Supplementary Methods, Tables and Figures

This appendix is a supplement to: Long-term survival follow-up for tebentafusp in previously treated metastatic uveal melanoma

Clinical trial registration number: NCT02570308

Contents

Sacco JJ, *et al. J Immunother Cancer* 2024; 12:e009028. doi: 10.1136/jitc-2024-009028

Supplementary Methods

Immunohistochemistry for gp100 was carried out using the Roche Ventana CONFIRM anti-melanosome (HMB45) mouse monoclonal primary antibody on the Ventana Discovery XT staining platform. An alkaline phosphatase detection system was used. Manufacturers guidelines were followed when developing the staining protocol.

Pre-treatment biopsies were collected as archival material or as screening samples. If no screening sample was available for a patient, then the most recently collected archival sample was used. In cases where there were multiple screening biopsies available, then the highest H-score was reported.

Sacco JJ, *et al. J Immunother Cancer* 2024; 12:e009028. doi: 10.1136/jitc-2024-009028

Supplementary Table 1. Baseline characteristics*

Characteristic	Phase 1 (N=19)	Phase 2 (N=127)	All patients (N=146)
Age, median (range), yrs	55 (34 – 73)	61 (25 – 88)	61 (25 – 88)
Male sex, n (%)	9 (47)	63 (50)	72 (49)
ECOG status, n (%)			
0	14 (74)	89 (70)	103 (71)
1	5 (26)	38 (30)	43 (29)
Lactate dehydrogenase > ULN, n (%)	11 (58)	74 (58)	85 (58)
Alkaline phosphatase > ULN, n (%)	10 (53)	37 (29)	47 (32)
Time from primary diagnosis to metastatic disease, median (range), yrs	2.8 (0.1 – 18.6)	3 (0 – 28)	3 (0 – 28)
Largest liver metastasis (ICR)†, n (%)			
≤3 cm	7 (37)	45 (35)	52 (36)
>3 – ≤8 cm	4 (21)	49 (39)	53 (36)
>8 cm	0	17 (13)	17 (12)
No target liver metastases or missing	8 (42)	16 (13)	24 (16)
Metastasis location (ICR)			
Hepatic only	7 (37)	52 (41)	59 (40)
Extrahepatic only	0	4 (3)	4 (3)
Hepatic & extrahepatic	5 (26)	71 (56)	76 (52)
Missing	7 (37)	0	7 (5)
Number of prior anti-cancer therapy regimens in metastatic setting			
0 prior lines	3 (16)	0	3 (2)
1 prior line	4 (21)	85 (67)	89 (61)
2+ prior lines	12 (63)	42 (33)	54 (37)

* Values in this table may differ from the primary analysis due to resolution of missing values or re-evaluation for this updated analysis

† Liver metastases measurements based on blinded, independent central review (ICR) of target liver lesions only (AJCC Cancer Staging 8th edition)

Supplementary Table 2. RECIST responses by overall survival

OS subgroup		RECIST best response*				
	n	PR	SD	MR†	PD	NE
< 1 yr	57	0	13	0	38	6
1 yr – < 2 yrs	33	1	14	1	16	1
2 yrs – < 3 yrs	30	2	16	5	6	1
≥ 3 yrs	26	4	14	5	3	0
Total	146	7	57	11	63	8

* RECIST responses per blinded, independent central review
† A minor response (MR) was defined as a reduction from baseline in the sum of longest diameters (or short axis for lymph nodes) of target lesions (mm) of 10–29%, where non-target lesion response was not unequivocal progression, and no new lesions were present.

PR, partial response; SD, stable disease; MR, minor response; PD, progressive disease; NE, non-evaluable

Supplementary Table 3. Overall survival by patient subgroup

Subgroup	n	Median OS, months (95% CI)	OS rates 1-year, % (95% CI)	OS rates 2-year, % (95% CI)	OS rates 3-year, % (95% CI)
Age, years					
< 65	92	21.2 (13.4-26.6)	67 (56-76)	43 (32-52)	21 (14-30)
≥ 65	54	13.3 (9.9-21.9)	54 (40-66)	35 (22-48)	27 (16-40)
18 – < 65	92	21.2 (13.4-26.6)	67 (56-76)	43 (32-52)	21 (14-30)
65 – < 75	38	16.8 (10.6-30.3)	57 (39-71)	41 (25-56)	32 (18-48)
≥ 75	16	10.3 (6.1-13.8)	47 (22-69)	20 (5-43)	-
Sex					
Female	74	21.9 (13.4-29.4)	64 (52-74)	45 (33-56)	30 (20-41)
Male	72	13.5 (11.6-22.8)	61 (48-71)	35 (24-46)	16 (8-25)
Region					
Europe	36	15.1 (8-28.8)	61 (43-75)	42 (26-57)	27 (13-42)
North America	110	17.7 (13.2-23.3)	63 (53-71)	39 (30-48)	22 (15-30)
ECOG performance status					
0	103	19.2 (13.3-28.5)	65 (55-74)	44 (34-53)	25 (17-34)
≥ 1	43	13.4 (9.8-22.5)	55 (39-68)	30 (17-44)	17 (7-30)
Baseline LDH					
≤ ULN	58	29.4 (22.9-37.1)	86 (74-93)	60 (46-72)	38 (25-51)
> ULN	85	11.4 (8.5-13.2)	46 (36-57)	25 (16-35)	12 (6-20)
Baseline ALP					
≤ ULN	99	24.6 (17.7-29.9)	73 (63-81)	51 (40-60)	29 (21-39)
> ULN	47	9.4 (4.5-12.3)	39 (25-53)	17 (8-29)	10 (3-20)
Baseline ALC					
< 1.0×10^9/L	29	10.3 (6.3-13.3)	43 (25-60)	18 (7-34)	-
≥ 1.0×10^9/L	117	22.5 (15.2-28.5)	67 (58-75)	45 (36-54)	28 (20-36)
Largest liver lesion (per investigator)					
< 3 cm	55	26.6 (17.7-30.3)	75 (61-84)	54 (40-66)	30 (18-42)
≥ 3 cm	79	12.3 (9.4-15.2)	52 (40-62)	26 (17-37)	15 (8-24)
No liver metastases	12	28.7 (6.6-NR)	75 (41-91)	58 (27-80)	42 (15-67)
Prior lines of therapy in metastatic setting					
0	3	51.2 (31.1-NR)	100 (100-100)	100 (100-100)	67 (5-95)
1	89	18.1 (13.1-23.3)	64 (53-73)	38 (28-48)	22 (14-32)
2	39	12.3 (7.9-22.5)	51 (35-66)	33 (19-48)	25 (12-39)
3	15	25.5 (8.5-29.6)	73 (44-89)	53 (26-74)	13 (2-35)
Prior checkpoint inhibitor					
No	43	13.5 (8-24.6)	56 (40-70)	36 (22-51)	20 (9-34)

Yes	103	17.7 (13.2-25.5)	65 (55-3)	41 (32-51)	24 (16-33)

ALC, absolute lymphocyte count; ALP, alkaline phosphatase; CI, confidence intervals; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; ULN, upper limit of normal

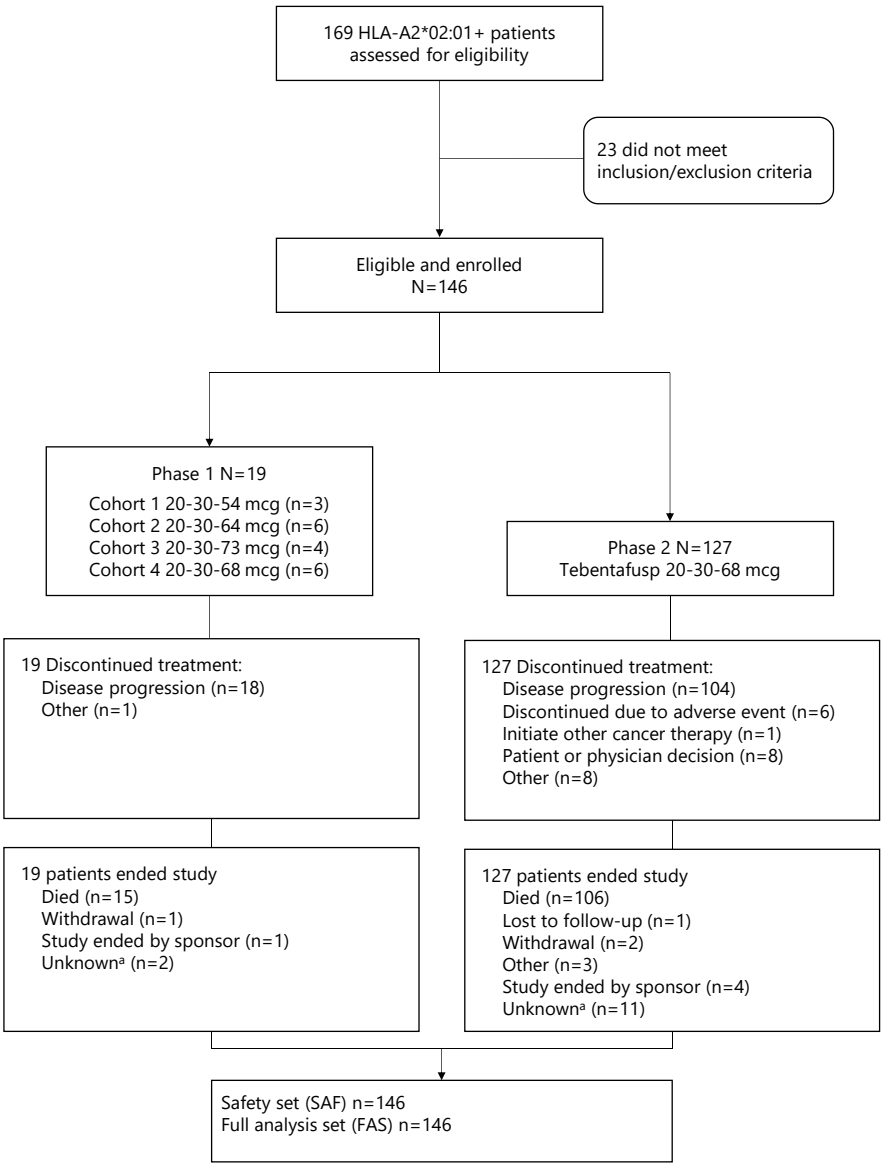
Supplementary Table 4. Baseline characteristics, RECIST responses and OS of ctDNA evaluable patients

	ctDNA level					
	Baseline (n = 117)		On-treatment change (n = 94)			
Characteristic	**Not detected**	**detected**	**Cleared**	**≥ 0.5 log (68%) decrease but not cleared**	**< 0.5 log decrease**	**increase**
Tumor burden (largest liver lesion)						
≤3 cm	11 (9)	31 (26)	8 (9)	7 (7)	7 (7)	8 (9)
3-8 cm	7 (6)	35 (30)	2 (2)	12 (13)	8 (9)	13 (14)
>8 cm	0	17 (15)	0	8 (9)	5 (5)	4 (4)
Missing	3 (3)	13 (11)	2 (2)	3 (3)	5 (5)	2 (2)
LDH						
≤ ULN	14 (12)	36 (31)	9 (10)	6 (6)	9 (10)	11 (12)
> ULN	7 (6)	60 (51)	3 (3)	24 (26)	16 (17)	16 (17)
ECOG						
0	15 (13)	71 (61)	10 (11)	19 (20)	22 (23)	18 (19)
1	6 (5)	25 (21)	2 (2)	11 (12)	3 (3)	9 (10)
Disease location						
Hepatic only	9 (8)	28 (24)	9 (10)	8 (9)	6 (6)	5 (5)
Hepatic & extrahepatic	12 (10)	66 (56)	3 (3)	21 (22)	19 (20)	21 (22)
RECIST response						
PR	2 (2)	4 (3)	1 (1)	1 (1)	0	2 (2)
MR	2 (2)	6 (5)	2 (2)	3 (3)		
SD	11 (9)	37 (32)	6 (6)	13 (14)	9 (10)	8 (9)
PD	6 (5)	48 (41)	3 (3)	13 (14)	15 (16)	17 (18)
NE	0	1 (1)	0	0	1 (1)	0
Gp100 expression						
Median H-score (gp100)	180	170	229	178	178	85

Supplementary Table 5. Composite terms for Rash, Hypotension and Liver Function Tests

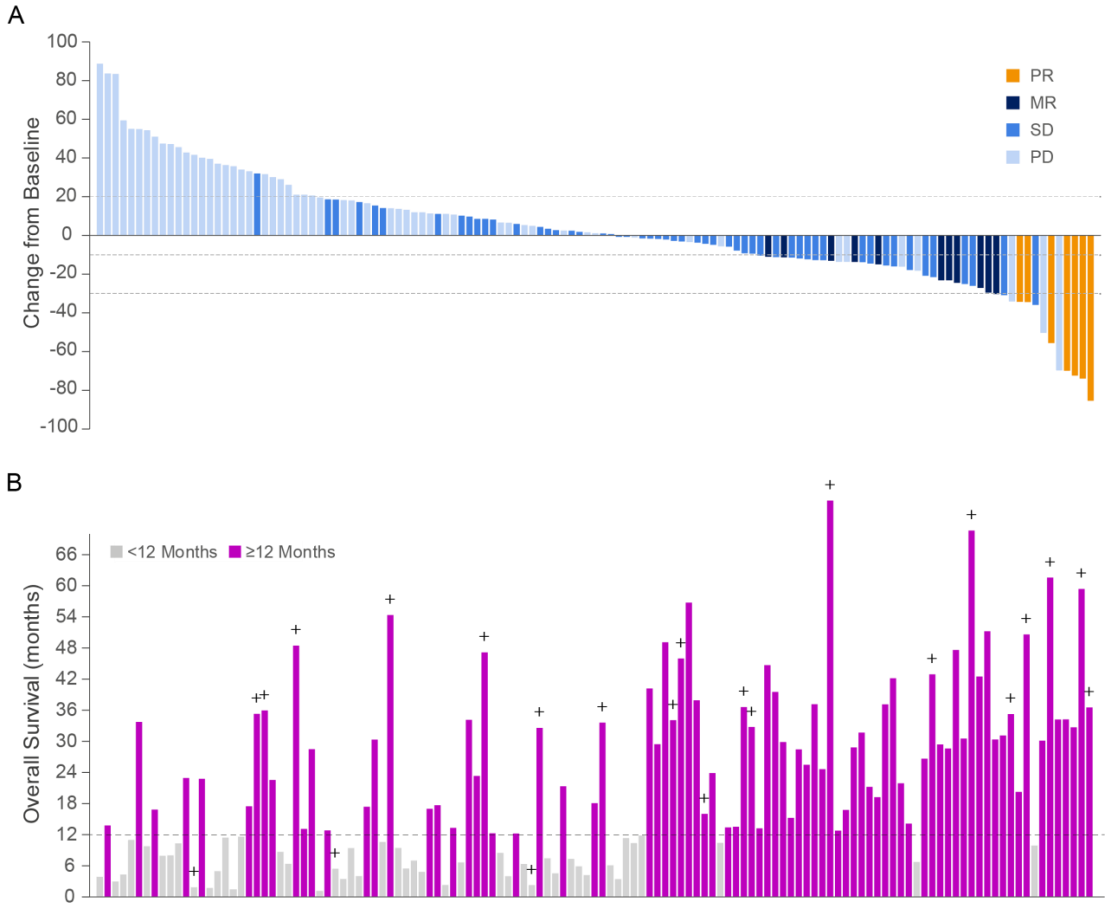
Composite term	Adverse event (any grade)
Rash	Blister, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Palmar-plantar erythrodysaesthesia syndrome, Papule, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Skin exfoliation, Urticaria
Liver Function Tests	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic pain, Hyperbilirubinaemia, Liver function test increased, Transaminases increased

Supplementary Figure 1



Supplementary Figure 1. CONSORT flowchart for the single-arm, open-label, phase 1/2 clinical trial with tebentafusp in patients with metastatic uveal melanoma. All patients who received at least one full or partial dose of study drug were included in the safety set. All patients who were assigned to treatment, and who received at least one full or partial dose of study drug, were included in the full analysis set (FAS). [a] Reason for ending study was not entered into the database.

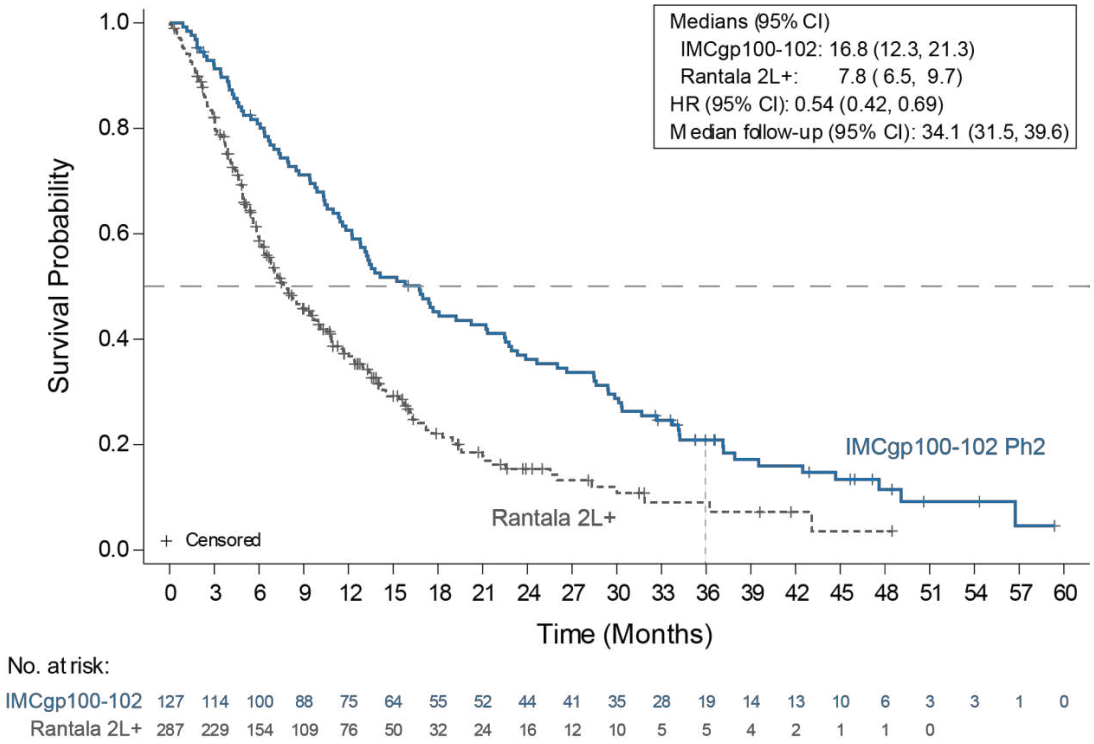
Supplementary Figure 2



Supplementary Figure 2. Clinical activity of tebentafusp. (A) Waterfall plot showing the best change in tumor size in all evaluable patients (n=127). 48% of patients had tumor reduction at any time. Tumor size was measured as the sum of longest diameters or short axis of the target lesions according to RECIST v1.1 by Independent Central Review. Best percent change in target lesion size was the maximum percent reduction from baseline or the minimum percent increase from baseline (in the absence of a reduction), up until disease progression or starting subsequent alternative cancer therapy. Complete response, partial response or minor response required confirmation at least 4 weeks later. Reference lines at 20%, -10%, and -30% mark target lesion response criteria for disease progression (PD), minor response (MR), and partial response (PR), respectively. SD, stable disease. **(B)** Overall survival in months is plotted for each patient (n=127). 65% of patients survived more than 12 months. + denotes censored. (A-B) Only patients with at least one evaluable post baseline

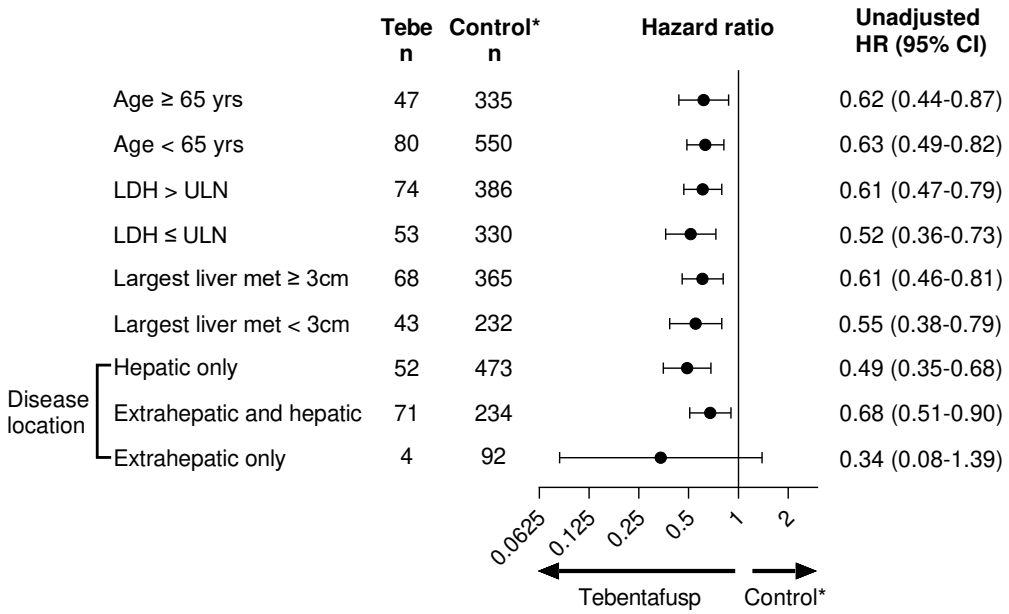
target lesion scan were included. Nineteen patients were not included due to non-measurable disease at baseline or no evaluable postbaseline target lesion scans. Evaluable post-baseline scans must be on or prior to disease progression or starting subsequent alternative cancer therapy to be considered.

Supplementary Figure 3



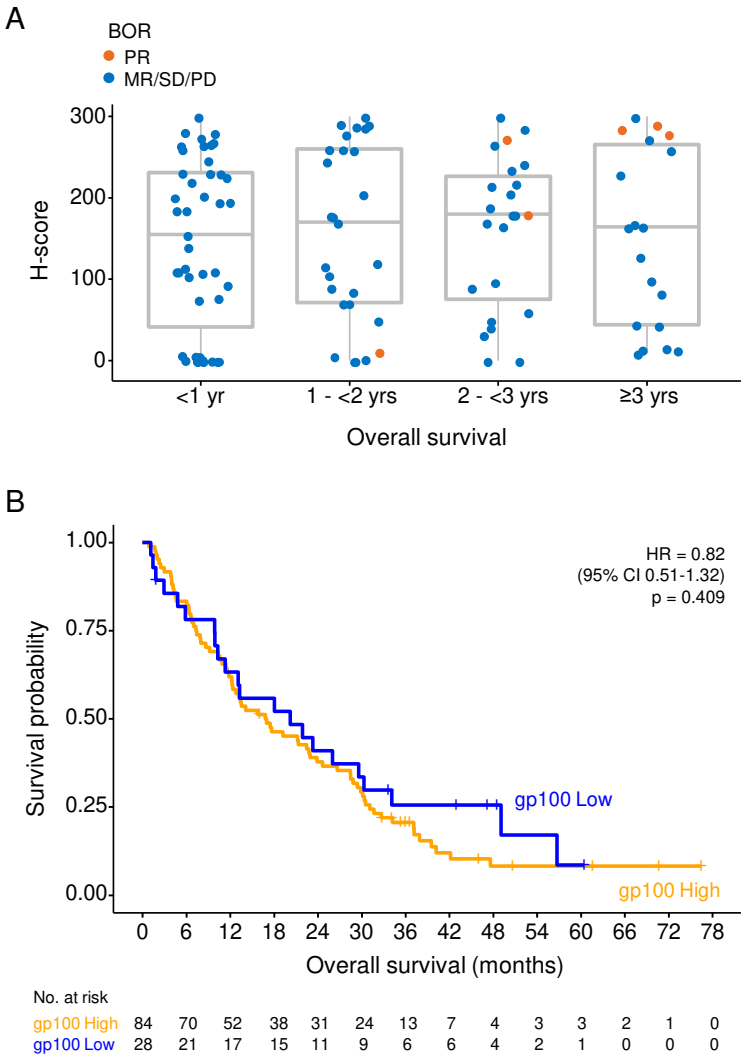
Supplementary Figure 3. OS with tebentafusp in 2L+ population compared to recent meta analysis. Digitized overlay of Kaplan–Meier estimates of overall survival for patients treated with tebentafusp in this study compared to 2L+ patients from a meta-analysis (Rantala et al. 2019). Parsing of data for 2L+ patients from 1L patients was only possible from the Rantala et al. meta-analysis.

Supplementary Figure 4



Supplementary Figure 4. OS subgroup analysis of tebentafusp from this study compared to a meta analysis in mUM. Unadjusted comparison of overall survival in known prognostic categories for tebentafusp from this study with historical control treatments from a recent meta analysis in mUM (Khoja et al. 2019). Data for this subgroup analysis was only available from the Khoja et al. meta-analysis and was obtained from digitized curves; the number of patients in each subgroup may not match the publication. *historical control treatments

Supplementary Figure 5



Supplementary Figure 5. Association between glycoprotein 100 (gp100) levels at baseline and overall survival. (A) Level of gp100 expression (H-score) at baseline was plotted for phase 2 patients (n = 127) with overall survival < 1 year (n = 43), 1 – <2 years (n = 27), 2 – <3 years (n=23) and ≥ 3 years (n = 19). Patients with a best overall response (BOR) of partial response (PR) are denoted in orange. (B) Kaplan-Meier analysis of overall survival according to gp100 level at baseline (low, n=28 or high, n=84, corresponding to the lowest quartile and above the lowest quartile of gp100 H-scores, respectively). The hazard

ratio (HR) and 95% confidence interval (CI) were calculated using a Cox proportional hazard model.