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MELANOMA AND OTHER SKIN TUMOURS

784O Adjuvant nivolumab (NIVO) alone or in combination with ipilimumab (IPI) versus placebo in stage IV melanoma with no evidence of disease (NED): Overall survival (OS) results of IMMUNED, a randomized, double-blind multi-center phase II DeCOG trial

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Background: The phase 2 study IMMUNED demonstrated significantly longer relapse-free survival (RFS) of NIVO alone or in combination with IPI compared to placebo in stage IV melanoma patients (pts) with NED after surgery or radiotherapy (Zimmer L, et al; Lancet 2020; 395:1558-68). Final RFS and first and final OS data are presented.

Methods: Pts aged ≥18 y with stage IV cutaneous or unknown primary melanoma with NED were randomly assigned 1:1:1 (stratified by trial site, site of metastasis and PD-L1 status) to *either* NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses followed by NIVO 3 mg/kg Q2W (56 patients) *or* NIVO 3 mg/kg Q2W (n=59) *or* matching placebo (n=52) for up to 1 year, or until disease recurrence, unacceptable toxicity, or withdrawal of consent. RFS (ITT-population) was the primary endpoint, time to progression, OS and safety secondary endpoints.

Results: At a median follow-up of 49.2 months, NIVO and NIVO+IPI continued to demonstrate superior RFS *vs* placebo (Table). Overall, 36 OS events had occurred. Median OS was not reached in either group, risk of death was significantly lower for NIVO+IPI *vs* placebo (HR 0.41, 95% CI, 0.17-0.99) but not for NIVO alone *vs* placebo (HR 0.75, 95% CI, 0.36-1.56). Most patients of the placebo group with progression (32/42) received anti-PD-1 antibody containing treatment as first subsequent systemic therapy either as crossover or outside the trial. Treatment-related adverse events of grade 3/4 remained largely unchanged (70.9% for NIVO+IPI, 28.6% for NIVO).

Conclusions: NIVO and NIVO+IPI continued to demonstrate improved RFS in stage IV patients at high risk of recurrence. OS was markedly improved for patients receiving NIVO+IPI compared with placebo. Use of subsequent anti-PD-1 based therapy was high in placebo pts and most likely impacted the OS comparison of NIVO mono *vs* placebo.

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Table: 784O

	RFS			OS		
	NIVO+IPI	NIVO	Placebo	NIVO+IPI	NIVO	Placebo
No. Events	18	38	42	7	13	16
1-year rate	75.3%	51.7%	32.2%	95.7%	92.2%	93.9%
2-year rate	66.5%	36.9%	15.0%	83.8%	75.3%	68.0%
3-year rate	64.2%	31.4%	15.0%	83.8%	75.3%	68.0%
4-year rate	64.2%	31.4%	15.0%	83.8%	72.6%	63.1%
Median (months)	NR	12.3	6.3	NR	NR	NR
HR (97.5% CI for RFS, 95% CI for OS) *vs*. PLA	**0.25** (0.13-0.48)	**0.60** (0.36-1.00)		**0.41** (0.17-0.99)	**0.75** (0.36-1.56)	
Log-rank p-value (*vs*. PLA)	<0.0001	0.0236		0.0396	0.4423	
HR (95% CI) NIVO+IPI *vs*. NIVO	**0.41** (0.23-0.72)			**0.55** (0.22-1.38)		
Log-rank p-value (*vs*. NIVO)	0.0013			0.1969		

HR: hazard ratio; CI: Confidence interval; NR: not reached.

785O PIVOT IO 001: First disclosure of efficacy and safety of bempegaldesleukin (BEMPEG) plus nivolumab (NIVO) vs NIVO monotherapy in advanced melanoma (MEL)

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Background: BEMPEG, an IL-2 prodrug, combined with NIVO, a PD-1 inhibitor, showed clinical activity with a manageable safety profile in patients (pts) with advanced MEL in the phase 1/2 PIVOT-02 study. These data supported initiation of the phase 3, randomized, open-label PIVOT IO 001 study (NCT03635983) evaluating BEMPEG + NIVO vs NIVO in advanced MEL. Here we report efficacy and safety of PIVOT IO 001.

Methods: Pts with previously untreated, unresectable or metastatic MEL were randomized 1:1 to receive BEMPEG 0.006 mg/kg IV + NIVO 360 mg IV Q3W or NIVO 360 mg IV Q3W, stratified by PD-L1 tumor cell expression, *BRAF* mutation status, and AJCC v8 M stage. Primary endpoints were objective response rate (ORR) and progression-free survival (PFS), both by blinded independent central review per RECIST v1.1, and overall survival (OS). Overall study α was 0.05, split with 0.001 for ORR, 0.03 for PFS, and 0.019 for OS. All α are 2-sided.

Results: 783 pts were randomized to BEMPEG + NIVO (n = 391) or NIVO (n = 392); baseline characteristics were balanced across arms. Median follow-up was 19.3 months (mo) and 11.6 mo for ORR and PFS, respectively. The ORR with BEMPEG + NIVO was 27.7% vs 36.0% with NIVO (2-sided $P = 0.0311$). Disease control rate was 56.1% with BEMPEG+ NIVO and 58.5% with NIVO. Median PFS with BEMPEG + NIVO was 4.17 mo (95% CI, 3.52—5.55) vs 4.99 mo (4.14—7.82) with NIVO; HR, 1.09 (97% CI, 0.88—1.35); $P = 0.3988$. Median OS was 29.67 mo (95% CI, 22.14—not reached [NR]) for BEMPEG + NIVO vs 28.88 mo (21.32—NR) with NIVO (HR, 0.94; 99.93% CI, 0.59—1.48; $P = 0.6361$). Grade 3—4 drug-related adverse events (AEs) and serious AEs were higher with BEMPEG + NIVO (21.7% and 10.1%) vs NIVO (11.5% and 5.5%). An AE of special interest, ischemic cerebrovascular events, was higher with BEMPEG + NIVO (2.6%) vs NIVO (0.8%). There were 3 BEMPEG + NIVO and 1 NIVO treatment-related deaths.

Conclusions: In pts with advanced MEL, BEMPEG + NIVO demonstrated no added clinical efficacy vs NIVO. Primary endpoints ORR, PFS, and OS did not meet the prespecified boundary for statistical significance. Increased toxicity was observed with BEMPEG + NIVO vs NIVO. Ongoing biomarker analysis may help further interpret study results.

Clinical trial identification: NCT03635983.

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786O Tumor biomarker analysis from COLUMBUS part 1: Encorafenib + binimetinib for BRAF V600E/K-mutant advanced or metastatic melanoma

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Background: In the randomized, 2-part, multicenter, open-label, phase 3 COLUMBUS study, encorafenib (enco) + binimetinib (bini)—approved in the US, EU, and other countries—and enco alone improved 5-year PFS and OS vs vemurafenib (vemu) in patients (pts) with *BRAF* V600E/K—mutant metastatic melanoma. We retrospectively investigated genetic and transcriptional correlates of response and intrinsic resistance to enco + bini in an exploratory biomarker (BM) analysis of COLUMBUS Part 1.

Methods: Baseline (BL) tumor samples were analyzed using the ACE ImmunoID NeXT whole exome and whole transcriptome sequencing assays (Personalis). PFS and OS were analyzed (data cutoff: 15 Sep 2020) based on treatment (tx) type and presence of specific genetic or transcriptomic alterations at BL. High tumor mutation burden (TMB) was defined as above median TMB [8.6 mutations (muts)/megabase].

Results: 366 tissue samples were successfully analyzed. We present results from the comparison of enco + bini (116 pts) vs vemu arms (130 pts). Median (m) PFS in the enco + bini and vemu arms was 14.9 and 5.7 mo, respectively (HR [95% CI], 0.55 [0.40—0.76]), and mOS was 34.8 and 18.6 mo, respectively (HR, 0.67 [0.50—0.90], similar to that observed in the safety cohort. PFS and OS by tx arm and BM status are shown in the table. High TMB, PD-L1 expression (exp), and IFNg signature were associated with longer PFS and OS in the enco + bini arm vs vemu arm. High ErbB2 exp and PI3KCA pathway muts were associated with shorter survival outcomes in the enco + bini arm vs the vemu arm.

Table: 786O

		Enco + bini vs vemu			
		mPFS, mo	HR; 95% CI	mOS, mo	HR; 95% CI
TMB, median	≤	9.2 vs 7.3	0.60; 0.39—0.94	26.0 vs 18.6	0.84; 0.56—1.27
	>	24.0 vs 5.7	0.49; 0.30—0.79	47.5 vs 16.9	0.53; 0.34—0.82
PD-L1 exp, median	≤	14.5 vs 5.7	0.56; 0.34—0.92	22.3 vs 19.4	0.86; 0.54—1.36
	>	33.2 vs 5.6	0.35; 0.20—0.61	67.3 vs 15.1	0.39; 0.23—0.65
IFNγ signature	-	14.5 vs 5.6	0.44; 0.27—0.72	26.0 vs 16.1	0.76; 0.48—1.19
	+	33.2 vs 7.3	0.41; 0.23—0.72	67.3 vs 16.9	0.41; 0.24—0.70
PI3K, PTEN, Akt, or mTOR	wt	18.7 vs 5.7	0.45; 0.30—0.66	41.8 vs 18.8	0.56; 0.39—0.79
	mut	7.5 vs 7.3	1.04; 0.56—1.93	12.5 vs 16.1	1.23; 0.71—2.13
ErbB2 exp, median	≤	34.9 vs 5.6	0.29; 0.17—0.50	67.3 vs 15.8	0.44; 0.26—0.72
	>	12.9 vs 7.3	0.63; 0.38—1.07	23.4 vs 18.6	0.74; 0.46—1.19

Conclusions: Pts with high immune-related signatures derived greater clinical benefit from enco + bini vs vemu. High ErbB2 exp and PI3KCA pathway muts are potential resistance mechanisms to enco + bini. Addition of checkpoint inhibitors or PI3KCA pathway—targeted therapies to enco + bini in selected pts may further improve clinical benefit for pts with *BRAF* V600E/K—mutant metastatic melanoma.

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787O Adjuvant immunotherapy with nivolumab (NIVO) versus observation in completely resected Merkel cell carcinoma (MCC): Disease-free survival (DFS) results from ADMEC-O, a randomized, open-label phase II trial

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Background: MCC is a rare, immunogenic but aggressive skin cancer. Even after complete resection and radiation relapse rates are high. PD-1/PD-L1 immune checkpoint inhibitors (ICI) showed clinical benefit in locally advanced MCC. ADMEC-O is the first trial to investigate the efficacy/safety of adjuvant PD-1 blockade by ICI in completely resected MCC, i.e. in a situation with no systemic Standard of Care.

Methods: This multicenter phase 2 trial enrolled MCC patients (pts) (any stage, ECOG PS 0-1) with tumor lesions completely resected within 12 weeks prior to a 2:1 randomization to *either* NIVO 480 mg Q4W for up to 1 year, *or* observation, stratified by stage of disease (AJCC I/II *vs*. III/IV), age (<65 *vs*. ≥65 years) and gender. DFS was the primary endpoint, overall survival (OS) and adverse events (AE) secondary endpoints. This planned interim analysis was triggered when the Last Patient In was followed for at least 1 year.

Results: From 03/2017 until 08/2020 179 pts (NIVO, n=118; observation, n=61) were enrolled from 20 centers (ITT population; 62% male, 68% ≥65 years, 67% stage III/IV), with baseline characteristics well balanced across both arms. At this interim analysis with a median follow-up of 24.3 months (IQR 19.2-33.4), all pts had ended treatment. DFS rates at 12 and 24 months favored NIVO with 87.9% *vs* 78.5%, and 86.9% *vs* 74.3%, respectively. OS results are not yet mature. Treatment was well tolerated, with 41% of NIVO pts and 31% of pts in the observation group experiencing grade 3/4 AEs; only 5% of pts discontinued due to adverse events. No treatment-related deaths were reported.

Table: 787O

	DFS		OS	
	NIVO	Observation	NIVO	Observation
No. of events (rate, %)	**17**/118 (14%)	**14**/61 (23%)	**10**/118 (8%)	**6**/61 (10%)
1-year rate	87.9%	78.5%	93.6%	96.5%
2-year rate	86.9%	74.3%	93.6%	91.9%
Median (months	NR	NR	NR	NR
HR (95% CI)*	**0.56** (0.28-1.15)		**0.78** (0.28-2.15)	
Log-rank p-value	0.109		0.628	

* HR: hazard ratio for the median provided by a univariate Cox model;
CI, Confidence interval; NR, not reached

Conclusions: In this first randomized trial for MCC, a hazard ratio for DFS of 0.56 (95% CI 0.28-1.15) in favor of NIVO was observed at a median follow-up of 2 years, suggesting clinical benefit in this unmet medical need. Remarkably, the spontaneous course of MCC was considerably better than historical data would have suggested.

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788O Association of pre-treatment ctDNA with disease recurrence and clinical and translational factors in patients with stage IIIB-D/IV melanoma treated with adjuvant immunotherapy (CheckMate 915)

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Background: In patients (pts) with resectable melanoma, circulating tumor DNA (ctDNA) detection post-resection may be useful to inform disease state and recurrence risk.

Methods: Post-resection pre-treatment plasma from 1127 pts with stage IIIB-D/IV resected melanoma treated with nivolumab + ipilimumab vs nivolumab in the phase 3 CheckMate 915 study (NCT03068455) was retrospectively evaluated for ctDNA status and level, using a tumor-guided, pt-specific panel of up to 200 variants (Invitae Personalized Cancer MonitoringÔ). Kaplan-Meier and Cox regression models were used to evaluate the association between ctDNA status and recurrence-free survival (RFS), alone and combined with baseline clinical factors and biomarkers, including interferon-γ, TMB, tumor PD-L1, CD8+ T cells, tumor thickness, ulceration, and lymph node involvement.

Results: Overall pre-treatment ctDNA prevalence was ∼16% (95% CI: 14%—18%) and similar across most baseline demographics. A trend of greater ctDNA+ prevalence in higher stage III substages of melanoma was observed (IIIB = 11% [35/333], IIIC = 18% [110/596], IIID = 41% [13/32]). Pre-treatment ctDNA was associated with an increased risk of recurrence (HR 1.87, 95% CI: 1.48—2.36; Table). No significant interaction between ctDNA status and treatment arm was seen (ratio of hazard ratios: 0.99, 95% CI: 0.63—1.57). Patients with ctDNA present exhibited a greater rate of recurrence, seen as early as week 13 of therapy (Table). Distant metastasis-free survival results were similar. In composite analyses, improved RFS prediction was observed after combining ctDNA with clinical factors and biomarkers.

Table: 788O RFS probability by pre-treatment ctDNA status in CheckMate 915 treated patients

Status	Number of pts (n)	13-week RFS (95% CI)	12-month RFS (95% CI)	24-month RFS (95% CI)
ctDNA+	183	72.3% (65—78.3)	58.4% (50.7—65.3)	45.5% (37.9—52.8)
ctDNA-	944	91.7% (89.7—93.3)	75.1% (72.1—77.8)	65.4% (62.1—68.4)

Conclusions: Pre-treatment ctDNA was associated with increased risk of early recurrence across treatment arms. ctDNA is a useful biomarker for combined analyses predicting outcome for adjuvant melanoma.

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789O Neoadjuvant cemiplimab in patients (pts) with stage II—IV (M0) cutaneous squamous cell carcinoma (CSCC): Primary analysis of a phase II study

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Background: CSCC is highly immune-responsive; a prior pilot study demonstrated a high rate of pathologic complete response (pCR) or major pathologic response (MPR, ≤10% viable tumor), using cemiplimab anti-programmed death 1 (PD-1) therapy in the neoadjuvant setting. Here, we present the primary analysis of a confirmatory, open-label, multicenter, Phase 2, single-arm trial of neoadjuvant cemiplimab in pts with resectable Stage II—IV (M0) CSCC.

Methods: Pts received cemiplimab 350 mg IV q3W for up to 4 doses before surgery. The primary endpoint was pCR rate per independent central pathologic review (ICPR). Key secondary endpoints included MPR rate per ICPR, objective response rate (ORR; complete response [CR] + partial response [PR]) per RECIST v1.1, investigator-assessed pCR and MPR, safety and tolerability.

Results: At data cutoff date of 01 Dec 2021, 79 pts were enrolled (67 male; median age 73.0 yrs [range, 66.0—81.0]; ECOG performance status 0 (n=60) and 1 (n=19) with stage II (n=5), III (n=38), or IV(M0) (n=36) disease; 62 pts received all 4 doses (median number of doses given (Q1:Q3), 4 (4:4); 70 pts underwent surgery. The study met its primary endpoint: pCR was observed in 40 (50.6%) pts (95% confidence interval [CI], 39.1—62.1%). MPR was observed in an additional 10 (12.7%) pts (95% CI, 6.2—22.0%). ORR was 68.4% (95% CI, 56.9—78.4) (5 CR, 49 PR, 16 stable disease, 8 progressive disease (PD), 1 non evaluable. Reasons 9 pts did not have surgery: 3 responders declined surgery, 2 lost to follow-up or noncompliance, 2 had inoperable PD, 2 due to AE. Fourteen (17.7%) pts experienced Grade ≥3 AE. Four pts died due to AEs: 1 exacerbation of cardiac failure, 2 myocardial infarctions, and 1 COVID-19 pneumonia. The most common AEs regardless of attribution (all grades) were fatigue (30.4%), rash maculo-papular (13.9%), diarrhea (13.9%) and nausea (13.9%).

Conclusions: The pCR + MPR of 63.3% by ICPR in pts with Stage II—IV (M0) CSCC is the highest observed in a multicenter anti-PD-1 neoadjuvant monotherapy study for any solid tumor type. The safety profile of neoadjuvant cemiplimab is consistent with previous anti-PD-1 monotherapy experience. Ongoing follow-up will describe disease-free survival.

Clinical trial identification: NCT04154943.

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790MO Phase I study of fianlimab, a human lymphocyte activation gene-3 (LAG-3) monoclonal antibody, in combination with cemiplimab in advanced melanoma (mel)

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Background: Concurrent blockade of LAG-3 may enhance efficacy of anti-programmed cell death-1 (PD-1) therapies. We present updated safety and clinical activity data from patients (pts) with advanced mel treated with concurrent anti-LAG-3 (fianlimab) and anti-PD-1 (cemiplimab).

Methods: This phase 1 study included pts with unresectable or metastatic mel (excluding uveal mel) who were anti—PD-(L)1 treatment naïve (expansion cohort [EC] 6) or anti—PD-(L) 1 experienced within 3 months of screening (EC7). Pts received fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks for 12 months (optional additional 12 months if clinically indicated). Tumour measurements were performed every 6 weeks for 24 weeks, then every 9 weeks.

Results: As of the 9 Feb 2022 data cutoff date, 40 EC6 and 15 EC7 pts were enrolled and treated with fianlimab + cemiplimab. For EC6 and EC7 cohorts respectively, median age was 69.5 and 59.0 years, 62.5% and 46.7% were male, 90.0% and 60.0% were White. Median treatment duration was 37.1 weeks (EC6) and 9.0 weeks (EC7). Grade $\geq$3 treatment-emergent adverse events (TEAEs) occurred in 37.5% (EC6) and 46.7% (EC7) of pts; serious TEAEs occurred in 32.5% (EC6) and 33.3% (EC7) of pts; 17.5% (EC6) and 13.3% (EC7) of pts discontinued treatment due to a TEAE. Rate of adrenal insufficiency (AI) was 12.5% (EC6) and 6.7% (EC7); none led to treatment discontinuation. Investigator-assessed objective response rate was 62.5% (6 complete responses; 19 partial responses [PRs]) in EC6 and 13.3% (2 PRs) in EC7 pts. Kaplan-Meier estimation of median progression-free survival was 14.2 (95% CI: 5.6—not estimated) months in EC6 and 1.4 (95% CI: 1.3—7.7) months in EC7 pts. Median duration of response had not been reached in both cohorts. LAG-3 and PD-L1 correlative biomarkers analysis will be included in the presentation.

Conclusions: Fianlimab + cemiplimab in advanced mel pts had a similar safety profile to anti—PD-1 agents; clinical activity in anti-PD-(L)1-naïve patients appears higher than previously reported for anti-PD-1 monotherapy or anti—LAG-3 + anti—PD-1. A phase 3 trial (NCT05352672) investigating fianlimab + cemiplimab in advanced mel pts is ongoing.

Clinical trial identification: NCT03005782.

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791MO Clinical and tumor characteristics of patients (pts) with recurrence after pathologic response upon neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) in stage III melanoma

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Background: Pathologic (path) response (resp) is an excellent surrogate marker for long-term recurrence-free survival after neoadjuvant (neoadj) IPI + NIVO in stage III melanoma. Few resp pts develop recurrence of disease, and their clinical characteristics and mechanisms of tumor immune escape are unknown.

Methods: In the OpACIN, OpACIN-neo and PRADO trials, pts with recurrence after path resp were identified. All pts received 2x IPI + NIVO neoadj (different dosing regimens) and surgery at week 6. Path resp was classified as major path response (MPR; $\leq$10% vital tumor) or path partial response (pPR; $>$10-$\leq$50% vital tumor). Multiplex immunofluorescence staining (CD3, CD8, CD20, CD68, FoxP3, Sox10, DAPI) of paired baseline and recurrent samples was performed. Tumor and stroma regions were classified and % staining-positive cells determined using HALO imaging software.

Results: In the three trials, 142 pts obtained path resp, of whom 11 (8%) had a recurrence (n=6/118 [5%] of MPR pts and n=5/24 [21%] of pPR pts). Clinical characteristics were comparable for pts with and without recurrence, except for more frequent BRAF-mutations (73% vs 35%, p=0.044) and less frequent MPR (55% vs 85%, p=0.009) in pts with recurrence. Five pts had a regional recurrence (45%) and 6 pts distant metastases (55%), median 6.7mo and 13.1mo post surgery, respectively. Matched baseline and recurrence multiplex data were available for 6 pts (3 pts had regional and 3 pts distant recurrence): 4 MPR and 2 pPR pts. The percentage of $CD3^+$, $CD8^+$, $FoxP3^+$ and $CD68^+$ cells was increased at recurrence in both pPR patients, while in 3/4 MPR pts tumor immune infiltration was decreased at recurrence. Additional spatial analyses defining the nearest neighbor cell will be presented at ESMO.

Conclusions: Obtaining MPR is a surrogate marker for having an excellent clinical outcome. BRAF-mutation and response depth seem associated with recurrence after resp to neoadj IPI + NIVO in stage III melanoma. Regional recurrences were diagnosed earlier than distant metastases. Multiplex staining shows a trend of in- or decrease of immune cell populations according to initial depth of response, although the data presented is based on small numbers.

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792MO Neoadjuvant pepinemab in combination with nivolumab and/or ipilimumab in resectable stage III melanoma

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Background: SEMA4D has broad immunomodulatory effects in the tumor microenvironment; blocking SEMA4D in combination with checkpoint inhibitors (CI) promotes immune infiltration, enhances T cell activity, and promotes tumor regression. We hypothesized that the combination of pepinemab (pepi), which targets SEMA4D, and CI will increase immunomodulatory effects and augment response to neoadjuvant therapy in stage III melanoma.

Methods: Patients with resectable stage IIIB/C/D melanoma were sequentially enrolled on one of four treatment cohorts (n = 8 each): pepi/nivolumab (nivo), pepi/ipilimumab (ipi), pepi/nivo/ipi or nivo alone. Two doses were given on days 1 and 21; surgery occurred on day 42. Patients received adjuvant nivo q4w to complete one year of treatment. Primary clinical endpoint was major pathologic response (pMR), including complete and near complete responses (pCR). Secondary endpoints included safety, surgical delays, ORR, RFS, EFS, and OS.

Results: All 32 patients received both doses of neoadjuvant therapy; 31 patients safely proceeded to surgery without delay (1 patient is awaiting surgery). Thirteen (41.9%) patients had a pMR. Rates of pMR in the pepi/nivo, pepi/ipi, pepi/nivo/ipi, and nivo arms were 37.5% (2 pCR, 1 near pCR), 12.5% (1 pCR), 75.0% (5 pCR, 1 near pCR), and 42.9% (2 pCR, 1 near pCR), respectively. Three patients did not get adjuvant therapy due to treatment-related severe adverse events: 1 pepi/nivo and 2 pepi/nivo/ipi patients. Two patients had progression following surgery but prior to adjuvant therapy; both had no pathologic response. At median follow up of 19.6 months, 12 patients (38.7%) had recurred. Four patients died of disease; all had no pathologic response. All patients receiving pepi/nivo/ipi are free from recurrence at median follow up of 19.8 months, including two without major responses. We will update toxicities, RFS, EFS and OS at presentation.

Conclusions: While neoadjuvant treatment is used routinely for resectable stage III melanoma, there is no consensus on the most appropriate regimen. The combination of pepi/nivo/ipi provides robust pathologic response, durable response, and suitable toxicity. Analysis of biomarker endpoints is ongoing and will inform further development of this regimen.

Clinical trial identification: NCT03769155.

Legal entity responsible for the study: The authors.

Funding: Vaccinex, Inc.; Bristol Myers Squibb.

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793P NeoPeLe: A phase II trial of neoadjuvant (NAT) pembrolizumab (Pembro) combined with lenvatinib (Lenva) in resectable stage III melanoma

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Background: Neoadjuvant anti-PD-1 (PD1) induces a pathological complete response (pCR) in 20% and any pathological response (pRR) in 34% of stage III pts, with durable survival in responders. Improvements are needed to overcome primary resistance. NeoPele sought to determine if additional clinical benefit can be achieved by adding lenva to pembro using the NAT platform in pts with stage III melanoma (NCT04207086).

Methods: 20 pts with resectable, RECIST measurable stage III nodal melanoma received 6 wks of NAT with pembro (200mg, IV, Q3W) and lenva (20mg, po, od), then a lymph node dissection (LND), then 46 wks pembro. CT + PET scans were performed at baseline and wk 6; CT was continued 12 wkly to 2 yrs. Primary endpoint was pCR

and pRR at wk 6. Secondary endpoints; RECIST RR at wk 6, event-free survival (EFS), relapse free survival (RFS), OS, toxicity and translational endpoints.

Results: At data cut off 31 Mar 2022, 20 pts analysed: 30% female, med age 64.7 yrs, 3 (15%) BRAF V600E, 8 (40%) NRAS, 10 (50%) clinical N1b. Med f/u was 11.2 months (95% CI 10.2 - 13.8). 8/20 (40%) pts had pCR and 15/20 (75%) had any path response (Table). Events occurred in 4 pts; 1 had brain metastasis prior to LND with pPR, and 3 post surgery with pNR. Most common toxicities were fatigue (9, 45%), hypertension (8, 40%), headache (6, 30%) and anorexia (5, 25%) due to lenva; 45% were gd 3/4, most commonly hypertension (5, 25%). Most common surgical events were seroma (4, 20%) and lymphoedema (7, 35%), with no DVTs. 4 pts interrupted lenva and 0 permanently discontinued during NAT. Post NAT surgical operability was the same or improved in 13 (65%) pts, and harder in 7 (35%). Longitudinal analysis of melanoma tissue, microenvironment and microbiome is ongoing.

Conclusions: A high pCR and pRR rate was observed with NAT pembro+lenva, higher than previous studies of PD1 alone. The trial and translational investigations are ongoing, and RFS and OS data will be collected.

Table: 793P

	Pembro+Lenva (n=20)
pRR pCR Near pCR pPR pNR	15 (75%) 8 (40%) 3 (15%) 4 (20%) 5 (25%)
RECIST ORR/CR	35% / 5%
No. Events	4 (20%)
No. Recurred/Progressed by pCR/near-pCR/pPR/pNR	0/0/1^/3
No. Death	1
1-yr EFS (95% CI)	80% (95% CI 64-99%)

^1 pt progressed in brain prior to surgery but had LND.

Clinical trial identification: NCT04207086.

Legal entity responsible for the study: Melanoma Institute Australia.

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794P Efficacy and tolerability of neoadjuvant treatment with T-VEC in difficult to resect primary basal cell carcinoma: A phase II clinical trial (NeoBCC)

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Background: Cutaneous basal cell carcinomas (BCCs) carry a high mutational burden and are accompanied by a regulatory T-cell-rich tumor microenvironment, which makes them an attractive target for oncolytic virotherapy. This is the first clinical trial to report data on the efficacy of Talimogene laherparepvec (T-VEC) in BCCs. We hypothesized that neoadjuvant treatment with T-VEC can reduce the size of difficult to resect primary BCCs to allow surgery without skin grafts or skin flaps.

Methods: In this exploratory phase II study, 18 patients (11 female, 7 male) with a difficult to resect BCC, defined as requiring a reconstructive skin flap or skin graft for wound closure, were included. The patients' median age was 76 years (range 51-94 years). T-VEC was administered intratumorally, according to the melanoma treatment schedule, with a total of 6 cycles (13 weeks). Pre- and posttreatment tumor samples were analyzed using multiplex immunofluorescence (mIF) and changes in immune and non-immune cells contributing to the tumor microenvironment were quantified.

Results: Between January 2020 and January 2022, 18 patients started therapy. 17 were included for the final analysis. Treatment was prematurely discontinued in 1 patient after 2 cycles because of treatment related fever, Grade 2 (CTCAE Version 5.0). The median follow-up was 15.9 months (range: 0.3-28.7 months). The mean tumor area reduction was 48.7%, respectively. The primary endpoint was reached since 9 (52.9%) out of 17 patients underwent surgery without a skin graft or skin flap. 6 patients (35.3%) had a CR, 4 (23.5 %) a PR, 7 (41.2%) a SD, whereas no patient showed a PD prior to surgery. T-VEC reprogrammed the immune cell landscape of BCCs, with an increasing number of CD8+ T-cells, CD79+ plasma cells and a decreasing number of CD4+FOXP3+ regulatory T-cells and CD68+ myeloid cells. The safety analysis set included all patients, that at least received one dose of T-VEC. 15 (83.3%) of 18 patients developed treatment related Grade 1 or 2 AEs. None of the patients had serious adverse events (SAEs). No tumor recurrence occurred.

Conclusions: Neoadjuvant treatment with T-VEC was well tolerated and showed high activity in difficult to resect primary BCC.

Clinical trial identification: EudraCT number 2018-002165-19.

Legal entity responsible for the study: The authors.

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795P A phase Ib trial of neoadjuvant oncolytic virus OrienX010 (ori) and anti-PD-1 toripalimab (tori) combo in patients (pts) with resectable stage IIIb-IV (M1a) acral melanoma

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Background: Acral melanoma responds poorly to anti-PD-1 monotherapy. Ori is a HSV-1 derived oncolytic virus expressing granulocyte-macrophage colony-stimulating factor, which has potentiated the efficacy of anti-PD-1 in acral melanoma in the metastatic setting. We conducted a phase Ib trial evaluating ori/tori in resectable stage IIIb-IV (M1a) acral melanoma (NCT04197882).

Methods: Pts received the neoadjuvant intralesional ori up to $8*10^7$pfu/mL*10mL combined with iv tori 3mg/kg every 2 wks*4—6 doses prior to surgery, followed by the adjuvant iv tori 3 mg/kg every 3 wks for 1 year. The primary endpoints included radiological (per RECIST 1.1) and pathological response rates. The secondary endpoints were 1/2-y recurrence-free survival (RFS) and safety.

Results: Thirty patients were enrolled between 07/2019 and 12/2020, with a median age of 57 y.o. (range 21-72), including 14 (47%) males; 12 (40%) with stage IIIB, 14 (47%) with IIIC, and 4 (13%) with IV (M1a) disease. By the last follow-up in 01/2022, all pts have completed the neoadjuvant part, 27 (90%) completed the surgery and tori adjuvant part (the remaining 3 abrogated surgeries due to disease progression). The median follow-up time was 19 months (IQR 15-25). The radiological and pathological (among those who underwent surgeries only) objective response rate was 36.7% (11/30) (95%CI 19.9-56.1) and 77.8% (21/27) (95%CI 57.7-91.4), and that of complete response rate was 3.3% (1/30) (95%CI 0-17.2) and 14.8% (4/27) (95%CI 4.2-33.7), respectively. The 1-y RFS rate was 80.0% (95%CI 66.9-95.7). This combo was well tolerated. Although all pts experienced adverse events (AEs), most were of grade 1/2 (25/30, 83%). Five patients (17%) developed grade 3 AEs, including 2 soft tissue infections, 1 transaminitis, 1 peripheral neuropathy and 1 neutropenia. No grade 4 AE was observed.

Conclusions: Neoadjuvant ori/tori achieved a high pathologic response rate, an impressive 1-y RFS rate, and was well-tolerated in patients with resectable stage IIIB-IV (M1a) acral melanoma. Although longer follow-up is in need, this combo warrants further evaluation in this melanoma subtype.

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Legal entity responsible for the study: Peking University Cancer Hospital and Institute.

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796P Neoadjuvant toripalimab plus axitinib in patients (pts) with resectable mucosal melanoma (MuM): Updated findings of a single-arm, phase II trial

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Background: Initial results of the single-arm, phase II trial (NCT04180995) showed neoadjuvant toripalimab (T) plus axitinib (A) in resectable MuM had pathologic responses rate (RR) of 28.6% (4/14, 2 pCR, 2pPR) with good tolerance. We presented the updated data of pathologic RR, RFS at 1.5-years and the multiplex immunohistochemistry (mIHC) analysis before and after surgery.

Methods: Eligible pts were aged 18 to 75 with histologically confirmed resectable MuM. As neoadjuvant therapy, pts received T 3 mg/kg Q2W plus A 5 mg BID for 8 weeks before surgery, then adjuvant T 3 mg/kg Q2W for 52 weeks after surgery. The primary end point is pathologic RR according to the International Neoadjuvant Melanoma Consortium (pCR+pPR). The secondary end point is RFS in ITT population. Tumor infiltrating lymphocytes were quantified by mIHC.

Results: From Aug 2019 to Oct 2021, 29 pts were included. Median age 62 years; M: F 27.6% : 72.4%; primary sites : 10 femal genital, 10 anorectal, 5 esophagus, 3 nasal and 1 oral cavity in which 31.0% localized disease, 65.5% regional lymphatic disease, and 3.5% oligometastatic disease. Till last follow up of Apr 2022, 24 pts had received surgery (local excision 8.3%, wide excision 91.7% and 5 pts inoperable for distant metastasis during neoadjuvant therapy), the pathologic RR was 27.6% (8/29, 4 pCR & 4 pPR). With a median follow up time of 17.5 m, 21 pts got recurrence (62.1% distant metastasis, 10.3% local-regional recurrence) , the median RFS was 11.7 m (95% CI: 6.6-16.9 m) , and it was 13.0 m vs. 6.2 m in responder vs. non-responder respectively . The median OS has not been reached. Neoadjuvant therapy was tolerable with grade 3-4 treatment related AEs of 20.7% (liver dysfunction 10.3%, hyperglycemia 6.9%, hypertension 3.4%, dyslipidemia 3.4% and CK increased 3.4%). 16 pts (4 responder, 12 non-responder) with tumor tissue samples at baseline and after surgery were collected to perform mIHC, It showed significant increase of infiltrating CD3+ ($P = 0.0063$) and CD3+CD8+ ($P = 0.0076$) T cells after neoadjuvant therapy.

Conclusions: Neoadjuvant T plus A in resectable MuM showed promising pathologic responses with significantly increased infiltrating CD3+ and CD3+CD8+ T cells, which supports further investigation.

Clinical trial identification: NCT04180995.

Legal entity responsible for the study: Peking University Cancer Hospital and Institute.

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797P Relapse-free survival (RFS) update and first translational analyses of DONIMI, a study testing personalized neoadjuvant domatinostat, nivolumab (NIVO) and ipilimumab (IPI) in stage III melanoma patients (pts) based on the interferon-gamma signature (IFN-γ sign) algorithm

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Background: In stage III melanoma, neoadjuvant (neoadj) IPI + NIVO induces high pathologic response rates (pRR 72-78%), which is associated with long-term RFS. Pts with a low baseline IFN-γ sign are less likely to respond (pRR 55%). Domatinostat (DOM), a class I histone deacetylase inhibitor, increased intratumoral T cell infiltration and the IFN-γ sign expression in melanoma. DONIMI tests neoadj combinations of NIVO ± IPI with DOM stratified according to the IFN-γ sign of baseline biopsies in stage IIIB-D nodal melanoma.

Methods: DONIMI randomized IFN-γ sign high pts to arm A (2 cycles NIVO) or arm B (2 cycles NIVO + DOM twice daily), and IFN-γ sign low pts to arm C (same regimen as arm B) or arm D (2 cycles NIVO + IPI + DOM once daily). Arm D expansion (D-exp) treated IFN-γ sign low pts with 2 cycles NIVO + IPI + DOM twice daily. Surgery was planned after 6 weeks. Adjuvant NIVO or dabrafenib + trametinib started at week 12 for 52 weeks. Safety/feasibility was the primary endpoint, pRR and RFS were secondary endpoints. RFS rates were calculated using a Kaplan-Meier based method. Baseline and week 3 gene expression signatures (GES) were examined using Nanostring nCounter Technologies.

Results: Between Jan 2020 - Oct 2021, 44 pts were enrolled. At data cutoff (Mar 18, 2022), median follow-up was 14.6 months. Clinical data are shown in the table.

Table: 797P

	Arm A (n = 10)	Arm B (n = 10)	Arm C (n = 10)	Arm D (n = 10)	Arm D-exp (n = 4)
Gr 3-4 trAEs within first 12 weeks	0 (0%)	2 (20%)*	4 (40%)*	2 (20%)	4 (100%)*
Surgery performed on time (week 6 ± 1 week)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	4 (100%)
pRR (≤50% viable tumor)	9 (90%)	8 (80%)	3 (30%)	4 (40%)	2 (50%)
12-month RFS	100%	100%	90%	63%	NA

* These gr 3-4 teatment-related adverse events were DOM-related rash, necessitating premature stop of DOM. All IFN-γ sign low pts (Arm C + D), with persistent low IFN-γ sign at week 3 were non-responders.

Conclusions: The IFN-γ sign adequately identified pts who are likely to benefit from NIVO ± DOM alone (IFN-γ high pts) vs pts who may need an alternative scheme (IFN-γ low pts). Treatment regimen of arm D-exp was not feasible; DOM was stopped early in all arm D-exp pts. Addition of DOM did not increase the pRR in IFN-γ low pts.

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798P NeoTrio – Optimal neoadjuvant (NAT) sequencing of anti-PD-1 and BRAF targeted therapy (TT) in BRAF mutant stage III melanoma: Results of histopathological analysis

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Background: Anti-PD-1 and BRAF TT improve survival for metastatic and resected stage III melanoma. TT shows favourable immunomodulatory changes early during treatment and may have synergistic effects with anti-PD-1. Hyalinised fibrosis (HF) is associated with pathological complete response (pCR) with NAT. We examined longitudinal biopsies from the NeoTrio trial exploring the optimal combination of dabrafenib + trametinib (D+T) and pembrolizumab (pembro) (NCT02858921).

Methods: 60 pts with resectable, RECIST measurable stage III $BRAF^{V600}$- mutant cutaneous melanoma were randomised 1:1:1 to 3 arms of 6 wks of NAT followed by therapeutic lymph node dissection (TLND): A) ALONE - pembro (200mg Q3W x 2); B) SEQ - D+T (150mg bd + 2mg od) for 1 wk followed by pembro (200mg x 2); C) CON - D+T+pembro (doses as SEQ). Primary endpoint was the pathological response rate and pCR at wk 6. Core biopsies were taken at baseline, wks 1 and 2 and TLND at wk 6 and examined for translational endpoints; lymphocyte density score (LDS), melanophages and HF.

Results: LDS significantly increased from baseline at wks 2 and 6 in SEQ and CON but not in ALONE. Melanophages significantly increased from baseline to wk 6 in ALONE, wk 2 and wk 6 in CON, but not in SEQ. All arms demonstrated a significant increase in HF at wk 6 from baseline. Across arms, HF was significantly increased in CON when compared to ALONE and SEQ while no significant difference was seen in HF in SEQ compared to ALONE. Increased melanophages were significantly associated with pCR in ALONE while increased HF was significantly associated with pCR in SEQ. LDS was not associated with pCR in any arm. Across all pts increased HF was significantly associated with pCR (Table).

Conclusions: HF was significantly increased in CON when compared to SEQ or ALONE and was strongly associated with pCR across all patients. While melanophages and LDS demonstrated a temporal increase, these changes were not significantly associated with pCR.

Clinical trial identification: NCT02858921.

Legal entity responsible for the study: Melanoma Institute of Australia, The University of Sydney.

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799P A pilot study of the neo-adjuvant use of vemurafenib plus cobimetinib in patients with BRAF mutant melanoma with palpable lymph node metastases

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Background: Melanoma patients with palpable nodal metastases have a very poor prognosis with the majority recurring within the first 2-3 years with survival ranging from 20-50% at 5 years. We aimed to ascertain that patients with a BRAF V600 mutation that receive vemurafenib and cobimetinib before surgery (neoadjuvantly) will have a higher probability of resectability, pathologic complete response, a lower risk of local recurrence and a longer DFS, PFS and OS.

Methods: This was a single arm, prospective, multi centre phase II study in patients with confirmed BRAF V600 mutated Stage IIIB and IIIC melanoma (AJCC 7^{th} Edition) with palpable nodal disease. Patients received vemurafenib 960mg PO BID and cobimetinib 60mg PO OD for 4 months prior to resection followed by 8 months of adjuvant therapy post-surgery. CTscans were performed at baseline and before resection and every 6 months for the first 3 years and yearly in year 4 and 5. Biopsies for correlative studies and diagnosis were performed at baseline prior to starting therapy. The primary outcomes were the proportion of patients achieving resectability, radiologic response as per RECIST and the proportion of patients achieving a pathological response. Secondary objectives were local-regional recurrence rates, DMFS, DFS and OS.

Results: Twenty-four patients were enrolled and received neoadjuvant vemurafenib and cobimetinib and 21 underwent resection. At time of surgery 1 (20%; 95% CI 0.15-24.87) had a complete response, 16 (80%; 95% CI 56.34-94.27) had a partial response, and 2 (10%; 95% CI 1.23-31.70) had stable disease. One patient progressed as per

Table: 798P

Arm	LDS	Melanophages	HF	Response (pCR/ nearpCR/pPR/pNR)
ALONE				6/2/3/7
*Response	-0.11% p=1.2	+20% p=0.009	+3.9% p=0.13	
**Wk 2	-0.08% p=1.2	+1.2% p=0.716	-0.5% p=1.13	
**Wk 6	+0.3% p=0.2	+7.9% p=0.02	+13% p<0.001	
SEQ				4/2/4/10
*Response	+0.6% p=0.1	-7.5% p=1.4	+7.1% p=0.05	
**Wk 2	+0.67% p=0.005	+1.9% p=0.52	-0.6% p=1.13	
**Wk 6	+0.57% p=0.018	+5.2% p=0.08	+7.5% p=0.04	
CON				10/1/5/3
*Response	+0.4% p=0.14	-6.1% p=1.4	+11.1% p=0.09	
**Wk 2	+0.7% p=0.003	+13% p=0.008	+9.9% p=1.15	
**Wk 6	+0.78% p=0.001	+19.5% p<0.001	+24.9% p<0.001	
ALL ARMS *Response	+0.3% p=0.09	+4% p=0.44	+9.2% p<0.001	

*Pathological response; pCR vs no pCR **Wk 2 and 6; change from baseline

RECIST but had a partial response upon resection. Following resection and pathological evaluation 12 (57%; 95% CI 34.02-78.18)) patients achieved a complete pathologic response, 8 (38%; 95% CI 18.11-61.56) had a partial pathologic response. Treatment related Grade 3-4 events occurred in 10 patients with no deaths due to AEs. Only 2 patients had a local recurrence. OS at 60 months was 63.9% (95% CI 43.5-93.8).

Conclusions: Neoadjuvant vemurafenib and cobimetinib led to all patients being resectable with a high response rate, pathologic response rate and low local recurrence rate in melanoma patients with palpable lymph nodes.

Clinical trial identification: NCT02036086.

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800P Number needed to treat (NNT) and number needed to harm (NNH) to estimate clinical efficacy and safety of new adjuvant (Adj) therapies for resected stage (St) II-III melanoma

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Background: NNT and NNH are simple, easy-to-read devices that allow to estimate magnitude of benefit and harm of a therapeutic intervention. This study aims to apply these numbers to describe efficacy and safety of pembrolizumab (Pembro) and dabrafenib plus trametinib (D-T) as Adj therapies in St II-III resected melanoma.

Methods: Three phase III trials evaluating Adj therapies in melanoma versus placebo (KEYNOTE-716 [KN-716], KEYNOTE-054 [KN-054] and COMBI-AD [C-AD]) were considered for data extraction. NNT for relapse-free survival (RFS) was calculated as the inverse of the absolute risk reduction, rounded up to the nearest whole number. NNH for grade $\geq$ 3 (AEG$\geq$3) and grade 5 adverse events (AEG5) was also calculated as the inverse of the absolute risk increase, rounded down to the nearest whole number. Calculations were performed in the overall population and in principal subgroups (SG), if feasible.

Results: NNTs and NNHs are listed in the table. In KN-716, lower NNT values were obtained in the T3b and T4a SG, as compared to overall population and T4b; oppositely, NNT tended to a slight decrease as the St worsened in both KN-054 and C-AD. NNTs were also a bit lower in the SG with macroscopic lymph node invasion (LNi) in KN-054 only and with both ulceration (ulc) and macroscopic LNi in KN-054 and C-AD. NNHs for AEG$\geq$3 were 3 for C-AD, 7 for KN-054 and 11 KN-716, while NNHs for AEG5 were very high across all trials.

Table: 800P NNT and NNH for melanoma Adj therapies

	C-AD	KN-054	KN-716
Experimental treatment	D-T	Pembro	Pembro
Population	St III *BRAF*-mutated	St III	St II
Overall	-	7	12
BRAF wild type	-	7	-
BRAF mutated	6	6	-
St IIIA	7	9[1]	-
St IIIB	5	7	-
St IIIC	5	6	-
St II - T3b	-	-	8
St II - T4a	-	-	10[1]
St II - T4b	-	-	27[1]
Microscopic LNi	5	9	-
Macroscopic LNi	5	6	-
No ulc/Microscopic LNi	7	9[1]	-
Ulc/Macroscopic LNi	4	5	-
AEG$\geq$3	3	7	11
AEG5	435	509[2]	-162

[1] no RFS benefit demonstrated at SG analysis [2] treatment-related AEG5.

Conclusions: Analyzing NNT and NNH offered us a simple, quick and useful overview on efficacy and safety of Pembro and D-T in this setting. If validated, these data may support their use in clinical decision-making process. Despite study limitations, we suggest that some clinical SG could have a little more favorable risk-to-benefit ratio.

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801P Neoadjuvant checkpoint inhibitor immunotherapy (IMT) for resectable mucosal melanoma (MM)

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Background: Neoadjuvant checkpoint inhibition (CPI) has recently demonstrated impressive outcomes in patients (pts) with stage 3 cutaneous melanoma. However, the safety, efficacy, and outcome of neoadjuvant CPI in pts with mucosal melanoma (MM) are not well studied as MM is a rare melanoma subtype. CPI such as combination nivolumab and ipilimumab achieves response rates of 37-43% in unresectable or metastatic MM but there is limited data regarding the efficacy of these agents in the preoperative setting. We hypothesize that neoadjuvant CPI is a safe and feasible approach for pts with resectable MM.

Methods: Under an institutionally approved research protocol, we identified adult MM pts with resectable disease who received neoadjuvant anti-PD1 +/- anti-CTLA4 between 2015 to 2019 at our institution. Clinical information include age, gender, presence of nodal involvement or satellitosis, functional status, pre-treatment LDH, tumor mutation status, and treatment data was collected. Outcomes include event free survival (EFS), overall survival (OS), objective response rate (ORR), pathologic response rate (PRR), and grade $\geq$3 toxicities were assessed.

Results: We identified 36 pts. Median age was 62; 58% were female. 78% of pts got anti-PD1 + anti-CTLA4. Node-positive disease or satellite lesions was present in 47% of pts. Primary sites of disease were anorectal (53%), urogenital (25%), head and neck (17%), and esophageal (6%). A minority of pts did not undergo surgery due to complete response (n=3, 8%) and disease progression (n=6, 17%), respectively. With a median follow up of 37.9 months, the median EFS was 9.2mo with 3-year EFS rate of 29%. Median OS had not been reached and 3-year OS rate was 55%. ORR was 47% and PRR was 35%. EFS was significantly higher for pts with objective response and for pts with pathologic response. OS was significantly higher for pts with pathologic response. Grade 3 toxicities were reported in 39% of pts.

Conclusions: Neoadjuvant CPI for resectable MM is a feasible approach with signs of efficacy and an acceptable safety profile. As there is currently no standard approach for resectable MM, this study supports further investigations using neoadjuvant therapy for these pts.

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802P Demography and clinical outcomes of adjuvant therapy in Spain: Results from GEM 1801 study

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Background: Approximately one-third of patients (pts) with stage III nodal disease will eventually develop metastatic disease and 17% will develop local unresectable relapse. The use of lymphadenectomy and adjuvant treatment (AT) for local disease is controversial.

Methods: Here we present the demographic characteristics and clinical outcomes of those pts receiving AT other than interferon, included in the prospective observational study GEM 1801.

Results: From 2018 to 2019, 400 locally advanced / metastatic melanoma pts were included, 54 pts (13.5%) received AT. Pts receiving AT were stage IIIA-B (18.5%), IIIC (42.6%), IIID-IV (38.9%) at inclusion according to AJCC 8th ed. Median age was 51.6 y (range: 23.3-86.6), 59.3% were male, and 57.4% BRAF mutated. Resection of the sentinel lymph node (LN) was performed in 72.2%. The median of resected LN was 2 (range: 1-5), of which a median of 1 LN (range: 1-2) was positive. Lymphadenectomy was performed in 55.6% pts, with a median of 14 LN (range: 2-40) resected, of which a median of 0 LN (range: 0-42) was positive. Immunotherapy (IT) was the prefered AT in 44 (81.5%) pts, targeted therapy (TT) in 10 (18.5%). With median follow-up of 36.1 m (95% CI: 29.9-39.2), 24 pts (44.4,%) continued without evidence of disease and 25 pts (46.3%) relapsed (29.6% intra-AT, 16.7% post-AT), 9.3% Not Evaluable. The median relapse-free survival (RFS) was 36.6 m (95% CI: 28.9-44.3).After relapse 19 (76%) pts received subsequent systemic treatments, 9 (36%) pts IT, 8 (32%) TT, and 2 (8%) other. The 24-m OS rate was 85.7% (95% CI: 76.5-96.1). Stratified analysis of RFS and OS is depicted in the table.

Table: 802P

		24-m RFS; % (95%CI)	24-m OS; % (95%CI)
Stage at diagnosis	IIIA-B	87.5 (67.3-100)	87.5 (67.3-100)
	IIIC	68.4 (50.4-92.9)	94.7 (85.2-100)
	IIID - IV	36.4 (20.9-63.2)	77.3 (61.6-96.9)
Lymphadenectomy	Yes	51.9 (36.1-74.6)	85.2 (72.8-99.7)
	No	70 (52.5-93.3)	90 (77.8-100)

Conclusions: Our data, as previously reported, suggest that lymphadenectomy previous to AT would have no impact on both RFS and OS in our population.

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803P Patient-reported outcomes in patients with resected, stage III BRAF V600+ melanoma treated with adjuvant dabrafenib + trametinib: COMBI-APlus study

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Background: COMBI-APlus, an open-label, phase 3b study, met its primary endpoint of significant reduction in composite pyrexia events compared with a historical control from COMBI-AD. Here, we report the patient-reported outcomes (PROs) during the 12-month adjuvant dabrafenib plus trametinib (D + T) treatment in patients (pts) with stage III BRAF V600+ melanoma after complete resection.

Methods: Eligible pts aged ≥18 years with resected stage III BRAF V600E/K—mutant melanoma received oral adjuvant D (150 mg twice daily) + T (2 mg once daily) for up to 12 months (mo). A 16-item melanoma subscale of the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) tool was used to assess the quality of life (QOL). Respondents were asked to score the statements related to their QoL with melanoma, based on a four-point response scale, with 4 being the best response. The FACT-M scores were assessed at baseline and at every month up to month 12. Time to first deterioration, which was defined as the time from inclusion in the study to the first decrease in QoL scores according to baseline score, and effect of age, stage, baseline score, visit, and status visit on PRO using a mixed-effect model were also evaluated.

Results: A total of 552 pts were enrolled and included in this analysis. The mean (SD) FACT-M score at baseline for all pts was 57.44 (5.203), which changed to 55.31 (7.392) at 6 months, and 56.02 (7.324) at 12 months. Overall, data of individual questions showed that pts were at their best state at most of the visits, with non-relapsed pts

showing better change in scores than relapsed pts. The minimal point of worsening was observed at point 5, and the median time for minimal worsening of melanoma-related symptoms was 5.55 mo. The mixed-effect model showed that the disease stage at baseline had a significant effect on the change in PRO score.

Conclusions: PRO data from COMBI-APlus study showed no clear worsening of QOL during the treatment unless there was a relapse. This implies that disease evolution but not treatment affects the QOL, supporting use of D + T as adjuvant treatment in pts with stage III BRAF V600+ melanoma after complete resection.

Clinical trial identification: NCT03551626.

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804P Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: 5-year results of the EORTC 1325-MG/Keynote-054 double-blinded phase III trial

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Background: We conducted the randomized phase 3 double-blind EORTC 1325/KEYNOTE-054 trial to evaluate pembrolizumab vs placebo in patients (pts) with resected high-risk stage III melanoma. At 3.5-year (yr) median follow-up, pembrolizumab improved recurrence-free survival (RFS) (hazard ratio [HR] 0.59; 95% CI 0.49-0.70, P<0.0001) and distant metastasis-free survival (DMFS) (HR 0.60, 95% CI 0.49-0.73, P<0.0001) as compared to placebo (Eggermont, TLO 2020).

Methods: Eligible pts included those ≥18 yrs of age with complete resection of cutaneous melanoma metastatic to lymph node(s), classified as AJCC-7 stage IIIA (at least one lymph node metastasis >1 mm), IIIB or IIIC (without in-transit metastasis). Between Aug-2015 until Nov-2016, 1019 pts were randomized to pembrolizumab 200 mg (N=514) or placebo (N=505) every 3 weeks for a total of 18 doses or until disease recurrence or unacceptable toxicity. The co-primary endpoints were RFS in the intention-to-treat (ITT) overall population and in pts with PD-L1-positive tumors. DMFS was a secondary and progression/recurrence-free survival 2 (PRFS2, time from randomization until the 2nd disease recurrence, a progression of the 1st recurrence, or death) an exploratory endpoint.

Results: Overall, 15%/46%/39% of pts had stage IIIA/IIIB/IIIC. By Jan 17, 2022, at approximately 5-yr median follow-up, 532 RFS, 470 DMFS and 382 PRFS2 events were reported. Pembrolizumab compared with placebo significantly prolonged RFS, DMFS and PRFS2 in the ITT population and in the PD-L1+ subgroup (N=853). Consistent improvements were observed across subgroups, in particular by AJCC staging and BRAF-mutation status.

Table: 804P

Endpoint	Population	Pembrolizumab*	Placebo*	HR**	95% CI HR**
RFS	ITT	55%	38%	0.61	0.51-0.72
RFS	PD-L1+	56%	40%	0.62	0.51-0.75
DMFS	ITT	61%	45%	0.62	0.52-0.75
DMFS	PD-L1+	62%	46%	0.63	0.51-0.77
PRFS2	ITT	68%	56%	0.65	0.53-0.80
PRFS2	PD-L1+	70%	58%	0.67	0.53-0.84

*: 5-yr rate **: stratified by stage at randomization.

Conclusions: At approximately 5-yr median follow-up, adjuvant pembrolizumab provided a clinically meaningful improvement in RFS, DMFS, and PRFS2 in resected high-risk stage III melanoma pts.

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805P Predicting recurrence-free survival for patients with stage II melanoma: A validated tool to guide selection for adjuvant systemic therapy

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Background: Keynote 716 has recently shown improved recurrence-free survival (RFS) for sentinel node-negative Stage IIB/C melanoma patients given adjuvant pembrolizumab. Accordingly, identification of patients most likely to benefit from adjuvant systemic therapy requires accurate, personalised risk prediction. The current AJCC 8th Edition (AJCC-8) estimates melanoma-specific survival (MSS). We developed and externally validated a tool for predicting RFS in stage II melanoma patients.

Methods: Development cohort clinicopathological data were extracted from the Melanoma Institute Australia (MIA) database for patients diagnosed with stage II melanoma (n=3243). Survival prediction models were developed using multivariable Cox regression analyses and externally validated using datasets from the Dutch national cancer registry (PALGA) (n=8631) and the MD Anderson Cancer Center (n=703). Predictive performance of the models was assessed using C-statistics, decision curve analysis and calibration plots.

Results: The development and validation C-statistics for the MIA prediction tool (Table) demonstrated good calibration and large, statistically-significant discrimination gains over the AJCC-8 stage groups, ranging from 8.3% to 12.2%. The MIA tool showed good performance using external datasets and was thus validated.

Conclusions: The MIA model for RFS demonstrated both good discrimination and calibration to predict survival for individual stage II melanoma patients at both 5 and 10 years, which held true on external validation using independent datasets from two different continents. This robust model provides clinicians with important data to guide recommendations for adjuvant immunotherapy, based on individual patients' risk-benefit ratios. An online tool will be available at *www.melanomarisk.org.au*.

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Table: 805P

RFS	C-statistics (95%CI)					
	Australian model			AJCC-8		
	Development	Validation		Development	Validation	
		Dutch	US		Dutch	US
5-Year	68.8% (66.8—70.8)	71.8% (70.6-73.0)	69.4% (65.2-73.6)	60.5% (58.6-62.5)	64.3% (63.2-65.5)	61.9% (57.8-66.0)
10-Year	71.7% (69.3-74.0)	74.0% (72.5-75.6)	69.7% (64.3-75.2)	59.5% (57.1-61.9)	62.3% (60.7-64.0)	61.3% (55.9-66.7)

806P Updated toxicity profile and relapse-free survival outcomes using an adapted pyrexia management algorithm in patients with resected stage III BRAF V600E/K-mutant melanoma treated with adjuvant dabrafenib plus trametinib in COMBI-APlus

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Background: COMBI-APlus (NCT03551626) evaluated an adapted pyrexia management algorithm in patients (pts) with resected stage III *BRAF* V600E/K-mutant melanoma treated with adjuvant dabrafenib plus trametinib (D + T). The study showed significant improvement in the composite pyrexia events compared to that in COMBI-AD. Here we report the updated long-term toxicity profile and relapse-free survival (RFS) from COMBI-APlus.

Methods: D + T was interrupted at the onset of pyrexia and resumed once pts were symptom-free. The primary end point was the composite rate of grade 3/4 pyrexia, hospitalization or permanent cessation due to pyrexia vs historical control from COMBI-AD (20%; 95% CI; 16.3—24.1).

Results: At a median (min—max) follow-up of 31.6 mo (24.9—38.6), median duration of D + T exposure for all enrolled pts (N=552) was 11.0 mo (0.03—12.42). The composite rate of grade 3/4 pyrexia, hospitalization, and permanent withdrawal due to pyrexia was 7.6% (95% CI; 5.5—10.1). Grade 3/4 pyrexia, hospitalization, and permanent discontinuation due to pyrexia occurred in 20 (3.6%), 24 (4.3%), and 12 (2.2%) pts, respectively. The median (interquartile range [IQR]) time to first onset of pyrexia was 22 days (11—70), and the median duration of first pyrexia event was 2 days (IQR, 2.0—4.0). A total of 542 (98.2%) pts experienced an adverse event (AE). Most AEs appeared in the first quarter of treatment, and >94% of them were fully resolved by end of the study. All pyrexia events were 100% resolved. Exposure-adjusted AEs in the first 3 months were 8.36 occurrences, which reduced to 3.51 in months 9—12; likewise, pyrexia occurrence was reduced from 1.68 to 0.73. Permanent discontinuation due to any AE occurred in 80 (14.5%) pts. At data cut-off (18 Nov 2021), RFS events were reported in 150 (27.2%) pts, whereas relapses occurred in 144 (26.1%) pts. The 12- and 18-mo RFS rates were 91.7 % (95% CI; 89.0—93.8) and 81.5 % (95% CI; 77.8—84.6), respectively.

Conclusions: After >2 years of follow-up, the adapted algorithm reduced the incidence of pyrexia-related toxicities compared to that in COMBI-AD, while D + T maintained RFS benefits.

Clinical trial identification: NCT03551626.

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807P Adjuvant anti-PD-1 monotherapy benefit varies across different ethnicities and melanoma subtypes

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Background: Although anti-programmed cell death receptor-1 (PD-1) monotherapy is a standard adjuvant treatment for melanoma patients underwent definitive surgery, their efficacy is evaluated mostly in Caucasians and cutaneous melanoma, it remains unclear in other ethnic groups and melanoma subtypes.

Methods: Clinical data for patients (pts) with resected stage II/III/IV melanoma treated with anti-PD-1 monotherapy both in and outside clinical trial settings between 2015 and 2021 was collected retrospectively from 6 independent institutions in the US, Australia, Japan and China. Survival outcomes (both recurrence free survival [RFS] and overall survival [OS]) were compared by ethnicity (Caucasian versus East-Asian/African) and by different melanoma subtypes (non-acral-cutaneous[NAC]/unknown primary[UP], acral and mucosal).

Results: In total 537 pts were included. Caucasians had significantly longer RFS and OS. Among different melanoma subtypes, NAC/UP had the best RFS and OS, followed by acral. Mucosal melanoma had the poorest survival outcomes. In NAC/UP subtypes, Caucasians had longer RFS (with significance) and OS (with marginal significance) than East Asian/African. In the multivariate analysis incorporating ethnicity, melanoma subtype, age, sex, stage, LDH, and BRAF mutation status, Caucasian ethnicity was independently correlated with significantly better RFS (HR 0.59; 95%CI 0.41-0.84; P=.004) and a trend towards better OS (HR 0.59, 95%CI 0.34-1.02; P=.06), while mucosal subtype independently associated with both poorer RFS (HR 2.43; 95%CI 1.55-3.80; P<.001) and OS (HR 2.97; 95%CI, 1.53-5.78; P=.001).

Table: 807P

	Entire Cohort					NAC/UP subtypes	
	Ethnicity		Mel Subtype			Ethnicity	
	Caucasian (n = 262)	East-Asian /African (n = 275)	NAC/UP (n = 352)	Acral (n = 83)	Mucosal (n = 102)	Caucasian (n = 246)	East-Asian /African (n = 106)
RFS							
1-y rate (%, 95% CI)	80 (76-86)	67 (62-73)	77 (73-82)	79 (70-88)	58 (49-69)	81 (76-86)	68 (60-78)
2-y rate (%, 95% CI)	70 (64-76)	49 (44-56)	66 (61-71)	57 (46-70)	40 (32-52)	71 (65-77)	53 (44-64)
P value	<.001		<.001			<.001	
OS							
2-y rate (%, 95% CI)	92 (88-95)	80 (75-86)	90 (87-94)	83 (74-92)	75 (67-85)	92 (89-96)	85 (78-93)
4-y rate (%, 95% CI)	83 (78-89)	55 (46-66)	82 (77-87)	57 (38-86)	46 (36-60)	84 (78-90)	78 (69-88)
P value	<.001		<.001			.07	

Conclusions: Ethnicity and melanoma subtype both contribute to survival discrepancies in melanoma patients undergoing adjuvant anti-PD-1 monotherapy. The somatic genetic and immunologic underpinning of these differences remain unclear and warrants further investigation.

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808P Postoperative adjuvant radiotherapy can reduce the local recurrence of nasal cavity and paranasal sinus mucosal melanoma: A prospective design, retrospective analysis and case–control study

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Background: Mucosal melanoma of the nasal cavity and paranasal sinuses (NPMM) is a highly aggressive disease. The role of postoperative adjuvant radiotherapy is controversial.

Methods: A database was prospectively designed for NPMM from Peking University Cancer Hospital. 300 patients between March 2009 and January 2020 were included and divided into SA (surgery alone, 158 patients) and SR group (surgery plus radiotherapy, 142 patients). Similarly and balanced system therapies were added into two groups. Postoperative radiotherapy was recommended, with a total dose of 65-70 Gy/30-35 fx to GTV and 60 Gy/30 Fx to CTV. The primary endpoint was relapse-free survival (RFS). The secondary endpoints included recurrence-free survival, distant metastasis-free survival (DMFS), and overall survival (OS).

Results: At a median follow-up of 50.0 months, The RFS in SA and SR groups were 9.8 and 15.2 months (HR: 0.714, 95% CI: 0.546-0.933, P = 0.014). The DMFS in SA and SR groups were 23.8 and 21.3 months (HR: 0.896, 95% CI: 15.7-31.9 vs. 13.3-29.3, P = 0.457). The OS in SA and SR groups was 31.0 and 35.1 months (HR: 0.816, 95% CI: 25.7-36.3 vs. 27.1-43.2, P = 0.178). For stage IVA patients, radiotherapy reduced the incidence of relapse by 0.43-fold with NPMM. For patients without adjuvant system therapy, radiotherapy reduced the incidence of recurrence by 0.85 times. Most adverse events were grade 1-2 and manageable.

Conclusions: Postoperative radiotherapy played a crucial role in the local control of NPMM, especially for patients with a local excision, observation only, T4a or IVA stages.

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809P Outcomes of patients with resected stage III/IV acral or mucosal melanoma treated with adjuvant anti-PD-1 therapy

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Background: Acral (AM) and mucosal melanomas (MM) are rare subtypes with a poor prognosis. In those with advanced disease anti-PD-1 (PD1) therapy has reduced activity compared to that seen in non-acral cutaneous melanoma. While adjuvant (adj) PD1 is used for resected stage III/IV AM and MM, there are no data regarding efficacy in these subgroups.

Methods: Patients with resected stage III or IV AM or MM from 19 centres were included. Baseline disease characteristics, disease recurrence characteristics and treatment outcomes-recurrence free survival (RFS) and distant metastasis free survival (DMFS) were examined. Comparison has been made to matched historical data of patients who did not receive adjuvant therapy from the Melanoma Institute Australia (MIA) database.

Results: 157 patients were identified, 100 (64%) Caucasian, 116 (74%) AM and 41 (26%) MM with a median age 65.5 (20-82) for AM and 59 (29-82)for MM. Of these patients 5 (5%) AM and 3 (7%) MM had resected stage IV disease. At a median follow up of 18 months, 65 (56%) AM and 29 (71%) MM had recurred. 34 (29%) of AM and 9 (22%) MM patients completed adjuvant PD1 therapy with 47 (41%) of AM and 19 (46%) of MM patients stopping adjuvant treatment due to recurrence. Median time to recurrence was 17.7 months for AM and 12.9 months for MM patients. First recurrence was locoregional alone in 33 (51%) of AM and 16 (55%) of MM patients . In those with resected stage III disease both median and landmark RFS and DMFS were not significantly different to that seen in the matched historical cohort (Table).

Table: 809P

	Acral		Mucosal	
	Adj PD1	Database matched	Adj PD1	Database matched
N	111	90	38	12
BRAF mutant %	18	-	7	-
Stage IIIC/D* %	65	-	75	-
Median RFS (months)	17.35	17.4	18.8	11.65
1yr landmark RFS %, (95% CI)	79 (70-88)	71 (62-82)	66 (43-99)	80 (60-100)
3yr landmark RFS % (95% CI)	48 (38-62)	47 (37-60)	-	-
Median DMFS (months)	31.95	25.9	23.65	14.5
3yr landmark DMFS % (95% CI)	78 (69-88)	80 (71-91)	53 (27-100)	70 (46-100)

*AJCCv8 cutaneous staging applied to AM/MM.

Conclusions: Resected AM and MM carries a poor prognosis irrespective of the use of adjuvant PD1. We did not observe an obvious benefit of adjuvant PD1 in RFS and DMFS compared to historical controls. Prospective studies in these subgroups are required to determine the utility of adjuvant PD1 therapy.

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810P PRESERV MEL: Real-world outcomes and health-related quality of life (HRQoL) in patients receiving adjuvant nivolumab for melanoma in Belgium and Luxembourg

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Background: Based on CheckMate 238 results, nivolumab was the first anti-programmed death-1 therapy reimbursed in Belgium and Luxemburg as an adjuvant treatment for adults with resected melanoma. This study aimed to describe effectiveness, safety and HRQoL of patients (pts) treated with adjuvant nivolumab in the real-world.

Methods: 152 pts (125 prospective, 27 retrospective) were enrolled by 31-Dec-2020. Relapse-free survival (RFS), time to treatment discontinuation (TTD), and adverse events (AEs) were assessed before treatment initiation (baseline) to the end of available follow-up. Kaplan-Meier methods were used to assess time-to-event endpoints. For 125 prospectively enrolled pts HRQoL was assessed at baseline and at 3, 6, 9, 12, 18, and 24 months (mo) using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, Functional Assessment of Cancer Therapy Melanoma (FACT-M) and EQ-5D-3L. Change from baseline was analysed using a mixed model for repeated measures.

Results: At a minimum follow-up of 11.5 mo (median 18.5 mo), 12- and 18-mo RFS was 77.3% (95% confidence interval [CI] 69.8-83.2) and 71.8% (95% CI 63.5-78.6), respectively. Median TTD was 11 mo; 35 pts (23%) discontinued due to any grade AE. Twenty-one pts (14%) had grade 3/4 treatment-related AEs, with no treatment-related deaths. Completion of the HRQoL scales ranged from 96% at baseline to 87% at 18-mo. At all timepoints (TP) EORTC QLQ-C30 function and symptom scores were below thresholds for clinical importance. No clinically meaningful changes were found for the QLQ-C30 Global QoL nor for the subscales compared to the minimally important difference (MID) estimates for melanoma pts. The FACT-M scores were stable; the melanoma surgery scale reached the MID for improvement as from mo 3. The EQ-5D visual analogue scale and utility index did not exceed the MID thresholds at any TP.

Conclusions: Real-world effectiveness and safety were consistent with CheckMate 238. HRQoL remained close to baseline values after adjuvant nivolumab initiation with no clinical meaningful changes over time, suggesting that adjuvant nivolumab does not impact HRQoL in a real-world setting.

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811P Three-years real-world evidence of adjuvant dabrafenib plus trametinib (DT) in patients with resected melanoma in Spain (GEM 1901 - DESCRIBE-AD)

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Background: DT combination has shown efficacy in the adjuvant setting for BRAF-mutated melanoma (BMM) patients (pts) in clinical trials. Previous reports from DESCRIBE-AD resulted in promising overall survival (OS) rates at 12 months.

Methods: An observational retrospective study was carried out in 25 GEM sites in Spain. Histologically confirmed and resected BMM pts previously treated with DT according to standard clinical practice in the adjuvant setting were included. Only surgical resection was allowed as a prior treatment to DT. DT discontinuation rate and time to treatment discontinuation were the primary objective. Secondary objectives included safety and efficacy of the combination. Here, we report 3-year results for OS.

Results: From 10/2020 to 03/2021, 65 pts were included. Median age was 58 years, 55% were male and 60%, 25%, and 14% had an ECOG PS 0/1/Uk respectively, one patient presented ECOG 3. Allocation of stage IIIA, IIIB and IIIC according to TNM AJCC 7th edition was 29%, 26% and 32%, respectively. There were 3 pts diagnosed at stage I/II but considered of risk, and 2 pts with stage IV but completely resected, all considered for adjuvant DT. Ulceration was present in 40%, Breslow ≥2 mm in 71%, and nodes were microscopically and macroscopically affected in 39% and 22% of pts,

respectively. Only 9.2% of pts discontinued DT prematurely due to toxicity and 21.2% had dose reductions to manage toxicity. After a median follow-up of 36.2 m (range: 13-51.1), the overall OS rate at 3-years was 83.5% (95% CI: 74.5-93.5). According to AJCC 7 stage at diagnosis, the 3-years OS rate was 95.2% (95% CI: 86.6-100), 75% (56-100), and 76.8% (60.7-97.2) for stage I-II-IIIA, IIIB, and IIIC-IV respectively. Throughout the study period 11 (16.9%) pts died, of which 10 died due to disease progression and one due to COVID-19 infection.

Conclusions: Adjuvant treatment with DT for melanoma achieved good treatment compliance and has proven efficacy in the real world. Adjuvant DT has a clinical impact in survival in line with previous clinical trial COMBI-AD.

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812P Early experiences in adjuvant treatment of melanoma: Real-world data on tolerability, safety and efficacy

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Background: Nivolumab, pembrolizumab, and dabrafenib plus trametinib are registered as adjuvant melanoma treatments since 2018. Randomized controlled trial results may not fully represent the benefits and risks of treatments in clinical practice. Therefore, the aim of this study was to evaluate real world experience with text-mining software on tolerability, safety and efficacy in patients treated for adjuvant melanoma.

Methods: Adult melanoma patients receiving adjuvant treatment between January 2019 and October 2021 in the Leiden University Medical Center, The Netherlands, were included. We retrospectively identified patients and collected data from electronic health records with text-mining software CTcue.

Results: A total of 122 patients were included: 55 patients treated with nivolumab (N), 48 with pembrolizumab (P), and 20 with dabrafenib plus trametinib (D+T). We found a significant difference in the reason to stop treatment (P-value = 0.0238): 48 (39%) patients completed their scheduled treatment (N: 22 (40%), P: 20 (42%), D+T: 6 (30%)); 20 (16%) patients had treatment-limiting toxicity (N: 9 (16%), P: 3 (6%), D+T: 8 (40%)), and recurrence was treatment-limiting in 28 (23%) patients (N: 15 (27%), P: 12 (25%), D+T: 1 (5%)). Treatment-limiting toxicity from D+T was primarily a combination of adverse events (AEs) including pyrexia and fatigue, which are mainly reversible. Most treatment-limiting AEs from immunotherapy were immune-related. The 1-year recurrence-free survival was 70.3% (95% CI: 58.1—85.0) with nivolumab, 72.4% (95% CI: 60—87.3) with pembrolizumab, and 83.0% (95% CI: 67.1—100) with D+T.

Conclusions: Adjuvant immunotherapy was better tolerated than D+T, comparable to data from clinical trials. Specifically for BRAF+-patients, physicians must weigh the higher risk of reversible treatment-limiting AEs of D+T against the risk of long-term immune-related AEs. For conclusions on efficacy, a longer follow-up period is needed.

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813P Time to development of central nervous system (CNS) metastases (mets) with atezolizumab (A) or placebo (P) combined with vemurafenib (V) + cobimetinib (C): Updated results from the phase III IMspire150 study

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Background: Primary analysis of the phase 3 IMspire150 study (NCT02908672) demonstrated improved progression-free survival with first-line combination treatment with A+V+C vs P+V+C in patients (pts) with previously untreated *BRAF*^{V600} mutation—positive advanced melanoma. At the time of primary analysis (median follow-up 18.9 months), numerically lower rates of interval development of CNS mets were also seen with A+V+C vs P+V+C. Here we report updated exploratory analyses of incidence and time to development of CNS mets with A+V+C vs P+V+C with longer follow-up in the IMspire150 study.

Methods: Eligible pts were randomized 1:1 to receive A+V+C or P+V+C. Pts received V+C in cycle 1; A or P were given on day 1 and 15 of each 28-day cycle starting from cycle 2 onwards. Incidence and time to development of CNS mets were evaluated in pts with no history of CNS mets at baseline confirmed by magnetic resonance imaging/computed tomography (MRI/CT). Follow-up MRI/CT assessments were performed during the study as clinically indicated. Time-to-event outcomes were estimated using the Kaplan-Meier method and competing risks analysis.

Results: 514 pts were randomly assigned to A+V+C (n=256) or P+V+C (n=258); 244 and 247 pts, respectively, had no history of CNS mets at baseline. With median follow-up of 29.8 months in the A+V+C arm and 22.8 months in the P+V+C arm, CNS mets had developed in 61/244 pts (25%) in the A+V+C arm and 70/247 pts (28%) in the P+V+C arm. Cumulative incidence of CNS mets as site of first progressive disease with A+V+C vs P+V+C was 16% vs 19%, 24% vs 26%, 25% vs 28%, and 28% vs 29% at 12, 24, 36, and 48 months, respectively (stratified hazard ratio [HR] 0.91; 95% CI, 0.64-1.29). Time to first CNS mets was delayed with A+V+C vs P+V+C (HR 0.80; 95% CI, 0.57-1.13). Median time from first detection of CNS mets until death was similar between A+V+C and P+V+C (median 5.3 vs 5.2 months; HR 0.96; 95% CI, 0.65-1.41).

Conclusions: Addition of A to V+C is associated with numerically lower rates for development of CNS mets. The observed risk reduction for CNS mets is consistent with the overall benefit observed for A+V+C in the IMspire150 study.

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814P Phase II study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC): Final analysis from EMPOWER-CSCC-1 groups 1, 2 and 3

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Background: Previous analyses from EMPOWER-CSCC-1 phase 2 study (NCT02760498) demonstrated substantial clinical benefit and an acceptable safety profile with cemiplimab in patients with locally advanced and metastatic CSCC. Here, we provide the final analysis from the study Groups 1, 2 and 3.

Methods: Patients received cemiplimab 3 mg/kg IV every 2 weeks for up to 96 weeks (Group 1, metastatic CSCC; Group 2, locally advanced CSCC) or cemiplimab 350 mg IV every 3 weeks for up to 54 weeks (Group 3, metastatic CSCC). The primary endpoint was objective response rate (ORR; complete + partial response) per independent central review (ICR). This is the final analysis and the final database lock occurred on 01 Mar 2022.

Results: A total of 193 patients were enrolled (Group 1, n=59; Group 2, n=78; Group 3, n=56). Tumour response per ICR, median progression-free survival (PFS) and overall survival (OS) (Table) remain generally consistent with the previous update (data cut-off: 11 Oct 2020). OS at 48 months is 61.8% (95% CI: 54.0-68.7). Overall median duration of response (DOR) was 41.3 months (Table). Fatigue (34.7%) was the most common treatment-emergent adverse event (TEAE) of any grade; hypertension (4.7%) was the most common Grade $\geq$3 TEAE.

Conclusions: The final update confirms the durable response, safety and efficacy of cemiplimab in patients with advanced CSCC. There were no new safety signals identified on longer follow-up. Cemiplimab remains a standard of care option for advanced CSCC.

Clinical trial identification: NCT02760498.

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Table: 814P

	Group 1 (mCSCC) 3 mg/kg Q2W (n=59)	Group 2 (laCSCC) 3 mg/kg Q2W (n=78)	Group 3 (mCSCC) 350 mg Q3W (n=56)	Total (n=193)
Median duration of follow-up, months, (range)	18.5 (1.1–41.0)	15.5 (0.8–43.2)	17.3 (0.6–43.4)	15.7 (0.6–43.4)
ORR, %, (95% CI)	50.8 (37.5–64.1)	44.9 (33.6–56.6)	46.4 (33.0–60.3)	47.2 (39.9–54.4)
Complete response, n (%)	12 (20.3)	10 (12.8)	11 (19.6)	33 (17.1)
Partial response, n (%)	18 (30.5)	25 (32.1)	15 (26.8)	58 (30.1)
Median DOR, months (95% CI)	NR (20.7–NE)	41.9 (20.5–54.6)	41.3 (40.8–46.3)	41.3 (38.8–46.3)
Median PFS, months (95% CI)	18.4 (7.3–53.2)	18.5 (11.1–43.8)	21.7 (3.8–43.3)	22.1 (10.4–32.3)
Median OS, months (95% CI)	57.7 (29.3–NE)	NR (58.3–NE)	48.4 (29.5–NE)	NR (56.0–NE)

CI, confidence interval; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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815P A single-arm, phase II clinical study of imatinib mesylate/toripalimab combo in patients (pts) with advanced melanoma harboring c-Kit mutation or amplification

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Background: Kit inhibitor monotherapy has moderated activity in melanoma harboring c-Kit aberrations (CKA) but with an unsatisfied objective response rate (ORR) of 23-26% and median progression free survival (mPFS) of 3.5-7.3mo. Thus we performed a phase II trial testing the imatinib mesylate/toripalimab (anti-PD-1 monoantibody) combo in pts with advanced melanoma harboring CKA. (NCT: 05274438).

Methods: This is a single-arm, single-center, phase II clinical trial involving 37 pts (treatment-naive or refractory to standard therapy excluding Kit inhibitors and anti-PD-1/L1) with advanced melanoma harboring CKA including two stages: 3 pts were enrolled starting with imatinib 400mg qd for 6 weeks, followed by imatinib 400mg qd combined with toripalimab 240mg per 3 weeks until disease progression or intolerable toxicity. If dose limiting toxicity (DLT) was not observed, the original dose was extended to 37 pts in stage II; if there was 1 DLT, pts was extended to 6 in stage I; if $\geq$2 DLT cases occurred, imatinib was reduced to 300mg qd and the "3+3" study was restarted. The primary endpoint was PFS and the secondary endpoints included ORR, disease control rate (DCR), overall survival (OS) and safety.

Results: From March 2021 to April 2022, no DLT was observed in the first 3 pts and another 17 pts enrolled. 17 pts were radiologically evaluable. The ORR was 58.8% (95% CI: 32.7-84.9%) and DCR was 82.4% (95% CI: 56.6-96.2%). The mPFS was not reached (NR). Notably, in pts harboring exon 11 mutations (n=10), the ORR was 90.0% (95% CI: 55.5-99.7%). In 9 treatment naive pts, the ORR was 55.6% (95% CI: 21.2-86.3). The incidence of grade $\geq$3 treatment-related adverse events was 20% (4/20), including rash (10.0%), aspartase transaminase elevation (5.0%), fatigue (5.0%) and interstitial pneumonia (5.0%). No treatment-related deaths was observed.

Conclusions: Imatinib mesylate/toripalimab combo was effective and well-tolerated in pts with advanced melanoma harboring c-kit aberrations. Longer follow-up and further patient recruitment are in need.

Clinical trial identification: NCT05274438.

Legal entity responsible for the study: Peking University Cancer Hospital.

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Disclosure: All authors have declared no conflicts of interest.

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816P Investigating surrogate endpoints (SE) for overall survival (OS) in first-line (1L) advanced melanoma: A pooled-analysis of immune checkpoint inhibitor (ICI) trials

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Background: ICIs transformed the treatment of advanced melanoma with substantial improvements in OS. Establishing valid SEs for OS enables earlier assessment of randomized controlled trials (RCTs) of ICIs due to lengthy follow-up required to observe mature OS data.

Methods: We examined progression-free survival (PFS), time-to-next treatment (TNT) and objective response rate (ORR) as potential SEs for OS in 1L advanced melanoma by pooling patient-level data from 4 RCTs (CheckMate [CM] 066, 067, 069 & 511) of nivolumab, ipilimumab, and their combinations. Individual-level (IL)-correlation measures - Spearman's (ρ) & Kendall's (τ) rank correlation coefficients for PFS and TNT, and an odds ratio (OR) for survival due to presence of objective response - were derived from copula models. For the trial-level (TL)-correlation, surrogacy equations and coefficients of determination (R^2) between the treatment effects on SEs and OS were estimated via regression. Primary analyses used all patients (n=1865) from all RCTs. Sensitivity of the results were tested with respect to BRAF-status and removal of CM 069 due to imbalances in subsequent systemic therapy and ICI use between the arms of this study.

Results: At the IL, ORR was strongly correlated with OS, whereas both PFS & TNT showed moderate correlation with OS. All SEs were moderately correlated with OS at the TL (Table). Removing CM 069 from the analyses only marginally affected IL-correlations ($\leq$ 0.01 change in ρ and τ, 4.5% change in the OR) but greatly strengthened TL-correlations for all SEs ($R^2 \geq 0.87$ with significantly narrower 95% CIs for all SEs). IL-correlations were insensitive to BRAF status, whereas TL-correlations were slightly stronger for the BRAF wild-type.

Table: 816P

Correlation	ρ [95% CI]	τ [95% CI]	R^2 [95% CI]
PFS - OS	0.72 [0.71, 0.73]	0.53 [0.49, 0.57]	0.71 [0.23, 1.00]
TNT - OS	0.77 [0.76, 0.78]	0.58 [0.55, 0.62]	0.75 [0.32, 1.00]
ORR - OS	**OR** 12.29 [9.78-14.80]		0.62 [0, 1.00]

Conclusions: With moderate-to-strong correlation to OS on both levels, all candidate SEs can assist predictions for OS benefits of ICIs with a range of uncertainty depending on BRAF-status and subsequent treatment patterns.

Clinical trial identification: CheckMate 066: NCT01721772, CheckMate 067: NCT01844505, CheckMate 069: NCT01927419, CheckMate 511: NCT02714218.

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817P Nivolumab (NIVO) + relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: Additional response outcomes from RELATIVITY-047

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Background: In the phase 2/3 RELATIVITY-047 trial, NIVO + RELA as a fixed-dose combination (FDC) significantly improved the primary endpoint of progression-free survival (PFS) and showed a clinically meaningful improvement in overall survival (OS), although not statistically significant, with a numerically higher confirmed objective response rate (ORR) vs NIVO in patients (pts) with previously untreated metastatic or unresectable melanoma. NIVO + RELA had a manageable safety profile with no new or unexpected safety signals. Here, we report additional response outcomes.

Methods: Pts were randomized 1:1 to NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg intravenously every 4 weeks. The primary endpoint of PFS per RECIST v1.1 was assessed by blinded independent central review (BICR). Secondary endpoints, to be tested in hierarchy, were OS and then ORR by BICR. Exploratory analyses were performed to further characterize tumor responses and associated outcomes.

Results: Pts received NIVO + RELA (n = 355) or NIVO (n = 359). Median follow-up was 19.3 months (mo). Confirmed ORR by BICR was 43.1% vs 32.6% and median time (range) to objective response was 2.8 mo (1.2—12.2 mo) vs 2.8 mo (1.7—20.1 mo) with NIVO + RELA vs NIVO, respectively. Among pts with an objective response, 88% responded within 20 weeks (second imaging scan) on NIVO + RELA vs 82% on NIVO. Median duration of response (DOR) was not reached in either arm. Among responders, the proportion of pts with a DOR of at least 12 (80% vs 85%) and 18 mo (75% vs 73%) was similar with NIVO + RELA vs NIVO, respectively. In both arms, PFS and OS were greater in responders vs nonresponders (Table). PFS and OS Kaplan-Meier curves by response will be presented.

Conclusions: Durable responses occurred in patients treated with either NIVO + RELA or NIVO, with numerically higher response rates for NIVO + RELA vs NIVO. In both arms, pts who responded to treatment had substantially improved PFS and OS vs nonresponders.

Clinical trial identification: NCT03470922.

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Table: 817P

	NIVO + RELA (N = 355)		NIVO (N = 359)	
	Responder	Nonresponder	Responder	Nonresponder
Patients, n	153	175	117	214
Median PFS by BICR, mo (95% CI)	NR (32.2—NR)	2.8 (2.8—3.0)	NR (32.7—NR)	2.8 (2.8—2.8)
PFS by BICR at 12 mo, % (95% CI)	87.4 (80.7—91.9)	14.2 (9.1—20.5)	86.9 (78.9—92.1)	10.6 (6.8—15.4)
Median OS, mo (95% CI)	NR (NR—NR)	19.2 (15.8—29.5)	NR (NR—NR)	17.0 (13.8—22.1)
OS at 12 mo, % (95% CI)	97.4 (93.2—99.0)	66.3 (58.7—72.8)	99.1 (94.1—99.9)	60.7 (53.8—67.0)

Responder: complete or partial response; Nonresponder: stable disease, progressive disease, noncomplete response or nonprogressive disease.
CI, confidence interval; NR, not reached.

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818P Phase II confirmatory study of cemiplimab (350mg IV Q3W) in patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): Study 1540 Group 6

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Background: While most patients (pts) diagnosed with CSCC are cured with local therapies, for the small percentage developing advanced CSCC the disease is life threatening with dismal prognosis. In a phase 1 (NCT02383212) and a pivotal phase 2 (NCT02760498) clinical trials, cemiplimab, an anti—programmed cell death receptor-1 [anti—PD-1], was the first systemic therapy to demonstrate significant antitumor activity in pts with advanced CSCC. Here, we report results from group 6 of the pivotal phase 2 trial, providing additional efficacy and safety data for cemiplimab monotherapy, 350 mg every 3 weeks (Q3W) up to 104 weeks, in patients with advanced CSCC.

Methods: Patients with advanced CSCC (metastatic [nodal or distant] or locally advanced) were treated with cemiplimab 350 mg intravenous (IV) Q3W for up to 108 weeks. The primary endpoint was objective response rate (ORR; complete response + partial response) per independent central review (ICR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS) by central and investigator review as well as safety and tolerability of cemiplimab.

Results: At data cut-off date of Oct 25 2021, 167 pts were enrolled, of which 165 pts received at least one dose of cemiplimab and were followed-up for a median of 8.71 months (range: 0.0 - 19.5). 5 of 167 pts received prior systemic therapies. Per ICR, ORR was 44.3% (74/167, 95% CI: 36.6%, 52.2%) with complete response in 5.4% (9/167), partial response in 38.9% (65/167), and DOR was not reached (95% CI: 13.0 months, not evaluable [NE]). Among treated patients, median PFS was 14.7 months (95% CI: 10.4, NE) and median OS was not reached (95% CI: 17.6 months, NE). The most common treatment-emergent adverse events (TEAEs) by any grade were fatigue (26.1%), diarrhoea and pruritus (each 21.2%), and nausea (17.0%). The most common grade $\geq$3 TEAEs were hypertension and pneumonia (each 3.6%), and general physical health deterioration (3.0%).

Conclusions: The group 6 primary analysis demonstrates a safety and efficacy profile that is consistent with that of the earlier groups of the study.

Clinical trial identification: NCT02760498.

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819P Efficacy of dabrafenib (D) trametinib (T) plus spartalizumab (S) by baseline site of metastases in patients (pts) with previously untreated BRAF V600-mutant unresectable or metastatic melanoma: Post hoc analysis of phase III COMBI-i trial

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Background: Pts with high tumour burden may benefit from adding anti-PD-1 to targeted therapy.[1] Although COMBI-i trial (NCT02967692) did not meet its primary endpoint for overall population, progression-free survival (PFS) was significantly longer with S (anti-PD-1) +DT vs placebo (PBO)+DT in pts with $\geq$3 metastatic (met) sites (hazard ratio [HR]=0.63; 95% confidence interval [CI] 0.46—0.87).[2] This post hoc analysis of COMBI-i examined S+DT vs PBO+DT based on met site.

Methods: In COMBI-i part 3, eligible pts were randomised 1:1 to receive either S+DT (n=267) or PBO+DT (n=265) until progression or unacceptable toxicity.[2] Post hoc analysis of PFS and overall survival (OS) was performed in pts with >2/>3 met sites and in pts with adrenal/bone/lung/liver mets at baseline. PFS and OS were summarised descriptively using Kaplan–Meier methods; HRs were estimated using cox regression models.

Results: At data cut off on 01 July 2020, median follow-up for COMBI-i part 3 was 27.2 months.[2] Among 531 pts with mets at baseline, n=179 had >2 met sites, n=93 had >3 met sites. Mets at baseline were reported in lung (n=250), liver (n=157), bone (n=57) and adrenal glands (n=33). In pts with >3 met sites, S+DT showed benefit vs PBO+DT in terms of PFS (HR=0.40; 95% CI 0.25–0.65) and OS (HR=0.50; 95% CI 0.28–0.87). Pts with >3 met sites and elevated lactate dehydrogenase (LDH) had longer PFS (HR=0.43; 95% CI 0.24–0.77) and OS (HR=0.42; 95% CI 0.21–0.84) with S+DT vs PBO+DT. Similar results were seen in pts with >2 met sites. PFS was longer with S+DT vs PBO+DT in pts with adrenal (HR=0.20; 95% CI 0.07–0.57), bone (HR=0.45; 95% CI 0.24–0.84) and lung mets (HR=0.59; 95% CI 0.43–0.80); 95% CIs for HR for PFS crossed 1 in pts with liver mets (HR=0.85) or those with isolated lung mets (n=33; HR=1.27).

Conclusions: Pts with >2 or >3 met sites with or without raised LDH derived benefit from adding S to DT, as did pts with lung, bone and adrenal involvement at baseline. Number and site of mets may be a useful guide for patient selection for triplet therapy. 1. Kim et al Front Immunol;11:629722. 2. Dummer et al JCO 2022;JCO2101601.

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820P Nivolumab (NIVO) +/- relatlimab (RELA) or ipilimumab (IPI) for patients (pts) with advanced treatment-naïve or -refractory basal cell carcinoma (BCC)

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Background: Standard therapies for pts with locally-advanced or metastatic BCC (aBCC) include hedgehog pathway inhibitors (HHi), limited by tolerability, and 2nd-line (2L) anti-PD-1, limited by suboptimal response rates (~20-30%). 1L anti-PD-1 efficacy data are limited to case reports, and anti-LAG-3 data have not been reported in BCC. The current study tests NIVO (anti-PD-1) alone in treatment-naïve and HHi-experienced pts, and NIVO+RELA (anti-LAG-3) or NIVO+IPI (anti-CTLA-4) in anti-PD-1-refractory aBCC (NCT03521830).

Methods: The primary endpoint was overall response rate (ORR) per RECIST v1.1. Treatment-naïve and HHi-experienced pts with aBCC received NIVO 480 mg IV q4 weeks (W) for ≤48W. Pts with stable disease (SD) at ≥36W or progressive disease (PD) on anti-PD-1 received NIVO 480 mg + RELA 480 or 960 mg IV q4W x 12, or NIVO 240 mg + IPI 1 mg/kg IV q3W x 4 then NIVO 480mg q4W x 7. H&E-stained tumor biopsy specimens taken 2-12W after treatment initiation or regimen change were scored for % residual viable tumor (RVT) [Stein, et al. *Ann Oncol*, 2019].

Results: 24 pts (5 metastatic) were enrolled 12/2018 – 3/2022, 22 of whom were evaluable. Pts received NIVO (n=15; 10 treatment-naïve), NIVO+RELA (n=8), or NIVO+IPI (n=1). Median follow-up was 9.9 mo (range 1.8 - 38.4). Toxicities associated with each regimen were consistent with previous experience. Complete or partial response (CR, PR) to NIVO was observed in 5/10 (50%) and 1/5 (20%) pts in the 1L and 2L settings, respectively. 9 pts had SD (median duration 8 mo). 6 evaluable pts received NIVO+RELA; PD (n=1), SD (n=4), PR (n=1, 0% RVT at 4W; this pt had SD >48W on 1L NIVO). One pt who received NIVO+IPI after HHi and NIVO had PD. No responses were seen in 5 pts with metastatic BCC regardless of cohort. In 14/15 pts who received NIVO or NIVO+RELA and underwent tumor biopsy at ≤12W, ≤35% RVT was associated with PR or CR.

Conclusions: 1L NIVO demonstrated an ORR of 50% among 10 pts with aBCC. NIVO+RELA mediated tumor regression in 1/6 anti-PD-1-refractory pts. ≤35% RVT in on-treatment biopsy was associated with response and warrants further exploration as a predictive biomarker. These preliminary findings in this ongoing trial support testing NIVO+RELA in treatment-naïve pts with aBCC.

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821P Safety and efficacy of infrequent tebentafusp treatment omissions in patients with metastatic uveal melanoma

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Background: Tebentafusp (tebe) (gp100×CD3) is the first TCR bispecific protein approved for treatment of a solid tumor (metastatic uveal melanoma, mUM). The IMCgp100-202 trial (NCT03070392) in untreated mUM demonstrated improved overall survival, HR=0.51. The most frequent treatment-related AEs (TRAEs), cytokine release syndrome (CRS) and rash, were consistent with mechanism of action and were most common in the first 3 weeks (wks). Once the target dose has been achieved after the first 3 intrapatient escalation doses, tebe is administered as outpatient. After the initial 3 wks, a subset of patients (pts) omitted at least one dose. Here, we assessed the impact on safety and efficacy of dose omissions that occurred beyond the initial 3 doses.

Methods: Planned dosing was 20 mcg (wk1), 30 mcg (wk2), and 68 mcg (wk3+). Omissions were required for certain AEs and also occurred for other elective reasons. Omissions beyond initial 3 wks were analyzed by reason, duration and safety (primarily CRS and rash) within 2 wks of restarting. CRS was evaluated per the ASCTC 2019 criteria. This analysis was conducted on the primary analysis (data cut-off 13Oct2020).

Results: 245 pts received tebe; median 23 doses. A total of 104 pts had omissions with 92/245 pts (38%) having an omission after the initial 3 wks. 56/92 pts (61%) had 1 omission; 14 pts had $>$ 3 omissions. Most omissions were due to elective/other reasons (71%) or AEs (29%). 72% of omissions were $\leq$ 2 wks; 7% of omissions were $>$ 3 wks. Upon restarting, majority of pts did not have G3 TRAE (91%), G2 CRS (93%) or G2+ rash (93%) within 14 days. However, 6 pts had G2 CRS within 14 days of restart and all had prior G2 CRS. 1 or 2 omissions did not have a significant impact on OS when controlling for immortal time bias. The small numbers of pts with omissions $>$ 3 wks duration limit the ability to evaluate impact on OS.

Conclusions: After reaching 68 mcg, patients receiving tebentafusp can have 1-2 omissions of $\leq$ 2 weeks duration with minimal impact on safety and efficacy. Treatment restart was typically outpatient (95%), without dose modification from most recent dose (98%) or steroid premedication (98%). G2 CRS was uncommon at restart, and occurred mostly in patients with preceding G2 CRS.

Clinical trial identification: NCT03070392.

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822P Phase II clinical trial: Safety and efficacy study of tocilizumab (Toci) in combination with ipilimumab (Ipi) 3mg/kg plus nivolumab (Nivo) 1mg/kg in patients (pts) with metastatic melanoma (MM)

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Background: The combination of Ipi + Nivo is frequently used as first line therapy in pts with MM, however, high rate of grade 3/4 immune related adverse events (irAEs) and treatment discontinuation pose a challenge for both physicians and pts. Our prior retrospective translational studies suggested that targeting interlukin-6 (IL-6) -Th17 pathway could be an effective approach to alleviate irAEs without hindering anti-tumor immunity. This supported initiation of phase II open-label, single center study (NCT04940299) to assess the safety and efficacy of adding Toci (anti-IL-6 receptor) to Ipi + Nivo for treatment naïve, unresectable stage III/IV MM.

Methods: A total of 35 MM pts will be enrolled; age $\geq$18 years (yrs), histologically confirmed locally advanced or MM including pts with stable asymptomatic brain mets. As of April 29, 2022, 18 pts were enrolled including 8 pts (45%) with stage IV M1c. Pts receive subcutaneous Toci 162 mg/2 weeks (wks) for 6 doses plus intravenously Ipi 3 mg/kg + Nivo 1 mg/kg/3 wks for up to 4 doses, then will continue Nivo 480 mg/4 wks up to 2 yrs. The primary objective includes safety and tolerability of this triplet. The secondary objectives include assessing the overall response rate (ORR) by RECIST v1.1. Longitudinal immune analysis of blood, tumor samples, and inflamed tissues will be performed to explore biomarkers of toxicity and tumor response.

Results: To date, 17 pts received at least 1 cycle of therapy and were evaluable for toxicity; 12 pts were evaluable for ORR. Follow-up ranged from 3 to 24 wks. Overall, 6 pts (35%) had grade 3 irAEs including diarrhea (n=5, 29%), elevated lipase (n=2, 11%), and elevated transaminases (n=1, 6%). Efficacy analysis demonstrated an ORR of 58% (1 CR and 6 PR) and disease control date of 75%. ORR in pts with elevated LDH was 44% (4/9 pts). One pt discontinued therapy due to toxicity; there have been no treatment-related deaths.

Conclusions: Our preliminary data of the combination of Toci plus Ipi3/Nivo1 is safe and well tolerated. The limited efficacy data reveal no negative impact of Toci on tumor immunity. Ongoing biomarker analysis will be presented to help further interpret study results.

Clinical trial identification: NCT04940299.

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823P A propensity score weighted comparison of tebentafusp or pembrolizumab versus combination ipilimumab and nivolumab in untreated metastatic uveal melanoma

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Background: Tebentafusp (tebe) demonstrated an overall survival (OS) benefit, HR 0.51, compared to investigator choice (IC) in a Ph3 trial in untreated metastatic uveal melanoma (mUM). 82% of the IC arm was pembrolizumab (pembro); ipilimumab + nivolumab (ipi + nivo) was not studied. The 1-yr OS rate for tebe and pembro were 73% and 59%, respectively, while the 1-yr OS rate for ipi + nivo in GEM-1402 was 52%. Using individual patient data (IPD), we conducted a propensity score (PS) weighted analysis to compare OS on tebe or pembro (IMCgp100-202) to ipi+nivo (GEM-1402) in untreated mUM.

Methods: Two analyses were conducted: 1) an initial match-adjusted indirect comparison (MAIC) of tebe or pembro with ipi+nivo and 2) a PS analysis of tebe with ipi+nivo. To adjust for differences in patient characteristics, PS from a logistic regression model were used to generate inverse probability of treatment weights (IPTW). OS was compared using weighted Cox models and Kaplan-Meier curves. The primary analysis was complete case with ATT (average treatment effect of the treated) weights. Sensitivity analyses used alternative missing data methods and weights.

Results: MAICs favored tebe vs ipi+nivo (HR 0.51, 95% CI 0.32-0.79) with no significant difference for pembro vs ipi+nivo (HR 0.74, 95% CI 0.45-1.21). 237 tebe and 45 ipi + nivo patients were included in the primary IPTW analysis. Key baseline covariates including LDH, ALP and ECOG were generally well balanced across treatments, with some differences in disease location. After IPT weighting, all key baseline characteristics were balanced. The IPTW adjusted OS favored tebe, HR 0.43 (95% CI 0.29-0.64); 1-yr OS 74% vs 50%, respectively. Sensitivity analyses showed consistent superior OS for tebe with all IPTW HRs <0.48. An IPTW analysis of pembro vs ipi + nivo based on full IPD will be presented.

Conclusions: Tebentafusp is the only therapy to demonstrate an OS benefit in previously untreated mUM against an IC arm that was mostly pembro. A patient-level propensity analysis comparison to ipi + nivo demonstrates a similarly strong OS benefit for tebentafusp. These data support initial use of tebentafusp in previously untreated HLA-A*0201+ mUM patients as the standard of care.

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824P Patterns of response/progression and management following progressive disease (PD) with anti-PD-(L)1 (PD(L)1) in patients (pts) with advanced Merkel cell carcinoma (MCC)

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Background: PD(L)1 has become 1st line therapy for advanced MCC, however resistance occurs in approximately half of pts. We aim to: (1) evaluate patterns and predictors of response/PD to PD(L)1; (2) study the management following PD to PDL1.

Methods: Advanced MCC pts treated with PD(L)1 at 13 international centres were included. Demographics, baseline characteristics, outcomes and subsequent treatments were examined. Multivariable analyses (MVA) identified factors associated with response.

Results: 171 MCC pts were included; 111 (65%) were male, median (med) age 75 years (range 38-92). 52 pts (30%) had a history of a malignancy other than complex skin cancer and 23 (13%) were immunosuppressed. 86 (50%) pts had visceral disease; 37 (22%) with bone, 30 (18%) with liver and 17 (10%) with lung metastases (mets). With a med follow-up of 31 months (mo; 95% CI, 21 — 40), the response rate (RR) was 60% (37% complete response [CR]) and 30% (n=52) had PD. In a MVA including demographics, sites of mets and full blood count, only higher haemoglobin and eosinophils were associated with response. Site-specific CR/partial response (PR) was most common in bone (68%) and liver mets (63%); while site-specific PD was most common in lymph nodes (LN; 27%) and subcutaneous (subcut; 24%) mets. 24-mo PFS and OS were 39% (95% CI, 32 - 49) and 61% (95% CI, 53 - 70), respectively. From 98 (57%) progressing pts; 56 (57%) had upfront PD or <6 mo of stable disease (SD) prior to PD (innate resistance = IR) and 42 (43%) had PD following CR/PR or SD>6 mo (acquired resistance = AR). 70 (71%) had subsequent treatment with 59 (61%) having systemic +/- local therapy (Table).

Table: 824P

Subsequent Systemic Therapy	N(%)	IR		AR	
		N(%)	RR	N(%)	RR
Carboplatin/Etoposide	20 (34)	13(65)	31%	7(35)	71%
PD(L)1	17 (29)	5 (29)	40%	12 (71)	50%
Ipilimumab + PD(L)1	5 (8)	4 (80)	50%	1 (20)	0%
Others	17 (29)				

Conclusions: Patterns of response/PD to PD(L)1 in MCC differ from other skin cancers with greater response in liver/bone versus LN/subcut, suggesting unique MCC biology.

Most IR pts received chemotherapy as subsequent therapy while AR pts were re-challenged with PD(L)1, and both demonstrated promising RR.

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825P CemiplimAb-rwlc Survivorship and Epidemiology (CASE): A prospective study of the safety and efficacy of cemiplimab in patients (pts) with advanced cutaneous squamous cell carcinoma (CSCC) in a real-world setting

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Background: Cemiplimab is the first programmed cell death-1 inhibitor approved for the treatment of pts with locally advanced or metastatic CSCC who are not candidates for curative surgery or curative radiation. Here, we describe demographics, effectiveness, and safety results of cemiplimab in a general population of pts with advanced CSCC enrolled in the CASE study (NCT03836105).

Methods: CASE is a real-world study evaluating the effectiveness, safety, disease evolution, survivorship, and quality of life of pts with advanced CSCC treated in 43 US academic and community centres. Pts had received cemiplimab 350 mg intravenously every 3 weeks per standard of care. Prospective data are captured using an electronic case report form and include demographics, disease characteristics, efficacy, and quality-of-life data. Investigator assessment of objective response rate (ORR), survival, and safety was conducted. Data collected between June 2019 and October 2021 are presented. Recruitment is ongoing.

Results: As of 1 Oct 2021, 188 pts were enrolled in the CASE study. Median age was 76.0 years (range, 33.0—98.0), 76.9% were male, 90.9% were White, and 36 (19.1%) were considered immunocompromised or immunosuppressed (IC/IS). Median duration of cemiplimab exposure for all pts was 22.1 weeks (quartile [Q] 1—Q3, 9.1—46.4; range, 0—117). Efficacy was evaluated in pts enrolled before Cycle 3 (n=164), when a clear treatment outcome could be established. ORR for the overall population was 42.1% (95% confidence interval [CI], 34.4—50.0) and for the IC/IS population (n=27) was 44.4% (95% CI, 25.5—64.7). Eight (4.3%) pts experienced a treatment-related serious adverse event and 47 (25.3%) experienced a treatment-related immune-related adverse event. Cemiplimab was generally well tolerated in IC/IS pts. In total, 95 (48.2%) pts discontinued treatment.

Conclusions: At this timepoint, the safety, tolerability, and effectiveness of cemiplimab in this real-world study of pts with advanced CSCC were consistent with results observed in the registration clinical trial (NCT02383212, NCT02760498).

Clinical trial identification: NCT03836105.

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826P Encorafenib and binimetinib followed by radiotherapy for patients with symptomatic BRAF mutated melanoma brain metastases: GEM1802/E-BRAIN clinical trial

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Background: Patients (pts) with symptomatic melanoma brain metastases (MBM) have very poor prognosis. For *BRAF* mutated (mut) targeted therapy achieves high intracranial response rate (iRR) but intracranial progression free survival (iPFS) is usually short. With immunotherapy iRR can be long lasting in asymptomatic pts but are less frequent in symptomatic ones, especially if they need steroids GEM1802/EBRAIN (NCT03898908) evaluates iRR with encorafenib and binimetinib (EB) and explores if adding brain radiotherapy (RDT) could improve the iPFS in pts with both asymptomatic and symptomatic *BRAF* mut MBM. We present final results for symptomatic pts.

Methods: 15 pts were treated with 2 months of EB at standard dose. If intracranial partial response (PR) or stable disease (SD), brain RDT (radiosurgery (SRS) or whole brain RDT (WBRT) was offered according to local guidelines followed by EB. For pts with complete response (CR) RDT could be spare and used in a later progressive disease (PD). iRR, iPFS, overall survival (OS) and QoL (QLQ-C30) were analyzed.

Results: Table summarizes ptś basal characteristics. iRR after 2 months of EB was 73.3% (6.7% CR and 66.7% PR) with 26.7% SD and no PD. 20% pts received SRS & 46.7% WBRT after 1st evaluation. With a median follow up of 11.8 months (m) (Range: 3.4-23.1) median iPFS was 9.3 m (95% CI: 7.6-NR) with 73.3 & 23.3% of pts progression free at 6 & 12m respectively. Median OS was 18.4m (95% CI: 12.1-NR) with 93.3, 72.7 & 62.3% of pts alive at 6, 12 & 18m respectively. 20% of pts experienced G3-4 toxicity from EB and 6.7% from RDT. Global health status, pain and insomnia scales improved compared to baseline at week 16 (p=0.014, 0.028 and 0.045 respectively).

Table: 826P

Median age (range)	49y (21-79)
Sex	60% female
Brain Tumor Burden (target lesions), mean (95%CI)	51.9 mm (32.9-70.9)
	%
>ULN LDH	33.3
Number of target BMs (1 vs 2-3 vs >3)	33.3 - 46.7 - 20
Extracranial disease	93.3
ECOG 0-1	86.6
Basal steroids	93.3
Previous systemic treatment	13.3

Conclusions: EB achieve a significant iRR in pts with symptomatic brain *BRAF* mut MBM and very bad prognosis factors (need for steroids and high intracranial tumor burden). Adding brain RDT is feasible and could help to improve the intracranial disease control provided by EB.

Clinical trial identification: NCT03898908.

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827P An open-label, multicenter, phase I study of RP2 as a single agent and in combination with nivolumab in patients with solid tumors: Safety, efficacy, and biomarker results

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Background: RP2 is an enhanced potency oncolytic herpes simplex virus (HSV) -1 expressing GM-CSF, a fusogenic protein (GALV-GP R-), and an anti-CTLA-4 antibody-like molecule that is being evaluated in an open-label, multicenter, phase 1 clinical trial as monotherapy and combined with nivolumab (nivo). Here, we present updated safety, efficacy, and biomarker data of RP2 ± nivo.

Methods: After determination of the RP2D (10^6 PFU/mL intratumorally (IT) once followed by up to 7 additional doses of 10^7 PFU/mL via IT), a cohort of 30 patients (pts) was enrolled and treated with RP2 combined with nivo (240 mg Q2W for 4 months from the second RP2 dose, then 480 mg Q4W for 20 months). Responses were assessed using modified RECIST v1.1.

Results: Objective responses with RP2 monotherapy were observed in 3 out of 9 pts including 1 CR for ≥15 months in mucoepidermoid carcinoma, 1 PR for ≥18 months in esophageal cancer with liver metastases, 1 PR in uveal melanoma with liver metastases that progressed at 15 months. Objective responses with RP2 + nivo treatment were 44.4% in cutaneous melanoma (4/9), 25% in uveal melanoma (2/8), and 33% in SCCHN (1/3) pts. All seven responding patients had previously failed anti-PD-1 therapy, with all but one response durable to date for >425 days. The most common adverse events (grade 1-2) were pyrexia, chills, influenza-like illness, fatigue, and pruritus. No grade 4-5 events were observed. Immunohistochemistry (IHC) analysis indicated robust increases in CD8 T cell influx, PD-L1 expression, and an increase in the CD8/foxp3+ cell ratio. Clinical responses were independent of baseline CD8 T cell infiltration, PD-L1 expression levels, and prior anti-PD-1 therapy status.

Conclusions: RP2 ± nivo demonstrated good tolerability and durable systemic responses in pts with difficult-to-treat, heavily pretreated and anti-PD-1 failed advanced cancers. These data continue to support the hypothesis that oncolytic delivery of anti-CTLA-4 into tumors, with accompanying antigen release, presentation and immune activation, can provide potent systemic anti-tumor effects.

Clinical trial identification: NCT04336241.

Legal entity responsible for the study: Replimune Inc.

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828P Effectiveness and safety of dabrafenib and trametinib in patients with BRAFV600 mutated metastatic melanoma in the real-world setting: Final results of the non-interventional COMBI-r study

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Background: Targeted therapies (TT) with BRAF/MEK inhibitors and immunotherapy (anti-PD-1 ± anti-CTLA-4 antibodies) have shown significant improvements of outcomes in patients (pts) with BRAFV600 mutated metastatic melanoma (mM) and are used routinely in clinical practice. However, real-world data is still limited, especially regarding effectiveness of TT in different therapy lines and subgroups that are usually excluded in phase III clinical trials, e.g. pts with brain metastases (BM). Therefore, the objective of the prospective non-interventional COMBI-r study was to assess the treatment of mM pts with dabrafenib and trametinib (D+T) regarding effectiveness across different therapy lines and subgroups.

Methods: In total, 504 pts at 55 German Skin Cancer Centers were enrolled in COMBI-r between Dec 2015 and Dec 2018. Following inclusion and exclusion criteria, 472 pts were included in the final analysis. During the first year on treatment, visits were scheduled every 3 months (mo), followed by half-yearly visits until the end of treatment (EoT), and two follow-up visits at 3 and 6 mo after EoT.

Results: 95.3% pts of the final analysis population entered the follow-up phase, while 81.4% pts suffered a progression and 56.1% died. Overall survival (OS) and progression-free survival (PFS) were analyzed by line of therapy (1L, 2L, ≥3L) with D+T. Outcomes were correlated with baseline demographics and clinical, laboratory and biological parameters, i.e., tumor dynamics, BM, elevated LDH, and ≥3 metastatic sites. Between therapy lines, no differences in BM development were observed and median PFS as well as median OS were comparable.

Table: 828P

	1L	2L	≥3L	Total
Median PFS [mo (95% CI)]	7.7 (6.6-9.1)	10.3 (7-11.8)	8.3 (6.3-11.4)	8.3 (7.1-9.3)
Median OS [mo (95% CI)]	17.5 (13.3-21.3)	20.2 (12-n/a)	19.8 (13.7-35.6)	18.3 (14.9-21.3)

Conclusions: Data from COMBI-r shed light on the real-world situation of mM pts treated with D+T and describe clinical outcomes stratified by established predictive factors. The final analysis points to D+T as an effective treatment strategy even in higher therapy lines for mM pts.

Clinical trial identification: Registry: Germany BfArM Registration Number: NIS 6690.

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829P A proof of concept study of sequential treatment with the HDAC inhibitor vorinostat plus BRAF and MEK inhibitors in BRAFV600 mutated melanoma

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Background: Development of resistance after median 12-14 months limits the clinical benefit of BRAF and MEK inhibitors in $BRAF^{V600}$ mutated melanoma. This acquired resistance is frequently caused by reactivation of the MAPK pathway by secondary mutations. It has been shown that short-term treatment (14d) with vorinostat was able to initiate apoptosis of the resistant tumor cells. We aimed to assess the anti-tumor activity of sequential treatment with vorinostat and BRAFi/MEKi in patients with $BRAF^{V600}$ melanoma who progressed after initial response to BRAFi/MEKi.

Methods: Eligible patients with BRAFi/MEKi resistant $BRAF^{V600}$ melanoma were treated with vorinostat 360 mg once daily in a 14-day cycle, followed by BRAFi/MEKi. In patients with clinical benefit upon treatment, additional cycles of vorinostat were allowed. The primary endpoint was an anti-tumor response rate of progressive lesions of at least 30% according to RECIST 1.1. Secondary endpoints included safety and tolerability, pharmacokinetics of vorinostat and translational molecular analyses.

Results: 25 patients (16M/9F, median age 56 years) with advanced, progressive BRAFi/MEKi resistant $BRAF^{V600}$ melanoma have initiated treatment with vorinostat. 21 patients were evaluable for response. Best objective response: 4 PR (confirmed in 3 pts, duration of response 6.2, 9.3 and 18.6 months), 4 SD (confirmed in 1 pt, duration 9.3 months) and 13 PD. Four patients received ≥ 2 cycles of vorinostat and 1 patient had an objective response upon this retreatment. Common reported adverse events were fatigue (24%), nausea (20%) and vomiting (12%) and were only grade 1/2. Preliminary results of ctDNA analysis (in first 6 pts) showed emerging secondary mutations in *NRAS* in two patients at time of BRAFi/MEKi resistance. Elimination of the NRAS mutation by vorinostat treatment was observed in one patient (best overall response: PD).

Conclusions: Intermittent treatment with vorinostat in patients with resistant $BRAF^{V600}$mutated melanoma is well tolerated. Although the primary endpoint of this study was not met, durable anti-tumor responses were observed in a minority of patients (14%). Translational research aiming to find predictive biomarkers for response is ongoing.

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Legal entity responsible for the study: The authors.

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830P Efficacy of immunotherapy in melanoma patients with symptomatic brain metastases treated with steroids: Initial report from the MEMBRAINS trial

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Background: Checkpoint inhibitor (CPI) treatment can induce intracranial responses in patients (pts) with melanoma metastasized to the brain (MM-BM), but very limited data exist for pts with symptomatic brain metastases as the use of corticosteroids for symptomatic relief excludes these patients from most clinical studies. The purpose of MEMBRAINS is to investigate whether treatment with CPI alone or after BRAF/MEK inhibitor induction can lead to clinical benefit for pts with MM-BM in need of steroid treatment.

Methods: This is an investigator-sponsored, multicenter, non-randomized multi-arm phase II trial. To be eligible, pts need to have MM-BM with a need for >10 mg prednisolone due to brain metastasis and a performance status 0-2. pts are enrolled in two steps; step 1) a pilot phase with enrollment of six pts in each arm, and step 2) an expansion phase with the option to enroll a total of 20 pts in a specific study arm, if at least one patient has clinical benefit defined as complete response, partial response (PR) or stable disease ≥ 6 months. Primary endpoints are progression-free survival (PFS) and overall survival (OS) rates at six months. Here we report from the pilot phase of three arms; C) ipilimumab and nivolumab (IPI-NIVO) for pts treated with a steroid dose of >10-25 mg prednisolone at baseline, D) IPI-NIVO and a steroid dose >25 mg prednisolone, or E) 4 week BRAF/MEK inhibitor induction period followed by switch to IPI-NIVO for BRAF mutated pts treated with a steroid dose of >10 mg prednisolone.

Results: A total of 18 pts were treated; six in each arm. One of six patient achieved objective response (PR) in arm C, none in arm D, and two of six patients (PR) in arm E. PFS rate at 6 months were 17% in arm C, 0% in arm D, and 33% in arm E. OS rate at 6 months was 50% in arm C, 33% in arm D, and 83% in arm E.

Conclusions: The prognosis of pts with MM-BM and a need for steroid is dismal. CPI treatment response can be obtained in pts on lower doses of steroid while daily doses of steroid above 25 mg appears incompatible with CPI benefit. However, in BRAF mutated pts a short induction treatment period with BRAF/MEK inhibitor, bridging a switch to CPI, seems to be a promising treatment strategy for this hard-to-treat patient subgroup.

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831P Outcomes of immune checkpoint inhibitors in patients with metastatic uveal melanoma treated with tebentafusp

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Background: Metastatic uveal melanoma (MUM) is a nearly universal fatal disease with limited treatment options. Tebentafusp, a novel bispecific immune mobilizing T cell receptor, provides an overall survival (OS) benefit for MUM in HLA-A*02:01 positive patients despite a low overall response rate (ORR). Immune checkpoint inhibitors (ICI) in first line therapy also have a low ORR but improved survival. Little is known about the outcomes of patients who receive sequential ICI and tebentafusp.

Methods: In this single center retrospective cohort study, we included patients with MUM treated with tebentafusp and ICI (anti PD1 +/- anti CTLA-4) between 2016-2021. Investigator-assessed ICI response rates (RR), progression free survival (PFS) and OS were analyzed and compared when used before or after tebentafusp. X^2, Fisher's exact and Mann-Whitney U tests were used to compare groups and Cox proportional hazards models were fitted. The Log-rank test was used to assess PFS and OS.

Results: Twenty patients were identified: 10 patients who received ICI following tebentafusp (T-I) and 10 patients treated with ICI prior to tebentafusp (I-T). Disease characteristics were similar amongst both groups (Table). Response rates for the T-I group were: partial response (PR): 10% (1), stable disease (SD): 30% (3) and progressive disease (PD): 60% (6). For the I-T group the corresponding rates were: SD: 20% (2) and PD: 80% (8), p = 0.63 between groups. Median PFS from ICI initiation was 2.86 months (95%CI 2.37-NA) for T-I and 2.35 months (95% CI 0.92-NA) for I-T, (p=0.046). Median OS from start of first treatment was 21.47 months (95% CI 15.78-NA) for T-I, and 16.88 months (95% CI 8.52-NA) for I-T (p=0.38).

Table: 831P

Covariate	ICI - Teb (n=10)	Teb - ICI (n=10)	p-value
Age			0.82
Median	60 (51 - 64)	57 (50 - 66)	
Sex			1
Female	4 (40)	5 (50)	
Male	6 (60)	5 (50)	
IV Stage			0.44
M1a	8 (80)	5 (50)	
M1b	1 (10)	3 (30)	
M1c	1 (10)	2 (20)	
ECOG			1
0	8 (80)	7 (70)	
1	2 (20)	3 (30)	
Extra Liver Mets			1
No	3 (30)	3 (30)	
Yes	7 (70)	7 (70)	
Increased LDH			0.63
No	8 (80)	6 (60)	
Yes	2 (20)	4 (40)	

Conclusions: In this small series, PD- 1 +/- CTLA-4 blocking antibodies may show better clinical efficacy in patients with MUM when administered after tebentafusp rather than before. A larger study is needed to confirm these data. Erica Koch Hein and Diana Paola Arteaga Ceballos contributed equally to this study.

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832P Treatment sequence with tebentafusp (tebe) and anti-PD1/ipilimumab (PD1+IPI) in HLA-A2*02:01 patients (pts) with metastatic uveal melanoma (mUM)

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Background: mUM has poor prognosis. Unlike cutaneous melanoma, PD1+IPI shows modest efficacy. In phase 2 trials median progression-free survival (mPFS) ranges between 3-5.5 mo. Tebe, a soluble T-cell receptor and CD3-directed bispecific fusion protein, resulted in prolonged overall survival (OS) (21.7 mo) in a phase 3 study, but median duration of response (mDOR) was short and PFS benefit modest. The optimal sequence of tebe and PD1+IPI is unknown.

Methods: Retrospective study from 12 cancer centers investigating the efficacy of the sequence of tebe followed by PD1+IPI (Group 1) to the converse sequence (Group 2). Primary endpoints: overall response rate (ORR), disease control rate (DCR) and PFS. Secondary endpoint: OS. Kaplan Meier method was used for time to event analyses. Log-rank test was used for differences between groups.

Results: 59 pts were included (26 in Group 1; 33 in Group 2); median age 54 yrs (16-80); 32 (54%) female; median f/u 26 mo (17-38). Differences of baseline characteristics between groups included hepatic + extra-hepatic (46% v 36%) mets, ECOG PS $\geq$1 (15% v 21%), LDH $>$ULN at baseline (42% v 24%) and time between tebe and PD1+IPI (and vice versa) (21 v 85 days). Total mPFS was similar in Group 1 and Group 2 (Table). Total mOS was numerically higher in group 2 (55.6 v 37.6 mo). ORR for PD1+IPI was 15% v 6%. Stable disease (SD) was more common in tebe (38% v 39%) than PD1+IPI (12% v 30%). DCR for tebe was similar in Group 1 and 2 (46% v 45%). 73% in Group 1 and 36% in Group 2 were treated beyond tebe PD. Gr 3/4 toxicities occurred in 19% v 30% for IPI+PD1 and 42% v 9% for tebe. Discontinuation due to toxicity was common in PD1+IPI (27% v 39%). PD was common reason for discontinuation in tebe (85% v 48%).

Conclusions: Tebe was active prior to or after PD1+IPI (DCR 46% v 45%). PD1+IPI showed similar efficacy in Group 1 and Group 2. After tebe failure, PD+IPI was active. Data collection is ongoing and additional information will be presented.

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833P Longer follow up of a real-world study of cemiplimab in advanced cutaneous squamous cell carcinoma: Focus on late toxicities and long term benefit

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Background: Cemiplimab is the first approved systemic treatment for patients with advanced cutaneous squamous cell carcinoma (cSCC). We have already reported previously acute toxicities and overall responses from a real-world experience of 18 Italian centers.

Methods: We analyzed the long-term follow up of the 134 patients previously analyzed in the retrospective, observational study REAL CEMI. We assessed late toxicities rate, considering treatment-related adverse events (trAEs) that occurred after at least 6 months since cemiplimab start, the updated objective response rate (ORR) and disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). We explored correlations between clinical outcomes and baseline clinical-pathological characteristics, and we carried out a descriptive analysis of patients who obtained a complete response (CR).

Results: At a median follow up (range 1-32) of 14 months, cemiplimab was ongoing in 29 patients (21,6%) with a median duration of treatment of 7 months (1-29+). Late trAEs occurred in 11,2% of cases, with a median time to onset of 12 months. Most of them were grade (G) 1/2 (73,3%), but two patients stopped cemiplimab due to a late adverse event (G3 maculopapular rash pemphigoid-like and G3 nausea and vomiting). Updated ORR was 58,9% and DCR was 72,4%. Median PFS was 9 (95% confidence interval (CI) 2.45-15.55) months and median OS was 21 (95% CI 9.41-32.59) months. In the multivariate analysis, the best response obtained, and Performance Status were found to be significantly related to both PFS and OS, while chronic intake of steroids was only related to PFS. Considering the subgroup of 26 (19,4%) patients with CR: median time to CR was 4 months (1-23) and median duration of treatment after obtaining CR 8 months (0-35+); at the data cut-off, 19 (73,1%) patients had stopped treatment with cemiplimab, and all these patients had ongoing complete response.

Table: 832P

		Group 1 Tebe followed by PD1+IPI (n=26)			Group 2 PD1+IPI followed by Tebe (n=33)		
		Total (both therapies)	Tebe	PD1+IPI	Total (both therapies)	Tebe	PD1+IPI
Treatment Duration (med, range)		-	7 mo (0-31)	2 mo (0-36)	-	6 mo (1-29)	2 mo (0-27)
ORR		-	2/26 (8%)	4/26 (15%)	-	2/33 (6%)	2/33 (6%)
DCR		-	12/26 (46%)	7/26 (27%)	-	15/33 (45%)	12/33 (36%)
PFS	mPFS mo (med, 95% CI)	28.4 (13.4-NR)	3.7 (2.8-10.1)	2.9 (2.4-NR)	20.7 (17.1-NR)	5.6 (4.7-10.8)	5.4 (2.7-9.3)
OS	1 yr OS (95% CI)	87% (74-100)	-	-	87% (76-100)	-	-
	2 yr OS (95% CI)	57% (39-83)	-	-	75% (58-96)	-	-
	3 yr OS (95% CI)	57% (39-83)	-	-	62% (40-96)	-	-
	mOS mo (med, 95% CI)	37.6 (22.4-NR)	-	-	55.6 (32.6-NR)	-	-

Conclusions: At a longer follow up of a real-world study, the activity of cemiplimab is confirmed, with a relatively low number of late toxicities. However, some trAEs may occur even after several months from the start of treatment. Complete response is often maintained for long time.

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834P Intracranial disease control and survival in patients with melanoma brain metastases (MBM) treated with radiation and immune checkpoint inhibitors (IO)

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Background: Combination immunotherapy with anti-PD1/CTLA4 is the standard for patients (pts) with MBM with the highest potential of long-term control. However, the utility of immunotherapy (IO) in delaying intracranial (IC) progression in pts with radiated MBM remains unexplored.

Methods: This retrospective study assessed pts with MBM who received radiation therapy (RT) followed by IO. Primary endpoints were overall survival (OS) and IC progression-free survival (IC-PFS), defined as the time from IO initiation to investigator-assessed IC progression or death. In pts who received IO following IC progression, we assessed the time from IO re-initiation to subsequent IC progression (second IC-PFS). Survival analyses were obtained using Log-Rank and Cox regression was applied to detect differences in specified subgroups. A p-value < 0.05 was statistically significant.

Results: 101 pts with MBM received IO after RT between 2010-2021. Median age was 58 (19-87) years; 60 (59%) were male. Skin and unknown primary melanomas comprised 66 (65%) and 18 (18%) pts, respectively. Molecular studies were available for 79 pts and 42 (53%) had *BRAF* V600 mutations. At MBM diagnosis, 30 (30%) pts had $\geq$ 3 brain lesions, 42 (42%) presented neurologic symptoms, and 27 (27%) had prior IO. Ninety-three (92%) pts had SRS, and 52 (52%) had IO in the first line metastatic setting. Following MBM diagnosis, 29 (29%) pts received anti-PD1, and 33 (33%) anti-PD1+CTLA4. Median follow up was 43.1 (0.8-107.9) months (mo), median OS was 18.1 mo (95% CI 11.3-24.8), and median IC-PFS was 8.9 mo (95% CI 4.1-13.7). Anti-PD1-based therapy favourably impacted OS and IC-PFS (Table). Among 22 pts who received IO after IC progression, median OS following IO resumption was 16 mo (95% CI 7.5-24.5). and median second IC-PFS was 11.3 mo (95% CI 0.3-22.9).

Table: 834P

	IC-PFS: HR (95% CI); *P*	OS: HR (95% CI); *P*
Anti-CTLA4	1	1
Anti-PD1+CTLA4	0.27 (0.15-0.48); < 0.001	0.25 (0.13-0.48); < 0.001
Anti-PD1	0.33 (0.18-0.59); < 0.001	0.32 (0.17-0.58); < 0.001
Anti-PD1+other	0.34 (0.12-0.99); 0.04	0.60 (0.23-1.57); 0.3

Conclusions: This data corroborates the activity of anti-PD1-based IO for pts with treated MBM and suggests ongoing IC activity beyond progression.

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835P Efficacy of checkpoint inhibitors and targeted therapy depending on the line of treatment in patients with advanced / metastatic melanoma

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Background: The use of targeted therapies (TT) and checkpoint inhibitors (IT) in patients with melanoma significantly prolonged survival, especially in the group of patients with BRAF-mutated melanoma. The aim of this study was to evaluate real-life outcomes of advanced melanoma second line therapy in TT-IT and IT-TT sequence with BRAFi/MEKi combination or anti-PD1 agent.

Methods: Consecutive patients with *BRAF* mutation-positive unresectable or metastatic melanoma treated sequentially with TT-IT (BRAF and MEK inhibitors then anti-PD-1 antibody) and IT-TT were included in the study, patients treated with IT or TT in the first line only without switch to another therapy were not included. All the basic factors and response to treatment were analyzed in 1st and 2nd lines. Data cut-off was 31/Jan/2022.

Results: In total 304 patients were enrolled. 207 (68%) patients were treated with TT-IT and 97 (32%) with IT-TT. The median age was 58 years. At the time of treatment initiation, there were no differences between the TT-IT and IT-TT groups in age, sex, primary lesion location, TMN stage, and presence of brain metastases. In the TT-IT group, there were significantly more patients in ECOG 2 and with elevated LDH. However, after 1st line TT no such differences were found at 2nd line treatment initiation. There were also no statistically significant difference in median PFS between 1st line TT (TT 1L) and 2nd line TT (TT 2L) - $p = 0.1628$; as well as for the 1st and 2nd line IT (IT 1L vs IT 2L) - $p = 0.2484$. More objective responses were achieved in the TT 1L and TT 2L groups than in the IT 1L and IT 2L groups, 56% and 57% vs. 15% and 20%, respectively. In the IT groups IT 1L and IT 2L PD was recorded in 59% and 61% at the time of analysis, respectively. There was no correlation between OR in 1st and 2nd line of treatment. 21 % of patient in TT-IT and 22% in IT-TT were enrolled in 3rd line.

Conclusions: There is no difference in PFS and treatment response for TT and IT depending on the 1st or 2nd line for BRAFi/MEKi and anti-PD1 therapies. *BRAF*-mutated patients treated with TT progressing on first line TT therapy are still candidates for IT, even in those patients with initially elevated LDH at 1st line therapy. New factors responsible for resistance to IT should be investigated.

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836P Outcome of PD-1 inhibitor therapy of advanced melanoma patients according to demographic factors in a real-world setting across Europe

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Background: Treatment with programmed cell death protein (PD-1) blocking antibodies substantially improves prognosis of melanoma patients. However, there is still limited evidence how baseline demographics influence treatment efficacy in real world practice.

Methods: This registry-based observational study evaluated the therapy outcome of 1046 melanoma patients who were treated with single agent PD-1 inhibitors in the advanced setting. Demographic and baseline variables were analysed in respect to differences in overall survival (OS), time to next treatment after PD-1 inhibitor treatment (TTNT) and other outcome variables.

Results: For melanoma-specific OS, many factors were not significantly relevant. However, among the statistically significant factors (age, ECOG, LDH, line of treatment and AJCC stages M1c and M1d) the age effect was of particular interest. When grouping patients into three age groups (<70/70-80/>80) there was a higher risk of melanoma related death for patients aged 70-80 years (multivariable HR (95% CI): 1.51 (1.02-2.2)) and patients older than 80 years (multivariable HR 1.78; 95% CI 1.04-3.0). Median melanoma specific OS was not reached for patients younger than 70 years, 33.6 (31.7—nr) months for patients between 70 and 80 years, and 30.3 (20.4—nr) for patients older than 80 years. For TTNT a significant effect of age could not be observed. Objective response rate (ORR) was slightly elevated in the age group 70-80 years (47%; $p = 0.04$) as compared to younger patients (39.6%) and patients older than 80 years (39.7%). Also, median PFS (95% CI) was 9.9 (7.6-14.1) months for patients younger than 70 years, 12.9 (8.6-18.4) months for patients between 70 and 80 years and 9.3 (6.9-12.3) for patients older than 80 years.

Conclusions: The different survival outcomes showed less benefit of PD-1 inhibitor therapy in patients older than 80 years compared to younger patients. The most likely explanation could be a generally reduced immunoreactivity with increasing age. However, ORR and PFS were slightly higher in the age group of 70-80 years as compared to younger patients. These results suggest a complex relationship between age and response to immune checkpoint inhibition.

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837P Real-world evidence of encorafenib (E) plus binimetinib (B) in unresectable advanced or metastatic BRAFV600-mut melanoma in Spain (GEM 2002 - BECARE)

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Background: Combined BRAF/MEK inhibitor therapy has demonstrated efficacy and tolerability in phase III clinical trials, and is standard of care for advanced / metastatic melanoma. However there is limited evidence in the real-world.

Methods: BECARE is a retrospective, non-interventional study that investigates real-world effectiveness and tolerability of encorafenib plus binimetinib in unresectable advanced / metastatic BRAFV600-mut melanoma in 21 sites from Spain. The primary objective is to characterize the population of patients (pts) receiving EB and their outcomes. The study includes melanoma pts treated according to standard clinical practice with EB in the first line or after progression to a first line with immune checkpoint inhibitors (ICI) for advanced or metastatic stage. Previous BRAF- and/or MEK- inhibitor treatment (other than adjuvant ended $\geq$ 6 m before EB) or chemotherapy was not allowed.

Results: From September 2021, 56 pts were included. Median age was 58 years (range: 25-89), 58.9% were male, 67.9% had ECOG 0, 96.4% had metastasis being 51.8% IVM1C, and 73.2% had $\geq$3 organs involved (Brain: 17.9%). LDH was elevated in 37.5% of pts. EB was administered as the second line after IT in 10 (17.9%) pts. The ORR to EB was 80.4%. With a median follow up of 13 m (range: 1.1-26.7), median PFS was 11.4 m (95% CI: 9.9-21.6) and 6.6 m (95% CI: 4.4-NR) for pts in first-line and after ICI, respectively. The 12-m OS rate was 72.3% (95% CI: 60.1-87) and 30% (95% CI: 11.6-77.3) for pts in first-line and after ICI, respectively. There were no deaths related to study treatment and most common grade 3-4 toxicities were ALT increased (5.4%), fatigue (3.4%) and diarrhea (1.9%).

Conclusions: EB showed similar efficacy in the real-world setting than in clinical trials, despite the population included pts with worse prognosis. Final OS results are awaited. The toxicity profile was consistent with previous experience.

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838P Patterns of response/progressive disease (PD) and management following PD with anti-PD-1 (PD1) in patients (pts) with advanced cutaneous squamous cell carcinoma (cSCC)

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Background: PD1 has become 1st line therapy for advanced cSCC however most pts have innate resistance (IR; upfront PD or PD after <6 months (mo) of stable disease [SD]) or acquired resistance (AR; PD after complete/partial response [CR/PR] or SD>6 mo). We aim to: (1) evaluate patterns of response/PD to PD1 therapy; (2) define a clinical predictive model of upfront PD; (3) study the management following PD to PD1.

Methods: Advanced cSCC pts treated with PD1 therapy at 8 international centres were included. Demographics, disease characteristics, full blood count, nature of PD, subsequent treatments and outcomes were examined. Multivariate analysis and backward elimination technique were used to build a model to predict upfront PD.

Results: 115 advanced cSCC pts were included; 89 (77%) were male, median (med) age was 79 years (range 42 - 94). 25 pts (22%) had a history of a malignancy other than complex skin cancer and 10 (9%) pts were immunosuppressed. 33 (29%) pts had visceral metastases (mets); 19 (17%) lung, 17 (15%) bone and 3 (3%) liver mets. With a med follow-up of 17 mo (95% CI, 15 -20), the response rate was 66% (n=76; 36% [n=41] CR). 17 pts (15%) had upfront PD, and the combination of clinical features (age, immunosuppression, primary site, white cell count, neutrophils, and monocytes) accurately identified these pts (AUC 73.6; 95% CI, 60.1 − 87.0). Site-specific CR/PR was most common in subcutaneous (subcut; 67%) and lymph node (LN; 67%) mets, while site-specific PD was most common in bone (18%) mets. 24-mo PFS and OS were 62% (95% CI, 52-74%) and 68% (95% CI, 59-80%), respectively. From 34 (30%) progressing pts, 20 (59%) had IR and 14 (41%) had AR. 22 (65%) had further therapy, from which 16 (73%) had systemic +/- local therapy. Cetuximab was the most common systemic therapy (31%; n=5) and 4 pts responded. 4 pts (25%) were re-challenged PD1 and only 1 patient responded.

Conclusions: PD-1 demonstrated high subcut/LN response but poor response in bone cSCC mets. The combination of clinical features accurately predicted upfront PD, and although numbers were low, cetuximab demonstrated activity as subsequent therapy for these pts following PD1.

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839P A retrospective study on the long-term survival and incidence of metachronous malignancies in advanced melanoma patients treated with immune checkpoint blockade (ICB)

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Background: ICB (ipilimumab [IPI], nivolumab [NIVO], pembrolizumab [PEMBRO] or IPI/NIVO) improves long-term (>5y) survival of patients (pts) with unresectable stage III/IV melanoma. The incidence of metachronous malignancies (MM) in this population has not been reported.

Methods: We reviewed the medical files of prospectively identified unresectable stage III/IV melanoma pts treated with ICB at the Universitair Ziekenhuis Brussel. The probability for progression-free survival (PFS) and overall survival (OS) were calculated starting from the date of first ICB administration (by Kaplan-Meier estimates). The incidence of events (: melanoma progression, death or MM) were calculated by 1-year intervals and normalized to the weeks of pts-follow-up during the interval.

Results: Of the 292 eligible pts, 153 (52%) were female. Median age at first ICB was 57y [24—93]. A total of 219 (46%) IPI, 216 (46%) PEMBRO, 19 (4%) NIVO, and 17 (4%) IPI/NIVO treatments were administered; 81 pts (28%) were treated with IPI only, 85 (29%) with PEMBRO or NIVO only, and 126 (43%) with IPI and NIVO or PEMBRO . Median ICB duration was 44w (range 3-528); ICB was stopped electively in the absence of PD or AE in 166 (35%) pts, following an AE in 84 (18%) pts, PD in 177 (37%) pts, death in 42 (8,9%) pts, and 4 (0.8%) pts were lost to follow-up. Median PFS- and OS were 47w [95% CI, 33—60] and 83w (95% CI, 48—117) respectively; 3- and 5-y PFS-rates were 33% [27—39] and 26% [21—32]; 3- and 5y OS-rates were 41% [35—47] and 33% [27—39]. A total of 22 MM (13 cutaneous, 9 non-cutaneous) were diagnosed in 17 pts (5.8%). All pts underwent treatment with curative intent, there were no deaths due to MM. At the time of diagnosis of MM, 19 out of 22 pts were in a CR of their melanoma and 5 were treated with ICB. During the first 4y after the start of ICB dosing, the normalized incidence of melanoma PD was numerically higher than the of MM, from the 5thy onwards, this ratio was inversed.

Conclusions: In this real-world study, long-term survival of ICB treated pts with unresectable stage III/IV melanoma resembles the outcome of prospective clinical trials. Beyond 5y, the incidence of melanoma PD is very low and numerically exceeded by a low-incidence of MM.

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840P Electronic patient-reported outcomes (ePROs) of adults with BRAF V600—mutant stage III-IV melanoma treated with dabrafenib + trametinib (D + T) collected using the Kaiku Health digital patient (pt) monitoring platform

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Background: D + T has shown long-term efficacy and a well-characterised safety profile in pts with *BRAF*-mutant melanoma in clinical trials; however, real-world evidence (RWE) is limited. ePROs compiled with digital solutions can allow for collection of symptom data, prompt reaction to medical events, and improved quality of life (QOL). Novartis and Kaiku Health codeveloped a platform for pts with high-risk stage III or unresectable/metastatic *BRAF* V600E/K—mutant melanoma to describe PROs during treatment with D + T and provide pt educational materials.

Methods: 40 to 100 pts will be enrolled during treatment with D + T and followed for $\geq$ 6 mo to collect longitudinal PRO and clinical data. The primary endpoint is incidence of key symptoms such as fever, chills, fatigue, and nausea. Secondary endpoints include frequency, severity, and duration of symptoms; platform feasibility and impact on treatment interruptions and/or reductions and time on treatment; and machine learning (ML) modelling aimed at predicting symptom onset and continuity.

Results: At data cutoff for the interim analysis (22 Mar 2022), 49 pts were enrolled from 5 sites. The adoption rate was 92%, with 45/49 invited pts registered, with 66% using the module for $\geq$ 12 wk. The majority (65%) used mobile versions, and 76% read electronic educational materials. 39/45 pts reported a total of 7217 symptoms using the module with a 71% average weekly compliance, and 39 pts completed $\geq$ 1 QOL questionnaire. Median time spent on questionnaires ranged from $\approx$ 2-3 minutes. Common symptoms were fatigue (82%), headache (56%), cough (51%), and muscle pain (51%). 10 pts reported 19 cases of acute fever and were monitored using a fever management algorithm until resolution. ML models predicted symptom onset and continuity for 9 symptoms with good to excellent performance.

Conclusions: Interim data suggest that modules are supporting pts while generating RWE, which opens the possibility of understanding safety profiles and QOL in this setting. Continued data collection and investigation of ML aim to better predict symptoms for earlier intervention.

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841P Effects of immune checkpoint inhibitor-based combination therapies on the gut microbiota in advanced melanoma patients

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Background: The combination of immune checkpoint inhibitors (ICIs) with molecular targeted drugs or chemotherapy has been explored to improve the clinical benefit of cancer therapy. However, the effect of combination therapy on the gut microbiota has not been characterized.

Methods: We retrospectively analyzed frozen fecal samples for gut microbiota genomic characterization. A total of 50 pantients' samples of advanced melanoma who received ICI-based therapy from Sun Yat-sen University Cancer Center were included. Fecal samples were collected at various time points during the immunotherapy. Total DNA was extracted from the fecal samples and sequenced. The filtered gut microbiome DNA reads were mapped to the integrated gene catalogue.

Results: We examined the longitudinal changes in gut microbiota composition in patients that received ICI monotherapy (anti-PD-1 therapy; n=23), combined ICI with chemotherapy [nab-paclitaxel (PTX) or temozolomide (TMZ); n=13], or molecular targeting drugs [vemurafenib, or lenvatinib/anlotinib (TKI); n=14]. In 7 patients who received both ICI monotherapy and combination therapies, we found reduced gut bacterial richness and alpha diversity upon ICI combination therapies. ICI combination therapies also altered gut bacterial species abundances more intensively than ICI monotherapy. The abundance of the *Bacteroides* genus was increased while the abundance of the *Eubacterium* and *Clostridium* genus were decreased after combination therapies. Furthermore, bacterial species characteristics of specific combination regimens were identified. *Akkermansia muciniphila* was found to be more abundant in ICI plus TKI, and *Clostridium disporicum* was more abundant in ICI plus TMZ compared with ICI alone. ICI plus PTX displayed higher abundance of *Parabacteroides* genus than all other groups. Several bacterial species including *Ruthenibacterium lactatiformans* were found to be enriched in ICI plus vemurafenib. Interestingly, *Ruthenibacterium lactatiformans* was found to be highly enriched in non-responders of ICI alone.

Conclusions: Our study points to a possible effect of ICI based combination therapies on the gut microbiota and provides implications for the treatment of advanced melanoma patients.

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842P A phase II trial of AU-011, an investigational, virus-like drug conjugate (VDC) for the treatment of primary indeterminate lesions and small choroidal melanoma (IL/CM) using suprachoroidal administration

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Background: Choroidal melanoma is the most common primary intraocular malignancy in adults. Many subjects with a melanocytic choroidal tumor of indeterminate malignancy (i.e., 'indeterminate lesion') or small choroidal melanoma (IL/CM) are monitored clinically or treated with radiotherapy, which may lead to severe and irreversible vision loss. AU-011 (belzupacap sarotalocan) is a virus-like drug conjugate (VDC) currently being investigated as a potential first-line vision-sparing treatment. The dual mechanism of action consists of AU-011 selectively binding to malignant melanoma cells, causing acute necrosis upon light activation and potential long term anti-tumor immunity. The current Phase 2 trial is designed to evaluate the safety and efficacy of AU-011 when administered via suprachoroidal (SC) injection. Trial design using SC administration and interim safety from the open-label dose escalation phase will be presented.

Methods: Phase 2, multicenter trial being conducted at 22 ocular oncology sites in the US. The trial included 6 single- and multiple-dose escalation cohorts to be followed by a randomized confirmatory phase. In dose escalation, adult subjects received up to 3 cycles of 3 weekly AU-011 treatments via SC administration with a maximum dose of 80µg with 2 laser applications.

Results: Preliminary safety results include 17 subjects in the dose escalation phase. The most common adverse events (AE) related to drug or laser were anterior chamber inflammation in 4 subjects, conjunctival hyperemia, eye pain, and punctate keratitis in 2 subjects each. There were no dose-limiting toxicities, treatment-related serious or grade 3/4 AEs, vitritis or serious AEs of vision loss. Two subjects developed 5 serious AEs unrelated to treatment.

Conclusions: Preliminary results indicate AU-011 to have a favorable safety profile, supporting its potential to be a first-line therapy for the treatment of IL/CM, especially in early-stage disease where observation may be commonly employed. Efficacy data including visual acuity and tumor control from the dose escalation phase will be reported later this year.

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843P Long-term survivors on tebentafusp in phase II trial of previously treated patients with metastatic uveal melanoma

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Background: The phase (Ph)3 IMCgp100-202 trial (NCT03070392) of tebentafusp (tebe) in untreated metastatic uveal melanoma (mUM) demonstrated improved overall survival (OS), HR=0.51. In the Ph2 IMCgp100-102 trial (Study 102; NCT02570308) in previously treated mUM, the estimated 2-yr and 3-yr tebe OS rates were 37% and 24% compared to 15% and 9%, respectively, from a meta-analysis (Rantala 2019). The OS benefit is not explained by RECIST responses alone. We describe the characteristics of tebe treated pts with long-term survival (OS $\geq$ 2 yrs) in Study 102.

Methods: 127 pts with 2L+ mUM received tebe during the expansion phase of Study 102, where treatment beyond initial RECIST progression (TBP) was allowed. The association between OS and baseline (BL) covariates, on-treatment RECIST response, baseline tumor biopsy and ctDNA changes were assessed (31Mar2021 data cut-off).

Results: With median follow-up of 29.9 months, 33% (42/127) of pts had OS $\geq$ 2 yrs, 79% of whom received TBP. 5 of 6 pts with PR were alive $\geq$ 2 yrs. 41% (25/61) of pts

with best response of PD had OS $\geq$ 1 yr, including 10 pts with OS $\geq$ 2 yrs. In a multivariate analysis of BL covariates, LDH $\leq$ ULN and ALP $\leq$ ULN were most strongly associated with OS $\geq$ 2 yrs. Lower BL serum ctDNA levels and a low tumor M2 macrophage:CD3 T cell ratio were strongly associated with OS $\geq$ 2 yrs. BL gp100 expression, prior IO therapy (including anti-PD1 +/- ipilimumab), time from initial diagnosis or metastatic disease, or size of largest liver lesion were not significant predictors of OS $\geq$ 2 yrs. 20% (14/69) of pts with largest liver lesion of $\geq$ 3 cm had OS $\geq$ 2 years. ctDNA reduction ($\geq$ 0.5 log) or clearance by Wk 9 were associated with long OS. Of 25 pts with OS $\geq$ 2 yrs and evaluable ctDNA, 52% (13/25) had $\geq$ 0.5 log ctDNA reduction, of whom 8 had ctDNA clearance. Most of the 13 pts had best RECIST response of PD or SD.

Conclusions: The strongest baseline predictors of OS $\geq$ 2 yrs on tebe were low serum LDH, ALP and ctDNA and, in tumors, a low M2 macrophage:CD3 T cell ratio. Other BL covariates, e.g., size of largest liver lesion, were not significant predictors. ctDNA reduction/clearance may be a better early surrogate of long OS than radiographic response.

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844P Efficacy and safety of lifileucel, an investigational autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma previously treated with anti-LAG3 antibody

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Background: Lifileucel showed durable responses in patients (pts) with advanced (unresectable/metastatic) melanoma in the post anti—PD-1 setting, with an ORR of 36% (Sarnaik JCO 2021). The recent approval of relatlimab (anti—LAG3 antibody) + nivolumab provides a new option for first-line (1L) treatment of advanced melanoma; however, ORR after exposure to this novel combination has been reported only for anti—CTLA-4—based therapies (11%; Menzies NEJM 2022).

Methods: In the phase 2, C-144-01 study (NCT02360579), pts with advanced melanoma were previously treated with immune checkpoint inhibitor(s) (ICI) and BRAF $\pm$ MEK inhibitors (if *BRAF V600* mutation-positive). We performed a retrospective exploratory analysis to assess efficacy and safety of lifileucel in pts enrolled in C-144-01 who progressed on/after anti-LAG3—containing therapy. ORR was assessed by investigators per RECIST v1.1.

Results: Thirteen pts received prior anti-LAG3 (12 with anti—PD-1; 1 with anti—PD-1 + anti—CTLA-4), with a median of 3 prior therapies. Anti-LAG3 was the last therapy prior to TIL therapy in 7 pts; 6 pts had other therapies after anti-LAG3 (eg, chemotherapy, ICI, targeted therapy). Anti-LAG3 was used in 1L in 4 pts; 9 pts received it post-progression. Median duration of anti-LAG3 therapy was 3.3 mo (range, 0.03—9.2 mo). ORR for lifileucel was 38.5% (5 partial responses); 3 responders had primary and 2 acquired resistance to anti-LAG3 + anti—PD-1. Responses were durable, with 60% of responses extending beyond 12 mo. Safety profile was consistent with prior reports; most common ($\geq$30%) grade 3/4 treatment-emergent adverse events were anemia (85%), thrombocytopenia (85%), febrile neutropenia (39%), leukopenia (31%), neutropenia (31%), and lymphopenia (31%).

Conclusions: Lifileucel showed an encouraging 38.5% ORR in pts with advanced melanoma refractory to prior anti-LAG3 + anti—PD-1 $\pm$ anti—CTLA-4. Similar to prior observations in pts after anti—PD-1 therapy, both primary and acquired anti-LAG3—resistant pts responded to lifileucel, suggesting that lifileucel outcomes may not be affected by prior anti-LAG3 therapy.

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845P Vidutolimod + pembrolizumab as 2L+ treatment in patients with anti–PD-1–refractory melanoma and adrenal insufficiency: Subgroup analyses of a phase Ib study

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Background: Corticosteroid replacement therapy (CRT) in patients (pts) with adrenal insufficiency (AI) could reduce the efficacy of immunotherapy. Vidutolimod (vidu) is an immunostimulatory virus-like particle containing a CpG-A Toll like receptor 9 (TLR9) agonist. In a phase 1b study in pts with anti–PD-1–refractory melanoma, vidu + pembrolizumab (pembro) showed promising clinical activity with an objective response rate (ORR) of 23.5% (95% CI, 15.5-33.1). This post hoc analysis assessed the safety and clinical activity in the subgroup of pts with AI on CRT.

Methods: This study (NCT02680184) enrolled adults with etastatic or unresectable cutaneous melanoma with progressive disease or stable disease after ≥12 weeks of anti–PD-1 treatment (tx), measurable disease per RECIST v1.1, ECOG PS 0/1, and ≥1 lesion accessible for intratumoral (IT) injection. This post hoc analysis included all pts who received IT vidu + IV pembro. Pts with AI were to receive CRT (prednisone-equivalent 5-10 mg daily) and prophylactic stress-dose steroids (50-100 mg hydrocortisone or equivalent orally every 8 hours) before and for 24-48 hours after vidu dosing. The primary objective was safety, and the key secondary objective was ORR.

Results: 159 pts received vidu + pembro. All pts had prior anti–PD-1 tx, and 74 pts (46.5%) had prior ipilimumab (ipi) tx. 148 pts (93.1%) had progressive disease on last anti–PD-1 tx. 20 pts (12.6%) had a medical history of AI; 19 of these pts (95.0%) had prior ipi tx. 5 additional pts (3.1%; 4 with prior ipi tx) were diagnosed with AI on study. Grade 3/4 tx-emergent adverse events were reported in 11 pts (55.0%) with prior AI and in 3 pts (60.0%) diagnosed with AI on study. No tx-related deaths occurred. The ORR was 28.0% (7/25; 95% CI, 12.1-49.4) in pts with AI.

Conclusions: The safety and ORR of vidu + pembro in pts with AI were consistent with the overall study population, suggesting that simultaneous corticosteroids for AI do not reduce the biologic activity of this combination. A phase 2 study to confirm the efficacy of vidu + anti–PD-1 in pts with PD-1 blockade–refractory melanoma is ongoing (NCT04698187).

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846P Triple combination of ipilimumab + nivolumab + anti-TNF in treatment naive melanoma patients: Final analysis of TICIMEL, a phase Ib prospective clinical trial

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Background: CTLA-4 and PD-1 inhibitors have been shown to improve Progression Free survival (PFS) and Overall Survival (OS) in advanced melanoma patients. TNF, which is produced upon immune checkpoint inhibitors, impedes ICI therapy efficacy in preclinical melanoma and colon cancer models. Indeed, we and others have published preclinical analyses showing that the systematic combination of anti-TNF with anti-PD-1 +/- anti-CTLA-4 may improve tolerability and efficacy of the treatment.We conducted a phase Ib clinical trial in advanced melanoma patients at our institution.

Methods: TICIMEL (NCT03293784) is an open label phase Ib clinical trial in treatment naive advanced melanoma patients with two parallel cohorts: ipilimumab/nivolumab/

certolizumab (C cohort) and ipilimumab/nivolumab/infliximab (I cohort). Fourteen patients were included in the safety part of the trial that has already been published and 19 patients were additionally included in the expansion part. The objective of the expansion part was to evaluate safety and to screen for preliminary anti-tumor activity of these combinations. We report the safety and activity results of all patients.

Results: Between January 2018 and November 2021 , 33 patients were included: 13 in the I cohort and 20 in the C cohort. One patient in the I cohort did not receive any treatment and was considered as not evaluable for both safety and activity. At the time of data cut-off, With a median follow-up of 20.2 months, one patient in each cohort remains on treatment and first tumor assessment was pending for 1 patient in the C cohort. Thirteen patients in the C cohort and 4 in the I cohort had drug-related G3/4 adverse events. Drug-related AE were mostly hepatobiliary, gastrointestinal and respiratory disorders. In the C and I cohorts, an objective response was observed in 12 patients (CR: 5; PR: 7) and 6 (CR: 2; PR: 4), respectively.

Conclusions: Our study shows that the systematic co-administration of anti-TNF and ipi+nivo is safe. Our final analysis shows that certo+nivo+ipi may have synergistic pharmacodynamic activities, with a promising response rate.

Clinical trial identification: NCT03293784.

Legal entity responsible for the study: The authors.

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847P Precision oncology for resistant acral, mucosal and cutaneous melanomas: A prospective broad high throughput genomics feasibility study

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Background: There are limited therapies for metastatic cutaneous, mucosal and acral melanomas (m) progressing after checkpoint (CPI) and BRAF/MEK (TKI) inhibitors. The Treat20 Plus study aimed to identify oncogenic drivers through high throughput genomics that could inform treatment recommendations ((Trec).

Methods: From 1.2016 - 1.2019, 54 resistant m were prospectively subjected to a comprehensive molecular analysis (WGS, WES, RNA seq), that allowed a molecular tumor board to make individualized treatment recommendations.

Results: Primary sites: cutaneous (34), mucosal (16), acral (4), PS 1(0-3), abnormal LDH (37), # of therapies 5(2-22) (surgery 2(0-18), irradiation 1 (0-5), CPI 2(1-5), TKI 0 (0-2), chemo 0(0-2). No Trec in 10 p (low purity 7, early PD 3). Trec in 44 p (81%) with 4 (0-5) / p, for a total of 108 Trec including inhibitors of MEK 27%, CDK4/6 23%, TKI 7%, MET 6%, MTOR 6%, EGFR, FGFR, RAS 5 %, ALK 4%, NOTCH and PARP 2%, IGFR, NTRK, IDO and ER 1%. Treatment realization made in 21/44 p (48 %). Non-realization was early PD (14), still on CPI (6), on chemo (1), no druggable mutation (2). Among the 21 treated p 1 CR, 4 PR (RR: 24 %; 9 % of whole cohort (wc)), 3 SD (Clinical benefit: 38 %; 15% of wc) and 13 PD. Duration of the clinical benefit ranged from 147-678+ d. Resistance to prior TKI were observed in 8/9 BRAF V600E p by BRAF fusion (1), splicing (1), NRAS mutation (4), PTEN (2), RB1 (1), CDKN2A loss (2). CPI resistance mutations were shown in B2M (1), SOCS1 (1), MDM2 (1) and MDM2 focal amplification (2), and homozygous deletion in PTEN (4), but no relevant JAK1, JAK2, IRF1, IFNGR1/2, PIAS4, EGFR, MDM4, EZH2 alterations. Responding p had BRAF 599delinsTT (1), BRAF G469S (1), cKIT (2) mutations and NTRK fusion (1). Stabilization: IGFR (1) MET overexpression (1), CDKN2A loss (1). Among the seven p without BRAF V600E, NRAS and NF1 mutation (triple-negative profile) six had a clinical benefit. PFS for the treated p: 2.26 months (95%CI: 0.00-4.98) and the OS for the 54 p: 8.7 months (95 % CI: 1.56-15.97).

Conclusions: For resistant acral, mucosal and cutaneous m, precision oncology was feasible with Trec in 81 % of p. It uncovered targetable alterations that led to a clinical benefit in 38 % of p mainly presenting with absence of BRAF V600E, NRAS and NF1 mutation.

Clinical trial identification: NCT05063058.

Legal entity responsible for the study: U. Keilholz.

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848P Second-line systemic treatment for patients with advanced melanoma: Results from the prospective real-world study GEM1801

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Background: Information regarding charatcteristics and outcomes of second line treatment for patients with advanced melanoma is scarce since no randomized clinical trials are published in the post-targeted and immunotherapy era. Real-world data studies are capital for benchmarking patientś outcomes in order to design clinical trials in this scenario.

Methods: GEM1801 is a prospective observational real-world study that currently has included 551 patients with advanced melanoma treated in 37 centers from the Spanish Melanoma Group (GEM). This is a descriptive analysis of basal characteristics, progression free survival (PFS) and overall survival (OS) from patients that received second line treatment in GEM1801.

Results: 186 (33.8%) patients received a second line (2L) treatment. For the 186 patients receiving 2L, with a median follow up of 6.4 months (m) (95% CI: 4.9-9.8), median PFS was 4.7 m (95% CI: 3.5-5.8) and median OS 11.3 m (95% CI: 8.6-13.4) from the beginning of 2L. Additionally, 63 (33.9%) patients received treatment

beyond 2L. Table summarizes the patients characteristics and their outcomes according to *BRAF* status and treatments. For the 365 (66.2%) patients that did not receive 2L, the reasons were: 249 (68.2%) no progression with first line; 110 (30.1%) death before 2L; 6 (1.6%) loss of follow up.

Table: 848P

CHARACTERISTIC AT 2L	*BRAF* Mutated N= 99	*BRAF* wildtype N= 82
SEX female N (%)	47 (47.5)	33 (40.2)
age (median, Rank)	59 (23-90)	69 (29-93)
ECOG 0-1 N (%)	87 (87.9)	78 (95.1)
LDH >UNL N (%)	34 (34.3)	26 (31.7)
M1C-D N (%)	62 (62.6)	40 (48.8)
2L targeted therapy (TT): N, (%)	44 (44.4)	2 (2.4)
TT mPFS, m (95% CI)	12.4 (6.1-NR)	2 (NA-NA)
TT mOS, m (95% CI)	20 (11.5-NR)	2.7 (NA-NA)
2L immunotherapy (IT): N (%)	46 (46.5)	34 (41.5)
IT mPFS, m (95% CI)	5.3 (2.9-10.8)	3.1 (2.3-8.2)
IT mOS, m (95% CI)	10.9 (3.7-NR)	12.5 (8.1-NR)
2L Chemotherapy (CT): N, (%)	4 (4)	29 (35.4)
CT mPFS, m (95% CI)	0.4 (0-NR)	3.2 (2.7-5.5)
CT mOS, m (95% CI)	0.6 (0.2-NR)	5.6 (3.9-15.2)
2L non specified: N (%)	5 (5.1)	13 (15.9)
Treatment beyond 2L N (%)	27 (27.8)	33 (39.3)

There are 5 patients with unknown *BRAF* status.

Conclusions: Second line treatment is still a difficult clinical scenario, especially for patients with *BRAF* wildtype melanoma and with *BRAF* mutated that progress after targeted therapy. The results, remarkably for PFS, need to be improved, thereby clinical trials participation is encouraged.

Clinical trial identification: NCT03605771.

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849P Time from primary melanoma to first distant recurrence in relation to survival outcomes in metastatic melanoma

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Background: Since the introduction of novel systemic therapies, the prognosis of advanced melanoma has greatly improved. Melanoma is known for its remarkably long time to first distant recurrence (TFDR), which can be decades in some patients and is attributed to immune-surveillance. We investigated the relationship between TFDR and outcomes upon systemic treatment for advanced melanoma.

Methods: Analyses were performed on prospectively registered data from advanced cutaneous melanoma patients treated with first line BRAF(/MEK) inhibition or immune checkpoint inhibition (ICI) from the nationwide Dutch Melanoma Treatment Registry. Patients with a known primary tumor date were included. The association between TFDR and progression free survival (PFS) and overall survival (OS) was assessed by Cox proportional hazard regression models with adjustment for age and type of therapy, both continuously (modelled linearly as well as flexibly using restricted cubic splines) and categorically.

Results: Patients received anti-PD-1-based treatment (n=1361 monotherapy and 483 in combination with anti-CTLA4) or BRAF(/MEK) inhibition (n=1618). Median follow-up was 32.8 months. Patients with a longer TFDR (>5 years) had a longer PFS (Hazard ratio (HR) 0.89, 95% confidence interval (CI) 0.81-0.98) and OS (HR 0.83, 95%CI 0.75-0.92) than patients with TFDR <2 years. When stratifying for treatment, patients with a TFDR > 5 years (Table) had a longer median OS in both treatment cohorts. Based on a flexible spline fit and compared to synchronous disease, the hazard of dying rapidly decreased with increasing TFDR until approximately 5 years (HR 0.87), after which the hazard of dying further decreased with increasing TFDR, but less strongly (HR 0.82 for a TFDR of 10 years and HR 0.79 for a TFDR of 15 years).

Conclusions: Patients with longer TFDR have a prolonged PFS and OS, irrespective of being treated with first line ICI or targeted therapy.

Legal entity responsible for the study: University Medical Centre Utrecht.

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Table: 849P Median PFS and OS stratified by systemic treatment for the different TFDR categories

		Time to first distant recurrence			Logrank P-value
		< 2 years	2-5 years	>5 years	
Immune checkpoint inhibition	**Median PFS, months (95%CI)**	7.3 (5.7-9.1)	9.2 (7.4-12.2)	10.0 (8.4-12.4)	0.412
	Median OS, months (95%CI)	25.0 (21.3-30.4)	29.2 (30.6-35.7)	37.3 (29.4-46.3)	0.014
BRAF(/MEK) inhibition	**Median PFS, months (95%CI)**	5.7 (5.4-6.2)	5.8 (5.4-6.3)	7.3 (6.4-8.1)	0.006
	Median OS, months (95%CI)	8.6 (7.4-9.8)	8.1 (7.4-9.0)	11.1 (10.2-12.2)	0.004

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850P A dynamic recurrence risk prediction tool for adjuvant therapy in stage III melanoma

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Background: Adjuvant treatment with dabrafenib/trametinib (dab/tram) and anti-PD-1 antibodies (PD1) reduce the risk of recurrence and distant-metastasis in patients with stage III melanoma. Applying stage and treatment-specific clinical trial data to patients at time points during the course of treatment to inform follow-up and prognostication is difficult. We therefore developed a risk-prediction tool to aid clinical management that provides recurrence risks, adjusted for time survived, for patients with resected stage III melanoma at commencement of therapy as well as at various timepoints thereafter.

Methods: Kaplan-Meier survival curves (recurrence-free and distant-metastasis free survival) information were extracted from three clinical trials (COMBI-AD, CheckMate-238, Keynote-054/EORTC-1325). Individual curves were digitalized separately, and individual patient data reconstructed. Recurrence (any, distant), and time to event were obtained for each individual. Conditional survival analysis estimated the risks of recurrence from commencement of treatment and for survivors at 3-monthly time points, stratified by stage and intervention.

Results: Data from 2032 patients with resected AJCC v8 stage IIIB-D melanoma treated with dab/tram (n=384, median F/U 61mo, 95% CI 60-63), PD1 (n=816, median F/U 41mo, 95% CI 40-42) or observation (n=832, median F/U 41mo, 95% CI 40-43) were derived. Example results are shown (Table). An online calculator was developed.

Table: 850P

AJCC v8 Stage	Adjuvant intervention	Overall risk of recurrence* with intervention (%)	Remaining risk of recurrence* (%) if recurrence free at:			
			6mo	12mo	24mo	36mo
IIIB	Observation	51%	42%	29%	10%	6%
	Dab/Tram	40%	41%	37%	20%	12%
	PD1	30%	20%	14%	10%	7%
IIIC	Observation	62%	53%	38%	18%	13%
	Dab/Tram	45%	51%	45%	23%	10%
	PD1	45%	35%	26%	14%	12%

* Risk over F/U period as referred to in the results. Differing follow up periods from different trials precludes accurate comparison of risk between interventions.

Conclusions: This tool provides risks of recurrence in an easy-access location, which should guide discussions with patients about their current risk of recurrence with or without therapy at baseline and during their treatment journey, and appropriate surveillance. More data will be incorporated as they become available, further increasing the accuracy of the tool over time.

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851P Frequency and clinical significance of homologous recombination deficiency gene mutations in non-cutaneous melanoma

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Background: Homologous recombination deficiency (HRD) refers to the state of tumor cells which received defects in DNA-damage repair mechanisms. The HRD phenotype encodes important proteins for DNA homologous recombination repair (HRR) which can serve as a biomarker of therapeutic efficacy. Here, we explored the frequency and clinical significance of HRD gene mutations in non-cutaneous melanoma to provide experience for clinical options.

Methods: The data of 978 Chinese non-cutaneous melanoma patients using next-generation sequencing techniques with 81 or 425 cancer-related genes were collected. Among them, 881 patients were detected with 81 genes and 97 with 425 genes. The survival analysis was used to find the correlations between HRR gene mutations and clinical outcomes.

Results: In non-cutaneous patients, 10.8% (106/978) patients were found the genomic alterations in HRR genes. The frequently mutated genes were ATM (3.9%), ARID1A (3.8%), BRCA2 (2.8%), BRCA1 (1.5%), BRIP1 (0.4%), ATR (0.1%), PALB2 (0.1%), ARID2 (0.1%), FANCA (0.1%) and RAD50 (0.1%). Among 106 patients with HRR gene mutation, 54.7% were males and 65.4% were under 65 years old. 8.0% (27/335) patients were acral melanoma, 9.6% (40/418) patients with mucosal melanoma, 15.2% (5/33) patients with uveal melanoma and 21.5% (34/158) patients with unknown melanoma. In addition, 28.3% had ulcer in primary sites. 21.7% were in stage IV and 4 patients were with M1a, 1 with M1b, 14 with M1c, 4 with M1d. From January 2008 to January 2022, 29 patients among 106 patients with HRR gene mutation died. The median follow-up time was 32.00 months (95% CI: 27.14-36.86 months) and the median overall survival was not reached. The 1-year, 3-year and 5-year survival rates were 92.8%, 63.8%, 55.6%, respectively.

Conclusions: ATM and ARID1A are the most common genomic alterations with HRR genes and patients with HRR gene mutations maybe get survival benefits from treatment.

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852P Does sex affect the efficacy of immune checkpoint inhibitors? A national Danish melanoma study

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Background: Immune checkpoint inhibitors (ICI) are current standard in treating metastatic melanoma. In melanoma, males are known to have a poorer prognosis compared to females. However, metanalysis have shown conflicting results regarding differences in ICI efficacy between females and males. In this study, we evaluate the efficacy of ICI in a real-world Danish metastatic melanoma population according to sex. The primary endpoint was progression-free survival (PFS). Secondary endpoint was overall survival (OS) and melanoma specific survival (MSS).

Methods: All patients treated with ICI (anti-PD-1 and/or anti-CTLA4) for metastatic melanoma in Denmark between 2011-2021 were identified in the Danish metastatic melanoma database. Only patients receiving ICI as first-line treatment were included. Baseline characteristics were evaluated according to ICI treatment for; age, ECOG performance status, lactate dehydrogenase (LDH), M-stage, BRAF status, the origin of melanoma (cutaneous or unknown primary melanoma), and granulocytes. Parameters for multivariate analysis were selected backwards, with a cutoff at 0.10.

Results: 1461 patients; 573 females and 888 males were identified. Baseline characteristics were significantly unbalanced between sex. A higher frequency of BRAF mutation and a lower age was found for females, however, also elevated LDH and advanced M stage. The median follow-up time for PFS was 51 months (95% CI 48-55). Multivariate analysis showed sex as a significant factor of efficacy with improved PFS for females (HR 1.16 (1.02-1.33), p=0.03). Females showed significantly better OS with a five-year survival of 46% (41%-51%) for females and 38% (34%-42%) for males. Multivariate analysis reinforced this significance with HR 1.29 (1.09-1.52). Five-year MSS rates were 49% (95% CI 44%-54%) for female and 45% (40%-49%) for male. Multivariate analysis showed significantly better MSS for females (1.20 (1.01-1.43), p=0.04).

Conclusions: This study represents a complete, national dataset of ICI-treated metastatic melanoma patients. Baseline characteristics were unbalanced between sexes. Despite adjustments for clinical, validated prognostic factors, sex remains an independent prognostic factor for PFS, OS, and MSS in this real-world cohort.

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853P TNF plasma levels in advanced melanoma patients treated with immune checkpoint inhibitors: Results from the MELANFα clinical study

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Background: Immune checkpoints inhibitors (ICI) targeting CTLA-4 and PD-1 have achieved unprecedented results in advanced melanoma patients. Mechanisms of resistance are not fully understood and predictive biomarkers of response are to be identified. TNF is a pleiotropic cytokine whose role in cancer can be detrimental and TNF blockade potentiates ICI efficacy in preclinical models.

Methods: MELANFα (NCT03348891) is a translational proof-of-concept, open-label, prospective, multicenter, cohort study of 60 advanced melanoma patients (ipilimumab+nivolumab; pembolizumab or nivolumab). Its primary objective was to study whether the evolution of plasma TNF between baseline (W0) and week 12 (W12) could identify patients presenting non-progressive disease at W12. Exploratory objectives were to monitor the pharmacodynamics of ICI on plasma cytokines (Meso Scale) and circulating T cells (flow cytometry). The disease control rate (DCR) was defined as complete response (CR) + partial response (PR) + stable disease (SD) ≥6 months.

Results: TNF plasma levels increased along therapy with a median of 0.804 pg/mL (range: 0.180-5.451) at W0 to 0.981 pg/mL (0.313-4.835) at W12 (p=0.0416) but the evolution from baseline was not associated with non-progressive disease at W12. Whereas TNF plasma levels at baseline did not differ in responders (R) and non-responders (NR), they were significantly higher at W12 (p = 0.0129) in NR (1.060 pg/mL; 0.403-4.835) versus R (0.713 pg/mL; 0.313-1.880). At W12, TNF and IL-6 plasma levels were positively correlated (r(s)=0.5769; p<0.0001) and IL-6 plasma levels tended (p=0.0562) to be increased in NR (2.016 pg/mL; 0.405-9.932) versus R (1.103 pg/mL; 0.314-8.813). At W12, the proportion of circulating central memory CD4 T cells was significantly increased in patients with DCR [median: 36.5% (22.1-55.1) versus 29.4% (7.6-47.2), p=0.0045].

Conclusions: Our results show that elevated TNF plasma levels along therapy is associated with a poorer clinical outcome and further point TNF as a putative target in combination with ICI in melanoma patients.

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854P Clinical features of acquired resistance (AR) in stage IV melanoma patients (pts) treated with immune checkpoint inhibition (ICI)

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Background: Long-term benefit of ICI in stage IV melanoma pts achieving response is often observed, although progression after initial response (AR) unfortunately regularly occurs. Limited evidence exists regarding clinical features, outcome and treatment of pts with AR. Therefore, this monocenter study retrospectively analysed pts with AR.

Methods: Stage IV melanoma pts treated at NKI between Jan 2013 and July 2021 and who developed AR after initial response upon ICI were included. AR is defined as progression after initial response (stable disease ≥6 months, partial response [PR] or complete response [CR]). Progression-free survival (PFS) from date of AR and from start date ICI (time to subsequent progression after treatment of AR [TTAR]) and overall survival (OS) from start date ICI were evaluated.

Results: 155 pts were identified with AR during ICI (n=50) and post ICI (n=105). Pts mostly developed AR after PR (67%) and CR (21%). Almost all CR pts belonged to the post ICI group, as opposed to the during ICI group (n=32 vs n=1). AR mostly occurred at isolated organ sites, but they were not specific for a site and were observed mainly in lymph nodes, lungs, brain and skin, with a median onset of 11mo after start of ICI. Pts received mostly local therapy alone (34%), switched systemic therapy (22%) or received combined local + systemic therapy (21%) as treatment of AR. Higher PFS, TTAR and OS rates were observed in pts developing AR post ICI, as compared to AR during ICI (median PFS 8mo vs 6mo, TTAR 26mo vs 22mo and OS 58mo vs 43mo). In the post ICI group PFS, TTAR and OS for CR were higher than for PR (median PFS 9mo vs 7mo, TTAR 35mo vs 22mo, OS not reached vs 55mo). For the various treatment strategies nearly all PFS rates were similar in both groups, except for continuation and restart of ICI. Restart of ICI resulted in the longest PFS, whereas continuation of ICI had the shortest PFS (12mo versus 6mo). This trend was also observed for TTAR and OS.

Conclusions: In general pts with AR have a good outcome, due to sufficient clinical management options of often solitary progression. Inferior clinical outcomes in the during ICI group compared to the post ICI group were observed, which can partly be due to patient selection as illustrated by the lack of pts with CR in the during ICI group.

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855P Whole blood transcriptomic profiling to predict response to immunotherapy in metastatic melanoma

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Background: While immune checkpoint inhibitors (ICI) have revolutionized treatment of metastatic melanoma (MM) patients, still 40−60% of patients do not achieve a clinical benefit. Tissue-based predictive biomarkers are not validated in MM, and non-invasive liquid biomarkers can be an alternative source. Whole-blood transcriptome has shown to identify early response to ICI in urothelial cancer, thus have a potential in the context of MM.

Methods: Whole blood samples from 29 patients with BRAF+ and high lactate hydrogenase MM were collected before and after 6 weeks of anti-PD1/CTLA4 treatment. Nineteen were classified as responders (R) (progression-free survival (PFS) $\geq$ 6 months) and 10 as non-responders (NR). Transcriptome profiles were generated by RNAseq and differentially expressed genes (DEG) identified by combining differential expression and multivariate analysis. Biological relevancy was assessed by over representation and gene network analysis and performance was evaluated by Sparse Partial Least Squares (SPLS) regression and cross validation.

Results: One hundred nineteen DEGs have been identified to predict ICI response at baseline (BL). The list is enriched for genes related to CD8 T-cells as well as interferon and TLR signaling, suggesting R and NR pts have different immune cell composition at BL. Seventy and 400 DEGs have been identified in NR and R, respectively, by comparing BL and on-treatment samples. Although cell proliferation genes were commonly identified in R and NR, suggesting ICI can exert an effect in both groups, genes associated to cell chemotaxis, anti-PD1/CTLA4 therapy targets and interferon-γ were found specifically associated to R, suggesting them as key processes for a durable response. SPLS model coupled with PFS analysis showed a highly significant difference at 6-month between the 2 patient strata (100% R vs 15% NR, $p<0.0001$).

Conclusions: Whole blood transcriptome profiling is a promising tool to identify predictive biomarkers of response to ICI in MM and to understand underlying biological processes. Future plans include biomarker validation on an independent sample cohort (under collection) to confirm performances and identified biological processes.

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856P Characterization of patients with brain metastases from metastatic uveal melanoma

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Background: Brain metastases (BM) occur rarely in patients with metastatic uveal melanoma (MUM). However, new therapies have improved survival of patients with MUM and development of extra-hepatic metastases is increasingly common. We aimed to describe the characteristics of patients with MUM who developed BM.

Methods: In this single-center retrospective study, we identified patients with MUM who presented BM at any time during their clinical course. We collected data regarding age at BM diagnosis, time to development of BM, next generation sequencing (NGS) and multiplex ligation-dependent probe amplification (MLPA) analyses, lines of therapy prior to BM diagnosis, and management of BM. Intracranial progression-free survival (IC-PFS) and overall survival (OS) from BM diagnosis were calculated by the Log-Rank method.

Results: From 2014 to 2021, 210 patients with MUM were identified; 22 (10.4%) developed BM. Median age at BM diagnosis was 59 years (49-80); 12 (55%) were male. Median number of systemic treatments prior to BM diagnosis was 2 (0-4) and included anti-PD1 + anti-CTLA4 in 4, anti-PD1 monotherapy in 8, and tebentafusp in 5 patients. Eleven (50%) patients had NGS data available and, following *GNAQ/11* mutations (11 patients), *BAP1* alterations were the most frequent (4 patients: p.Val171Cysfs*12, p.Thr93_Ala95del, p.S58fs*4, and p.Glu653* each). Three patients had MLPA analysis, and all had chromosome 3 monosomy and 8q gain. Median time from diagnosis of MUM to BM was 16.6 months (0-147). Fifteen (68%) patients had an incidental diagnosis, and 17 (77%) had $<$ 3 BM. Mean size of the largest lesion was 15.9 mm (SD 2.4). Twelve (55%) patients were treated with SRS, and 6 (27.5%) had WBRT. Fourteen (63%) patients received systemic therapy following BM diagnosis, which included anti-PD1 + anti-CTLA4 in 2, anti-PD1 monotherapy in 4, and tebentafusp in 1. From BM diagnosis, median IC-PFS was 4.2 months (95% CI 3.7-4.8), and median OS was 7.4 months (95% CI 3.1-11.7).

Conclusions: BM in patients with MUM tend to occur late in the course of disease. Molecular high-risk features are frequent in this population. Surveillance with neuroimaging in patients with long-term control of disease may be warranted.

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857P Precision oncology and tumor mutational burden (TMB) in Merkel cell carcinoma (MCC): An analysis of the AACR Project Genie real-world database

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Background: Merkel cell carcinoma is an aggressive neuroendocrine tumor of the skin. Phenotypes include a low mutation and high mutation variant. Standard of care treatments for MCC include cytotoxic chemotherapy and immune checkpoint inhibitors. Presently, there are no targeted therapy options for MCC, however the AACR Project Genie is a large multi-institutional international database of genomic samples of tumors uniquely suited to evaluate rare tumors.

Methods: Individual patient data from AACR Genie versions 11.1 were accessed from the cBioPortal. Variables of interest include demographic data, alterations annotated by OncoKB therapeutic evidence level, and TCGA PanCancer pathway alterations. TMB was estimated was classified by mutations/Megabase as low ($<$2), intermediate (2-16), or high ($>$16).

Results: 313 MCC patients were identified from the database. Patients were 34.2% (n=107) female. Patients identified race as 91.7% (n=287) white, 2.2% (n=7) African American, and 0.6% (n=2) Asian. Sampled tissue originated from primary tumor in 55% (n=172) verses metastases in 41.9% (n=131). TMB-Low was present in 49.8% (n=156), TMB-Intermediate in 27.5% (n=86), and TMB-high in 24.7 (N=71). The median number of oncogenic alterations were 0 in TMB-Low, 1 in TMB-Intermediate, and 9 in TMB-High. Level 1-3 alterations (alterations supported by trial or evidence in other tumors) were present in 5.1% (n=9) of solid tumors while only 15.1% (n=13) of hematologic malignancies. Level 3A/B alterations (FDA approved drug for use in a biomarker approved indication or approved drug in another indication) were present in 48% (n=34) of TMB-high, 15% (n=13) of TMB-intermediate, and 5% (n=8) of TMB-low. HRAS (n=3; 2%) alterations more frequent in TMB-Low. Alterations frequent in TMB-High were PIK3CA (N=10; 20%), BRCA1/2 (n=7; 14%), PDGFRA (n=3; 6%), ATM (n=4; 8%), and TSC1/2 (n=2; 4%), CHEK1/2 (n=2; 4%), and PTCH1 (n=2; 4%).

Conclusions: While most targetable mutations in MCC were likely passenger alterations in relation to tumor mutational status, there is a subset of MCC which have actionable alterations. These alterations support enrollment or treatment of MCC with targeted therapies.

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858P Automated detection of melanoma: Comparing a convolutional neural network (CNN) approach with an algorithm assessing disorder in the pattern of pigmented lesions, intended to mimick onco-dermatologists' visual analysis

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Background: Among Computer Aided Diagnosis (CAD) systems for melanoma detection, CNN behaves as a "black box", using a huge number of unknown features from a lesion's image to come to a classification and where no expert input can be implemented. Conversely of hand-crafted methods, the expert is selecting features to be used for the lesions' classification. Most of these hand-crafted algorithms were based on ABCD criteria (asymmetry, border, color, diameter). However the unconscious process leading onco-dermatologists to arbitrate between nevi and melanoma is more likely based on a global cognitive assessment, which we hypothesize to be an overall perception of order/disorder in the pattern of pigmented lesions. Our objective was to design an hand-crafted model based on the concept of ordered/disordered pattern, and to assess its performances by comparison to a CNN model, for the classification melanoma *versus* nevus.

Methods: We trained and tested 2 algorithms on a dermoscopic images dataset of 1533 melanomas and 6124 nevi. First, we developped The "Disorder model" based on a hand-crafted method, we extracted 4 specific features to characterize melanoma disorder named entropy, skewness, standard deviation and kurtosis, from 4 colors spaces. The classification of melanoma *versus* nevi was based on a statistical clustering method (KNN algorithm). Second, we developped a CNN model on the same dataset.

Results: Performances of the CNN model yielded: AUC 0.89, sensitivity 86%, specificity 75%, balanced accuracy 81%. The "Disorder model" reached similar high performances: AUC 0.91, sensitivity 91%, specificity 74%, balanced accuracy 82.5%. A statistical $\chi 2$ test revealed that entropy, characterizing color disorder, was the most discriminative feature for melanoma detection.

Conclusions: This study shows that an algorithm attempting to mimick human brain ability, using a few features to assess the disorder pattern in pigmented lesions, can reach a level of performance for melanoma detection equivalent to CNN-based algorithm, which is using much more features. Entropy seems to be a key feature to assess pattern disorder of pigmented lesions.

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859P The influence of hematologic malignancies on response to immune checkpoint inhibition in patients with advanced melanoma

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Background: Patients diagnosed with hematologic malignancies (HM) have a higher risk of developing subsequent solid tumors, such as melanoma. Patients with HM were mostly excluded from clinical trials but could derive less benefit from immune checkpoint inhibition due to disease or treatment-related T- or B-cell dysfunction.

Methods: All advanced stage IIIc and IV melanoma patients treated with anti-PD-1 or ipilimumab-nivolumab between 2015 and 2021 were included from the prospective nationwide Dutch Melanoma Treatment Registry. Progression-free survival (PFS), overall survival (OS), and melanoma-specific survival (MSS) were analyzed for patients with HM (HM+) and without HM (HM-). A cox model was used to account for confounders associated with PFS and OS.

Results: Fifty-seven HM+ patients and 2506 HM- patients were included. Twenty-two patients were diagnosed with leukemia, 26 with malignant lymphoma, three with multiple myeloma, and six had a different type of HM. Forty-four percent received curative treatment for their HM. In the anti-PD-1 cohort, median PFS was 2.8 months for HM+ and 9.9 months for HM- ($p=0.01$). MSS was 41.2 months for HM+ and 58.1 months for HM- ($p=0.00086$). In multivariable analysis, the presence of a HM was significantly associated with a higher risk of melanoma progression (HR_{adj} 1.68; 95%CI 1.24-2.29; $p<0.001$) and death (HR_{adj} 1.76; 95%CI 1.25-2.47; $p<0.001$). Median PFS, OS, and MSS for anti-PD-1 and ipilimumab-nivolumab can be seen in the table.

Table: 859P Median progression-free survival, overall survival, and melanoma-specific survival in months, stratified by hematologic malignancy and treatment type

	Median PFS in months (95% CI)	Median OS in months (95% CI)	Median MSS in months (95% CI)
Anti-PD-1 and HM+ (n=46)	2.8 (2.6-7.3)	12.8 (6.2-NR)	41.2 (12.8-NR)
Anti-PD-1 and HM (n=1717)	9.9 (8.6-11.8)	31.0 (28.5-35.0)	58.1 (47.5-NR)
Ipilimumab-nivolumab and HM+ (n=11)	2.3 (2.0-NR)	4.6 (2.4-NR)	4.6 (2.4-NR)
Ipilimumab-nivolumab and HM- (n=789)	6.9 (5.5-9.2)	31.7 (22.1-39.0)	46.1 (33.4-NR)

Conclusions: Patients with hematologic malignancy and advanced melanoma show significantly worse melanoma-related survival than patients with advanced melanoma alone. Larger numbers of patients are needed to look into the different subtypes of HM.

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860P The IOpener study: Tyrosine kinase activity in peripheral lymphocytes to predict durable response to immune checkpoint inhibition in patients with advanced melanoma

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Background: Immune checkpoint inhibitors (ICIs) have improved survival outcomes for patients with melanoma. Unfortunately, only a minority of patients experiences durable responses, while ICI treatment is accompanied with high toxicity rates and treatment costs. In an effort to predict ICI response, we have previously shown the predictive value of blood-based kinase profiling (Hurkmans et al. JITC 2020). The aim of this prospective study is to identify whether tyrosine kinase activity profiling can predict ICI response in patients with advanced melanoma.

Methods: Patients with irresectable stage III or IV melanoma were included in this multicenter study. Peripheral blood mononuclear cells (PBMCs) were isolated before start of anti-PD-1 treatment. Tyrosine kinase activity profiles of PBMCs were measured using a micro-array comprising 144 different peptide-substrates for tyrosine kinases (Pepscan). Durable response was set as a partial or complete response (RECIST v1.1) $\leq$1 year after treatment initiation and lasting for $\geq$6 months.

Results: The classification model was established based on the tyrosine kinase activity profiles determined in a calibration cohort (N = 71) and applied to an independent validation cohort (N = 75). The validated model had an predictive accuracy (correct classification rate) of 64% (CI_{95} = 52-75%). This accuracy strongly improved (up to 76%; CI_{95} = 60-89%) when only treatment-naive patients or patients without brain metastases at baseline were included in the validated model (38 out of 75 patients). In addition, for the subgroup of treatment-naive patients, the kinome analysis showed a significant difference in the progression-free survival between patients predicted as being a responder versus non-responders.

Conclusions: Tyrosine kinase activity profiling predicts a durable response to ICIs for patients with advanced melanoma. In clinical practice, the model can be further improved when applied in a particular sub-population of patients with melanoma and when used in combination with existing (bio)markers. Finally, after validation of our findings in an ongoing extension study, the final aim is to implement the kinome analysis clinically.

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861P Association of genetic variants in JAK/STAT signaling pathway with cutaneous melanoma susceptibility

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Background: Janus kinase signal transducer and activator of transcription (JAK/STAT) signaling pathway is involved in cell proliferation, angiogenesis, apoptosis inhibition, metastasis, and immune suppression. Due to these multiple functions, this pathway regulates cutaneous melanoma (CM) development and progression. The JAK1, JAK2 and STAT3 proteins are encoded by polymorphic genes. This study aimed to verify whether single-nucleotide variants (SNVs) in *JAK1* (c.1648+1272G>A, c.991-27C>T), *JAK2* (c.-1132G>T, c.-139G>A) and *STAT3* (c.*1671T>C, c.-1937C>G) altered risk, clinicopathological aspects, survival of CM patients, as well as protein activity.

Methods: CM patients (N = 248) and controls (N = 274) were included in this study. Genotyping was performed by real-time polymerase chain reaction (PCR) and *JAK1*, *JAK2* and *STAT3* expression was assessed by quantitative PCR (qPCR). *STAT3* c.-1937C>G SNV was investigated by luciferase, qPCR, western blot, apoptosis, and cell cycle assays in SKMEL-28 cells with CC or GG genotype. In addition, fourteen melanoma cell lines with different genotypes were used to analyze STAT3 expression with non-intervention.

Results: Individuals with *STAT3* c.*1671TT and c.-1937CC genotypes, and TC haplotype of both SNVs were under 2.0-fold increased risk of CM. Specific *JAK1*, *JAK2* and *STAT3* combined genotypes were associated with up to 4.0-fold increased risk of CM. Higher luciferase activity (4,013.34 *vs.* 2,463.32 arbitrary unit (AU); $p = 0.009$), *STAT3* expression by qPCR (649.20 *vs.* 0.04 AU; $p = 0.003$) and western blot (1.69 *vs.* 1.16 AU; $p = 0.01$), and percentage of cells in S phase of cell cycle (57.54 *vs.* 30.73 %; $p = 0.04$) were more frequent in SKMEL-28 with *STAT3* c.-1937CC than with GG genotype. CM cell lines with CC genotype presented higher STAT3 protein levels than those with GG genotype (1.93 *versus* 1.27 AU, $p = 0.0027$).

Conclusions: Our data present for the first-time preliminary evidence that *JAK1*, *JAK2* and *STAT3* SNVs alter risk and clinical aspects of CM patients. If validated in a further epidemiological study, our data can be used to select individuals at high-risk of CM, who should receive special attention in tumor prevention and early detection.

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862P Incidence of hypothyroidism following the use of various immune checkpoint inhibitor regimens in melanoma patients: Meta-analysis

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Background: Among the endocrinopathies the incidence of thyroid disfunction in cancer patients receiving immune checkpoint inhibitors (ICHs) is the highest. The aim of this study was to evaluate the risk of treatment-related hypothyroidism across different ICH regimens that are applied for advanced melanoma treatment. PubMed was searched for phase 2 and 3 randomised clinical trials (RCTs) dedicated to the treatment of advanced melanoma with different ICH regimens. The articles were published from 1/1/2010 until 31/12/2020. 10 RCTs were selected from 124 articles and assessed for the overall risk of bias.

Methods: 10 selected RCTs with 13 different advanced melanoma ICH treatment regimens, that involved a total of 7012 patients, were simultaneously compared using Bayesian network meta-analysis with Markov chain Monte Carlo simulation with non-informative prior distribution and random-effects generalized linear models. Pooled odds ratios (ORs) with 95% credible intervals (CrIs) were used to estimate the risk of hypothyroidism. The ranking of regimens was established using the surface under the cumulative ranking curve (SUCRA).

Results: Overall, comparing the most clinically applied ICH regimens for advanced melanoma treatment such as nivolumab, 3 mg/kg, every 2 weeks, pembrolizumab, 200 mg, every 3 weeks, and the combination of nivolumab, 1 mg/kg, and ipilimumab, 3 mg/kg, every 3 weeks, the lowest risk of any grade treatment-related hypothyroidism AE was associated with pembrolizumab (SUCRA, 97.9%). Although there were no statistically significant differences between these treatments according to ORs with 95% CrIs, the overall SUCRA ranking revealed a tendency that nivolumab (SUCRA, 39.2%) was associated with lower risk of any grade treatment-related hypothyroidism AE than the nivolumab in combination with ipilimumab (SUCRA, 23.7%). No significant differences were identified between treatment regimens associated with severe (grade 3-5) hypothyroidism AE.

Conclusions: Obtained SUCRA ranking tendencies suggest that for patients with advanced melanoma, who have a risk of hypothyroidism, pembrolizumab, 200 mg, every 3 weeks, may be the preferred treatment regimen among the compared ICH.

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863P Elderly patients (pts) with advanced melanoma: Results from the prospective real-world study GEM1801

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Background: Cutaneous melanoma (CM) is suffering an increase in incidence and mortality in recent decades, especially in elderly pts, who experience different biological behavior. Management of CM in elderly pts is conditioned by limited expectations of survival, quality of life and a high incidence of comorbidities. These abstract reviews the treatment elections and the outcomes of elderly pts in the real world setting in Spain, specifically in a prospective manner.

Methods: GEM1801 is a prospective cohort study that analyzes the clinical and pathological disease presentation patterns, the different lines of treatment choices and the health outcomes derived from treatments. Here we focus on elderly pts diagnosed with advanced CM and the first line (1L) of treatment choice.

Results: 357 pts were included since August 2018 to January 2019 from 35 hospitals in Spain, 146 ≥70 y. A survival cutoff was made by March 2022. 57.4% pts were male; median age was 78.3 y (range: 70.2-95.2). 60.1% were cutaneous, 9.5% acral, and 2.7% uveal. 8.1% were unresectable stage IIIB/C/D and 91.9% stage IV (33.8% A, 15.5% B, 27.8% C and 14.9% D). ECOG was 0-1 in 75.6%; LDH levels were normal in 49.3%, elevated in 39.3% (UK: 11.5%). BRAF was mutated in the 34.5% of elderly pts. Median survival follow up was 21.3 months (range: 1.3-46.9) with 36.5% pts alive at time of analysis. Median overall survival was 23.4 m (95% CI: 18.1-30.1) for pts ≥70 y. Table summarizes the 1L options according to BRAF status and age.

Table: 863P

	BRAF -		BRAF +	
Treatment type; n (%)	≥70; N= 95	All; N= 156	≥70; N= 51	All; N = 170
Immunotherapy (IT)	77 (90.6)	148 (94.9)	9 (18)	51 (30.0)
PD-1 / PD-L1 IT	68 (80)	115 (73.7)	9 (18)	36 (21.2)
Dual IT or other IT	9 (10.6)	33 (19.4)	0 (0)	15 (8.8)
Targeted Therapy (TT)	-	-	40 (80)	109 (64.1)
Chemotherapy	1 (1.2)	1 (0.6)	0 (0)	2 (1.2)
Other, Clinical trials	7 (8.2)	7 (4.5)	1 (2)	7 (4.1)

Conclusions: Survival results of elderly pts are consistent with results of modern clinical trials. Either for the overall population or elderly pts in Spain, TT is the most frequent 1L choice in BRAF + pts. Monotherapy with anti PD-1 is the most frequent IT 1L choice.

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864P Prognostic impact of MARCO and OAS1 expression in metastatic melanoma patients treated with anti-PD1: A proteomics and transcriptomics retrospective analysis

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Background: Immune checkpoint inhibitors (ICIs) have rapidly altered the treatment landscape of metastatic melanoma patients. Despite the durability of response to ICI[1,2], many patients with initial response develop resistance[3]. One potential way to overcome the mechanisms of resistance is to identify molecular signatures associated with response to treatment. Here, we are presenting the results of an integrated deep proteomic and transcriptomic analysis from biopsies of metastatic melanoma patients prior anti-PD1 treatment. The combination of whole proteome profiling with targeted transcriptomics allowed for identification of a molecular response signature specific to anti-PD1 therapy.

Methods: Formalin-fixed paraffin-embedded (FFPE) tumor biopsy tissues were used for unbiased whole proteome profiling using Biognosys' TrueDiscovery™ platform and analyzed using an optimized data-independent acquisition (DIA) LC-MS workflow. A deep spectral library was generated, and proteins were quantified using Spectronaut™ software (Biognosys). From the same tumor tissue, RNA was extracted and subjected to transcriptomic analysis with NanoString nCounter using the Pan-Cancer IO 360 panel. Statistical analysis was conducted with R.

Results: Patients were stratified into two groups: those who received clinical benefit (CR/PR or SD>1 year, n= 13) and those with no clinical benefit (PD or SD<1 year, n= 9). Response evaluation was done using RECIST criteria. For each sample 8,536 proteins and 770 RNA were evaluated with an overlap of 419 genes for which both proteomic and transcriptomic data were profiled. In the combined analysis, we found concordant levels for protein and RNA expression, such as STAT2 that is lower in responder group. However, other biomarker candidates such as MARCO and OAS1 showed a higher expression on protein level and a lower RNA expression in the responders.

Conclusions: Combination of deep and proteomics approaches with targeted transcriptomics assays provides a comprehensive image of responses to anti-PD1 treatment in metastatic melanoma patients. Identified candidates show striking changes in responder and non-responder groups and need further investigations.

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865P TNFRSF1B gene variants on susceptibility, clinicopathological aspects, and prognosis of patients with cutaneous melanoma

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Background: Regulatory T lymphocytes (Treg) modulate the destruction of abnormal cells through the binding of tumor necrosis factor (TNF) to tumor necrosis factor receptor 2 (TNFR2) on its surface. The TNFR2 is encoded by the *TNFRSF1B* polymorphic gene, and therefore, healthy individuals may be at distinct risks of CM and CM patients may have tumors of different behaviors. This study aimed to evaluate the roles of *TNFRSF1B* c.587T>G, c.*188A>G, c.*215C>T, and c.*922C>T single nucleotide variants (SNVs) in risk, clinicopathological aspects, and survival of CM patients.

Methods: Genotypes from 433 CM patients and 502 controls were identified by real-time polymerase chain reaction, and gene expression was analyzed by quantitative PCR. Interaction between miR-96 and miR-1271 with 3'-UTR of *TNFRSF1B* gene was evaluated by luciferase reporter assay.

Results: Individuals with c.587TT genotype and individuals aged less than 54 years and with c.587TT genotype were under 1.41- and 1.81-fold increased risks of developing MC, respectively. Patients with c.*922CT or TT genotype, c.587TG or GG + c.*922CT or TT genotype, and TATT haplotype had 2.09, 2.16, and 1.86 more chances of presenting tumor progression, and 2.38, 3.01, and 1.97 more chances of evolving to death due to CM, respectively. *TNFRSF1B* expression was higher in individuals with c.*922TT genotype than in individuals with c.*922CC genotype (2.57 arbitrary units (AUs) ± 0.96 standard deviation (SD) *versus* 1.95 AUs ± 1.22 SD; $P = 0.01$). MiR-1271 showed more efficient binding with *TNFRSF1B* 3'-UTR region encoded by the C allele than by T allele of c.*922C>T SNV (71 *versus* 107%; $P = 0.02$).

Conclusions: The data present preliminary evidence that *TNFRSF1B* c.587T>G and c.*922C>T inherited abnormalities alter risk and clinical aspects of CM, and act as independent prognostic factors in CM. If validated in a further epidemiological study, our data can be used to select individuals at high-risk of CM, who should receive special attention in tumor prevention and early detection, and to select CM patients of high risk, who should receive distinct treatment.

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866P Inflammation proteins associated with worse clinical outcome to treatment with anti-PD1 in metastatic cutaneous melanoma

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Background: In the last decade, treatment with the immune checkpoint inhibitors (ICI) anti-PD-1 and anti-CTLA-4 has improved overall survival (OS) for patients with metastatic cutaneous melanoma (CMM). However, only a subset of patients has long-term benefit from ICI. We have recently identified 43 potential prognostic/predictive proteins in an unbiased proteomics approach in plasma from patients with metastatic CMM. Increased levels of inflammation proteins were associated with shorter progression free survival (PFS) for patients receiving ICI (Karlsson et al Cancer Res. 81(9):2545-2555, 2021). However, in the unbiased proteomics analysis we only detect high-abundant plasma proteins. The aim of this study is to search for predictive biomarkers among low-abundant inflammation proteins in plasma from patients with metastatic CMM receiving anti-PD1.

Methods: Fifty-nine patients were included in the study between 2015 and 2019, 20 females and 39 males. The median age was 70 years old (range 31 – 84). All patients had metastatic CMM (21 M1a, 15 M1b, 17 M1c, 6 M1d). Anti-PD1 was first line treatment for 58/59 patients (one patient received anti-PD1 as 2nd line). Pretreatment plasma samples were analyzed using the OLINK target 96 inflammation platform.

Results: In the OLINK analysis, baseline expression of CXCL9, TNFRSF9, IL-15RA, CX3CL1 and MSP-2 were found to significantly increase with age (adjusted p-value <0.05). Higher IL8 expression was significantly associated with increasing M1 stage (adjusted p-value <0.05) and shorter OS (HR 2.51, 95% CI 1.19-5.29, p-value 0.012) but not with PFS (HR 1.51, 95% CI0.81-2.82, p-value 0.20). IL8, EN-RAGE/S100A12, IL10-RA and DNER were significantly associated with poorer OS (adjusted p-value <0.05). In addition, EN-RAGE/S100A12 expression also correlated to baseline LDH levels (normal vs elevated).

Conclusions: Our findings suggest that a panel of inflammation proteins may predict worse clinical outcome for patients with metastatic CMM receiving anti-PD1. These proteins warrant further investigation as potential additional therapeutic targets.

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867P The association between polygenic risk of autoimmune disease, progression-free survival (PFS), and pathway-level transcriptomic signatures predictive of anti-PD1 response in melanoma

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Background: Germline variation may influence anti-tumour immune responses. Recent studies suggest that polygenic scores (PGS) for autoimmune disease risk are associated with immune-related adverse events in patients (pts) treated with anti-PD(L)-1 therapy (anti-PD1) but the role of PGS in melanoma remains unexplored. We evaluated associations between PGS for vitiligo (VIT) and hypothyroidism (HYPOT) and melanoma molecular and clinical traits.

Methods: PGS for VIT (42 variants) and HYPOT (134 variants) were derived from genome-wide association studies of 29,752 VIT/HYPOT cases + 423,473 controls. The Cancer Genome Atlas (TCGA) melanoma pts (TCGA SKCM; n = 443) were assigned PGS for VIT/HYPOT using their blood genotypes and associations between PGS and tumour gene expression, immune cell infiltrates, and survival examined. Tumour infiltration of 22 immune cell types was quantified by CIBERSORT. Gene expression changes in Hallmark pathways were evaluated by gene set enrichment analysis (GSEA), with false discovery rate (FDR) control. Cox models adjusted for age, sex, and stage were used for survival analyses. PGS-linked differentially expressed pathways in TCGA SKCM were assessed for association by GSEA with anti-PD1 response in on-treatment biopsies with transcriptomic data in an independent cohort of 54 melanoma pts.

Results: In TCGA SKCM, increased polygenic risks of VIT and HYPOT were associated with longer PFS (HR, 95% CI: VIT 0.84, 0.74-0.95; HYPOT 0.90, 0.80-1.01). VIT PGS was associated with increased CD8+ T cells (P = 0.03) and downregulated expression of the G2M cell cycle pathway (FDR = 6e-4). HYPOT PGS was associated with upregulation of interferon α (FDR = 3e-7) and γ (FDR = 2e-6) pathways. Genes driving pathway enrichments in TCGA SKCM were associated with anti-PD1 response on evaluation for expression in on-treatment samples in the independent cohort (FDR < 0.005).

Conclusions: PGS for autoimmune disease associate with PFS and intra-tumour pathway-level transcriptomic changes predictive of anti-PD1 response in melanoma. Since germline PGS can be measured pre-treatment, this may inform prognosis and patient selection if replicated in larger cohorts.

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868P System biology approach to normal tissue protection in cytotoxic cancer therapy: Experimentally validated gene/signaling basis – melanoma as case study

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Background: About 20% of human population recovers from asymptomatic malignancy without treatment, this process is known as spontaneous regression of tumors. There the host has effective immune system, eliminating tumor cells, but protecting normal tissue. Here we develop systems biology approach for analyzing normal tissue protection process, synchronized with tumor regression. We validate our approach by experimental findings.

Methods: We develop a computational System Biology model of coupled differential equations for tumor lysis, keeping normal tissue protected, as estimated by minimization of quadratic toxicity function. We mathematically obtain the temporal variation in level of 3 components which preserve normal tissue: Natural Killer (NK) cells, Circulating Leucocytes, and Interleukin (IL-2). Using microarray analysis of melanoma regression, and bio-informatics modelling, we investigate the temporal profiling and signaling pathways of normal tissue protection as tumor regresses. We also find out the gene expression signature related to the above 3 components.

Results: From mathematical model we find temporal behavior of the normal cell protecting components: (1) *Natural Killer cell activation*: Saturation function; (2) *Interleukin-2 activation*: Uniform function. (3) *Circulating Leucocyte activation*: Saturation function. We use quadratic least damage principle to characterise tumor regression dynamics that would be optimal for host, producing minor damage to normal tissue. Utilizing IPA assessment, our microarray analysis shows temporal behavior of gene expression levels corroborating the above 3 components: NK Signaling pathway (*KLRK1, TVB1* genes), IL-2 Signaling pathway (genes *IL2RG, CD74*), Leukocyte vascular Signaling activity (genes *CCL5, TAC*). Finally, we validate our mathematical model by the experimental findings (Smirnov statistical test satisfied; 5% a).

Conclusions: Normal tissue protection is enabled by chronologically phased alteration of IL-2, NK cells, and circulation leucocytes. Using minimization-maximization algorithm, one may optimize temporal scheduling of chemotherapy/immunotherapy, so that drug-induced side-effects minimize.

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869P PAK4 as a potential marker for poor response to immunotherapy in melanoma patients

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Background: Despite remarkable clinical success with immune checkpoint inhibitor (ICI) therapy targeting the PD-1 pathway for the treatment of melanoma some patients still remain unresponsive to immunotherapy. Using an unbiased mass spectrometry (LC-MS) discovery-based approach we identified a panel of protein biomarkers that correlated with ICI therapy response, one of which was the p21-activated kinase 4 (PAK4) which we found to be significantly elevated in non-responding tumor biopsies. This finding is in line with a previously published study where PAK4 was reported to be enriched in non-responding tumor biopsies and its inhibition was shown to improve PD-1 blockade (Abril-Rodriguez *et al. Nat Cancer* **1,** 46–58 (2020)). For an in-depth analysis of PAK4 in these same patient samples, we followed up with spatial tissue analysis using a multiplexed immunofluorescence (mIF) platform to gain information on PAK4 mechanisms in melanoma patients treated with ICI therapy.

Methods: FFPE tumor samples were firstly used for unbiased whole proteome profiling using TrueDiscovery™, a data-independent acquisition (DIA) LC-MS technology. Baseline patient samples were classified as responders (n = 9) or non-responders (n = 15) based on the response at 3 months post ICI-treatment. Subsequently, the same patient samples were analyzed by an 18-marker custom panel using MultiOmyx™, a multiplexed immunofluorescence (mIF) assay utilizing a pair of conjugated Cyanine dye-labeled antibodies per round of staining coupled with the deep-learning-based cell classification platform NeoLYTX.

Results: PAK4 was found to be elevated in tumor samples from non-responder patients by both unbiased proteomics analysis, as well as MultiOmyx mIF analysis. Furthermore, we observed a clear difference in the correlation to other immune cells between the two patient groups by MultiOmyx analysis, PAK4 density being negatively correlated to T cells and TAMs only in non-responders, while positively correlated to MDSCs only in responders.

Conclusions: Analysis of the 24 FFPE samples from metastatic melanoma patients treated with ICI therapy stratified into responders and non-responders lead to the identification of PAK4 as a potential marker for poor response to immunotherapy in melanoma patient samples.

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870P Systemic levels of the soluble co-inhibitory and co-stimulatory immune checkpoint molecules in basal cell carcinoma

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Background: Although co-inhibitory immune checkpoint proteins are primarily involved in promoting inhibitory cell-cell interactions in adaptive immunity, especially tumor immunity, the soluble cell-free variants of these molecules are also detectable in the circulation of cancer patients where they retain immunosuppressive activity. Nevertheless, little is known about the systemic levels of these soluble co-inhibitory immune checkpoints in patients with various subtypes of basal cell carcinoma (BCC), which is the most invasive and treatment-resistant type of this most commonly occurring malignancy.

Methods: We have measured the systemic concentrations of five prominent co-inhibitory immune checkpoints, namely CTLA-4, LAG-3, PD-1/PD-L1 and TIM-3, as well as those of C-reactive protein (CRP) and vitamin D (VD), in a cohort of patients ($n = 40$) with BCC, relative to those of a group of control participants ($n = 20$), using the combination of multiplex bead array, laser nephelometry and ELISA technologies, respectively. Additionally, in the subsequent study, we measured co-stimulatory checkpoints (CD27, CD28, CD40, ICOS, GITR, GITRL, CD86 and CD80), co-inhibitory checkpoints (PD-1, PD-L1, CTLA-4, TIM-3, LAG-3, BTLA-4) and dual checkpoints (TRL-2 and HVEM).

Results: The median systemic concentrations of CRP and VD were comparable between the two groups; however, those of all five immune checkpoints were significantly elevated ($P = 0.0184 - P < 0.00001$), with those of CTLA-4 and PD-1 being highly correlated ($r = 0.87$; $P < 0.00001$). The levels of CD27, CD28, CD40 and other immune checkpoint levels will be presented at the time of the meeting as this study is ongoing.

Conclusions: This novel finding identifies the existence of systemic dysregulation in BCC and underscores the therapeutic promise of immune checkpoint targeted therapy, as well as the potential of these immune checkpoint molecules to serve as prognostic/predictive biomarkers in BCC.

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871P Predictive role of neutrophil-lymphocyte ratio (NLR) in patients (pts) with metastatic melanoma: A post hoc exploratory analysis from phase III COMBI-i trial

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Background: An elevated NLR is associated with poor survival in pts with a variety of solid cancers, including those treated with immunotherapies. Based on literature, NLR ≥ 5 was identified as a cutoff for NLR elevation in the metastatic setting. This post hoc exploratory analysis from COMBI-i trial aimed at evaluating the potential predictive role of NLR in pts with BRAFV600—mutant advanced melanoma who received spartalizumab + dabrafenib + trametinib (Sparta-DabTram) versus (vs) placebo + dabrafenib + trametinib (placebo-DabTram).

Methods: All pts enrolled in COMBI-i trial (NCT02967692) were included in this analysis (Sparta-DabTram, n=267; placebo-DabTram, n=264). NLR values at baseline and subsequent treatment (Tx) cycles (up to cycle 7) were calculated and analyzed, along with other variables, and correlated with progression-free survival (PFS) using Kaplan—Meier curve.

Results: Baseline NLR values ranged from 2 to 4 for most of the pts in either of the Tx arms that reduced to 1-3 upon Tx. Survival tree analysis indicated that in pts receiving placebo-DabTram, the threshold NLR value obtained through mathematical model was associated with poor PFS outcome in pts with baseline NLR ≥ 1.693 (n=114) vs <1.693 (n=19). In pts with NLR ≥ 1.693, those with sum of the longest diameter (mm) ≥ 61 (n=43) had worst PFS outcome. Baseline NLR ≥ 1.693 was associated with poor PFS outcome in placebo-DabTram arm vs Sparta-DabTram arm. Literature-based cutoff for baseline NLR ≥ 5 was associated with shorter mPFS in placebo-DabTram arm (n=37) vs Sparta-DabTram arm (n=40; hazard ratio, 0.642 [95% confidence interval, 0.377-1.1]).

Conclusions: The findings from this study suggest that NLR is an independent factor predicting poor PFS outcome in pts with metastatic melanoma treated with the combination of immune checkpoint inhibitors and targeted therapy. Sparta-DabTram showed benefit in pts with poor prognostic factors, such as increased NLR and sum of target lesions compared to placebo-DabTram arm. The predictive value of NLR and the selected threshold will have to be validated in future studies.

Clinical trial identification: NCT02967692.

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872P Ipilimumab-induced gastrointestinal and hepatic immune-related adverse events: A national cohort

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Background: There is a paucity of population-based data regarding ipilimumab-induced gastrointestinal and hepatic immune-related adverse events (irAE) during cutaneous melanoma treatment. We examined the risk and predictors of gastrointestinal and hepatic irAE in a national cohort of patients diagnosed with cutaneous melanoma.

Methods: This retrospective study used Surveillance, Epidemiology and End Results - Medicare linked data of patients diagnosed with cutaneous melanoma between the years 2010 and 2015 treated with ipilimumab or other therapies. We excluded patients with preexisting gastrointestinal and hepatic conditions. Our endpoint was time to gastrointestinal and hepatic irAE after treatment. We used multivariable competing-risk analysis adjusted for death of any cause within one year of treatment as a competing event to estimate the risk of gastrointestinal and hepatic irAE. Then, we used a stepwise competing-risk model to assess the predictors of having at least one gastrointestinal and hepatic irAE among patients treated with ipilimumab. The covariates included were patient demographics, disease stage, prevalent autoimmune disease, history of hypertension, anticoagulant use, end-stage renal disease, steroid use, and Charlson Comorbidity Index.

Results: Overall, 620 out of 31,234 (2%) patients were treated with ipilimumab. Incidence rates of gastrointestinal and hepatic irAE among patients who received ipilimumab and controls were 32.3 and 4.0 per 1,000 person-years, respectively. Receiving ipilimumab was associated with an increased risk of gastrointestinal and hepatic irAE compared to controls (HR: 10.18, 95% CI: 8.11-12.78, p<.001). Other predictors of gastrointestinal and hepatic irAE are found in the table.

Table: 872P Significant predictors of gastrointestinal and hepatic immune-related adverse events

	Entire Cohort (n = 31,234)			Ipilimumab Cohort (n = 620)		
Covariant	Hazard Ratio †	95 % Confidence Interval	p-value	Hazard Ratio ‡	95 % Confidence Interval	p-value
Ipilimumab	10.18	8.11 — 12.78	<.001	NA	NA	NA
Year of Diagnosis	0.88	0.84 — 0.91	<.001	-	-	-
Gender	1.20	1.04 — 1.38	=.011	-	-	-
Charlson Comorbidity Index	1.48	1.09 — 2.01	=.011	-	-	-
Autoimmune Disease	1.53	1.25 — 1.88	<.001	0.26	0.09 — 0.83	=.023
Hypertension	1.53	1.28 — 1.83	<.001	-	-	-
Anticoagulant	1.34	1.11 — 1.60	=.002	-	-	-

- Not significant at 0.05 threshold † Competing risk model (Fine & Gray method) ‡ Stepwise competing risk model.

Conclusions: Patients treated with ipilimumab had higher risk of gastrointestinal and hepatic irAE than controls.
Among patients who received ipilimumab, history of autoimmune disease was associated with lower risk of irAE.

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873P Feasibility of a comprehensive ambulatory monitoring platform during immunotherapy for advanced melanoma: CAMP-IT trial

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Background: Ambulatory monitoring using wearable devices combined with online symptom monitoring in a home-based setting could improve quality of care for patients during imunotherapy. The aim of this study was to evaluate the feasibility of the online CAMP-IT platform and explore the first results of the Fitbit and patient-reported outcome (PRO) data generated by the platform.

Methods: Consenting patients with advanced melanoma, scheduled to receive treatment with immune checkpoint inhibitors (ICIs) were connected to the platform consisting of Fitbit, smart thermometer, and smartphone app for 12 weeks after start of ICIs. Participants were asked to complete a weekly PRO-CTCAE survey (15 items) in the app, take daily temperature measurements and wear the Fitbit continuously. Weekly averages of Fitbit-measured daily steps were calculated and changes over time were analyzed using linear mixed effect models. Feasibility was determined in terms of compliance rates with questionnaires and temperature measurements (> 75%) and for Fitbit use recording at least 100 steps for at least 75% of assigned days. At follow-up, satisfaction was scored on a 0-10 scale.

Results: A total of 41 out of 44 eligible patients were included. Median age was 59 (range 30-74) years and 51% was female. Metastatic disease was present in 44% of patients and 32% received combination ICI therapy. Mean compliance with temperature measurements, PRO-CTCAE surveys and Fitbit was 76%, 86%, and 96%, resp. Mean daily steps in week 1 was 6997 (SD 3306) and did not decrease significantly over time (p =0.72). Grade 3 AEs occurred in 43% of patients and the most commonly reported grade 3 AEs were fatigue (30%), headache (20%), and shortness of breath (15%). Presence of grade 3 AEs was accompanied with significant lower activity levels in matching weeks compared with absence (median steps: 5269 vs 7911, resp., p <0.001). Overall satisfaction rating was 7.5.

Conclusions: The use af a comprehensive ambulatory monitoring platform is feasible and acceptable in patients receiving ICIs for advanced melanoma. Combining objective data from wearable devices with PROs offers new possibilities in ambulatory monitoring of AEs. Future studies should examine their value in early detection of AEs.

Clinical trial identification: NL8827 (21-08-2020).

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874P The economic burden of surviving malignant melanoma

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Background: This cost-of-illness study analyses the socio-economic burden of malignant melanoma survivorship for the ten years following initial treatment in Germany during 2000, 2010, and 2020.

Methods: We developed a patient-level micro-costing approach that considers direct and indirect medical expenses resulting from cancer follow-ups to estimate the economic spending on malignant melanoma survivorship. The frequency of recommended follow-up procedures was obtained from German guidelines. Direct medical expenses were derived from literature and official scales of tariffs, whilst indirect expenses were estimated based on opportunity costs. Follow-up-related costs were estimated in a cohort of 1,000 patients. Expenditure arising for patients, healthcare providers (including physicians and nurses), and insurers were combined to calculate societal costs.

Results: Mean ten-year follow-up costs for the society amounted to 5,081€ (95% CI: 4,164-6,151) for stage IA, 8,957€ (95% CI: 7,642-10,539) for stage IB-IIB, and 12,434€ (95%CI: 10,843-14,242) for stage IIC-IV malignant melanoma survivors in 2020. Total societal expenditure surged by +17% from 2000 to 2020 (p<0.001). Costs were shifted from patients and physicians to insurers, who reduced their reimbursement rates from 29% in 2000 to 21% in 2000. Resources consumption comprised physician-

patient consultations and self-examinations (65%), blood tests (5%), diagnostic imaging (9%), and travel expenditure (21%). Expenses mainly arose during the first two years after initial treatment, which entailed more frequent and resource-intensive consultations (years 1-2: 37%, years 3-5: 34%, years 6-10: 29%).

Conclusions: The introduction of general practitioner-led screenings, improved diagnostics, and novel anti-cancer medicines decreased cancer mortality rates; ultimately leading to a surge in the population of cancer survivors. This study highlights the rising socio-economic burden of malignant melanoma survivorship. Policy makers should explore risk-stratified follow-ups to provide more personalized care for survivors. Individualized, evidence-based, and insurance-covered follow-ups are required to early detect side-effects, metastasis, and secondary malignancies.

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875P Trends in melanoma incidence among women living in North-East Italy 2000-2020: Population-based study

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Background: Among Italian people under 50 years of age, cutaneous melanoma (CM) represents the third most common incident cancer in women. This study aims to describe trends in CM incidence among women residing in Friuli Venezia Giulia region (FVG), North-East Italy from 2000 to 2020.

Methods: A descriptive study was conducted using de-identified data from the population-based regional Cancer Registry. To describe CM incidence among women residing in FVG from 2000 to 2020, descriptive statistics and age-standardized incidence rates (ASR) were estimated according to calendar period, age at diagnosis, histology, cancer site and stage. To assess temporal trends, annual percent change (APC) in rates, and 95% confidence intervals (CI), were computed using Joinpoint regression analysis.

Results: etween 2000 and 2020, 3292 CM cancer cases were newly diagnosed among women residing in FVG. ASR were stable until 2013 (APC=1.4, IC95%: -0.2 to 3.1), they increased from 2013 to 2018 (APC= 13.5%, IC95%: 4.7 to 22.9), and they thereafter slightly decreased (not significantly) until 2020 (APC=-13.1, IC95%: -31.2%-+9.7%). Increased ASR (/105 per year) were documented for all age classes: from da 10.5 to 18.0 cases for women aged < 50; from 23.3 to 49.3 cases for those aged 50-69; and from 33.2 to 54.4 cases for those aged 70+. The trunk turned out to be the anatomic site with the highest increase in incidence rates, from 4.4 cases/105 per year in 2000-2004 to 11,4 cases/105 per year in 2015-2019. The proportion of CM diagnosed in advanced stage (Breslow thickness $>$ 4mm) decreased from 13,6% in 2008 to 4,7% in 2020.

Conclusions: CM incidence increased among women of all ages living in FVG,from 2000 to 2018, with a slight decrease in 2019-2020. These results support the importance of enhancing primary and secondary prevention programs among FVG women.

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876P An observational retrospective study on microsatellite instability (MSI) in metastatic melanoma

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Background: Microsatellite instability (MSI) has been reported in skin melanoma and is thought to be a progression dependent phenomenon seen predominantly on metastases. However, a paucity of data is available about frequency, predictive and prognostic value of MSI in melanoma, in particular using the pentaplex panel of markers approved for colon cancer. Primary aim of this study was to provide a descriptive analysis of the presence of MSI in distant melanoma metastases, regardless of BRAF status and type of first-line treatment.

Methods: The study retrospectively reviewed a consecutive series of patients with stage IV melanoma who were treated from January 2011 to December 2018 at the Academic Hospital of Udine, Italy. Archival tumor tissue of the metastases was available for all patients and the sample temporally closest to the first-line treatment start was selected to evaluate MSI status with a pentaplex panel of mononucleotides markers (NR-27, NR-21, NR-24, BAT-25, and BAT-26). The study protocol was approved by the Ethical Committee of the Italian Friuli-Venezia Giulia Region (protocol n. 0025936) and written informed consent for analysis on archival tissue was obtained for all the alive patients.

Results: Overall, we included 90 patients: 63.3% males and 36.7% females. Median age at the first-line treatment start for stage IV melanoma was 68 years (range 30-87). In detail, 18.9%, 15.6%, 41.1% and 24.4% presented with stage M1a, M1b, M1c and M1d, respectively, of which 18 had *de novo* metastatic disease. A BRAF V600 mutation was present in 44.4% of cases and in 28.9% of patients LDH value was above the upper normal limit. The metastases sample was most frequently obtained from skin and subcutaneous tissue (30.0%), followed by lymph nodes (28.9%), lung (17.8%), liver (6.7%), central nervous system (5.6%) and other sites (11.0%). Microsatellite stability (MSS) was detected in 81 of 82 (98.8%) evaluable metastatic tissue samples.

Conclusions: A low frequency of MSI (1.2%) in distant melanoma metastases was found in our retrospective observational study. In order to evaluate the possible predictive and prognostic role of MSI in metastatic melanoma, further research is needed.

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877P Characteristics of malignant cutaneous adnexal tumors in a single-institution study

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Background: Malignant cutaneous adnexal tumors (MCATs) comprise a heterogeneous group of rare neoplasms. Little is known about their natural history, with limited information regarding prognostic factors and long-term outcomes described.

Methods: In this single-center retrospective cohort study, we included patients diagnosed with MCATs between 2014 and 2021. Clinicopathologic variables and outcome measures were analyzed. X^2, Fisher's exact and Mann-Whitney U tests were used to compare groups and Cox proportional hazards models were fitted. The log-rank test was used to assess recurrence free survival (RFS) and overall survival (OS).

Results: We identified 114 patients with MCATs. Characteristics are displayed in table. The most frequent histological subtypes were porocarcinoma in 41 (36%), sebaceous carcinoma in 28 (25%) and eccrine carcinoma in 17 (15%) patients. Porocarcinoma was significantly associated with organ-transplant and hematological cancer ($p=0.03$), and other skin cancers ($p < 0.01$). Disease recurred following surgical resection in 24 patients (21%) and median RFS was 68 months (95% CI 45.7-90.3). Head and neck tumors ($p=0.05$), larger size ($p=0.04$) and higher stage ($p<0.01$) were associated with increased risk of recurrence. Among 49 patients with stage I, 34 underwent completion of surgical resection after excisional biopsy, and it was associated with a

longer OS (HR: 0.26 95% CI 0.08-0.78 p=0.01). Only 13 (11%) patients had stage IV disease at diagnosis, and the most common site of metastasis was the lung. Median OS for stage IV was 37 months (95%CI 20.6-53.3) (median follow-up 17 months). Median follow-up was 24 months for patients with localized disease and median OS was not reached (95% CI NE).

Table: 877P

	MCATs - n (%)
Age (years) — median (range)	73 (27-95)
Sex male	75 (66)
Histology groups Sweat gland Sebaceous Follicular	83 (73) 28 (25) 3 (2)
Primary site Head and neck Trunk Extremities	73 (64) 15 (13.2) 26 (22.8)
Comorbidities Organ transplant Hematological cancer Other skin cancer	25 (22) 8 (7) 54 (47)

Conclusions: Patients with MCATs have a good prognosis when detected early and are adequately resected. Careful dermatological surveillance in immunosuppressed patients is warranted.

Legal entity responsible for the study: The authors.

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Disclosure: E.C. Koch: Financial Interests, Personal, Invited Speaker: Novartis, MSD; Financial Interests, Personal, Advisory Board: Novartis, MSD; Financial Interests, Institutional, Other, Funding: Alamos Gold Inc.; Financial Interests, Institutional, Research Grant: Novartis. M. Vilbert: Financial Interests, Institutional, Funding: Alamos Gold Inc. T. Pimentel Muniz: Financial Interests, Institutional, Research Grant: Novartis; Financial Interests, Institutional, Funding: Alamos Gold Inc. S. Saibil: Financial Interests, Personal, Advisory Board: Novartis. A. Spreafico: Financial Interests, Personal, Advisory Board: Merck, Bristol Myers Squibb, Oncorus, Janssen, Medison & Immunocore; Financial Interests, Institutional, Research Grant: Novartis, Bristol Myers Squibb, Symphogen AstraZeneca/MedImmune, Merck, Bayer, Surface Oncology, Northern Biologics, Janssen Oncology/Johnson & Johnson, Roche, Regeneron, Alkermes, Array Biopharma/Pfizer, GSK, Oncorus, Treadwell, Amgen. M.O. Butler: Financial Interests, Personal, Advisory Board: Bristol Myers Squibb, EMD Serono, GlaxoSmithKline, Immunocore, Merck, Novartis, Pfizer, Sanofi; Financial Interests, Institutional, Research Grant: Merck; Financial Interests, Personal, Other, Safety Review Board: Adaptimmune, GlaxoSmithKline. All other authors have declared no conflicts of interest.

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878P Improved proteome coverage for cancer plasma-derived extracellular vesicles (pEVs) using high-resolution isoelectric focusing (HiRIEF) LC-MS

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Background: The pEVs have strong potential to be used as clinical biomarkers in various pathological conditions by providing unique, additional proteomics information that could not be obtained from plasma alone. Our study provides an advanced proteomics workflow for in-depth proteome profiling and detection of disease-specific proteins present in plasma and pEVs.

Methods: Size-exclusion chromatography-based columns were used for EV isolation from plasma. The particle size, concentration, and distribution of pEVs were characterized using the Coomassie brilliant blue protein gel staining, nanoparticle tracking analysis, and flow cytometry bead-based assay. For workflow optimization pEVs (healthy donor plasma) proteome was generated using long-gradient (LG) and HiRIEF methods. The workflow performance was validated using a cohort of 6 metastatic melanoma (MM) and 6 lung adenocarcinoma (LUAD) patients. HiRIEF pre-fractionation and tandem mass tags (TMT)-16plex based peptide quantification, was used to generate cancer pEVs and corresponding albumin-depleted plasma proteomes.

Results: We achieved high proteome coverage in pEVs, and detected traditional EV-marker proteins (CD81, CD9, HSPA8, FLOT1/2, LGALS3BP, HSP90AA1/AB1), ESCRTs, and several other EV-specific proteins associated to cargo selection, trafficking/sorting, and exosome biogenesis. Some well-known clinical biomarkers for LUAD and MM, as well as many other cancer-related proteins, were present in the cancer cohort plasma and pEVs. The differentially expressed proteins (DEPs) in pEVs and plasma show no overlap, supporting the unique protein information carried by pEVs in plasma. Some of the DEPs identified in pEVs and plasma are frequently reported as prognostic biomarkers for LUAD and MM.

Conclusions: We present an optimized workflow for extensive proteome profiling of plasma and pEVs in parallel using the advanced HiRIEF LC-MS method. The workflow exhibits high proteome coverage and the ability to detect potential disease-specific markers in pEVs enriched from clinical plasma samples.

Legal entity responsible for the study: Cancer Proteomics Mass Spectrometry Group.

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Disclosure: All authors have declared no conflicts of interest.

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879P Whole-genome landscape of head and neck melanomas in East Asia (China)

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Background: Head and neck melanomas are a heterogeneous group of tumors that may arise from abnormal melanocytes in various sites, such as scalp of the head, conjunctiva, nasal pharyngeal and oral cavity.Despite their close anatomical location, melanomas from different sites of the head and neck have widely different histological structures, biological behaviors, genetic characteristics, and prognosis. However, researches on genomic landscape of head and neck melanoma in East Asian patients are still sparse.

Methods: We performed whole-genome sequencing (WES) and clinical profiling on 40 head and neck melanoma samples, including 8 conjunctival melanoma of the eyes, 7 scalp of the head, 10 nasal and 15 oral cavity. All the samples were derived from East Asian populations.

Results: We show that tumors from eyes and head tended to harbor more substitution/indel (SNVs) than those from nasal and oral. Percent of the genome affected by copy number variants was no significant differences among the four sites. Head and neck melanomas samples had more genetic aberations in genes within the RTK-RAS pathway and NOTCH pathway. BRAF, NRAS were identified as significantly mutated genes (SMGs).Eyes and head tumors had consistent mutational signature, while the oral and nasal tumors had similar mutationnal signature. The number and type of structural rearrangements varied dramatically among the four sites, suggesting the implication of distinctive mutational processes. Somatic arm level CNV alterations including amplification at chromosomes 1q, 6p, 7 and deletions at chromosomes 6q, 10, 13q, 16q, 18p, 19.Significantly amplified regions, included those containing 1q22(MUC1), 3p13(MITF), 4q12(KIT), 5p15.33 (TERT), 6p23, 7p22.1(RAC1), 8q24.3(MYC), 9q34.3(NOTCH1),11q14.1(PAK1,GAB2), 12q14.1(CDK4), 17q25.1, 20q13.2. as well as deleted regions 3q22.2, 6q26, 9p21.3-24.3(CDKN2A,CDKN2B), 10q26.13, 11q23.3, 16p12.1, 11q22.3(ATM).

Conclusions: Here, we provided a detailed view of the genomic landscape of East Asian head and neck melanomas at different sites, which might extend our current understanding of head and neck melanoma.

Legal entity responsible for the study: Peking University Cancer Hospital and Institute.

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880P Phase II trial of the cyclin dependent kinase 4/6 inhibitor SHR6390 in patients with advanced head and neck mucosal melanoma harboring CDK4 amplification

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Background: Mucosal melanoma (MM) is a rare but devastating subtype of melanoma with 5-year survival rates ranging from only 16% to 25%. Our previous studies have demonstrated robust anti-tumor effects of CDK 4/6 inhibitors in head and neck MM (HNMM) patients (pts) derived xenograft models with CDK4 amplification. We performed a phase II study to determine the efficiency and safety of SHR6390, a CDK4/6 inhibitor, in pts with HNMM harboring CDK4 amplification.

Methods: In this phase II trial, advanced recurrent and/or metastatic HNMM pts with CDK4 amplification were treated with SHR6390 125 mg once daily for 21 consecutive days in 28-day cycles. The primary endpoint was disease control rate (DCR) per RECIST

v1.1, which included complete response (CR), partial response (PR), stable disease (SD). Secondary endpoints included safety, objective response rate (ORR) and progression free survival (PFS).

Results: Up to Apr 2022, 17 pts who have failed ≥1 prior therapies were enrolled in this study. The median age of the pts was 56 years (ranged 29-73 years), 8 pts (47.1%) were male. All pts had ECOG PS 1, 10 pts (58.8%) had received chemotherapy treatment, and 11 pts (64.7%) had received prior PD-1 inhibitor therapy. Of 15 evaluable pts, 11 pts had SD and the best clinical response was a PR in one pt. The PR is still ongoing for more than 13 months (tumor shrinkage >80%). The ORR and DCR were 6.7% and 80.0%, respectively. With a median follow-up of 10.1 months, the estimated median PFS was 5.5 months, and the median OS was not reached. At data cutoff, 7 pts remained on treatment. Treatment-related adverse events (TRAEs) occurred in 100.0% of pts, and most TRAEs were grade 1-2. The most frequent AEs were neutrophil count decreased (64.7%), white blood cell count decreased (64.7%), and fatigue (41.2%). Only 1 pt experienced grade 3 neutrophil count decreased and white blood cell count. No grade 4/5 AEs were reported.

Conclusions: This study showed that SHR6390 was well-tolerated and appeared to be effective in HNMM pts harboring CDK4 amplification, which hints that it's worthy to further explore SHR6390 in combination with other drugs in the systemic treatment of advanced MM.

Clinical trial identification: ChiCTR2000031608.

Legal entity responsible for the study: The authors.

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881TiP NEOplus: A phase II study of neoadjuvant lenvatinib and pembrolizumab in resectable mucosal melanoma

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Background: Mucosal melanoma is a rare type of melanoma in the Caucasian population and a dominate subtype in Asia, which generally carries a worse prognosis than cutaneous melanoma. Surgery remains the primary therapeutic intervention for mucosal melanoma. Pembrolizumab showed modest objective response rate (ORR, 13%) in advanced mucosal melanoma in the Chinese population (NCT02628067). Recent study has also demonstrated neoadjuvant therapy with pembrolizumab could lead to pathological response which associated with reduced risk of recurrence and improved survival. Lenvatinib is also a kinase inhibitor that inhibits the kinase activities of VEGFR1,2, 3, which has been approved by the FDA for differentiated thyroid cancer, advanced renal cell carcinoma and hepatocellular carcinoma. This trial hypothesize that neoadjuvant combination of pembrolizumab and lenvatinib may enhance anti-tumor activity and prolong RFS and OS in resectable mucosal melanoma.

Trial design: NEOplus(NCT04622566) is a single-arm, open-label phase 2 trial evaluating the efficacy and safety of neoadjuvant with lenvatinib and pembrolizumab in resectable mucosal melanoma. Newly diagnosed resectable mucosal melanoma patients without any previous anti-cancer treatment may be included. Twenty-six patients will be enrolled in this study and will received pembrolizumab (200mg IV, Q3W) in combination with lenvatinib (20mg QD) for 6 weeks before surgery. Pembrolizumab (200mg IV, Q3W) will be as adjuvant treatment for 15 cycles until the disease progresses or intolerable toxicity. The primary endpoint is complete pathologic response (pCR), which is defined as no residual tumor cells in tumor bed or lymph nodes. Secondary endpoints are pathologic response which include pCR, MPR and pPR (MPR was defined as less than 10% of residual viable tumor cells. pPR was defined as less than 50% residual viable tumor cells); relapse-free survival (RFS), overall survival (OS) and safety etc. Enrollment began in Oct 2021.

Clinical trial identification: NCT04622566.

Legal entity responsible for the study: The authors.

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882TiP Subcutaneous vs intravenous nivolumab in patients with melanoma following complete resection

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Background: Nivolumab (NIVO), a programmed death-1 immune checkpoint inhibitor, is approved globally as an effective treatment across multiple cancer types. Several studies are investigating subcutaneous (SC) NIVO, co-formulated with recombinant human hyaluronidase PH20 (rHuPH20), as it may benefit patients, clinicians, and the healthcare system. Patients with cancer often prefer SC over IV administration. SC dosing may alleviate the need for IV vein ports, lower the risk of dosing errors, allow more patient flexibility, and reduce dose preparation and administration times, thereby optimizing occupancy in infusion centres. In CheckMate 8KX, SC NIVO + rHuPH20 was well tolerated in patients with different solid tumours and exposures were comparable to IV NIVO 3 mg/kg Q2W (from historical data). Investigations of SC NIVO vs IV NIVO in patients with clear cell renal cell carcinoma (phase 3 CheckMate 67T study) or melanoma following complete resection are ongoing.

Trial design: CheckMate 6GE is a multicentre, randomized, open-label, phase 3 study evaluating the pharmacokinetic (PK) noninferiority of SC NIVO + rHuPH20 vs IV NIVO in patients with melanoma following complete resection. Inclusion criteria are stage IIIA/B/C/D or stage IV melanoma, complete resection ≤ 12 weeks before randomization or treatment assignment, and ECOG performance status ≤ 1. Key exclusion criteria include a history of uveal/mucosal melanoma, untreated/unresected CNS metastases, concurrent malignancy or history of prior malignancy active ≤ 2 years before randomization or treatment assignment, known or suspected autoimmune disease, serious/uncontrolled medical disorder 4 weeks before screening, and prior immunotherapy. Patients (N ≈ 286) are randomized (1:1) to receive SC NIVO or IV NIVO in part 1 (stratified by stage [IIIA/B vs IIIC/D/IV] and weight [< 80 kg vs ≥ 80 kg]) or enrolled in the part 2 PK cohort. PK, safety, efficacy, immunogenicity, and cancer treatment satisfaction will be evaluated (Table).

Table: 882TiP

Primary endpoints
Time-averaged NIVO serum concentration over the first 28 days
C_{min} at steady state
Secondary endpoints
Safety and tolerability, eg, AEs, serious AEs, immune-mediated AEs, death, administration-related reactions, laboratory abnormalities
Recurrence-free survival
Overall survival
Additional PK parameters: C_{min} on Day 28, C_{max} after the first dose, time to C_{max} after the first dose, C_{max} at steady state, time-averaged NIVO serum concentration at steady state
Immunogenicity (anti-NIVO and neutralizing antibodies)
Cancer Treatment Satisfaction Questionnaire

AE, adverse event; C_{max}, maximum NIVO serum concentration; C_{min}, minimum NIVO serum concentration.

Clinical trial identification: NCT05297565.

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883TiP A phase I/II open-label study (IOV-GM1-201) of TALEN-mediated PD-1 inactivated autologous tumor-infiltrating lymphocytes (TIL; IOV-4001) in patients with advanced melanoma and NSCLC

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Background: Adoptive cell therapy with TIL has demonstrated efficacy in patients (pts) with advanced solid tumors, including melanoma (Sarnaik JCO 2021) and NSCLC (Schoenfeld SITC 2021). IOV-4001 is a TALEN®-mediated *PDCD-1* knockout autologous TIL cell therapy product. Preclinical studies suggest that PD-1 inactivation by *PDCD-1* gene knockout may enhance TIL cell therapy efficacy, with similar quality attributes and phenotypes to those of non-edited TIL (Natarajan AACR 2022).

Trial design: This first-in-human phase 1/2, open-label, nonrandomized, multicenter study (NCT05361174; open to enrollment) will enroll ~53 adult pts. During the phase 1 portion, enrollment and dose level decisions will be based on emerging safety and tolerability data in a 28-day dose-limiting toxicity (DLT) observation period. Cohort 1 will include pts with unresectable/metastatic melanoma that has progressed during/within 12 wks of last anti−PD-1/PD-L1 dose (pts must have also received a BRAF ± MEK inhibitor if *BRAF V600* mutation-positive). Cohort 2 will include pts with advanced NSCLC who have received ≤3 prior therapies and whose disease progressed either: (1) during/within 12 wks after last anti−PD-1/PD-L1 dose (pts without oncogene-driven mutations) or (2) during/after ≥1 targeted therapy and either platinum doublet chemotherapy or during/within 12 wks after last anti−PD-1/PD-L1 dose (pts with oncogene-driven tumors). Pts must have ECOG PS ≤1, ≥1 resectable lesion(s) (≥1.5 cm), ≥1 remaining RECIST-measurable lesion(s) and recovered from prior surgery/anticancer treatment-related AEs (grade ≤1). IOV-4001 is generated from resected tumor in a centralized GMP process. The regimen includes non-myeloablative lymphodepletion, IOV-4001 infusion, and a short course of high-dose IL-2. The primary endpoints of phases 1 and 2 are safety (DLTs and AEs) and objective response rate per RECIST v1.1, respectively. Secondary endpoints include complete response rate, duration of response, disease control rate, progression-free survival, overall survival, feasibility, and additional safety.

Clinical trial identification: NCT05361174.

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884TiP A phase Ib/II multicenter, randomized, umbrella study evaluating novel treatment combinations in melanoma (MORPHEUS-MELANOMA)

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Background: Immune checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) have improved overall survival (OS) in patients (pts) with advanced melanoma, and neoadjuvant ICIs can induce tumor regression in pts with resectable melanoma. Targeting other co-inhibitory receptors, such as lymphocyte activation gene-3 (LAG-3) or T cell immunoglobulin and ITIM domain (TIGIT), or combining agents targeting multiple immune evasion mechanisms may enhance antitumor activity.

Trial design: MORPHEUS-MELANOMA (NCT05116202) is a phase 1b/2 multicenter, randomized, open-label, umbrella study in pts with treatment-naive, resectable stage III (Cohort 1) or previously treated stage IV (Cohort 2) melanoma. Cohort 1 pts will be randomized to receive 6 weeks of neoadjuvant treatment in 1 of 3 experimental arms (RO7247669 [bispecific anti−PD-1/anti−LAG-3], atezolizumab [anti−PD-L1] + tiragolumab [anti−TIGIT], or RO7247669 + tiragolumab) or a comparator arm (nivolumab 3 mg/kg [anti−PD-1] + ipilimumab 1 mg/kg [anti−CTLA-4]). Pts will be stratified by region (Australia vs Rest of World) and lactate dehydrogenase (≤ vs > ULN). Cohort 2 pts will receive experimental treatment with RO7247669 + tiragolumab until unacceptable toxicity or loss of clinical benefit; new arms may be added as new treatments become available. The study will enroll ~61-191 pts, including ≥ 6 pts in a safety run-in phase in Cohort 2. Experimental arms will enroll in a preliminary phase (20 pts per arm) and an expansion phase (20 additional pts per arm). Primary end point for Cohort 1 is pathologic response rate at surgery by independent review; secondary end points are pathologic response by local assessment, event-free survival, recurrence-free survival, OS, objective response rate (ORR), and safety. Primary end point for Cohort 2 is ORR by investigator assessment; secondary end points are progression-free survival, OS, duration of response, disease control rate, and safety. Biopsies will be collected at baseline, in cycle 2 (both cohorts), and at surgery (Cohort 1). The study is currently enrolling, with 21 sites planned in Australia, Europe, and USA.

Clinical trial identification: NCT05116202.

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885TiP The I-PACE study: Imgatuzumab in PAtients with advanCEd cutaneous squamous cell carcinoma (aCSCC)

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Background: Imgatuzumab (formerly known as GA201, RO5083945) is a humanized monoclonal antibody against the epidermal growth factor receptor (EGFR), glyco-engineered for enhanced antibody-dependent cellular cytotoxicity (ADCC). It exhibited superior ADCC compared with cetuximab which translated into prolonged survival in several murine xenograft models. Its clinical anti-tumor activity and manageable safety profile as monotherapy and in combination with chemotherapy was demonstrated in previous trials that enrolled 296 patients with advanced solid tumors, including colorectal, head and neck and non-small cell lung cancers. aCSCC overexpresses EGFR and lacks effective treatments after anti-PD-1 failure.

Trial design: This is an open-label, multicenter, single-arm phase 2 study to investigate activity, safety, tolerability, immunogenicity, pharmacokinetics, pharmacodynamics and quality of life of imgatuzumab monotherapy in patients with aCSCC. The primary endpoint is overall response rate assessed by an Independent Central Review Committee. The study is conducted according to a two-stage, optimal Simon's design. Imgatuzumab will be given at the dose of 1,400 mg as an intravenous infusion on Day 1, 8, and subsequently every two weeks. Key eligibility criteria include (a) metastatic (regional or distant) disease or locally advanced disease not amenable for any therapy having curative potential, (b) measurable disease as per the Study Response Criteria (SRC), (c) patients must have received systemic treatment with anti-PD1 agents for advanced disease, unless medically contraindicated (d) no more than two prior lines of systemic treatment for advanced disease (e) no prior anti-EGFR therapy for advanced disease, (f) adequate organ function, (g) availability of tumor tissue sample (archival specimen or fresh biopsy material) at screening. It is estimated that 87 patients will be enrolled in total across 5 countries (Australia, USA, France, Germany, Canada).

Clinical trial identification: NCT04985825.

Legal entity responsible for the study: Pega-One S.A.S.

Funding: Pega-One S.A.S.

Disclosure: C. Robert: Financial Interests, Personal, Advisory Board: BMS, Roche, Pierre Fabre, Novartis, Sanofi, MSD, AstraZeneca, Pfizer. F.L. Day: Financial Interests, Personal, Advisory Board: Amgen; Non-Financial Interests, Institutional, Other, IMP provision to investigator-initiated clinical trial: Bristol Myers Squibb, AstraZeneca. R.D. Hofheinz: Financial Interests, Personal, Advisory Board: Amgen, BMS, MSD, Sanofi, Roche, AstraZeneca, Lilly, Roche, Merck, Daichi. P. Chrom: Financial Interests, Personal, Member: Pega-One S.A.S. S. Heeger: Financial Interests, Personal, Full or part-time Employment: Pega-One S.A.S. D. Rischin: Financial Interests, Institutional, Research Grant, Funding: Regeneron Pharmaceuticals, Inc., Sanofi, Kura Oncology, Roche, Merck Sharp & Dohme, Bristol Myers Squibb, GlaxoSmithKline, Pega-One S.A.S., ALX Oncology; Non-Financial Interests, Personal, Advisory Board: Merck Sharp & Dohme, Regeneron Pharmaceuticals, Inc., Sanofi, GlaxoSmithKline. All other authors have declared no conflicts of interest.

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886TiP Recombinant human adenovirus type 5 combined with anti-PD-1 monoclonal antibody in the treatment of patients with advanced melanoma with previous immunotherapy failure: A single-site, single-arm, prospective study

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Background: Treatment for advanced melanoma after progression on immunotherapy is limited. H101, a recombinant human type 5 adenovirus with the deletion of E1B and E3 gene, which is the world's first approved oncolytic virus product in China, and has been reported to have anti-tumor activity in some solid tumors. However, there was little evidence regarding the effect of H101 on advanced melanoma. Therefore, we aimed to explore the effect and safety of H101 intra-tumor injection combined with anti-programmed death-1 (anti-PD-1) monoclonal antibody in the treatment of advanced melanoma with previous immunotherapy failure, and to further provide a new method for clinical treatment of melanoma.

Trial design: In this single-site, single-arm, prospective study, it is estimated 10 patients with advanced melanoma with previous immunotherapy failure who receive treatment of H101 combined with anti-PD-1 monoclonal antibody are required. Based on individual conditions, H101 are intratumorally injected on day 1 of every cycle, two weeks for a cycle, with 4 cycles totally. In addition, anti-PD-1 are administered intravenously within 48 hours after H101 injection, with a dosage of 3mg/kg. The injection dose of H101 is determined by the maximum tumor diameter: 5.0×1011 virus particles (vp) (1 vial) for tumor diameter between 1cm and 4cm, and 1×1012 vp (2 vials) for tumor diameter between 4cm and 8cm. The primary endpoint is objective response rate (ORR). The secondary endpoints include duration of response (DOR), disease control rate (DCR), overall survival (OS), quality of life (QOL) and adverse events (AEs). The AEs are monitored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0). Study data will be collected using electronic case report form (eCRF) and managed using the electronic data capture system (EDC). Patients are now not yet recruiting and the estimated study duration are 3 years.

Clinical trial identification: Chinese Clinical Trial Registry (Registration No: ChiCTR2200055931).

Legal entity responsible for the study: The authors.

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