Supplementary Appendix

Supplement to: Hassel JC, Piperno-Neumann S, Rutkowski P, et al. Three-year overall survival with tebentafusp in metastatic uveal melanoma. N Engl J Med 2023;389:2256-66. DOI: 10.1056/NEJMoa2304753

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Contents

Methods for exploratory endpoints

ctDNA analysis

Serum samples, collected at baseline and at week 9 on-treatment were used to assess the level of circulating tumour DNA. Changes in ctDNA levels at week 9 versus baseline were measured for all patients treated with tebentafusp with serum samples available at both time points (ctDNA evaluable; n=202) using a custom panel of mutations commonly found in uveal melanoma (GNAQ Q209L/P; GNA11 Q209L; SF3B1 K700E, R625L/H/C; PLCB4 D630N/Y/V; CYSLTR2 L129Q; and EIF1AX G15D). BAP1 was not included due to a lack of hotspot mutation and because BAP1 alterations are nearly always present in the context of other uveal melanoma mutations, particularly GNAQ or GNA11. ctDNA was amplified by multiplex PCR and analysed by next-generation sequencing (performed by Natera Inc).

Tumor mutation analysis

The relationship between tumor mutational burden (TMB) in biopsies and overall survival was explored in patients with available biopsies. DNA was extracted from FFPE sections and libraries for sequencing were generated using the Illumina ExomeSeq all exon v6 kit. Paired end fragments of 100 bp in length were sequenced (50 million reads per sample) using the Illumina NovaSeq system. Reads were aligned using BWA-MEM (Burrows–Wheeler aligner – maximal exact match) v0.7.15. and mapped to the GRCh38 primary assembly provided by Ensembl. Duplicate reads were flagged using the MarkDuplicate function of Picard to prevent variant call errors. Somatic variants were called using MuTect2 (GATK Somatic SNVs and INDELs 4.1.6.0) with inclusion of a panel of normals. Ensembl Variant Effect Predictor v101 was used for variant annotation and filtering to retain nonsynonymous alterations. Tumor mutation burden was calculated as the number of nonsynonymous somatic alterations per total targeted coding region.

Because only 5 patients had TMB greater than the generally accepted threshold of 10 mutations / megabase,[1] we evaluated overall survival in the upper quartile of TMB (≥0.9 mutations / megabase) versus the lower three quartiles (<0.9 mutations / megabase) using Kaplan Meier methods.

Statistical analysis

Pre-specified and post-hoc analyses were evaluated with hazard ratios and 95% confidence intervals from unstratified Cox regression models but only if the proportional-hazards assumption was met,[2] which did not occur in three instances outlined in the table below. The ad hoc analysis of overall survival among patients with a best response of progressive disease reported previously[3] was replicated for this analysis using a landmark approach whereby overall survival was measured starting

from Day 100 and patients were categorized based on their best response by that time (Table S6). The exploratory analysis of overall survival among ctDNA evaluable patients treated with tebentafusp was also conducted using a landmark approach whereby overall survival was measured starting from Week 9 and patients were categorized based on their percent change in ctDNA level from baseline. A 50% reduction threshold was used based on analysis of the Phase 2 trial and literature.[4–6]

Comparisons for which the proportional hazards assumption was not met

			PH assumption test*	Median OS, months† (95% CI)	
Comparison	**Figure**	**Hazard ratio (95% CI)**	**p-value**		
ctDNA cleared vs ctDNA not cleared	Fig. 3B	0.32 (0.21 - 0.5)	0.008	29.6 (23 – 37)	10.2 (8.3 – 13.2)
Tebentafusp vs control for patients with TMB <0.9 mutations/megabase	Fig. S3B	0.51 (0.35-0.74)	0.002	21.6 (18.4 – 25.5)	8.3 (5.8 – 14.4)
Baseline ctDNA undetectable vs baseline ctDNA detectable	Fig. S11	0.49 (0.35 - 0.69)	0.021	27.3 (24.1 - 34.3)	18.4 (14.8 - 22.5)

* Proportional hazards assumption was tested according to Lin et al.[2] with the supremum test p-values derived from Kolmogorov Smirnoff test.
† Median overall survival (OS) and 95% confidence intervals (CI) are included for comparison in the absence of a hazard ratio
TMB, tumor mutational burden

Figure S1 – CONSORT diagram

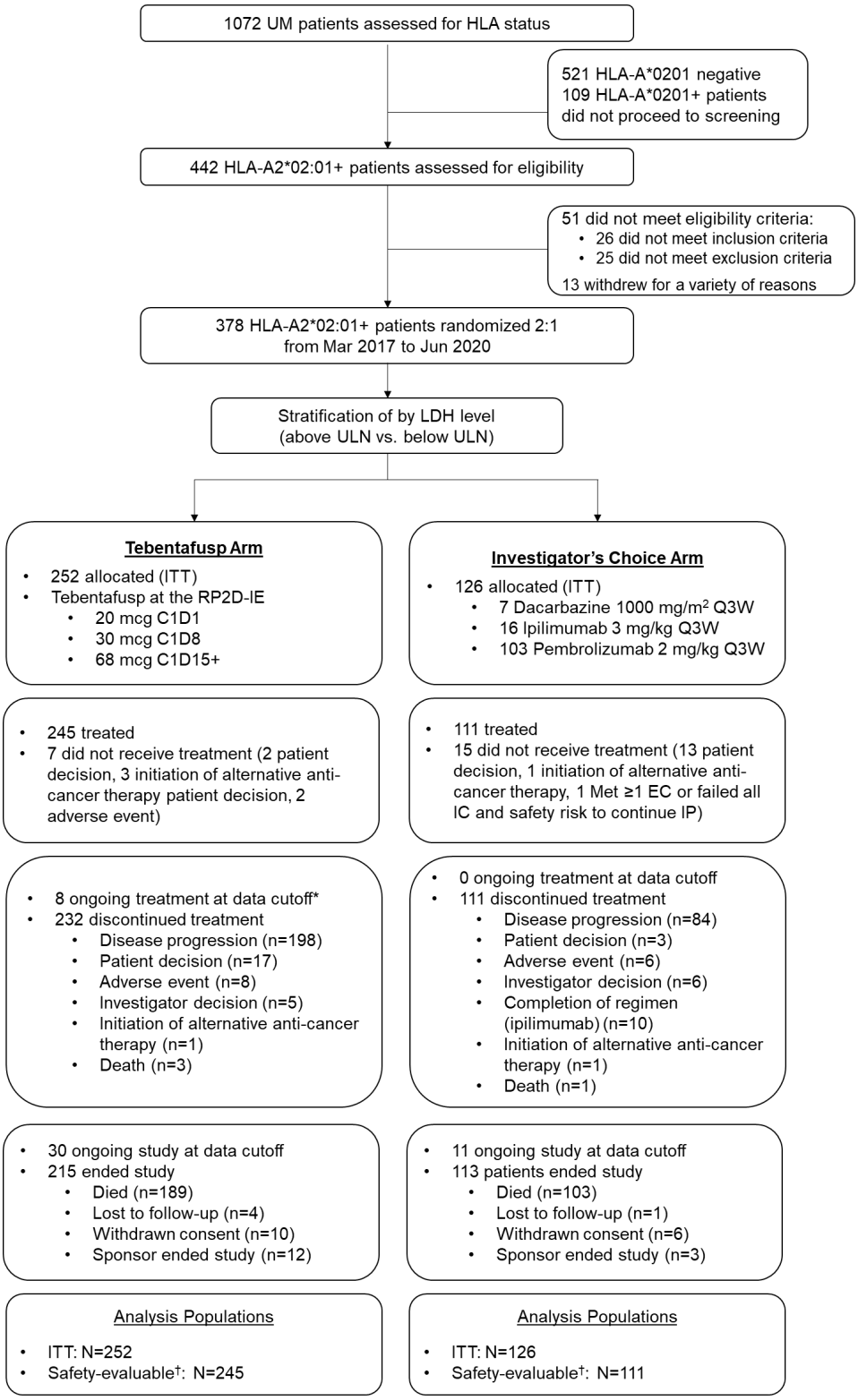


Figure S1. Study design, participant enrolment and disposition in the intention-to-treat (ITT) population after 3-years of follow-up. *End of treatment page was not completed for these 8 patients; 6 of these 8 patients transferred to the early access program. †Includes all patients who received ≥1 dose of study treatment.

Figure S2 – Prespecified subgroup analysis of overall survival in the intention-to-treat population

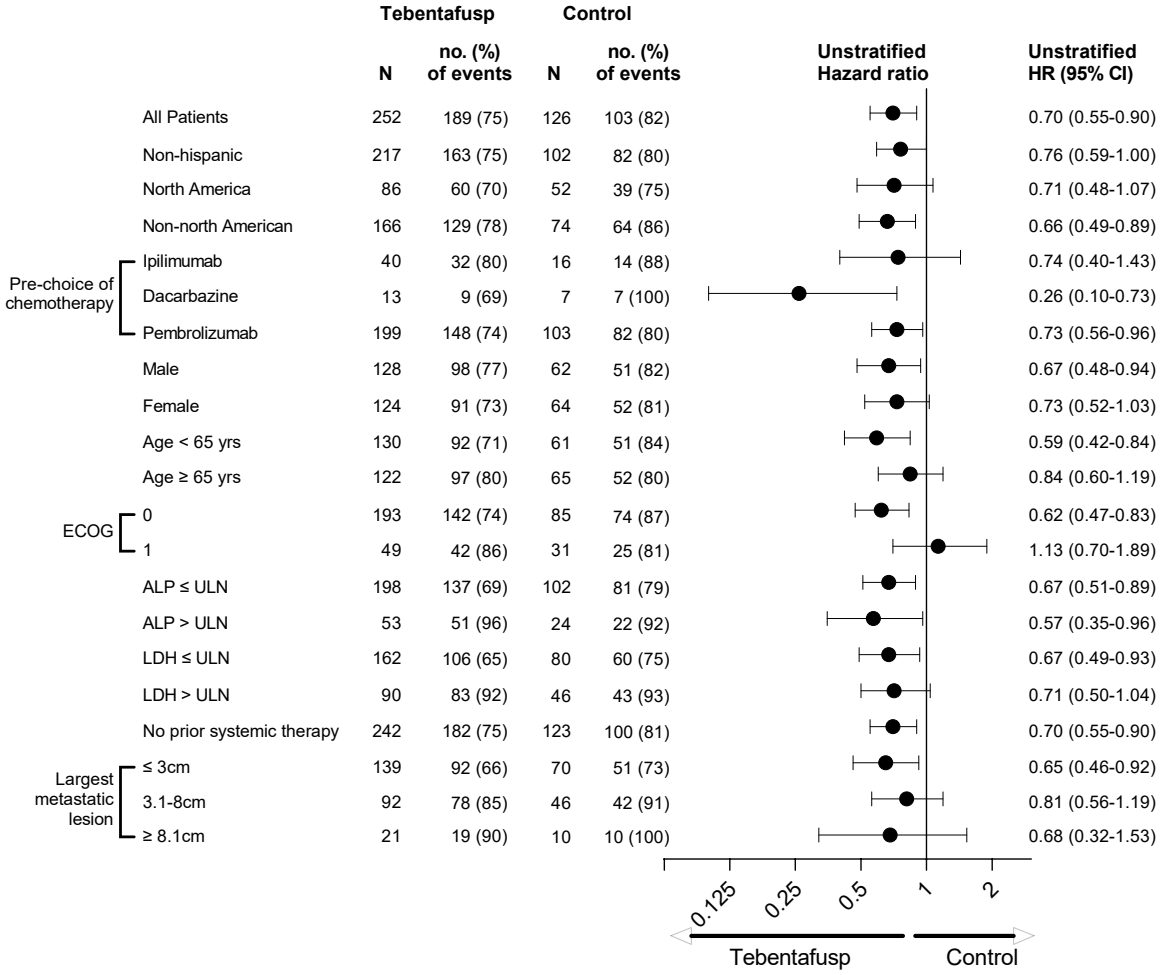


Figure S2. Forest plot of unstratified hazard ratios and 95% confidence intervals for overall survival in prespecified subgroups of patients, according to various baseline characteristics.

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal

Figure S3 – Association between tumor mutational burden and overall survival

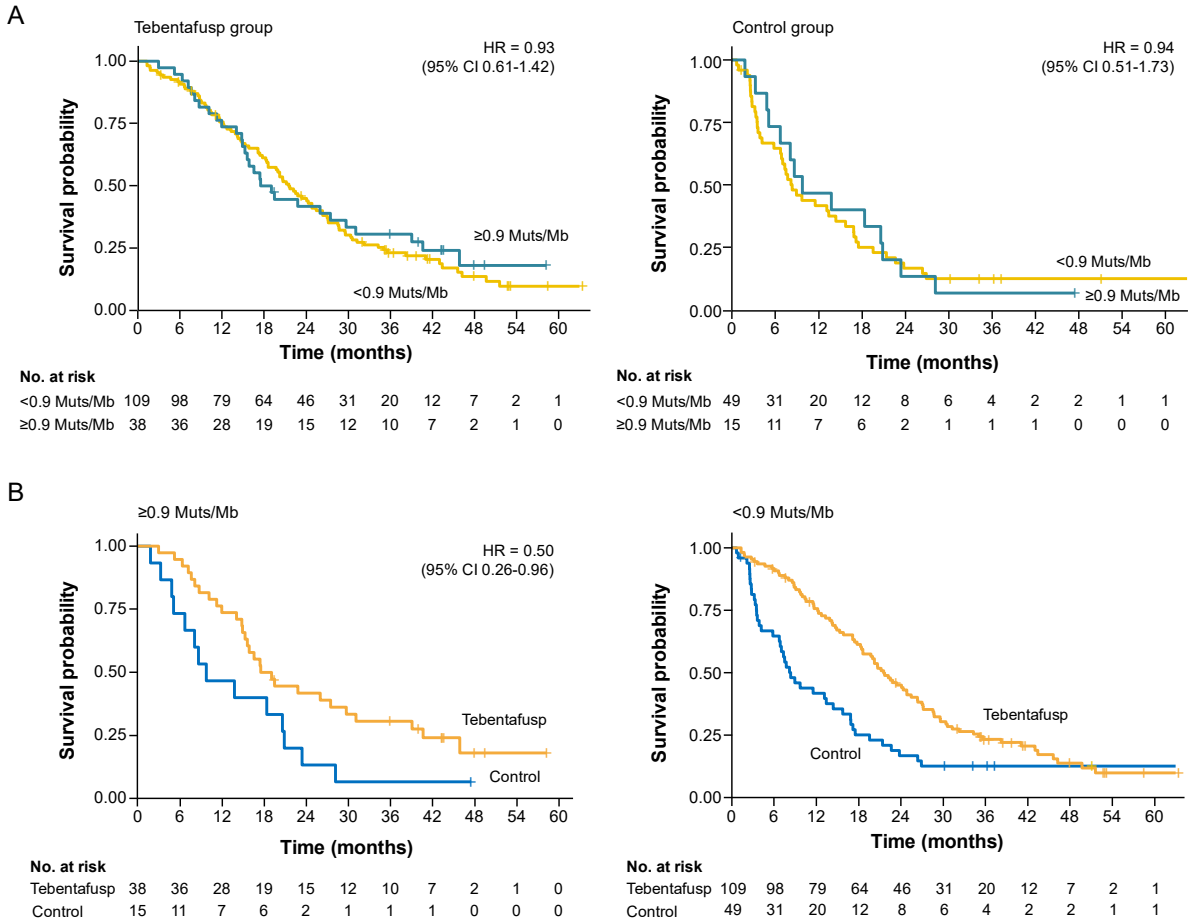


Figure S3. Kaplan-Meier estimate of overall survival from time of randomization in (A) tebentafusp and control groups by TMB ≥0.9 mutations / megabase (upper quartile) versus <0.9 mutations / megabase (lower 3 quartiles) and (B) in patients with TMB values ≥0.9 mutations / megabase and <0.9 mutations / megabase by treatment group.

Figure S4 – Overall survival in patients who crossed over to receive tebentafusp

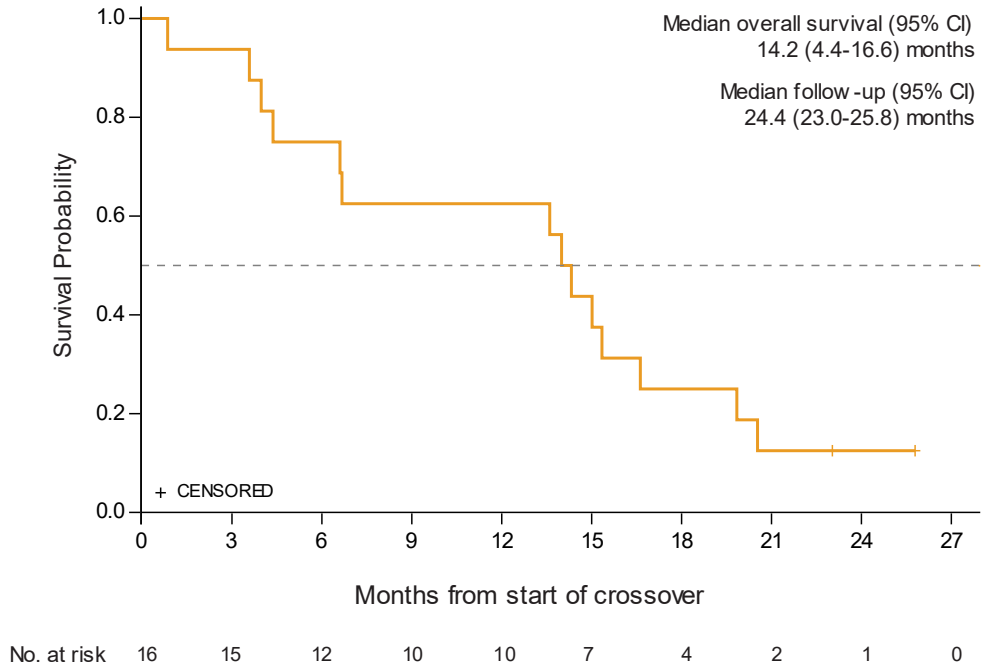


Figure S4. Kaplan-Meier estimate of overall survival from start of crossover in patients from the control group who crossed over to tebentafusp following the primary analysis.

Figure S5 – Overall survival and treatment duration in patients with a best response of CR or PR

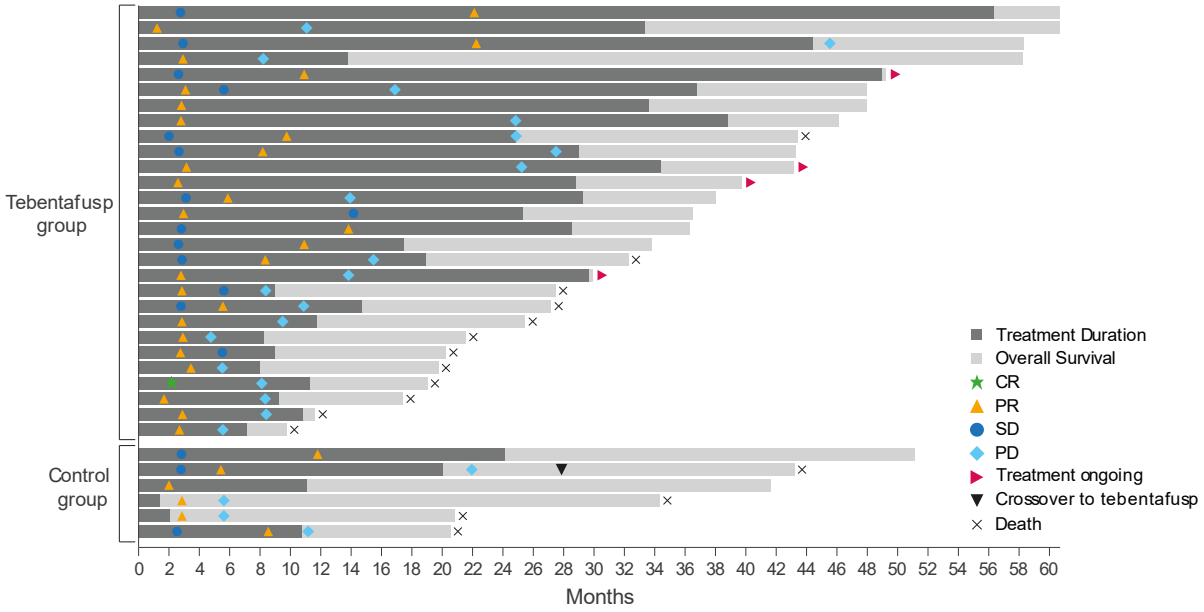


Figure S5. Swimlane plot of overall survival and duration of treatment for patients with an overall best response of complete response or partial response by RECIST v1.1. The response data presented for each patient in the figure represents an individual timepoint response that occurred at the corresponding visit assessment. Representative visits are highlighted to indicate changes in visit response (e.g., first PD). A visit response is derived for each timepoint by comparing to baseline and, where applicable, the previous minimum. Per RECIST v1.1, a timepoint response of SD after PR is not included in calculation of best overall response.

Figure S6 – Overall survival and treatment duration in patients with a best response of stable disease

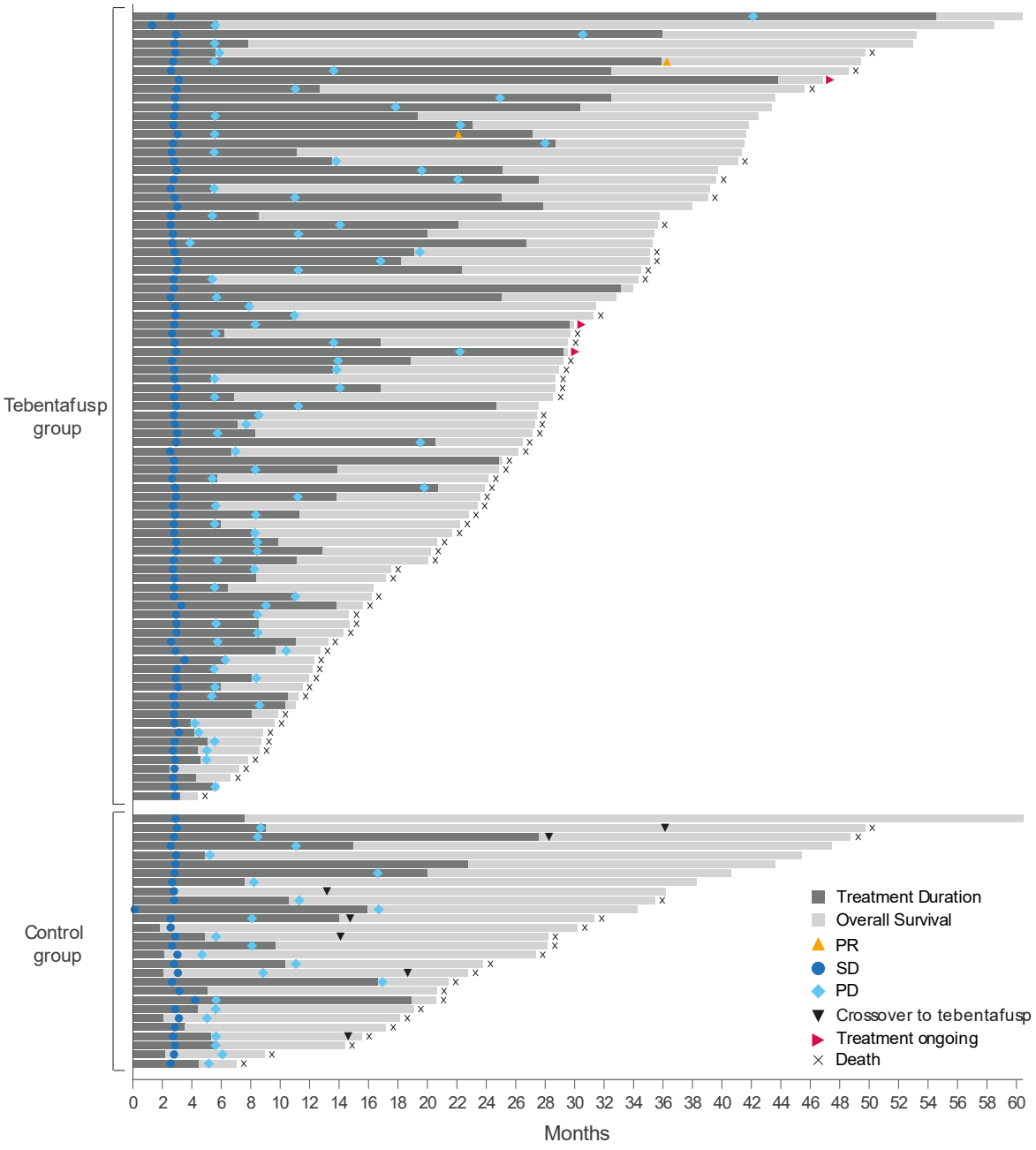


Figure S6. Swimlane plot of overall survival and duration of treatment for patients with a best response of stable disease by RECIST v1.1. The response data presented for each patient in the figure represents an individual timepoint response that occurred at the corresponding visit assessment. Representative visits are highlighted to indicate changes in visit response (e.g. first PD). A visit response is derived for each timepoint by comparing to baseline and, where applicable, the previous minimum. Per RECIST v1.1, a timepoint response of PR after PD is not included in calculation of best overall response.

Figure S7 – Best percent change in tumor size from baseline

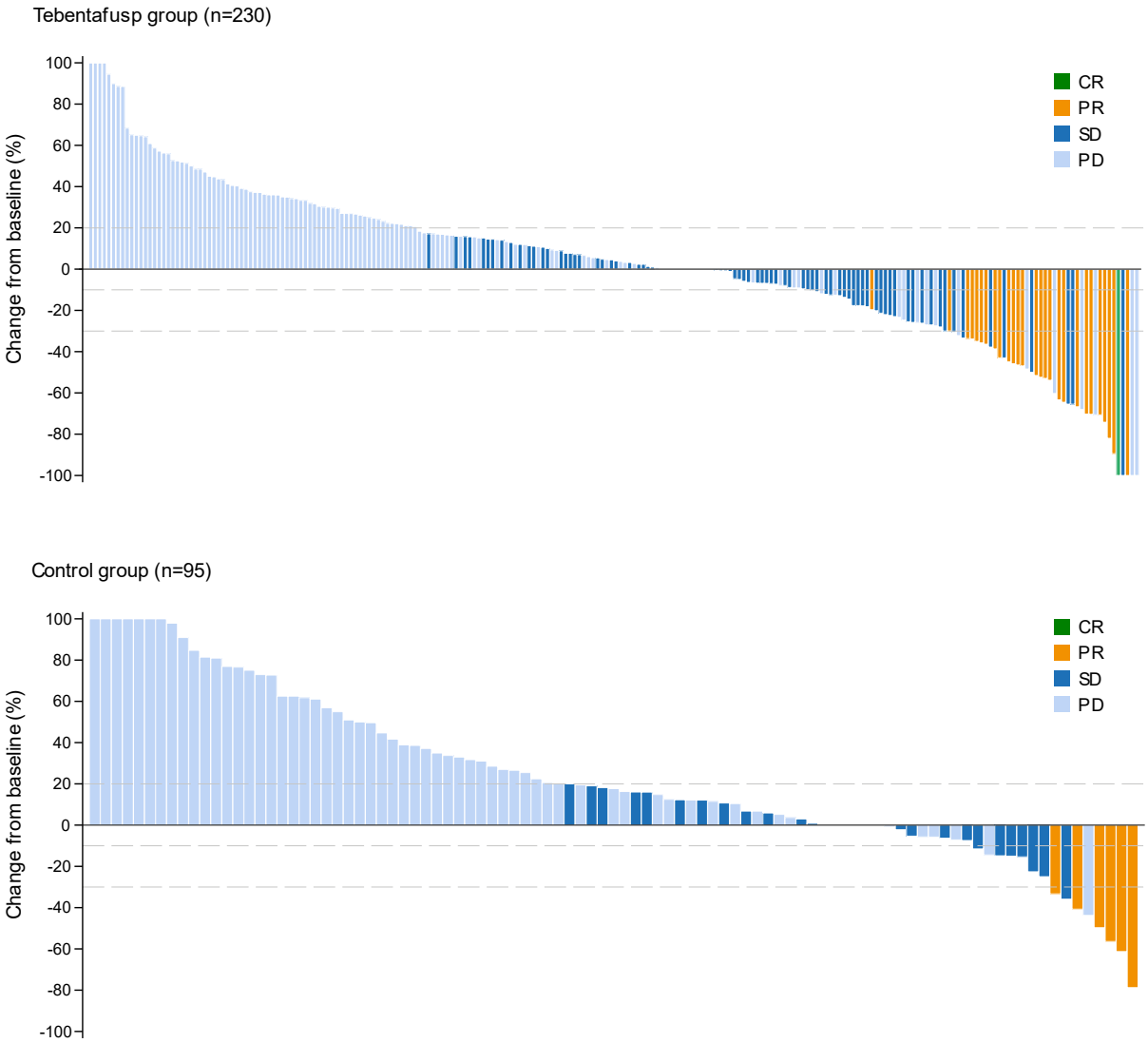


Figure S7. Best percent change in tumor size from baseline. Tumor size is measured as the sum of longest diameters or short axis of the target lesions according to RECIST version 1.1. Best percent change in target lesion size is the maximum percent reduction from baseline or the minimum percent increase from baseline before starting any new anti-cancer treatment. Changes of more than 100% were truncated at 100%. Reference lines at 20%, -10% and -30% mark target lesion response criteria for disease progression, minor response, and partial response, respectively. **(A)** In the tebentafusp group, 54% of patients with tumor increase and 40% of patients with tumor shrinkage. **(B)** In the control group, 70% of patients with tumor increase and 24% of patients with tumor shrinkage.

Figure S8 – Overall survival and treatment duration in patients with a best response of progressive disease

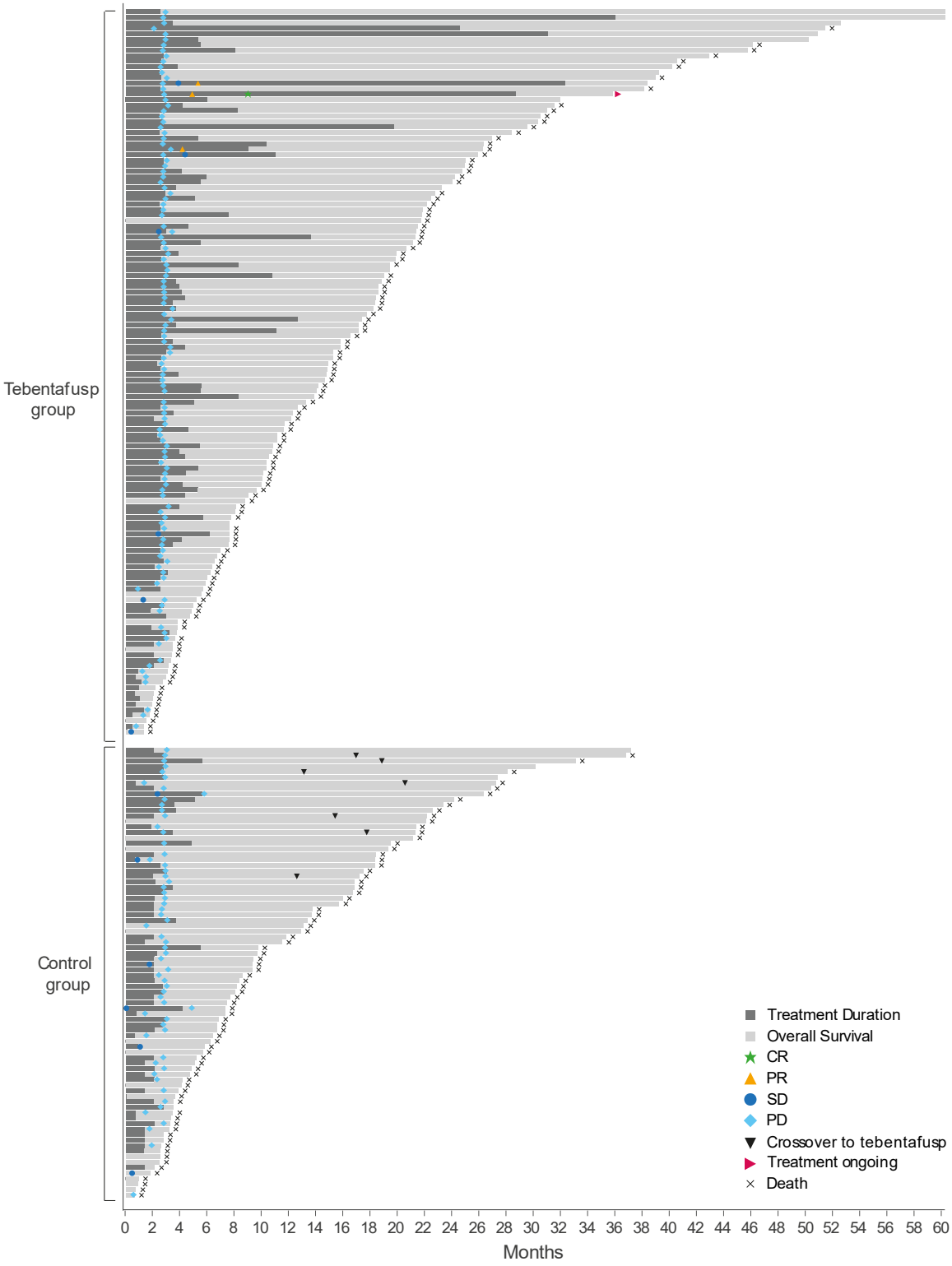


Figure S8. Swimlane plot of overall survival and duration of treatment for patients with a best response of progressive disease by RECIST v1.1. The response data presented for each patient represents the individual timepoint responses that occurred at each visit assessment. A visit response is derived for each timepoint assessed by comparing to baseline and where applicable the previous minimum.

Figure S9 – Post Day 100 Overall Survival in Patients with Best Overall Response of Complete / Partial Response or Stable Disease

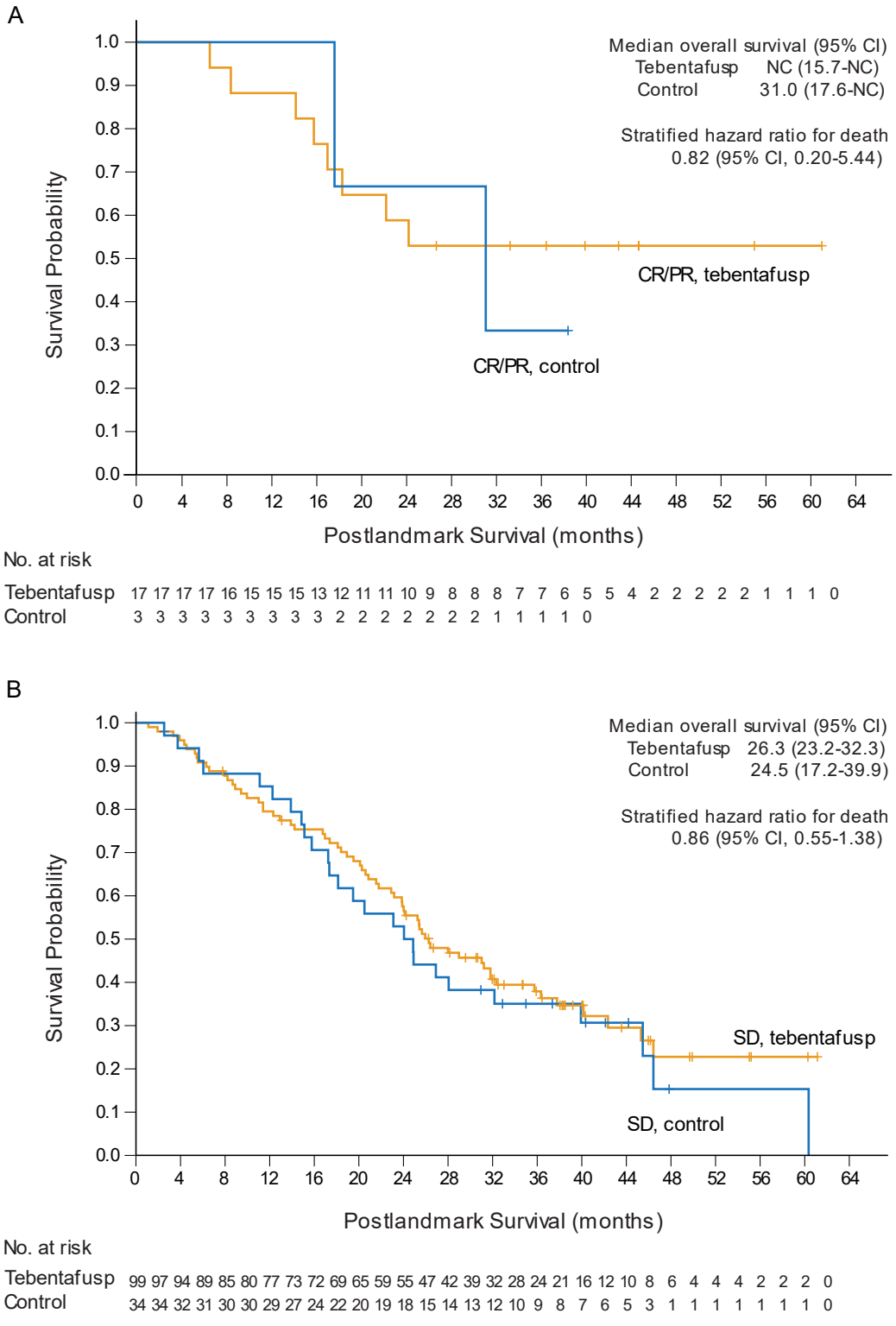


Figure S9. Kaplan-Meier estimates of overall survival in patients with best overall response prior to the landmark (day 100) of A) complete / partial response (CR/PR) or B) stable disease (SD) by RECIST v1.1.

Figure S10 – Overall survival in ctDNA evaluable patients treated with tebentafusp compared with the intention-to-treat population

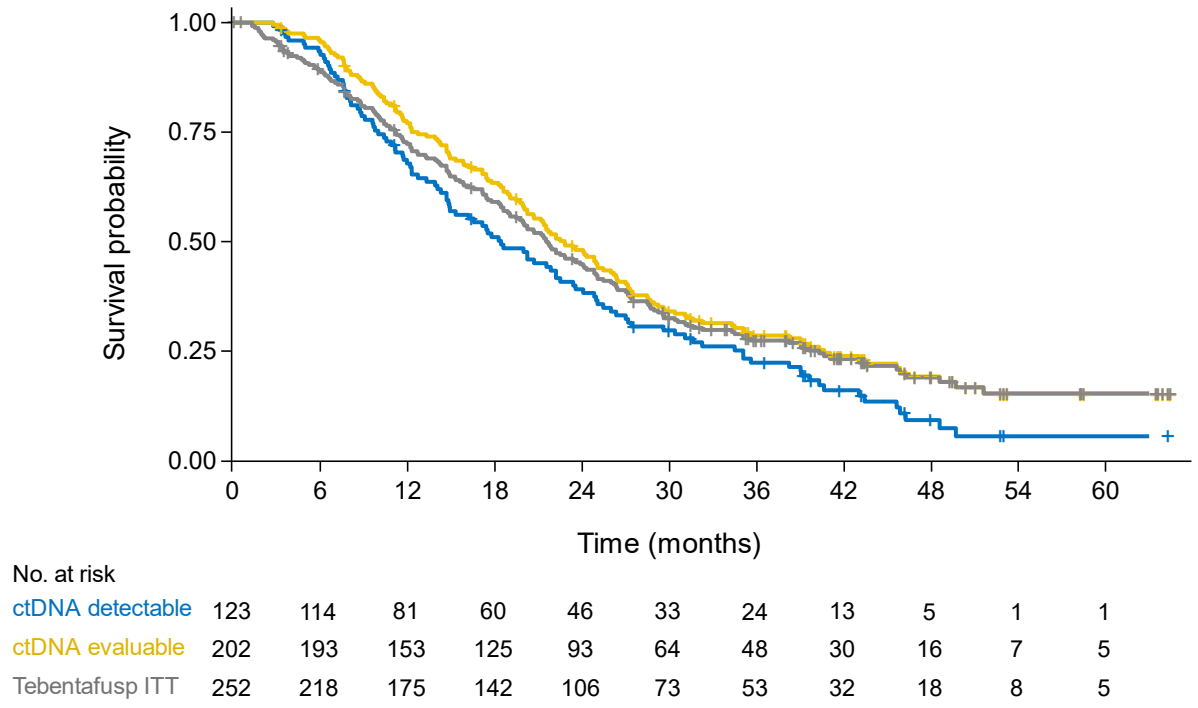
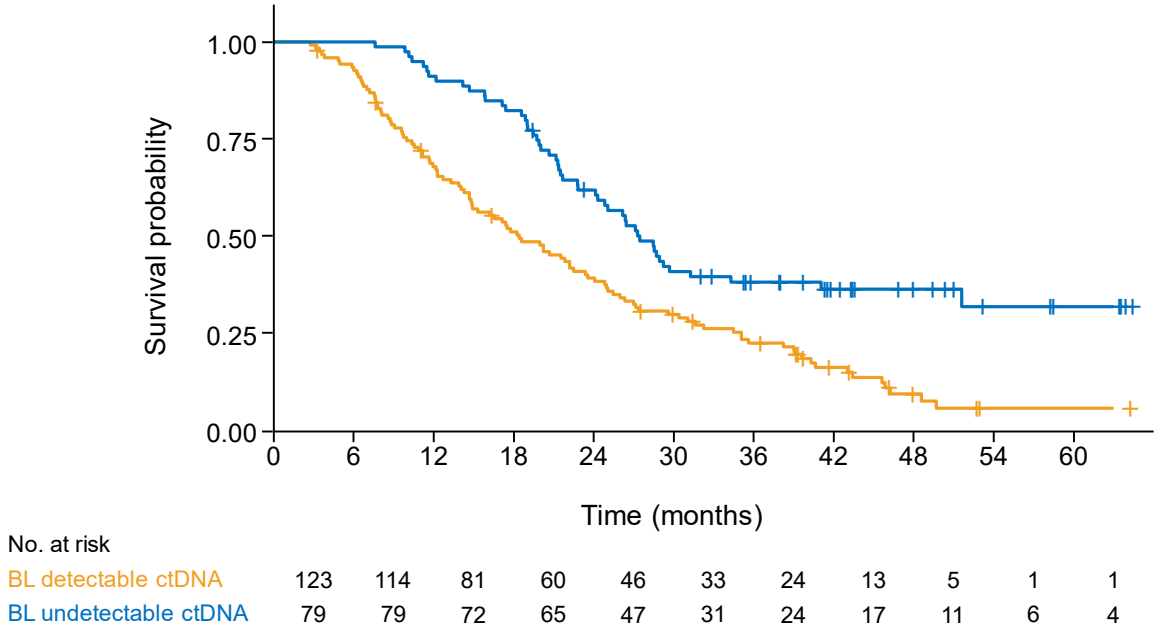


Figure S10. Kaplan-Meier estimate of overall survival from start of randomization in patients from the tebentafusp group who were evaluable for ctDNA (n=202) or had detectable ctDNA at baseline (n=123) compared to all patients randomized to the tebentafusp arm (N=252; ITT, intention-to-treat).

Figure S11 – Overall survival in tebentafusp-treated patients with and without detectable ctDNA at baseline



No. at risk											
BL detectable ctDNA	123	114	81	60	46	33	24	13	5	1	1
BL undetectable ctDNA	79	79	72	65	47	31	24	17	11	6	4

Figure S11. Kaplan-Meier estimates of overall survival from start of randomization in patients from the tebentafusp group with or without detectable ctDNA at baseline. BL, baseline

Figure S12 – Post week 9 overall survival in tebentafusp-treated patients with and without detectable ctDNA at baseline and week 9

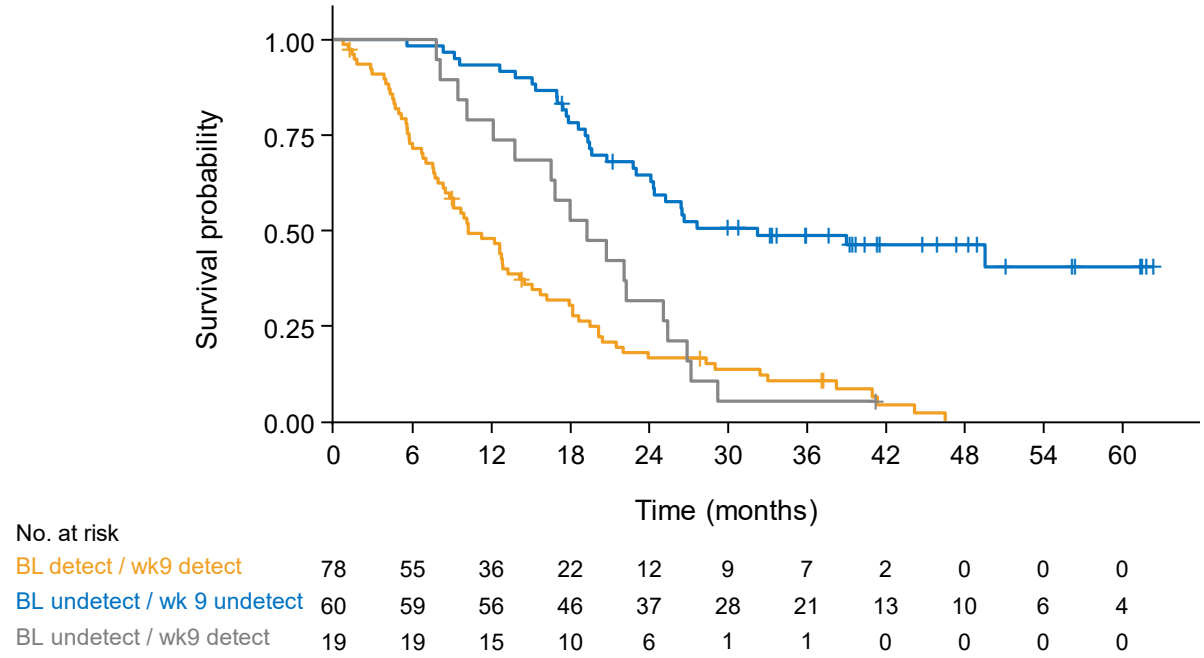


Figure S12. Overall survival from week 9 in patients with detectable ctDNA at baseline and week 9 compared to patients without detectable ctDNA at baseline with or without detectable ctDNA at week 9. BL, baseline

Table S1 – Demographics and disease characteristics of patients at baseline

Characteristic	Tebentafusp				Investigator's choice (Control group) (N=126)
	All patients (N=252)	ctDNA evaluable (N=202)	Detectable ctDNA at baseline (N=123)	Undetected ctDNA at baseline (N=79)	
Median age (range) — yr	64 (23, 92)	64 (23, 81)	65 (36, 80)	63 (23, 81)	66 (25, 88)
Male sex — no. (%)	128 (51)	102 (50)	67 (54)	35 (44)	62 (49)
Time since primary diagnosis — median (range) — yr	2.9 (0.1, 25.1)	2.9 (0.1, 25)	2.8 (0.1, 25)	2.9 (0.1, 20)	2.4 (0.1, 36.1)
ECOG performance status — no. (%)					
0	193 (77)	163 (81)	94 (76)	69 (87)	85 (68)
1	49 (19)	35 (17)	26 (21)	9 (11)	31 (25)
2	0	0	0	0	1 (1)
Missing	10 (4)	4 (2)	3 (2)	1 (1)	9 (7)
Elevated baseline LDH level (>ULN) — no. (%)	90 (36)	61 (30)	51 (41)	10 (13)	46 (37)
Largest metastatic lesion* — no. (%)					
M1a (≤3.0 cm)	139 (55)	117 (58)	58 (47)	59 (75)	70 (56)
M1b (3.1 – 8.0 cm)	92 (37)	73 (36)	53 (43)	20 (25)	46 (37)
M1c (≥ 8.1 cm)	21 (8)	12 (6)	12 (10)	0	10 (8)
Metastasis location — no. (%)					
Hepatic only	129 (51)	109 (54)	60 (49)	49 (62)	59 (47)
Extrahepatic only	9 (4)	6 (3)	3 (2)	3 (4)	10 (8)
Hepatic & extrahepatic	113 (45)	87 (43)	60 (49)	27 (34)	55 (44)
Missing	1 (0.4)	0	0	0	2 (2)
Prior surgical therapy in the metastatic setting — no. (%)	23 (9)	20 (10)	11 (9)	9 (11)	8 (6)

*AJCC Cancer Staging 7th edition

Table S2 – Demographic and disease characteristics of crossover patients

	Crossover patients (N=16)	
Characteristic	**At baseline**	**At crossover**
Median age (range), yr	65 (36-88)	66 (37-89)
Age ≥65 yrs, n (%)	8 (50)	8 (50)
Male, n (%)	8 (50)	8 (50)
ECOG performance status score, n (%)*		
0	14 (88)	13 (81%)
1	2 (13)	3 (19%)
Lactate dehydrogenase >ULN, n (%)†	2 (13)	9 (56)
Largest metastatic lesion, n (%)‡		
≤3.0 cm, stage M1a	10 (63)	9 (56)
3.1 to 8.0 cm, stage M1b	6 (38)	6 (38)
≥8.1 cm, stage M1c	0 (0)	1 (6)
Location of metastasis, n (%)		
Hepatic only	11 (69)	
Extrahepatic only	1 (6)	
Hepatic and extrahepatic	4 (25)	
Previous surgical therapy for metastatic disease, n (%)	1 (6)	
Pre-randomization choice of chemotherapy, n (%)		
Ipilimumab	2 (13)	
Dacarbazine	0 (0)	
Pembrolizumab	14 (88)	
Median duration of cross-over treatment (range), mo	4.3 (0.3-16.6)	

* The Eastern Cooperative Oncology Group (ECOG) performance-status scale ranges from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates no symptoms, 1 mild symptoms, and 2 moderate symptoms.

† ULN denotes the upper limit of the normal range. Percentages may not sum to 100 because of rounding.

‡ Lesions were assessed with the use of the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer.

Table S3 – Subsequent therapies*

Therapy class, n (%)	Tebentafusp (N=252)	Investigator's choice of therapy (Control group)			
		Control patients (N=126)	Pembrolizumab (N=103)	Ipilimumab (N=16)	Dacarbazine (N=7)
Any systemic therapy	148 (59)	73 (58)	61 (59)	9 (56)	3 (43)
Chemotherapy	44 (18)	18 (14)	14 (14)	2 (13)	2 (29)
Immunotherapy	131 (52)	58 (46)	49 (48)	6 (38)	3 (43)
Anti-CTLA4 monotherapy	16 (6)	9 (7)	8 (8)	1 (6)	0 (0)
Anti-PD(L)1 monotherapy	62 (25)	21 (17)	16 (16)	2 (13)	3 (43)
Anti-PD(L)1 + anti-CTLA4	72 (29)	20 (16)	18 (18)	2 (13)	0 (0)
Anti-PD1/ Other†	1 (0)	2 (2)	2 (2)	0 (0)	0 (0)
Other Immunotherapy	16 (6)	25 (20)	23 (22)	2 (13)	0 (0)
Tebentafusp	0 (0)	24 (19)	22 (21)	2 (13)	0 (0)
Other†	16 (6)	2 (2)	2 (2)	0 (0)	0 (0)
Targeted therapy	20 (8)	14 (11)	11 (11)	1 (6)	2 (29)
Other systemic therapies	4 (2)	2 (2)	2 (2)	0 (0)	0 (0)
Radiotherapy	35 (14)	23 (18)	18 (17)	4 (25)	1 (14)
Local therapy - excluding radiotherapy	27 (11)	22 (18)	15 (15)	7 (44)	0 (0)
Surgery	1 (0)	1 (1)	1 (1)	0 (0)	0 (0)
Other therapies	4 (2)	1 (1)	1 (1)	0 (0)	0 (0)

* Patients may have received more than one anti-cancer therapies following discontinuation of study therapy.
† Other therapies include: All other therapeutic products, antineoplastic and immunomodulating agents, CAR-T cells, CDX-1140, investigational antineoplastic drugs, M6223, relatlimab, talimogene laherparepvec, tiragolumab

Table S4 – Rates of overall survival and progression free survival in the ITT population

	Overall survival		Progression free survival	
Rate (%)	Tebentafusp (N=252)	Control (N=126)	Tebentafusp (N=252)	Control (N=126)
1-year	72%	60%	17%	9%
2-year	45%	30%	8%	3%
3-year	27%	18%	4%	0%

Table S5 – Univariate analysis of baseline factors and overall survival in the tebentafusp group

		Univariate	
Parameter		**n**	**Hazard Ratio (95% CI)**
Sex	Female	124	0.85 (0.64, 1.13)
ECOG	0	193	0.42 (0.30, 0.60)
Age	<65 yrs	130	0.77 (0.58, 1.03)
LDH level	LDH ≤ ULN 250 U/L (n, %)	162	0.25 (0.18, 0.33)
ALP level	ALP ≤ ULN	198	0.32 (0.23, 0.44)
Largest liver lesion	≤ 3cm	139	0.16 (0.10, 0.27)
Largest liver lesion	3.1-8.0 cm	92	0.39 (0.24, 0.65)
Time since primary diagnosis in years	Continuous, per 1 year increase	252	0.95 (0.92, 0.99)

Abbreviations: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal

Table S6 – Summary of patients alive at Day 100 by response type

Category	Best Overall Response	Tebentafusp (n=235)	Control (n=108)
Best Overall Response	CR/PR	28 (12%)	6 (6%)
	SD	87 (37%)	28 (26%)
	PD	118 (50%)	68 (63%)
	NE	2 (1%)	6 (6%)
Best Overall Response prior to Day 100	CR/PR	17 (7%)	3 (3%)
	SD	99 (42%)	34 (31%)
	PD	104 (44%)	53 (49%)
	NE	15 (6%)	18 (17%)

Table S7 – Treatment-related adverse events in the as-treated population

Tebentafusp (N=245)			Investigator's choice (control group) (N=111)		
Adverse event, n (%)	**Any grade (≥20%)***	**Grade 3-4 (≥2%)***	**Adverse event, n (%)**	**Any grade (≥20%)***	**Grade 3-4 (≥2%)***
Any	244 (100)	116 (47)	Any	91 (82)	20 (18)
Cytokine release syndrome†	*217 (89)*	*2 (1)*	Rash‡	30 (27)	0
Rash‡	204 (83)	46 (19)	Fatigue	28 (25)	1 (1)
Pyrexia	187 (76)	11 (5)	Pruritus	25 (23)	0
Pruritus	171 (70)	11 (5)	Diarrhea	16 (14)	3 (3)
Chills	120 (49)	2 (1)	Lipase increased	8 (7)	6 (5)
Nausea	110 (45)	3 (1)			
Fatigue	103 (42)	7 (3)			
Hypotension	93 (38)	9 (4)			
Dry skin	72 (29)	0			
Vomiting	66 (27)	1 (0)			
Erythema	59 (24)	0			
Headache	53 (22)	1 (0)			
Aspartate aminotransferase increased	52 (21)	14 (6)			
Hair color changes	50 (20)	0			
Alanine aminotransferase increased	49 (20)	9 (4)			
Lipase increased	36 (15)	9 (4)			
Lymphopenia	23 (9)	7 (3)			
Hyperbilirubinemia	22 (9)	5 (2)			
Hypophosphatemia	20 (8)	8 (3)			
Hypertension	17 (7)	10 (4)			

*Related adverse events reported in ≥20% incidence for events at any grade or ≥2% of grade 3-4

† Cytokine release syndrome was graded according to 2019 American Society for Transplantation and Cellular Therapy consensus grading.[21]

‡ Rash is a composite term for a list of skin-related adverse events (Table S7)

Table S8 – Treatment-emergent adverse events in the as-treated population

	Tebentafusp (N=245)	Investigator's Choice (control group) (N=111)
Preferred Term, n (%)	**Any grade (≥ 10%)**	**Any grade (≥ 10%)**
Any TEAE	245 (100%)	107 (96%)
Pyrexia	189 (77%)	9 (8%)
Pruritus	172 (70%)	28 (25%)
Rash	136 (56%)	20 (18%)
Fatigue	127 (52%)	40 (36%)
Chills	126 (51%)	6 (5%)
Nausea	125 (51%)	30 (27%)
Hypotension	95 (39%)	3 (3%)
Rash maculo-papular	79 (32%)	11 (10%)
Dry skin	77 (31%)	4 (4%)
Headache	77 (31%)	12 (11%)
Vomiting	75 (31%)	10 (9%)
Oedema peripheral	71 (29%)	4 (4%)
Abdominal pain	66 (27%)	17 (15%)
Diarrhoea	66 (27%)	22 (20%)
Aspartate aminotransferase increased	63 (26%)	12 (11%)
Erythema	63 (26%)	1 (1%)
Arthralgia	62 (25%)	19 (17%)
Alanine aminotransferase increased	58 (24%)	13 (12%)
Abdominal pain upper	56 (23%)	14 (13%)
Back pain	53 (22%)	11 (10%)
Skin exfoliation	53 (22%)	2 (2%)
Cytokine release syndrome	51 (21%)	0
Decreased appetite	51 (21%)	16 (14%)
Hair colour changes	50 (20%)	0
Constipation	48 (20%)	14 (13%)
Cough	46 (19%)	12 (11%)
Vitiligo	44 (18%)	4 (4%)
Hypertension	41 (17%)	8 (7%)
Lipase increased	40 (16%)	8 (7%)
Asthenia	37 (15%)	9 (8%)
Dyspnoea	35 (14%)	7 (6%)
Dizziness	33 (14%)	9 (8%)
Paraesthesia	30 (12%)	1 (1%)
Hyperbilirubinaemia	29 (12%)	10 (9%)
Hypophosphataemia	28 (11%)	2 (2%)
Myalgia	28 (11%)	7 (6%)
Anaemia	27 (11%)	7 (6%)
Insomnia	27 (11%)	6 (5%)
Blood alkaline phosphatase increased	26 (11%)	2 (2%)

	Tebentafusp (N=245)	Investigator's Choice (control group) (N=111)
Preferred Term, n (%)	**Any grade (≥ 10%)**	**Any grade (≥ 10%)**
Lymphopenia	26 (11%)	3 (3%)
Periorbital oedema	26 (11%)	1 (1%)
Face oedema	25 (10%)	2 (2%)
Flushing	25 (10%)	1 (1%)
Pain in extremity	25 (10%)	4 (4%)
Hypothyroidism	3 (1%)	14 (13%)
Hyperthyroidism	2 (1%)	12 (11%)

Table S9 – Serious adverse events

System organ class / Preferred term	Tebentafusp (N=245) Any grade n (%)	Investigator's Choice (control group) (N=111) Any grade n (%)
Any TEAE	79 (32%)	24 (22%)
Infections and infestations	6 (2%)	2 (2%)
Anorectal infection	0	1 (1%)
Appendicitis	1 (0.4%)	0
COVID-19	1 (0.4%)	0
COVID-19 pneumonia	1 (0.4%)	0
Diverticulitis	1 (0.4%)	0
Erysipelas	1 (0.4%)	0
Pneumonia	0	1 (1%)
Pneumonia mycoplasmal	0	1 (1%)
Salmonella sepsis	1 (0.4%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (2%)	1 (1%)
Brain neoplasm malignant	1 (0.4%)	0
Metastases to abdominal cavity	0	1 (1%)
Metastases to liver	1 (0.4%)	0
Tumour pain	2 (1%)	0
Blood and lymphatic system disorders	1 (0.4%)	0
Anaemia	1 (0.4%)	0
Immune system disorders	25 (10%)	0
Anaphylactic reaction	1 (0.4%)	0
Cytokine release syndrome	24 (10%)	0
Endocrine disorders	0	1 (1%)
Hypopituitarism	0	1 (1%)
Metabolism and nutrition disorders	2 (1%)	3 (3%)
Dehydration	0	2 (2%)
Failure to thrive	1 (0.4%)	0
Hyperglycaemia	0	1 (1%)
Tumour lysis syndrome	1 (0.4%)	0
Psychiatric disorders	1 (0.4%)	1 (1%)
Mental status changes	1 (0.4%)	1 (1%)
Nervous system disorders	6 (2%)	2 (2%)
Brain oedema	1 (0.4%)	0
Dizziness	1 (0.4%)	0
Intracranial mass	0	1 (1%)
Motor dysfunction	1 (0.4%)	0
Presyncope	1 (0.4%)	0
Seizure	0	1 (1%)
Spinal cord compression	1 (0.4%)	0
Transient ischaemic attack	1 (0.4%)	0
Eye disorders	3 (1%)	1 (1%)
Diplopia	1 (0.4%)	0
Optic ischaemic neuropathy	1 (0.4%)	0

System organ class / Preferred term	Tebentafusp (N=245) Any grade n (%)	Investigator's Choice (control group) (N=111) Any grade n (%)
Uveitis	0	1 (1%)
Vitreous haemorrhage	1 (0.4%)	0
Cardiac disorders	4 (2%)	1 (1%)
Acute myocardial infarction	1 (0.4%)	0
Angina pectoris	1 (0.4%)	0
Cardiac failure congestive	1 (0.4%)	0
Left ventricular dysfunction	0	1 (1%)
Myocardial infarction	1 (0.4%)	0
Vascular disorders	6 (2%)	0
Hypotension	6 (2%)	0
Respiratory, thoracic and mediastinal disorders	5 (2%)	6 (5%)
Cough	0	1 (1%)
Dyspnoea	1 (0.4%)	0
Pleurisy	0	1 (1%)
Pneumonitis	1 (0.4%)	1 (1%)
Pulmonary embolism	2 (1%)	3 (3%)
Pulmonary oedema	1 (0.4%)	0
Sleep apnoea syndrome	0	1 (1%)
Gastrointestinal disorders	8 (3%)	7 (6%)
Abdominal pain	3 (1%)	3 (3%)
Abdominal pain upper	1 (0.4%)	0
Colitis	0	1 (1%)
Diarrhoea	0	1 (1%)
Enteritis	0	1 (1%)
Gastritis	0	1 (1%)
Nausea	5 (2%)	1 (1%)
Vomiting	2 (1%)	0
Hepatobiliary disorders	7 (3%)	3 (3%)
Biliary obstruction	1 (0.4%)	0
Hepatic failure	1 (0.4%)	0
Hepatic necrosis	1 (0.4%)	0
Hepatic pain	1 (0.4%)	1 (1%)
Hepatomegaly	0	1 (1%)
Hepatotoxicity	2 (1%)	0
Hyperbilirubinaemia	1 (0.4%)	3 (3%)
Hypertransaminasaemia	1 (0.4%)	0
Skin and subcutaneous tissue disorders	15 (6%)	0
Dermatitis	1 (0.4%)	0
Pruritus	1 (0.4%)	0
Rash	5 (2%)	0
Rash maculo-papular	4 (2%)	0
Rash papular	2 (1%)	0
Skin reaction	1 (0.4%)	0
Urticaria	1 (0.4%)	0
Musculoskeletal and connective tissue disorders	0	2 (2%)
Bone pain	0	1 (1%)

	Tebentafusp (N=245)	Investigator's Choice (control group) (N=111)
System organ class / Preferred term	**Any grade n (%)**	**Any grade n (%)**
Pathological fracture	0	1 (1%)
Renal and urinary disorders	2 (1%)	0
Acute kidney injury	1 (0.4%)	0
Renal failure	1 (0.4%)	0
General disorders and administration site conditions	8 (3%)	2 (2%)
Asthenia	1 (0.4%)	0
Chills	1 (0.4%)	0
Fatigue	1 (0.4%)	0
General physical health deterioration	1 (0.4%)	0
Pain	1 (0.4%)	0
Pyrexia	7 (3%)	2 (2%)
Investigations	2 (1%)	1 (1%)
Alanine aminotransferase increased	1 (0.4%)	0
Amylase increased	1 (0.4%)	0
Aspartate aminotransferase increased	1 (0.4%)	0
Lipase increased	0	1 (1%)
Injury, poisoning and procedural complications	3 (1%)	1 (1%)
Fall	0	1 (1%)
Multiple fractures	1 (0.4%)	0
Patella fracture	1 (0.4%)	0
Procedural pain	1 (0.4%)	0

Table S10 – Treatment-emergent adverse events in crossover patients

	Crossover patients (N=16)	
Adverse event, n (%)	**Any grade (≥20%)**	**Grade 3-4 (≥10%)**
Any	16 (100)	10 (63)
Pruritus	12 (75)	2 (13)
Pyrexia	9 (56)	1 (6)
Chills	8 (50)	0 (0)
Rash*	8 (50)	3 (19)
Fatigue	6 (38)	1 (6)
Vomiting	6 (38)	0 (0)
Alanine aminotransferase increased	5 (31)	1 (6)
Blood alkaline phosphatase increased	5 (31)	1 (6)
Anemia	5 (31)	1 (6)
Aspartate aminotransferase increased	5 (31)	0 (0)
Abdominal pain	5 (31)	0 (0)
Nausea	5 (31)	0 (0)
Cytokine release syndrome	4 (25)	0 (0)
Hypotension	4 (25)	0 (0)
Constipation	4 (25)	0 (0)

* Rash composite terms includes: Blister, Dermatitis, Rash, Rash macular, Rash maculo-papular

Table S11 – Composite terms for Rash, Hypotension and Liver Function Tests

Composite term	Adverse event (any grade)
Rash	Blister, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Dermatitis contact, Dermatosis, Drug eruption, Eczema, Eczema eyelids, Erythema multiforme, Exfoliative rash, Interstitial granulomatous dermatitis, Lichenoid keratosis, Palmar-plantar erythrodysaesthesia syndrome, Papule, Psoriasis, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash vesicular, Seborrhoea, Seborrhoeic dermatitis, Skin abrasion, Skin erosion, Skin exfoliation, Skin irritation, Skin plaque, Solar dermatitis, Urticaria
Hypotension	Blood pressure decreased, Hypotension
Liver Function Tests	Alanine aminotransferase increased, Ascites, Aspartate aminotransferase increased, Blood bilirubin increased, Coagulation factor V level decreased, Gamma-glutamyltransferase increased, Hepatic failure, Hepatic necrosis, Hepatic pain, Hepatocellular injury, Hepatotoxicity, Hyperbilirubinaemia, Hypertransaminasaemia, Immune-mediated hepatitis, Jaundice, Prothrombin level decreased, Prothrombin time prolonged, Transaminases increase

References

1. Aggarwal C, Ben-Shachar R, Gao Y, et al. Assessment of Tumor Mutational Burden and Outcomes in Patients With Diverse Advanced Cancers Treated With Immunotherapy. JAMA Netw Open 2023;6(5):e2311181.

2. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 1993;80(3):557–72.

3. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. New Engl J Med [Internet] 2021;385(13):1196–206. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34551229

4. Carvajal RD, Butler MO, Shoushtari AN, et al. Clinical and molecular response to tebentafusp in previously treated patients with metastatic uveal melanoma: a phase 2 trial. Nat Med [Internet] 2022;28(11):2364–73. Available from: https://www.ncbi.nlm.nih.gov/pubmed/36229663

5. Zhang Q, Luo J, Wu S, et al. Prognostic and Predictive Impact of Circulating Tumor DNA in Patients with Advanced Cancers Treated with Immune Checkpoint Blockade. Cancer Discov [Internet] 2020;10(12):1842–53. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32816849

6. Vega DM, Nishimura KK, Zariffa N, et al. Changes in Circulating Tumor DNA Reflect Clinical Benefit Across Multiple Studies of Patients With Non–Small-Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. JCO Precis Oncol [Internet] 2022;6(6):e2100372. Available from: https://pubmed.ncbi.nlm.nih.gov/35952319/