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Brain metastasis and survival outcomes after first-line therapy in metastatic melanoma: a multicenter DeCOG study on 1704 patients from the prospective skin cancer registry ADOREG

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ABSTRACT

Background Despite the availability of effective systemic therapies, a significant number of advanced melanoma patients develops brain metastases. This study investigated differences in incidence and time to diagnosis of brain metastasis and survival outcomes dependent on the type of first-line therapy.

Methods Patients with metastatic, non-resectable melanoma (AJCCv8 stage IIIC–V) without brain metastasis at start of first-line therapy (1L-therapy) were identified from the prospective multicenter real-world skin cancer registry ADOREG. Study endpoints were incidence of brain metastasis, brain metastasis-free survival (BMFS), progression-free survival (PFS), and overall survival (OS).

Results Of 1704 patients, 916 were BRAF wild-type (BRAF*wt*) and 788 were BRAF V600 mutant (BRAF*mut*). Median follow-up time after start of 1L-therapy was 40.4 months. BRAF*wt* patients received 1L-therapy with immune checkpoint inhibitors (ICI) against CTLA-4+PD-1 (n=281) or PD-1 (n=544). In BRAF*mut* patients, 1L-therapy was ICI in 415 patients (CTLA-4+PD-1, n=108; PD-1, n=264), and BRAF+MEK targeted therapy (TT) in 373 patients. After 24 months, 1L-therapy with BRAF+MEK resulted in a higher incidence of brain metastasis compared with PD-1±CTLA-4 (BRAF+MEK, 30.3%; CTLA-4+PD-1, 22.2%; PD-1, 14.0%). In multivariate analysis, BRAF*mut* patients developed brain metastases earlier on 1L-therapy with BRAF+MEK than with PD-1±CTLA-4 (CTLA-4+PD-1: HR 0.560, 95% CI 0.332 to 0.945, p=0.030; PD-1: HR 0.575, 95% CI 0.372 to 0.888, p=0.013). Type of 1L-therapy, tumor stage, and age were independent prognostic factors for BMFS in BRAF*mut* patients. In BRAF*wt* patients, tumor stage was independently associated with longer BMFS; ECOG Performance status (ECOG-PS), lactate dehydrogenase (LDH), and tumor stage with OS. CTLA-4+PD-1 did not

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although systemic therapy of metastatic melanoma has advanced dramatically, it is unclear at present, which treatment strategy is preventing the development of brain metastases best and if that treatment is also associated with the best overall survival.

WHAT THIS STUDY ADDS

⇒ To address this, we assessed a prospectively collected real-world multicenter patient cohort with 1704 melanoma patients for the time until occurrence of brain metastases, progression-free and overall survival.

⇒ In our cohort, first-line therapy with BRAF+MEK targeted therapy led to faster development of brain metastases than PD-1±CTLA-4 immune checkpoint inhibition (ICI) in BRAF V600 mutant patients.

⇒ In BRAF V600 mutant patients, CTLA-4+PD-1 ICI resulted in better overall survival compared with PD-1 ICI or BRAF+MEK inhibitor therapy, while in BRAF wild-type patients there was no difference in the occurrence of brain metastases and overall survival between treatment with PD-1 monotherapy and CTLA-4+PD-1 combined ICI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underline that survival outcomes have to be assessed separately for BRAF*mut* and BRAF*wt* patients, and that ICI, particularly CTLA-4+PD-1, should be preferably chosen as first-line therapy in BRAF*mut* melanoma patients without MBM.

result in better BMFS, PFS, or OS than PD-1 in BRAF*wt* patients. For BRAF*mut* patients, multivariate Cox regression revealed ECOG-PS, type of 1L-therapy, tumor stage, and LDH as independent prognostic factors for PFS and OS. 1L-therapy with CTLA-4+PD-1 led to longer OS than PD-1 (HR 1.97, 95% CI 1.122 to 3.455, p=0.018) or BRAF+MEK (HR 2.41, 95% CI 1.432 to 4.054, p=0.001), without PD-1 being superior to BRAF+MEK.

Conclusions In BRAF*mut* patients 1L-therapy with PD-1±CTLA-4 ICI resulted in a delayed and less frequent development of brain metastasis compared with BRAF+MEKTT. 1L-therapy with CTLA-4+PD-1 showed superior OS compared with PD-1 and BRAF+MEK. In BRAF*wt* patients, no differences in brain metastasis and survival outcomes were detected for CTLA-4+PD-1 compared with PD-1.

BACKGROUND

Outcome of melanoma patients has improved dramatically in the last decade. Immune checkpoint inhibitors (ICIs) directed against CTLA-4 (ipilimumab) or PD-1 (nivolumab, pembrolizumab) or their combination can be applied as systemic therapies in all advanced melanoma patients. Melanoma patients with an activating *BRAF V600* mutation (BRAF*mut*) can alternatively receive a targeted therapy (TT) with inhibitors of the RAS-RAF-MEK-ERK (MAPK) signaling pathway. The current standard of care is the combination of BRAF plus MEK inhibitors (BRAF+MEK), based on randomized phase III trials demonstrating improved survival of the combination compared with BRAF monotherapy.[1–3] Monotherapy with ipilimumab (CTLA-4) has shown inferior response and survival rates compared with PD-1 monotherapy (PD-1) or the combined therapy with ipilimumab and nivolumab (CTLA-4+PD-1) and is therefore no longer considered standard of care.[4] Recently, in a large retrospective study, our group could not detect differences in survival outcomes in 450 melanoma patients with brain metastases (MBM) who received different first-line therapies in addition to different types of radiotherapy.[5] Prospective studies without additional locoregional therapies in MBM patients, as well as a meta-analysis, showed higher intracranial effectiveness and better survival outcomes with first-line therapy with CTLA-4+PD-1 compared with PD-1.[6–8] In melanoma patients without MBM it is currently unclear, which treatment strategy is preventing the development of MBM best. This question is of utmost importance, since MBM account for around 50% of melanoma-related deaths.[9] Recent results of two prospective studies have shown better overall survival (OS) with the use of ICIs as first-line and TT as second-line therapy in metastatic BRAF*mut* patients.[10 11] At present, we do not know if TT or ICI as first-line therapy results in better prevention and delay of MBM and if this results in better survival. While several ongoing prospective randomized clinical trials address the question of the optimal sequence in metastatic patients, it has to be considered that a number of patients die—frequently by occurrence of MBM—reducing the chance to receive an effective second-line therapy.

The aim of this study was to compare survival outcomes and onset of MBM occurrence depending on different systemic treatment options (PD-1 or CTLA-4+PD-1 ICI, BRAF+MEKTT) in BRAF wild-type (BRAF*wt*) and BRAF*mut* melanoma patients starting their first-line therapy without MBM in a prospectively collected multicenter real-world patient cohort.

PATIENTS AND METHODS

Study design

Patients with advanced, non-resectable melanoma (AJCCv8 stage IIIC–IV) without brain metastasis at start of their first-line therapy (1L-therapy) treated with inhibitors of PD-1 (nivolumab, pembrolizumab), CTLA-4 (ipilimumab), the combination of both (ipilimumab+nivolumab), or BRAF+MEK (dabrafenib+trametinib, vemurafenib+cobimetinib, encorafenib+binimetinib) between January 2011 and January 2022 were identified from the prospective multicenter skin cancer registry ADOREG of the German Dermatologic Cooperative Oncology Group. Patients with ocular melanoma, patients with non-resectable stage IIIA/B disease, and patients who received BRAF inhibitors without a MEK inhibitor were excluded from this analysis. Data on patient and tumor characteristics, as well as baseline parameters of the first and second non-adjuvant systemic treatment were collected. Best overall response as assessed by the investigators was categorized as complete response, partial response, stable disease, mixed response and progressive disease according to RECIST V.1.1.[12–14] Tumor stagings were performed at baseline and every 3 months thereafter by CT scan of the chest and abdomen and an MRI scan of the brain. Study endpoints were time until the first diagnosis of brain metastasis (brain metastasis-free survival, BMFS), progression-free (PFS) and OS.

Statistical analysis

Univariate and multivariate Cox proportional hazards regression analyses were performed to assess the impact of baseline patient and tumor characteristics and therapeutic measures on BMFS, PFS and OS. The following parameters were included into the univariate and multivariate analyses: sex, age, type of therapy, Eastern Cooperative Oncology Group performance status (ECOG-PS), lactate-dehydrogenase (LDH) serum levels, disease stage by AJCCv8 (IIIB/C, IV M1a, IV M1b, IV M1c), and previous adjuvant therapy with ICI or BRAF+MEK inhibitors. Median follow-up time was calculated as time from start of first non-adjuvant systemic therapy till death or last patient contact. BMFS was defined as time from start

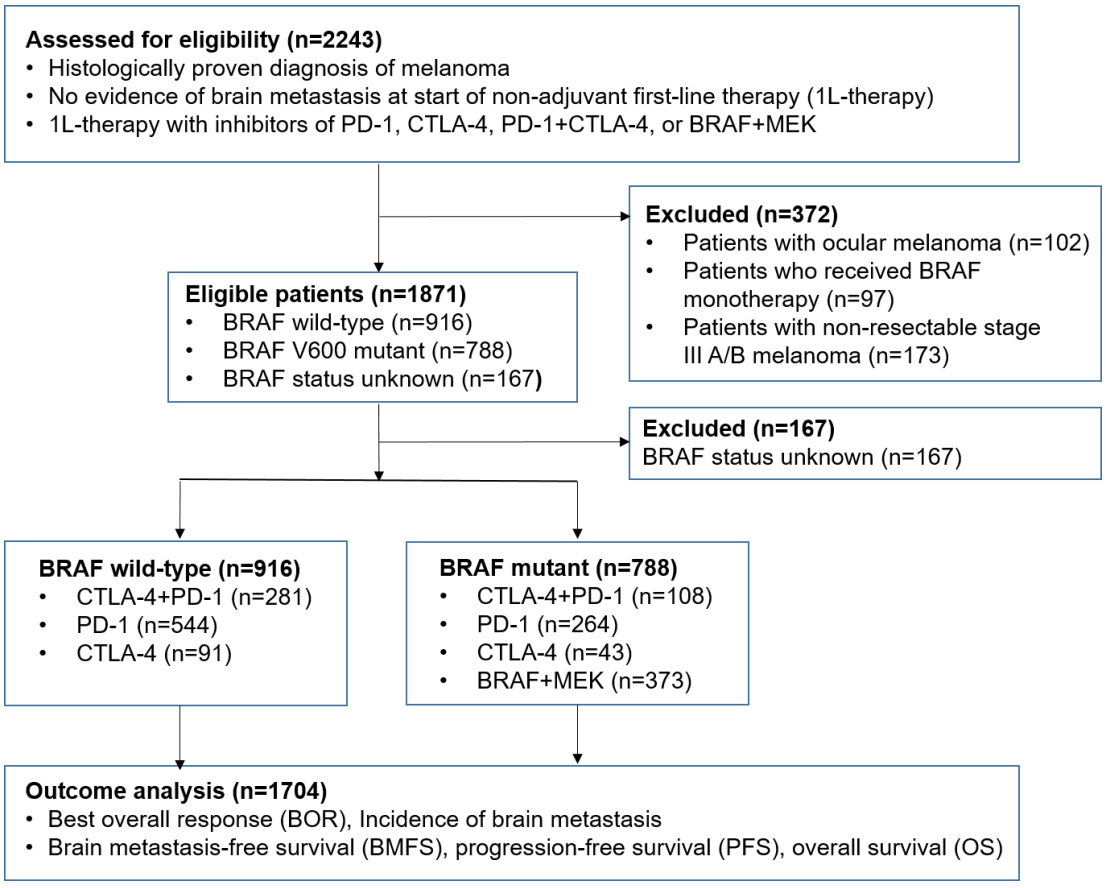

Figure 1 Study flow. A total of 2243 patients from 33 skin cancer centers were identified in the prospective multicenter ADOREG registry. Of these, 1704 patients could be included in the outcome analysis.

of first non-adjuvant systemic therapy until first detection of brain metastasis or last patient contact (censored BMFS), PFS as time from start of systemic therapy until disease progression or last patient contact (censored PFS) and OS as time from start of systemic therapy until death or last patient contact (censored OS). Kaplan-Meier estimates were used for BMFS, PFS and OS calculation; differences between groups were assessed by two-sided log-rank tests. P values <0.05 were considered statistically significant. Patients with missing data were excluded from the respective analyses. Statistical analyses were performed with IBM SPSS Statistics V.27.

RESULTS

Patient characteristics

Data freeze was February 1, 2022. From 2243 patients identified in the ADOREG registry, 1871 met all study inclusion criteria. Additional 167 patients were excluded because of an unknown BRAF mutational status. A detailed study flow is provided in figure 1.

The resulting 1704 patients were used for all further analyses, and had a median follow-up time of 40.4 (range: 0.1–119.8) months after start of 1L-therapy. A total of 930 (54.6%) of these patients had received a subsequent second-line therapy. With regard to pretreatment, 67 (3.9%) patients had received an adjuvant therapy for stage III, and 127 (7.5%) patients for stage IV melanoma (three patients received both). For detailed patient characteristics see table 1.

A total of 788 patients were BRAF*mut*, and 916 were BRAF*wt*. As expected, BRAF*wt* patients were older and encomprised 64 (6.8%) patients with mucosal melanoma, compared with only 4 (0.5%) patients with mucosal melanoma in the BRAF*mut* patient group. 60.5% (n=477) of BRAF*mut* patients and 49.5% (n=453) of BRAF*wt* patients received a second-line therapy. Median OS was similar for BRAF*mut* and BRAF*wt* patients (36.44 vs 37.39 months, p=0.922).

BRAF wild-type patients

Two hundred and eighty-one (30.7%) BRAF*wt* patients received CTLA-4+PD-1, 544 (59.4%) PD-1, and 91 (9.7%) CTLA-4 ICI as 1L-therapy. For detailed characteristics of BRAF*wt* patients, see online supplemental table S1A. Patients who received CTLA-4+PD-1 were significantly younger than patients who received PD-1 (age ≤65 years: 56.2% vs 26.7%). Patients who received CTLA-4+PD-1 showed a better PS compared with those who received PD-1 monotherapy (ECOG-PS>0: 55.5% vs 48.0%), while patients with very high levels of serum LDH also received more often CTLA-4+PD-1 (serum LDH ≥2 x ULN: 31.0% vs 21.9%). In addition, patients who received combination ICI had more advanced

Table 1 Baseline characteristics and therapy outcome of first-line therapy (all patients; n=1704)

	All patients n=1704 (100%)	BRAF wild-type n=916 (100%)	BRAF mutant n=788 (100%)
Age			
≤65 years	780 (45.8)	344 (37.6)	436 (55.3)
>65 years	924 (54.2)	572 (62.4)	352 (44.7)
Gender			
Male	1055 (61.9)	577 (63.0)	478 (60.7)
Female	649 (38.1)	339 (37.0)	310 (39.3)
Site of primary			
Cutaneous	1422 (83.4)	751 (80.3)	671 (87.3)
Mucosal	68 (4.0)	64 (6.8)	4 (0.5)
Unknown primary	214 (12.6)	118 (12.9)	96 (12.2)
BRAF status			
V600 wild-type	916 (50.0)	916 (100.0)	0 (0.0)
V600 mutation	788 (41.0)	0 (0.0)	788 (100.0)
Previous adjuvant therapy in stage III			
None	1637 (96.1)	886 (96.7)	752 (95.4)
Immune checkpoint inhibitors	34 (2.0)	19 (2.1)	15 (1.9)
BRAF+MEK inhibitors	4 (0.2)	0 (0.0)	3 (0.4)
Interferon-alpha	27 (1.6)	11 (1.2)	16 (2.0)
Blinded (clinical trial)	2 (0.1)	0 (0.0)	2 (0.3)
Previous adjuvant therapy in stage IV			
None	1577 (92.5)	847 (92.5)	730 (92.6)
Immune checkpoint inhibitors	68 (4.0)	46 (5.0)	22 (2.8)
BRAF+MEK inhibitors	13 (0.8)	0 (0.0)	13 (1.6)
Interferon-alpha	32 (1.9)	16 (1.7)	16 (2.0)
Blinded (clinical trial)	7 (0.4)	3 (0.3)	4 (0.5)
Chemotherapy	7 (0.4)	4 (0.4)	3 (0.4)
ECOG performance status			
0	790 (46.4)	446 (48.7)	344 (43.7)
1	215 (12.6)	124 (13.5)	91 (11.5)
≥2	62 (3.6)	31 (3.4)	31 (3.9)
Unknown	637 (37.4)	315 (34.4)	322 (40.9)
Serum LDH			
Normal (≤ULN)	811 (47.6)	459 (50.1)	352 (44.7)
Elevated (>ULN)	890 (52.2)	455 (49.7)	435 (55.2)
>2xULN	492 (28.9)	232 (25.3)	260 (33.0)
Unknown	3 (0.2)	2 (0.2)	1 (0.1)
Stage (AJCCv8)			
IIIC/D	274 (16.1)	149 (16.3)	125 (15.9)
IV M1a	173 (10.2)	84 (9.2)	89 (11.3)
IV M1b	411 (24.1)	239 (26.1)	172 (21.8)
IV M1c	821 (48.2)	430 (46.9)	391 (49.6)
IV M1a-c, not specified	25 (1.5)	14 (1.5)	11 (1.4)
First non-adjuvant therapy regimen			

Continued

Table 1 Continued

	All patients n=1704 (100%)	BRAF wild-type n=916 (100%)	BRAF mutant n=788 (100%)
CTLA-4+PD-1	389 (22.8)	281 (30.7)	108 (13.7)
PD-1	808 (47.4)	544 (59.4)	264 (33.5)
BRAF+MEK	373 (21.9)	0 (0.0)	373 (47.3)
CTLA-4	134 (7.9)	91 (9.9)	43 (5.5)
Best overall response			
CR	211 (12.4)	106 (11.6)	105 (13.3)
PR	294 (17.3)	144 (15.7)	150 (19.0)
SD	215 (12.6)	115 (12.6)	100 (12.7)
PD	602 (35.3)	354 (38.6)	248 (31.5)
Mixed response	65 (3.8)	35 (3.8)	30 (3.8)
Unknown	317 (18.6)	162 (17.7)	155 (19.7)
Therapy end reason			
Planned stop	182 (10.7)	108 (11.8)	74 (9.4)
Toxicity	300 (17.6)	178 (19.4)	122 (15.5)
Disease progression	707 (41.5)	357 (39.0)	350 (44.4)
Patient wish	75 (4.4)	43 (4.7)	32 (4.1)
Other	164 (9.6)	93 (10.2)	71 (9.0)
Ongoing	248 (14.6)	120 (13.1)	128 (16.2)
Lost to follow-up	27 (1.6)	17 (1.9)	11 (1.4)
Progression			
No	732 (43.0)	387 (42.2)	345 (43.8)
Yes	972 (57.0)	529 (57.8)	443 (56.2)
Second-line therapy			
No	774 (45.4)	463 (50.5)	311 (39.5)
Yes	930 (54.6)	453 (49.5)	477 (60.5)
Death			
No	1003 (58.9)	540 (59.0)	463 (58.8)
Yes	701 (41.1)	376 (41.0)	325 (41.2)
Development of brain metastases			
No	1317 (77.3)	745 (81.3)	572 (72.6)
Yes	387 (22.7)	171 (18.7)	216 (27.4)
Progression-free survival			
Median in months (95% CI)	6.7 (5.85 to 7.49)	5.78 (4.77 to 6.80)	7.98 (6.83 to 9.14)
Overall survival			
Median in months (95% CI)	36.93 (32.47 to 41.39)	37.39 (30.91 to 43.87)	36.44 (29.98 to 42.90)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, partial response.

disease stages (56.6% stage IV M1c) compared with patients who received PD-1 monotherapy (41.9% stage IV M1c). The objective response rate was 32.0% for CTLA-4+PD-1, 27.2% for PD-1, and 13.2% for CTLA-4. First-line therapy was stopped significantly more often because of toxicity in patients who received CTLA-4+PD-1 (32.0% vs 12.3%), whereas in patients who received PD-1 therapy, therapy was ended more often due to disease progression (27.4% vs 44.1%). Disease progression occurred in 47.0% (CTLA-4+PD-1), 60.3%

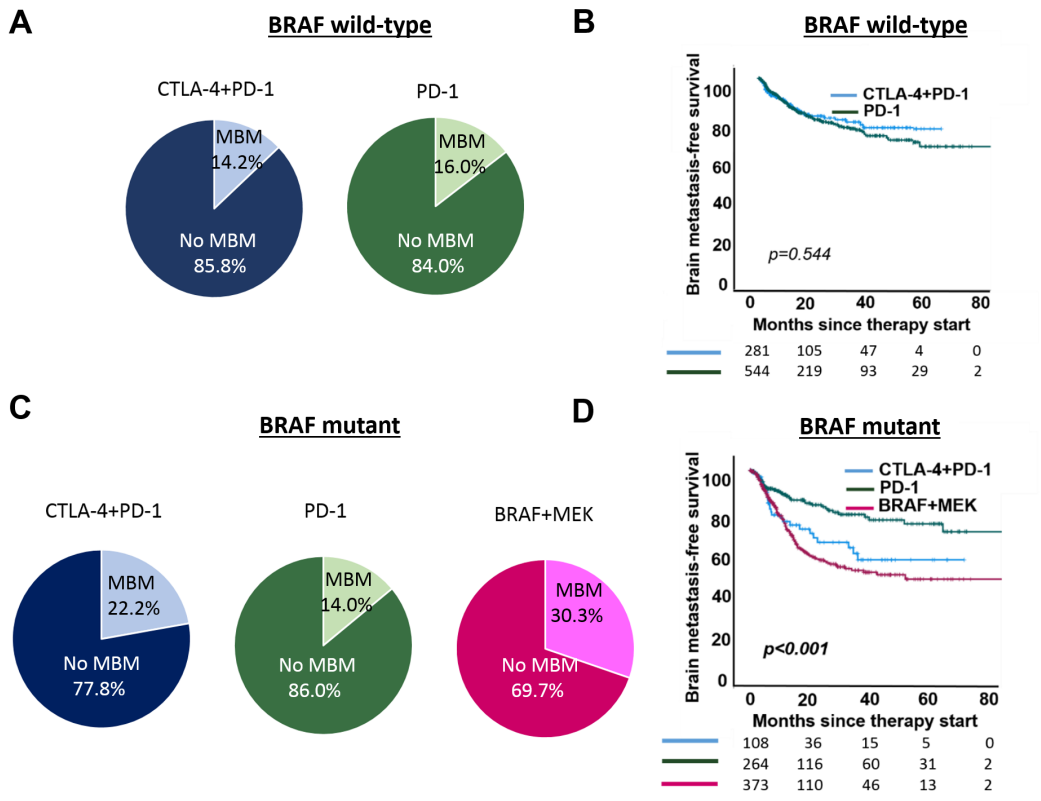

Figure 2 Development of brain metastasis on different types of first-line therapy in BRAF mutant and BRAF wild-type melanoma patients. (A, C) Incidence of brain metastasis at 24 months after start of first-line therapy, and (B, D) brain metastasis-free survival. The log-rank test was used to compare between groups; p<0.05 was considered significant.

(PD-1) and 75.8% (CTLA-4). At 24 months after start of 1L-therapy, the incidence of MBM was 14.2% with CTLA-4+PD-1, 16.0% with PD-1 and 24.2% with CTLA-4 (figure 2). Median OS was not reached for CTLA-4+PD-1, 34.56 (95% CI 28.00 to 41.12) months for PD-1, and 37.39 (95% CI 21.99 to 52.79) months for CTLA-4 (online supplemental table S1B).

Univariate Cox regression analysis showed an association of ECOG-PS, serum LDH, tumor stage, and type of 1L-therapy with OS, and of tumor stage and therapy type with PFS; for details see online supplemental table S2 and figure 3. For BMFS, only tumor stage was significantly prognostic (online supplemental table S3).

Multivariate Cox regression analysis in BRAF*wt* patients including age, gender, ECOG-PS, serum LDH, previous adjuvant therapy with ICI or BRAF+MEK, tumor stage, and type of 1L-therapy (CTLA+PD-1, PD-1 or CTLA-4; table 2) identified ECOG-PS>0 (0 vs 1: HR 1.821, 95% CI 1.350 to 2.456, p<0.001; 0 vs 2: HR 2.510, 95% CI 1.433 to 4.247, p=0.001), elevated serum LDH (not elevated vs elevated: HR 1.433, 95% CI 1.10 to 1.851, p=0.006), and tumor stage (IV M1c vs IV M1a: HR 0.558, 95% CI 0.320 to 0.972, p=0.039; IV M1c vs IV M1b: HR 0.625, 95% CI 0.454 to 0.862, p=0.002), but not the type of 1L-therapy (CTLA-4+PD-1 or PD-1) as independent prognostic factors for OS. First-line therapy with CTLA-4 (CTLA-4+PD-1 vs CTLA-4: HR 2.346, 95% CI 1.469 to 3.747, p<0.001, CTLA-4 vs PD-1: HR 0.466, 95% CI 0.299 to 0.727, p=0.001), and higher tumor stage (IV M1c vs IV M1b: HR 0.640, 95% CI 0.489 to 0.837, p=0.001) were independently prognostic for a shorter PFS. Only tumor stage could be identified as an independent prognostic factor for BMFS (stage IV M1c vs stage IIIC/D: HR 0.359, 95% CI 0.181 to 0.711, p=0.003; stage IV M1c vs stage IV M1a: HR 0.158, 95% CI 0.039 to 0.646, p=0.010; table 3).

BRAF-mutant patients

Thirteen point seven % (n=108) of BRAF*mut* patients received CTLA-4+PD-1, 33.5% (n=264) received PD-1, 43 (5.5%) received CTLA-4, and 373 (47.3%) received BRAF+MEK as 1L-therapy (online supplemental table S4A). Of 373 patients who received BRAF+MEK as first-line therapy, 257 (68.9%) received dabrafenib+trametinib, 62 (16.6%) vemurafenib+cobimetinib and 54 (14.5%) encorafenib+binimetinib. Patients who received CTLA-4+PD-1 were significantly younger than patients with other therapy types (age ≤65 years: 77.8% CTLA-4+PD-1, 43.6% PD-1, 56.6% BRAF+MEK, and 60.5% CTLA-4), while patients treated with BRAF+MEK had significantly higher serum LDH levels (>2× ULN: 40.8% BRAF+MEK, 29.6% CTLA-4+PD-1, 23.5% PD-1, and 32.6% CTLA-4). Patients who received CTLA-4+PD-1 or BRAF+MEK had more advanced disease stages than patients who received PD-1 or CTLA-4 monotherapy

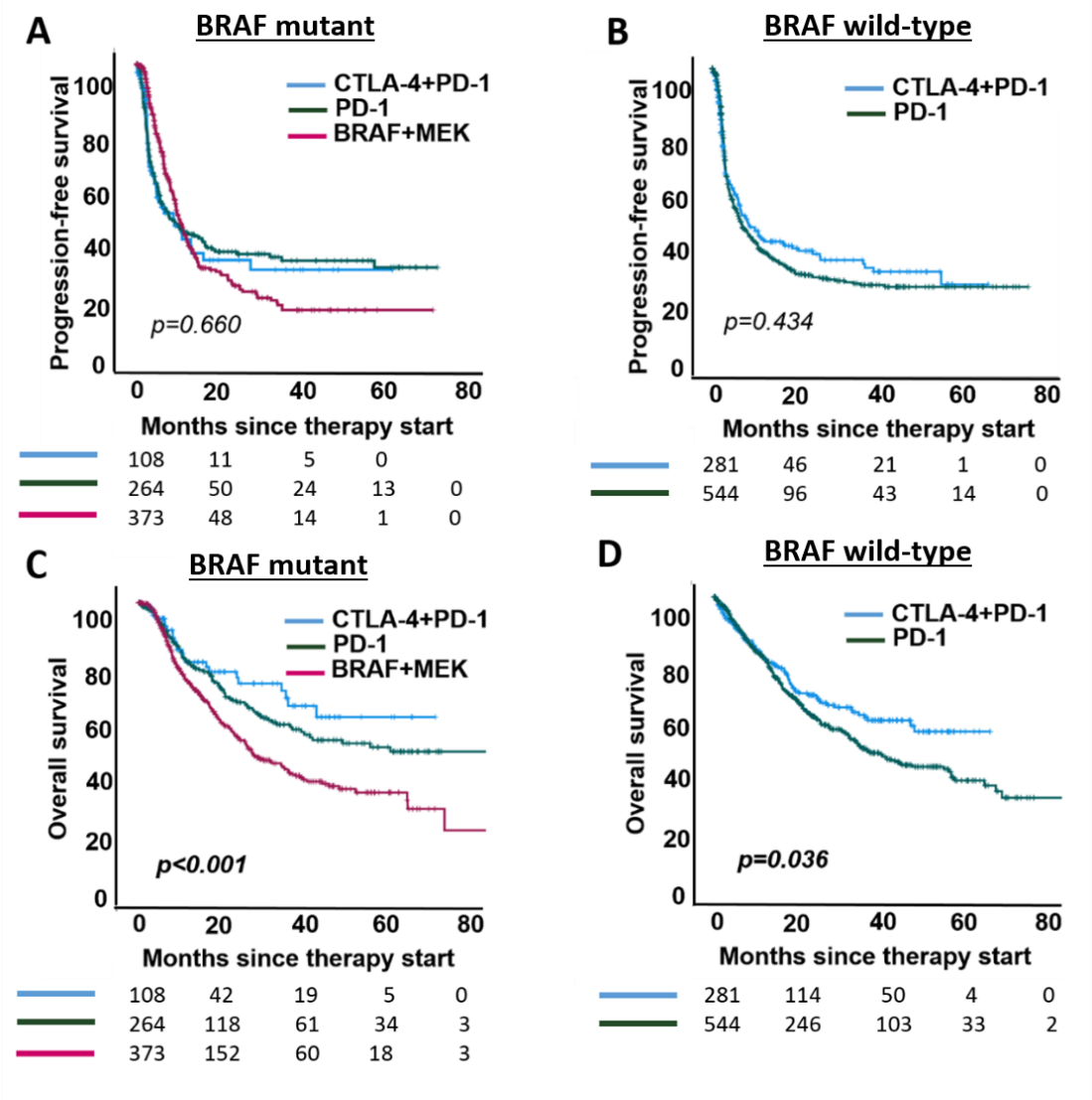

Figure 3 Kaplan-Meier curves showing progression-free and overall survival for first-line therapy in BRAF mutant and BRAF wild-type melanoma patients. (A, B) Progression-free survival; (C, D) overall survival. The log-rank test was used to compare between groups; p<0.05 was considered significant.

(stage IV M1c: 60.2% CTLA-4+PD-1, 57.4% BRAF+MEK, 36.4% PD-1, and 37.2% CTLA-4). Objective response rate was 36.4% for BRAF+MEK, 32.6% for PD-1, 28.7% for CTLA-4+PD-1, and 4.7% for CTLA-4, with a high number of best responses not reported. 26.9% of patients who received CTLA-4+PD-1 stopped therapy because of toxicity, compared with only 8.3% with PD-1, 17.4% with BRAF+MEK, and 14% with CTLA-4. In contrast, 31.5% of patients treated with CTLA-4+PD-1, 48.5% of patients treated with PD-1, 45.8% of patients treated with BRAF+MEK, and 37.2% of patients treated with CTLA-4 discontinued 1L-therapy because of disease progression. Disease progression occurred in 43.5% of patients who received CTLA-4+PD-1, in 58.7% of patients who received PD-1, in 56.0% of patients who received BRAF+MEK, and in 74.4% of patients who received CTLA-4. Median PFS was highest for BRAF+MEKTT (9.46; 95% CI 8.341 to 10.583 months) compared with CTLA-4+PD-1 (8.74; 95% CI 2.83 to 14.65) months), PD-1 (5.95 months; 95% CI 4.24 to 7.66), and CTLA-4 (2.14; 95% CI 2.048 to 2.223 months) ICI. Median OS was not reached for CTLA-4+PD-1 and for PD-1 monotherapy, and was 26.28 (95% CI 21.1 to 31.5) months for BRAF+MEKand 34.92 (95% CI 3.3 to 41.4) months for CTLA-4. At 24 months after start of 1L-therapy, BRAF+MEKTT revealed a higher incidence of MBM compared with PD-1±CTLA-4 ICI (CTLA-4+PD-1: 22.2%, PD-1: 14.0%, BRAF+MEK: 30.3%, CTLA-4: 44.2%, figure 2, online supplemental table S4B).

Univariate Cox regression analysis revealed ECOG-PS, serum LDH, tumor stage, and type of 1L-therapy as associated with PFS and OS; for details see online supplemental table S5 and figure 3. Age, tumor stage, and type of systemic therapy were associated with BMFS (online supplemental table S6).

In the multivariate Cox regression analysis (table 4), we detected ECOG-PS>0 (ECOG-PS=1: HR 1.740, 95% CI 1.221 to 2.479, p=0.001; ECOG-PS=2: HR 2.513, 95% CI 1.541 to 4.099, p<0.001), elevated serum LDH (HR 1.464,

Table 2 Multivariate Cox regression analysis for progression-free and overall survival in BRAF-wild-type patients

Parameters included (patient no)	Overall survival N=593 HR (95% CI) p value	Progression-free survival N=593 HR (95% CI) p value
Gender (reference: male)		
Male vs female (380 vs 213)	1.256 (0.965 to 1.634) 0.090	1.055 (0.844 to 1.319) 0.639
Age (reference: ≤65 years)		
≤65 vs >65 years (203 vs 390)	0.843 (0.632 to 1.123) 0.243	0.843 (0.663 to 1.072) 0.163
BRAF status (reference: wild-type)		
Wild-type vs BRAF V600 mutant	n.a.	n.a.
ECOG performance status (reference :0)		
0 vs 1 (442 vs 123)	**1.821 (1.350 to 2.456) <0.001**	1.209 (0.923 to 1.584) 0.169
0 vs ≥2 (442 vs 28)	**2.510 (1.483 to 4.247) 0.001**	1.407 (0.855 to 2.316) 0.180
Serum LDH (reference: normal)		
Normal vs elevated	**1.433 (1.110 to 1.851) 0.006**	1.226 (0.988 to 1.520) 0.064
Primary adjuvant drug therapy with immune checkpoint blockade (reference: no)		
No vs yes (547 vs 46)	0.922 (0.493 to 1.725) 0.800	1.025 (0.668 to 1.573) 0.910
Tumor stage (reference: M1c)		
M1c vs stage III C/D (294 vs 97)	0.693 (0.470 to 1.020) 0.063	0.811 (0.595 to 1.06) 0.185
M1c vs stage IV M1a (294 vs 45)	**0.558 (0.320 to 0.972) 0.039**	0.639 (0.402 to 1.017) 0.059
M1c vs stage IV M1b (294 vs 157)	**0.625 (0.454 to 0.862) 0.004**	**0.640 (0.489 to 0.837) 0.001**
Type of first systemic therapy (reference:CTLA-4+PD-1)		
CTLA-4+PD-1 vs PD-1 (181 vs 377)	1.179 (0.857 to 1.621) 0.311	1.093 (0.838 to 1.425) 0.510
CTLA-4+PD-1 vs CTLA-4 (181 vs 35)	1.175 (0.707 to 1.954) 0.533	**2.346 (1.469 to 3.747) <0.001**
(reference:CTLA-4)		
CTLA-4 vs PD-1 (35 vs 377)	1.003 (0.626 to 1.607) 0.990	**0.466 (0.299 to 0.727) 0.001**

Significant values are in bold.
LDH, lactate dehydrogenase; n.a, not applicable.

95% CI 1.087 to 1.970, p=0.012), tumor stage of IV M1c (III C/D: HR 0.481, 95% CI 0.261 to 0.884, p=0.018; IV M1a: HR 0.450, 95% CI 0.262 to 0.774, p=0.004) as independently negatively associated with OS, and 1L-therapy with CTLA-4+PD-1 as independently positively associated with OS (PD-1: HR 1.969, 95% CI 1.122 to 3.455, p=0.018; CTLA-4: HR 3.948, 95% CI 1.743 to 8.942, p=0.001; BRAF+MEK: HR 2.409, 95% CI 1.432 to 4.054, p=0.001). ECOG-PS>0, elevated serum LDH, tumor stage of IV M1c, and 1L-therapy with CTLA-4 showed an independent negative association with PFS. Independent prognostic factors for longer BMFS found by multivariate analysis were age >65 years (HR=0.632 compared with age ≤65 years; 95% CI 0.431 to 0.927, p=0.019) and tumor stage IV M1a (HR 0.294, 95% CI 0.1133 to 0.651, p=0.003) compared with stage IV M1c, while 1L-therapy with BRAF+MEK was negatively associated with BMFS compared with CTLA-4+PD-1 (HR 0.60, 95% CI 0.332 to 0.945; p=0.030) and PD-1 (HR 0.575, 95% CI 0.372 to 0.888; p=0.013; table 5). A subgroup analysis revealed no differences for PFS or OS when comparing the three different BRAF+MEK combinations in the multivariate analysis (online supplemental table S11A,B).

Brain metastases

BRAF*mut* patients developed MBM significantly more often than BRAF*wt* patients (27.4% (n=216) vs 18.7% (n=171) MBM, table 1). Median time till development of MBM was not reached in both groups, while mean time till development of MBM was 66.5 months for BRAF*mut* and 83.0 months for BRAF*wt* patients (p<0.001). With regard to 1L-therapy, 16.0% (n=45) of BRAF*wt* patients treated with CTLA-4+PD-1, 18.9% (n=103) of patients treated with PD-1, and 25.3% (n=23) of patients treated with CTLA-4 developed MBM during follow-up (online supplemental table S1A), compared with 25.0% (n=27) of BRAF*mut* patients treated with CTLA-4+PD-1, 17.0% (n=45) treated with PD-1, 33% (n=123) treated with BRAF+MEKand 48.8% (n=21) treated with CTLA-4 (online supplemental table S4A). In BRAF*mut* patients, median time till development of MBM was 51.8 months for BRAF+MEK, 39.2 months for CTLA-4 and not reached for CTLA-4+PD-1 or PD-1 (p<0.001), whereas it was not reached for BRAF*wt* patients on treatment with CTLA-4+PD-1, PD-1 or CTLA-4. In the Kaplan-Meier survival analysis, we noticed that in *BRAFmut* patients ICI therapy with CTLA-4+PD-1 resulted in a more rapid development

Table 3 Multivariate Cox regression analysis for brain metastasis-free survival in BRAF-wild-type patients

Parameters included (patient no)	Brain metastasis-free survival N=583 HR (95% CI) p value
Gender (reference: male)	
Male vs female (380 vs 213)	1.106 (0.748 to 1.635) 0.614
Age (reference: ≤65 years)	
≤65 vs >65 years (203 vs 390)	0.784 (0.521 to 1.178) 0.241
BRAF status (reference: wild-type)	
Wild-type vs BRAF V600 mutant	n.a.
ECOG performance status (reference :0)	
0 vs 1 (442 vs 123)	1.463 (0.927 to 2.308) 0.102
0 vs ≥2 (442 vs 28)	1.232 (0.445 to 3.410) 0.688
Serum LDH (reference: normal)	
normal vs elevated (312 vs 281)	1.367 (0.939 to 1.992) 0.103
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no)	
No vs yes (556 vs 47)	1.246 (0.564 to 2.752) 0.587
Tumor stage (reference: M1c)	
M1c vs stage III C/D (294 vs 97)	**0.359 (0.181 to 0.711) 0.003**
M1c vs stage IV M1a (294 vs 45)	**0.158 (0.039 to 0.646) 0.010**
M1c vs stage IV M1b (294 vs 157)	0.782 (0.511 to 1.198) 0.259
Type of first systemic therapy (reference:CTLA-4+PD-1)	
CTLA-4+PD-1 vs PD-1 (181 vs 377)	1.093 (0.703 to 1.700) 0.692
CTLA-4+PD-1 vs CTLA-4 (181 vs 35)	0.898 (0.394 to 2.046) 0.798
(reference:CTLA-4)	
CTLA-4 vs PD-1 (35 vs 377)	1.217 (0.551 to 2.689) 0.626

Significant values are in bold.
LDH, lactate dehydrogenase; n.a., not applicable.

of MBM compared with PD-1-treated patients, while this was not visible in the *BRAFwt* cohort (figure 2). No differences for BMFS where detected when comparing the three different BRAF+MEK combinations in the multivariate analysis.

Therapy sequence

Next we wanted to assess, if a certain therapy sequence of first-line and second-line therapy is associated with improved BMFS or OS. Altogether, 930 patients with known BRAF mutational status had received a second-line therapy. These patients were significantly younger than patients who did not receive second-line therapy. They also had more often received CTLA-4 or BRAF+MEK as 1L-therapy. Patients with second-line therapy developed MBM more often than patients without second-line therapy (for details, see online supplemental table S7). A total of 477 (51.3%) patients who received second-line therapy were BRAF*mut,* and 453 (48.7%) were BRAF*wt* (online supplemental table S8).

Multivariate Cox regression analysis including therapy sequence revealed ECOG-PS>0 (ECOG-PS=1: HR 1.745, 95% CI 1.090 to 2.795, p=0.021, ECOG-PS=2: HR 3.146, 95% CI 1.656 to 5.975, p<0.001) as negatively associated with OS for BRAF*mut* patients (online supplemental table S10). Additionally, the sequence of BRAF+MEK followed by CTLA-4+PD-1 was negatively associated with OS when compared with CTLA-4+PD-1 followed by BRAF+MEK (HR 1.988, 95% CI 1.026 to 3.852, p=0.042). For BMFS the sequence of BRAF+MEK followed by CTLA-4+PD-1 was inferior to PD-1 followed by BRAF+MEK. In BRAF*wt* patients, the sequence of CTLA+PD-1 and PD-1 did not affect OS or BMFS (online supplemental table S9).

DISCUSSION

In our present study, we analyzed a large prospectively collected real-world cohort of advanced melanoma patients, who started non-adjuvant 1L-therapy in the absence of brain metastases. This specific setting was chosen to test for differences in time from therapy start until first diagnosis of brain metastases in different types of 1L-therapy. Our findings demonstrate that in BRAF*mut* patients 1L-therapy with BRAF+MEK TT is associated with shorter BMFS compared with 1L-therapy with ICI (CTLA-4+PD-1 or PD-1 alone), independent of other prognostically relevant factors. In addition, our multivariate analysis showed that 1L-therapy with CTLA-4+PD1 leads to better OS than 1L-therapy with PD-1, CTLA-4 or BRAF+MEK. In contrast, these correlations could not be demonstrated in the multivariate analysis for PFS, which showed only inferiority of CTLA-4 monotherapy compared with all other types of 1L-therapy. Also, in the multivariate analysis, we could not detect significant differences in survival outcomes of BRAF*wt* patients who received combined or single-agent PD-1 based ICI.

Our study shows a significantly higher incidence of MBM in BRAF*mut* patients who received BRAF+MEK as 1L-therapy compared with those patients who received first-line ICI. Melanoma is one of the cancers with the highest risk to develop brain metastases, accounting for approximately 6%–11% of all metastatic brain lesions.[15] Several studies tried to predict the risk of development of MBM, but these comparisons were performed between patients who developed brain metastases in earlier stages independent of therapies.[16–18] Frenard *et al* compared the development of MBM in a small cohort of 52 patients who received ipilimumab with a cohort of patients who received vemurafenib, and found no difference in risk of developing brain metastases between both cohorts.[19] A French group analyzed 293 melanoma patients without brain metastases who were treated with either anti-PD-1 or anti-PD-L1 antibodies or other systemic therapies (including BRAF inhibitors and chemotherapy) and found a lower incidence of MBM in the PD-1 group compared with patients treated with other therapies.[20] The results of this study are weakened by the fact, that BRAF*mut* patients were not assessed separately in the multivariate analysis

Table 4 Multivariate Cox regression analysis for progression-free and overall survival in BRAF-mutant patients

Parameters included (patient no)	Overall survival HR (95% CI) p value N=451	Progression free-survival HR (95% CI) p value N=462
Gender (reference: male)		
Male vs female (281 vs 182; 280 vs 182)	0.987 (0.730 to 1.334) 0.931	0.965 (0.748 to 1.245) 0.785
Age (reference: ≤65 years)		
≤65 vs >65 years (259 vs 204; 258 vs 204)	1.093 (0.807 to 1.481) 0.564	0.792 (0.606 to 1.036) 0.089
BRAF status (reference: BRAF+MEK)		
BRAF V600 mutant vs wild-type	n.a.	n.a.
ECOG performance status (reference: 0)		
0 vs 1 (342 vs 91; 341 vs 91)	**1.740 (1.221 to 2.479) 0.002**	**1.457 (1.059 to 2.003) 0.021**
0 vs ≥2 (342 vs 30; 341 vs 30)	**2.513 (1.541 to 4.099) <0.001**	1.420 (0.884 to 2.280) 0.147
Serum LDH (reference: normal)		
Normal vs elevated (221 vs 242; 221 vs 241)	**1.464 (1.087 to 1.970) 0.012**	**1.330 (1.033 to 1.712) 0.027**
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no)		
No vs yes (421 vs 42; 420 vs 42)	1.104 (0.615 to 1.982) 0.740	1.095 (0.678 to 1.770) 0.710
Tumor stage (reference: M1c)		
M1c vs stage III C/D (240 vs 53; 239 vs 53)	**0.481 (0.261 to 0.884) 0.018**	**0.576 (0.359 to 0.925) 0.022**
M1c vs stage IV M1a (240 vs 55; 239 vs 55)	**0.450 (0.262 to 0.774) 0.004**	**0.534 (0.349 to 0.817) 0.004**
M1c vs stage IV M1b (240 vs 115; 239 vs 115)	0.876 (0.618 to 1.242) 0.457	**0.615 (0.448 to 0.844) 0.003**
Type of first systemic therapy (reference: *BRAF+MEK*)		
BRAF+MEK vs CTLA-4+PD-1 (214 vs 74; 213 vs 74)	**0.415 (0.247 to 0.698) 0.001**	1.098 (0.745 to 1.620) 0.636
BRAF+MEK vs PD-1 (214 vs 161; 213 vs 161)	0.817 (0.583 to 1.146) 0.242	**1.550 (1.150 to 2.089) 0.004**
BRAF+MEK vs CTLA-4 (214 vs 14; 213 vs 14)	1.639 (0.830 to 3.235) 0.154	**8.233 (4.045 to 16.755) <0.001**
(reference:CTLA-4+PD-1)		
CTLA-4+PD-1 vs PD-1 (74 vs 161; 74 vs 161)	**1.969 (1.122 to 3.455) 0.018**	1.411 (0.928 to 2.146) 0.108
CTLA-4+PD-1 vs CTLA-4 (74 vs 14; 74 vs 14)	**3.948 (1.743 to 8.942) 0.001**	**7.495 (3.470 to 16.188) <0.001**
CTLA-4+PD-1 vs BRAF+MEK (74 vs 214; 74 vs 213)	**2.409 (1.432 to 4.054) 0.001**	0.910 (0.617 to 1.343) 0.636

Significant values are in bold.
LDH, lactate dehydrogenase; n.a., not available.

and patients treated with BRAF+MEK were not compared directly to patients treated with PD-1. A retrospective study by Wang *et al* assessed BMFS in a cohort of BRAF*mut*, but not BRAF*wt* patients, receiving ICI or BRAF+MEK TT.[21] This work showed a prolonged BMFS for patients who received ICI as 1L-therapy compared with patients who received BRAF+MEK. These findings were based on propensity scored matching of single variables and not on a multivariate Cox regression analysis including all important prognostic variables as in our analysis.

Why 1L-therapy with BRAF+MEK TT leads to a faster and more frequent development of MBM than ICI in BRAF*mut* patients is unclear yet. It is known, that while BRAF+MEK therapy shows good intracranial responses, the duration of these responses is relatively short.[22] While there are data from a prospective phase II study on the effectiveness of dabrafenib+trametinib on MBM, such data is lacking for vemurafenib+cobimetinib or encorafenib+binimetinib. We did not detect differences in survival outcomes with the three different BRAF+MEK combinations in a subgroup analysis, but it has to be kept in mind, that the majority of our patients received dabrafenib+trametinib and that the other two groups were rather small.

Findings from different studies showed that MBM have distinct molecular features such as increased activation of the PI3K-AKT pathway and larger fractions of dysfunctional CD8+T cells with distinct expression of immune checkpoints compared with extracerebral metastases.[23 24] This might explain why intracerebral effectiveness of BRAF+MEK is lower than outside the brain. In addition, Seifert *et al*[25] showed in vitro that cerebrospinal fluid reduced cell death mediated by BRAF inhibitors. Interestingly, recently Wang *et al* demonstrated in a murine melanoma model that only a short sequence of PD-1 therapy followed by BRAF+MEK treatment was sufficient to suppress MBM development and improve the survival of the animals which was accompanied by

Table 5 Multivariate Cox regression analysis for brain metastasis free-survival in BRAF-mutant patients

Parameters included (patient no)	Brain metastasis-free survival HR (95% CI) p value N=456
Gender (reference: male)	
Male vs female (281 vs 182)	0.991 (0.690 to 1.421) 0.959
Age (reference: ≤65 years)	
≤65 vs >65 years (259 vs 204)	**0.632 (0.431 to 0.927) 0.019**
BRAF status (reference: wild-type)	
Wild-type vs BRAF V600 mutant	n.a.
ECOG performance status (reference :0)	
0 vs 1 (342 vs 91)	1.499 (0.949 to 2.369) 0.083
0 vs ≥2 (342 vs 30)	1.249 (0.637 to 2.448) 0.517
Serum LDH (reference: normal)	
Normal vs elevated (221 vs 242)	1.229 (0.857 to 1.764) 0.262
Primary adjuvant drug therapy with immune checkpoint blockade or BRAF+MEK inhibitors (reference: no)	
No vs yes (421 vs 42)	0.787 (0.395 to 1.568) 0.496
Tumor stage (reference: M1c)	
M1c vs stage III C/D (240 vs 53)	0.567 (0.283 to 1.135) 0.109
M1c vs stage IV M1a (240 vs 55)	**0.294 (0.133 to 0.651) 0.003**
M1c vs stage IV M1b (240 vs 115)	1.053 (0.700 to 1.584) 0.805
Type of first systemic therapy (reference: BRAF+MEK)	
BRAF+MEK vs CTLA-4+PD-1 (214 vs 74)	**0.560 (0.332 to 0.945) 0.030**
BRAF+MEK vs PD-1 (214 vs 161)	**0.575 (0.372 to 0.888) 0.013**
BRAF+MEK vs CTLA-4 (214 vs 14)	1.432 (0.607 to 3.380) 0.413
(reference:CTLA-4+PD-1)	
CTLA-4+PD-1 vs PD-1 (74 vs 161)	1.026 (0.562 to 1.875) 0.932
CTLA-4+PD-1 vs CTLA-4 (74 vs 14)	2.556 (0.982 to 6.653) 0.054
CTLA-4+PD-1 vs BRAF+MEK (74 vs 214)	**1.785 (1.059 to 3.011) 0.030**

Significant values are in bold.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; n.a, not applicable.

T cell clonal expansion in intra- and extracranial metastases.[26] These observations support our finding, that ICI as 1L-therapy are associated with better intracranial effectiveness and longer BMFS in BRAF*mut* patients. In the BRAF*mut* patients of our studied cohort, 1L-therapy with BRAF+MEK was associated with a significantly prolonged PFS compared with PD-1 and CTLA-4, but not to CTLA-4+PD-1. This observation is in line with the known higher primary resistance rate to PD-1 monotherapy compared with BRAF+MEK or CTLA-4+PD-1. The observed superior OS with CTLA-4+PD-1 compared with BRAF+MEK did not result from superior PFS of CTLA-4+PD1, which could be explained by a better response to second-line therapies in BRAFmut patients progressing on 1L-therapy with CTLA-4+PD-1, which is most often BRAF+MEK, compared with those progressing on 1L-therapy with BRAF+MEK, who mainly receive ICI as second-line treatment. Our findings for OS are in line with the recently published results of the randomized phase III trial *Dreamseq*.[11] This study evaluated the sequential non-adjuvant therapy with ipilimumab+nivolumab followed by dabrafenib+trametinib in comparison to the converse sequence in BRAF*mut* melanoma. It has to be considered though, that the numbers of treated patients in the sequential arms of this study were very small. Nevertheless, an exploratory analysis of survival data from the most relevant clinical trials on BRAF+MEKTT and ICI therapy performed by us also led to similar results: a comparison of the mean PFS and OS data at 3 years after treatment start revealed a clear superiority of ICI vs TT as 1L-therapy (3year OS 41.3% for BRAF+MEK, 49.9% for PD-1, and 58.4% for CTLA-4+PD-1).[27] A similar trend was detected in the 3-arm randomized prospective *SECOMBIT* trial.[10] Patients who received first-line therapy with encorafenib+binimetinib followed by second-line therapy with ipilimumab+nivolumab showed a slightly lower OS at 2 years (65%) compared with patients with the converse sequence (73%) in this trial. In addition, there was a so-called

"sandwich"-arm with an 8 week run-in phase followed by ipilimumab+nivolumab until progression and then switch to TT. OS for this arm was in between the two other arms (69%). All differences were not statistically significant, but showed a clear trend. A recent update confirmed these findings at 37.1 months median follow-up.[28] The real-world findings of our present study now underline these retrospectively obtained findings and those of the prospective *Dreamseq* and *SECOMBIT* trials. In addition, several studies have reported immunological changes in the tumor microenvironment after progression on TT, which can explain the inferior clinical activity of ICI as second-line therapy after progression to BRAF+MEK.[29–31] In line with this and the results of our study, a recent study compared patients with MBM who received CTLA-4+PD-1 as first-line therapy or after progression on BRAF+MEK.[32] There, treatment with CTLA-4+PD-1 after progression on BRAF+MEK showed a very low response rate which was associated with an enrichment in genes from the innate anti-PD-1 resistance signature (IPRES).

Another remarkable observation made in our present study is that a significant number of patients did not receive a second-line therapy. Further analyzing this interesting point, we found several reasons for this: (1) good response to 1L-therapy which does not make a second therapy necessary, (2) rapid tumor progression on 1L-therapy with fast deterioration of overall health status ruling out the start of a second-line therapy, (3) adverse events of 1L-therapy that make a second-line therapy impossible, or (4) patient wish. This finding of a high rate of patients never receiving second-line therapy underlines the importance of the right choice for an optimal 1L-therapy. When only considering 1L-therapy, in our study OS was significantly better in BRAF*mut* patients who received CTLA-4+PD-1 compared with all other treatment types. Moreover, this superiority was independent of other prognostically relevant factors such as age, ECOG-PS, serum LDH, and disease stage). While in BRAF*mut* patients OS on 1L-therapy with CTLA-4+PD-1 was superior compared with PD-1 alone, this difference was not detectable for BRAF*wt* patients. A similar finding was reported in the *Checkmate-067* trial. In that study, the 6.5 years OS rates for BRAF*wt* patients were 46% on CTLA-4+PD-1 and 42% on PD-1, while in BRAF*mut* patients they were 57% on CTLA-4+PD-1 and 43% on PD-1.[33] This separation of OS curves in BRAF*mut* patients treated with CTLA-4+PD-1 or PD-1 was already visible in the 4 years analysis.[34] On one hand, this OS difference could be explained by the availability of BRAF+MEK TT as an efficient second-line therapy option in these patients, which BRAF*wt* patients do not have. On the other hand, different features in tumor biology and immunology intrinsic to these different types of melanoma might probably contribute to this effect, since BRAF activation is associated with the production of immunosuppressive cytokines, downregulation of MHC-class-I molecules, reduced T cell recognition, and a higher number of myeloid-derived suppressor cells and regulatory T cells, leading to a more immunosuppressive tumor microenvironment and a stronger immune escape of tumor cells in BRAF*mut* melanoma.[35 36]

Our study is not without limitations. Despite the large number of patients, the retrospective nature of this study has clear limitations: while we tried to account for many important prognostically relevant parameters, information on some parameters such as the sum and the biggest diameter of tumor burden and organ dysfunction by metastasis could not be included into the multivariate analysis, since they were not recorded in the registry. While LDH is one important marker of tumor burden, these parameters could have influenced treatment selection and therefore prognosis as well. Organ dysfunction or metastasis of critical organs, for example, could have prompted treating physicians to select treatment with TT instead of ICI, because of their faster treatment effect. In addition, in our real-world cohort, 50% of patients had elevated serum levels of LDH of whom more than half had very highly elevated levels (>2× ULN). This explains a significantly lower ORR to ICI and TT than reported for patients in most prospectively randomized trials, which has to be kept in mind, when results of such studies are compared with ours. It also has to be considered, that during the long time period over which the data was collected (2011–2021) not all therapeutic options were always similarly available. Particularly between 2011 and 2016, there were less approved therapeutic options available than nowadays. This could have influenced treatment outcomes and decisions toward first-line and second-line therapies. To partially account for this, we excluded patients who received BRAF monotherapy as 1L-therapy from this study, because the BRAF+MEK combination has become standard of care due to its better efficacy and tolerability. We also did not detect any significant differences for OS for the different time periods (before and after approval of the different therapies, online supplemental figure S1) other than for ipilimumab, which has not been used as first-line therapy any more since approval of PD-1 based ICI). In addition, a high number of missing values for the ECOG-PS reduced the number of patients that could be assessed in the multivariate analysis. Nevertheless, due to our high patient number, we could still analyze different subgroups and therapy sequences with robust statistical results. Further, the rather low incidence of MBM in the entire cohort (22.7%) has to be kept in mind, when interpreting the data for BMFS with different therapy sequences in the multivariate analysis. Because of much higher patient numbers for 1L-therapy than for second-line therapy, analyses of outcomes with 1L-therapy are suited better to show smaller differences between groups. Lastly, in our cohort, only a small number of patients received adjuvant therapy for stage III and IV disease, which can be explained by the long time period covered. Nowadays, most stage III patients receive adjuvant therapy with ICI or BRAF+MEK TT, which influences selection and effectiveness of first-line treatment in the non-adjuvant setting. This has to be kept in mind, when

interpreting our data and drawing conclusions from it for treatment selection.

Altogether, our analysis of a large real-world cohort of melanoma patients demonstrates a faster and more frequent development of brain metastasis in BRAF*mut* patients treated first-line with BRAF+MEKTT, and prolonged OS in BRAF*mut* patients treated first-line with CTLA-4+PD-1 compared with PD-1 or BRAF+MEK. Moreover, we did not detect improved OS or BMFS in BRAF*wt* patients treated with combined ICI compared with PD-1 alone. These findings underline that survival outcomes have to be assessed separately for BRAF*mut* and BRAF*wt* patients, and that ICI, particularly CTLA-4+PD-1, should be preferably chosen as first-line therapy in BRAF*mut* melanoma patients without MBM.

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Correction: *Brain metastasis and survival outcomes after first-line therapy in metastatic melanoma: a multicenter DeCOG study on 1704 patients from the prospective skin cancer registry ADOREG*

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