Supplementary Material

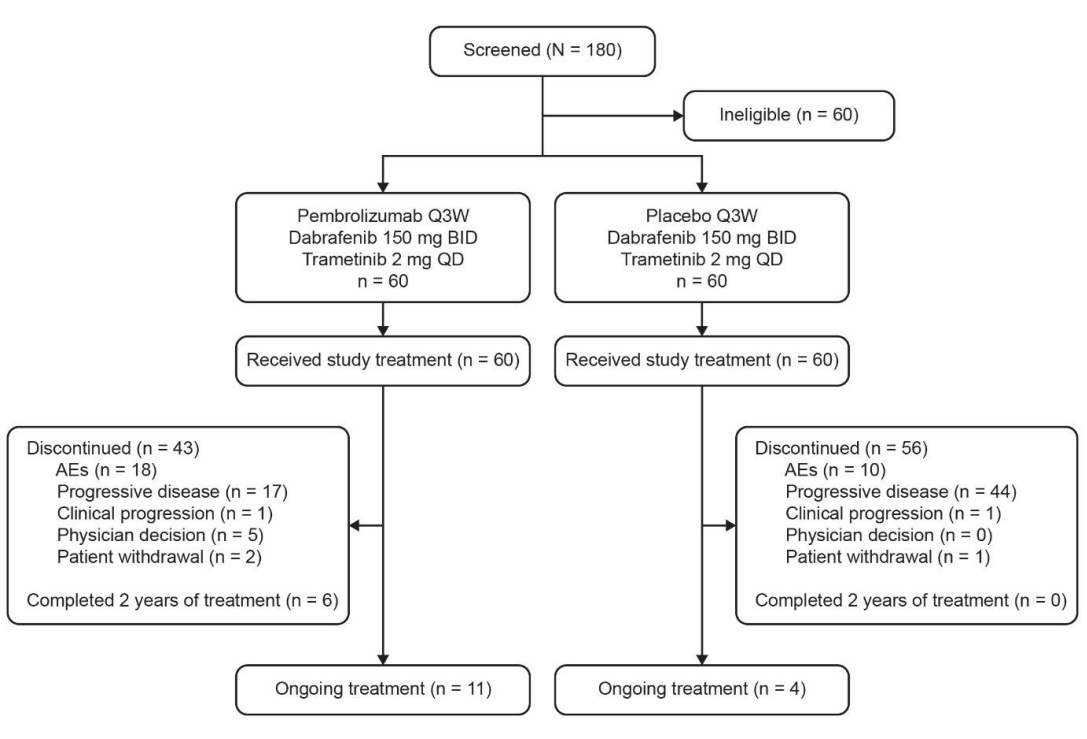
Methods

Duration of follow-up was defined as the time from randomization to the date of death or the date of database cutoff if the patient is still alive.

Immune-mediated adverse events were selected from a prespecified list and defined as events of unknown cause associated with drug exposure and consistent with an immune event.

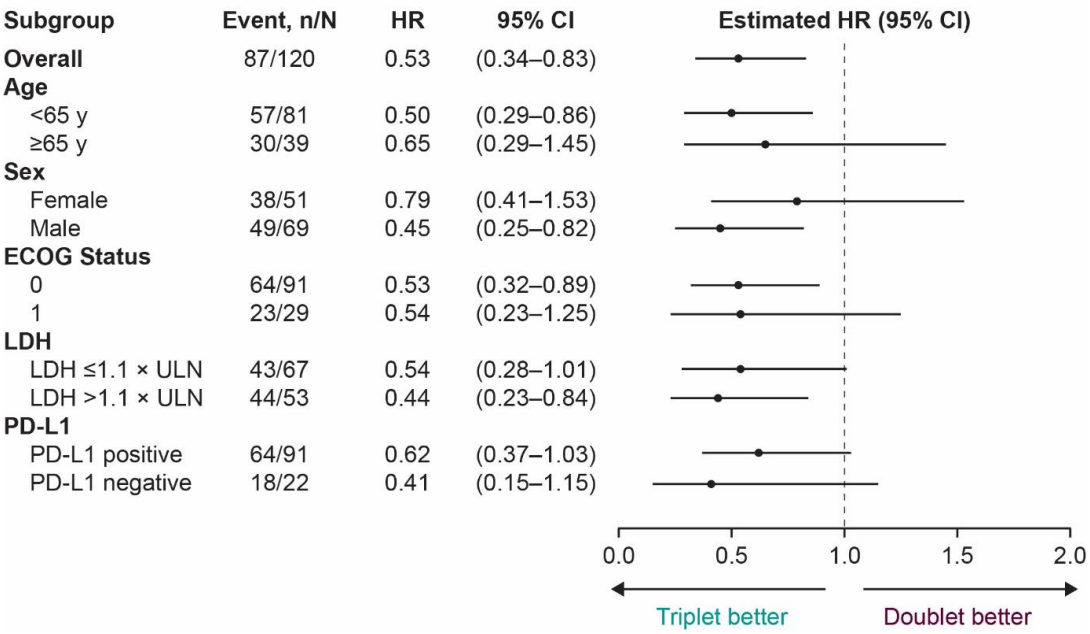
Ferrucci PF, *et al. J Immunother Cancer* 2020; 8:e001806. doi: 10.1136/jitc-2020-001806

Figure S1 Patient flow diagram.



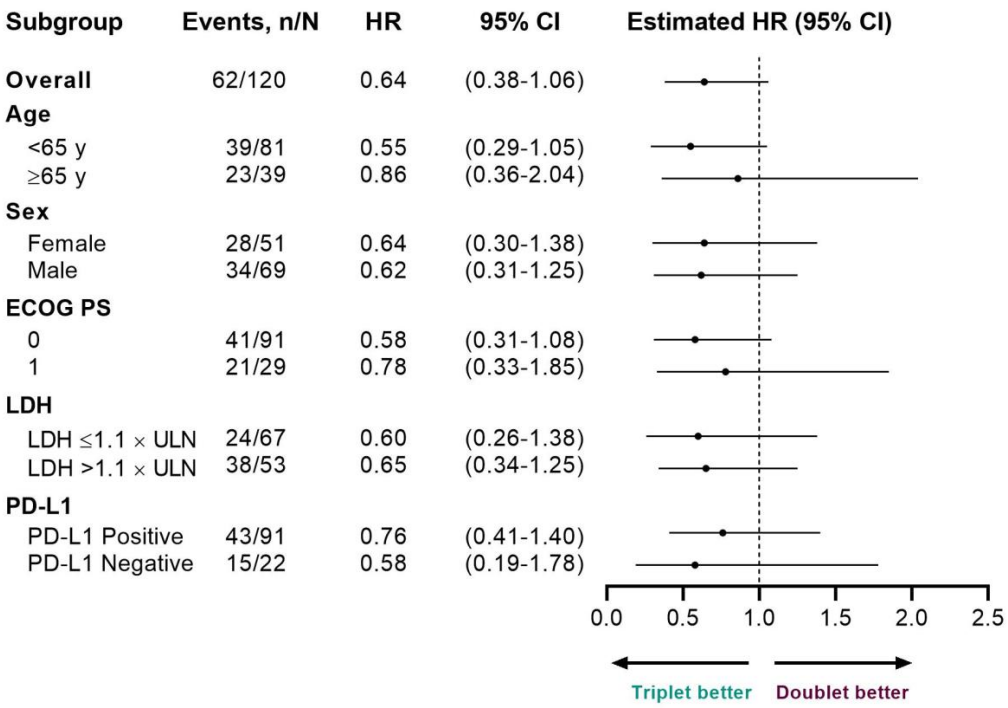
AEs, adverse events; BID, twice daily; Q3W, every 3 weeks; QD, once daily.

Figure S2 Kaplan-Meier estimates of progression-free survival in key subgroups.



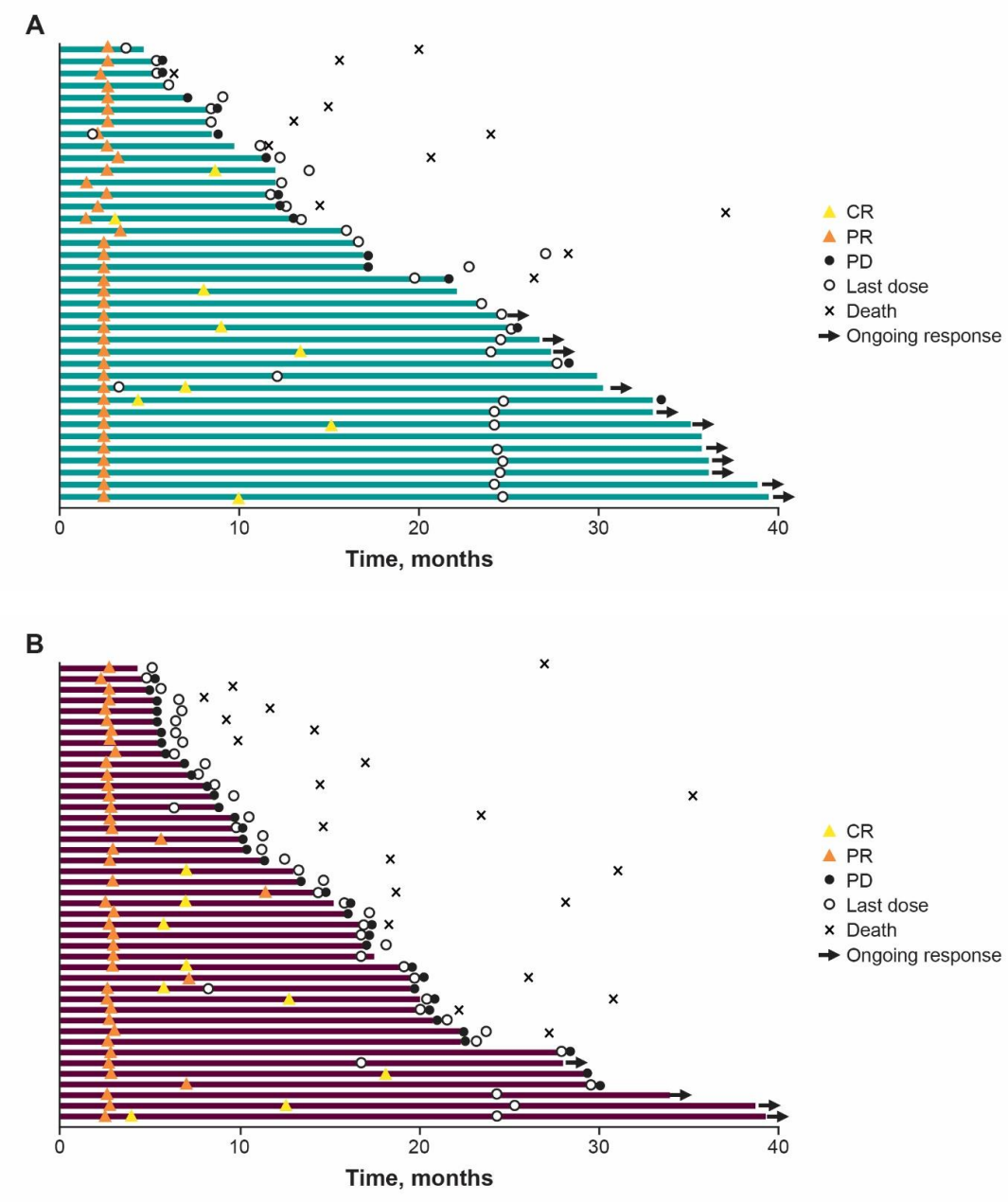
Progression-free survival was defined as time from randomization to disease progression or death, whichever came first. Median progression-free survival was based on Kaplan-Meier estimate per investigator assessment. The hazard ratios and 95% confidence intervals were calculated using a Cox regression model with treatment as a covariate and stratified by ECOG performance status (0 vs 1) and LDH (>1.1× ULN vs ≤1.1× ULN); because of the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1× ULN strata, these strata were combined. PD-L1 positive status was defined as >1% staining in tumor and adjacent immune cells by immunohistochemistry using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). CI, confidence interval; Doublet, placebo plus dabrafenib plus trametinib; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; Triplet, pembrolizumab plus dabrafenib plus trametinib; ULN, the upper limit of normal.

Figure S3 Kaplan-Meier estimates of overall survival in key subgroups.



Overall survival was defined as time from randomization to death due to any cause. Median overall survival was based on Kaplan-Meier estimate. The hazard ratios and 95% confidence intervals were calculated using a Cox regression model with treatment as a covariate and stratified by ECOG performance status (0 vs 1) and LDH (>1.1× ULN vs ≤1.1× ULN); because of the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1× ULN strata, these strata were combined. PD-L1 positive status was defined as >1% staining in tumor and adjacent immune cells by immunohistochemistry using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). CI, confidence interval; Doublet, placebo plus dabrafenib plus trametinib; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; Triplet, pembrolizumab plus dabrafenib plus trametinib; ULN, the upper limit of normal.

Figure S4 Time to response and time to progression in patients (A) in the triplet arm (pembrolizumab plus dabrafenib and trametinib) and (B) in the doublet arm (placebo plus dabrafenib and trametinib).



Response and progression were based on investigator assessment per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation in Solid Tumors, version 1.1.

Figure S5 Best percentage reduction in tumor line length from baseline by investigator assessment in patients with measurable disease at baseline. (**A**) Triplet therapy (pembrolizumab plus dabrafenib plus trametinib). (**B**) Doublet therapy (placebo plus dabrafenib plus trametinib).

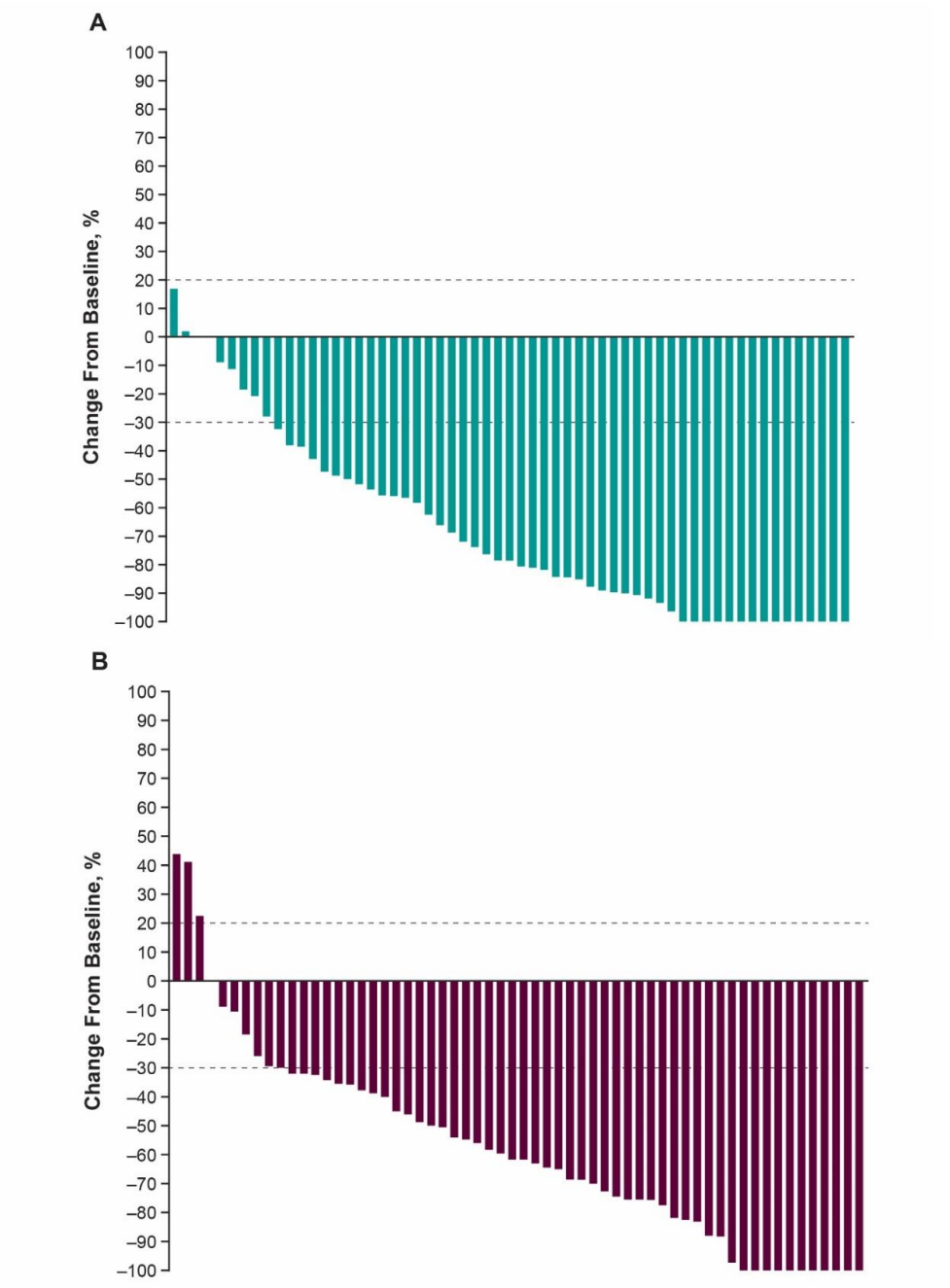


Table S1 Principal investigators and their affiliated sites

Country	Institution	Investigator
USA	University of California Los Angeles	Antoni Ribas
USA	Goshen General Hospital	Sachin Agarwal
USA	Texas Oncology PA	Charles Cowey
Canada	Jewish General Hospital	Wilson Miller
Canada	Sunnybrook Research Institute	Teresa Petrella
Canada	Hotel Dieu de Quebec, CHUQ	Felix Couture
Italy	Istituto dei tumori Fond. G. Pascale	Paolo Ascierto
Italy	Istituto Nazionale Tumori	Michele Del Vecchio
Italy	Azienda Ospedaliera Universitaria Senese	Michele Maio
Italy	IRCCS A.O.U. San Martino - IST	Francesco Spagnolo
Italy	European Institute of Oncology	Pier Francesco Ferrucci
Israel	Sheba Medical Center	Jacob Schachter
Israel	Hadassah Ein Karem Jerusalem	Michal Lotem
Israel	Rambam Health Care Campus	Karen Drumea
Denmark	Herlev og Gentofte Hospital	Eva Ellebaek
Denmark	Herlev og Gentofte Hospital	Inge Svane
Denmark	Odense Universitetshospital	Lars Bastholt
Denmark	Aarhus University Hospital	Henrik Schmidt
Australia	Gallipoli Medical Research Centre	Victoria Atkinson
Australia	Melanoma Institute Australia	Georgina Long
Australia	Westmead Hospital	Matteo Carlino
New Zealand	Auckland City Hospital	Michael McCrystal

Table S2 Baseline characteristics (intention-to-treat population)

	Pembrolizumab + dabrafenib + trametinib n=60	**Placebo + dabrafenib + trametinib n=60**
Age, median (range), years	54 (18–82)	58 (21–83)
Sex, n (%)		
Female	27 (45.0)	24 (40.0)
Male	33 (55.0)	36 (60.0)
ECOG PS,* n (%)		
0	47 (78.3)	44 (73.3)
1	13 (21.7)	16 (26.7)
Stage at study entry, n (%)		
IIIB	1 (1.7)	1 (1.7)
IIIC	0 (0.0)	2 (3.3)
IV	59 (98.3)	57 (95.0)
Metastatic stage, n (%)		
M1a	2 (3.3)	10 (16.7)
M1b	8 (13.3)	9 (15.0)
M1c	49 (81.7)	38 (63.3)
Location of metastases, n (%)		
≤2 sites	24 (40.0)	29 (48.3)
>2 sites	36 (60.0)	31 (51.7)
Brain metastases, n (%)		
Yes	1 (1.7)	1 (1.7)
No	59 (98.3)	59 (98.3)
BRAF mutation status, n (%)		

V600K	8 (13.3)	11 (18.3)
V600E	52 (86.7)	49 (81.7)
Baseline PD-L1 status, n (%)		
PD-L1 negative†	10 (16.7)	12 (20.0)
PD-L1 positive	47 (78.3)	44 (73.3)
Missing	3 (5.0)	4 (6.7)
LDH level, n (%)		
≤1.1× ULN	33 (55.0)	34 (56.7)
>1.1× ULN	27 (45.0)	26 (43.3)
Previous radiation, n (%)	9 (15.0)	6 (10.0)
Previous therapy, n (%)		
Adjuvant	8 (13.3)	5 (8.3)
Neoadjuvant	1 (1.7)	1 (1.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

*ECOG PS assessment at day 1 of cycle 1 was included in the determination of baseline.

†PD-L1 positive status was defined as ≥1% staining in tumor and adjacent immune cells by immunohistochemistry using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).

Table S3 Drug exposure (all-subjects-as-treated population)

	Pembrolizumab + dabrafenib + trametinib n=60	**Placebo + dabrafenib + trametinib n=60**
Pembrolizumab/placebo, median (range)		
Months	7.4 (0.0–24.9)	8.8 (0.7-24.4)
Number of administrations	12 (1–36)	13 (2–36)
Dabrafenib, median (range)		
Months	12.4 (0.4–40.0)	9.1 (1.1–41.0)
Number of administrations	702 (26–2514)	560 (64–2474)
Trametinib, median (range)		
Months	12.4 (0.2–40.0)	9.1 (1.1–41.0)
Number of administrations	344 (7–1176)	276 (27–1202)

Table S4 Patients with adverse events leading to treatment discontinuation

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
Pembrolizumab + dabrafenib + trametinib arm						
1	Hepatitis	2.14 weeks	2	Y (pembro, T, D)	Discontinued (pembro, T, D)	Resolved
2	Peripheral edema	1.68 months	2	Y (T)	Discontinued (T)	Resolved
	Peripheral edema	1.61 months	1	Y (T)	Discontinued (T)	Resolved
	Face edema	1 week	1	Y (T)	Discontinued (T)	Resolved
	Tubulointerstitial nephritis	2.99 months	3	Y (pembro, T, D)	Discontinued (pembro, D)	Resolved
	Hypercalcemia	5 days	2	Y (pembro, T, D)	Discontinued (pembro, D)	Resolved
3	Hypoesthesia	2.92 months	3	Y (pembro)	Discontinued (pembro)	Resolved
4	Transaminases increased	2.46 months	3	Y (T, D)	Discontinued (pembro, T, D)	Resolved
5	Pneumonitis	3.45 months	3	Y (pembro)	Discontinued (pembro) Interrupted (T, D)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
6	Sepsis	1.84 months	4	Y (T, D)	Discontinued (pembro) Reduced (T, D)	Resolved
	Myalgia	1.29 weeks	3	None	Discontinued (T, D)	Sequelae
7	Pneumonitis	2.4 months	5	Y (pembro)	Discontinued (pembro, T, D)	Fatal
8	Pneumonitis	1.43 weeks	3	Y (pembro)	Discontinued (pembro) Interrupted (T, D)	Resolved
9	Detachment of retinal pigment epithelium	1.48 months	3	Y (T)	Discontinued (T) Interrupted (D)	Resolved
	Skin lesion	1.58 months	1	Y (D)	Discontinued (D)	Resolved
10	Pneumonitis	1.05 months	2	Y (pembro, T, D)	Discontinued (pembro, T, D)	Resolved
11	Drug-induced liver injury	3.68 months	3	Y (pembro, T, D)	Discontinued (pembro, T, D)	Resolved
12	Nausea	3 days	2	Y (T, D)	Discontinued (pembro, T, D)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
	Periorbital edema	1.28 months	2	Y (T, D)	Discontinued (pembro, T, D)	Resolved
13	Pneumonitis	1.64 months	3	Y (pembro)	Discontinued (pembro) Reduced (T, D)	Resolved
14	Back pain	Continuing	3	None	Discontinued (pembro, T, D)	Not resolved
15	Increased ALT	Continuing	4	Y (pembro, T, D)	Discontinued (pembro)	Not resolved
	Increased AST	Continuing	3	Y (pembro, T, D)	Discontinued (pembro, T, D)	Not resolved
	Increased GGT	2.6 months	3	Y (pembro, T, D)	Discontinued (pembro)	Resolved
	Increased blood ALP	2.29 weeks	1	Y (pembro, T, D)	Discontinued (pembro)	Resolved
16	Dermatitis	7.79 months	2	Y (pembro, T, D)	Discontinued (T, D) Interrupted (pembro)	Resolved
	Diarrhea	Continuing	3	Y (pembro)	Discontinued (pembro)	Not resolved
17	Pyrexia	4 days	1	Y (T, D)	Discontinued (T, D)	Resolved
	Peripheral motor	1.91 months	3	Y (pembro)	Discontinued (pembro)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
	neuropathy					
18	Increased ALT	2.71 weeks	1	Y (T, D)	Discontinued (pembro) Reduced (T, D)	Resolved
	Increased AST	2.73 months	3	Y (T, D)	Discontinued (pembro) Reduced (T, D)	Resolved
19	Increased ALT	1.12 months	1	Y (pembro, T, D)	Discontinued (pembro, T, D)	Resolved
	Increased AST	2.71 weeks	3	Y (pembro, T, D)	Discontinued (pembro, T, D)	Resolved
20	Hypophysitis	5.22 months	3	Y (T, D)	Discontinued (pembro) Interrupted (T, D)	Resolved
	Drug-induced liver injury	3.75 months	3	Y (pembro, T, D)	Discontinued (T, D)	Resolved
	Pyrexia	6 days	3	Y (D)	Discontinued (T, D)	Resolved
21	Death	23 hours	5	None	Discontinued (pembro, T, D)	Fatal
22	Transaminases	1.43 weeks	3	Y (pembro, D)	Discontinued (pembro, T, D)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
	increased					
23	Increased ALT	1.87 months	3	Y (pembro, D)	Discontinued (pembro, T, D)	Resolved
	Increased AST	1.45 months	3	Y (pembro, D)	Discontinued (pembro, T, D)	Resolved
	Increased blood ALP	4 weeks	3	Y (pembro, D)	Discontinued (pembro, T, D)	Resolved
24	Myalgia	2.29 weeks	1	Y (T, D)	Discontinued (pembro, T, D)	Resolved
25	Headache	3 days	1	Y (pembro, T, D)	Discontinued (pembro)	Resolved
	Chills	23 hours	1	Y (pembro, T, D)	Discontinued (pembro) Interrupted (T, D)	Resolved
	Pneumonitis	4 days	3	Y (pembro)	Discontinued (pembro) Interrupted (T, D)	Resolved
26	Pneumonitis	Continuing	2	Y (pembro)	Discontinued (pembro)	Not resolved
27	Autoimmune hepatitis	1.41 months	2	Y (pembro, T, D)	Discontinued (pembro) Reduced (T, D)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
28	Colitis	7.92 months	3	Y (pembro)	Discontinued (pembro) Interrupted (T, D)	Resolved
Placebo + dabrafenib + trametinib arm						
1	Dermatitis acneiform	2.04	2	Y (placebo, T, D)	Discontinued (D)	Resolved
2	Pneumonitis	Continuing	2	Y (T, D)	Discontinued (placebo, T, D)	Not resolved
3	Breast cancer	Continuing	3	None	Discontinued (placebo, T, D)	Not resolved
4	Increased ALT	2 weeks	3	Y (placebo, T, D)	Discontinued (placebo, T, D)	Resolved
	Increased AST	2 weeks	3	Y (placebo, T, D)	Discontinued (placebo, T, D)	Resolved
	Increased blood ALP	1.43 weeks	2	Y (placebo, T, D)	Discontinued (placebo, T, D)	Resolved
	Increased GGT	1.43 weeks	3	Y (placebo, T, D)	Discontinued (placebo, T, D)	Resolved
5	Drug-induced liver injury	1.18 months	3	Y (placebo, T, D)	Discontinued (T, D) Interrupted (placebo)	Resolved
	Uveitis	9 months	3	Y (placebo)	Discontinued (placebo)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
					Reduced (T, D)	
6	Liver function test increased	3.14 weeks	3	Y (placebo, T, D)	Discontinued (placebo, T, D)	Resolved
7	Acute motor axonal neuropathy	Continuing	3	Y (placebo)	Discontinued (placebo, T, D)	Resolved
8	Fluid retention	11.01 months	3	Y (T)	Discontinued (placebo, T, D)	Resolved
9	Hepatitis	1.14 weeks	3	Y (placebo, T, D)	Discontinued (placebo) Interrupted (T, D)	Resolved
10	Increased AST	2.14 weeks	3	Y (T, D)	Discontinued (placebo, T, D)	Resolved
	Increased GGT	4.67 weeks	3	Y (T, D)	Discontinued (placebo, T, D)	Resolved
11	Diarrhea	5.32 months	2	Y (placebo, T, D)	Discontinued (T, D) Interrupted (placebo)	Resolved
	Fungal skin infection	2.04 months	2	None	Discontinued (T, D)	Resolved

Patient	Adverse event	Duration	Toxicity grade	Related to treatment (Y/N)	Action taken	Outcome
12	Joint swelling	5.98 months	2	Y (D)	Discontinued (T, D)	Resolved

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, dabrafenib; GGT, gamma-glutamyltransferase; N, no; pembro, pembrolizumab; T, trametinib; Y, yes.