

## Supplementary material

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

	<b>BRAF wildtype CTLA-4+PD-1 N=281 (100%)</b>	<b>BRAF wildtype PD-1 N=544 (100%)</b>	<b>BRAF wildtype CTLA-4 N=91 (100%)</b>
<b>Age</b>			
≤65 years	158 (56.2)	145 (26.7)	41 (45.1)
>65 years	123 (43.3)	399 (73.3)	50 (54.9)
<b>Gender</b>			
Male	188 (66.9)	329 (60.5)	60 (65.9)
Female	93 (33.1)	215 (39.5)	31 (34.1)
<b>Previous adjuvant therapy in stage III</b>			
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)
<b>Previous adjuvant therapy in stage IV</b>			
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)
<b>ECOG performance status</b>			
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)
<b>Serum LDH</b>			
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)
<b>Stage (AJCCv8)</b>			
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)
<b>Best overall response</b>			
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)
<b>Therapy end reason</b>			
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)

<b>Progression</b>			
No	149 (53.0)	216 (39.7)	22 (24.2)
Yes	132 (47.0)	328 (60.3)	69 (75.8)
<b>Death</b>			
No	195 (69.4)	307 (56.4)	53 (58.2)
Yes	86 (30.6)	237 (43.6)	38 (41.8)
<b>Development of brain metastases</b>			
No	236 (84.0)	441 (81.1)	68 (74.7)
Yes	45 (16.0)	103 (18.9)	23 (25.3)
<b>Progression-free survival</b>			
Median in months (95% CI)	6.93 (4.14-9.73)	6.44 (4.930-7.95)	2.10 (2.014-2.191)
<b>Overall survival</b>			
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.

	<b>BRAF wildtype All n=916 (100%)</b>	<b>BRAF wildtype CTLA-4+PD-1 N=281 (N=100%)</b>	<b>BRAF wildtype PD-1 N=544 (N=100%)</b>	<b>BRAF wildtype CTLA-4 N=91 (N=100%)</b>
<b>Frequency of brain metastasis</b>				
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.

<b>Parameters included</b> (patient number)	<b>Progression-free survival</b> <b>Hazard ratio (95% CI) P-value</b>	<b>Overall survival</b> <b>Hazard ratio (95% CI) P-value</b>
<b>Gender (reference: male)</b> male versus female (577 vs.339)	1.092 (0.916-1.300) 0.326	1.208 (0.982-1.486) 0.074
<b>Age (reference: ≤65 years)</b> ≤65 versus >65 years (344 vs. 572)	0.880 (0.738-1.049) 0.154	1.052 (0.852-1.298) 0.637
<b>BRAF status (reference: mutant)</b> BRAF V600 mutant versus wildtype	n.a.	n.a.
<b>ECOG performance status (reference: 0)</b> 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	<b>1.772 (1.331-2.359) &lt;0.001</b> <b>2.673 (1.619-4.414) &lt;0.001</b>
<b>Serum LDH (reference: normal)</b> normal versus elevated (459 vs. 455)	1.173 (0.989-1.392) 0.067	<b>1.495 (1.220-1.833) &lt;0.001</b>
<b>Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no)</b> no versus yes (847 vs. 69)	1.072 (0.770-1.491) 0.681	0.882 (0.562-1.385) 0.586
<b>Tumor stage (reference: M1c)</b> 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)	<b>0.700 (0.569-0.862) 0.001</b>	<b>0.669 (0.522-0.858) 0.002</b>
<b>Type of first systemic therapy (reference:CTLA-4+PD-1)</b>		
CTLA-4+PD-1 versus PD-1 (281 vs. 544)	1.049 (0.857-1.284) 0.641	<b>1.287 (1.005-1.647) 0.045</b>
CTLA-4+PD-1 versus CTLA-4 (281 vs. 91)	<b>2.880 (2.141-3.875) &lt;0.001</b>	1.173 (0.828-1.664) 0.369
<b>(reference:CTLA-4)</b>		
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
<b>Gender (reference: male)</b> male versus female (577 vs. 339)	0.933 (0.681-1.280) 0.669
<b>Age (reference: ≤65 years)</b> ≤65 versus >65 years (344 vs. 572)	0.852 (0.628-1.155) 0.302
<b>BRAF status (reference: wildtype)</b> wildtype versus BRAF V600 mutant	n.a.
<b>ECOG performance status (reference :0)</b> 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
<b>Serum LDH (reference: normal)</b> normal versus elevated (470 vs. 465)	1.159 (0.857-1.567) 0.337
<b>Pre-treatment with adjuvant immune checkpoint blockade or BRAF+MEK inhibitors (reference: no)</b> No versus yes (847 vs. 69)	0.681 (0.335-1.385) 0.289
<b>Tumor stage (reference: M1c)</b> 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)	<b>0.507 (0.310-0.830) 0.007</b> <b>0.288 (0.126-0.657) 0.003</b> 0.797 (0.567-1.120) 0.192
<b>Type of first systemic therapy (reference:CTLA-4+PD-1)</b> 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
<b>(reference:CTLA-4)</b> 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%)
<b>Age</b>				
≤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)

<b>Gender</b>				
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)
<b>Previous adjuvant therapy in stage III</b>				
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)
<b>Previous adjuvant therapy in stage IV</b>				
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)
<b>ECOG performance status</b>				
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)
<b>Serum LDH</b>				
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)
<b>Stage (AJCCv8)</b>				
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)
<b>Best overall response</b>				
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)
<b>Therapy end reason</b>				
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)
<b>Progression</b>				
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)
<b>Death</b>				
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)
<b>Development of brain metastases</b>				
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)
<b>Progression-free survival</b>				

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)
<b>Overall survival</b> 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.**

	<b>BRAF mutant All n=788 (100%)</b>	<b>BRAF mutant CTLA-4+PD-1 n=108 (100%)</b>	<b>BRAF mutant PD-1 n=264 (100%)</b>	<b>BRAF mutant BRAF+MEK N=373 (100%)</b>	<b>BRAF mutant CTLA-4 N=43 (100%)</b>
<b>Frequency of brain metastasis</b>					
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.**

<b>Parameters included</b> (patient number)	<b>Progression-free survival</b> Hazard ratio (95% CI) P-value		<b>Overall survival</b> Hazard ratio (95% CI) P-value	
<b>Gender (reference: male)</b> male versus female (478 vs.310)	0.935 (0.772-1.133)	0.495	0.947 (0.757-1.185)	0.634
<b>Age (reference: ≤65 years)</b> ≤65 versus >65 years (436 vs.352)	0.926 (0.767-1.118)	0.423	1.184 (0.951-1.472)	0.130
<b>BRAF status (reference: wildtype)</b> wildtype versus BRAF V600 mutant	n.a.		n.a.	
<b>ECOG performance status (reference: 0)</b> 0 versus 1 (344 vs. 91) 0 versus ≥2 (336 vs. 31)	<b>1.359 (1.007-1.833)</b> 1.499 (0.963-2.333)	<b>0.045</b> 0.073	<b>1.739 (1.244-2.432)</b> <b>2.857 (1.798-4.540)</b>	<b>0.001</b> <b>&lt;0.001</b>
<b>Serum LDH (reference: normal)</b> normal versus elevated (352 vs. 435)	<b>1.309 (1.083-1.581)</b>	<b>0.005</b>	<b>1.451 (1.163-1.810)</b>	<b>0.001</b>
<b>Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no)</b> no versus yes (731 vs. 57)	0.961 (0.655-1.409)	0.837	0.970 (0.617-1.525)	0.895
<b>Tumor stage (reference: M1c)</b> 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)	<b>0.643 (0.481-0.860)</b> 0.735 (0.538-1.004) <b>0.702 (0.550-0.895)</b>	<b>0.003</b> 0.053 <b>0.004</b>	<b>0.579 (0.409-0.830)</b> <b>0.490 (0.330-0.730)</b> <b>0.703 (0.532-0.928)</b>	<b>0.003</b> <b>&lt;0.001</b> <b>0.013</b>
<b>Type of first systemic therapy (reference: BRAF+MEK)</b> 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) <b>(reference: CTLA-4+PD-1)</b>	1.148 (0.836-1.600) 1.099 (0.891-1.355) <b>4.537 (3.087-6.667)</b>	0.394 0.376 <b>&lt;0.001</b>	<b>0.483 (0.315-0.740)</b> <b>0.653 (0.509-0.838)</b> 0.893 (0.602-1.325)	<b>0.001</b> <b>0.001</b> 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)	<b>3.953 (2.499-6.251)</b>	<b>&lt;0.001</b>	<b>1.848 (1.075-3.180)</b>	<b>0.026</b>
CTLA-4+PD-1 versus BRAF+MEK (108 vs. 371)	0.871 (0.634-1.196)	0.394	<b>2.070 (1.351-3.171)</b>	<b>0.001</b>

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	
<b>Gender (reference: male)</b> male versus female (478 vs.310)	1.038 (0.790-1.363)	0.789
<b>Age (reference: ≤65 years)</b> ≤65 versus >65 years (436 vs.352)	<b>0.669 (0.505-0.885)</b>	<b>0.005</b>
<b>BRAF status (reference: wildtype)</b> wildtype versus BRAF V600 mutant	n.a.	
<b>ECOG performance status (reference: 0)</b> 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
<b>Serum LDH (reference: normal)</b> normal versus elevated (352 vs. 435)	1.234 (0.942-1.616)	0.127
<b>Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK/BRAF+MEK inhibitors (reference: no)</b> no versus yes (731 vs. 57)	1.088 (0.654-1.810)	0.746
<b>Tumor stage (reference: M1c)</b> 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)	<b>0.421 (0.260-0.682)</b>	<b>&lt;0.001</b>
	<b>0.369 (0.212-0.641)</b>	<b>&lt;0.001</b>
	0.864 (0.630-1.186)	0.475
<b>Type of first systemic therapy (reference: BRAF+MEK)</b> 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
	<b>0.441 (0.313-0.622)</b>	<b>&lt;0.001</b>
	1.193 (0.751-1.896)	0.466
<b>(reference:CTLA-4+PD-1)</b> 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)	<b>0.561 (0.348-0.905)</b>	<b>0.018</b>
	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%)
<b>Age</b>		
≤65 years	295 (38.1)	485 (52.2)
>65 years	479 (61.9)	445 (47.8)
<b>Gender</b>		
male	486 (62.8)	569 (61.2)
female	288 (37.2)	361 (38.8)

<b>ECOG performance status</b>		
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)
<b>Serum LDH</b>		
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)
<b>AJCC Stage at first-line therapy start</b>		
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)
<b>BRAF status</b>		
V600 wildtype	463 (59.8)	453 (48.7)
V600 mutant	311 (40.2)	477 (51.3)
<b>Best response to first-line therapy</b>		
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)
<b>First-line therapy end reason</b>		
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)
<b>Progression</b>		
No	498 (64.3)	234 (25.2)
Yes	276 (35.7)	696 (74.8)
<b>Death</b>		
No	577 (74.5)	426 (45.8)
Yes	197 (25.5)	504 (54.2)
<b>Brain metastasis</b>		
No	706 (91.2)	611 (65.7)
Yes	68 (8.8)	319 (34.3)
<b>First-line therapy</b>		
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)
<b>Gender</b>			
male	569 (61.2)	286 (60.0)	283 (62.5)
female	361 (38.8)	191 (40.0)	170 (37.5)
<b>ECOG performance status</b>			
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)
<b>Serum LDH</b>			
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)
<b>AJCC Stage at first-line therapy start</b>			
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)
<b>BRAF status</b>			
V600 wildtype	472 (50.8)	n.a.	n.a.
V600 mutant	458 (49.2)		
<b>Therapy sequence</b>			
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
<b>Gender (reference: male)</b> male versus female	1.030 (0.527-2.012) 0.932	0.696 (0.270-1.791) 0.452
<b>Age (reference: ≤65 years)</b> ≤65 versus >65 years	0.402 (0.160-1.009) 0.052	0.743 (0.230-2.401) 0.619
<b>BRAF status (reference: wildtype)</b> wildtype versus BRAF V600 mutant	n.a.	n.a.
<b>ECOG performance status (reference :0)</b> 0 versus 1 0 versus ≥2	<b>2.104 (1.002-4.418) 0.049</b> n.a.	1.113 (0.344-3.605) 0.858 n.a.
<b>Serum LDH (reference: normal)</b> 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
<b>Tumor stage (reference: M1c)</b> 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
<b>Therapy sequence (reference: PD-1_CTLA-4+PD-1)</b>  <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 <b>9.870 (3.494-27.879) 0.001</b>	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
<b>Gender (reference: male)</b> male versus female	1.242 (0.832-1.854) 0.290	1.282 (0.815-2.017) 0.283
<b>Age (reference: ≤65 years)</b> ≤65 versus >65 years	1.242 (0.832-1.854) 0.290	0.751 (0.456-1.238) 0.262
<b>BRAF status (reference: wildtype)</b> wildtype versus BRAF V600 mutated	n.a.	n.a.
<b>ECOG performance status (reference :0)</b> 0 versus 1 0 versus ≥2	<b>1.745 (1.090-2.795) 0.021</b> <b>3.146 (1.656-5.975) &lt;0.001</b>	1.417 (0.809-2.481) 0.223 1.264 (0.521-3.067) 0.605
<b>Serum LDH (reference: normal)</b> 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
<b>Tumor stage (reference: M1c)</b> 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
<b>Therapy sequence (reference:CTLA-4+PD-1_BRAF+MEK)</b>  <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 <b>1.988 (1.026-3.852) 0.042</b> 1.863 (0.955-3.633) 0.068 <b>None</b>	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	<b>10.391 (1.245-86.740) 0.031</b>	None
<b>(reference: PD-1_BRAF+MEK)</b>		
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	<b>1.896 (1.013-3.548) 0.045</b>
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.**

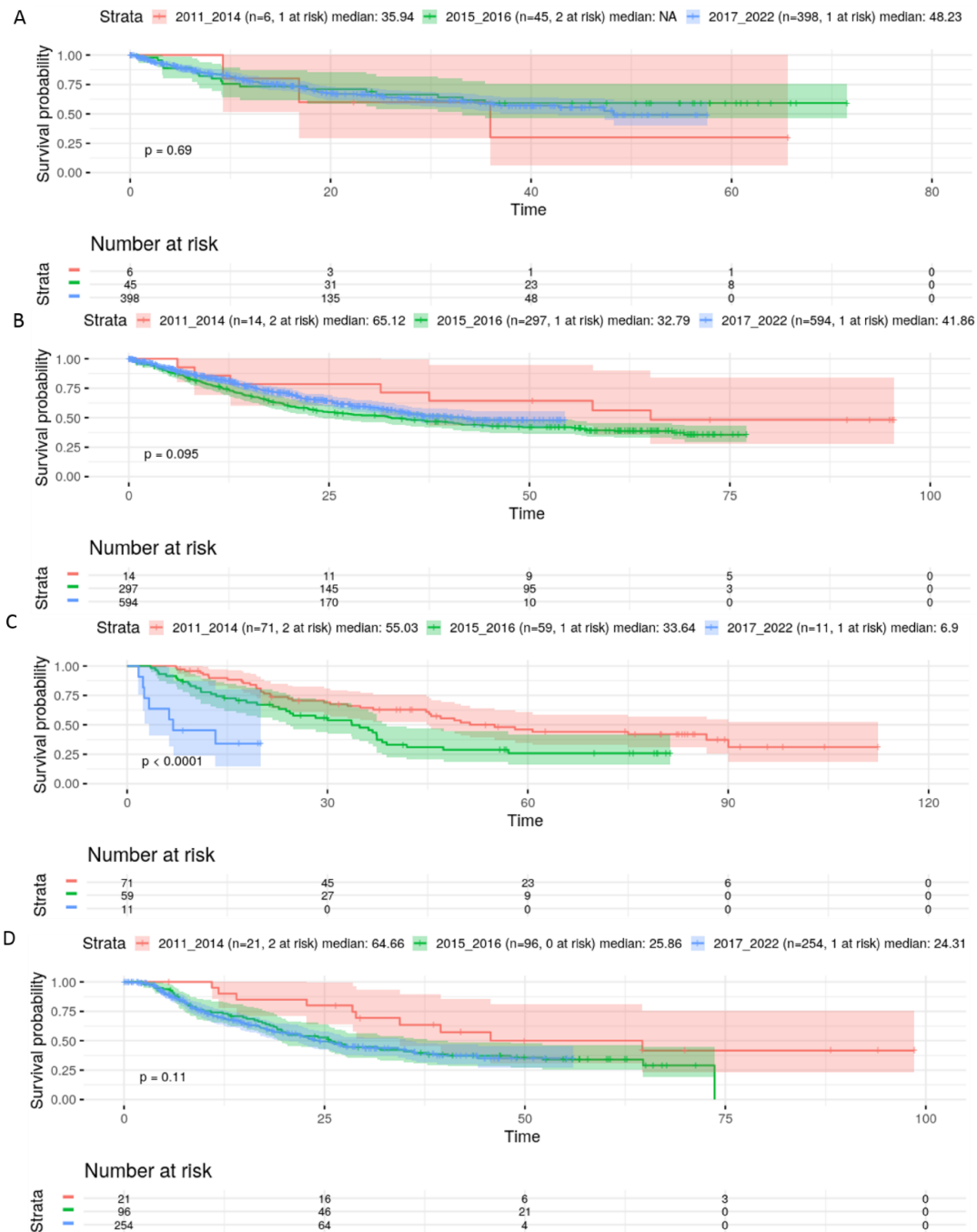
	dabrafenib+trametinib	vemurafenib+cobimetinib	encorafenib+binimetinib
<b>Brain metastasis</b>			
No	170 (66.1%)	40 (64.5%)	40 (74.1%)
Yes	87 (33.9%)	22 (35.5%)	14 (25.9%)

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

<b>Tumor stage (reference: M1c)</b>				
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	<b>0.323 (0.113-0.926)</b>	<b>0.035</b>
M1c vs. Stage IV M1b (126 vs. 43)	0.830 (0.487-1.416)	0.494	0.664 (0.350-1.261)	0.211
<b>BRAF+MEK inhibitor regimen (reference: dabrafenib+trametinib)</b>				
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.**