

Supplementary material

Table S1a: Baseline characteristics and therapy outcome of first-line therapy (BRAF wildtype patients; n=916).

	BRAF wildtype CTLA-4+PD-1 N=281 (100%)	BRAF wildtype PD-1 N=544 (100%)	BRAF wildtype CTLA-4 N=91 (100%)
Age			
≤65 years	158 (56.2)	145 (26.7)	41 (45.1)
>65 years	123 (43.3)	399 (73.3)	50 (54.9)
Gender			
Male	188 (66.9)	329 (60.5)	60 (65.9)
Female	93 (33.1)	215 (39.5)	31 (34.1)
Previous adjuvant therapy in stage III			
None	268 (95.4)	531 (97.6)	86 (94.5)
Immune checkpoint inhibitors	11 (3.9)	6 (1.1)	2 (2.2)
Interferon-alpha	2 (0.7)	7 (1.3)	3 (3.3)
blinded	0 (0.0)	0 (0.0)	0 (0.0)
Previous adjuvant therapy in stage IV			
None	255 (90.7)	511 (93.9)	81 (89.0)
Immune checkpoint inhibitors	24 (8.5)	19 (3.5)	3 (3.3)
Interferon-alpha	1 (0.4)	12 (2.2)	3 (3.3)
Blinded	1 (0.4)	2 (0.4)	0 (0.0)
Chemotherapy	0 (0.0)	0 (0.0)	4 (4.4)
ECOG performance status			
0	156 (55.5)	261 (48.0)	29 (31.9)
1	24 (8.5)	95 (17.5)	5 (5.5)
≥2	7 (2.5)	22 (4.0)	2 (2.2)
unknown	94 (33.5)	166 (30.5)	55 (60.4)
Serum LDH			
Normal (≤ULN)	132 (47.0)	281 (51.7)	46 (50.5)
Elevated (>ULN)	149 (53.0)	262 (48.2)	44 (48.4)
>2xULN	87 (31.0)	119 (21.9)	26 (28.9)
unknown		1 (0.2)	1 (1.1)
Stage (AJCCv8)			
IIIC/D	28 (10.0)	113 (20.8)	8 (8.8)
IV M1a	27 (9.6)	42 (7.7)	15 (16.5)
IV M1b	59 (21.0)	156 (28.7)	24 (26.4)
IV M1c	159 (56.6)	228 (41.9)	43 (47.3)
Stage IV M1a-c, not specified	8 (2.8)	5 (0.9)	1 (1.1)
Best overall response			
CR	31 (11.0)	73 (13.4)	2 (2.2)
PR	59 (21.0)	75 (13.8)	10 (11.0)
SD	26 (9.3)	82 (15.1)	7 (7.7)
PD	83 (29.5)	210 (38.6)	61 (67.0)
Mixed response	14 (5.0)	21 (3.9)	0 (0.0)
Unknown	68 (24.0)	83 (15.3)	11 (12.1)
Therapy end reason			
Planned stop	28 (10.0)	55 (10.1)	27 (29.7)
Toxicity	90 (32.0)	67 (12.3)	21 (23.1)
Disease progression	77 (27.4)	240 (44.1)	40 (44.0)
Patient wish	7 (2.5)	36 (6.6)	0 (0.0)
Other	26 (9.3)	62 (11.4)	0 (0.0)
Ongoing	47 (16.7)	73 (13.4)	0 (0.0)
Lost to follow-up	6 (2.1)	11 (2.0)	0 (0.0)

Progression			
No	149 (53.0)	216 (39.7)	22 (24.2)
Yes	132 (47.0)	328 (60.3)	69 (75.8)
Death			
No	195 (69.4)	307 (56.4)	53 (58.2)
Yes	86 (30.6)	237 (43.6)	38 (41.8)
Development of brain metastases			
No	236 (84.0)	441 (81.1)	68 (74.7)
Yes	45 (16.0)	103 (18.9)	23 (25.3)
Progression-free survival			
Median in months (95% CI)	6.93 (4.14-9.73)	6.44 (4.930-7.95)	2.10 (2.014-2.191)
Overall survival			
Median in months (95% CI)	Not reached	34.56 (28.00-41.12)	37.39 (21.99-52.79)

Table S1b: Frequency of brain metastasis in BRAF wildtype patients.

	BRAF wildtype All n=916 (100%)	BRAF wildtype CTLA-4+PD-1 N=281 (N=100%)	BRAF wildtype PD-1 N=544 (N=100%)	BRAF wildtype CTLA-4 N=91 (N=100%)
Frequency of brain metastasis				
During complete FU time	171 (18.7)	45 (16.0)	103 (18.9)	23 (25.3)
Within 12 months after therapy start	113 (12.3)	31 (11.0)	64 (11.8)	18 (19.8)
Within 24 months after therapy start	149 (16.3)	40 (14.2)	87 (16.0)	22 (24.2)
Within 36 months after therapy start	161 (17.6)	43 (15.3)	95 (17.5)	23 (25.3)

Table S2: Univariate Cox regression analysis for progression-free and overall survival in BRAF-wildtype patients.

Parameters included (patient number)	Progression-free survival Hazard ratio (95% CI) P-value	Overall survival Hazard ratio (95% CI) P-value
Gender (reference: male) male versus female (577 vs.339)	1.092 (0.916-1.300) 0.326	1.208 (0.982-1.486) 0.074
Age (reference: ≤65 years) ≤65 versus >65 years (344 vs. 572)	0.880 (0.738-1.049) 0.154	1.052 (0.852-1.298) 0.637
BRAF status (reference: mutant) BRAF V600 mutant versus wildtype	n.a.	n.a.
ECOG performance status (reference: 0) 0 versus 1 (446 vs. 124) 0 versus ≥2 (446 vs. 31)	1.131 (0.871-1.468) 0.356 1.452 (0.900-2.343) 0.127	1.772 (1.331-2.359) <0.001 2.673 (1.619-4.414) <0.001
Serum LDH (reference: normal) normal versus elevated (459 vs. 455)	1.173 (0.989-1.392) 0.067	1.495 (1.220-1.833) <0.001
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no) no versus yes (847 vs. 69)	1.072 (0.770-1.491) 0.681	0.882 (0.562-1.385) 0.586
Tumor stage (reference: M1c) M1c versus Stage III C/D (430 vs. 149) M1c versus Stage IV M1a (430 vs. 84)	0.815 (0.638-1.042) 0.103 0.773 (0.558-1.071) 0.121	0.757 (0.560-1.023) 0.070 0.759 (0.520-1.108) 0.154

M1c versus Stage IV M1b (430 vs. 239)	0.700 (0.569-0.862) 0.001	0.669 (0.522-0.858) 0.002
Type of first systemic therapy (reference:CTLA-4+PD-1)		
CTLA-4+PD-1 versus PD-1 (281 vs. 544)	1.049 (0.857-1.284) 0.641	1.287 (1.005-1.647) 0.045
CTLA-4+PD-1 versus CTLA-4 (281 vs. 91)	2.880 (2.141-3.875) <0.001	1.173 (0.828-1.664) 0.369
(reference:CTLA-4)		
CTLA-4 versus PD-1 (91 vs. 544)	0.364 (0.279-0.475) <0.001	1.097 (0.809-1.486) 0.551
n.a., not applicable		

Table S3: Univariate Cox regression analysis for brain metastasis-free survival in BRAF-wildtype patients.

Parameters included (patient number)	Brain metastasis-free survival Hazard ratio (95% CI) P-value
Gender (reference: male) male versus female (577 vs. 339)	0.933 (0.681-1.280) 0.669
Age (reference: ≤65 years) ≤65 versus >65 years (344 vs. 572)	0.852 (0.628-1.155) 0.302
BRAF status (reference: wildtype) wildtype versus BRAF V600 mutant	n.a.
ECOG performance status (reference :0) 0 versus 1 (446 vs. 124) 0 versus ≥2 (446 vs. 31)	1.390 (0.899-2.150) 0.138 1.179 (0.432-3.129) 0.748
Serum LDH (reference: normal) normal versus elevated (470 vs. 465)	1.159 (0.857-1.567) 0.337
Pre-treatment with adjuvant immune checkpoint blockade or BRAF+MEK inhibitors (reference: no) No versus yes (847 vs. 69)	0.681 (0.335-1.385) 0.289
Tumor stage (reference: M1c) M1c versus Stage III C/D (430 vs. 149) M1c versus Stage IV M1a (430 vs. 84) M1c versus Stage IV M1b (430 vs. 239)	0.507 (0.310-0.830) 0.007 0.288 (0.126-0.657) 0.003 0.797 (0.567-1.120) 0.192
Type of first systemic therapy (reference:CTLA-4+PD-1) CTLA-4+PD1 versus PD-1 (281 vs. 544) CTLA-4+PD-1 versus CTLA-4 (281 vs. 91)	1.080 (0.761-1.533) 0.667 1.156 (0.698-1.915) 0.572
(reference:CTLA-4) CTLA-4 versus PD-1 (91 vs.544)	0.934 (0.593-1.470) 0.768
n.a., not applicable	

Table S4a: Baseline characteristics and therapy outcome of first-line therapy (BRAF mutant patients; n=788).

	BRAF mutant CTLA-4+PD-1 n=108 (100%)	BRAF mutant PD-1 n=264 (100%)	BRAF mutant BRAF+MEK N=373 (100%)	BRAF mutant CTLA-4 N=43 (100%)
Age				
≤65 years	84 (77.8)	115 (43.6)	211 (56.6)	26 (60.5)
>65 years	24 (22.2)	149 (56.4)	162 (43.4)	17 (39.5)

Gender				
Male	72 (66.7)	165 (62.5)	218 (58.4)	23 (53.5)
Female	36 (33.3)	99 (37.5)	155 (41.6)	20 (46.5)
Previous adjuvant therapy in stage III				
None	104 (96.3)	253 (95.8)	355 (95.2)	40 (93.0)
Immune checkpoint inhibitors	1(0.9)	1 (0.4)	13 (3.5)	0 (0.0)
BRAF+MEK inhibitors	1(0.9)	1(0.4)	1 (0.3)	0 (0.0)
Interferon-alpha	2(1.9)	8 (3.0)	3 (0.8)	3 (7.0)
blinded	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)
Previous adjuvant therapy in stage IV				
None	101 (93.5)	250 (94.7)	342 (91.7)	37 (86.0)
Immune checkpoint inhibitors	2(1.9)	1 (0.4)	18 (4.8)	1 (2.3)
BRAF+MEK inhibitors	4 (3.7)	3 (1.1)	5 (1.3)	1 (2.3)
Interferon-alpha	0 (0.0)	6(2.3)	7 (1.9)	3 (7.0)
Blinded	1 (0.9)	2 (0.8)	0 (0.0)	1 (2.3)
Chemotherapy	0 (0.0)	2 (0.8)	1(0.3)	0 (0.0)
ECOG performance status				
0	57 (52.8)	123 (46.6)	149 (39.9)	15 (34.9)
1	13 (12.0)	35 (13.3)	43 (11.5)	0 (0.0)
≥2	5 (4.6)	4 (1.5)	22 (5.9)	0 (0.0)
unknown	33 (30.6)	102 (38.6)	159 (42.6)	28 (65.1)
Serum LDH				
Normal (≤ULN)	46 (42.6)	143 (54.2)	136 (36.5)	27 (62.8)
Elevated (>ULN)	62 (57.4)	120 (45.5)	237 (63.5)	16 (37.2)
>2xULN	32 (29.6)	62 (23.5)	152 (40.8)	14 (32.6)
unknown	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Stage (AJCCv8)				
IIIC/D	8 (7.4)	54 (20.5)	57 (15.3)	6(14.0)
IV M1a	12 (11.1)	36 (13.6)	33 (8.8)	8(18.6)
IV M1b	21 (19.4)	77 (29.2)	63 (16.9)	11(25.6)
IV M1c	65 (60.2)	96 (36.4)	214 (57.4)	16 (37.2)
Stage IV, not specified	2 (1.9)	1 (0.4)	6(1.6)	2 (4.7)
Best overall response				
CR	7 (6.5)	52 (19.7)	46 (12.3)	0 (0.0)
PR	24 (22.2)	34 (12.9)	90 (24.1)	2(4.7)
SD	13 (12.0)	34 (12.9)	47 (12.6)	6(14.0)
PD	30 (27.8)	93 (35.2)	98 (26.3)	27(62.8)
Mixed response	8 (7.4)	10 (3.8)	12 (3.2)	0 (0.0)
Unknown	26 (24.1)	41 (15.5)	80 (21.4)	8(18.6)
Therapy end reason				
Planned stop	12 (11.1)	30 (11.4)	16 (4.3)	16 (37.2)
Toxicity	29 (26.9)	22 (8.3)	65 (17.4)	6 (14.0)
Disease progression	34 (31.5)	128 (48.5)	171 (45.8)	16 (37.2)
Patient wish	1 (0.9)	16 (6.1)	15 (4.0)	0 (0.0)
Other	11 (10.2)	26 (9.8)	30 (8.0)	4 (9.3)
Ongoing	19 (17.6)	37 (14.0)	72 (19.3)	0 (0.0)
Lost to follow-up	2 (1.8)	5 (1.9)	4 (1.1)	0 (0.0)
Progression				
No	61 (56.5)	109 (41.3)	164 (44.0)	11 (25.6)
Yes	47 (43.5)	155 (58.7)	209 (56.0)	32 (74.4)
Death				
No	84 (77.8)	169 (64.0)	196 (52.5)	14 (32.6)
Yes	24 (22.2)	95 (36.0)	177 (47.5)	29 (67.4)
Development of brain metastases				
No	81 (75.0)	219 (83.0)	250 (67.0)	22 (51.2)
Yes	27 (25.0)	45 (17.0)	123 (33.0)	21 (48.8)
Progression-free survival				

Median in months (95% CI)	8.74 (2.83-14.65)	5.947 (4.24-7.66)	9.462 (8.341-10.583)	2.136 (2.048-2.223)
Overall survival Median in months (95% CI)	Not reached	Not reached	26.28 (21.1-31.5)	34.92 (3.3-41.4)

Table S4b: Frequency of brain metastasis in BRAF mutant patients.

	BRAF mutant All n=788 (100%)	BRAF mutant CTLA-4+PD-1 n=108 (100%)	BRAF mutant PD-1 n=264 (100%)	BRAF mutant BRAF+MEK N=373 (100%)	BRAF mutant CTLA-4 N=43 (100%)
Frequency of brain metastasis					
During complete FU time	216 (27.4)	27 (25.0)	45 (17.0)	123 (33.0)	21 (48.8)
Within 12 months after therapy start	148 (18.8)	19 (17.6)	30 (11.4)	83 (22.3)	16 (37.2)
Within 24 months after therapy start	193 (24.5)	24 (22.2)	37 (14.0)	113 (30.3)	19 (44.2)
Within 36 months after therapy start	208 (26.4)	27 (25.0)	41 (15.5)	120 (32.2)	20 (46.5)

Table S5: Univariate Cox regression analysis for progression-free and overall survival in BRAF-mutant patients.

Parameters included (patient number)	Progression-free survival Hazard ratio (95% CI) P-value		Overall survival Hazard ratio (95% CI) P-value	
Gender (reference: male) male versus female (478 vs.310)	0.935 (0.772-1.133)	0.495	0.947 (0.757-1.185)	0.634
Age (reference: ≤65 years) ≤65 versus >65 years (436 vs.352)	0.926 (0.767-1.118)	0.423	1.184 (0.951-1.472)	0.130
BRAF status (reference: wildtype) wildtype versus BRAF V600 mutant	n.a.		n.a.	
ECOG performance status (reference: 0) 0 versus 1 (344 vs. 91) 0 versus ≥2 (336 vs. 31)	1.359 (1.007-1.833) 1.499 (0.963-2.333)	0.045 0.073	1.739 (1.244-2.432) 2.857 (1.798-4.540)	0.001 <0.001
Serum LDH (reference: normal) normal versus elevated (352 vs. 435)	1.309 (1.083-1.581)	0.005	1.451 (1.163-1.810)	0.001
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no) no versus yes (731 vs. 57)	0.961 (0.655-1.409)	0.837	0.970 (0.617-1.525)	0.895
Tumor stage (reference: M1c) M1c versus Stage III C/D (391 vs. 125) M1c versus Stage IV M1a (391 vs. 89) M1c versus Stage IV M1b (391 vs. 172)	0.643 (0.481-0.860) 0.735 (0.538-1.004) 0.702 (0.550-0.895)	0.003 0.053 0.004	0.579 (0.409-0.830) 0.490 (0.330-0.730) 0.703 (0.532-0.928)	0.003 <0.001 0.013
Type of first systemic therapy (reference: BRAF+MEK) BRAF+MEK versus CTLA-4+PD-1 (371 vs. 108) BRAF+MEK versus PD-1 (371 vs. 264) BRAF+MEK versus CTLA-4 (371 vs. 43) (reference: CTLA-4+PD-1)	1.148 (0.836-1.600) 1.099 (0.891-1.355) 4.537 (3.087-6.667)	0.394 0.376 <0.001	0.483 (0.315-0.740) 0.653 (0.509-0.838) 0.893 (0.602-1.325)	0.001 0.001 0.574

CTLA-4+PD-1 versus PD-1 (108 vs. 264)	0.958 (0.691-1.328)	0.795	1.352 (0.864-2.116)	0.187
CTLA-4+PD-1 versus CTLA-4 (108 vs. 43)	3.953 (2.499-6.251)	<0.001	1.848 (1.075-3.180)	0.026
CTLA-4+PD-1 versus BRAF+MEK (108 vs. 371)	0.871 (0.634-1.196)	0.394	2.070 (1.351-3.171)	0.001

n.a., not applicable

Table S6: Univariate Cox regression analysis for brain metastasis free-survival in BRAF-mutant patients.

Parameters included (patient number)	Brain metastasis-free survival Hazard ratio (95% CI) P-value	
Gender (reference: male) male versus female (478 vs.310)	1.038 (0.790-1.363)	0.789
Age (reference: ≤65 years) ≤65 versus >65 years (436 vs.352)	0.669 (0.505-0.885)	0.005
BRAF status (reference: wildtype) wildtype versus BRAF V600 mutant	n.a.	
ECOG performance status (reference: 0) 0 versus 1 (344 vs. 91) 0 versus ≥2 (336 vs. 31)	1.222 (0.792-1.887)	0.365
	1.645 (0.855-3.163)	0.136
Serum LDH (reference: normal) normal versus elevated (352 vs. 435)	1.234 (0.942-1.616)	0.127
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK/BRAF+MEK inhibitors (reference: no) no versus yes (731 vs. 57)	1.088 (0.654-1.810)	0.746
Tumor stage (reference: M1c) M1c versus Stage III C/D (391 vs. 125) M1c versus Stage IV M1a (391 vs. 89) M1c versus Stage IV M1b (391 vs. 172)	0.421 (0.260-0.682)	<0.001
	0.369 (0.212-0.641)	<0.001
	0.864 (0.630-1.186)	0.475
Type of first systemic therapy (reference: BRAF+MEK) BRAF+MEK versus CTLA-4+PD-1 (373 vs. 108) BRAF+MEK versus PD-1 (373 vs. 264) BRAF+MEK versus CTLA-4 (373 vs. 43)	0.786 (0.518-1.193)	0.259
	0.441 (0.313-0.622)	<0.001
	1.193 (0.751-1.896)	0.466
(reference:CTLA-4+PD-1) CTLA-4+PD-1 versus PD-1 (108 vs. 264) CTLA-4+PD-1 versus CTLA-4 (108 vs. 43) CTLA-4+PD-1 versus BRAF+MEK (108 vs. 371)	0.561 (0.348-0.905)	0.018
	1.517 (0.857-2.684)	0.152
	1.271 (0.838-1.929)	0.259

n.a., not applicable

Table S7: Baseline and therapy characteristics of patients with and without second-line therapy

	Patients without second-line therapy N=774 (100%)	Patients with second-line therapy N=930 (100%)
Age		
≤65 years	295 (38.1)	485 (52.2)
>65 years	479 (61.9)	445 (47.8)
Gender		
male	486 (62.8)	569 (61.2)
female	288 (37.2)	361 (38.8)

ECOG performance status		
0	370 (47.8)	420 (45.2)
1	95 (12.3)	120 (12.9)
≥2	36 (4.7)	26 (2.8)
unknown	273 (35.3)	364 (39.1)
Serum LDH		
Normal (≤ULN)	364 (47.0)	447 (48.1)
Elevated (>ULN)	410 (53.0)	480 (51.6)
>2xULN	241 (31.1)	251 (27.0)
unknown	0 (0.0)	3 (0.3)
AJCC Stage at first-line therapy start		
III C/D	140 (18.1)	134 (14.4)
IV M1a	76 (9.8)	97 (10.4)
IV M1b	196 (25.3)	215 (23.1)
IV M1c	344 (44.4)	477 (51.3)
IV not specified	18 (2.3)	7 (0.8)
BRAF status		
V600 wildtype	463 (59.8)	453 (48.7)
V600 mutant	311 (40.2)	477 (51.3)
Best response to first-line therapy		
CR	161 (20.8)	50 (5.4)
PR	146 (18.9)	148 (15.9)
SD	97 (12.5)	118 (12.7)
PD	137 (17.7)	465 (50.0)
MR	27 (3.5)	38 (4.1)
unknown	206 (26.6)	111 (11.9)
First-line therapy end reason		
Disease progression	133 (17.2)	574 (61.7)
Toxicity	125 (16.1)	175 (18.8)
Ongoing	245 (31.7)	0 (0.0)
Planned stop	94 (12.1)	88 (9.5)
Lost to follow-up	26 (3.4)	0 (0.0)
Patient wish	58 (7.5)	17 (1.8)
Other	93 (12.0)	76 (8.1)
Progression		
No	498 (64.3)	234 (25.2)
Yes	276 (35.7)	696 (74.8)
Death		
No	577 (74.5)	426 (45.8)
Yes	197 (25.5)	504 (54.2)
Brain metastasis		
No	706 (91.2)	611 (65.7)
Yes	68 (8.8)	319 (34.3)
First-line therapy		
CTLA-4+PD-1	211 (27.3)	178 (19.1)
PD-1	403 (52.1)	405 (43.5)
CTLA-4	15 (1.9)	119 (12.8)
BRAF+MEK	145 (18.7)	228 (24.5)

Table S8: Therapy sequence in patients with second-line therapy

	All patients N=930 (100%)	BRAF mutant N=477 (100%)	BRAF wildtype N=453 (100%)
Age			

≤65 years	485 (52.2)	282 (59.1)	203 (44.8)
>65 years	445 (47.8)	195 (40.9)	250 (55.2)
Gender			
male	569 (61.2)	286 (60.0)	283 (62.5)
female	361 (38.8)	191 (40.0)	170 (37.5)
ECOG performance status			
0	420 (45.2)	207 (43.4)	213 (47.0)
1	120 (12.9)	59 (12.4)	61 (13.5)
≥2	26 (2.8)	19 (4.0)	7 (1.5)
unknown	364 (39.1)	192 (40.3)	172 (38.0)
Serum LDH			
Normal (≤ULN)	447 (48.1)	209 (43.8)	238 (52.5)
Elevated (>ULN)	480 (51.6)	267 (56.0)	213 (47.0)
>2xULN	251 (27.0)	155 (32.5)	96 (21.2)
unknown	3 (0.3)	1 (0.2)	2 (0.4)
AJCC Stage at first-line therapy start			
III C/D	134 (14.4)	64 (13.4)	70 (15.5)
IV M1a	97 (10.4)	55 (11.5)	42 (9.3)
IV M1b	215 (23.1)	99 (20.8)	116 (25.6)
IV M1c	477 (51.3)	255 (53.5)	222 (49.0)
IV not specified	7 (0.8)	4 (0.8)	3 (0.7)
BRAF status			
V600 wildtype	472 (50.8)	n.a.	n.a.
V600 mutant	458 (49.2)		
Therapy sequence			
CTLA-4+PD-1_BRAF+MEK	42 (4.5)	42 (8.8)	
PD-1_BRAF+MEK	91 (9.8)	91 (19.1)	
BRAF+MEK_CTLA-4+PD-1	73 (7.8)	73 (15.3)	
BRAF+MEK_PD-1	79 (8.5)	79 (16.6)	
CTLA-4+PD-1_PD-1	74 (8.0)	13 (2.7)	61 (13.5)
PD-1_CTLA-4+PD-1	55 (5.9)	11 (2.3)	44 (9.7)
PD-1_CTLA-4	54 (5.8)	2 (0.4)	52 (11.5)
others	462 (50.3)	166 (34.8)	296 (65.3)

n.a., not applicable

Table S9: Multivariate Cox regression analysis for brain metastasis-free and overall survival in BRAF-wildtype patients including therapy sequence.

Parameters included (patient number)	Overall survival N= 100 Hazard ratio (95% CI) P-value	Brain metastasis-free survival N=100 Hazard ratio (95% CI) P-value
Gender (reference: male) male versus female	1.030 (0.527-2.012) 0.932	0.696 (0.270-1.791) 0.452
Age (reference: ≤65 years) ≤65 versus >65 years	0.402 (0.160-1.009) 0.052	0.743 (0.230-2.401) 0.619
BRAF status (reference: wildtype) wildtype versus BRAF V600 mutant	n.a.	n.a.
ECOG performance status (reference :0) 0 versus 1 0 versus ≥=2	2.104 (1.002-4.418) 0.049 n.a.	1.113 (0.344-3.605) 0.858 n.a.
Serum LDH (reference: normal) normal versus elevated	1.405 (0.704-2.805) 0.335	0.570 (0.236-1.379) 0.213
Primary adjuvant drug therapy with immune checkpoint blockade or		

BRAF+MEK inhibitors (reference: no) Yes	n.a.	3.256 (0.319-33.260) 0.319
Tumor stage (reference: M1c) M1c vs. Stage III C/D M1c vs. Stage IV M1a M1c vs. Stage IV M1b	1.509 (0.569-4.004) 0.408 0.446 (0.122-1.634) 0.223 0.689 (0.300-1.582) 0.380	0.234 (0.046-1.191) 0.080 n.a. 0.364 (0.118-1.110) 0.078
Therapy sequence (reference: PD-1_CTLA-4+PD-1) <i>PD-1_CTLA-4+PD-1 vs. CTLA-4+PD-1_PD-1</i> <i>PD-1_CTLA-4+PD-1 vs. PD-1_CTLA-4</i>	2.330 (0.700-7.751) 0.168 9.870 (3.494-27.879) 0.001	0.401 (0.103-1.561) 0.188 2.401 (0.846-6.815) 0.100

n.a., not applicable

Table S10: Multivariate Cox regression analysis for brain metastasis-free and overall survival in BRAF-mutant patients including therapy sequence.

Parameters included (patient number)	Overall survival N= 205 Hazard ratio (95% CI) P-value	Brain metastasis free-survival N=205 Hazard ratio (95% CI) P-value
Gender (reference: male) male versus female	1.242 (0.832-1.854) 0.290	1.282 (0.815-2.017) 0.283
Age (reference: ≤65 years) ≤65 versus >65 years	1.242 (0.832-1.854) 0.290	0.751 (0.456-1.238) 0.262
BRAF status (reference: wildtype) wildtype versus BRAF V600 mutated	n.a.	n.a.
ECOG performance status (reference :0) 0 versus 1 0 versus ≥2	1.745 (1.090-2.795) 0.021 3.146 (1.656-5.975) <0.001	1.417 (0.809-2.481) 0.223 1.264 (0.521-3.067) 0.605
Serum LDH (reference: normal) normal versus elevated	1.191 (0.804-1.764) 0.383	1.299 (0.814-2.071) 0.273
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no) Yes	0.898 (0.343-2.348) 0.826	0.888 (0.329-2.398) 0.815
Tumor stage (reference: M1c) M1c vs. Stage III C/D M1c vs. Stage IV M1a M1c vs. Stage IV M1b	0.533 (0.223-1.273) 0.157 0.511 (0.240-1.091) 0.083 1.260 (0.809-1.961) 0.307	0.747 (0.299-1.864) 0.532 0.655 (0.270-1.585) 0.348 1.323 (0.786-2.224) 0.292
Therapy sequence (reference:CTLA-4+PD-1_BRAF+MEK) <i>CTLA-4+PD-1_BRAF+MEK vs. PD-1_BRAF+MEK</i> <i>CTLA-4+PD-1_BRAF+MEK vs. BRAF+MEK_CTLA-4+PD-1</i> <i>CTLA-4+PD-1_BRAF+MEK vs. BRAF+MEK_PD-1</i> <i>CTLA-4+PD-1_BRAF+MEK vs. PD-1_BRAF+MEK</i>	1.547 (0.797-3.004) 0.197 1.988 (1.026-3.852) 0.042 1.863 (0.955-3.633) 0.068 None	0.750 (0.371-1.517) 0.423 1.421 (0.728-2.776) 0.303 1.095 (0.540-2.219) 0.801 0.179 (0.023-1.391) 0.100

CTLA-4+PD-1_BRAF+MEK vs. PD-1_CTLA-4+PD-1	0.272 (0.035-2.140) 0.216	0.213 (0.027-1.683) 0.142
CTLA-4+PD-1_BRAF+MEK vs. PD-1_CTLA-4	10.391 (1.245-86.740) 0.031	None
(reference: PD-1_BRAF+MEK)		
PD-1_BRAF+MEK vs. CTLA-4+ PD-1_BRAF+MEK	0.646 (0.333-1.255) 0.197	1.334 (0.659-2.699) 0.423
PD-1_BRAF+MEK vs. BRAF+MEK_CTLA-4+PD-1	1.285 (0.760-2.172) 0.349	1.896 (1.013-3.548) 0.045
PD-1_BRAF+MEK vs. BRAF+MEK_PD-1	1.204 (0.732-1.981) 0.465	1.460 (0.786-2.714) 0.231
PD-1_BRAF+MEK vs. CTLA-4+PD-1_PD-1	n.a.	0.238 (0.031-1.812) 0.166
PD-1_BRAF+MEK vs. PD-1_CTLA-4+PD-1	0.176 (0.024-1.314) 0.090	0.238 (0.037-2.172) 0.225
PD-1_BRAF+MEK vs. PD-1_CTLA-4	6.716 (0.836-53.924) 0.073	n.a.

Table S11a: Incidence of Brain metastasis in BRAF mutant patients with BRAF+MEK targeted therapy.

	dabrafenib+trametinib	vemurafenib+cobimetinib	encorafenib+binimetinib
Brain metastasis			
No	170 (66.1%)	40 (64.5%)	40 (74.1%)
Yes	87 (33.9%)	22 (35.5%)	14 (25.9%)

Table S11b: Multivariate Cox regression analysis for brain metastasis-free and overall survival in BRAF-mutant patients with BRAF+MEK inhibitor therapy.

Parameters included (patient number)	Overall survival N= 373		Brain metastasis-free survival N=373	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Gender (reference: male) male versus female (125 vs.89)	0.797 (0.510-1.244)	0.318	1.124 (0.685-1.847)	0.643
Age (reference: ≤65 years) ≤65 versus >65 years (123 vs.91)	1.235 (0.814-1.872)	0.321	0.795 (0.481-1.312)	0.369
BRAF status (reference: wildtype) wildtype versus BRAF V600 mutant	n.a.		n.a.	
ECOG performance status (reference :0) 0 versus 1 (149 vs.43) 0 versus ≥2 (149 vs.22)	1.944 (1.167-3.236)	0.011	1.503 (0.804-2.810)	0.202
	2.060 (1.132-3.750)	0.018	1.142 (0.509-2.565)	0.747
Serum LDH (reference: normal) normal versus elevated (87 vs. 127)	0.770 (0.440-1.348)	0.360	1.037 (0.641-1.676)	0.884
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no) Yes (186 vs. 28)	0.973 (0.471-2.012)	0.942	0.626 (0.277-1.415)	0.260

Tumor stage (reference: M1c)				
M1c vs. Stage III C/D (126 vs. 25)	0.519 (0.217-1.240)	0.140	0.772 (0.333-1.788)	0.545
M1c vs. Stage IV M1a (126 vs. 20)	0.424 (0.178-1.008)	0.052	0.323 (0.113-0.926)	0.035
M1c vs. Stage IV M1b (126 vs. 43)	0.830 (0.487-1.416)	0.494	0.664 (0.350-1.261)	0.211
BRAF+MEK inhibitor regimen (reference: dabrafenib+trametinib)				
dabrafenib+trametinib vs. vemurafenib+cobmetinib (139 vs. 34)	0.770 (0.440-1.348)	0.360	0.942 (0.501-1.770)	0.852
dabrafenib+trametinib vs. encorafenib+binimetinib (139 vs. 41)	1.296 (0.676-2.485)	0.436	1.648 (0.835-3.251)	0.150

n.a., not applicable

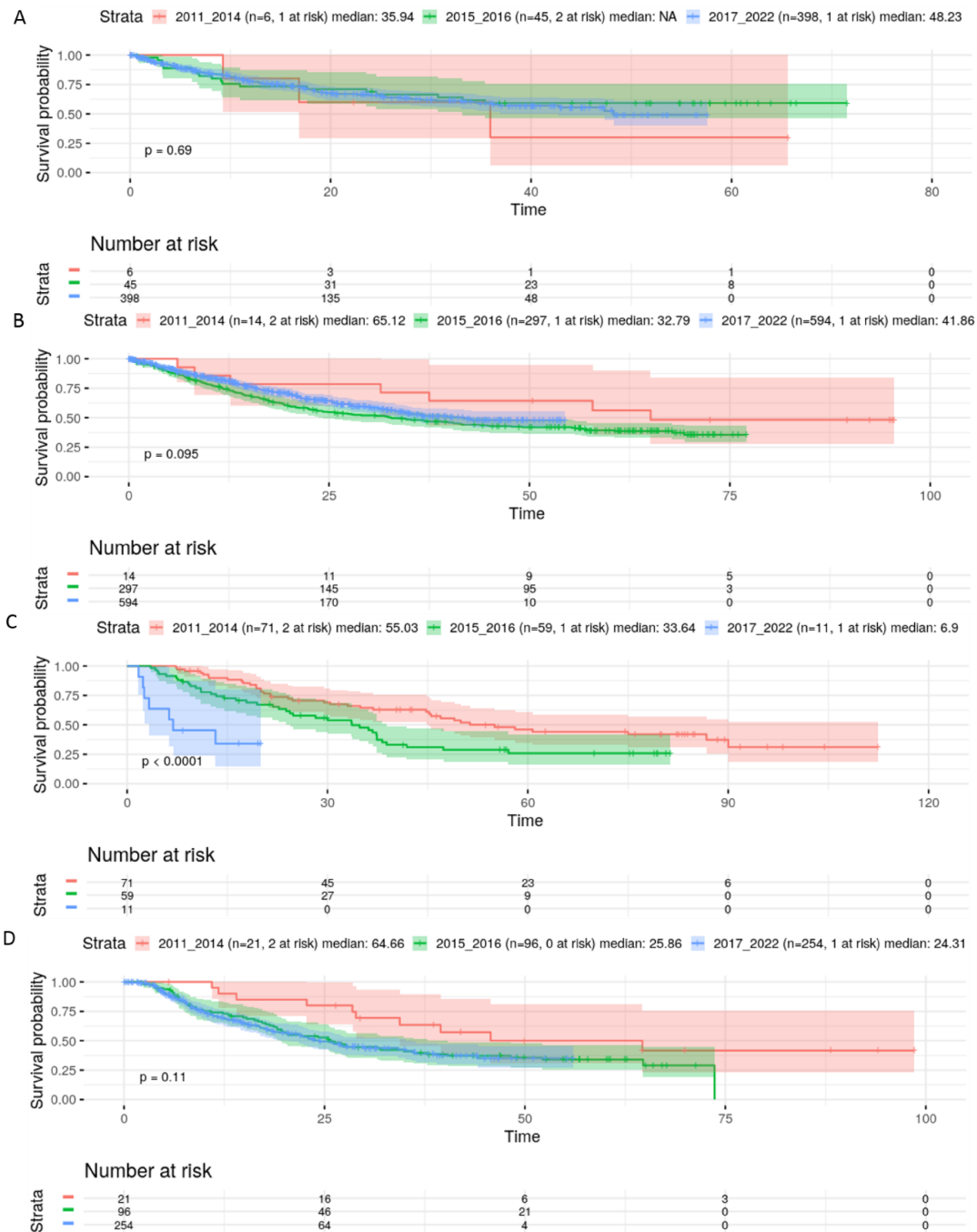


Figure S1. Kaplan-Meier curves showing overall survival for first-line systemic therapy in all patients by year of first-line therapy start. A CTLA-4+PD-1, B PD-1, C CTLA-4 and D BRAF+MEK. The log-rank test was used to compare between groups; $p < 0.05$ was considered significant.