dose and includes a third Gp of pts with mCSCC treated with cosibelimab 1200 mg Q3W (Gp 3).

Results: As of the 31 March 2023 data cutoff, 192 pts were enrolled and treated (78 in Gp 1, 58 in Gp 2 and 56 in Gp 3), and 109 pts were eligible for long-term efficacy assessment (78 in Gp 1 and 31 in Gp 2). With a median duration of follow-up of 29.3 months (range: 0.4-52.0) for Gp 1 and 24.1 months (range: 2.8-37.3) for Gp 2, ORR per ICR was 50.0% (95% CI: 38.5-61.5) and 54.8% (95% CI: 36.0-72.7), respectively. The complete response rate was 12.8% and 25.8% for Gp 1 and 2, respectively. Median duration of response has not been reached in either Gp, with a probably of maintaining response at 24 months of 72.1% and 80.2% for Gp 1 and 2, respectively. The most common adverse events (AEs) by any grade (Gr) were fatigue (22.9%), anemia (20.3%), constipation (16.1%) and diarrhea (15.1%); Gr $\geq$ 3 were anemia (5.2%) and lipase increased (3.1%). 3.6% of pts experienced a Gr 3 immune-related AE (no Gr $\geq$ 4).

Conclusions: Cosibelimab demonstrates robust objective response and complete response rates in advanced CSCC, with manageable safety and notable low rates of overall and severe immune-related AEs.

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1137P Efficacy of LNS8801 in melanoma patients with prior immune-related adverse events from immune-checkpoint inhibitors

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Background: LNS8801 is an agonist of the G-protein coupled estrogen receptor (GPER). LNS8801 treatment increases melanocytic differentiation, reduces c-Myc protein levels, inhibits tumor proliferation, and increases immune recognition of cancer cells. In the first-in-human study, LNS8801 was safe and tolerable, without serious adverse events or dose limiting toxicities (NCT04130516).

Methods: Patients with immune checkpoint inhibitor (ICI)-refractory cutaneous melanoma (CM), prior immune-related adverse events (irAEs), and subsequent progression were enrolled. Patients received LNS8801 (125 mg, QD, PO) (NCT04130516). Endpoints included safety and tolerability, pharmacokinetics, pharmacodynamics, and disease control rate (DCR, CR+PR+SD). Presence of a consensus, fully functional, germline GPER sequence was assessed as a predictive biomarker.

Results: As of 05/01/2024, 9 patients were treated. All patients received prior PD-1 and CTLA-4 directed ICIs and had prior irAEs that warranted ICI discontinuation. 7 of 9 patients had AEs possibly related to study drug (n=5 with grades 1-2 and n=2 with grade 3), with only AST/ALT elevation occurring in >1 patient (G3 and G1). Overall, 8 patients were evaluable, 5 of 8 patients have had stable disease, resulting in a DCR of 63%. Consensus germline GPER (C/C) was present in 5 of 8 sequenced patients. Of patients positive for this biomarker, 4 of 5 had stable disease (DCR 80%), with a preliminary median progression-free survival of 9 months. This includes a patient that is on treatment for over 4 years with resolution of all soft-tissue nontarget lesions and no evidence of active disease in the residual bone-associated target lesion or elsewhere by PET/CT.

Conclusions: LNS8801 is safe and tolerable and demonstrates encouraging activity in patients with ICI treatment-refractory CM and prior irAEs. Consensus germline GPER is a promising predictive biomarker for benefit and continues to be associated with improved outcomes in patients treated with LNS8801. These data support further development of LNS8801 as a therapy for patients with CM who can no longer tolerate ICI therapy. Further validation of the consensus biomarker to predict response is warranted.

Clinical trial identification: NCT04130516.

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1138P A prospective study of patients with immune checkpoint inhibitor-induced hepatitis: Management outcome and association with liver injury subtype, immune infiltration, and clinical parameters

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Background: Immune-related hepatitis (ir-hepatitis) ranks among the most frequent adverse events of immune checkpoint inhibitors (ICIs). Characterizing ir-hepatitis subtypes and treatment responses can provide valuable implications for guiding treatment decisions and prognostication.

Methods: This prospective, interventional study includes 34 patients with biopsy-verified grade 3-4 ir-hepatitis. All patients received methylprednisolone 2 mg/kg for at least 72 hours. Ursodeoxycholic acid (UDCA) was added in mixed and cholestatic subtypes, and mycophenolate mofetil (MMF) in patients with insufficient response to steroids. Drug-induced liver injury (DILI) subtypes were determined using Hy's law. Multiplex immunohistochemistry (mIHC) for CD3, CD8, FoxP3, CD20, CD56/NKp46 was performed on all liver biopsies. Single-cell RNA sequencing of peripheral blood samples was used to characterize immunological responses.

Results: Twenty of 34 patients (59%) with ir-hepatitis responded to steroids, while six (18%) were steroid-unresponsive and needed treatment with MMF. Eight (24%) patients had steroid-dependent ir-hepatitis, obtaining an initial response to steroids but relapsed during tapering needing MMF. Patients with insufficient steroid-response received significantly higher accumulated doses of steroids. Alcohol consumption was the only patient characteristic significantly related to treatment outcome (p=0.042). Patients with mixed DILI were most likely to respond to steroids (72%), while only half of patients with hepatocellular and cholestatic DILI responded. Cholestatic DILI had the worst prognosis in relation to recovery from ir-hepatitis and risk of cancer progression and death. mIHC revealed significantly increased T cell infiltration including cytotoxic, helper, and regulatory T cells.

Conclusions: Almost half of the patients who developed ICI-induced ir-hepatitis had an insufficient response to steroids and needed MMF. Patients with mixed DILI were more likely to respond to steroids and UDCA, requiring lower cumulative steroid doses. MIHC revealed high T cell infiltration in the liver among patients with ir-hepatitis.

Clinical trial identification: NCT04810156.

Legal entity responsible for the study: The authors.

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1139TiP IDE196 (darovasertib) in combination with crizotinib versus investigator's choice of treatment as first-line therapy in HLA-A2 negative metastatic uveal melanoma

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Background: Activating mutations in *GNAQ* & *GNA11* (*GNAQ/11*), the Gα subunits of certain G protein-coupled receptors, have been observed in >90% of patients (pts) with uveal melanoma (UM) and are considered genetic disease drivers. These mutations are present in other solid tumors, including cutaneous and mucosal melanoma, and are recorded in The Cancer Genome Atlas (TCGA) and FoundationOne databases. IDE196 (Darovasertib, previously known as LXS196) is a selective protein kinase C inhibitor which has demonstrated preliminary anti-tumor activity in patients with metastatic UM (MUM). In a phase I/II study the combination of IDE196+ crizotinib (a MET inhibitor) demonstrated an objective response rate (ORR) of 45% in treatment-naïve patients with MUM. The purpose of this study is to determine clinical and safety outcomes of IDE196 in combination with crizotinib in adult participants with HLA-A2 negative MUM.

Trial design: Study IDE196-002 (NCT05987332) is a phase II/3, multi-arm, multi-stage, multicenter, global, open-label study for first-line therapy for HLA-A*02:01 negative patients with MUM who will be randomized to receive either IDE196 + crizotinib or investigator's choice of treatment (ipilimumab + nivolumab, pembrolizumab or dacarbazine). Approximately 260 and 120 MUM pts will be enrolled in phase II (phase IIa and 2b) and phase III portions of the study, respectively. The primary endpoints of the phase IIa portion are to determine the recommended phase II dose of IDE196 + crizotinib for expansion in the phase IIb portion of the trial and to compare the Progression Free Survival (PFS) of IDE196 + crizotinib vs the investigator's choice per RECIST 1.1, as assessed by the Blinded Independent Central Review (BICR) committee. Secondary endpoints include ORR, disease control rate (DCR), safety and pharmacokinetics parameters. The primary endpoint of the phase III portion is to compare IDE196 + crizotinib to investigator's choice of treatment with respect to overall survival (OS).

Clinical trial identification: NCT05987332.

Legal entity responsible for the study: IDEAYA Biosciences.

Funding: IDEAYA Biosciences.

Disclosure: M.O. Butler: Financial Interests, Personal, Advisory Board: BMS, Merck, Novartis, Adaptimmune, Iovance, GSK, Sanofi, laRoche Possey, Pfizer, Medison, IDEAYA, Regeneron; Financial Interests, Personal, Invited Speaker: BMS, Merck, Novartis, Sanofi, Pfizer; Financial Interests, Personal, Advisory Board, Safety Review Committee: Adaptimmune; Financial Interests, Institutional, Other, Conduct Clinical Trial: TCR2, Novartis, Sanofi, Immunocore, GSK, Pfizer, Merck, Bristol Myers Squibb, Regeneron, AstraZeneca, Adaptimmune, IDEAYA Biosciences, Amgen, Instil Bio, Turnstone Biologics, Iovance, Ankara; Financial Interests, Institutional, Research Grant, support clinical trial: Merck; Financial Interests, Institutional, Funding, support clinical trial: Takara Bio; Financial Interests, Institutional, Funding, support quality improvement project: Novartis. B. Chmielowski: Financial Interests, Personal, Other, DMC: Nektar; Financial Interests, Personal, Advisory Board: Novartis, Delcath Systems, Instil Bio, Replimune; Financial Interests, Institutional, Local PI, Clinical trial support: Bristol Myers Squibb, Macrogenics, Karyopharm Therapeutics, Infinity Pharmaceuticals, Advenchen Biotherapeutics, Xencor, Compugen, Iovance, PACT Pharma, RAPT Therapeutics, Immunocore, Ascentage, Atreca, Replimune, IDEAYA Biosciences, Instil Bio; Financial Interests, Institutional, Local PI, clinical trial support: Adagene, TriSalus Life Sciences, Kinnate Biopharma, PTC Therapeutics, Xilio Therapeutics, Kezar Life Sciences. R. Dummer: Financial Interests, Personal, Other, Consulting and/or advisory role: Novartis, Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, MaviVAX SA, T3 Pharma, Pfizer, Simcere. M.S. Carlino: Financial Interests, Personal, Advisory Board, Consultant Advisor: MSD, BMS, Novartis, Amgen, Oncosec, Merck, Sanofi, Ideaya, Pierre Fabre, Eisai, Nektar, Regeneron. M. Mckean: Financial Interests, Institutional, Other, Consulting: Pfizer, Castle Biosciences, IQVIA, Merck, Moderna; Financial Interests, Institutional, Research Grant: Acentage Pharma Group, Bicycle Therapeutics, Dragonfly Therapeutics, Epizyme, Exelixis, Genentech, GSK, IDEAYA Biosciences, Ikena Oncology, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Moderna, NBE Therapeutics, Novartis, Oncorus, Plexxicon, Prelude Therapeutics, Regeneron, Sapience Therapeutics, Seattle Genetics, Tizona Therpeutics, TMUNITY Therapeutics, TopAlliance Biosciences, Aadi Biosciences, Alpine Immune Sciences, Arcs Biosciences, Arvinas, ASCO, Astellas, Bayer, BioMed Valley Discoveries, BioNTech, C4 Therapeutics, EMD Serono, Erasca, Foghorn Therapeutics, G1 Therapeutics, Gilead Sciences, ImmVira Pharma, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Mereo BioPharma, Metabomed, Nektar, OncoC4, PACT Pharma, Pfizer, Poseida, Pyramid Biosciences, Scholar Rock, Synthrox, Takeda Pharmaceuticals, Teneobio, Tempest Therapeutics, Xilio, Aulos Bioscienc, Boehringer Ingelheim Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, InconVir, Jazz Pharmaceutical, Krystal Biotech, NucMito Pharmaceuticals, OnKure, Remix Therapeutics. J. Moser: Financial Interests, Personal, Advisory Board: BMS, Amunix, Thirona Bio, Adagene, IQVIA, Incyte, Boxer Capital, Oberland Capital; Financial Interests, Personal, Other, Consultant: Imaging Endpoints; Financial Interests, Personal, Invited Speaker: Immunocore, Caris Life Sciences; Financial Interests, Personal, Other, Molecular Tumor Board Member: Caris Life Sciences; Financial Interests, Institutional, Coordinating PI: Novocure; Financial Interests, Institutional, Local PI: Genentech, Alpine Immune Sciences, Amgen, Trishula Therapeutics, FujiFilm, ImmunSensor, Simcha Therapeutics, Repertoire Immune Sciences, Nektar Therapeutics, Synthorx Inc, Istari Oncology, Ideaya Biosciences, Rubius Therapuetics, University of Arizona, Senwha Biosciences, Storm Therapuetics, Werewolf Therapeutics, Fate Therapuetics, Y-mab Therapuetics, Agenus; Financial Interests, Personal, Local PI: Bioeclipse Therapeutics. S. Khan: Financial Interests, Personal, Advisory Board: Castle Biosciences, Replimmune Inc. K.B. Kim: Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, Merck, Novartis; Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb; Financial Interests, Personal, Stocks/Shares: Arvinas, Cryoport; Financial Interests, Institutional, Funding, Moderna has provided funding to the institution for conducting a clinical trial of Moderna's drug: Moderna; Financial Interests, Institutional, Local PI: Bristol Myers Squibb, Merck, Regeneron, Iovance Biotherapeutics, ImmunoCore, Astex Pharmaceuticals, Ideaya Biosciences, Summit Pharmaceuticals. J. Lutzky: Financial Interests, Personal, Other, reviewed grant applications for department of defense: general dynamics; Financial Interests, Personal, Advisory Board: Regeneron, Immunocore; Financial Interests, Personal, Other, safety monitoring committee: agenus, Celldex; Financial Interests, Institutional, Research Grant, Funding for institutional trial: BMS; Financial Interests, Institutional, Local PI: Trisalus, Takeda, Vyriad, Tango, Immunocore, Replimune, Oncohost, Dragonfly, Iovance, Ideaya. M. Shackleton: Financial Interests, Personal, Invited Speaker, Have given paid lectures about melanoma management: Novartis, Pierre Fabre; Financial Interests, Personal, Advisory Board, Have given paid lectures about melanoma management: MSD, BMS; Financial Interests, Personal, Advisory Board: Roche; Non-Financial Interests, Advisory Role, Advised regarding TGA and PBAC approval of avelumab for Merkel Cell Cancer: Merck; Non-Financial Interests, Advisory Role: Ideaya. V.G. Atkinson: Financial Interests, Personal, Advisory Board: BMS, MSD, Novartis, Pierre Fabre, QBiotics; Financial Interests, Personal, Invited Speaker: BMS, MSD, Novartis, Pierre Fabre, Limbic; Financial Interests, Personal, Other, Travel Support: BMS; Financial Interests, Personal, Other, Travel support: Pierre Fabre; Financial Interests, Personal, Other, Advisory Board: Immunocore. D. Beaupre: Financial Interests, Personal, Full or part-time Employment, Employee: Ideaya; Financial Interests, Personal, Stocks/Shares, Stock: Ideaya; Non-Financial Interests, Leadership Role, CMO of organization: Ideaya; Non-Financial Interests, Institutional, Proprietary Information, Access to company confidential information: Ideaya. G.W. Cole Jr: Financial Interests, Personal, Full or part-time Employment: Ideaya Biosciences; Financial Interests, Personal, Stocks/Shares: Ideaya Biosciences; Non-Financial Interests, Member: ASCO. H. Patel: Financial Interests, Personal, Full or part-time Employment, Medical Director or Clinical Research and Pharmacovigilance: Heron Therapeutics; Financial Interests, Personal, Full or part-time Employment, Sr Medical Director: Ideaya Biosciences; Financial Interests, Personal, Stocks/Shares: Ideaya Biosciences. M. Orloff: Financial Interests, Personal, Invited Speaker: Immunocore; Financial Interests, Personal, Advisory Board: replimune, Ideaya, Delcath, Immunocore; Financial Interests, Institutional, Local PI: Immunocore, Ideaya, Ascentage, Foghorn, Iovance, Linneaus, trisalus. All other authors have declared no conflicts of interest.

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1140TiP **Safe stop IPI-NIVO trial: Early discontinuation of nivolumab upon achieving a complete or partial response in patients with irresectable stage III or metastatic melanoma treated with first-line ipilimumab-nivolumab**

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Background: Patients with irresectable stage III or metastatic melanoma presenting with poor prognostic factors are usually treated with combination therapy of the immune checkpoint inhibitors (ICIs) ipilimumab and nivolumab. This combination therapy is associated with severe immune related adverse events (irAEs) in about 60% of patients. In current clinical practice, patients with a tumor response are usually treated with ICIs for years, while durable tumor responses have been observed after early discontinuation of treatment. To improve quality of life for patients, a shorter treatment duration of ICIs is preferred. The objective of the Safe Stop IPI-NIVO trial is to evaluate whether early discontinuation of ICIs is safe in patients with irresectable stage III or metastatic melanoma who are treated with combination therapy.

Trial design: The Safe Stop IPI-NIVO trial is a nationwide, multicenter, prospective, single-arm, interventional study in the Netherlands (NCT05652673). A total of 80 patients with irresectable stage III or metastatic melanoma who are treated with combination therapy of ipilimumab-nivolumab and have a complete or partial response (CR/PR) according to RECIST v1.1 will be included to early discontinue maintenance therapy with anti-PD-1. The primary endpoint is the rate of ongoing response at 12 months after start of ICI. Secondary endpoints include ongoing response at 24 months, disease control at different time points, melanoma specific and overall survival, the incidence of irAEs and health-related quality of life. After inclusion in the trial, follow up will be conducted for five years and will include laboratory measurements, imaging for response evaluation and questionnaires on the health-related quality of life (HRQoL). These HRQoL questionnaires consist of the EuroQoL EQ-5D-5L, the FACT-Melanoma, the Cancer Worry Scale and the Institute for Medical Technology Assessment resource use questionnaires. In May 2024, the study was open for inclusion in 12 Dutch melanoma centers and 21 patients were included.

Clinical trial identification: NCT05652673.

Legal entity responsible for the study: Erasmus Medical Center.

Funding: Transformatiedeal of the Dutch Federation of University Medical Centres.

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