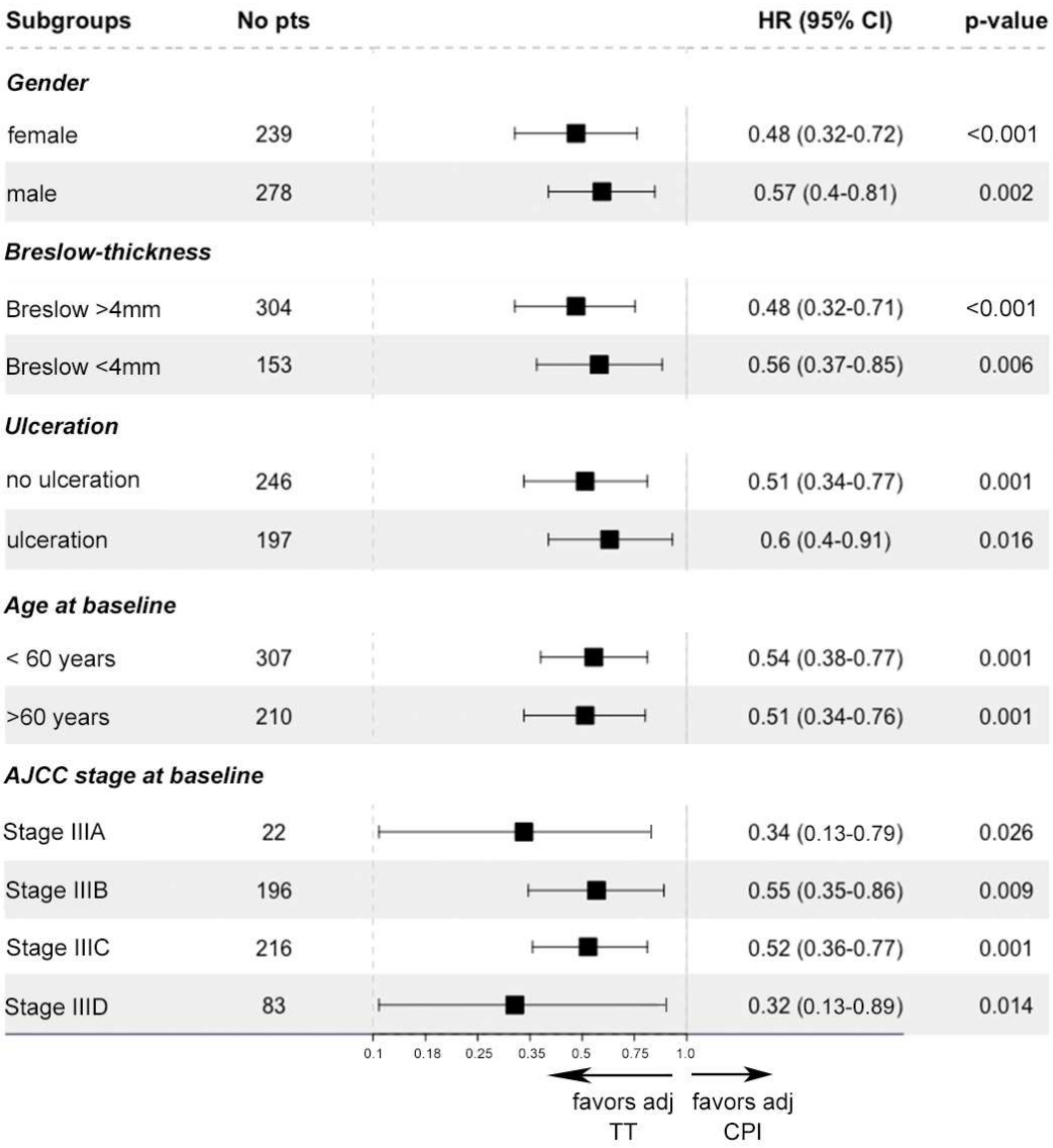
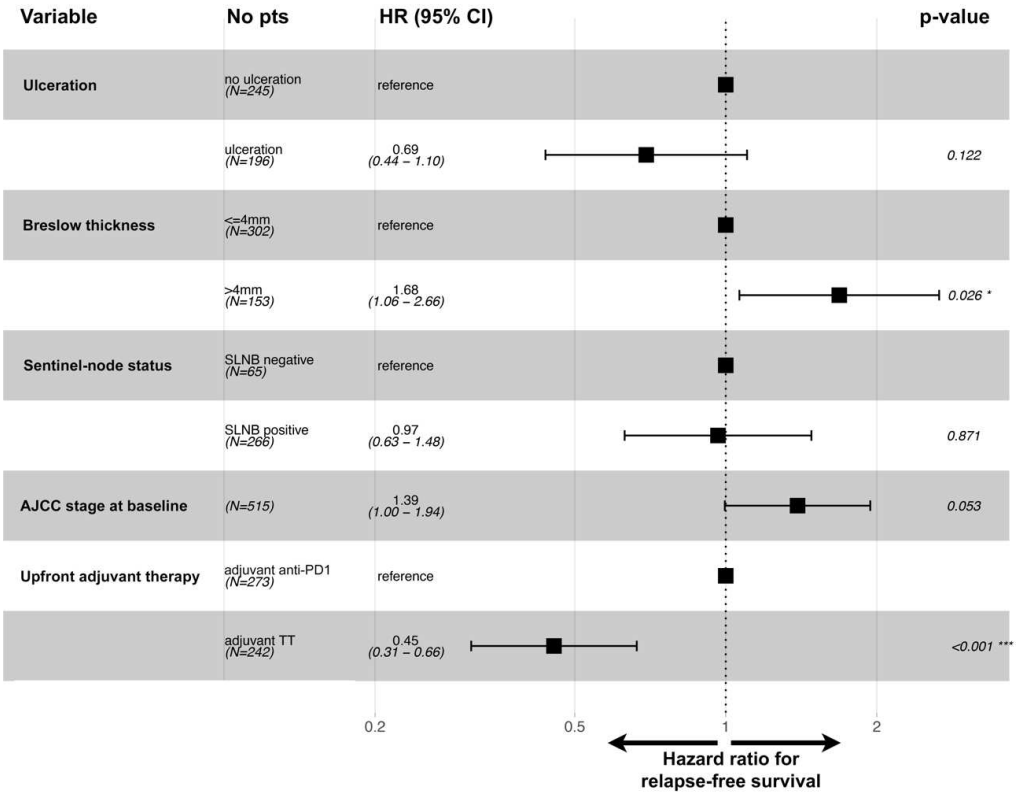
Supplementary Material

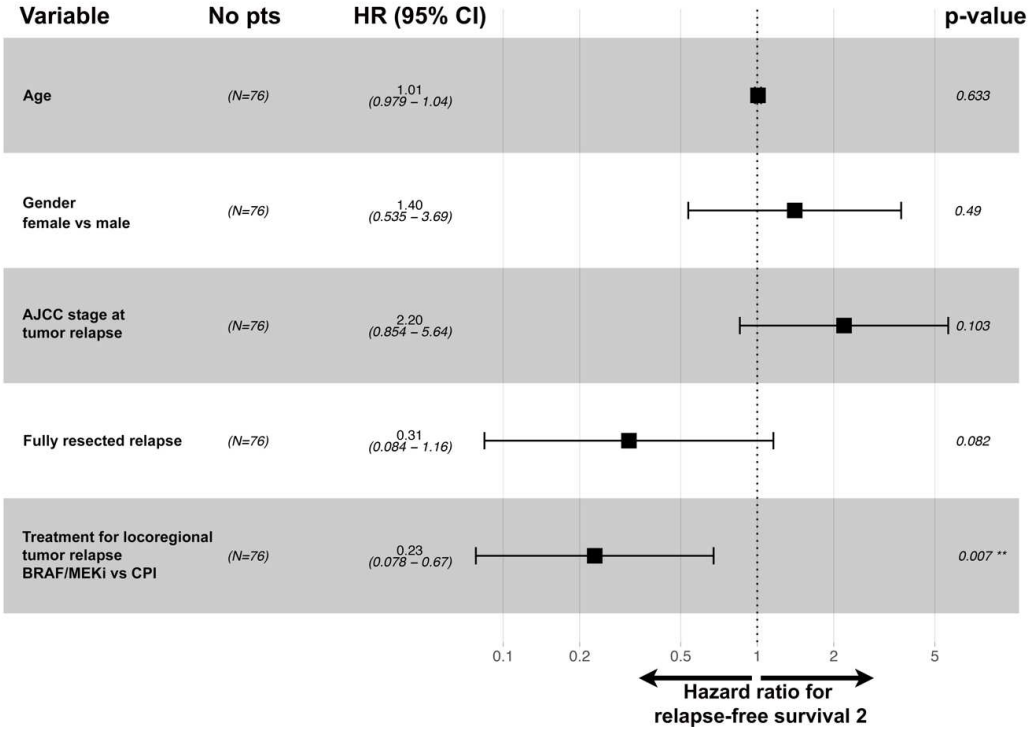
1.1. Supplementary Figures



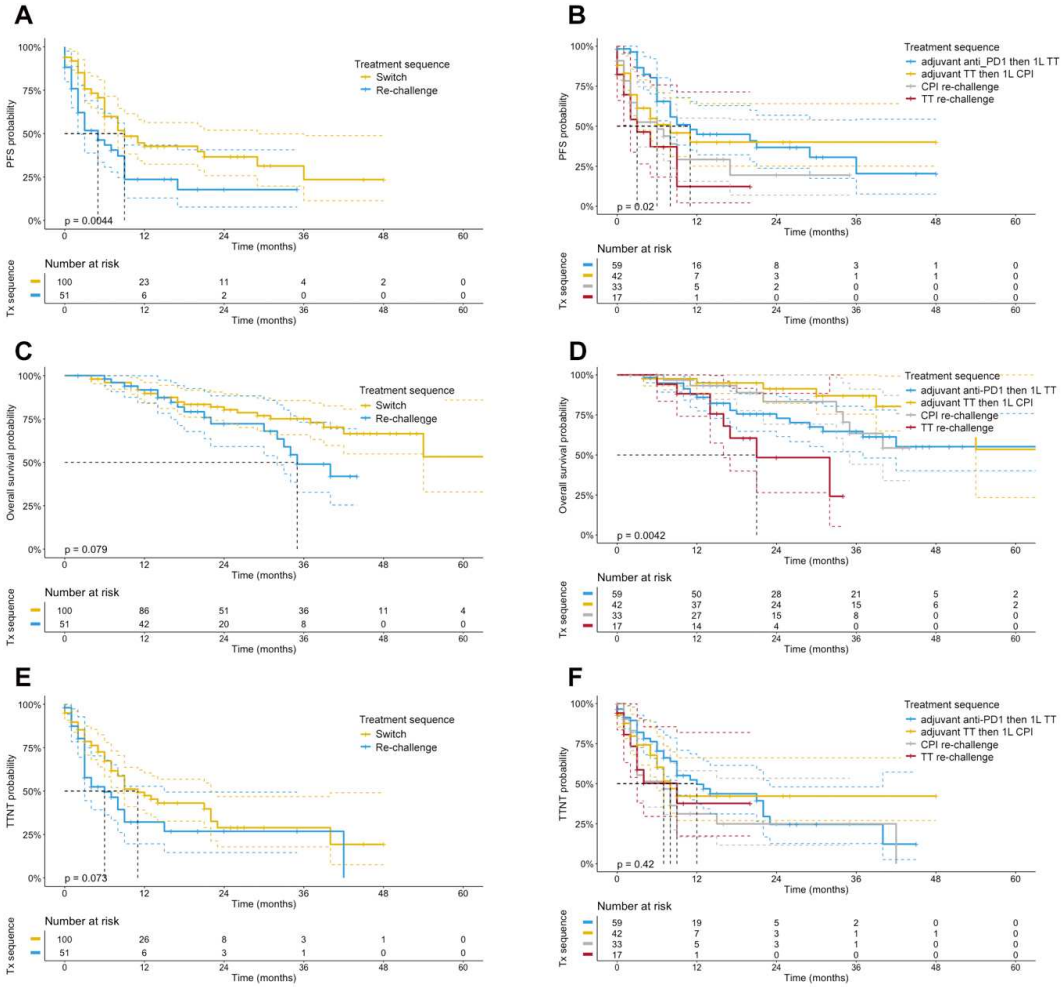
Supplementary Figure 1: Forest plot depicting hazard ratios for recurrence-free survival stratified by upfront adjuvant treatment in selected subgroups. It can be found that upfront adjuvant TT reduces the risk of tumor relapse in each of the investigated subgroups as compared to adjuvant CPI therapy.



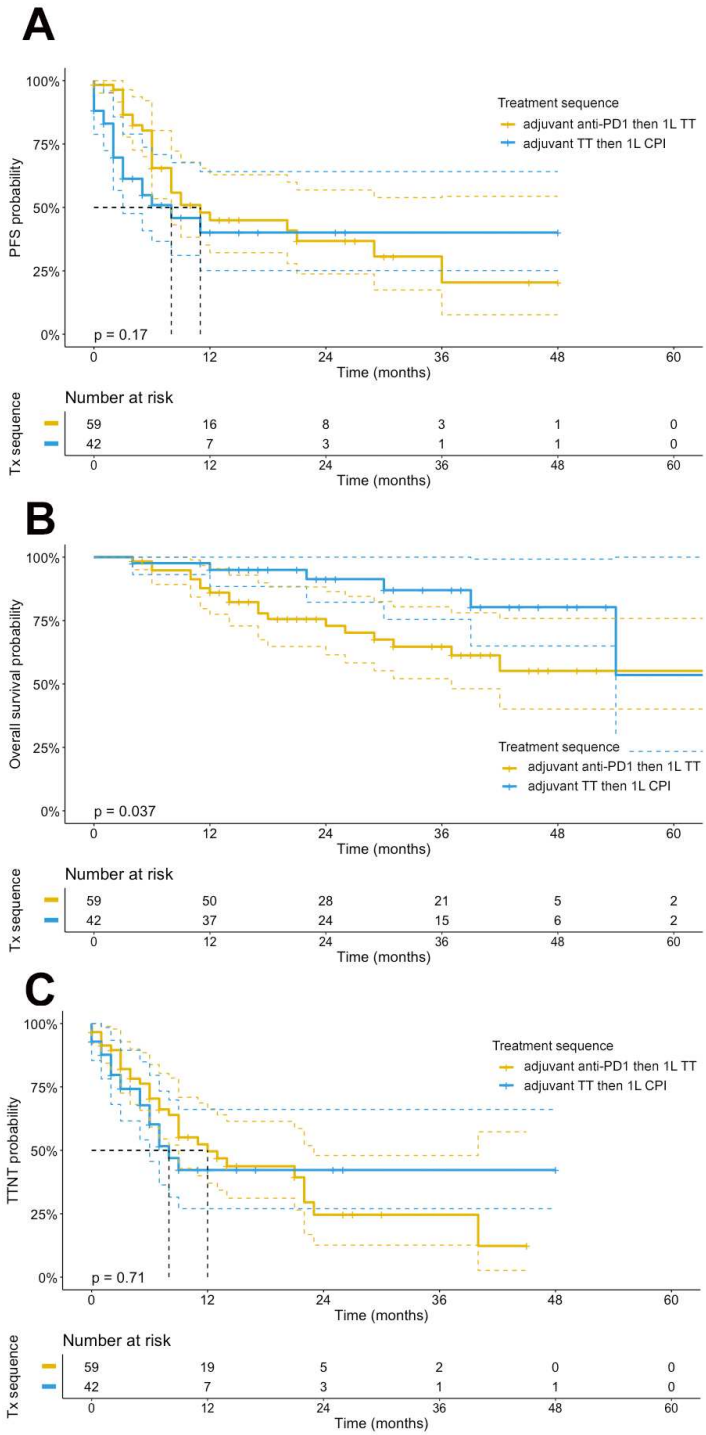
Supplementary Figure 2: Multivariate Cox-regression model investigating factors affecting recurrence-free survival for the overall patient cohort (n=515). In this multivariate model we included factors that were significantly associated with tumor recurrence in univariate testing. This multivariate Cox-regression analysis revealed that patients given adjuvant TT were at lower risk of tumor recurrence (HR: 0.45; 95% CI: 0.31-0.66) and patients with thick primary tumors (HR: 1.68; 95% CI: 1.06-2.66) and with increasing AJCC stage (HR: 1.39; 95% CI: 1.0-1.94) were at higher risk of subsequent tumor recurrence. All variables were classified as categorial variables, except for AJCC stage at baseline (continuous). *Abbreviations: CI = confidence interval; HR = hazard ratio; SLNB = sentinel-lymph node biopsy; TT = BRAF/MEK-directed targeted therapy.*



Supplementary Figure 3: Multivariate Cox-regression model investigating factors affecting recurrence-free survival 2 after locoregional tumor relapse and second systemic therapy (n=76). In this multivariate model we observed that patients who were treated with TT for locoregional tumor relapse were at lower risk of another tumor recurrence (HR: 0.23; 95% CI: 0.078-0.67, p=0.007). Also, we found that patients who underwent complete resection of locoregional tumor relapse prior to initiation of second adjuvant treatment were at lower risk of subsequent tumor relapse (HR: 0.31; 95% CI: 0.084-1.16, p=0.082). All variables were classified as categorical variables, except for Age and AJCC stage at tumor relapse (continuous). *Abbreviations: CI = confidence interval; CPI = checkpoint-inhibitor therapy; HR = hazard ratio; TT = BRAF/MEK-directed targeted therapy.*

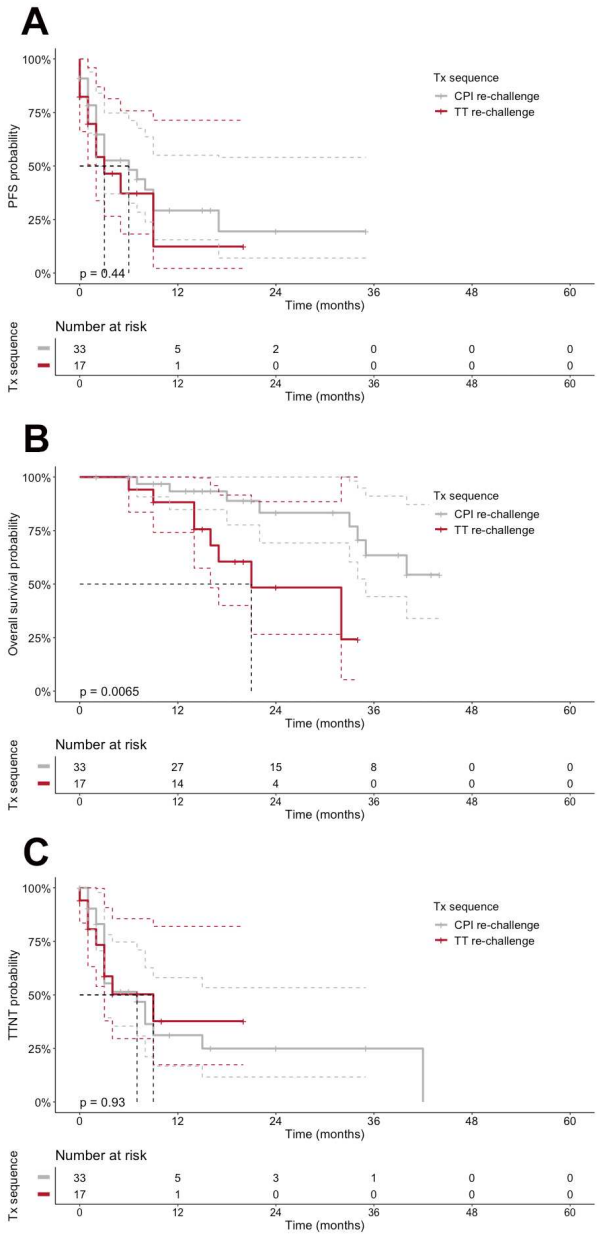


Supplementary Figure 4: Kaplan Meier survival plots comparing the outcomes from treatment sequences stratified by patients who switched treatment modalities between adjuvant therapy and first-line treatment for metastatic stage IV or who received the same treatment modality in the metastatic setting (re-challenge). Results show that a switching treatment modalities between adjuvant therapy and first metastatic treatment particularly resulted in longer median PFS (9 months, 95% CI: 5.2-12.8 vs 5 months, 95% CI: 1.3-8.7, p=0.004), although median OS (35.0 months vs NR, p=0.079) and TTNT (median TTNT: 11 months, 95% CI: 8.2-22.8 vs 6 months, 95% CI: 3.1-15.3, p=0.073) were not significantly different between the two treatment regimens (C, E). More specifically we observed that patients with a re-challenge of 1L BRAF/MEKi after failure of adjuvant TT showed the least favorable survival data. These patients presented with a median PFS of 3.0 months (95% CI: 0-6.2) as compared to 8.0 months (95% CI. 1.3-14.7) for patients switching to 1L CPI after previous TT-failure. Patients who received first-line treatment with CPI following failure of upfront adjuvant anti-PD1 therapy had a median PFS of 6.0 months (95% CI: 1.5-10.5), whereas patients who switched to 1L BRAF/MEKi upon adjuvant CPI failure had a median PFS of 11.0 months (95% CI: 5.5-16.5). Similarly median OS was significantly shorter for patients with BRAF/MEKi re-challenge with a median OS of 21.0 months (95%CI: 14.5-45.5), while median OS was not reached for all other subgroups (p=0.004). TTNT did not differ significantly between the investigated subgroups. *Abbreviations: 1L = first-line; CPI = checkpoint-inhibitor therapy; PFS = progression-free survival; TTNT = time-to-next treatment; TT = BRAF/MEK-directed targeted therapy.*

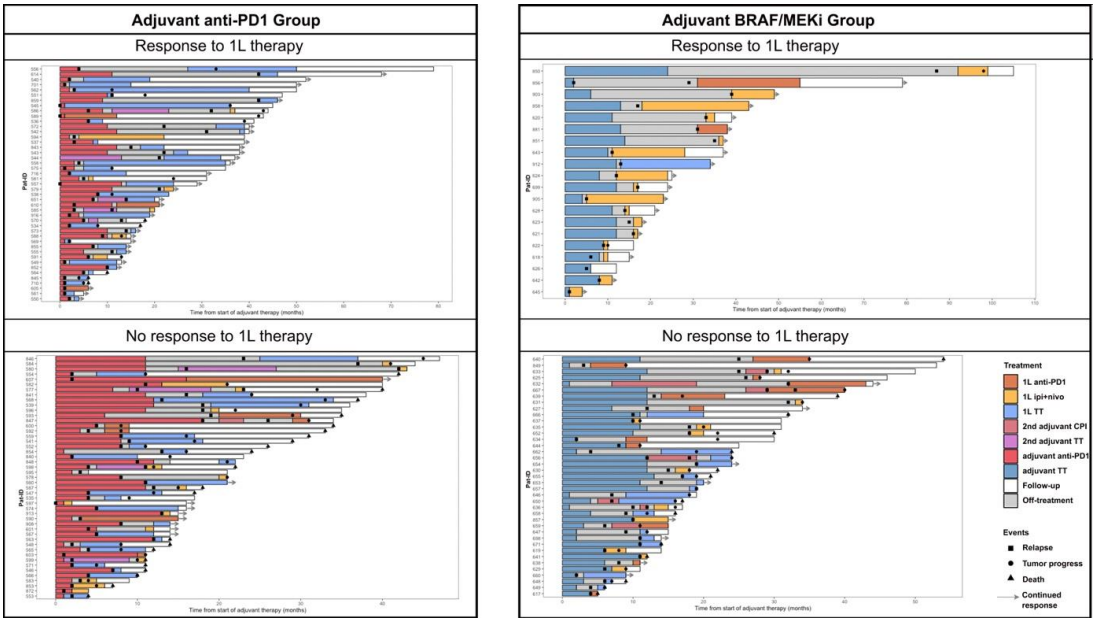


Supplementary Figure 5: Kaplan Meier survival plots for patients with distant tumor recurrence upon adjuvant therapy who switched treatment modalities after adjuvant treatment failure. Patients who received upfront adjuvant TT followed by first-line CPI showed a significantly longer median OS as compared to patients who switched to first-line BRAF/MEKi following adjuvant anti-PD1 failure (NR for both groups, p=0.037). However, median TTNT (median: 12.0 vs 8.0 months, p=0.71) and median PFS (11.0, 95% CI: 5.5-16.5 vs 8.0 months, 95% CI: 1.3-14.7, p=0.17) were not significantly different between both groups. *Abbreviations: CPI = checkpoint-inhibitor*

therapy; PFS = progression-free survival; TTNT = time-to-next treatment; TT = BRAF/MEK-directed targeted therapy.



Supplementary Figure 6: Kaplan Meier survival plots for patients who progressed to metastatic stage IV and were given either CPI or BRAF/MEK-directed TT both in the adjuvant and first-line metastatic setting (re-challenge). Re-challenge with CPI resulted in a longer PFS (median PFS: 6 months, 95% CI: 1.5-10.5 vs 3 months, 95% CI: 0-6.2, p=0.44) compared to patients that were received 1L BRAF/MEKi after adjuvant TT failure, albeit these findings were below statistical significance. By contrast, re-challenge with CPI was associated with a significantly prolonged median OS (21.0 months, 95% CI: 16.5-45.5 vs NR, p=0.0065). *Abbreviations: CPI = checkpoint-inhibitor therapy; PFS = progression-free survival; TTNT = time-to-next treatment; Tx sequence = treatment sequence; TT = BRAF/MEK-directed targeted therapy.*



Supplementary Figure 7: Swimmer´s plot illustrating the course of disease, the duration of adjuvant treatment regimens and subsequent treatments for locoregional tumor relapse and metastatic stage IV in patients who developed distant metastasis stratified by adjuvant regimen and response to first-line treatment for stage IV disease. Swimmer´s plots depict the sequential administration of adjuvant and first-line (1L) treatment regimens (CPI = red; ipi + nivo = yellow and BRAF/MEK-directed TT = blue; time off treatment is shown in grey and follow-up with second and third line treatments following 1L therapy is shown in white). In addition, time of first (and second) tumor recurrence, progressive disease during 1L therapy and patients without a tumor progression following 1L therapy initiation ("Continued response") are presented with the given icons. Responses to 1L ipi+nivo were most frequently associated with durable responses in both adjuvant treatment groups. By contrast, response to TT-re-challenge was low for patients with adjuvant BRAF/MEKi therapy. *Abbreviations: 1L = first-line; CPI = checkpoint inhibitor therapy; TT = BRAF/MEK-directed targeted therapy.*

1.2. Supplementary Tables

Table 1: Definition of real-world endpoints used in this study.

Endpoint	Outcome
Primary	
Progression-free survival (PFS)	The time interval from start of first-line treatment for metastatic stage IV to physician-reported date of progression, death date or start date of a new treatment due to progression of disease (whichever event occurred first). Patients without a progression event or date of death were censored at the date of last contact.
Real-world tumor response (rwTR)	Best tumor response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according real-world response assessments[1]. (The best therapy response was measured by the clinical assessments in the medical record and decision of the interdisciplinary tumor board as captured within the ADOReg database).
Real-world tumor response rate (rwTRR)	The proportion of patients with a complete response or partial response based on real-world response assessments relative to all patients initiating treatment.
Real-world tumor control rate (rwTCR)	The proportion of patients who had a complete response, partial response, or stable disease based on real-world response assessments
Secondary	
Recurrence-free survival (RFS)	The time interval from start of upfront adjuvant therapy to date of first locoregional or distant tumor recurrence or death, whichever occurred first. Patients alive and without tumor relapse at the date of last contact were censored.
Distant metastasis free survival (DMFS)	The time interval from start of initial adjuvant therapy to date of first documentation of distant tumor recurrence or death, whichever occurred first.
Relapse-free survival 2 (RFS2)	The time interval from start of second adjuvant therapy to date of locoregional or distant tumor recurrence or death, whichever occurred first. Patients alive and without second tumor relapse at the date of last contact were censored.
Cumulative PFS (cPFS)	The time interval from start of upfront adjuvant therapy to date of tumor progression or death following initiation of second treatments, regardless if second treatment was initiated for locoregional tumor relapse or stage IV disease. Patients alive and without tumor progression following second treatments were censored.
Time-to-next treatment (TTNT)	The time interval from start of upfront adjuvant therapy to date of next systemic anti-tumor therapy or death, whichever occurred first.
Treatment-related adverse events	Adverse events during CPI therapy or TT that were treated as clinically indicated and retrospectively graded according to the Common Terminology Criteria for Adverse Events, version 5.0 (28). Only AEs ≥grade II were evaluated because low grade AEs may not be documented thoroughly in routine clinical practice.
Overall survival (OS)	The time interval from start of upfront adjuvant therapy to date of death. Patients alive at the date of last contact were censored.
Treatment lines	
Adjuvant re-treatment	Second adjuvant treatment for locoregional tumor recurrence (AJCC stage III disease). Patients with resected locoregional recurrence, were referred to as adjuvant re-treatment that includes a switch from adjuvant TT to adjuvant anti-PD1 or vice versa or a re-treatment of either TT or CPI in the adjuvant setting.
1L treatment	Initial treatment for metastatic stage IV disease irrespective of the number of treatment lines the patient previously received for locoregional recurrence (stage III)

[1] Complete response: complete resolution of all visible disease; partial response: disease still present, with partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease; stable disease: no change in overall size of visible disease or mixed response; progressive disease: substantial increase in the overall size of all visible tumor lesions or occurrence of new tumor lesions.

Supplementary Table 2. Baseline patient characteristics of the patient cohort who received adjuvant therapy outside of clinical trials and not for resected stage IV disease.

Clinicopathological features	Overall cohort	Upfront adjuvant anti-PD1 therapy	Upfront adjuvant BRAF/ MEKi	*p*-value
Total number of patients	495	259	236	
Median age at start of adjuvant treatment (yrs, 95% CI)	58.0 (56.7-59.3)	56.0 (55.2-58.7)	59.0 (57.3-61.0)	0.088
Gender				0.93
- Female	228 (46.1%)	120 (46.3%)	108 (45.8%)	
- Male	267 (53.9%)	139 (53.7%)	128 (54.2%)	
Primary tumor characteristics				
Mean Breslow thickness (95% CI)[1]	3.7 mm (3.4-4.0)	3.4mm (3.0-3.7)	4.0mm (3.5-4.5)	**0.038**
Ulceration[2]	189 (44.6%)	96 (43.2%)	93 (46.0%)	0.625
Localization of primary tumor				0.059
- Head/neck area	49 (9.9%)	30 (11.6%)	19 (7.9%)	
- Lips, Ear, Eyelid	8 (1.6%)	4 (1.5%)	4 (1.7%)	
- Torso	198 (40.0%)	108 (41.7%)	90 (38.1%)	
- Upper limb	66 (13.3%)	33 (12.7%)	33 (14.0%)	
- Lower limb	137 (27.7%)	72 (27.8%)	65 (27.5%)	
- other	7 (1.4%)	0	7 (3.0%)	
- CUP	30 (6.1%)	12 (4.6%)	18 (7.6%)	
Tumor subtypes				**-**
- Cutaneous melanoma	442 (89.3%)	235 (90.7%)	207 (87.7%)	
- ALM	11 (2.2%)	3 (1.2%)	8 (3.4%)	
- Mucosal melanoma	1 (0.2%)	0	1 (0.4%)	
- CUP	30 (6.1%)	12 (4.6%)	18 (7.6%)	
- other	11 (2.2%)	9 (3.5%)	2 (0.8%)	
Sentinel lymph node biopsy	320 (64.6%)	164 (63.3%)	156 (66.1%)	0.249
- positive[3]	268 (80.4%)	132 (80.5%)	127 (80.9%)	
Completing lymph node dissection	65 (13.1%)	35 (13.5%)	30 (12.7%)	0.961
Adjuvant radiotherapy	61 (12.3%)	30 (11.6%)	31 (13.1%)	0.682
BRAF-mutation subtype				-
- BRAF V600E	373 (75.4%)	184 (71.0%)	189 (80.1%)	
- BRAF V600K	56 (11.3%)	27 (10.4%)	29 (12.3%)	
- BRAF V600D	11 (2.2%)	8 (3.1%)	3 (1.3%)	
- BRAF V600R	2 (0.4%)	2 (0.8%)	0	

BRAF-mutation, non-specified	53 (10.7%)	38 (14.7%)	15 (6.4%)	
Adjuvant treatment				
Initial adjuvant treatment - Nivolumab - Pembrolizumab - Dabrafenib+Trametinib	 167 (33.7%) 92 (18.6%) 236 (47.7%)	 167 (64.5%) 92 (35.5%) 0	 0 0 236	
Baseline AJCC stage - IIIA - IIIB - IIIC - IIID - III unspecified	 75 (15.2%) 189 (38.2%) 207 (41.8%) 19 (3.8%) 5 (1.0%)	 38 (14.7%) 106 (40.9%) 101 (39.0%) 9 (3.5%) 5 (1.9%)	 37 (15.7%) 83 (35.2%) 106 (44.9%) 10 (4.2%) 0	0.140
Mean treatment duration (95% CI)	8.2 months (7.8-8.6)	7.5 months (7.0-8.1)	9.0 months (8.4-9.5)	**<0.001**
Ongoing treatment	23 (4.6%)	6 (2.2%)	17 (7.2%)	**0.011**
Treatment-related adverse events > CTCAE grade 2	68 (13.7%)	34 (13.1%)	34 (14.4%)	0.230
Treatment cessation due to toxicity	105 (21.2%)	43 (16.2%)	62 (26.7%)	**0.011**
Regular completion of adjuvant therapy	212 (42.8%)	98 (37.8%)	114 (48.3%)	**0.023**
Tumor relapse - During adjuvant therapy - After adjuvant therapy	225 (45.5%) 116 (51.6%) 109 (48.4%)	141 (54.4%) 89 (63.1%) 52 (36.9%)	84 (35.6%) 27 (32.1%) 57 (67.9%)	**<0.001**
Median relapse-free survival (95% CI)	26.0 months (20.5-31.5)	17.0 months (11.9-22.1)	31.0 months (26.0-36.0)	**<0.001**
1-year relapse-free survival (95%CI)	-	56.5% (50.7-62.9%)	79.1% (74.0-84.6%)	**-**
Initial locoregional tumor relapse - Cutaneous/soft tissue - Lymph node - Not specified	72 42 (58.3%) 29 (40.3%) 1 (1.4%)	52 29 (55.8%) 23 (44.2%) 0	20 13 (65.0%) 6 (30.0%) 1 (5.0%)	0.197
Progression to stage IV disease	170 (34.3%)	102 (39.4%)	68 (28.8%)	**0.014**
Distant-metastasis-free survival (95% CI)	41.0 months (35.8-46.2)	41.0 months (29.2-52.8)	39.0 months (NA)	**0.012**
1-year distant-metastasis free survival (95% CI)	-	71.8% (66.5-77.6%)	83.1% (78.3-88.2%)	**-**
Median Time-to-next treatment	28.0 months	20.0 months	33.0 months	**<0.001**

(95% CI)	(22.9-33.1)	(14.3-25.7)	(26.6-39.4)	
Follow-up				
Median follow-up upon start of initial adjuvant therapy (95% CI)	20.0 months (18.5-21.5)	22.0 months (19.8-24.2)	19.0 months (17.1-20.9)	0.061
Median overall survival (95% CI)	NR	NR	NR	0.171
3-year OS rate (95% CI)	-	79.8% (72.8-87.5%)	86.7% (80.1-93.8%)	-
Deceased	51 (10.3%)	33 (12.7%)	18 (7.6%)	0.075

[1] Breslow thickness was available for 441 patients (231 for adjuvant anti-PD1 and 208 for TT); [2] Ulceration was available for 424 patients (222 for adjuvant anti-PD1 and 202 for TT); [3] data on sentinel-node biopsies were available for 320 patients (164 for adjuvant anti-PD1 and 156 for adjuvant TT) and positivity rate was calculated from the available data. *Abbreviations: ALM = acral-lentiginous melanoma; CI = confidence interval; CUP = carcinoma of unknown primary; OS = overall survival; TT = BRAF/MEK-directed targeted therapy; yrs = years*

Supplementary Table 3: Treatment outcomes of patients who underwent adjuvant anti-PD1 or BRAF/MEK-directed therapy outside of clinical trials.

Outcome parameter	Adjuvant CPI	Adjuvant TT
Tumor recurrence Number (%) 95% CI	 141 (54.4%) 48.2-60.6%	 84 (35.6%) 29.5-42.1%
Disease progression to stage IV Number (%) 95% CI	 102 (59.4%) 33.4-45.6%	 68 (28.8%) 23.1-35.0%
MBM before start of 1L therapy Number (%) 95% CI	 20 (7.8%) 4.8-11.7%	 29 (12.3%) 8.4-17.2%
Hepatic metastases before start of 1L therapy Number (%) 95% CI	 24 (9.3%) 6.0-13.5%	 14 (5.9%) 3.3-9.8%
Multifocal metastatic disease Number (%) 95% CI	 28 (10.8%) 7.3-15.2%	 25 (10.6%) 7.0-15.2%
Cessation of adjuvant therapy for intolerance Number (%) 95% CI	 43 (16.6%) 12.3-21.7%	 62 (26.3%) 20.8-32.4%
Cessation of adjuvant therapy for tumor recurrence Number (%) 95% CI	 91 (35.1%) 29.3-41.3%	 31 (13.1%) 8.1-18.1%

Supplementary Table 4: Univariate Cox regression analysis for relapse-free survival

Variables	**Subgroups**	**HR**	**95% CI**	***p*-value**

Age (years)	≤60 vs >60	1.05	0.80-1.37	0.73
Gender	Female vs Male	0.86	0.66-1.12	0.27
Ulceration	Yes vs no	1.25	0.94-1.67	0.13
Subtype	Cutaneous MM	0.86	0.57-1.30	0.47
	CUP	1.16	0.69-1.96	0.57
	Non-CM	1.14	0.62-2.09	0.68
Breslow (mm)	≤4mm vs >4mm	1.82	1.37-2.42	**<0.001**
Positive SLN	Yes vs no	0.83	0.55-1.26	0.38
Adjuvant RTx	Yes vs no	2.23	1.6-3.1	**<0.001**
Tumor stage at	IIIA	0.60	0.39-0.92	**0.018**
baseline	IIIB	0.86	0.65-1.13	0.27
	IIIC	1.17	0.90-1.52	0.25
	IIID	3.53	2.17-5.74	**<0.001**
Adjuvant regimen	TT vs anti-PD1	0.54	0.41-0.70	**<0.001**

Abbreviations: CM = cutaneous melanoma; MM = malignant melanoma; TT = BRAF/MEK-directed targeted therapy; RTx = radiotherapy; SLN = sentinel lymph node.

Supplementary Table 5: Treatment outcomes of patients who developed locoregional tumor recurrence.

Clinicopathological features	Overall cohort	Second treatment with CPI	Second treatment with TT	*p*-value

Total number of patients	76[1]	18	40	
Median time to locoregional recurrence	10.0 months (8.3-11.7)	7.0 months (3.9-10.1)	16.0 months (8.3-23.6)	**0.002**
Upfront adjuvant therapy				**<0.001**
- Anti-PD1 inhibitors	54 (71.0%)	4 (22.2%)	37 (94.9%)	
- BRAF/MEKi	22 (28.9%)	14 (77.8%)	3 (5.1%)	
AJCC stage at tumor recurrence				0.781
- IIIB	23 (30.2%)	7 (38.9%)	11 (27.5%)	
- IIIC	45 (59.2%)	9 (50.0%)	24 (60.0%)	
- IIID	8 (10.5%)	2 (11.1%)	5 (12.5%)	
A Treatment of locoregional tumor recurrence				
Fully resected tumor recurrence	58/76 (76.3%)	14/18 (77.8%)	37/40 (92.5%)	0.187
Treatment for locoregional recurrence	58/76 (76.3%)			-
- Ipilimumab + Nivolumab	2 (3.5%)	2 (11.1%)	0	
- Nivolumab	7 (12.3%)	7 (38.9%)	0	
- Pembrolizumab	9 (15.8%)	9 (50.0%)	0	
- Dabrafenib±Trametinib	39 (68.4%)	0	40 (100%)	
Mean treatment duration (95% CI)	7.0 months (5.8-8.3)	5.8 months (3.4-8.3)	7.6 months (6.0-9.1)	0.256
Ongoing treatment	21 (36.2%)	5 (27.8%)	16 (40.0%)	-
Reasons for treatment cessation				-
- Tumor recurrence	11 (19.0%)	6 (33.3%)	4 (10.0%)	
- Regular	19 (33.3%)	5 (27.8%)	14 (35.0%)	
- Intolerance	5 (8.8%)	1 (5.6%)	4 (10.0%)	
- other	3 (5.3%)	1 (5.6%)	2 (5.0%)	
Treatment-related adverse events > CTCAE grade 2	6 (10.5%)	1 (5.5%)	5 (12.5%)	0.73
Tumor recurrence	21 (36.2%)	10 (55.6%)	11 (27.5%)	0.075
Median relapse-free survival 2 (95% CI)	24.0 months (6.5-41.6)	6.0 months (3.2-8.7)	24.0 months (8.6-39.4)	**0.001**
Median cumulative progression-free survival (95% CI)	49 months (24.3-73.7)	28.0 months (18.6-37.4)	49.0 months (37.5-60.5)	0.111
Distant tumor recurrence	15 (25.9%)	5 (27.8%)	10 (25.0%)	1.0
Median time to next treatment	8.0 months (5.9-10.1)	5.0 months (2.4-7.6)	9.0 months (5.6-12.4)	0.09
B Survival outcomes for patients with second adjuvant therapy upon locoregional tumor				

recurrence				
Second adjuvant treatment - Adjuvant anti-PD1 - Adjuvant ipi+nivo - Adjuvant DT	 12 (23.5%) 2 (3.9%) 37 (72.5%)	 12 (85.7%) 2 (14.3%) 0	 0 0 37 (100%)	-
Site of resection - Lymph node - Cutaneous/subcutaneous	 18 (35.3%) 33 (64.7%)	 4 (28.6%) 10 (71.4%)	 14 (37.8%) 23 (62.2%)	0.240
Tumor recurrence	17/51 (33.3%)	7/14 (50%)	10/37 (27.0%)	0.183
Median relapse-free survival after second adjuvant therapy	24.0 months (9.6-38.3)	6.0 months (1.7-10.3)	41.0 months (21.0-61.0)	**0.009**
Median time to next treatment	9.0 months (7.2-10.8)	5.0 months (0.1-9.9)	9.0 months (5.9-12.1)	0.078
C Survival outcomes for patients with second adjuvant therapy upon distant metastasis				
- Ipilimumab+Nivolumab - Pembrolizumab - Nivolumab - Dabrafenib±Trametinib	4 (21.1%) 2 (10.5%) 3 (15.8%) 10 (52.6%)	4 (44.4%) 2 (22.2%) 3 (33.3%) 0	0 0 0 10	**-**
Site of resection - Distant lymph node - Brain - Lung - Skin - Other	 6 2 4 5 2	 2 (22.2%) 1 (11.1%) 3 (33.3%) 2 (22.2%) 1 (11.1%)	 4 (40%) 1 (10%) 1 (10%) 3 (30%) 1 (10%)	**-**
Tumor recurrence	11/19 (57.9%)	5/9 (55.5%)	6/10 (60.0%)	0.33
Median relapse-free survival after second adjuvant therapy	9.0 months (6.2-11.8)	9.0 months (2.0-16.0)	11.0 months (5.2-16.8)	0.428
Median time to next treatment	21.0 months (8.7-33.3)	9.0 months (0.7-17.3)	29.0 months (NA)	0.234

[1,2,3] Patients not listed did not receive any systemic treatment for locoregional tumor recurrence yet. Among the 18 patients without systemic treatment for locoregional tumor recurrence 6 were treated with surgical removal of locoregional recurrence. *Abbreviations: CI = confidence interval; CPI = checkpoint-inhibitor therapy; DT = dabrafenib+trametinib; NA = not available; TT = BRAF/MEK-directed targeted therapy.*

Supplementary Table 6: Treatment for patients that developed metastatic stage IV disease upon failure of adjuvant therapy stratified by first-line treatments (n=179).

Clinicopathological features	First-line CPI monotherapy	First-line ipi+nivo	First-line TT	*p*-value

Patient number	23	52	76	-
Upfront adjuvant therapy - Adjuvant anti-PD1 - Adjuvant DT	 10 (43.5%) 13 (56.5%)	 23 (44.2%) 29 (55.8%)	 59 (77.6%) 17 (22.4%)	**<0.001**
Prior adjuvant treatment for locoregional tumor recurrence	2 (8.7%)	8 (15.3%)	3 (3.9%)	0.238
Multifocal metastatic disease (>2 distant organ metastases)	8 (34.8%)	14 (26.9%)	32 (42.1%)	0.220
Brain metastasis at start of metastatic treatment	5 (21.7%)	25 (48.1%)	18 (23.7%)	**0.009**
Elevated LDH serum levels (>245 U/l) at start 1L therapy[1]	6 (50.0%)	14 (35.0%)	24 (49.0%)	0.385
Elevated S100 serum levels (>0.105µg/ml) at start 1L therapy[2]	7 (58.3%)	25 (62.5%)	35 (71.5%)	0.554
Treatment for metastatic stage IV disease				
First-line treatment for stage IV - Ipilimumab + Nivolumab - Nivolumab - Pembrolizumab - Ipilimumab - Vemurafenib±Cobimetinib - Dabrafenib±Trametinib - Encorafenib±Binimetinib	 0 11 (47.9%) 11 (47.9%) 1 (4.2%) 0 0 0	 52 0 0 0 0 0 0	 0 0 0 0 1 (1.3%) 39 (51.3%) 36 (47.4%)	-
Mean treatment duration (95% CI)	6.9 months (4.9-9.8)	2.9 months (1.7-4.1)	8.9 months (6.3-11.5)	**<0.001**
Ongoing treatment	7 (30.4%)	19 (36.5%)	28 (37.3%)	0.870
Real-world tumor response rate[3]	3/21 (14.3%)	15/38 (39.5%)	28/57 (49.1%)	**0.018**
Real-world tumor control rate[3]	14/21 (66.7%)	24 (63.2%)	44 (77.2%)	0.306
Treatment-related adverse events > CTCAE grade 2	1 (4.3%)	16 (30.7%)	10 (13.2%)	**0.045**
Treatment cessation due to toxicity	2 (8.7%)	10 (19.2%)	16 (21.3%)	0.432
Tumor progression	14 (60.9%)	26 (50%)	40 (52.6%)	0.717
Median progression-free survival (95% CI)	5.0 months (0-10.1)	7.0 months (3.7-10.3)	9.0 months (6.5-11.5)	0.422
Median time to next treatment (95% CI)	9.0 months (0-18.9)	7.0 months (4.7-9.3)	11.0 months (7.1-14.9)	0.357
Treatment lines for stage IV disease				0.877

- One treatment line - >1 treatment line(s)	13 (56.5%) 10 (43.5%)	30 (57.7%) 22 (42.3%)	45 (59.2%) 31 (40.8%)	
Follow-up				
Median follow-up upon upfront adjuvant therapy	40.0 months (30.3-49.7)	24.0 months (15.3-32.7)	35.0 months (22.9-47.1)	0.131
Median overall survival upon upfront adjuvant therapy (95% CI)	54.0 months (32.4-75.6)	NR	42.0 months (NA)	**0.049**
Median overall survival upon initiation of 1L therapy (95% CI)	27.0 months (25.6-28.4)	NR	24.0 months (9.6-38.4)	0.708

[1,2] LDH serum and S100 levels at baseline were available for 101 patients (12 for CPI monotherapy, 40 for ipi+nivo and 49 for TT; [3]tumor responses were available for 116 patients (21 for CPI monotherapy, 24 for ipi+nivo and 57 for TT). *Abbreviations: 1L = first-line; CI = confidence interval; CPI = checkpoint-inhibitor therapy; DT = dabrafenib+trametinib; NR = not reached; TT = BRAF/MEK-directed targeted therapy.*

Supplementary Table 7: Baseline patient characteristics and response to first-line treatment stratified by the treatment regimens applied for patients with progress to stage IV disease. Group 1 was defined by patients who received upfront adjuvant anti-PD1 treatment and BRAF/MEKi following distant metastasis, whereas patients in group 2 first received upfront adjuvant therapy with dabrafenib+trametinib and subsequently switched to 1L CPI for metastatic stage IV. Patients in groups 3 and 4 received upfront adjuvant treatment either with anti-PD1 (group 3) or BRAF/MEKi (group4) and were re-treated with these agents in the metastatic first-line setting.

Outcome	**Response to 1L**	**Response to**	**Response**	**Response to**	***p*-**

	BRAF±MEKi therapy (group 1)	**1L CPI therapy (group 2)**	**to CPI re-challenge (group 3)**	**BRAF±MEK re-challenge (group 4)**	**value**
Number of patients	59	42	33	17	
Best tumor response (%)					**0.037**
Complete response (CR)	13 (28.3%)	5 (14.7%)	3 (12.0%)	1 (9.1%)	
Partial response (PR)	14 (30.4%)	5 (14.7%)	5 (20.0%)	0	
Stable disease (SD)	12 (26.1%)	14 (41.2%)	6 (24.0%)	4 (36.4%)	
Progressive disease (PD)	7 (15.2%)	10 (29.4%)	11 (44.0%)	6 (54.5%)	
NA[1]	13	8	8	6	
Tumor response rate (TRR)[1]					**0.004**
Number (%)	27 (58.7%)	10 (29.4%)	8 (32.0%)	1 (9.1%)	
95% CI	43.2-73.0%	15.1-47.5%	14.9-53.5%	0.2-41.3%	
Tumor control rate (TCR)[1]					**0.013**
Number (%)	39 (84.8%)	24 (70.6%)	14 (56.0%)	5 (45.5%)	
95% CI	71.1-93.7%	52.5-84.9%	34.9-75.6%	16.7-76.6%	
Tumor progress					0.486
Number (%)	29 (49.2%)	20 (47.6%)	20 (60.6%)	11 (64.7%)	
95% CI[1]	35.9-62.5%	32.0-63.6%	42.1-77.1%	38.3-85.8%	
Elevated LDH serum[2] levels at baseline					**0.038**
Number (%)	16 (41.0%)	15 (46.9%)	5 (25.0%)	8 (80.0%)	
95% CI	25.6-57.9%	29.1-65.3%	8.7-49.1%	44.4-97.5%	
Liver metastases at baseline, no (%)	20 (33.9%)	7 (16.7%)	5 (15.2%)	6 (35.3%)	0.084
Brain metastases at baseline, no (%)	11 (18.3%)	20 (48.8%)	10 (29.4%)	7 (38.9%)	**0.011**
Multifocal metastatic disease, no (%)	24 (40.7%)	16 (38.1%)	6 (18.2%)	8 (47.1%)	0.094
Resected stage IV disease	10 (17.0%)	8 (19.1%)	1 (3.0%)	0	0.385
Ongoing 1L therapy Number, no (%)	21 (35.6%)	18 (42.9%)	8 (24.2%)	7 (43.8%)	0.345
Treatment-related AE > CTCAE grade 2	9 (15.2%)	9 (21.4%)	8 (24.2%)	1 (5.9%)	0.724
Cessation due to toxicity, no (%)	13 (22.0%)	4 (9.5%)	8 (24.2%)	3 (18.8%)	0.296

[1] Data on tumor responses was available for 116 patients (46 for 1L BRAF/MEKi, 34 for 1L CPI, 25 for CPI re-challenge and 11 for TT re-challenge), [2] data on LDH serum levels at baseline were available for 101 patients (39 for 1L BRAF/MEKi; 32 for 1L CPI; 10 for TT re-challenge and 20 for CPI re-challenge)

Supplementary Table 8: Univariate Cox-regression analysis for overall survival in patients that developed distant metastasis upon adjuvant treatment failure.

Variables	Subgroups	HR	95% CI	*p*-value
Age (years)	>60 vs ≤60	3.89	2.22-6.8	**<0.001**
Gender	Female vs Male	0.71	0.41-1.23	0.22
Ulceration	Yes vs no	2.47	1.32-4.60	**0.005**
Breslow (mm)	>4mm vs ≤4mm	1.35	0.77-2.36	0.30
LDH at baseline	Elevated vs normal	1.28	0.61-2.67	0.51
MBM at baseline	Yes vs no	1.98	1.14-3.41	**0.015**
Hepatic metastases at baseline	Yes vs no	2.34	1.35-4.04	**0.003**
Number metastatic sites	>2 vs ≤2	2.55	1.49-4.36	**<0.001**
Resection status	Resected stage IV vs non-resected stage IV disesae	0.53	0.26-1.09	0.082
Adjuvant regimen	TT vs anti-PD1	0.84	0.48-1.47	0.53
1L regimen	Adjuvant anti-PD1 > 1L TT vs Adjuvant TT > 1L CPI	2.56	1.02-6.43	**0.045**
	Adjuvant anti-PD1 > 1L TT vs Adjuvant anti-PD1 > 1L CPI	0.88	0.58-1.34	0.56
	Adjuvant anti-PD1 > 1L TT vs Adjuvant TT > 1L TT	0.48	0.20-1.13	0.092
	TT re-challenge vs CPI re-challenge	4.21	1.38-12.84	**0.011**

Abbreviations: 1L = first-line; CPI = checkpoint inhibitor therapy; MBM = melanoma brain metastasis; TT = BRAF/MEK-directed targeted therapy

Supplementary Table 9: Multivariate Cox-regression analysis for overall survival in patients that developed distant metastasis upon adjuvant treatment failure.

Variables	Subgroups	HR	95% CI	*p*-value
Gender	Female vs Male	0.80	0.32-2.01	0.64
Age	>60 years vs <60 years	2.66	1.01-7.0	**0.048**
MBM at baseline	Yes vs no	1.81	0.76-4.31	0.18
Number of metastatic sites	Multifocal vs Oligofocal	3.19	1.28-7.99	**0.013**
Treatment sequence	Adjuvant anti-PD1 > 1L TT vs Adjuvant TT > 1L CPI	2.72	1.0-7.3	**0.047**

Abbreviations: 1L = first-line; CPI = checkpoint inhibitor therapy; MBM = melanoma brain metastasis; TT = BRAF/MEK-directed targeted therapy

Supplementary Table 10: Univariate Cox-regression analysis for progression-free survival in patients that developed distant metastasis upon adjuvant treatment failure.

Variables	Subgroups	HR	95% CI	*p*-value
Age (years)	>60 vs ≤60	1.42	0.93-2.17	0.108
Gender	Female vs Male	0.62	40-0.96	**0.028**
Ulceration	Yes vs no	2.10	1.31-3.36	**0.002**
Breslow (mm)	>4mm vs ≤4mm	1.17	0.74-1.83	0.51
LDH at baseline	Elevated vs normal	1.53	0.90-2.61	0.11
MBM at baseline	Yes vs no	1.60	1.03-2.48	**0.037**
Hepatic metastases at baseline	Yes vs no	2.11	1.34-.3.31	**0.001**
Number metastatic sites	>2 vs ≤2	2.18	143-3.32	**<0.001**
Resection status	Resected stage IV vs Non-resected stage IV disease	0.75	0.41-1.39	0.36
Response to 1L therapy	Response vs no response	0.27	0.15-0.47	**<0.001**
Adjuvant regimen	TT vs anti-PD1	1.41	0.92-2.17	0.12
Treatment sequence	Adjuvant anti-PD1 > 1L TT vs Adjuvant TT > 1L CPI	0.68	0.38-1.21	0.19
	Adjuvant anti-PD1 > 1L CPI vs Adjuvant anti-PD1 > 1L TT v	1.41	1.06-1.89	**0.019**
	Adjuvant TT > 1L TT vs Adjuvant anti-PD1 > 1L TT	2.99	1.46-6.13	**0.003**
	TT re-challenge vs CPI re-challenge	1.31	0.63-2.73	0.476

Abbreviations: 1L = first-line; CPI = checkpoint inhibitor therapy; MBM = melanoma brain metastasis; TT = BRAF/MEK-directed targeted therapy

Supplementary Table 11: Multivariate Cox-regression analysis for progression-free survival in patients that developed distant metastasis upon adjuvant treatment failure.

Variables	Subgroups	HR	95% CI	*p*-value
Gender	Female vs Male	0.75	0.35-1.59	0.45
Age (years)	≤60 vs >60	0.86	0.41-1.79	0.69
Ulceration	Yes vs No	1.89	0.95-3.77	0.069
Number of metastatic sites	Multifocal vs Oligofocal	4.25	2.06-8.76	**<0.001**
Treatment sequence	Adjuvant anti-PD1 > 1L TT vs Adjuvant TT > 1L CPI	0.48	0.23-0.98	**0.045**

Abbreviations: 1L = first-line; CPI = checkpoint inhibitor therapy; TT = BRAF/MEK-directed targeted therapy