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Supplementary Data

Supplementary Table 1: Sites of metastases at the start of PD1+/-IPI stratified by treatment type.

Characteristics	Anti-PD-1 monotherapy (N = 115)	Anti-PD-1 + anti-CTLA-4 (N = 85)	P-value
Brain Metastasis (n, %)			
No	71 (61.7%)	30 (35.3%)	**0.0004**
Yes	44 (38.3%)	55 (64.7%)	
Lung Metastasis (n, %)			
No	50 (43.5%)	39 (45.9%)	0.8460
Yes	65 (56.5%)	46 (54.1%)	
Liver Metastasis (n, %)			
No	79 (68.7%)	57 (67.1%)	0.9267
Yes	36 (31.3%)	28 (32.9%)	
GI[1] Metastasis (n, %)			
No	99 (86.1%)	70 (82.4%)	0.6005
Yes	16 (13.9%)	15 (17.6%)	
Bone Metastasis (n, %)			
No	80 (69.6%)	57 (67.1%)	0.8233
Yes	35 (30.4%)	28 (32.9%)	
Adrenal Metastasis (n, %)			
No	97 (84.3%)	72 (84.7%)	1.0000
Yes	18 (15.7%)	13 (15.3%)	
Soft tissue Metastasis (n, %)			
No	73 (63.5%)	65 (76.5%)	0.0704
Yes	42 (36.5%)	20 (23.5%)	
LN[2] Metastasis (n, %)			
No	32 (27.8%)	40 (47.1%)	**0.0080**
Yes	83 (72.2%)	45 (52.9%)	
Spleen Metastasis (n, %)			

[1] GI, gastrointestinal.
[2] LN, Lymph node.

Characteristics	Anti-PD-1 monotherapy (N = 115)	Anti-PD-1 + anti-CTLA-4 (N = 85)	P-value
No	105 (91.3%)	79 (92.9%)	0.8743
Yes	10 (8.7%)	6 (7.1%)	
Subcutaneous Metastasis (n, %)			
No	76 (66.1%)	69 (81.2%)	**0.0276**
Yes	39 (33.9%)	16 (18.8%)	

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Supplementary Table 2. Univariable and multivariable logistic regression of Objective response.

Variable	Univariate		Multivariable (†)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex				
Female	1	0.8293		
Male	1.07 (0.57, 2.00)			
BRAF mutation status				
V600E	1	1.0000		
Other	1.00 (0.51, 1.95)			
ECOG PS[3] at BRAF/MEKi start				
0	1	0.3006		
≥1	0.73 (0.40, 1.33)			
AJCC[4] staging at BRAF/MEKi start				
III/M1a/M1b	1	0.0667		
M1c/M1d	0.55 (0.29, 1.04)			
LDH[5] at BRAF/MEKi start				
UNL	1	0.0918		
>UNL	0.58 (0.31, 1.09)			
Overall Best Response[6] with BRAF/MEKi				
CR/PR	1	0.8070		
SD/PD	1.09 (0.54, 2.21)			
Number of progressive lesions after BRAF/MEKi				
1	1	0.0770		

[3] ECOG PS, Eastern Cooperative Oncology Group performance status.
[4] AJCC, American Joint Committee on Cancer.
[5] LDH, Lactate dehydrogenase.
[6] Overall Best Response: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Variable	Univariate		Multivariable (†)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
2	0.42 (0.16, 1.10)			
≥3	0.47 (0.23, 0.96)			
Progressing brain metastases at PD1+/-IPI start				
No	1	**0.0376**	1	0.0789
Yes	0.50 (0.26, 0.96)		0.53 (0.27, 1.08)	
Progressing liver metastases at PD1+/-IPI start				
No	1	0.5001		
Yes	0.72 (0.28, 1.85)			
Any steroids to control symptoms due to progression				
No	1	0.1896		
Yes	0.42 (0.11, 1.54)			
Duration of BRAF/MEKi treatment (months)				
	1.01 (0.99, 1.03)	0.3849		
Reason to BRAF/MEKi cessation				
Progressive disease	1	0.0589		
Elective	1.91 (0.98, 3.72)			
Interval between BRAF/MEKi and PD1+/-IPI (weeks)				
	1.01 (1.00, 1.02)	0.1776		
Age at PD1+/-IPI start (years)				
	0.99 (0.97, 1.01)	0.3904		
ECOG at PD1+/-IPI start				
0	1	**0.0021**	1	**0.0056**
≥1	0.39 (0.21, 0.71)		0.38 (0.19, 0.75)	
AJCC Staging at PD1+/-IPI start				
III/M1a/M1b	1	0.1652		

Variable	Univariate		Multivariable (†)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
M1c/M1d	0.60 (0.29, 1.24)			
Brain metastasis at PD1+/-IPI start				
No	1	0.1725		
Yes	0.67 (0.37, 1.19)			
Lung metastasis at PD1+/-IPI start				
No	1	0.3680		
Yes	1.31 (0.73, 2.35)			
Liver metastasis at PD1+/-IPI start				
No	1	0.0584		
Yes	0.53 (0.28, 1.02)			
GI metastasis at PD1+/-IPI start				
No	1	0.7325		
Yes	1.15 (0.52, 2.52)			
Bone metastasis at PD1+/-IPI start				
No	1	**0.0359**	1	0.0791
Yes	0.49 (0.25, 0.95)		0.49 (0.22, 1.09)	
Adrenal metastasis at PD1+/-IPI start				
No	1	0.2026		
Yes	0.57 (0.24, 1.35)			
Soft tissue metastasis at PD1+/-IPI start				
No	1	0.6743		
Yes	0.87 (0.47, 1.64)			
LN metastasis at PD1+/-IPI start				
No	1	0.3708		
Yes	1.32 (0.72, 2.43)			
Spleen metastasis at PD1+/-IPI start				
No	1	0.3449		
Yes	0.57 (0.18, 1.83)			

Variable	Univariate		Multivariable (†)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Subcutaneous metastasis at PD1+/-IPI start				
No	1	0.1673		
Yes	1.56 (0.83, 2.95)			
LDH at PD1+/-IPI start				
UNL	1	0.1145		
>UNL	0.62 (0.35, 1.12)			
Treatment				
PD1	1	0.4748		
IPI+PD1	1.24 (0.69, 2.21)			

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Supplementary Table 3. Univariable and multivariable Cox regression of Progression-free Survival.

Variable	Univariable		Multivariable (†)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex				
Female	1	0.7038		
Male	0.94 (0.67, 1.31)			
BRAF mutation status				
V600E	1	0.9877		
Other	1.00 (0.70, 1.43)			
ECOG PS at BRAF/MEKi start				
0	1	0.7866		
≥1	1.04 (0.76, 1.44)			
AJCC staging at BRAF/MEKi start				
III/M1a/M1b	1	**0.0222**	1	0.5735
M1c/M1d	1.53 (1.06, 2.19)		1.16 (0.69, 1.97)	
LDH at BRAF/MEKi start				
UNL	1	0.0608		
>UNL	1.36 (0.99, 1.89)			
Overall Best Response with BRAF/MEKi				
CR/PR	1	0.8247		
SD/PD	0.96 (0.66, 1.39)			
Number of progressive lesions after BRAF/MEKi				
1	1	0.2781		
2	1.28 (0.79, 2.08)			
≥3	1.37 (0.93, 2.03)			
Progressing brain metastases at PD1+/-IPI start				

Variable	Univariable		Multivariable (†)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
No	1	**0.0017**	1	0.9434
Yes	1.71 (1.22, 2.38)		1.03 (0.49, 2.15)	
Progressing liver metastases at PD1+/-IPI start				
No	1	0.4926		
Yes	1.17 (0.74, 1.85)			
Any steroids to control symptoms due to progression				
No	1	0.4835		
Yes	1.22 (0.70, 2.11)			
Duration of BRAF/MEKi treatment (months)	1.00 (0.99, 1.01)	0.7568		
Reason to BRAF/MEKi cessation				
Progressive disease	1	**0.0021**	1	0.4002
Elective	0.52 (0.34, 0.79)		0.75 (0.39, 1.46)	
Interval between BRAF/MEKi and PD1+/-IPI (weeks)	0.99 (0.99, 1.00)	0.1494		
Age at PD1+/-IPI start (years)	1.00 (0.99, 1.01)	0.4287		
ECOG at PD1+/-IPI start				
0	1	**0.0011**	1	**0.0017**
≥1	1.73 (1.24, 2.40)		1.78 (1.24, 2.55)	
AJCC Staging v8 at PD1+/-IPI start				
III/M1a/M1b	1	**0.0257**	1	0.2110
M1c/M1d	1.61 (1.06, 2.46)		0.63 (0.34, 1.27)	
Brain metastasis at PD1+/-IPI start				
No	1	**0.0072**	1	0.1261
Yes	1.53 (1.12, 2.09)		1.84 (0.84, 4.00)	
Lung metastasis at PD1+/-IPI start				
No	1	0.4023		
Yes	0.88 (0.64, 1.20)			

Variable	Univariable		Multivariable (†)	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Liver metastasis at PD1+/-IPI start				
No	1	**0.0079**	1	**0.0368**
Yes	1.56 (1.12, 2.16)		1.56 (1.03, 2.35)	
GI metastasis at PD1+/-IPI start				
No	1	0.6263		
Yes	1.11 (0.73, 1.70)			
Bone metastasis at PD1+/-IPI start				
No	1	**0.0117**	1	0.1062
Yes	1.52 (1.10, 2.11)		1.41 (0.93, 2.14)	
Adrenal metastasis at PD1+/-IPI start				
No	1	0.1365		
Yes	1.38 (0.90, 2.10)			
Soft tissue metastasis at PD1+/-IPI start				
No	1	0.9884		
Yes	1.00 (0.72, 1.40)			
LN metastasis at PD1+/-IPI start				
No	1	0.8364		
Yes	0.97 (0.70, 1.34)			
Spleen metastasis at PD1+/-IPI start				
No	1	0.1608		
Yes	1.46 (0.86, 2.49)			
Subcutaneous metastasis at PD1+/-IPI start				
No	1	0.5355		
Yes	0.90 (0.63, 1.27)			
LDH at PD1+/-IPI start				
UNL	1	0.1311		
>UNL	1.27 (0.93, 1.74)			

	Univariable		Multivariable (†)	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatment				
PD1	1	0.6951		
IPI+PD1	0.94 (0.69, 1.29)			

Supplementary Table 4. Univariable and multivariable Cox regression of Overall Survival.

Variable	Univariable		Multivariable (†)	
	HR	**P-value**	**HR**	**P-value**
Sex				
Female	1	0.6790		
Male	1.09 (0.73, 1.61)			
BRAF mutation status				
V600E	1	0.7083		
Other	1.08 (0.72, 1.63)			
ECOG PS at BRAF/MEKi start				
0	1	0.1297		
≥1	1.33 (0.92, 1.92)			
AJCC staging v8 at BRAF/MEKi start				
III/M1a/M1b	1	0.0592		
M1c/M1d	1.52 (0.98, 2.36)			
LDH at BRAF/MEKi start				
UNL	1	**0.0197**	1	0.0915
>UNL	1.56 (1.07, 2.27)		1.41 (0.95, 2.10)	
Overall Best Response with BRAF/MEKi				
CR/PR	1	0.8720		
SD/PD	1.04 (0.68, 1.59)			
Number of progressive lesions after BRAF/MEKi				
1	1	0.2683		
2	0.87 (0.47, 1.58)			
≥3	1.29 (0.82, 2.02)			
Progressing brain metastases at PD1+/-IPI start				

Variable	Univariable		Multivariable (†)	
	HR	**P-value**	**HR**	**P-value**
No	1	0.2102		
Yes	1.28 (0.87, 1.88)			
Progressing liver metastases at PD1+/-IPI start				
No	1	0.1360		
Yes	1.47 (0.89, 2.45)			
Any steroids to control symptoms due to progression				
No	1	0.5720		
Yes	1.21 (0.63, 2.32)			
Duration of BRAF/MEKi treatment (months)	0.98 (0.96, 1.00)	0.0536		
Reason to BRAF/MEKi cessation				
Progressive disease	1	**0.0058**	1	**0.0105**
Elective	0.49 (0.30, 0.81)		0.50 (0.30, 0.85)	
Interval between BRAF/MEKi and PD1+/-IPI (weeks)	1.00 (0.99, 1.00)	0.2727		
Age at PD1+/-IPI start (years)	1.01 (1.00, 1.02)	0.1263		
ECOG at PD1+/-IPI start				
0	1	**<.0001**	1	**<.0001**
≥1	2.85 (1.88, 4.34)		3.10 (1.99, 4.82)	
AJCC Staging v8 at PD1+/-IPI start				
III/M1a/M1b	1	0.0799		
M1c/M1d	1.58 (0.95, 2.65)			
Brain metastasis at PD1+/-IPI start				
No	1	0.2017		
Yes	1.27 (0.88, 1.83)			
Lung metastasis at PD1+/-IPI start				
No	1	0.9416		
Yes	0.99 (0.68, 1.42)			

Variable	Univariable		Multivariable (†)	
	HR	P-value	HR	P-value
Liver metastasis at PD1+/-IPI start				
No	1	**0.0041**	1	**0.0032**
Yes	1.73 (1.19, 2.52)		2.04 (1.27, 3.28)	
GI metastasis at PD1+/-IPI start				
No	1	0.9150		
Yes	0.97 (0.58, 1.63)			
Bone metastasis at PD1+/-IPI start				
No	1	**0.0015**	1	0.5803
Yes	1.83 (1.26, 2.66)		1.14 (0.71, 1.85)	
Adrenal metastasis at PD1+/-IPI start				
No	1	0.7081		
Yes	1.10 (0.67, 1.80)			
Soft tissue metastasis at PD1+/-IPI start				
No	1	0.9568		
Yes	1.01 (0.68, 1.49)			
LN metastasis at PD1+/-IPI start				
No	1	0.1957		
Yes	1.30 (0.87, 1.93)			
Spleen metastasis at PD1+/-IPI start				
No	1	0.1213		
Yes	1.61 (0.88, 2.92)			
Subcutaneous metastasis at PD1+/-IPI start				
No	1	0.6495		
Yes	1.10 (0.73, 1.64)			
LDH at PD1+/-IPI start				
UNL	1	**0.0034**	1	0.1518
>UNL	1.96 (1.25, 3.09)		1.35 (0.89, 2.05)	

Variable	Univariable		Multivariable (†)	
	HR	P-value	HR	P-value
Treatment				
PD1	1	0.2603		
IPI+PD1	0.81 (0.55, 1.17)			

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Supplementary Table 5. Univariate and Multivariable Logistic Regression to identify the subgroup of patient with progressive disease as best response to anti-PD1+/-anti-CTLA-4 after BRAF/MEKi.

Variable	Univariate		Multivariable		Predictive Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender						
Female	1	0.8675				
Male	1.05 (0.58, 1.93)					
Age at BRAF/MEKi start						
	1.01 (0.99, 1.03)	0.3522				
ECOG PS at BRAF/MEKi start						
0	1	0.2214				
>=1	1.44 (0.80, 2.57)					
AJCC staging at BRAF/MEKi start						
III/M1a/M1b	1	0.0876	1	0.9363		
M1c/M1d	1.73 (0.92, 3.25)		0.96 (0.34, 2.74)			
Overall Best Response with BRAF/MEKi						
CR/PR	1	0.5383				
SD/PD	1.24 (0.62, 2.50)					
LDH at BRAF/MEKi start						
UNL	1	0.0742	1	0.1984		
>UNL	1.73 (0.95, 3.16)		1.69 (0.76, 3.76)			
Number of progressive lesions at PD1+/-IPI start						
1	1	0.1087	1	0.1761		
2	1.60 (0.65, 3.92)		2.46 (0.88, 6.89)			
>=3	2.16 (1.06, 4.40)		1.93 (0.82, 4.55)			
Progressing brain metastases at PD1+/-IPI start						
No	1	0.0356	1	0.4593	1	0.0787
Yes	1.96 (1.05, 3.67)		1.73 (0.41, 7.35)		1.83 (0.93, 3.60)	
Progressing liver metastases at PD1+/-IPI start						

	Univariate		Multivariable		Predictive Model	
Variable	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
No	1	0.4278				
Yes	1.44 (0.58, 3.56)					
Any steroids to control symptoms due to progression						
No	1	0.2302				
Yes	2.05 (0.63, 6.66)					
Age at PD1+/-IPI start (years)						
	1.01 (0.99, 1.03)	0.4051				
ECOG at PD1+/-IPI start						
0	1	0.0094	1	0.0170	1	**0.0086**
>=1	2.17 (1.21, 3.90)		2.40 (1.17, 4.94)		2.42 (1.25, 4.70)	
BRAF mutation status						
V600E	1	0.7408				
Other	0.90 (0.47, 1.71)					
Duration of BRAF/MEKi treatment (months)						
	0.99 (0.97, 1.01)	0.3570				
Reason for BRAF/MEKi cessation						
Recurrence/PD	1	0.0245	1	0.5426		
Elective	0.46 (0.24, 0.91)		0.69 (0.21, 2.27)			
Interval between BRAF/MEKi and PD1+/-IPI (days)						
	1.00 (1.00, 1.00)	0.3342				
AJCC Staging at PD1+/-IPI start						
III/M1a/M1b	1	0.2039	1	0.2765		
M1c/M1d	1.59 (0.78, 3.26)		0.48 (0.13, 1.81)			
Brain metastasis at PD1+/-IPI start						
No	1	0.1107	1	0.5551		
Yes	1.58 (0.90, 2.79)		1.58 (0.35, 7.24)			
Lung metastasis at PD1+/-IPI start						
No	1	0.4928				

Variable	Univariate		Multivariable		Predictive Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Yes	0.82 (0.47, 1.45)					
Liver metastasis at PD1+/-IPI start						
No	1	0.0724	1	0.5516		
Yes	1.77 (0.95, 3.29)		1.31 (0.54, 3.19)			
GI metastasis at PD1+/-IPI start						
No	1	0.9937				
Yes	1.00 (0.46, 2.18)					
Bone metastasis at PD1+/-IPI start						
No	1	0.0099	1	0.1560	1	**0.0494**
Yes	2.32 (1.22, 4.41)		1.93 (0.78, 4.78)		2.13 (1.00, 4.54)	
Adrenal metastasis at PD1+/-IPI start						
No	1	0.1161	1	0.7705		
Yes	1.95 (0.85, 4.48)		1.17 (0.40, 3.47)			
Soft tissue metastasis at PD1+/-IPI start						
No	1	0.3470				
Yes	1.34 (0.73, 2.48)					
LN metastasis at PD1+/-IPI start						
No	1	0.7113				
Yes	0.90 (0.50, 1.61)					
Spleen metastasis at PD1+/-IPI start						
No	1	0.7042				
Yes	1.23 (0.43, 3.52)					
Subcutaneous metastasis at PD1+/-IPI start						
No	1	0.3528				
Yes	0.74 (0.40, 1.39)					
LDH at PD1+/-IPI start						
UNL	1	0.0695	1	0.3883		
>UNL	1.70 (0.96, 3.02)		1.39 (0.66, 2.91)			
Treatment						

Variable	Univariate		Multivariable		Predictive Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
PD1	1	0.7064				
IPI+PD1	0.90 (0.51, 1.58)					

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Supplementary Table 6. Univariate and Multivariable Logistic Regression to identify the subgroup of long-term survivors (OS > 3 years) with anti-PD1+/-anti-CTLA-4 after BRAF/MEKi.

Variable	Univariate		Multivariable		Clinical Models	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Gender						
Female	1	0.3224				
Male	0.69 (0.33, 1.43)					
Age at BRAF/MEKi start						
	0.97 (0.95, 0.99)	0.0167				
ECOG PS at BRAF/MEKi start						
0	1	0.6306				
>=1	0.84 (0.41, 1.71)					
AJCC staging at BRAF/MEKi start						
III/M1a/M1b	1	0.0151	1	0.8857		
M1c/M1d	0.39 (0.19, 0.84)		0.91 (0.24, 3.40)			
Overall Best Response with BRAF/MEKi						
CR/PR	1	0.4566				
SD/PD	0.71 (0.30, 1.73)					
LDH at BRAF/MEKi start						
UNL	1	0.0386	1	0.3930		
>UNL	0.44 (0.20, 0.96)		0.62 (0.20, 1.87)			
Number of progressive lesions at PD1+/-IPI start						
1	1	0.6257				
2	1.19 (0.41, 3.42)					
>=3	0.76 (0.32, 1.80)					
Progressing brain metastases at PD1+/-IPI start						
No	1	0.1349	1	0.7650		
Yes	0.56 (0.26, 1.20)		1.38 (0.17, 11.46)			
Progressing liver metastases at PD1+/-IPI start						

Variable	Univariate		Multivariable		Clinical Models	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
No	1	0.1280	1	0.5097		
Yes	0.37 (0.10, 1.33)		0.45 (0.04, 4.89)			
Any steroids to control symptoms due to progression						
No	1	0.6464				
Yes	0.73 (0.19, 2.80)					
Age at PD1+/-IPI start (years)						
	0.97 (0.95, 1.00)	0.0265	0.98 (0.94, 1.01)	0.2170		
ECOG at PD1+/-IPI start						
0	1	0.0003	1	0.0107	1	**<.0001**
>=1	0.25 (0.12, 0.53)		0.25 (0.09, 0.73)		0.19 (0.09, 0.44)	
BRAF mutation status						
V600E	1	0.1282	1	0.0804		
Other	0.49 (0.20, 1.23)		0.30 (0.08, 1.16)			
Duration of BRAF/MEKi treatment (months)						
	1.05 (1.02, 1.09)	0.0038	1.05 (1.00, 1.11)	0.0488		
Reason for BRAF/MEKi cessation						
Recurrence/PD	1	0.7504				
Elective	1.16 (0.46, 2.90)					
Interval between BRAF/MEKi and PD1+/-IPI (days)						
	1.00 (1.00, 1.00)	0.7170				
AJCC Staging at PD1+/-IPI start						
III/M1a/M1b	1	0.1155	1	0.0658		
M1c/M1d	0.50 (0.21, 1.19)		5.50 (0.89, 33.82)			
Brain metastasis at PD1+/-IPI start						
No	1	0.1696	1	0.0478		
Yes	0.61 (0.30, 1.24)		0.10 (0.01, 0.98)			
Lung metastasis at PD1+/-IPI start						
No	1	0.3473				
Yes	1.41 (0.69, 2.89)					

Variable	Univariate		Multivariable		Clinical Models	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Liver metastasis at PD1+/-IPI start						
No	1	0.0020	1	0.0390	1	**0.0005**
Yes	0.23 (0.09, 0.58)		0.16 (0.03, 0.91)		0.16 (0.06, 0.45)	
GI metastasis at PD1+/-IPI start						
No	1	0.5448				
Yes	1.33 (0.53, 3.38)					
Bone metastasis at PD1+/-IPI start						
No	1	0.0020	1	0.0978		
Yes	0.23 (0.09, 0.58)		0.29 (0.07, 1.26)			
Adrenal metastasis at PD1+/-IPI start						
No	1	0.3864				
Yes	0.63 (0.22, 1.80)					
Soft tissue metastasis at PD1+/-IPI start						
No	1	0.9688				
Yes	0.99 (0.47, 2.08)					
LN metastasis at PD1+/-IPI start						
No	1	0.6514				
Yes	0.84 (0.40, 1.77)					
Spleen metastasis at PD1+/-IPI start						
No	1	0.2952				
Yes	0.44 (0.09, 2.06)					
Subcutaneous metastasis at PD1+/-IPI start						
No	1	0.2565				
Yes	0.62 (0.27, 1.42)					
LDH at PD1+/-IPI start						
UNL	1	0.0009	1	0.2383		
>UNL	0.27 (0.13, 0.59)		0.54 (0.19, 1.51)			
Treatment						
PD1	1	0.8952				

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Variable	Univariate		Multivariable		Clinical Models	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
IPI+PD1	0.95 (0.46, 1.96)					

Supplementary Table 7. Proportion of any grade immune-related adverse events (AE) by treatment type.

Any grade immune-related adverse events	Anti-PD1 (n=115)			Anti-PD1 + anti-CTLA-4 (n=85)		
Grade	**< G3**	**≥ G3**	**Any**	**< G3**	**≥ G3**	**Any**
Diarrhea/colitis (n, %)	9 (8%)	0	9 (8%)	9 (11%)	13 (15%)	22 (26%)
Hepatitis (n, %)	2 (2%)	3 (3%)	5 (4%)	8 (9%)	9 (11%)	17 (20%)
Skin toxicity (n, %)	16 (14%)	0	16 (14%)	19 (22%)	1 (1%)	20 (24%)
Hypophysitis, thyroiditis (n, %)	8 (7%)	0	8 (7%)	11 (13%)	1 (1%)	12 (14%)
Pneumonitis	4 (3%)	1 (1%)	5 (4%)	3 (4%)	0	3 (4%)
Nephritis (n, %)	1 (1%)	0	1 (1%)	0	1 (1%)	1 (1%)
Pyrexia (n, %)	5 (4%)	0	5 (4%)	2 (2%)	1 (1%)	3 (4%)
Arthritis/myalgias (n, %)	12 (10%)	0	12 (10%)	2 (2%)	0	2 (2%)
Others (n, %)	10 (9%)	2 (2%)	12 (10%)	8 (9%)	5 (6%)	13 (15%)

Subgroup	n/N (%)		Odds ratio	
	IPI+PD-1	PD-1	(95% CI)	
All patients	**33/85 (39%)**	**39/115 (34%)**	**1.24 (0.69, 2.21)**	
Gender				
Male	26/59 (44%)	24/78 (31%)	1.77 (0.88, 3.58)	
Female	7/26 (27%)	15/37 (41%)	0.54 (0.18, 1.60)	
Age				
<60	23/56 (41%)	18/46 (39%)	1.08 (0.49, 2.40)	
≥60	10/29 (34%)	21/69 (30%)	1.20 (0.48, 3.02)	
BRAF mutation status				
V600E	27/70 (39%)	27/80 (34%)	1.23 (0.63, 2.40)	
Other	6/15 (40%)	12/35 (34%)	1.28 (0.37, 4.45)	
ECOG				
0	21/43 (49%)	21/43 (49%)	1.00 (0.43, 2.33)	
≥1	10/34 (29%)	18/70 (26%)	1.20 (0.48, 3.00)	
Duration of BRAF/MEKi treatment				
≤7 months	18/46 (39%)	16/51 (31%)	1.41 (0.61, 3.25)	
>7 months	15/39 (38%)	23/64 (36%)	1.11 (0.49, 2.54)	
Reason to BRAF/MEKi cessation				
Progressive disease	22/64 (34%)	28/90 (31%)	1.16 (0.59, 2.29)	
Other	11/21 (52%)	11/25 (44%)	1.40 (0.44, 4.49)	
Interval between BRAF/MEKi and PD1+/-IPI				
≤10 days	17/52 (33%)	17/46 (37%)	0.83 (0.36, 1.91)	
>10 days	16/33 (48%)	22/69 (32%)	2.01 (0.86, 4.70)	
AJCC Staging				
III/M1A/M1B	2/5 (40%)	15/32 (47%)	0.76 (0.11, 5.15)	
M1C/M1D	31/80 (39%)	24/83 (29%)	1.56 (0.81, 2.99)	
Progressing liver metastases at PD1+/-IPI				
No	22/58 (38%)	29/88 (33%)	1.24 (0.62, 2.48)	
Yes	4/12 (33%)	3/13 (23%)	1.67 (0.29, 9.71)	
Progressing brain metastases at PD1+/-IPI				
No	12/26 (46%)	25/64 (39%)	1.34 (0.53, 3.36)	
Yes	14/44 (32%)	7/37 (19%)	2.00 (0.71, 5.65)	
LDH				
UNL	17/39 (44%)	24/59 (41%)	1.13 (0.50, 2.56)	
>UNL	16/45 (36%)	14/52 (27%)	1.50 (0.63, 3.56)	

0   0.5   1   1.5   2

Favour PD-1 | Favour IPI+PD-1

Supplementary Figure 1. Forest plot showing the objective response subgroup analysis.

Supplemental material

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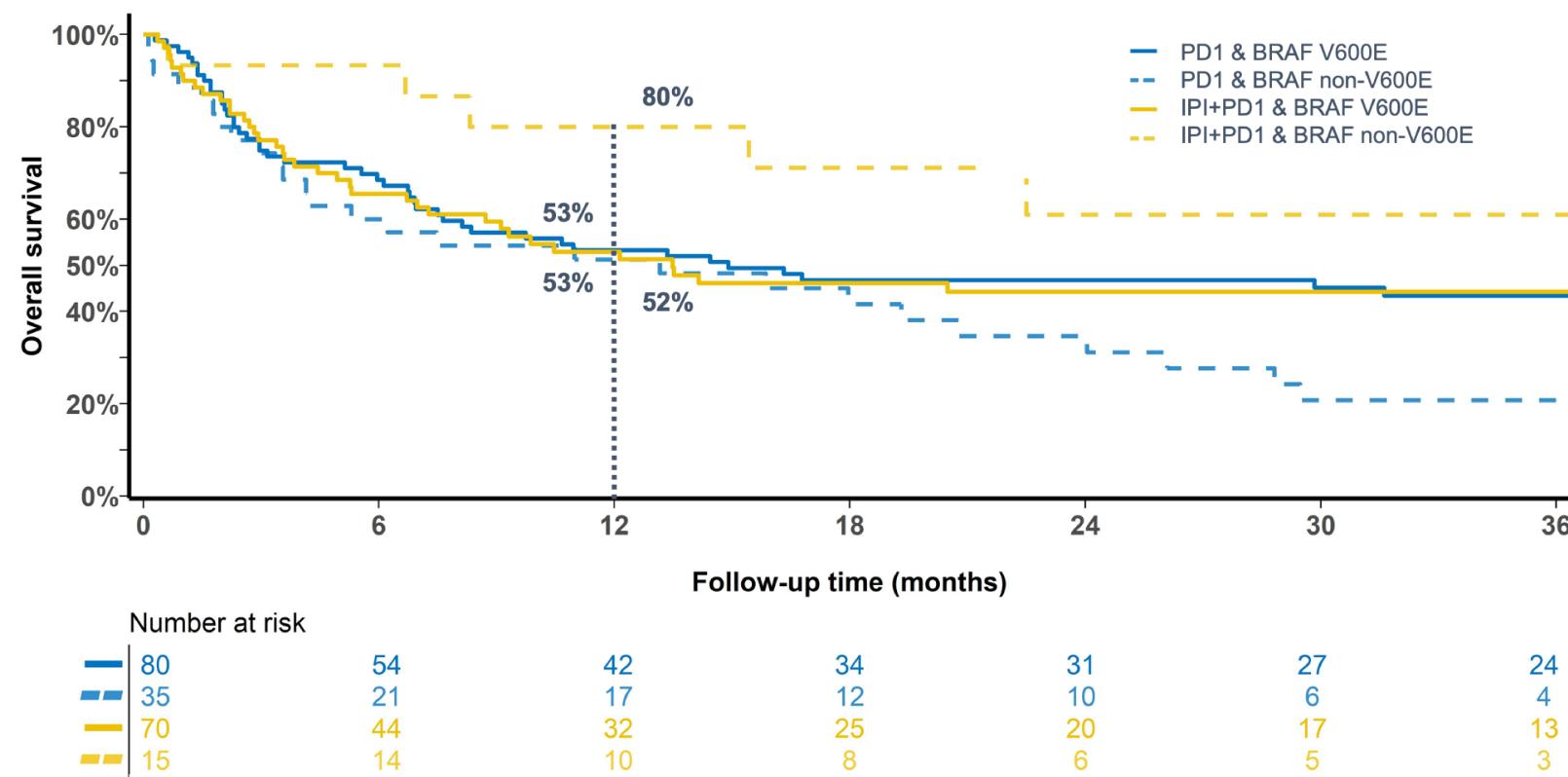
Supplementary Figure 2. Kaplan Meier curves showing overall survival stratified by treatment (PD1 vs IPI+PD1) and BRAF mutation type (V600E vs non-V600E).

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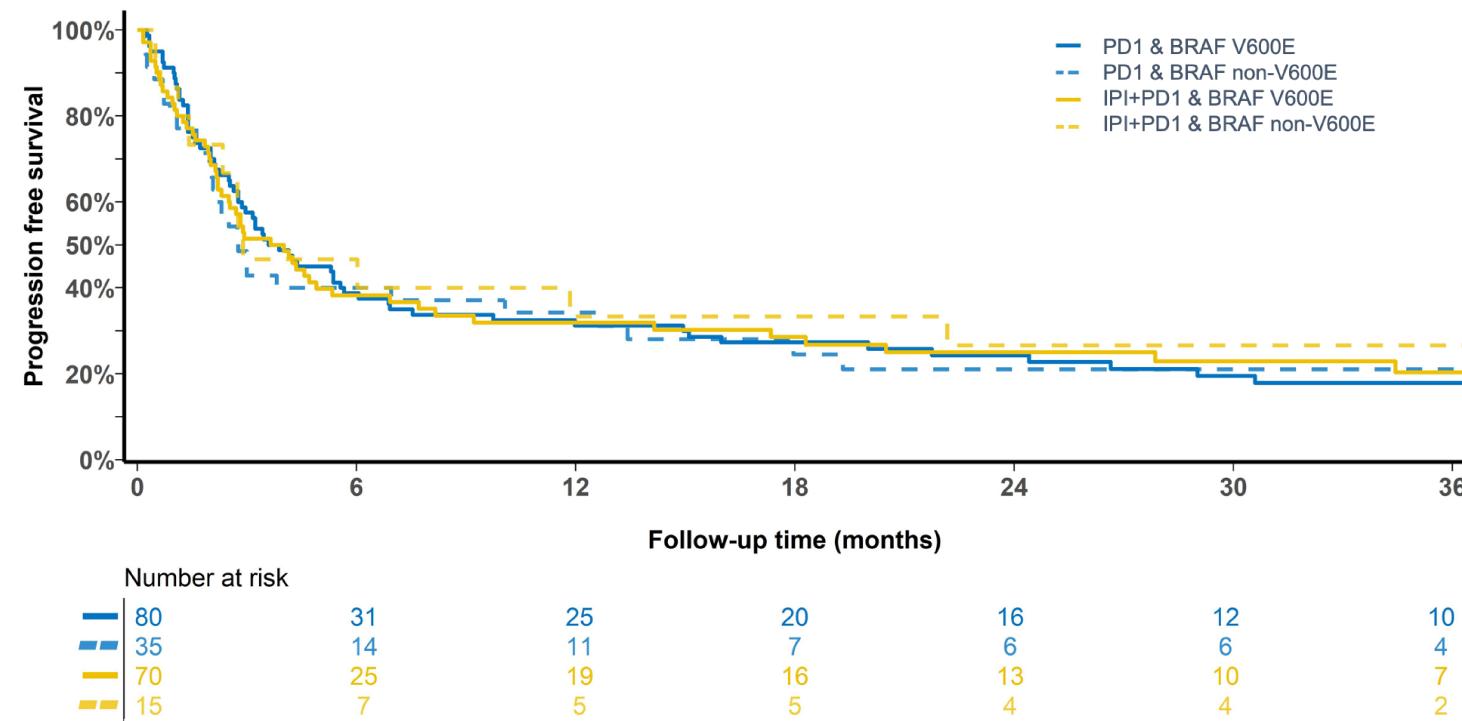
Supplementary Figure 3. Kaplan Meier curves showing progression-free survival stratified by treatment (PD1 vs IPI+PD1) and BRAF mutation type (V600E vs non-V600E).
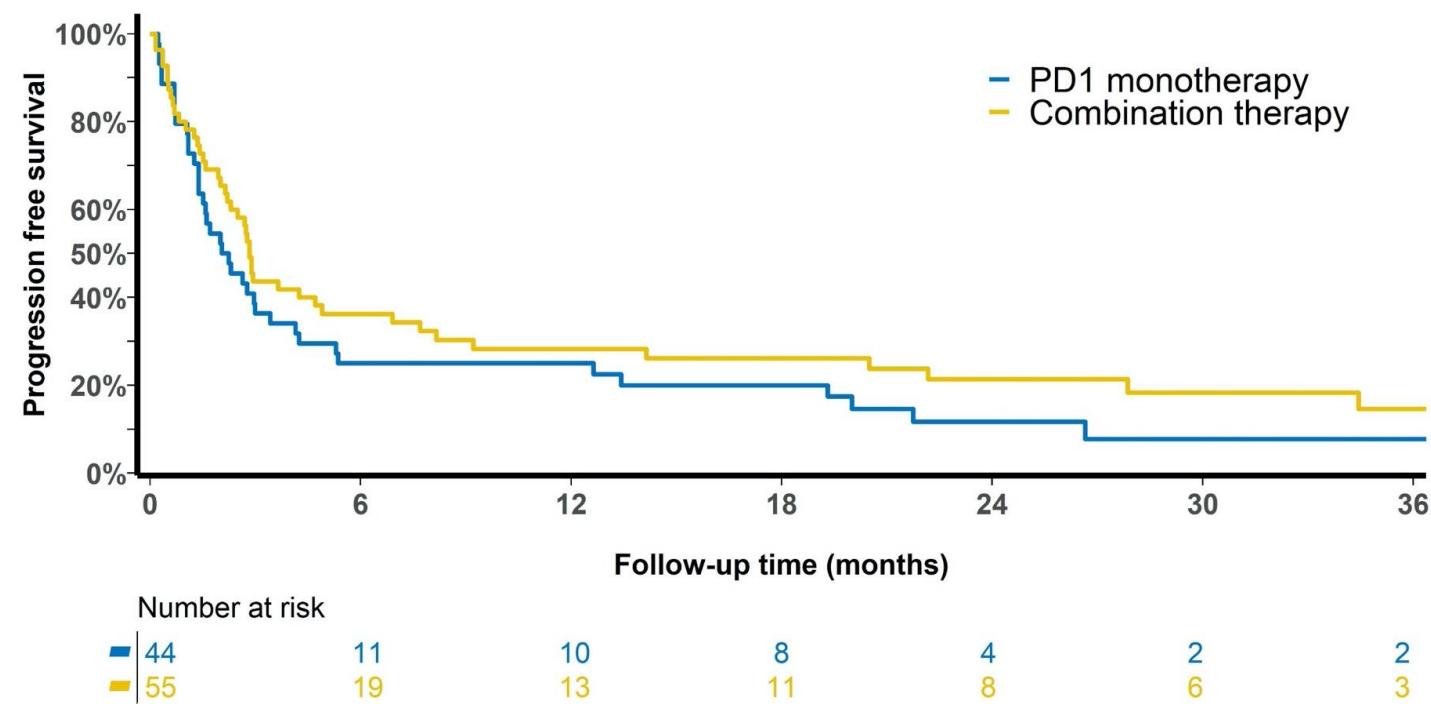
Supplementary Figure 4. Kaplan Meier curves showing progression-free survival for the subgroup of patients with brain metastases stratified by treatment (PD1 vs IPI+PD1).
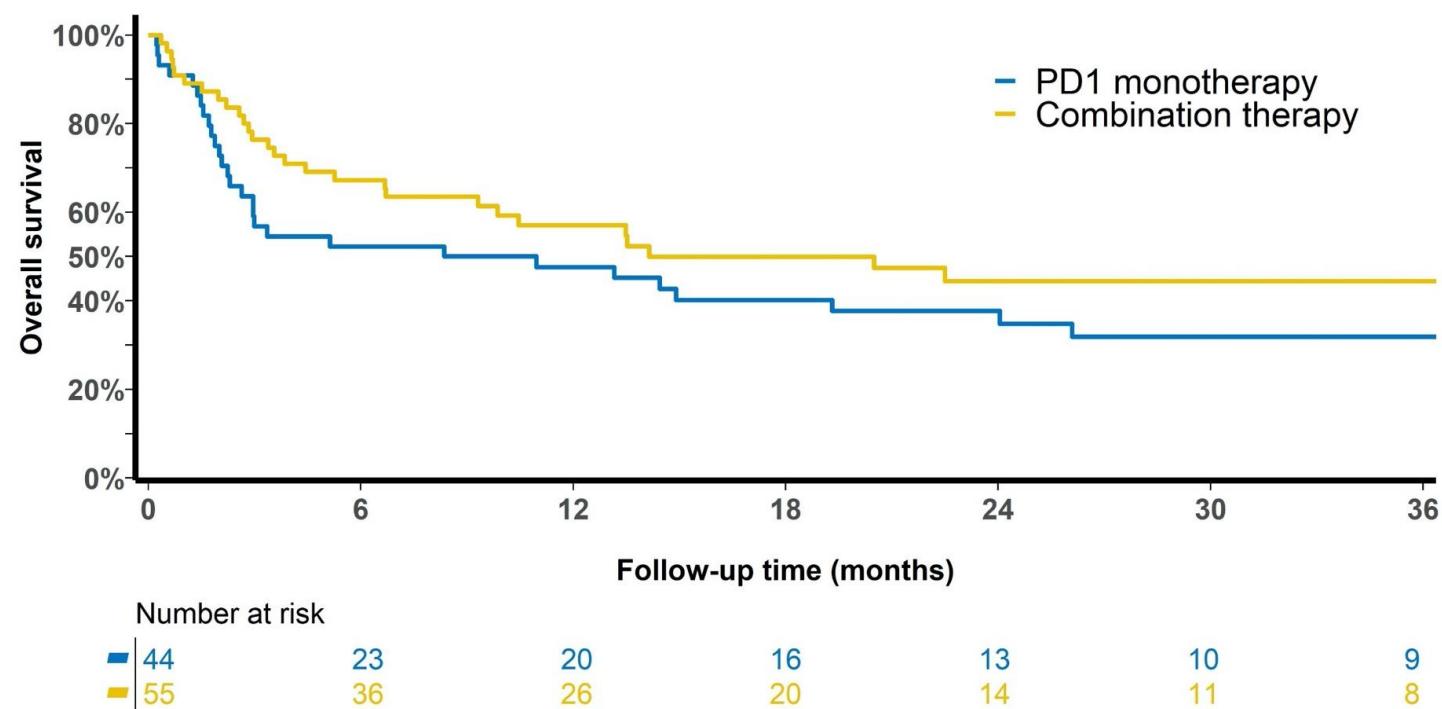
Supplementary Figure 5. Kaplan Meier curves showing overall survival for the subgroup of patients with brain metastases stratified by treatment (PD1 vs IPI+PD1).