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Treatment management for *BRAF*-mutant melanoma patients with tumor recurrence on adjuvant therapy: a multicenter study from the prospective skin cancer registry ADOREG

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ABSTRACT

Background Adjuvant therapy with immune-checkpoint inhibitors (CPI) or BRAF/MEK-directed targeted therapy (TT) improves recurrence-free survival (RFS) for patients with advanced, *BRAF*V600-mutant (*BRAF*mut) resected melanoma. However, 40% of these patients will develop distant metastases (DM) within 5 years, which require systemic therapy. Little data exist to guide the choice of upfront adjuvant therapy or treatment management upon DM. This study evaluated the efficacy of subsequent treatments following tumor recurrence upon upfront adjuvant therapy.

Methods For this multicenter cohort study, we identified 515 *BRAF*mut patients with resected stage III melanoma who were treated with PD-1 inhibitors (anti-PD1) or TT in the adjuvant setting. Disease characteristics, treatment regimens, details on tumor recurrence, subsequent treatment management, and survival outcomes were collected within the prospective, real-world skin cancer registry ADOReg. Primary endpoints included progression-free survival (PFS) following DM and best tumor response to first-line (1L) treatments.

Results Among 515 eligible patients, 273 patients received adjuvant anti-PD1 and 242 adjuvant TT. At a median follow-up of 21 months, 54.6% of anti-PD1 patients and 36.4% of TT patients recurred, while 39.6% (anti-PD1) and 29.3% (TT) developed DM. Risk of recurrence was significantly reduced in patients treated with TT compared with anti-PD1 (adjusted HR 0.52; 95% CI 0.40 to 0.68, p<0.001). Likewise, median RFS was significantly longer in TT-treated patients (31 vs 17 months, p<0.001). Patients who received TT as second adjuvant treatment upon locoregional recurrence had a longer RFS2 as compared with adjuvant CPI (41 vs 6 months, p=0.009). Patients who recurred at distant sites following adjuvant TT showed favorable response rates (42.9%) after switching to 1L ipilimumab+nivolumab (ipi+nivo). Patients with DM during adjuvant anti-PD1 achieved response rates of 58.7% after switching to 1L TT and 35.3% for 1L ipi+nivo. Overall, median PFS was significantly longer in patients who switched treatments for stage IV disease (median PFS 9 vs 5 months, p=0.004).

Conclusions *BRAF*mut melanoma patients who developed DM upon upfront adjuvant therapy achieve favorable tumor control and prolonged PFS after switching treatment modalities in the first-line setting of stage IV disease. Patients with locoregional recurrence benefit from complete resection of recurrence followed by a second adjuvant treatment with TT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the approval of effective adjuvant treatment regimens for patients with advanced, resected *BRAF*-mutant melanoma, 40% of patients will eventually develop distant metastasis. There are little data available which treatment strategy might allow for optimal survival outcomes following locoregional and distant tumor recurrence during or after adjuvant therapy.

BACKGROUND

The treatment landscape for advanced melanoma patients has been significantly

WHAT THIS STUDY ADDS

⇒ In this study, we show in a large, multicenter real-world patient cohort with resected *BRAF*-mutant melanoma that adjuvant targeted therapy (TT) resulted in a significant reduction of the risk of tumor recurrence compared with adjuvant anti-PD1 treatment.

⇒ Patients who recurred locoregionally benefit from a complete resection of locoregional tumor recurrence followed by a second adjuvant treatment with BRAF/MEK-inhibitors.

⇒ Patients who recurred at distant sites following upfront adjuvant anti-PD1 therapy achieved favorable tumor responses when switching to first-line TT or first-line ipi+nivo, whereas patients who developed distant metastasis upon adjuvant TT achieved highest response rates after switching to first-line ipi+nivo.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our data suggest that adjuvant TT can preferably be chosen in patients with resected, BRAF-mutant melanoma to prevent tumor recurrence. Patients who relapse at distant sites achieve favorable survival outcomes when switching treatments between adjuvant therapy and first-line therapy in the metastatic setting.

improved by the advent of BRAF/MEK-directed targeted therapy (TT) and immune-checkpoint inhibitors (CPIs). Given the success of CPI and TT in the metastatic setting,[1–3] recent studies tested the efficacy of adjuvant CPI and BRAF/MEK inhibitors for resected stage III/IV melanoma.

Nine large randomized controlled trials of CPI and TT in the adjuvant setting have been completed so far and continue to mature.[4] The EORTC-18071 and E1609 trial examined adjuvant treatment with ipilimumab (ipi), which demonstrated both an improved recurrence-free survival (RFS) and overall survival (OS).[5 6] Due to the high rates of severe treatment-related adverse events (AE of grade 3 or higher: 45%) observed in these trials, adjuvant ipi is rarely used in clinical practice. The subsequent Keynote-054 and Checkmate-238 trials evaluated the efficacy of pembrolizumab (Pb)[7 8] and nivolumab (nivo)[9 10] in the adjuvant setting for patients with resected stage III melanoma. Both trials observed a significantly prolonged RFS and better toxicity profiles with severe AE occurring in 14% of patients but did not report a significant OS benefit yet.

In addition, two trials examined the use of adjuvant TT for patients with *BRAF*-mutant resected melanoma: The BRIM-8 trial investigated the efficacy of adjuvant single-agent vemurafenib compared with placebo but did not reach statistical significance with regard to the prespecified endpoint of disease-free survival and thus single-agent vemurafenib is not recommended for adjuvant melanoma therapy.[11] By contrast, the COMBI-AD trial, which tested adjuvant dabrafenib+trametinib (DT) for resected, *BRAF*-mutant stage III melanoma met its primary endpoint of RFS, which was significantly longer as compared with placebo and thus DT has become a standard treatment option for patients with resected stage III melanoma.[12–14] Similar to Keynote-054 and Checkmate-238 adjuvant DT did, however, not meet its prespecified significance criteria with regard to improved OS at last interim analysis.

Although adjuvant anti-PD1 and TT significantly improved RFS, more than 50% of patients will eventually relapse and almost 40% of patients will recur at distant sites requiring the administration of subsequent treatments to re-initiate tumor control.[4] In particular, it has been found that 35% and 39% of patients treated with adjuvant DT or adjuvant Pb will develop distant metastases (DM) within 5 years.[7 12] Despite the significant number of patients with (distant) tumor recurrence, there are little data available on the outcomes of patients with *BRAF*mut melanoma who relapse after adjuvant therapy and which treatments might show the best efficacy following either locoregional recurrence or DM.[15 16]

In this multicenter, real-world cohort study, we evaluated the treatment management and outcome of patients who developed locoregional and DM upon adjuvant melanoma therapy and analyzed the efficacy of subsequent treatments following failure of upfront adjuvant therapy. Also, we describe the efficacy of upfront adjuvant therapy with PD-1 inhibitors as compared with adjuvant TT for patients with resected *BRAF*-mutant melanoma.

PATIENTS AND METHODS

Study design and data source

Patients with *BRAF*V600 positive resected stage III melanoma (defined by American Joint Committee on Cancer, AJCC, version 8 criteria), who received adjuvant treatment for at least 1 month or at least one dose of adjuvant anti-PD-1 therapy were identified from the prospective multicenter skin cancer registry ADOREG of the German Dermatologic Cooperative Oncology Group.[17] The ADOReg platform collects healthcare data on skin cancer patients from 59 skin cancer centers, 50 of which contributed to the current study. Details on treatment and outcome specifics were recorded in an unidentifiable, pseudonymized form at the patient level.

Patient cohort

At data request (08/2022), 9326 patients with malignant melanoma were identified within the ADOREG database with follow-up (FU) until data cut-off in August 2022. Thereof, 744 patients with *BRAF*-positive, resected stage III/IV melanoma received at least one dose of adjuvant anti-PD-1 (nivo or Pb) or 1 month of BRAF/MEKi (DT) therapy between January 2014 and July 2022. For subsequent analysis, we excluded patients with ongoing adjuvant treatment who had an FU of less than 11 months. Patients who were off adjuvant treatment for other reasons than recurrence or intolerance and were not lost to FU were included in the analysis if FU was at least 6 months (Consolidated Standards of Reporting Trials, CONSORT, diagram in figure 1).

Clinical data on baseline patient and tumor characteristics, as well as adjuvant treatment specifics, toxicity

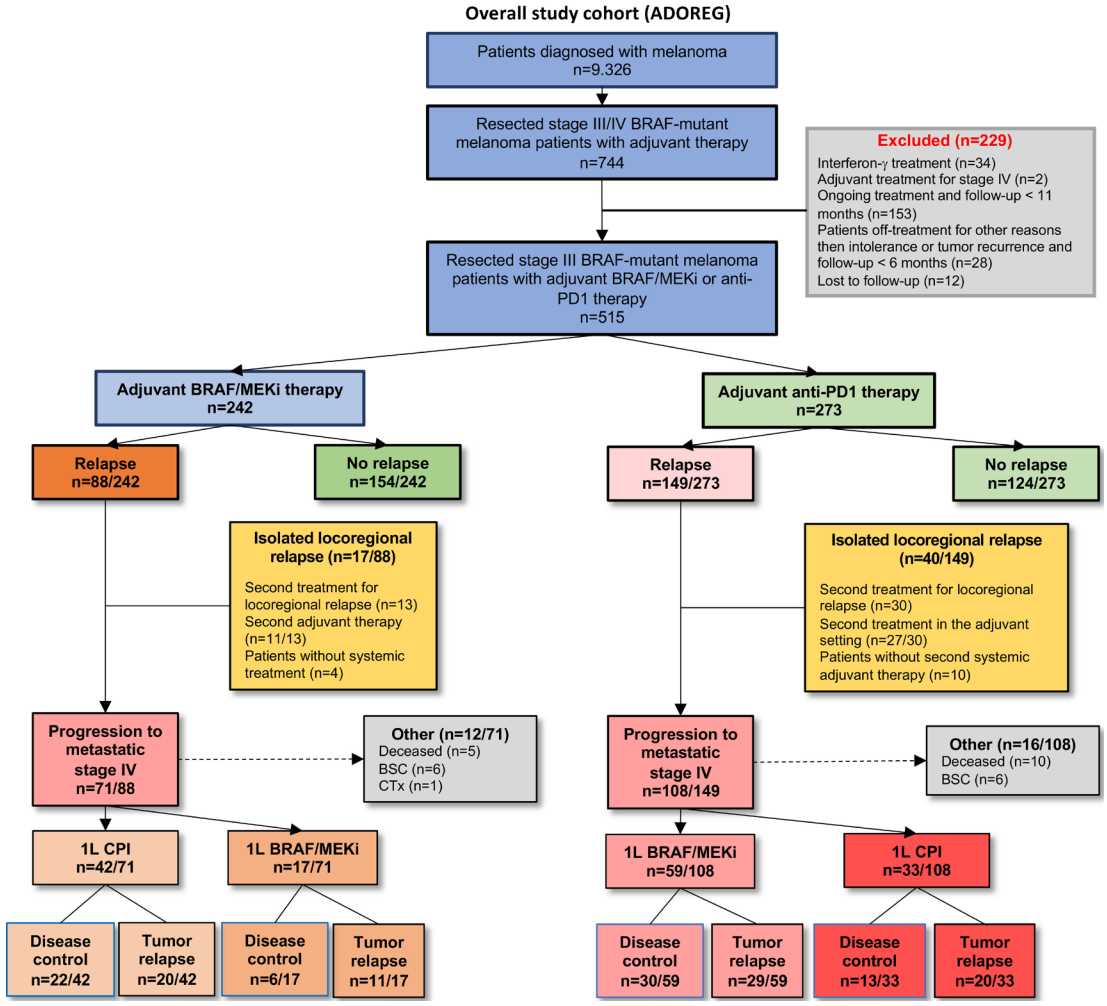

Figure 1 CONSORT diagram of patients investigated in the study. In this ADOREG study, we investigated patients who received adjuvant BRAF/MEKi therapy (n=242) or adjuvant anti-PD1 therapy (n=273). Among patients receiving adjuvant BRAF/MEKi therapy 154 did not show any tumor recurrence in the observation period, while among the 71 patients who progressed to stage IV and received subsequent systemic treatments 28 patients achieved disease control without disease progression at the time of data cut-off. By contrast, among all patients who received adjuvant anti-PD1 treatment, 124 patients did not show a tumor recurrence. Among patients who progressed to metastatic stage IV upon adjuvant anti-PD1 treatment (n=108) 43 achieved disease control without disease progression at the time of data cut-off. Patients who progressed to metastatic stage IV and who did not receive CPI or TT either received best-supportive care (BSC) including locoregional treatments such as surgery or TVEC or deceased prior to initiation of systemic treatments. CONSORT, Consolidated Standards of Reporting Trials; CPI, checkpoint inhibitor; TT, targeted therapy; TVEC, Talimogene laherparepvec.

classified according to CTCAE criteria, the time, pattern and resection status of recurrence, subsequent disease management (ie, additional adjuvant treatments following resectable recurrence or treatments for non-resectable disease) and survival outcomes were collected. Regional cutaneous, soft tissue and lymph node metastases were recorded as locoregional recurrences, all other as DM. Date of recurrence was used to stratify patients into those who relapsed during adjuvant treatment ('ON'), or after discontinuation of adjuvant treatment ('OFF'). Primary endpoints of this study were progression-free survival (PFS) and real-world tumor response following first-line therapy for metastatic stage IV upon adjuvant treatment failure. PFS was calculated from the start of first-line (1L) treatment for metastatic stage IV until disease progression or death from any cause. Real-world tumor response as assessed by the investigators was categorized into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) as described earlier.[18]

Secondary endpoints included RFS, distant-metastasis free survival (DMFS), severe treatment related adverse events (SAE), second RFS (RFS2), cumulative PFS (cPFS), and OS as defined in online supplemental table 1. RFS was calculated from the start of adjuvant therapy until first recurrence or death from any cause. New primary melanomas were not considered a recurrence. For RFS analysis, we excluded patients who received adjuvant treatment within a clinical trial setting (n=20). RFS2 was calculated from the start of second adjuvant therapy until recurrence or death from any cause. cPFS was calculated from the start of upfront adjuvant therapy until tumor

progression upon second treatment (cPFS) regardless if second treatment was for locoregional recurrence or stage IV disease. OS was calculated as the time from adjuvant treatment start to death from any cause. Patients who did not meet the endpoint were censored at date of last FU. Time-to-next treatment (TTNT) was included as an additional outcome parameter due to its role as a reliable surrogate for OS in real-world datasets.[18]

Statistical analysis

Descriptive statistics were used to analyze baseline characteristics. Testing for equality between subgroups was performed using Student's t-test and Fisher's exact test. For categorial variables, 95% CI were calculated using the Clopper-Pearson method. We employed Kaplan-Meier survival plots to illustrate median survival probabilities and to explore associations between the different treatment conditions. Survival curves were compared using a log-rank test. Median duration of FU was calculated using the reverse Kaplan-Meier method. Univariate and multivariate Cox's proportional hazards regression analyses were applied to assess the impact of baseline patient and tumor characteristics, as well as treatment modalities on survival outcomes. Multivariate analysis was calculated for significant variables by the univariate test or by a priori selection for biological relevance to evaluate their conjoint, independent effects on RFS or OS. Adjusted survival curves for RFS were calculated based on the multivariate Cox-regression model in R.[19] In all cases, two-tailed p values were calculated and considered significant for p<0.05. SPSS V.27, RStudio (V.1.3.1093), and GraphPad PRISM V.5 were used for all analyses. Swimmer plots were created using the swimplot package (RStudio V.1.3.1093).

RESULTS

Patient characteristics

Data were extracted for 515 eligible patients who received adjuvant therapy between January 2014 and July 2022. Among this cohort, we identified 237 patients who relapsed (46.2%) within the FU period. This cohort was used to analyze the primary endpoints, including PFS and best response to 1L treatments following DM. Details on baseline characteristics of this cohort are summarized in table 1.

The median patient age in the cohort with adjuvant treatment failure was 58 years and there was a slight male dominance of patients (56.1%). 89.3% of patients presented with primary cutaneous melanoma. 47.7% of patients presented with ulcerated primary cutaneous melanomas and a mean Breslow thickness of 3.6 mm. Patients who were treated after 2018 were staged according to the 2018 (Eighth Edition) AJCC Melanoma staging criteria, while patients who received adjuvant therapy before 2018 were reclassified according to AJCC 8 criteria. Patients in the investigated cohort showed predominantly stage IIIB (35.9%) and IIIC (45.1%) disease.

Thirty-three patients underwent completing lymph node dissection (13.9%) prior to adjuvant therapy initiation. Upfront adjuvant treatments included nivo (40.9%), Pb (21.9%) or DT (37.1%). Mean adjuvant treatment duration was 8.3 months. One hundred and thirty patients prematurely discontinued adjuvant therapy due to disease progression (54.9%). In particular, patients who received upfront adjuvant anti-PD1 therapy more often ceased therapy for tumor recurrence as compared with patients given upfront adjuvant DT (65.8% vs 36.4%, p<0.001). Meanwhile 61 patients (25.2%) were able to complete the regular 12-month schedule of adjuvant therapy and 34 patients discontinued for toxicity reasons (14.3%).

Among the 239 patients who relapsed within the FU period, 179 patients developed metastatic stage IV disease (74.9%). Tumor recurrence mainly occurred within or shortly after (<6 months) discontinuation of adjuvant therapy (85.3%). Of note, patients who received adjuvant DT commonly relapsed after discontinuation of adjuvant therapy (68.2%) while patients with adjuvant anti-PD1 therapy relapsed significantly more often during adjuvant treatment (63.1%).

Within the investigated cohort of patients with adjuvant treatment failure, median RFS was 8.0 months (95% CI 6.6 to 9.4). Patients who were treated with upfront adjuvant DT presented with a significantly longer RFS as compared with patients given adjuvant anti-PD1 (median RFS 11.0 vs 6.0 months, p<0.001). Similarly, median TTNT was significantly longer for patients treated with adjuvant DT (median TTNT 16.0 vs 9.0 months, p<0.001). Median DMFS was 13.0 months (95% CI 10.6 to 15.4) and did not show statistically significant differences between both adjuvant treatment groups.

Most patients who relapsed (83.1%) received at least one subsequent systemic treatment. Among the 179 patients who progressed to non-resectable stage III or stage IV disease 155 received systemic therapies (86.7%) and 71 patients received more than one subsequent treatment line for metastatic disease. At data cut-off median OS that has not been reached, while 55 patients (22.8%) deceased.

Adjuvant BRAF/MEKi therapy is associated with longer relapse-free survival for *BRAF*-mutant melanoma patients

Given the observation that patients who received upfront adjuvant TT had a longer time to initial recurrence (TTR) within our primary study cohort, we next compared the efficacy of upfront adjuvant DT and adjuvant anti-PD1 therapy within the overall patient cohort excluding patients who were treated outside of clinical trials (n=495/515). Patients' characteristics were mostly balanced in the two groups at baseline (online supplemental table 2), although patients given adjuvant DT presented with thicker tumors and more often received adjuvant therapy for longer than 12 months due to intermittent discontinuation for intolerance. At data cut-off, 141 patients had recurred in the adjuvant anti-PD1 group

Table 1 Baseline characteristics of patients who relapsed upon upfront adjuvant therapy (n=237)

Clinicopathological features	Overall cohort	Adjuvant anti-PD1 therapy	Adjuvant BRAF/MEKi	P value
Total no of patients	237	149	88	
Median age (years, 95% CI)	58.0 (56.6 to 59.0)	56.0 (55.0 to 58.4)	59 (57.2 to 60.8)	0.07
Gender				0.346
Female	104 (43.9%)	69 (46.3%)	35 (39.8%)	
Male	133 (56.1%)	80 (53.7%)	53 (60.2%)	
Primary tumor characteristics				
Mean Breslow thickness (95% CI)*	3.6 mm (3.3 to 3.9)	3.3 mm (3 to 3.6)	4 mm (3.5 to 4.5)	**0.027**
Ulceration†	94 (47.7%)	56 (45.9%)	38 (50.7%)	0.558
Tumor subtypes				*
Cutaneous melanoma	209 (89.3%)	132 (88.6%)	77 (87.5%)	
ALM	7 (3.0%)	4 (2.7%)	3 (3.4%)	
CUP	15 (6.3%)	9 (6.0%)	6 (6.8%)	
Other	6 (2.5%)	4 (2.7%)	2 (2.3%)	
Completing lymph node dissection	33 (13.9%)	20 (13.4%)	13 (14.8%)	*
Adjuvant radiotherapy	47 (19.9%)	28 (18.9%)	19 (21.6%)	0.618
BRAF-mutation subtype				0.354
BRAF V600E	173 (73.0%)	103 (69.1%)	70 (79.5%)	
BRAF V600K	29 (12.2%)	19 (12.8%)	10 (11.4%)	
BRAF V600D/R	8 (3.3%)	6 (4.0%)	2 (2.3%)	
BRAF-mutation, non-specified	27 (11.4%)	21 (14.1%)	6 (6.8%)	
Upfront adjuvant treatment				
Upfront adjuvant treatment				–
Nivolumab	97 (40.9%)	97 (65.1%)	0	
Pembrolizumab	52 (21.9%)	52 (34.9%)	0	
Dabrafenib+trametinib	88 (37.1%)	0	88	
Baseline AJCC stage				0.32
IIIA	24 (10.1%)	18 (12.1%)	6 (6.8%)	
IIIB	85 (35.9%)	55 (36.9%)	30 (34.1%)	
IIIC	107 (45.1%)	64 (43.0%)	43 (48.9%)	
IIID	18 (7.6%)	9 (6.0%)	9 (10.2%)	
III unspecified	3 (1.3%)	3 (2.0%)	0	
Mean treatment duration (95% CI)	8.3 months (7.9 to 8.7)	7.6 months (7.1 to 8.1)	9.1 months (8.5 to 9.6)	**<0.001**
Adverse events>CTCAE grade 2	32 (13.5%)	20 (13.4%)	12 (13.6%)	0.365
Treatment cessation due to toxicity	34 (14.3%)	16 (10.7%)	18 (20.5%)	0.054
Regular completion of treatment	61 (25.7%)	30 (20.1%)	31 (35.2%)	**0.014**
Tumor recurrence				**<0.001**
During adjuvant therapy	122 (51.5%)	94 (63.1%)	28 (31.8%)	
After adjuvant therapy	115 (48.5%)	55 (36.9%)	60 (68.2%)	
Median RFS in months (95% CI)	8 (6.6 to 9.4)	6 (4.0 to 8.0)	11 (8.7 to 13.3)	**<0.001**
Initial locoregional recurrence	76 (32.4%)	54 (36.2%)	22 (26.1%)	0.214
Cutaneous/soft tissue	43 (56.6%)	29 (53.7%)	14 (63.6%)	
Lymph node	32 (42.1%)	25 (46.3%)	7 (31.8%)	
Not specified	1 (1.3%)	0	1 (4.5%)	
Progression to stage IV disease	179 (75.5%)	108 (72.5%)	71 (80.7%)	0.164

Continued

Table 1 Continued

Clinicopathological features	Overall cohort	Adjuvant anti-PD1 therapy	Adjuvant BRAF/MEKi	P value
Median DMFS in months (95% CI)	13 (10.6 to 15.4)	12 (8.5 to 15.4)	15 (11.5 to 18.5)	0.346
Median TTNT in months (95% CI)	11 (9.2 to 12.8)	9 (6.3 to 11.7)	15 (11.8 to 18.1)	**<0.001**
Treatment management of locoregional tumor recurrence				
Fully resected locoregional relapse	58/76 (76.3%)	42/54 (77.8%)	16/22 (72.7%)	0.257
AJCC stage at locoregional relapse				0.887
IIIB	23 (30.3%)	17 (31.5%)	6 (27.2%)	
IIIC	45 (59.2%)	32 (59.3%)	13 (59.1%)	
IIID	8 (10.5%)	5 (9.3%)	3 (13.6%)	
Second systemic treatment	58	41	17	**<0.001**
Anti-PD1	16 (20.8%)	4 (9.7%)	12 (75.0%)	
Ipilimumab+nivolumab	2 (2.6%)	0	2 (12.5%)	
Dabrafenib+trametinib	40 (52.6%)	37 (90.2%)	3 (13.6%)	
Second tumor recurrence	28 (36.8%)	20 (37.0%)	8 (36.4%)	*
Median cPFS in months (95% CI)	41 (21.9 to 60.1)	41 (12.8 to 69.2)	NR	0.376
Treatment for metastatic stage IV disease				
Initial treatment for metastatic stage	155/179 (87%)	93/108 (86.4%)	62/71 (87.3%)	–
Ipilimumab+nivolumab	52/155 (33.5%)	23 (24.7%)	29 (46.8%)	
Anti-PD1	22/155 (14.2%)	9 (9.7%)	13 (21.0%)	
Ipilimumab	1/155 (0.6%)	1 (1.1%)	0	
BRAF±MEK inhibitors	76/155 (49.0%)	59 (63.5%)	17 (27.4%)	
Other (CTx, surgery)	4/155 (2.6%)	1 (1.1%)	3 (4.7%)	
None	24/179 (13.4%)	15/108 (13.9%)	9 (12.7%)	
Brain metastasis at 1L therapy start	52 (29.1%)	21 (19.4%)	31 (43.7%)	**<0.001**
Elevated serum LDH (>245 U/L)‡	44 (43.1%)	21 (35.0%)	23 (54.8%)	0.067
Real-world tumor response rate§	47/125 (37.6%)	35/75 (46.7%)	12/50 (24.0%)	**0.014**
Real-world tumor control rate§	87/125 (69.6%)	55/75 (73.3%)	32/50 (64.0%)	0.322
Tumor progression	88 (49.2%)	52 (48.1%)	36 (50.7%)	*
Median PFS in months (95% CI)	8.0 (6.3 to 9.7)	8.0 (6.4 to 9.6)	5.0 (2.4 to 7.6)	0.097
Follow-up				
Median FU in months (95% CI)	27 (22.3 to 31.7)	24 (17.8 to 30.2)	28 (22.1 to 33.9)	0.491
Median overall survival (95% CI)	NR	NR	NR	0.552
3-year OS rate in % (95% CI)	–	80.5 (73.9 to 87.6)	87.4 (81.3 to 94)	–
Deceased	54 (22.8%)	35 (23.5%)	19 (21.6%)	0.873

Statistically significant differences between patients receiving adjuvant anti-PD1 therapy or adjuvant BRAF/MEKi therapy are indicated in bold values (p<0.05)
*Breslow thickness was available for 205 patients (128 for adjuvant anti-PD1 and 77 for TT).
†Ulceration was available for 197 patients (122 for adjuvant anti-PD1 and 75 for TT).
‡LDH serum levels at baseline were available for 101 patients (61 for adjuvant anti-PD1 and 42 for TT).
§Tumor responses were available for 125 patients (75 for adjuvant anti-PD1 and 50 for TT).
AJCC, American Joint Committee on Cancer; ALM, acral-lentiginous melanoma; cPFS, cumulative progression-free survival; CTx, chemotherapy; CUP, cancer of unknown primary; DMFS, distant-metastasis free survival; LDH, lactate-dehydrogenase; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; TT, targeted therapy; TTNT, time to next treatment.

(54.4%) and 84 patients (35.6%, p<0.001) in the adjuvant DT group. Among patients with recurrence, initial relapse was more common at a distant site than at a locoregional site for both groups (online supplemental table 2). Overall, patients with adjuvant anti-PD1 therapy were more likely to develop metastatic stage IV disease (p=0.012). However, patients receiving adjuvant TT were more likely to develop melanoma brain metastases (MBM) (7.8% vs 12.3%, p<0.002) (online supplemental table 3). In general, the most frequent sites of DMs

were lung (42.4%), distant lymph nodes (35.9%), brain (28.8%) and liver (22.4%).

Among all *BRAF*-mutant, stage III melanoma patients who were treated outside of clinical trials, we observed a significantly longer median RFS for those given adjuvant DT as compared with patients with anti-PD1 therapy (31.0 months, 95% CI 26.0 to 36.0 vs 17.0 months, 95% CI 11.9 to 22.1, p<0.001) (HR, for relapse or death adjusted for age, gender and AJCC stage at baseline: 0.51; 95% CI 0.39 to 0.68, p<0.001, see figure 2). Further subgroup analyses confirmed a significant RFS benefit for adjuvant DT among most investigated subgroups (see online supplemental figure 1).

While the majority of patients with adjuvant CPI therapy recurred during adjuvant therapy (ON) (63.1% vs 32.1%), patients in the TT group did mainly relapse after cessation of adjuvant therapy (OFF) (67.9 vs 36.9%, p<0.001) and particularly within 6 months after cessation of adjuvant therapy (41.7% vs 29.1%, p<0.001). In line, we observed a longer DMFS for the TT group (HR adjusted for age, gender and AJCC stage at baseline: 0.66; 95% CI 0.48 to 0.90; p=0.008). However, OS did not significantly differ between both adjuvant cohorts (figure 3). Among the 220 patients who completed the 12-month schedule of adjuvant therapy without tumor recurrence, we detected no survival benefit for adjuvant DT (median RFS: 42.0 vs 35.0 months, p=0.705 and median DMFS: NR). Similarly, among the 105 patients who discontinued upfront adjuvant treatment for intolerance we could not detect a survival benefit for adjuvant DT (median RFS: 39.0 months vs NR, p=0.74).

Clinical factors associated with tumor recurrence following adjuvant therapy

To identify factors that are associated with recurrence among patients who were treated for resected melanoma outside of clinical trials, we conducted univariate Cox-regression analyses. Univariate analysis revealed that patients with ulcerated and primary tumors thicker than 4.0 mm, patients with a more advanced AJCC stage at baseline, and patients who received adjuvant anti-PD1 therapy were at higher risk of recurrence (see online supplemental table 4). These results were confirmed in a multivariate Cox regression model that identified Breslow thickness, AJCC stage v2018 and adjuvant anti-PD1 to be significantly associated with RFS (see online supplemental figure 2).

Treatment management for patients with locoregional tumor recurrence: Second adjuvant BRAF/MEK-directed TT results in longer relapse-free survival following resectable tumor recurrence compared with adjuvant checkpoint blockade

Among 239 patients who recurred within the FU period 76 patients presented with a locoregional recurrence that manifested as in-transit metastases (56.6%) or lymph-node metastases (42.1%) (online supplemental table 5). Among these, 19 patients first recurred locoregionally before progressing to stage IV disease. At the time of recurrence, the majority of patients showed at least AJCC stage IIIC disease (59.2%). Locoregional recurrence was resected in 58 patients and thereof 51 received subsequent second-line adjuvant treatments with either single-agent anti-PD1 (n=12), ipi+nivo (n=2) or DT (n=37). In general, most patients switched treatments after upfront adjuvant treatment failure (online supplemental table 5B). Five patients did not undergo resection of locoregional recurrence but received anti-PD1 treatment (n=2) or DT (n=3) and two patients underwent incomplete resection of recurrence.

Median duration of second treatment was 7 months with 21 patients still receiving treatment at the time of data cut-off. Patients who received CPI for locoregional recurrence most frequently ceased therapy due to disease progression (33.3%). By contrast, 35.0% of patients given DT for locoregional recurrence were able to complete the 12-month schedule of treatment. Similar to upfront adjuvant treatment, SAEs were more often seen for patients treated with DT (12.8% vs 5.5%). Following the introduction of the second systemic treatment, 21 patients relapsed (36.2%) with 15 patients recurring at distant sites (71.4%). Patients who received BRAF/MEKi as second systemic treatment showed a significantly longer RFS2 (24.0 months 95% CI 8.6 to 39.4 vs 6.0 months, 95% CI 3.2 to 8.7, p=0.001) as compared with patients given CPI (adjusted HR for gender, age, AJCC stage at recurrence and resection status: 0.25, 95% CI 0.09 to 0.71, p=0.009) (see figure 4A and online supplemental figure 3). Overall, patients who received upfront adjuvant DT had a prolonged cPFS compared with patients treated with upfront CPI, although below statistical significance (median cPFS: 49.0 vs 28.0 months, p=0.111) (figure 4B).

Given previous reports indicating that complete resection of recurrence followed by a second adjuvant treatment might result in favorable survival outcomes for patients with locoregional recurrence,[16] we evaluated whether patients with resected recurrence may benefit from a second adjuvant treatment with DT as compared with adjuvant CPI therapy. Overall, 70 patients underwent complete resection of the first recurrence and subsequently received a second adjuvant treatment. Among these 70 patients, 51 underwent complete resection for locoregional recurrence and 19 had a resection of DM (online supplemental table 5B,C). Patients with locoregional recurrence who received adjuvant DT for a second time presented with a longer RFS (median RFS2: 41.0 months, 95% CI 21.0 to 61.0 vs 6.0 months, 95% CI 1.4 to 10.6, p=0.009) as compared with adjuvant CPI (see figure 4C). Patients who received adjuvant DT following resected stage IV disease showed a longer RFS as compared with patients given adjuvant CPI, as well, albeit this association was below statistical significance (median RFS2: 11.0 vs 9.0 months, p=0.428). Further analysis showed that in this subgroup of resected stage IV melanoma patients adjuvant ipi+nivo reduced the risk of another recurrence as compared with adjuvant anti-PD1 therapy (tumor recurrence: 25% vs 80%) resulting

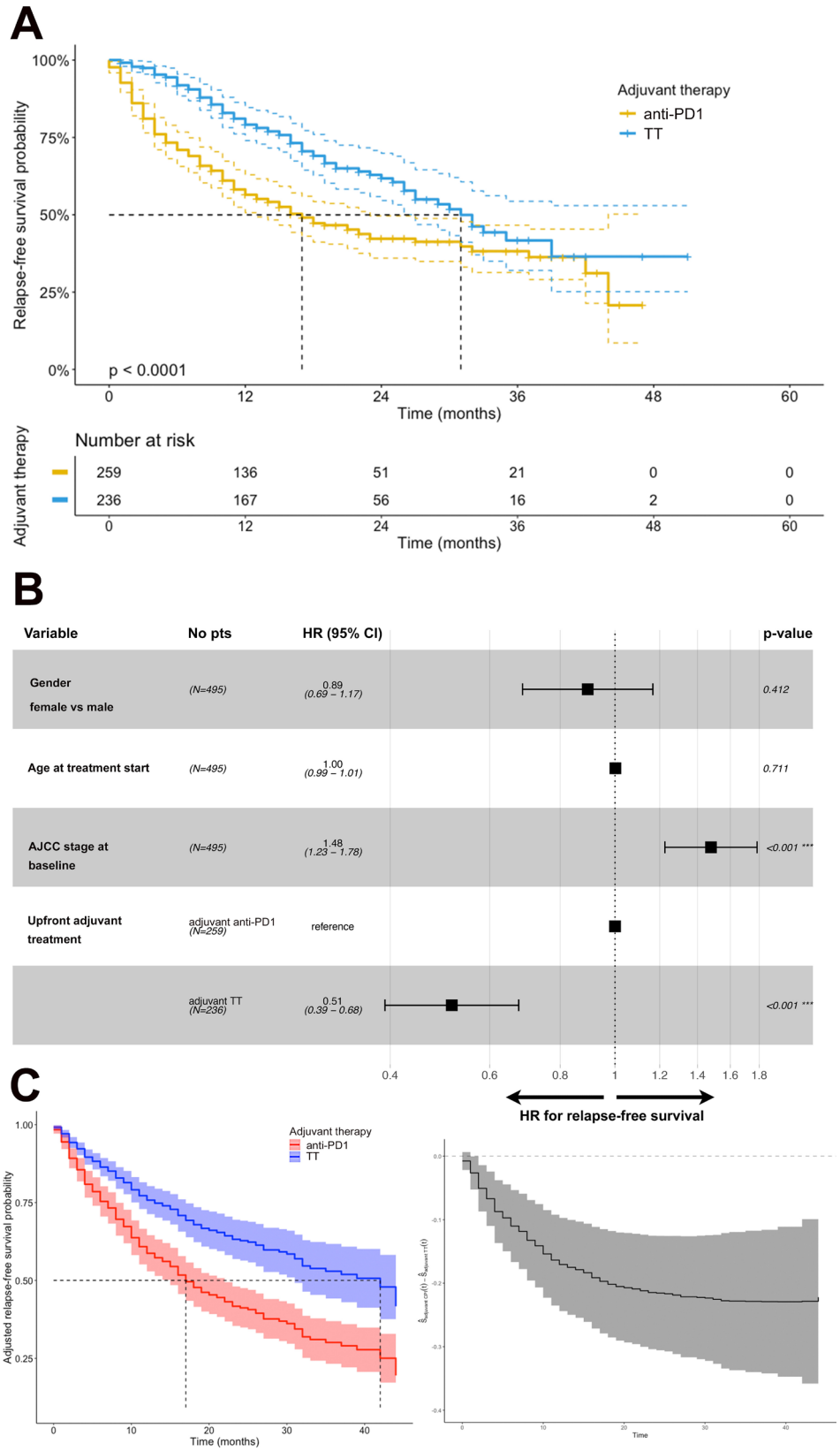

Figure 2 Survival outcomes for patients with resected stage III melanoma who were treated outside of clinical trials stratified by primary adjuvant therapy. (A) Median recurrence-free survival was significantly longer for patients given adjuvant TT (31.0 months, 95% CI 26.0 to 36.0 vs 17.0 months, 95% CI 11.9 to 22.1, p<0.001) as compared with adjuvant anti-PD1 therapy. (B) Forest plot illustrating results of multivariate Cox regression for recurrence-free survival and corresponding HR. (C) Cox-adjusted Kaplan-Meier curves for recurrence-free survival (bottom, left) and time point differences in adjusted RFS between patients treated with upfront adjuvant anti-PD1 as compared with upfront adjuvant TT. AJCC, American Joint Committee on Cancer; RFS, recurrence-free survival; TT, targeted therapy. Significance levels: *p<0.05, **p<0.01, ***p<0.001.

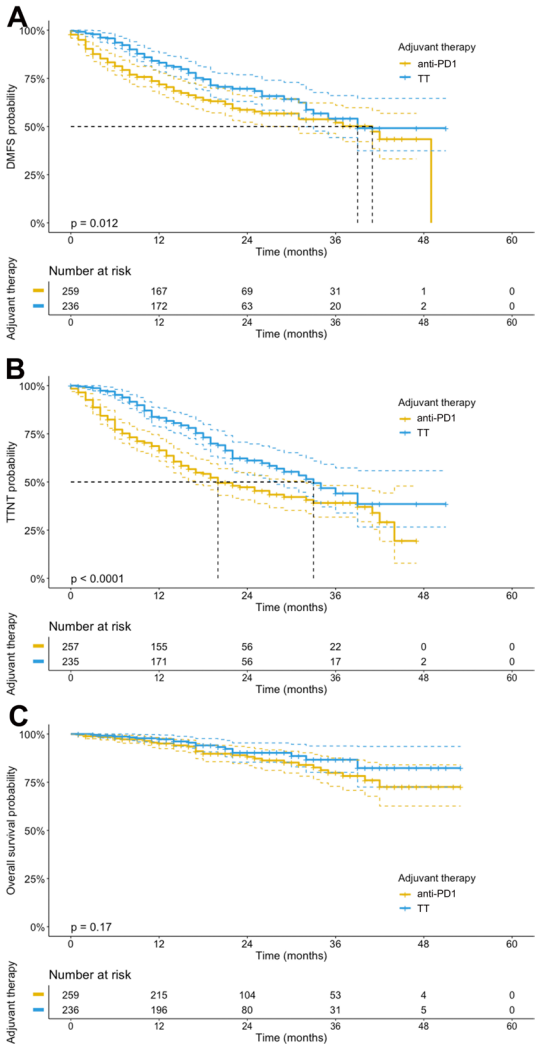

Figure 3 Kaplan-Meier survival curves depicting distant metastasis free survival (A), time-to-next treatment (B) and overall survival (C) stratified by adjuvant therapy. Result show that median distant-metastasis-free survival (39.0 months, 95% CI 31.0 to NR vs 41.0 months, 95% CI 29.2 to 52.8, p=0.012) and TTNT (33.0, 95% CI 26.6 to 39.4 vs 20.0 months, 95% CI 14.3 to 25.7, p<0.001) were significantly longer for adjuvant TT. By contrast, median overall survival was not reached in both groups. TTNT, time-to-next treatment; TT, targeted therapy.

in a prolonged RFS (median RFS2: NR vs anti-PD1: 3.0 months, 95% CI 0.8 to 5.1 vs adjuvant DT: 11.0 months, 95% CI 5.2 to 16.8, p=0.366) (see figure 4D).

Survival outcomes following DMs during adjuvant therapy

The majority of patients (n=179) who relapsed during adjuvant therapy developed DM in the course of the disease that required the introduction of first-line treatments for stage IV disease. Among patients with DM median time to first DM was 9.0 months. Patients who received upfront adjuvant DT had a longer median time to DM (11.0 vs 7.0 months, p=0.017). Following DM first-line treatments were administered in 155 patients. Thereof, 151 patients received either first-line CPI or first-line BRAF/MEKi (details on patients with DM stratified by first-line treatments are summarized in (online supplemental table 6).

Patients who received upfront adjuvant CPI and developed DM most commonly switched to 1L TT for metastatic stage IV (encorafenib+binimetinib, n=25; DT, n=34), whereas 34 patients received 1L CPI. Among patients with CPI re-administration, 1L ipi+nivo (n=23) was more common, while single-agent CPI was almost exclusively administered in patients who recurred ON adjuvant CPI therapy (n=9/10). Besides, 1 patient received intralesional talimogene laherparepvec and 15 patients did not receive systemic treatments by the time of data cut-off.

Patients with DM after adjuvant TT mainly switched to 1L CPI therapy (ipi+nivo, n=29; nivo, n=7; Pb, n=6), whereas 1L BRAF/MEKi was administered in a minority of 17 patients. Nine patients were not given any subsequent treatments by the time of data cut-off, while three patients received chemotherapy or underwent stage IV surgery only.

We examined treatment outcomes for all patients who progressed to metastatic stage IV and stratified patients by the sequence in which systemic treatments were given in the adjuvant and metastatic setting: Here, we observed that patients with a re-challenge of either CPI or TT had a shorter PFS as compared with patients who switched treatments (median PFS: 9.0, 95% CI 5.2 to 12.8 vs 5.0 months, 95% CI 1.3 to 8.7, p=0.004) (online supplemental figure 4). In particular, we observed the weakest response and shortest PFS for patients given a re-challenge of BRAF/MEKi (online supplemental tables 7,10 and 11). In line, median OS was shorter in this subset of patients (median OS: NR vs 21.0 months, p<0.001) (online supplemental tables 8,9). Subsequently, we stratified our analysis according to the individual treatment sequences. Here, we found that a re-challenge with CPI was associated with favorable tumor control and prolonged PFS as compared with TT re-challenge (online supplemental figures 4,6). By contrast, upfront adjuvant TT followed by 1L CPI or vice versa resulted in similar survival outcomes (online supplemental figure 5). Given the observation that neither treatment switching strategy significantly favored survival outcomes, we next sought to determine the treatment-specific outcomes following distant recurrence for each individual treatment sequence stratified by initial adjuvant therapy (details on the individual treatment sequences are provided in (online supplemental figure 7).

Patterns of distant tumor recurrence and treatment outcomes for patients with upfront adjuvant CPI therapy

Among 108 patients who developed DM the TTR following upfront adjuvant CPI was 5.0 months and median time to DM was 7.0 months. Most of those patients recurred *ON* adjuvant CPI (62.7%) at a median of 4.0 months (95% CI 3.0 to 5.0 months), whereas patients who recurred *OFF* adjuvant CPI recurred at a median of 13.0 months (95% CI 9.9 to 16.1, p<0.001). Of note, only a minority of

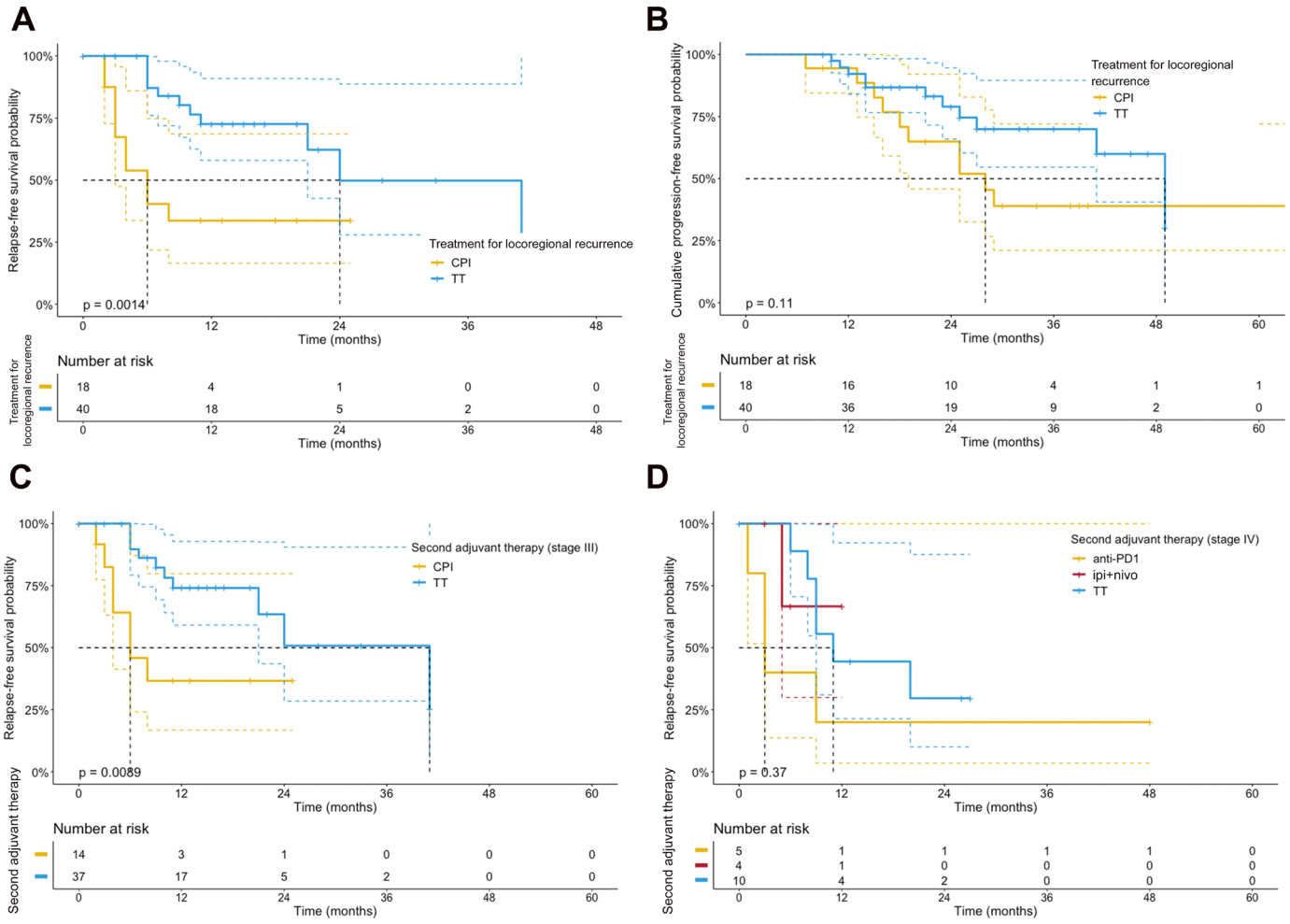

Figure 4 Survival outcomes after re-introduction of systemic treatments for locoregional tumor recurrence. Following locoregional tumor recurrence systemic treatment with TT prolonged RFS as compared with CPI therapy (median RFS2: 24.0 months, 95% CI 8.6 to 39.4 vs 6.0 months, 95% CI 3.2 to 8.7, p=0.001) (A). As most patients switched treatment modalities upon locoregional recurrence there was no statistically significant difference in cumulative progression-free survival between patients who received CPI or TT as second treatment (median cPFS: 49.0 vs 28.0 months, p=0.11) (B). Patients with fully resected locoregional recurrence, who received a second adjuvant treatment with TT showed a significantly longer RFS as compared with patients who received a second adjuvant CPI therapy (median RFS2: 41.0 vs 6.0 months, p=0.009) (C). By contrast, patients who received a second adjuvant treatment for resected stage IV disease presented with a shorter RFS compared with patients with adjuvant treatment for resected stage III. Also, for these patients no statistically significant RFS has been observed between either adjuvant anti-PD1, BRAF/MEKi or ipi+nivo (median RFS3: 3 vs 11 months vs NR, p=0.37) (D). cPFS, cumulative progression-free survival; CPI, checkpoint inhibitor; RFS, recurrence-free survival; TT, targeted therapy.

patients who completed the 12-month schedule of adjuvant CPI therapy developed DM during FU (n=16/103, 15.5%).

Most patients presented with oligometastatic disease (≤2 sites of metastasis) at the time of distant recurrence. Common sites of DM were lung (42.6%), lymph nodes (38.0%), liver (24.1%), brain (19.4%) and bones (21.3%). Of note, most patients with MBM subsequently received 1L ipi+nivo, whereas patients who received 1L BRAF/MEKi more often showed multifocal disease before treatment start. In the following, we evaluated responses to 1L treatments and assessed survival outcomes for this subgroup. The median FU of these patients was 35 months (95% CI 27.9 to 42.1) calculated from the start of adjuvant therapy and 16 months from the start of 1L therapy (95% CI 10.3 to 21.7).

The real-world tumor response rate (rwTRR) for patients who switched from adjuvant CPI to BRAF/MEKi was 58.7% and real-world tumor control rate (rwTCR) was 84.8% (online supplemental table 7). Response rates and median PFS (8 vs 9 months, p=0.73) were numerically higher for patients who recurred OFF adjuvant CPI, compared with those who relapsed ON therapy, although below statistical significance. Patients with adjuvant anti-PD1 failure who received 1L treatment with ipi+nivo showed a rwTRR of 35.3% (n=6/17), and three of the responders showed ongoing tumor remissions. Among patients receiving 1L ipi+nivo rwTCR was 58.8%. Again, responses were more frequently found for patients who recurred OFF adjuvant CPI treatment. By contrast, rwTRR for a re-challenge with single agent CPI was low with only 25.0% of patients responding, regardless of the time of

Table 2 Response to first-line treatments following distant metastasis after failure of adjuvant anti-PD1 treatment

	Single-agent CPI	Ipi+nivo	BRAF/MEKi
N	10	23	59
Recurred ON anti-PD1	9	12	40
Recurred OFF anti-PD1	1	11	19
Median follow-up	34 months (17.0–51.0)	24 months (9.4–38.6)	37 months (34.3–39.7)
rwTRR, N (%)			
Total*	2/8 (25.0)	6/17 (35.3)	27/46 (58.7)
Recurred ON anti-PD1	2/7 (28.6)	4/12 (33.3)	17/30 (56.7)
Recurred OFF anti-PD1	0/1	2/5 (40)	10/16 (62.5)
Tumor progression, N (%)	6/10 (60)	14/23 (60.9)	29/59 (49.2)
Median PFS (95% CI)	3 months (0 to 11.1)	6 months (1.6 to 10.4)	11 months (5.5 to 16.5)
Median OS† (95% CI)	27 months (14.1 to 39.9)	NR	36.0 months (NA)

*Response rates to 1L systemic therapy following DM were deemed assessable if patients did not receive any prior systemic treatments for metastatic stage, had measurable disease for assessment and underwent radiological and clinical response assessment. Response assessments for patients with DM following adjuvant anti-PD1 failure were available for 69 patients (eight for single-agent CPI; 17 for ipi+nivo and 46 for BRAF/MEKi therapy).
†OS was calculated from the start of 1L therapy.
CPI, checkpoint inhibitor; DM, distant metastasis; NA, not available; NR, not reported; OS, overall survival; PFS, progression-free survival; rwTRR, real-world tumor response rate.

DM. Importantly, the two patients who responded to a re-challenge with single-agent CPI relapsed within the first month of adjuvant CPI therapy and thus it is likely that response to single-agent CPI at metastatic stage might have already been mediated by adjuvant CPI therapy. Furthermore, among the 10 patients who received a re-challenge with single-agent CPI only 8 patients had available response assessments and a single patient was given single-agent CPI following DM OFF adjuvant CPI, allowing for little comparison of single-agent CPI efficacy between patients with DM ON versus OFF adjuvant therapy (table 2).

Patterns of distant tumor recurrence and treatment outcomes for patients with upfront adjuvant BRAF/MEK-inhibitor therapy

Among 71 patients who recurred at distant sites following adjuvant TT median TTR and median time to first distant recurrence were 11.0 months. Most patients with DM recurred OFF adjuvant TT (66.2%) at a median of 15.0 months (95% CI 12.1 to 17.9 months), whereas patients who recurred ON adjuvant TT had a median RFS of 8.0 months (95% CI 6.1 to 9.9, p<0.001). Only a minority of patients who completed the 12-month schedule of adjuvant DT (n=22/117, 18.8%) developed DM thereafter. Also, we observed that patients who completed adjuvant TT before DM had a significantly longer RFS (19.0 months, 95% CI 16.7 to 21.3 vs 9.0 months, 95% CI 7.7 to 10.3; p<0.001) as compared with patients who discontinued adjuvant DT prematurely.

Most patients with DM presented with oligometastatic disease (63.4%). Common sites of DM for patients who recurred upon adjuvant TT were lungs (43.7%), lymph nodes (33.8%), brain (43.7%) and bones (18.3%). Patients who developed DM following upfront adjuvant TT showed largely comparable characteristics before 1L treatment initiation, although patients given 1L ipi+nivo more often presented with MBM. Median FU was 25.0 months (95% CI 20.6 to 29.4) calculated from the start of upfront adjuvant therapy and 9.0 months (95% CI 4.8 to 13.2) following initiation of 1L treatments.

In contrast to the efficacy results reported for patients with failure of adjuvant CPI, we observed that patients who received upfront adjuvant TT achieved favorable responses only after switching from adjuvant TT to 1L CPI, whereas few patients responded to a re-challenge with BRAF/MEKi (see table 3). In particular, we identified only one patient who responded to BRAF/MEKi re-challenge (9.1%). Also, PFS and OS were short, regardless of whether DM occurred ON or OFF adjuvant therapy. By contrast, patients who switched from adjuvant TT to 1L CPI therapy and 1L ipi+nivo in particular, showed response rates of 42.9% with durable responses (>12 months) found in 80% of responding patients. In line, median OS following initiation of 1L therapy was significantly longer for patients switching from adjuvant TT to 1L ipi+nivo (9 months vs NR months, p=0.002). Of note, patients who developed DM OFF adjuvant TT were unlikely to respond to subsequent 1L single-agent CPI (0%) but showed clinical activity for 1L ipi+nivo (46.2%).

DISCUSSION

The approval of adjuvant TT and anti-PD1 antibodies resulted in a substantial prolongation of RFS for patients with resected *BRAF*-mutant melanoma. Given the lack of direct comparisons and compelling evidence to support the use of either anti-PD1 or TT in the adjuvant setting,

Table 3 Response to first-line treatments following distant metastasis after failure of adjuvant BRAF/MEK-directed targeted therapy

	Single-agent CPI	Ipi+nivo	BRAF/MEKi
N	13	29	17
Recurred ON TT	3 (23.0%)	11 (37.9%)	3 (17.6%)
Recurred OFF TT	10 (69.9%)	18 (62.1%)	14 (82.4%)
Median follow-up	40 months (25.1–54.9)	24 months (14.6–33.4)	24 months (15.7–24.3)
rwTRR, N (%)†			
Total	1/13 (7.7%)	9/21 (42.9%)	1/11 (9.1%)
Recurred ON TT	1/3 (33.3%)	3/8 (37.5%)	0/3
Recurred OFF TT	0/10	6/13 (46.2%)	1/8 (12.5%)
Tumor progression, N (%)	8/13 (61.2%)	12/21 (57.1%)	11/17 (64.7%)
Median PFS (95% CI)	5 months (0 to 12.9)	NR (NA)	3 months (0 to 6.2)
Median OS* (95% CI)	26 months (NA)	NR	9 months (4.1 to 14.0)

Response rates to 1L systemic therapy following DM were deemed assessable if patients did not receive any prior systemic treatments for metastatic stage, had measurable disease for assessment and underwent radiological and clinical response assessment.
*Overall survival was calculated from the start of 1L therapy.
†Response assessments for 1L therapy upon adjuvant TT failure were available for 45 patients (13 for single-agent CPI; 21 for ipi+nivo and 11 for BRAF/MEKi therapy).
CPI, checkpoint inhibitor; DM, distant metastasis; NA, not available; NR, not reported; OS, overall survival; PFS, progression-free survival; rwTRR, real-world tumor response rate; TT, targeted therapy.

it is currently unclear which regimen is most effective in preventing recurrence. Therefore, the decision between TT and CPI is often made based on patient characteristics and the preference of the treating physician. Many clinicians favor adjuvant anti-PD1 due to more durable responses observed in the metastatic setting that were recently confirmed in the DREAMSeq trial that evaluated the upfront use of ipi+nivo as compared with TT.[20] However, it is noteworthy that treatment regimens in the adjuvant setting differ in their biological effects and clinical administration from those observed in the metastatic setting. In particular, while TT is administered continuously or until disease progression in the metastatic setting, thereby imposing a high risk of acquired MAPKi-resistance or even cross-resistance to CPI therapy, the shorter duration of adjuvant TT might allow for favorable immunomodulation within the tumor microenvironment and tumor control without the substantial long-term risk of acquired resistance.[21 22] On the other hand, locoregional lymph node metastasis imposes an immune tolerance state that may mitigate the efficacy of adjuvant CPI.[23] In line, a recent subgroup analysis by Lodde *et al* and a propensity matched analysis by Wouters *et al* reported that adjuvant DT showed superior RFS outcomes in a real-world cohort of resected melanoma patients when compared with adjuvant anti-PD1 therapy.[24 25]

Our analysis confirms this important observation in a cohort of *BRAF*-mutant, resected stage III melanoma patients: Specifically, we were able to show that adjuvant TT significantly prolonged both RFS (median RFS: 31 vs 17 months, p<0.001) and DMFS. While this favorable outcome was observed across all investigated subgroups and after adjusting for clinical parameters such as age, gender and AJCC stage further FU studies will be necessary to dissect the long-term effects of adjuvant therapy particularly for OS. Our results are also in line with prospective trials, such as the Checkmate-238 and COMBI-AD which demonstrated a 1-year RFS-rate of 70% vs 88%.[9 12]

In addition to preventing recurrence, other relevant factors when deciding between adjuvant anti-PD1 or TT are response and survival following initiation of subsequent treatments. Despite the significant prolongation of RFS for patients treated with adjuvant TT, we did not detect a significant OS benefit of adjuvant TT, which can partly be attributed to the yet limited FU time. However, we reasoned that a poor response to subsequent treatment lines might additionally contribute to the lack of survival benefit. Therefore, as the central part of our analysis, we further evaluated the characteristics of tumor response and survival on adjuvant treatment failure.

Here, our results show that patients who developed locoregional recurrence benefit from a second adjuvant treatment with DT as compared with adjuvant CPI following complete resection of locoregional recurrence. These results corroborate findings from a previous multicenter study for patients who were treated with adjuvant BRAF/MEKi and showed favorable survival outcomes following complete resection of locoregional recurrence and subsequent adjuvant TT.[16] Our data also stress the previously formulated ESMO consensus recommendations that switching treatment agents for patients with resected relapse should be preferred over continuing treatment with the same agent after recovery from surgery.[26]

In patients with DM, it has previously been shown that systemic treatments can result in meaningful

tumor control, but response rates varied by drug class and whether patients recurred ON or OFF adjuvant therapy.[15 16] In particular, Owen *et al* observed a weak response rate for patients who relapsed ON adjuvant anti-PD1 therapy, whereas 40% of patients responded to a re-challenge of CPI if recurrence occurred after anti-PD1 cessation.[15] By contrast, response to subsequent TT was high with 79% of patients responding to TT if patients recurred ON anti-PD1 therapy and 88% responded to TT if recurrence occurred OFF anti-PD1 therapy. While we also observed high response rates to 1L BRAF/MEKi after failure of adjuvant anti-PD1 therapy, we detected weak responses to a re-challenge with single-agent CPI in the metastatic setting. This indicates that switching from adjuvant CPI to subsequent 1L BRAF/MEKi therapy is a valuable treatment option in case of DM and highlights the clinical observation that progression ON adjuvant treatment results in a low likelihood of significant clinical benefit if re-exposed to the same agent.[27] Additionally, we observed that adjuvant CPI-failure might not necessarily confer resistance to first-line treatment with ipi+nivo,[28] as ipi+nivo yielded response rates of 30%–40% depending on the time of DM. Therefore, a change in treatment agent either to 1L ipi+nivo or TT may be preferred in patients who relapse ON or OFF adjuvant CPI.

For patients who recurred during adjuvant TT on the other hand, a more recent report by Bhave *et al* described that these patients remained sensitive to subsequent CPI therapy, with response rates of approximately 60%.[16] Results from our multicenter study confirm that patients who develop DM upon adjuvant TT profit from switching to CPI in the metastatic setting, although we detected stronger and more durable responses for patients who received 1L ipi+nivo. As opposed to the low response rates seen for second-line CPI after previous failure of 1L BRAF/MEKi therapy for stage IV disease, our data demonstrate substantially better response and survival outcomes of 1L CPI following DM upon adjuvant TT for stage III melanoma. This indicates that the biology and immunogenicity of melanoma who recurs in the adjuvant setting may be different as compared with disease progression in metastatic stage IV.[22 29 30] A potential explanation might be that patients who are treated with TT in the metastatic setting are continuously treated until PD and might thus acquire cross-resistance to CPI. By contrast, patients treated with adjuvant TT infrequently relapse during treatment, with most recurrences occurring OFF adjuvant TT. Finally, our results demonstrate that response rates to TT re-challenge after previous failure of adjuvant TT were low, which is in line with a previous reports on the efficacy of TT re-challenge in the metastatic setting[31 32] and findings of Bhave *et al* in the adjuvant setting.[16] Importantly, the efficacy of TT re-challenge in our cohort was significantly lower as seen in a first-line setting,[3] which strongly suggests that patients who recur at distant sites any time during adjuvant TT benefit from switching to 1L ipi+nivo. However, it remains to be determined whether acquired resistance to MAPKi can be reversible after longer treatment interruptions or in case of distant tumor relapse >6 months after adjuvant treatment cessation as previously suggested.[27]

When interpreting the results of our analysis, limitations to be considered are the retrospective nature and the relatively short FU period. Given that survival curves converge in this investigation at approximately 36 months further FU data will particularly be necessary to evaluate OS data and will allow for more precise conclusions on RFS for patients who did not recur for at least 24 months. Also, the number of patients who were treated with a second adjuvant therapy following resected locoregional or distant recurrence was limited and requires further investigation. Due to the non-randomized nature of our study and the small number of patients with stage IIIA and IIID disease interpretation of subgroup analysis requires caution. Measurement of response to subsequent therapy was performed by the treating clinician, rather than centralized review and FU imaging was done according to the standards of the different participating centers, which might result in variations in timing of tumor assessment and response evaluation. Also, the small number of patients who were re-treated with single-agent CPI after DM OFF adjuvant therapy limits the significance of our results regarding treatment efficacy after previous anti-PD1 failure and further studies will be necessary to evaluate the efficacy of 1L ipi+nivo versus single-agent CPI in this setting.

Overall, this multicenter study provides important insights into the efficacy of upfront adjuvant therapy with TT or CPI and subsequent treatment options following locoregional and distant recurrence in a large real-world cohort of *BRAF*-mutant melanoma patients: first, we found that adjuvant TT reduces the risk of locoregional and distant recurrence after a FU of 21 months. Second, our results demonstrate a favorable response for patients who switched to 1L ipi+nivo following distant recurrence upon adjuvant TT, whereas patients who recurred at distant sites during adjuvant anti-PD1 achieved similar response and survival rates for switching to 1L BRAF/MEKi or ipi+nivo. In contrast to previous reports, we found that response rates and survival outcomes to 1L treatments following adjuvant treatment failure were weaker compared with treatment naïve patient cohorts, indicating that DM upon adjuvant therapy might impact subsequent treatment responses. Hence, there remains a strong need to identify the optimal treatment sequence particularly for patients who are at high risk of DM. Here, the additional use of biomarkers may help to guide treatment decisions in the future; for example, low tumor mutational burden (TMB) is associated with favorable RFS in patients treated with adjuvant TT.[12 13] By contrast, high TMB and concomitant IFNγ expression were associated with favorable survival outcomes to adjuvant anti-PD1 therapy.[8 10]

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