Supplementary Methods, Tables and Figures

This appendix is a supplement to: Hamid et al. Tebentafusp in Combination with Durvalumab and/or Tremelimumab in Patients with Metastatic Cutaneous Melanoma: A Phase 1 Study

Clinical trial registration number: NCT02535078

Contents

Supplementary Table 1. Dose levels of Tebentafusp, Durvalumab and Tremelimumab by Arm

Arm	Dose Level cohort	Tebentafusp Dose	Durvalumab Dose	Tremelimumab Dose
Arm 1	-1[a]	10 mcg	1 mg/kg	-
	1 (starting dose)	17 mcg	3 mg/kg	-
	2	30 mcg[b]	3 mg/kg	-
	3	40 mcg[b]	3 mg/kg	-
	4	40 mcg[b]	10 mg/kg	-
	5	50 mcg[b]	10 mg/kg	-
	6	58 mcg[b]	10 mg/kg	-
	7	68 mcg[b]	10 mg/kg	-
	8	68 mcg[b,c]	20 mg/kg[c]	-
Arm 2	-1[a]	10 mcg	-	0.5 mg/kg
	1 (starting dose)	17 mcg	-	1 mg/kg
	2	30 mcg[b]	-	1 mg/kg
	3	40 mcg[b]	-	1 mg/kg
	4	40 mcg[b]	-	3 mg/kg
	5	50 mcg[b]	-	3 mg/kg
	6	50 mcg[b]	-	10 mg/kg
Arm 3	-1[a]	10 mcg	1 mg/kg	0.5 mg/kg
	1 (starting dose)	17 mcg	3 mg/kg	0.5 mg/kg
	2	30 mcg[b]	3 mg/kg	0.5 mg/kg
	3	40 mcg[b]	3 mg/kg	0.5 mg/kg
	4	40 mcg[b]	10 mg/kg	0.5 mg/kg
	5	40 mcg[b]	10 mg/kg	1 mg/kg
	6	50 mcg[b]	10 mg/kg	1 mg/kg
	7	50 mcg[b]	15 mg/kg	1 mg/kg
	8	50 mcg[b]	20 mg/kg	1 mg/kg

[a] Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level.
[b] Beginning with Cohort 2, the dose administered at Cycle 1 Day 1 (C1D1) was capped at 20 mcg and C1D8 was capped at 30 mcg. Dosing at the cohort dose level then commenced at C1D15. Dosing at C1D1 and C1D8 was always capped at 20 mcg and 30 mcg, respectively, at cohort level 2 and beyond.
[c] Dose escalation of tebentafusp in Arm 1 beyond 68 mcg was to occur in 10 mcg increments until MTD or RP2D has been defined; the durvalumab dose was capped at 20 mg/kg.

Supplementary Table 2. Dose Limiting Toxicity Definitions

DLTs include any AE of NCI CTCAE Grade 3 or higher occurring during the DLT observation period, for which relationship to study treatment cannot be ruled out, with the following modifications:

Adverse Event	Dose-Limiting Toxicity Definition
Hematology	≥ Grade 3 lymphopenia in the presence of an infection indicating clinically significant lymphopenia is a DLT Grade 4 neutropenia persisting > 5 days after onset or associated with infection is a DLT ≥ Grade 3 febrile neutropenia is a DLT Grade 4 anemia is a DLT Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with ≥ Grade 3 bleeding is a DLT
Hepatic	Elevated total bilirubin (> 2 × ULN) with concurrent ALT and/or AST elevation (> 3 × ULN) with no clear alternate etiology (eg, biliary obstruction with elevated alkaline phosphatase) is a DLT ALT and/or AST elevation (> 5-8 × ULN if baseline was normal or > 5-8 × baseline if baseline was abnormal) or isolated bilirubin elevation (> 3-5 × ULN if baseline was normal; > 3-5 × baseline if baseline was abnormal) that does not resolve to ≤ Grade 1 within 7 days of onset is a DLT ALT and/or AST elevation (> 8 × ULN if baseline was normal; > 8 × baseline if baseline was abnormal) or bilirubin elevation (> 5 × ULN if baseline was normal; > 5 × baseline if baseline was abnormal) is a DLT
Gastrointestinal	Grade 3 nausea, vomiting, or diarrhea persisting for > 2 days after onset, despite optimal therapy, is a DLT
Pneumonitis	Grade 2 pneumonitis that is symptomatic and/or limiting instrumental ADL for > 7 days after onset despite treatment with corticosteroids is a DLT ≥ Grade 3 pneumonitis of any duration is a DLT
Hypotension	Grade 3 hypotension that does not resolve to ≤ Grade 1 within 6 hours of onset, despite optimal therapy, is a DLT Grade 4 hypotension of any duration and with any management is a DLT
Hypertension	Grade 3 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg) persisting > 7 days despite treatment is a DLT Grade 4 hypertension of any duration is a DLT
Fever/Infection	Grade 3 infection in the absence of neutropenia that persists > 72 hours after onset is a DLT Grade 4 infection of any duration is a DLT Fever > 40.0°C that persists > 48 hours after onset is a DLT
Colitis	≥ Grade 3 colitis of any duration is a DLT
Tumor flare	Grade 3 inflammatory reaction at a tumor site associated with a local anti-tumor immune response that does not resolve to Grade ≤ 2 within 7 days is a DLT
Electrolytes	Grade 3 electrolyte abnormalities that persist > 72 hours despite treatment and are clinically significant are DLT Any other Grade 4 electrolyte abnormality of any duration is a DLT
Adverse skin reaction/Rash and/or photosensitivity	Grade 3 adverse skin reaction and/or rash and/or pruritis that persists > 7 days after onset is a DLT Grade 4 cutaneous toxicity of any duration is a DLT
Injection site reaction	≥ Grade 3 injection site reaction of any duration is a DLT
Fatigue	≥ Grade 3 fatigue that persists > 7 days after onset is a DLT
Other imAE/irAE	Any Grade 3 imAE/irAE related to a vital organ, including any neurologic imAE/irAE or nephritis, is a DLT If not otherwise specified, a Grade 3 imAE/irAE that does not resolve to ≤ Grade 1 within 14 days of onset despite optimal treatment is a DLT Grade 4 imAE/irAE of any duration is a DLT

Infusion-related reaction	Grade 3 infusion-related reaction that does not resolve to ≤ Grade 2 within 6 hours of onset despite optimal medical management is a DLT Any Grade 4 infusion reaction is a DLT
Cytokine release syndrome*	Grade 3 cytokine release syndrome that does not resolve to ≤ Grade 2 within 6 hours of onset despite optimal medical management is a DLT Grade 4 cytokine release syndrome of any duration is a DLT
Other AEs	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in the DLT period, may be considered to be DLTs by the investigators and sponsor, even if not NCI CTCAE Grade 3 or higher

ADL = activities of daily living, AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C#D# = Cycle # Day #; DLT = dose limiting toxicity; imAE/irAE = immune-mediated adverse event / immune-related adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

* CRS was graded per 2019 ASTCT consensus criteria

Supplementary Table 3. Tebentafusp related adverse events

Preferred Term	Arm 1 Tebentafusp + Durvalumab (n=43) No. (%)	Arm 2 Tebentafusp + Tremelimumab (n=13) No. (%)	Arm 3 Tebentafusp + Durvalumab + Tremelimumab (n=29) No. (%)	Efficacy Population (N=72) No. (%)	Overall (≥5%) (N=85) No. (%)
Any TEAE related to tebentafusp	43 (100%)	13 (100%)	28 (97%)	71 (99%)	84 (99%)
Rash	29 (67%)	7 (54%)	23 (79%)	52 (72%	59 (69%)
Pruritus	28 (65%)	8 (62%)	17 (59%)	45 (63%)	53 (62%)
Pyrexia	22 (51%)	5 (39%)	11 (38%)	33 (46%)	38 (45%)
Fatigue	20 (47%)	4 (31%)	13 (45%)	33 (46%)	37 (44%)
Dry skin	13 (30%)	3 (23%)	3 (10%)	16 (22%)	19 (22%)
Nausea	13 (30%)	0	6 (21%)	19 (27%)	19 (22%)
Periorbital oedema	10 (23%)	2 (15%)	7 (24%)	17 (24%)	19 (22%)
Rash maculo-papular	12 (28%)	3 (23%)	3 (10%)	15 (21%)	18 (21%)
Chills	9 (21%)	3 (23%)	5 (17%)	14 (19%)	17 (20%)
Vitiligo	8 (19%)	2 (15%)	5 (17%)	13 (18%)	15 (18%)
Vomiting	9 (21%)	1 (8%)	5 (17%)	14 (19%)	15 (18%)
Oedema peripheral	6 (14%)	3 (23%)	5 (17%)	11 (15%)	14 (17%)
Hair color changes	7 (16%)	0	6 (21%)	13 (18%)	13 (15%)
Skin exfoliation	9 (21%)	1 (8%)	3 (10%)	12 (17%)	13 (15%)
Diarrhoea	3 (7%)	3 (23%)	6 (21%)	9 (13%)	12 (14%)
Face oedema	8 (19%)	2 (15%)	2 (7%)	10 (14%)	12 (14%)
Erythema	7 (16%)	0	4 (14%)	11 (15%)	11 (13%)
Lipase increased	5 (12%)	1 (8%)	5 (17%)	10 (14%)	11 (13%)
Arthralgia	4 (9%)	1 (8%)	5 (17%)	9 (13%)	10 (12%)
Alanine aminotransferase increased	4 (9%)	1 (8%)	4 (14%)	8 (11%)	9 (11%)
Blood alkaline phosphatase increased	3 (7%)	0	5 (17%)	8 (11%)	8 (9%)
Hypotension	5 (12%)	0	3 (10%)	8 (11%)	8 (9%)
Myalgia	4 (9%)	1 (8%)	3 (10%)	7 (10%)	8 (9%)
Peripheral swelling	4 (9%)	3 (23%)	1 (3%)	5 (7%)	8 (9%)
Tachycardia	5 (12%)	0	3 (10%)	8 (11%)	8 (9%)
Aspartate aminotransferase increased	4 (9%)	1 (8%)	2 (7%)	6 (8%)	7 (8%)
Dizziness	3 (7%)	1 (8%)	3 (10%)	6 (8%)	7 (8%)
Flushing	4 (9%)	0	3 (10%)	7 (10%)	7 (8%)
Headache	3 (7%)	1 (8%)	3 (10%)	6 (8%)	7 (8%)
Amylase increased	4 (9%)	0	2 (7%)	6 (8%)	6 (7%)
Decreased appetite	4 (9%)	0	2 (7%)	6 (8%)	6 (7%)
Abdominal pain	2 (5%)	0	3 (10%)	5 (7%)	5 (6%)
Alopecia	2 (5%)	1 (8%)	2 (7%)	4 (6%)	5 (6%)
Cough	1 (2%)	1 (8%)	3 (10%)	4 (6%)	5 (6%)
Cytokine release syndrome	3 (7%)	0	2 (7%)	5 (7%)	5 (6%)
Hypomagnesaemia	3 (7%)	0	2 (7%)	5 (7%)	5 (6%)
Skin hyperpigmentation	2 (5%)	1 (8%)	2 (7%)	4 (6%)	5 (6%)
Skin hypopigmentation	4 (9%)	1 (8%)	0	4 (6%)	5 (6%)

Preferred Term	Arm 1 Tebentafusp + Durvalumab (n=43) No. (%)	Arm 2 Tebentafusp + Tremelimumab (n=13) No. (%)	Arm 3 Tebentafusp + Durvalumab + Tremelimumab (n=29) No. (%)	Efficacy Population (N=72) No. (%)	Overall (≥5%) (N=85) No. (%)

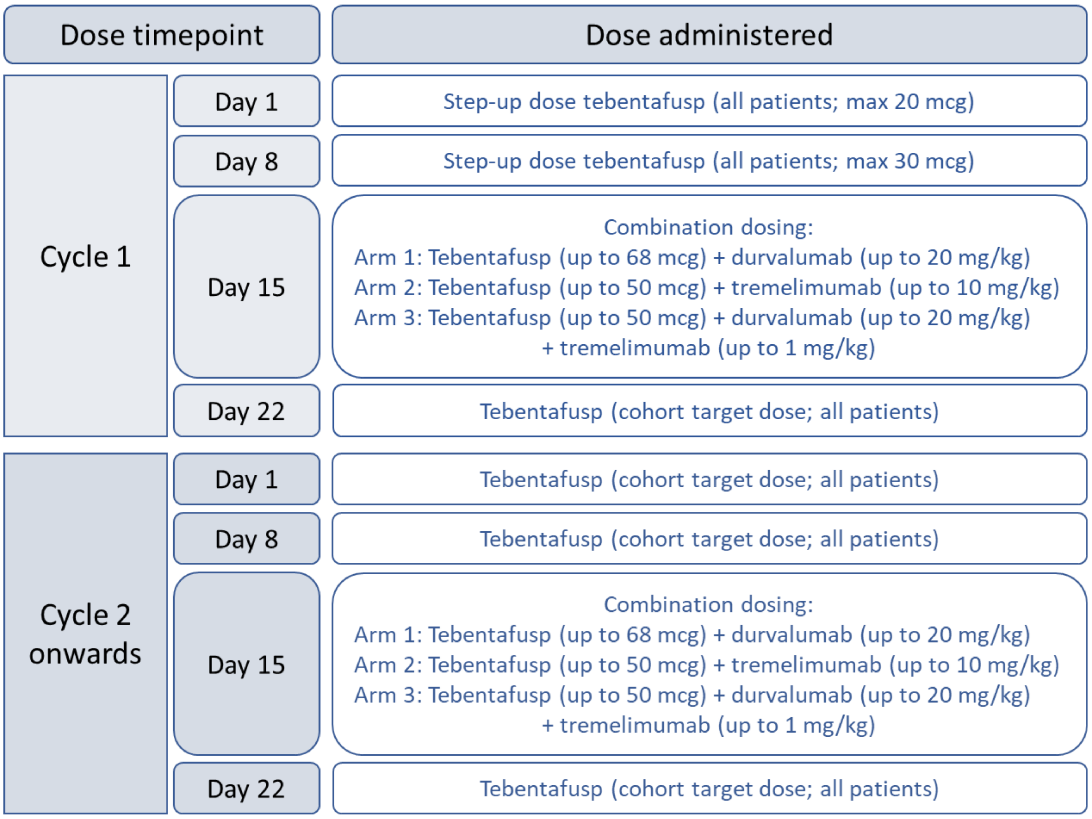
TEAE = Treatment-Emergent Adverse Event.
Patients with multiple TEAEs per PT are counted only once in each row.
Adverse events are coded using MedDRA version 23.1.
For a given treatment period (initial or restart), treatment-emergent adverse events are defined as any adverse event with a start date from day of first dose of study treatment (in that period) up to 90 days after last dose of study treatment (in that period) or until start of alternative cancer therapy post treatment end date (in the relevant period), whichever occurs first.
Number (%) of patients are sorted by descending frequency in the Overall column (Phase Ib) for PT.

Supplementary Table 4. Durvalumab or Tremelimumab related adverse events

Preferred Term	Tebentafusp + Durvalumab (n=43) No. (%)	Tebentafusp + Tremelimumab (n=13) No. (%)	Tebentafusp + Durvalumab + Tremelimumab (n=29) No. (%)	Efficacy Population (N=72) No. (%)	Overall (≥5%) (N=85) No. (%)
Any TEAE related to durvalumab or tremelimumab	35 (81%)	7 (54%)	25 (86%)	60 (83%)	67 (79%)
Fatigue	14 (33%)	3 (23%)	7 (24%)	21 (29%)	24 (28%)
Rash	10 (23%)	4 (31%)	10 (35%)	20 (28%)	24 (28%)
Pruritus	11 (26%)	4 (31%)	7 (24%)	18 (25%)	22 (26%)
Pyrexia	9 (21%)	1 (8%)	4 (14%)	13 (18%)	14 (17%)
Vitiligo	7 (16%)	2 (15%)	3 (10%)	10 (14%)	12 (14%)
Hair colour changes	6 (14%)	0	5 (17%)	11 (15%)	11 (13%)
Lipase increased	5 (12%)	1 (8%)	5 (17%)	10 (14%)	11 (13%)
Nausea	6 (14%)	1 (8%)	4 (14%)	10 (14%)	11 (13%)
Diarrhoea	3 (7%)	2 (15%)	5 (17%)	8 (11%)	10 (12%)
Arthralgia	4 (9%)	1 (8%)	3 (10%)	7 (10%)	8 (9%)
Dry skin	6 (14%)	1 (8%)	1 (3%)	7 (10%)	8 (9%)
Rash maculo-papular	5 (12%)	2 (15%)	1 (3%)	6	8 (9%)
Amylase increased	5 (12%)	0	2 (7%)	7 (10%)	7 (8%)
Chills	4 (9%)	1 (8%)	2 (7%)	6	7 (8%)
Alanine aminotransferase increased	2 (5%)	1 (8%)	3 (10%)	5	6 (7%)
Blood alkaline phosphatase increased	2 (5%)	0	4 (14%)	6	6 (7%)
Abdominal pain	1 (2%)	1 (8%)	3 (10%)	4	5 (6%)
Aspartate aminotransferase increased	1 (2%)	1 (8%)	3 (10%)	4	5 (6%)
Periorbital oedema	4 (9%)	0	1 (3%)	5	5 (6%)
Vomiting	3 (7%)	0	2 (7%)	5	5 (6%)

TEAE = Treatment-Emergent Adverse Event.
Patients with multiple TEAEs per PT are counted only once in each row.
Adverse events are coded using MedDRA version 23.1.
For a given treatment period (initial or restart), treatment-emergent adverse events are defined as any adverse event with a start date from day of first dose of study treatment (in that period) up to 90 days after last dose of study treatment (in that period) or until start of alternative cancer therapy post treatment end date (in the relevant period), whichever occurs first.
Number (%) of patients are sorted by descending frequency in the Overall column (Phase Ib) for PT.

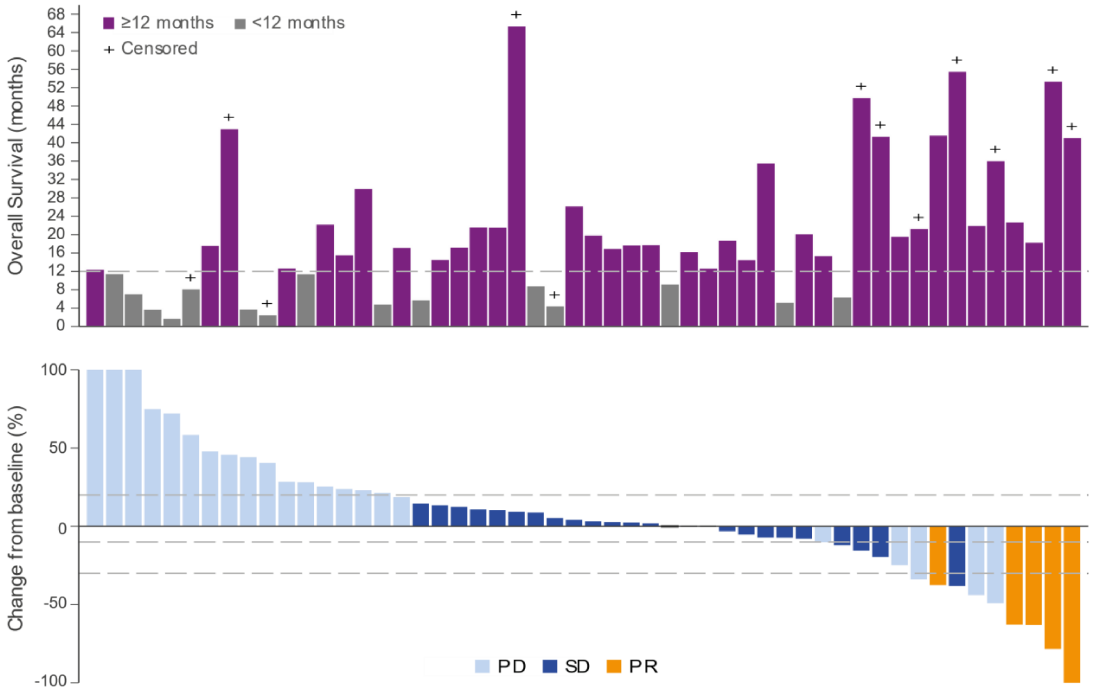
Supplemental Figure 1. Treatment regimen



Supplemental Figure 1. Treatment regimen

Tebentafusp was administered in weekly (QW) IV doses with each treatment cycle consisting of 4 weeks. Combination dosing with durvalumab and / or tremelimumab administered once monthly (Q4W) beginning on day 15 of each cycle. In the first cycle, patients first received step-up doses of tebentafusp on day 1 and day 8. From cycle 1 day 15 onwards, patients received the target dose of tebentafusp determined by the cohort level in each Arm outlined in supplementary Table S1. In Arm 2, tremelimumab was dosed Q4W (Day 15 of each cycle) for 7 doses (Cycles 1-7) followed by dosing every Q12W until treatment discontinuation. In Arm 3, tremelimumab was dosed Q4W (Day 15 of each cycle) for 4 doses (Cycles 1-4) only.

Supplemental Figure 2. Overall survival and best change in tumor size from baseline in patients who progressed on anti-PD(L)1 prior to receiving tebentafusp in combination with durvalumab +/- tremelimumab

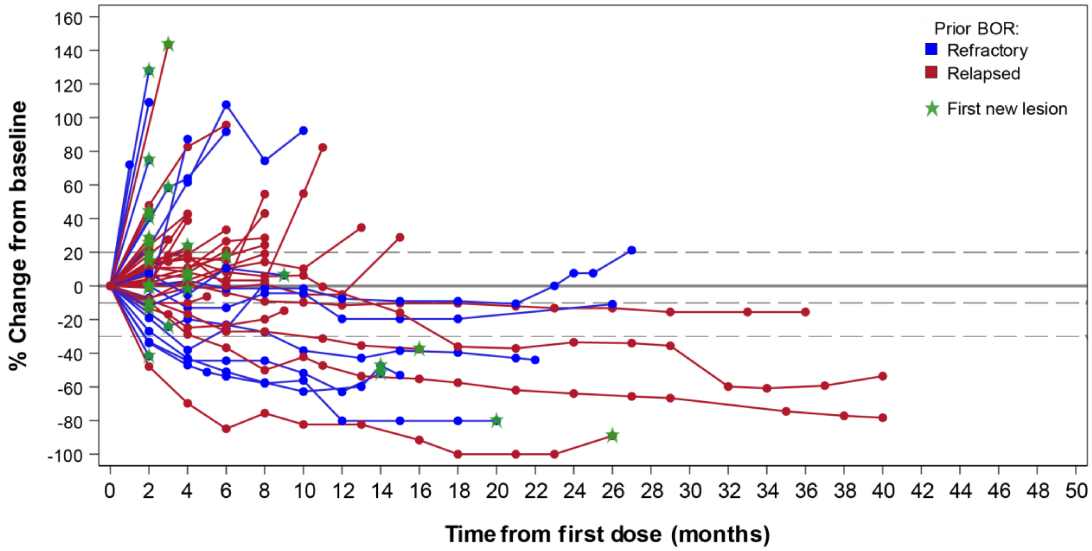


Supplemental Figure 2. Overall survival and best change in tumor size from baseline in patients who progressed on anti-PD(L)1 prior to receiving tebentafusp in combination with durvalumab +/- tremelimumab

(A) Overall survival in months is plotted for each evaluable patient (n=52). + denotes censored. (A-B) Data are presented only for those patients for whom BOR to previous anti-PD(L)1 therapy was known and only patients with at least one evaluable post baseline target lesion scan were included. Six patients overall 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. **(B)** Waterfall plot showing the best change in tumour size (n=52). 37% of patients had tumour 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 investigator assessment. 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. Tumor shrinkage is shown regardless of whether new lesions identified. Reference lines at 20%

and -30% mark target lesion response criteria for disease progression (PD), partial response (PR), respectively. SD, stable disease.

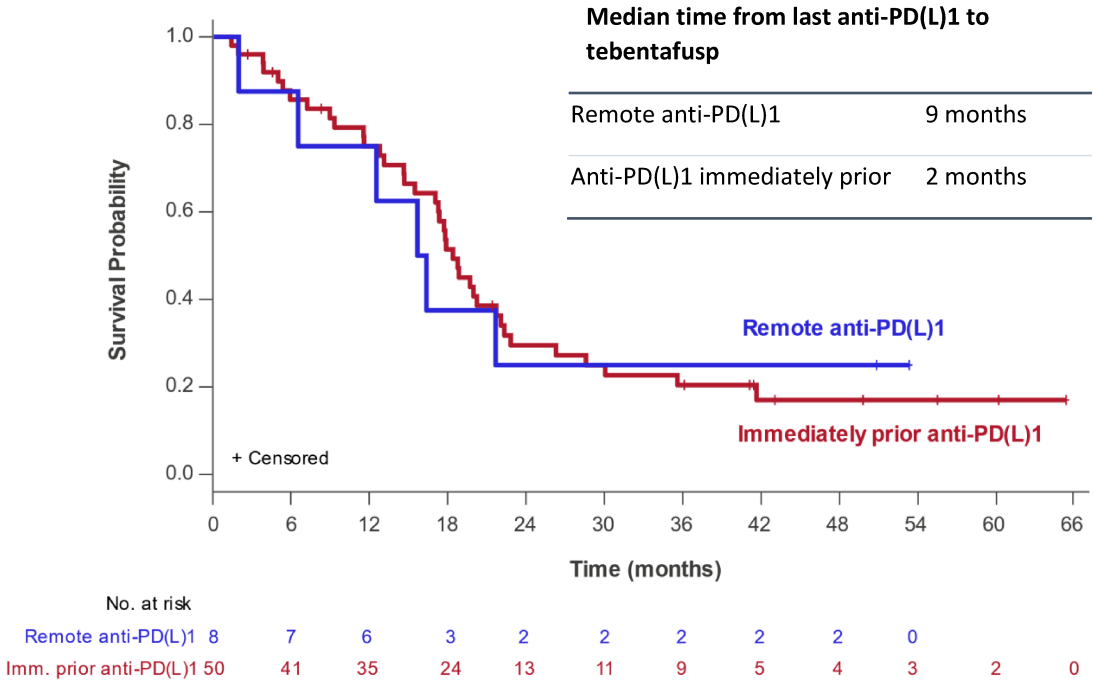
Supplemental Figure 3. Tumor kinetics according to prior anti-PD(L)1 resistance/refractory status



Supplemental Figure 3. Tumor kinetics according to prior anti-PD(L)1 relapsed/refractory status

Spider plot showing percent change in tumor size for patients with known best overall response to prior anti-PD(L)1 therapy. Tumor size is measured as the sum of longest diameters or short axis of the target lesions according to RECISTv1.1 by investigator opinion. Only patients with baseline and at least one evaluable post-baseline target lesion scans are included (n=52). Tumor shrinkage is regardless of whether new lesions identified; Relapsed = best response CR/PR/SD to prior PD(L)1, Refractory = best response of PD to prior anti-PD(L)1).

Supplemental Figure 4. OS by whether prior anti-PD(L)1 therapy was remote or most recent therapy



Supplementary Figure 4. OS by whether prior anti-PD(L)1 therapy was remote or most recent therapy. Kaplan-Meier estimates of overall survival for patients in Arms 1 and 3 (tebentafusp + durvalumab +/- tremelimumab; n=58) who progressed on prior anti-PD(L)1 prior to enrolment by timing of anti-PD(L)1 therapy. Remote = Patients received prior anti-PD(L)1 but it was not most recent therapy prior to enrolment (median time from last anti-PD(L)1 was 9 months); Immediately prior = anti-PD(L)1 was most recent therapy prior to enrolment (median time from last anti-PD(L)1 was 2 months).