Journal for ImmunoTherapy of Cancer

Impact of radiotherapy and sequencing of systemic therapy on survival outcomes in melanoma patients with previously untreated brain metastasis: a multicenter DeCOG study on 450 patients from the prospective skin cancer registry ADOREG

Cindy Franklin ,[1] Peter Mohr,[2] Leonie Bluhm,[2] Imke Grimmelmann,[3] Ralf Gutzmer,[4] Friedegund Meier,[5] Marlene Garzarolli,[5] Michael Weichenthal ,[6] Claudia Pfoehler,[7] Rudolf Herbst,[8] Patrick Terheyden ,[9] Jochen Utikal,[10] Jens Ulrich,[11] Dirk Debus,[12] Sebastian Haferkamp,[13] Martin Kaatz,[14] Andrea Forschner ,[15] Ulrike Leiter,[15] Dorothee Nashan,[16] Alexander Kreuter ,[17] Michael Sachse,[18] Julia Welzel,[19] Lucie Heinzerling,[20] Frank Meiss,[21] Carsten Weishaupt,[22] Thilo Gambichler ,[23] Gerhard Weyandt,[24] Edgar Dippel,[25] Kerstin Schatton,[26] Eren Celik,[27] Maike Trommer ,[27] Iris Helfrich,[28] Alexander Roesch,[28] Lisa Zimmer,[28] Elisabeth Livingstone,[28] Dirk Schadendorf,[28] Susanne Horn,[28,29] Selma Ugurel [28]

To cite: Franklin C, Mohr P, Bluhm L, *et al*. Impact of radiotherapy and sequencing of systemic therapy on survival outcomes in melanoma patients with previously untreated brain metastasis: a multicenter DeCOG study on 450 patients from the prospective skin cancer registry ADOREG. *Journal for ImmunoTherapy of Cancer* 2022;**10**:e004509. doi:10.1136/jitc-2022-004509

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-2022-004509).

Accepted 04 April 2022

For numbered affiliations see end of article.

Correspondence to
Dr Cindy Franklin;
cindy.franklin@uk-koeln.de

ABSTRACT

Background Despite of various therapeutic strategies, treatment of patients with melanoma brain metastasis (MBM) still is a major challenge. This study aimed at investigating the impact of type and sequence of immune checkpoint blockade (ICB) and targeted therapy (TT), radiotherapy, and surgery on the survival outcome of patients with MBM.

Method We assessed data of 450 patients collected within the prospective multicenter real-world skin cancer registry ADOREG who were diagnosed with MBM before start of the first non-adjuvant systemic therapy. Study endpoints were progression-free survival (PFS) and overall survival (OS).

Results Of 450 MBM patients, 175 (38.9%) received CTLA-4+PD-1 ICB, 161 (35.8%) PD-1 ICB, and 114 (25.3%) BRAF+MEKTT as first-line treatment. Additional to systemic therapy, 67.3% of the patients received radiotherapy (stereotactic radiosurgery (SRS); conventional radiotherapy (CRT)) and 24.4% had surgery of MBM. 199 patients (42.2%) received a second-line systemic therapy. Multivariate Cox regression analysis revealed the application of radiotherapy (HR for SRS: 0.213, 95% CI 0.094 to 0.485, p<0.001; HR for CRT: 0.424, 95% CI 0.210 to 0.855, p=0.016), maximal size of brain metastases (HR for MBM >1 cm: 1.977, 95% CI 1.117 to 3.500, p=0.019), age (HR for age >65 years: 1.802, 95% CI 1.016 to 3.197, p=0.044), and ECOG performance status (HR for ECOG ≥2: HR: 2.615, 95% CI 1.024 to 6.676, p=0.044)

KEY MESSAGES

⇒ Despite the advent of new systemic therapies, the prognosis of patients with melanoma brain metastases (MBM) remains poor.

⇒ Data from recent prospective trials showed effectiveness of targeted therapy and immune checkpoint blockade, but these studies did not include concomitant radiotherapy and while they have shown that combined CTLA-4 and PD-1 blockade is superior in MBM patients compared with PD-1 monotherapy, there have been no comparisons between the outcome with targeted therapy with BRAF/MEK inhibitors and immunotherapy and their optimal therapy sequence in MBM patients yet.

⇒ Our study in a large real-world patient cohort with 450 patients reveals stereotactic radiotherapy as an independent factor for better overall survival (OS) in MBM patients.

⇒ When comparing immune checkpoint blockade with combined CTLA-4 and PD-1 blockade, PD-1 monotherapy and targeted therapy with BRAF/MEK inhibitors, the type of first-line therapy did not lead to a difference in OS in the multivariate analysis of our patient cohort.

⇒ Our data show the importance of applying additional radiotherapy to systemic therapy in MBM patients.

as independent prognostic factors of OS on first-line therapy. The type of first-line therapy (ICB vs TT) was not independently prognostic. As second-line therapy BRAF+MEK showed the best survival outcome compared with ICB and other therapies (HR for CTLA-4+PD-1 compared with BRAF+MEK: 13.964, 95% CI 3.6 to 54.4, p<0.001; for PD-1 vs BRAF+MEK: 4.587 95% CI 1.3 to 16.8, p=0.022 for OS). Regarding therapy sequencing, patients treated with ICB as first-line therapy and BRAF+MEK as second-line therapy showed an improved OS (HR for CTLA-4+PD-1 followed by BRAF+MEK: 0.370, 95% CI 0.157 to 0.934, p=0.035; HR for PD-1 followed by BRAF+MEK: 0.290, 95% CI 0.092 to 0.918, p=0.035) compared with patients starting with BRAF+MEK in first-line therapy. There was no significant survival difference when comparing first-line therapy with CTLA-4+PD-1 ICB with PD-1 ICB.

Conclusions In patients with MBM, the addition of radiotherapy resulted in a favorable OS on systemic therapy. In BRAF-mutated MBM patients, ICB as first-line therapy and BRAF+MEK as second-line therapy were associated with a significantly prolonged OS.

BACKGROUND

Historically, due to low intracerebral efficacy of cytotoxic chemotherapies,[1] the treatment of melanoma brain metastases (MBM) was based on surgical excision, stereotactic radiosurgery (SRS), or whole brain radiotherapy (WBRT) being associated with poor survival outcomes of affected patients.[2 3] Recently published results from randomized trials designed for patients with MBM have shown intracranial effectiveness of BRAF+MEK inhibition (BRAF+MEK)[4] and immune checkpoint blockade (ICB), particularly with the combination of CTLA-4+PD-1 inhibitors (CTLA-4+PD-1).[5–7] Nevertheless, there are no results of head-to-head trials yet, comparing the survival of ICB versus BRAF+MEK, and their optimal sequence as first-line and second-line therapies in patients with MBM. Regarding radiotherapy, SRS can effectively treat single MBM but cannot prevent the occurrence of new intracranial lesions. The optimal timing of SRS, before, during, or after systemic therapy is also still a matter of debate. In patients with multiple MBM, conventional WBRT is often applied, despite its high toxicity and its unclear benefit for the patients' survival.

The aim of this study was to assess the outcome of different systemic treatments (ICB, BRAF+MEK) with or without locoregional treatments (SRS, conventional radiotherapy, and surgery) in first-line and second-line therapy of patients with MBM in a prospectively collected multicenter real-world patient cohort.

PATIENTS AND METHODS

Study design

Melanoma patients with MBM who received first-line non-adjuvant systemic treatment with inhibitors of CTLA-4+PD-1 (ipilimumab + nivolumab), PD-1 (nivolumab, pembrolizumab) or BRAF+MEK (dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib) between January 2013 and January 2021 were identified from the prospective multicenter skin cancer registry ADOREG of the German Dermatologic Cooperative Oncology Group. For study inclusion, MBM had to be diagnosed before start of the first non-adjuvant systemic treatment. Data on patient and tumor characteristics, as well as baseline parameters of the first and second non-adjuvant systemic treatment were collected. The number and maximal size of MBM, the presence of symptoms from MBM, and the intake and dose of dexamethasone for symptomatic MBM were additionally collected. For patients with radiotherapy of MBM, the type (SRS or conventional), and the timing (before or after start of systemic therapy) were determined. Since we could not distinguish between WBRT and postoperative radiotherapy of the tumor cavity, we assessed the effect of conventional radiotherapies (CRT) in general in this study. Best response as assessed by the investigators was categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to RECIST V.1.1.[8–10] Best overall response (BOR), best extracranial response (BER), and best intracranial (BIR) response to treatment were assessed retrospectively by the investigators. Study endpoints were progression-free survival (PFS) and overall survival (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 PFS and OS. The following parameters were included into the univariate and multivariate analyses: sex, age, type of therapy, BRAF mutation status, ECOG performance status (ECOG-PS), serum LDH, number and maximal size of MBM, dexamethasone intake, application and type of radiotherapy for MBM (SRS and CRT), and surgery of MBM. OS was defined as time from start of systemic therapy until death or last patient contact (censored OS); PFS as time from start of systemic therapy until disease progression or last patient contact (censored PFS). Kaplan-Meier estimates were used for PFS and OS calculation; differences between groups were assessed by two-sided log-rank test. 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 and treatment response

Data freeze was February 1st, 2021. From 458 patients identified, 450 met the study inclusion criteria. These 450 patients had a median follow-up time of 33.4 (range: 0–93.3) months after start of the first systemic therapy. One hundred and ninety-nine patients (44.2 %) received a second-line therapy. A detailed study flow is provided in figure 1. Of 450 patients eligible for analysis, 63.3% (n=285) were male and 54.9% (n=274) were ≤65 years old. An activating BRAF V600E/K mutation was detected in 48.7% (n=219). For detailed patient characteristics, see table 1. The median time from first diagnosis of

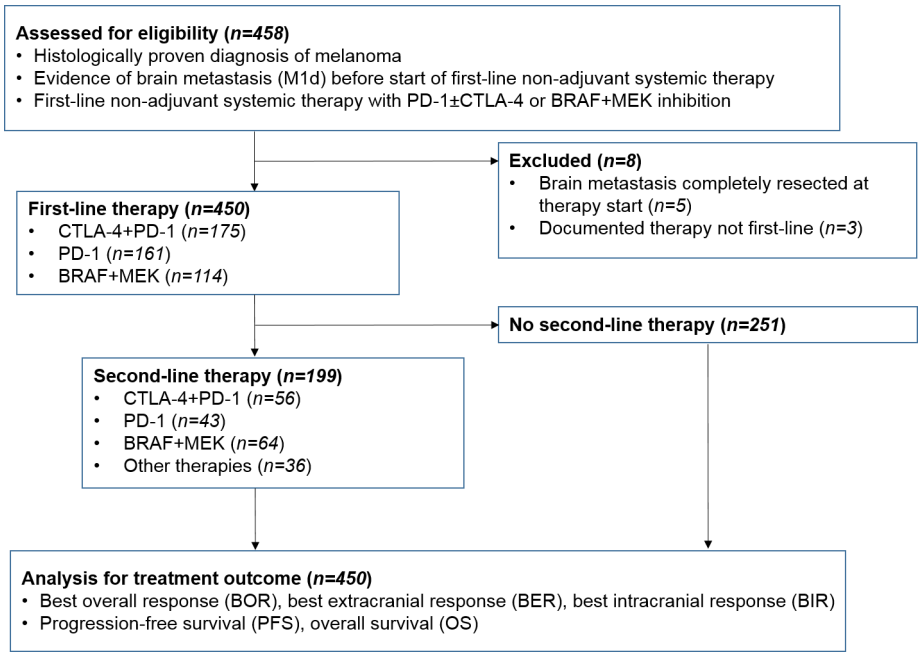

Figure 1 Study flow. Four hundred and fifty-eight patients from 35 skin cancer centers were identified in the prospective multicenter ADOREG registry. Of these, 450 patients were eligible for analysis.

melanoma until first diagnosis of brain metastasis was 20 (range: 0–391) months; the median time from first diagnosis of brain metastasis until start of first systemic therapy was 35 (range: 1–8594) days.

For first-line non-adjuvant therapy, 175 (38.9%) patients received CTLA-4+PD-1 ICB, 161 (35.8%) received PD-1 ICB, and 114 (25.3%) were treated with BRAF+MEK (dabrafenib + trametinib: 82 patients; vemurafenib + cobimetinib: 19 patients; encorafenib + binimetinib: 13 patients). The baseline characteristics for BRAF-mutated patients were comparable with those of the overall cohort (online supplemental table S1). Sixty-three (28.8%) of BRAF-mutated patients received a first-line therapy with CTLA-4+PD-1, 42 (19.2%) PD-1 and 114 (52.1%) BRAF+MEK. One hundred and ninety-nine patients (44.2%) of the total cohort received a second-line therapy that consisted of CTLA-4+PD-1 in 56 (28.1%), PD-1 in 43 (21.6%), BRAF+MEK in 64 (32.2%), and other therapy types including chemotherapy in 36 (18.1%) patients (for details, see online supplemental table S2). The median duration of first-line systemic therapy was 3.2 (range: 0–70.9) months and of second-line systemic therapy 2.4 (range: 0–39.4) months.

At baseline of first systemic therapy, 18% (n=81) of patients had only MBM, in 48.4% (n=218) one to two extracranial organs, and in 33.6% (n=151) three or more extracranial organs were additionally affected. A percentage of 25.3% (n=114) of patients had a solitary brain metastasis, 24.7% (n=111) had oligometastatic disease with 2–4 MBM, and 34.9% (n=157) had multiple (≥5) MBM. In 15.1% (n=68) of patients, the number of MBM was unknown. A percentage of 26.2% (n=118) of patients had symptomatic MBM, 64.7% (n=291) were asymptomatic, and in 9.1% (n=41) this information was missing. Ninety-five (21.1%) patients received dexamethasone at therapy start, 126 (28%) during the first 3 months of systemic therapy, and 89 (19.8%) patients after the first 3 months of systemic therapy. The median dose of dexamethasone at therapy start was 5.5 (range: 0.5–32) mg, and the median maximal dose within the first 3 months was 8 (range: 0.5–32) mg.

BOR of all first-line therapies was 9.3% (n=42) CR, 26.7% (n=120) PR, 13.8% (n=62) SD, 42.0% (n=189) PD, and 8% (n=36) unknown (table 1). Intracranial and extracranial objective response rates were similar, with 30% (n=135) of patients showing PD as BIR compared with 23.6% (n=106) as BER. BOR was 30.6% (n=54) for CTLA-4+PD-1, 38.5% (n=62) for PD-1, and 40.4% (n=46) for BRAF+MEK. A percentage of 52.9% (n=238) of patients stopped first-line therapy due to disease progression, and 18% (n=81) because of side effects. Discontinuation rates due to toxicity were 30.9% (n=54) for CTLA-4+PD-1, 11.8% (n=19) for PD-1, and 6.7% (n=7) for BRAF+MEK.

With regard to radiotherapy, 30.4% (n=137) of patients received SRS, 30.0% (n=135) CRT, 6.9% SRS and CRT (n=31), and 32.7% (n=147) no radiotherapy (online supplemental table S3). Sixty-eight (15.1%) patients received SRS during first-line systemic therapy, and 37 (8.2%) within 1 month before therapy start. Forty-one (9.1%) patients received CRT during first-line systemic therapy and 52 (11.6%) within 1 month before therapy start. The median total dose was 25.3± (range: 7–58) gray for SRS and 34.6 (range: 6–60) gray for CRT. Surgical resection of MBM was performed in 110 patients (24.4%). Eigty-five of those had MBM surgery with consecutive radiotherapy, and 25 had surgery only; one patient received five consecutive surgical resections of MBM.

Table 1 First-line treatment of patients with melanoma brain metastasis: baseline characteristics and therapy outcome

	All patients n=450 (100%)	CTLA-4+PD-1 n=175 (100%)	PD-1 n=161 (100%)	BRAF+MEK n=114 (100%)
Age				
≤65 years	274 (54.9)	102 (58.3)	73 (45.3)	72 (63.2)
>65 years	203 (45.1)	73 (41.7)	88 (54.7)	42 (36.8)
Gender				
Male	285 (63.3)	109 (62.3)	96 (59.6)	80 (70.2)
Female	165 (36.7)	66 (37.7)	65 (40.4)	34 (29.8)
Site of primary				
Cutaneous	357 (79.3)	139 (79.4)	127 (78.9)	91 (79.8)
Mucosal	5 (1.1)	2 (1.1)	3 (1.9)	0 (0.0)
Uveal	4 (0.9)	1 (0.6)	3 (1.9)	0 (0.0)
Unspecified or unknown	84 (18.6)	33 (18.9)	28 (17.4)	23 (20.2)
BRAF status				
V600 wildtype	191 (42.4)	85 (48.6)	106 (65.8)	0 (0.0)
V600E/K mutation	219 (48.7)	63 (36.0)	42 (26.1)	114 (100.0)
Unknown	40 (8.9)	27 (15.4)	1 (8.1)	0 (0.0)
Previous adjuvant therapy stage III				
Yes	78 (17.3)	30 (17.1)	32 (19.9)	16 (14.0)
No	372 (82.7)	145 (82.9)	129 (80.1)	98 (86.0)
Previous adjuvant therapy stage IV				
Yes	20 (4.4)	6 (3.4)	8 (5.0)	6 (5.3)
No	430 (95.6)	169 (96.6)	153 (95.0)	108 (94.7)
ECOG performance status				
0	164 (36.4)	83 (47.4)	51 (31.7)	30 (26.3)
1	84 (18.7)	26 (14.9)	38 (23.6)	20 (17.5)
≥2	30 (6.7)	8 (4.6)	9 (5.6)	13 (11.4)
Unknown	172 (38.2)	58 (33.1)	63 (39.1)	51 (44.7)
Serum LDH				
Normal (≤ULN)	146 (32.4)	57 (32.6)	62 (38.5)	27 (23.7)
Elevated (>ULN)	199 (44.2)	73 (41.7)	72 (44.7)	54 (47.4)
>10× ULN	43 (9.6)	17 (9.7)	12 (7.5)	14 (12.3)
Unknown	105 (23.3)	45 (25.7)	27 (16.8)	33 (28.9)
Extracranial affected organ sites				
0	81 (18.0)	31 (17.7)	32 (19.9)	18 (15.8)
1–2	218 (48.4)	89 (50.9)	77 (47.8)	52 (45.6)
≥3	151 (33.6)	55 (31.4)	52 (32.3)	44 (38.6)
Number of brain metastases				
1	114 (25.3)	47 (26.9)	40 (24.8)	27 (23.7)
2–4	111 (24.7)	42 (24.0)	41 (25.5)	28 (24.6)
≥5	157 (34.9)	56 (32.0)	61 (37.9)	40 (35.1)
Unknown	68 (15.1)	30 (17.1)	19 (11.8)	19 (16.7)
Maximal size of brain metastases				
≤1 cm	127 (28.2)	51 (29.1)	46 (28.6)	30 (26.3)
>1 cm	136 (30.2)	47 (26.9)	47 (29.2)	42 (36.8)
Unknown	187 (41.6)	77 (44.0)	68 (42.2)	42 (36.8)
Maximal size of brain metastases				
No	291 (64.7)	118 (67.4)	106 (65.8)	67 (58.8)
Yes	118 (26.2)	42 (24.0)	37 (23.0)	39 (34.2)
Unknown	41 (9.1)	15 (8.6)	18 (11.2)	8 (7.0)
Dexamethasone intake at therapy start				

Continued

Table 1 Continued

	All patients n=450 (100%)	CTLA-4+PD-1 n=175 (100%)	PD-1 n=161 (100%)	BRAF+MEK n=114 (100%)
No	314 (69.8)	127 (72.6)	114 (70.8)	73 (64.0)
Yes	95 (21.1)	35 (20.0)	28 (17.4)	32 (28.1)
Unknown	41 (9.1)	13 (7.4)	19 (11.8)	9 (7.9)
Radiotherapy of brain metastases				
None	147 (32.7)	61 (34.9)	47 (29.2)	39 (34.2)
Stereotactic	137 (30.4)	46 (26.3)	52 (32.2)	39 (34.2)
Conventional	135 (30.0)	56 (32.0)	50 (31.1)	29 (25.4)
Stereotactic and conventional	31 (6.9)	12 (6.9)	12 (7.5)	7 (6.1)
Surgery of brain metastases				
No	340 (75.6)	134 (76.6)	122 (75.8)	84 (73.7)
Yes	110 (24.4)	41 (23.4)	39 (24.2)	30 (26.3)
Best overall response				
CR	42 (9.3)	12 (6.9)	24 (14.9)	6 (5.3)
PR	120 (26.7)	42 (24.0)	38 (23.6)	40 (35.1)
SD	62 (13.8)	20 (11.4)	23 (14.3)	19 (16.7)
PD	189 (42.0)	82 (46.9)	66 (41.0)	41 (36.0)
Unknown	36 (8.0)	19 (10.9)	10 (6.2)	8 (7.0)
Best extracranial response				
NED	35 (7.8)	12 (6.9)	15 (9.3)	8 (7.0)
CR	51 (11.3)	14 (8.0)	25 (15.5)	12 (10.5)
PR	105 (23.3)	37 (21.1)	33 (20.5)	35 (30.7)
SD	75 (16.7)	28 (16.0)	20 (12.4)	27 (23.7)
PD	106 (23.6)	47 (26.9)	39 (24.2)	20 (17.5)
Unknown	78 (18.3)	37 (21.1)	29 (18.0)	12 (10.5)
Best intracranial response				
CR	70 (15.6)	24 (13.8)	35 (22.7)	11 (9.7)
PR	104 (23.1)	35 (20.0)	31 (19.3)	38 (33.3)
SD	60 (13.3)	24 (13.7)	17 (10.6)	19 (16.7)
PD	135 (30.0)	58 (33.1)	46 (28.6)	31 (27.2)
Unknown	81 (18.0)	34 (19.4)	32 (19.9)	15 (13.2)
Therapy end reason				
Planned stop	7 (1.6)	1 (0.6)	6 (3.7)	0 (0.0)
Toxicity	81 (18.0)	54 (30.9)	19 (11.8)	7 (6.1)
Disease progression	238 (52.9)	69 (39.4)	86 (53.4)	85 (74.6)
Patient wish	16 (3.6)	3 (1.7)	9 (5.6)	5 (4.4)
Other	36 (8.0)	12 (6.9)	17 (10.6)	6 (5.3)
Ongoing	65 (14.4)	33 (18.9)	20 (12.4)	11 (9.6)
Lost to follow-up	7 (1.5)	3 (1.7)	4 (2.5)	0 (0.0)
Progression				
No	120 (26.7)	63 (36.0)	40 (24.8)	17 (14.9)
Yes	330 (73.3)	112 (64.0)	121 (75.2)	97 (85.1)
Death				
No	236 (52.4)	112 (64.0)	82 (50.9)	42 (36.8)
Yes	214 (47.6)	63 (36.0)	79 (49.1)	72 (63.0)
Progression-free survival				
Median in months (95% CI)	4.7 (3.9 to 5.6)	3.9 (2.3 to 5.5)	5.4 (2.0 to 8.8)	5.0 (4.3 to 5.8)
Overall survival				
Median in months (95% CI)	21.5 (16.9 to 26.0)	Not reached	26.6 (12.0 to 40.5)	16.5 (8.9 to 24.1)

CR, complete response; LDH, lactate dehydrogenase; NED, no evidence of disease; PD, progressive disease; PR, partial response; SD, stable disease; ULN, upper level of norm.

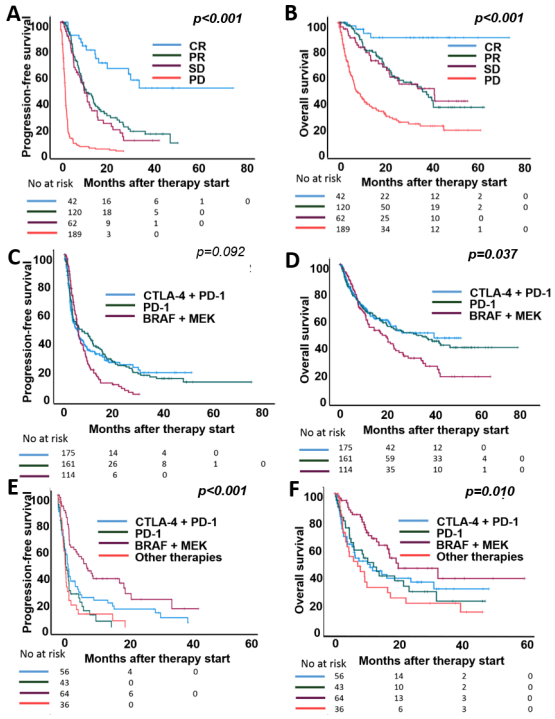

Figure 2 Kaplan-Meier curves showing progression-free and overall survival for first-line and second-line systemic therapy in melanoma patients with brain metastases. (A and B) Best overall response to first-line therapy (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease); (C and D) type of first-line therapy; (E and F) type of second-line therapy. The log-rank test was used to compare between groups; p<0.05 was considered significant. The p value states that there is a difference between the groups calculated by the log-rank test.

Survival on first-line systemic therapy in patients with MBM

At database closure, 330 of the total 450 patients (73.3%) had progressed on first-line therapy, and 236 patients (52.4%) had died. The median PFS was 4.7 (range: 0.0–74.8) months, and the median OS was 21.5 (range: 0.0–74.8) months. PFS and OS were strongly correlated with BOR (figure 2A,B), being best for patients who achieved a CR. Similar correlations were found for BIR and BER, with higher median OS times for BER than for BIR. Median PFS was 3.9 months for CTLA-4+PD-1, 5.4 months for PD-1, and 5.0 months for BRAF+MEK; median OS was not reached for CTLA-4+PD-1, 26.6 months for PD-1, and 16.5 months for BRAF+MEK (table 1; figure 2C,D). Patients with symptomatic MBM showed a decreased median OS (CTLA-4+PD-1: 11.7 months, PD-1: 8.6 months, BRAF+MEK inhibition: 14.3 months) compared with patients with asymptomatic MBM (CTLA-4+PD-1: not reached, PD-1: 36.9 months, BRAF+MEK inhibition: 20.1 months) with an objective intracranial response rate of 36.4% for symptomatic and 44% for asymptomatic patients. Additional survival rates of selected patient groups at 6, 12, and 24 months can be found in table 2. Survival outcomes were similar when BRAF-mutated patients were assessed separately (online supplemental figure S1).

In the univariate Cox regression analysis of survival on first-line systemic therapy, we found the following significant prognostic factors for OS: number of MBM, maximum size of MBM, ECOG-PS, serum LDH, symptoms of MBM, dexamethasone intake, dexamethasone dose, number of affected extracranial organs, presence and type of radiotherapy, surgery of MBM, type of systemic therapy, and type of second-line systemic therapy. For PFS, we found these significant prognostic factors: ECOG-PS, serum LDH, presence of symptomatic MBM, dexamethasone intake, number of affected extracranial organs, radiotherapy, timing of SRS, type of systemic first-line therapy, and type of second-line therapy. For details of the univariate analyses, see online supplemental table S4, figures 2A–F and 3A–F, and online supplemental figure S2A-F and figure S3A-F.

After adjusting for confounders using the multivariate Cox regression analysis, we found radiotherapy (HR 0.213 for SRS vs none, p<0.001; HR 0.424 for CRT versus none, p=0.016), maximal size of MBM (HR 1.977 for size >1 cm, p=0.019), age (HR 1.8 for age >65 years, p=0.044) and ECOG-PS (HR 2.615 for ECOG-PS ≥2, p=0.044) as independent prognostic factors for OS on first-line therapy in patients with MBM (table 3). We did not detect any independent prognostic factors for PFS.

Radiotherapy and surgical resection of MBM

With regard to radiotherapy, patients who received additional SRS showed a significantly improved median OS (36.4 months) on first-line systemic therapy compared with patients without any radiotherapy of MBM (19.5 months) or to patients who received CRT (16.9 months) (figure 3A,B). While the median OS on CTLA-4+PD-1 was not reached in patients treated with SRS and with no radiotherapy, it was 20.2 (range: 0.5–46.0) months with CRT. In patients treated with PD-1, additional SRS led to a median OS of 38.7 (range: 1.1–75.1) months, whereas CRT revealed 15.1 (range: 0.0–55.5) and no radiotherapy 19.8 (range: 0.0–54.9) months. Patients treated with BRAF+MEK inhibition showed median OS of 24.7 (range: 2.3–63.2) months with SRS, 17.0 (range: 0.7–58.2) months with CRT, and 8.3 (range: 0.0–41.5) months without radiotherapy. Median PFS with SRS was 5.7 months for patients treated with CTLA-4+PD-1 and 5.5 months for patients treated with PD-1 or BRAF+MEK inhibition.

The presence and type of radiotherapy of MBM were detected as the strongest independent prognostic parameters in the multivariate Cox proportional hazard model (table 3). Regarding the timing of radiotherapy, patients who received SRS during systemic treatment showed a significantly favorable PFS, but not OS, compared with patients receiving SRS within 1 month before systemic therapy (median PFS 5.5 vs 2.9 months, p=0.028, figure 3E,F). This difference was significant in the ICB cohort only (ICB: median PFS 8.8 (SRS during) vs 2.8 months (SRS before); BRAF+MEK inhibition: median PFS 4.5 (SRS during) versus 6.8 (SRS before) months.

Table 2 Selected overall survival (OS) rates in patients with melanoma brain metastasis

	6 months OS rate (deceased; at risk)	12 months OS rate (deceased; at risk)	24 months OS rate (deceased; at risk)	Median OS (months)	P value (log-rank test)
Total patient cohort (n=450 pts)	76.0% (92; 292)	57.9% (150; 206)	37.0%(191; 112)		
First-line systemic therapy					
CTLA-4+PD-1 (n=175)	74.3% (35; 101)	57.5% (51; 69)	33.7% (61; 31)	nr	p=0.037
PD-1 (n=161)	75.9% (35; 110)	61.9% (53; 86)	44.3% (68; 54)	26.6	
BRAF+MEK (n=114)	78.6% (22; 81)	52.6% (46; 51)	29.2% (62; 27)	16.5	
Symptomatic brain metastases					
No (n=291)	80.5% (48; 198)	62.7% (84; 141)	43.1% (107; 81)	30.8	p<0.001
Yes (n=118)	65.1% (37; 69)	45.0% (55; 45)	22.7% (68; 20)	11.5	
Radiotherapy of brain metastases					
None (n=147)	65.5% (40; 76)	45.5% (55; 46)	25.6% (61; 21)	19.5	p<0.001
Stereotactic (n=137)	89.0% (13; 105)	73.0% (30; 82)	52.1% (45; 49)	36.4	
Conventional (n=135)	69.7% (36; 83)	51.3% (55; 58)	33.3% (68; 34)	17.0	
Surgery of brain metastases					
No (n=340)	72.0% (80; 206)	54.7% (119; 144)	33.6% (150; 76)	20.1	p=0.031
Yes (n=110)	87.8% (12; 86)	66.3% (31; 62)	46.8% (41; 36)	36.4	
Second-line systemic therapy					
CTLA-4+PD-1 (n=56)	58.8% (21; 30)	39.1% (28; 18)	27.3% (31; 13)	10.4	p=0.010
PD-1 (n=43)	59.5% (15; 22)	41.2% (19; 15)	21.8% (25; 7)	10.5	
BRAF+MEK (n=64)	84.5% (9; 49)	63.3% (18; 31)	26.5% (25; 9)	19.7	
Others (n=36)	48.3% (15; 14)	28.6% (20; 8)	17.9% (23; 5)	7.3	

P values from log-rank test comparing the median OS values; p<0.05 was considered significant.
NR, not reached.

The number of SRS (one vs multiple), or whether SRS was applied as single exposure or fractionated did not show a relevant survival difference.

Regarding surgery of MBM, the excision of brain metastases was significantly associated with a favorable OS but not PFS as compared with patients with no surgery (median 36.4 vs 20.1 months, p=0.031, figure 3C,D).

Survival on second-line systemic therapy in patients with MBM

Next, we compared the baseline characteristics of patients who died after first-line therapy to those who received a second-line therapy. Patients who received second-line therapy were significantly younger, had a better ECOG-PS, less often elevated serum LDH, less symptomatic MBM, and fewer and smaller MBM (for details, see table 4). A larger fraction of patients who received second-line therapy also received radiotherapy (SRS 38.7% vs 15.2%). Interestingly, patients who died after first-line therapy had been more often treated with PD-1 and less often with BRAF+MEK (41.9% vs 24.8%) compared with patients who received a second-line therapy (29.1% vs 36.2%).

For second-line therapy in patients with MBM, we detected the following significant factors for OS using an univariate Cox regression analysis (online supplemental table S5): ECOG-PS, presence of symptomatic MBM, intake of dexamethasone within first 3 months of second therapy, dexamethasone dose at start of second systemic therapy and therapy with BRAF+MEK as second-line therapy compared with all other therapy regimens. ECOG-PS, presence of symptomatic MBM, dexamethasone within the first 3 months of systemic therapy and BRAF+MEK as second-line therapy were also significant parameters for PFS.

We then performed a multivariate Cox regression analysis (online supplemental table S6) of survival on second-line therapy, which showed an ECOG-PS of 0 at therapy start and treatment with BRAF+MEK as independent prognostic factors for longer OS. The same parameters were also independently prognostic of PFS on second-line therapy.

One hundred and thirty-seven of 219 (62.6%) patients with an activating BRAF mutation and 59 of 191 (30.9%) BRAF wildtype patients received a second-line therapy. Presuming that the therapy sequence influences OS, we performed univariate and multivariate Cox regression analyses for all possible therapy sequences in the entire patient cohort. When referred to BRAF+MEK as first-line therapy without subsequent therapies, the following

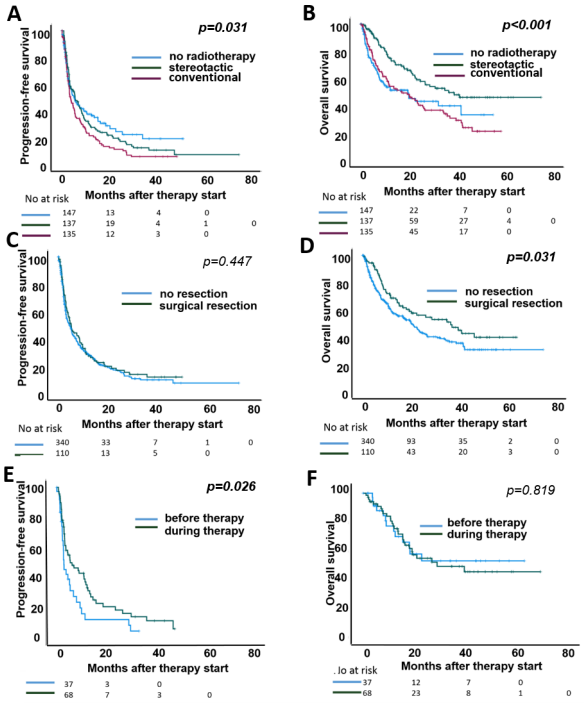

Figure 3 Kaplan-Meier curves showing progression-free and overall survival on first-line systemic therapy in melanoma patients with brain metastases with or without additional radiotherapy or surgical resection. (A and B) radiotherapy (RT) in addition to systemic therapy; (C and D) surgical resection of brain metastases in addition to systemic therapy; (E and F) timing of stereotactic radiotherapy in addition to systemic therapy (before: RT within 1 month before start of systemic therapy; during: RT while systemic therapy ongoing). The log-rank test was used to calculate differences between groups; p<0.05 was considered significant. The p value states that there is a difference between the groups calculated by the log-rank test.

sequences were favorable in the univariate analysis: CTLA-4+PD-1 followed by no further therapy (HR 0.578, p=0.034) or followed by BRAF+MEK (HR 0.322, p=0.001), and PD-1 followed by no therapy (0.519, p=0.009), by CTLA-4+PD-1 (HR 0.316, p=0.002) or BRAF+MEKhour 0.407, p=0.027). In the multivariate analysis (online supplemental table S7), including age, gender, ECOG-PS, LDH, radiotherapy and therapy sequence, an ECOG-PS of 0 (HR 1.536, p=0.039 for ECOG ≥1), SRS (HR 0.474, p=0.008 compared with no radiotherapy) and CTLA-4+PD-1 or PD-1 both followed by BRAF+MEK (HR 0.370, p=0.035; HR 0.290, p=0.035 respectively), as well as PD-1 followed by CTLA-4+PD-1 (0.333, p=0.046) were independent prognostic parameters for increased OS.

DISCUSSION

The results of our present study reveal an impact of additional radiotherapy, maximal size of brain metastases, age and performance score on the outcome of systemic treatment of MBM. Interestingly, the favorable survival effect of radiotherapy is detectable for SRS as well as for CRT. Our data underline a particular importance of SRS additional to systemic treatment in patients with MBM, with no regard to the type of systemic treatment. Patients with SRS showed longer median survival and SRS was confirmed as independent prognostic factor for OS in our multivariate analysis. An improved survival on SRS had also been detected in the univariate analysis of a recent study by Amaral *et al*[11] in MBM patients treated with CTLA-4+PD-1, but type of treatment and addition of radiotherapy were not included in that study's multivariate analysis to adjust for confounders. Notably, the number of MBM in our cohort did not show an independent prognostically relevant effect (when comparing 1, 2–4 and ≥5 metastases), which might be explained by the fact that SRS is nowadays applied in patients with up to 10–15 brain metastases and not restricted to patients with ≤5 MBM anymore. This finding is in line with a study by Rauschenberg *et al*[12] that included type of radiotherapy and number of brain metastasis in the multivariate analysis with only type of radiotherapy, but not the number of brain metastasis (when comparing 1, 2–3 and >3) being an independently prognostic factor.

Whether SRS before or after initiation of systemic therapy is more beneficial is still unclear though. SRS can eradicate inhibitory T cells in the tumor microenvironment that otherwise dampen the immune response.[13 14] Most studies dealing with this question focused on CTLA-4 monotherapy and assessed intracranial response rate or time to cerebral progression. Several smaller studies and meta-analyses showed improved OS of patients treated with ICB and concomitant (±1 month before or after therapy start) SRS when compared with ICB and non-concomitant SRS.[15–17] In our overall cohort, when focusing only on patients who received SRS up to 1 month before or after first-line systemic therapy, we detected a significantly higher median PFS, but not OS, for patients who received SRS during systemic therapy compared with those who received SRS up to 1 month before. This difference could only be detected in patients treated with ICB as first-line treatment.

Although SRS has been restricted to lesions ≤3 cm diameter in the past, a fractionated SRS approach allows treatment of bigger and critically located metastases now.[18 19] SRS has largely replaced surgery and postsurgical conventional radiation, but the optimal timing of SRS is still a matter of debate.[20 21] Compared with surgery and postsurgical radiation, SRS has many advantages, in particular reduction of intraoperative seeding of viable tumor cells, but does not allow histopathological analysis of the metastasis.[22 23] Since locoregional control is as good if more than five metastases are treated by SRS compared with fewer,[24] more and more centers are currently treating up to 15 MBM with SRS.[25] Nevertheless, the occurrence of new distant intracranial metastases cannot be reduced by this way; therefore, hippocampal-avoidant conventional WBRT is often performed. Several randomized controlled trials showed no improved OS but reduced intracranial relapse rates with WBRT.[26–28] Reduction of intracranial relapse can improve the

Table 3 Multivariate Cox regression analysis for progression-free survival (PFS) and overall survival (OS) on first-line systemic therapy in melanoma patients with brain metastasis

Parameters included	PFS HR (95% CI) P value	OS HR (95% CI) P value
Gender (reference: male)		
Male versus female	0.993 (0.627 to 1.572) 0.975	0.978 (0.554 to 1.724) 0.938
Age (reference: ≤65 years)		
≤65 versus >65 years	0.945 (0.569 to 1.569) 0.828	**1.802 (1.016 to 3.197) 0.044**
BRAF status (reference: wildtype)		
Wildtype versus BRAFV600E/K	0.756 (0.420 to 1.360) 0.350	0.839 (0.406 to 1.734) 0.636
ECOG-PS (reference: 0)		
0 versus 1	0.899 (0.518 to 1.563) 0.707	1.404 (0.753 to 2.617) 0.286
0 versus ≥2	1.446 (0.594 to 3.521) 0.416	**2.615 (1.024 to 6.676) 0.044**
Serum LDH (reference: normal)		
Normal versus elevated	1.415 (0.863 to 2.321) 0.168	1.291 (0.711 to 2.342) 0.401
Number of brain metastases (reference: 1)		
1 versus 2–4	1.361 (0.738 to 2.509) 0.324	1.208 (0.557 to 2.620) 0.633
1 versus ≥5	1.000 (0.559 to 1.786) 0.999	0.940 (0.445 to 1.983) 0.870
Maximal size of brain metastases (reference: ≤1 cm)		
≤1 cm versus >1 cm	0.837 (0.531 to 1.319) 0.443	**1.977 (1.117 to 3.500) 0.019**
Dexamethasone intake at therapy start (reference: no)		
No versus yes	0.903 (0.470 to 1.737) 0.760	1.159 (0.547 to 2.457) 0.700
Number of affected extracranial organ sites (reference: 0)		
0 versus 1–2	0.968 (0.509 to 1.837) 0.920	0.834 (0.385 to 1.844) 0.669
0 versus ≥3	0.944 (0.487 to 1.837) 0.865	0.839 (0.406 to 1.734) 0.636
Radiotherapy (reference: none)		
None versus stereotactic	0.647 (0.334 to 1.251) 0.195	**0.213 (0.094 to 0.485)<0.001**
None versus conventional	1.033 (0.551 to 1.936) 0.920	**0.424 (0.210 to 0.855) 0.016**
Surgery of brain metastases (reference: no)		
No versus yes	0.794 (0.429 to 1.471) 0.463	2.117 (0.947 to 4.731) 0.068
Type of systemic therapy (reference: BRAF+MEK besides*)		
BRAF+MEK versus CTLA-4+PD-1	1.259 (0.606 to 2.615) 0.537	0.995 (0.433 to 2.290) 0.991
BRAF+MEK versus PD-1	1.290 (0.587 to 2.831) 0.526	0.536 (0.221 to 1.300) 0.168
CTLA-4+PD-1 versus PD-1*	1.024 (0.607 to 1.728) 0.928	0.538 (0.273 to 1.063) 0.074

P<0.05 was considered significant. Significant values in bold letters.
*Reference: CTLA-4+PD-1.

patients' health-related quality of life, while the side effects of WBRT can impair it. Therefore, the necessity of WBRT, especially in asymptomatic patients, has been highly debated. In our study, CRT showed a positive effect on OS in the multivariate analysis, which included also the size and number of MBM. It has to be kept in mind that in the CRT group we could not differentiate between WBRT and postoperative CRT of the tumor cavity. Nevertheless, we clearly distinguished between SRS and conventional radiotherapy and only included patients who received conventional radiotherapy in the CRT cohort. Since metastasectomy is usually followed by postoperative radiotherapy of the tumor cavity (in our study in 77.3%), but metastasectomy itself did not have a favorable effect on survival in the multivariate analysis, it is not likely that this beneficial effect can be attributed to postoperative radiotherapy of the tumor cavity. Although these data are preliminary, they suggest that there might be a survival benefit for patients with CRT additional to systemic therapy compared with systemic therapy alone, which may be explained by increased immunogenic cell death induced by radiotherapy.[29–32] Therefore, the indication for CRT has to be carefully discussed individually with every patient.

Toward safety of SRS combined with ICB, four patients of our cohort reported with radionecrosis. There is controversial data about the increased risk of adverse radiation effects such as radionecrosis in patients treated concomitantly with ICB and SRS[33–35] including a meta-analysis of the literature (mainly MBM patients), indicating that the

Table 4 Baseline and therapy characteristics of patients who received second-line therapy compared with patients who died before second-line therapy

	All patients n=450 (100%)	Patients who received second-line therapy n=199 (100%)	Patients who died before second-line therapy n=105 (100%)
Age			
≤65 years	274 (54.9)	131 (65.8)	49 (46.7)
>65 years	203 (45.1)	68 (34.2)	56 (53.3)
Gender			
Male	285 (63.3)	122 (61.3)	65 (61.9)
Female	165 (36.7)	77 (38.7)	40 (38.1)
Site of primary			
Cutaneous	357 (79.3)	162 (81.4)	84 (80.0)
Mucosal	5 (1.1)	1 (0.5)	2 (1.9)
Uveal	4 (0.9)	2 (1.0)	1 (1.0)
Unspecified or unknown	84 (18.6)	34 (17.1)	18 (17.1)
BRAF status			
V600 wildtype	193 (42.9)	59 (29.6)	57 (54.3)
V600E/K mutation	217 (48.2)	137 (68.8)	36 (34.3)
Unknown	40 (8.9)	3 (1.5)	12 (11.4)
Previous adjuvant therapy in stage III			
Yes	78 (17.3)	41 (20.6)	15 (14.3)
No	372 (82.7)	158 (79.4)	90 (85.7)
Previous adjuvant therapy in stage IV			
Yes	20 (4.4)	9 (4.5)	5 (4.8)
No	430 (95.6)	190 (95.5)	100 (95.2)
ECOG performance status			
0	164 (36.4)	77 (38.7)	30 (28.6)
1	84 (18.7)	29 (14.6)	27 (25.7)
≥2	30 (6.7)	15 (7.5)	11 (10.5)
Unknown	172 (38.2)	78 (39.2)	37 (35.2)
Serum LDH			
Normal (≤ULN)	146 (32.4)	70 (35.2)	28 (26.7)
Elevated (>ULN)	199 (44.2)	78 (39.2)	64 (61.0)
>10× ULN	43 (9.6)	19 (9.5)	24 (9.6)
Unknown	105 (23.3)	51 (25.6)	13 (12.4)
Extracranial affected organ sites			
0	81 (18.0)	30 (15.1)	23 (21.9)
1–2	218 (48.4)	104 (52.3)	42 (40.0)
≥3	151 (33.6)	65 (32.7)	40 (38.1)
Number of brain metastases			
1	114 (25.3)	63 (31.7)	17 (16.2)
2–4	111 (24.7)	47 (23.6)	32 (30.5)
≥5	157 (34.9)	56 (28.1)	44 (41.9)
Unknown	68 (15.1)	33 (16.6)	12 (11.4)
Maximal size of brain metastases			
≤1 cm	127 (28.2)	62 (31.2)	21 (20.0)
>1 cm	136 (30.2)	55 (27.6)	40 (38.1)
Unknown	187 (41.6)	82 (41.2)	44 (41.9)
Symptomatic brain metastases			
No	291 (64.7)	140 (70.4)	52 (49.5)
Yes	118 (26.2)	43 (21.6)	45 (42.9)
Unknown	41 (9.1)	16 (8.0)	8 (7.6)
Radiotherapy of brain metastases			

Continued

Table 4 Continued

	All patients n=450 (100%)	Patients who received second-line therapy n=199 (100%)	Patients who died before second-line therapy n=105 (100%)
None	147 (32.7)	34 (17.1)	46 (43.8)
Stereotactic	137 (30.4)	77 (38.7)	16 (15.2)
Conventional	135 (30.0)	68 (34.2)	36 (34.3)
Stereotactic and conventional	31 (6.9)	20 (10.1)	7 (6.7)
Surgery of brain metastases			
No	340 (75.6)	141 (70.9)	84 (80.0)
Yes	110 (24.4)	58 (29.1)	21 (20.0)
Type of first-line systemic therapy			
CTLA-4+PD-1	175 (38.9)	69 (34.7)	35 (33.3)
PD-1	161 (35.8)	58 (29.1)	44 (41.9)
BRAF+MEK	114 (25.3)	72 (36.2)	26 (24.8)
Best overall response			
CR	42 (9.3)	7 (3.5)	3 (2.9)
PR	120 (26.7)	59 (29.6)	11 (10.5)
SD	62 (13.8)	28 (14.1)	19 (12.4)
PD	189 (42.0)	97 (48.7)	63 (65.7)
Unknown	36 (8.0)	8 (4.0)	9 (8.6)
Best extracranial response			
NED	35 (7.8)	11 (5.5)	12 (11.4)
CR	51 (11.3)	14 (7.0)	3 (2.9)
PR	105 (23.3)	60 (30.2)	8 (7.6)
SD	75 (16.7)	40 (20.1)	16 (15.2)
PD	106 (23.6)	49 (24.6)	44 (41.9)
Unknown	78 (18.3)	25 (12.6)	22 (21.0)
Best intracranial response			
CR	70 (15.6)	17 (8.5)	10 (9.6)
PR	104 (23.1)	51 (25.6)	12 (11.4)
SD	60 (13.3)	32 (16.1)	11 (10.5)
PD	135 (30.0)	75 (37.7)	44 (41.9)
Unknown	81 (18.0)	24 (12.1)	28 (26.7)
Therapy end reason			
Planned stop	7 (1.6)	1 (0.5)	0 (0.0)
Toxicity	81 (18.0)	41 (20.6)	12 (11.4)
Disease progression	238 (52.9)	147 (73.9)	79 (75.2)
Patient wish	16 (3.6)	4 (2.0)	2 (1.9)
Other	36 (8.0)	6 (3.0)	10 (9.5)
Ongoing	65 (14.4)	0 (0.0)	0 (0.0)
Lost to follow-up	7 (1.5)	0 (0.0)	2 (1.9)
Progression			
No	120 (26.7)	14 (7.0)	6 (5.7)
Yes	330 (73.3)	185 (93.0)	99 (94.3)
Death			
No	236 (52.4)	90 (45.2)	0 (0.0)
Yes	214 (47.6)	109 (54.8)	105 (100.0)
Progression-free survival			
Median in months (95% CI)	4.7 (3.9 to 5.6)	3.8 (2.7 to 5.0)	2.1 (1.9 to 2.3)
Overall survival			
Median in months (95% CI)	21.5 (16.9 to 26.0)	23.9 (19.8 to 28.0)	19.5 (6.6 to 32.4)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

risk of adverse effects is not increased.[17] BRAF+MEK inhibition is known to increase the general risk of bleeding.[36] However, as reported in previous studies[12 37 38] concomitant treatment with BRAF+MEK inhibition and SRS was safe in our study.

With regard to systemic therapy, recently published treatment recommendations for MBM recommend CTLA-4+PD-1 as first-line treatment.[39] In line with this recommendation, our univariate results revealed that patients receiving BRAF+MEK inhibition as first-line therapy showed a significantly shorter median OS than those receiving PD-1 based ICB. However, these effects could not be demonstrated in the multivariate model, suggesting that the univariately significant difference between treatment types could be caused by poorer prognostic baseline characteristics in patients treated with BRAF+MEK inhibition (ECOG ≥2: 11.4% for BRAF+MEK inhibition vs 5.6% for CTLA-4+PD-1% and 4.6% for PD-1; symptomatic MBM 34.2% for BRAF+MEK inhibition vs 23.0% for PD-1% and 24.0% for CTLA-4+PD-1).

In our investigated cohort, patients receiving CTLA-4+PD-1 showed a significantly shorter median PFS than patients receiving PD-1 (3.9 vs 5.4 months) in the univariate analysis. Herewith our data oppose the results for median PFS from the prospective randomized phase II ABC trial,[5] which showed significantly improved PFS in patients treated with CTLA-4+PD-1 compared with PD-1 (median PFS 5.4 months compared with 2.5 months) for asymptomatic MBM with no prior radiotherapy and no steroid intake. In that study, median PFS for CTLA-4+PD-1 in treatment-naïve patients was not yet reached after 5 years compared with 2.5 months for PD-1. In our real world, not randomized patient cohort, CTLA-4+PD-1 treated patients were younger (patients ≤65 years 58.3% vs 45.3%) and in better performance state (ECOG-PS 0 47.4% vs 31.7%) than patients treated with PD-1, with otherwise equal distribution of prognostically relevant patient characteristics. Therefore, a better outcome in the CTLA-4+PD-1 group in our study would be expected. The difference in median PFS observed by us could be explained by confounding factors, especially by additional SRS. Interestingly, when only assessing the patients treated with SRS, the median PFS in our cohort was similar for systemic therapy with CTLA-4+PD-1, PD-1, and BRAF+MEK inhibition. Patients in arm A and B in the ABC trial did not receive concomitant radiotherapy; therefore, these patients would be better comparable with patients in our cohort who did not receive radiotherapy together with systemic therapy. In patients without radiotherapy for MBM, the median OS rates in our study were in line with the OS results of the ABC trial with median OS for CTLA-4+PD-1 not being reached after 5 years, and 26.1 months for nivolumab in asymptomatic patients. Nevertheless, although our study suggests that patients receiving PD-1 monotherapy and SRS can have survival outcomes comparable with CTLA-4+PD-1, considering the shortcomings of a retrospective analysis, this has to be addressed and assessed in a prospective randomized trial before drawing conclusions from it for daily clinical practice. So far, clinical trials with MBM patients (not addressing effects of concomitant radiotherapy though) show a clearly superior outcome with CTLA-4+PD-1 compared with PD-1 monotherapy.

Toward therapy sequencing, our results suggest that PD-1 based ICB in first-line therapy followed by BRAF+MEK inhibition as second-line therapy shows the best OS outcome in patients with MBM. We could also show that BRAF+MEK inhibition is the most favorable second-line therapy in patients with MBM compared with other therapies such as chemotherapy, but also to CTLA-4+PD-1 and PD-1. This could be due to the fact that in clinical practice BRAF+MEK is often applied to MBM patients with worse prognostic parameters who need a fast-acting therapy and that patients with better baseline characteristics receive ICB. In fact, several baseline characteristics in the group of patients who received targeted therapy as first-line therapy in our study were associated with a worse prognosis compared with the group who received ICB as first-line therapy. It also has to be noted that the patient numbers in the different systemic therapy sequences were not big enough to include them into the multivariate Cox regression analysis with all prognostic parameters of interest. We therefore evaluated the therapy sequences in a separate multivariate analysis focusing on the most important prognostic factors only. Nevertheless, the patient numbers in the single groups were small, limiting its validity. Additionally, it has to be kept in mind that a large number (23.3%) of patients died before receiving a second-line therapy. Interestingly, while the percentage of patients with CTLA-4+PD-1 and CRT was similar in patients who received a second-line therapy compared with those who died after the first-line therapy, a significantly higher fraction of the patients who died before second-line therapy did not show an activating BRAF-mutation and were treated with PD-1 without additional radiotherapy as first-line treatment, while a significantly larger fraction of patients who received a second-line therapy received BRAF+MEK inhibitors and also SRS as first-line treatment. Therefore, although the sequence of BRAF+MEK inhibition as second-line therapy seems to be more favorable, it has to be kept in mind that there is also a fraction of patients who died after first-line therapy comprising a large fraction of BRAF wildtype patients with unfavorable baseline characteristics who received PD-1 monotherapy without additional radiotherapy.

Patients with symptomatic MBM in our study cohort showed a decreased median OS compared with patients with asymptomatic MBM. Of note, in symptomatic patients, median OS on BRAF+MEK inhibition was slightly better compared with PD-1 and CTLA-4+PD-1, while for asymptomatic patients, it was significantly decreased compared with ICB. In the Checkmate 204 trial, a small cohort of 18 symptomatic patients showed a poor intracranial response rate to CTLA-4+PD-1 (22.2% CR, PR or SD >6 months),[6] with two of six patients who received corticosteroids showing an objective intracranial

response. Median PFS was 1.2 months and median OS 8.7 months in these patients. Similarly, symptomatic patients treated with PD-1 in the ABC trial (n=15) had a median PFS of 2.6 months and median OS of 5.1 months, but an intracranial response rate of only 6%. In comparison, the intracranial objective response rate for dabrafenib + trametinib in the Combi-MB trial was 59% with a short duration of response of 4.5 months and median OS of 11.5 months in 17 symptomatic MBM patients.[4] Altogether, in our studied real-world patient cohort, symptomatic MBM patients showed higher intracranial response rates compared with symptomatic MBM patients reported in prospective clinical trials, which could be explained by small numbers of MBM patients in these trials, as well as the additional radiotherapy received in most cases of our cohort. Taken together, these data suggest that targeted therapy with BRAF+MEK inhibition is more favorable as first-line therapy in symptomatic than asymptomatic patients, most probably because of the rapid treatment effect and high response rate. Moreover, our data show that additional SRS is beneficial to achieve an intracranial response and prolonged survival in symptomatic patiens. Additionally, we could show that while the intake of dexamethasone generally impairs the treatment outcome of ICB, as also reported in previous studies,[40 41] this negative effect is enhanced by the dose of dexamethasone, with doses of <4 mg resulting in better OS.

It has been reported, mainly in historical cohorts of patients with MBM that surgical resection of single MBM can be beneficial; however, in most studies, a clear impact of MBM surgery on OS could not be shown[42 43] or only if compared with patients with no systemic treatment at all.[44] In a historic analysis by Eigentler *et al*, for example, local treatment with SRS or surgical resection was an independently prognostic factor for survival compared with other treatments (WBRT and chemotherapy) in patients with a single brain metastasis. Compared with our study, that study did not separately assess the effects of SRS and metastasectomy.[45] One retrospective study showed a statistically relevant survival benefit for patients with surgical resection before immunotherapy versus immunotherapy alone in a smaller heterogeneous cohort with different immunotherapy regimens.[46] In our real-world cohort of patients with ICB and targeted therapy, surgical resection of MBM was also significantly associated with improved OS in the univariate analysis, however not in the multivariate analysis. Hence, improved survival may rather be attributable to selection bias, since surgery is often performed in patients with solitary or oligometastatic MBM. Indeed, in our study, solitary metastases were detected in 40.4% of patients with surgical resection versus 26.4% in patients who did not receive surgical resection.

Limitations of this study are its retrospective data evaluation and the high percentage of missing data for some important prognostic parameters of MBM. More comprehensive statistical analyses of subgroups would require a higher total patient number. Therefore, parameters like the timing of SRS before or during systemic therapy could not be included into the multivariate analysis, and an additional multivariate analysis including fewer prognostically relevant parameters had to be performed to assess the independent prognostic value of the therapy sequence. Additionally, the median OS for CTLA-4+PD-1, a type of treatment that had been approved for melanoma later than BRAF+MEK inhibition, has not been reached yet, hereby impairing comparability of groups. Nevertheless, compared with other retrospective studies, we have excluded patients who received previous systemic therapies, and therefore, we are able to show a clear effect of our analyzed parameters on first-line therapy.

In conclusion, this study shows that SRS combined with systemic therapy is beneficial in MBM and should be an integral part of the therapeutic management of patients with MBM. Our results favor the sequence of ICB as first-line and BRAF+MEK as second-line therapy. Also, we could show a possible survival benefit of CRT when combined with systemic therapy.

Since retrospectively analyzed data have always to be treated with caution, because the quality of the documented data is never as high as in a prospectively randomized study, more and larger prospectively conducted clinical studies with an adequately high number of patients with MBM taking into account all prognostically relevant parameters are warranted to further answer the question of the optimal therapy sequence of ICB and BRAF+MEK inhibition together with SRS. Generally, these trials should separately assess different patient scenarios (BRAF-mutated and BRAF-wildtype, oligometastastic MBM versus multiple metastases, asymptomatic versus symptomatic and patients without extracranial organ affection versus few or many affected extracranial organs) and should incorporate SRS with all systemic therapy regimens.

Author affiliations
[1]Department of Dermatology and Venereology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[2]Department of Dermatology, Elbe Kliniken Buxtehude, Buxtehude, Germany
[3]Department of Dermatology, Hannover Medical School, Hannover, Germany
[4]Department of Dermatology, Muehlenkreiskliniken Minden and Ruhr University Bochum, Minden, Germany
[5]Skin Cancer Center at the University Cancer Centre Dresden and National Center for Tumor Diseases, Dresden, Germany; Department of Dermatology, University Hospital Carl Gustav Carus, Dresden, Germany
[6]Department of Dermatology, Skin Cancer Center, Schleswig-Holstein University Hospital, Campus Kiel, Kiel, Germany
[7]Department of Dermatology, Saarland University Medical School, Homburg/Saar, Germany
[8]Department of Dermatology, HELIOS Klinikum Erfurt, Erfurt, Germany
[9]Department of Dermatology, University of Lübeck, Lübeck, Germany
[10]Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany; Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Heidelberg, Germany
[11]Department of Dermatology and Skin Cancer Center, Harzklinikum Dorothea Christiane Erxleben, Quedlinburg, Germany
[12]Department of Dermatology, Nuremberg General Hospital, Paracelsus Medical University, Nuremberg, Germany
[13]Department of Dermatology, University Hospital Regensburg, Regensburg, Germany
[14]Department of Dermatology, SRH Wald-Klinikum Gera, Gera, Germany

[15]Department of Dermatology, University Hospital Tübingen, Tübingen, Germany
[16]Department of Dermatology, Hospital of Dortmund, Dortmund, Germany
[17]Department of Dermatology, Venereology and Allergology, HELIOS St. Elisabeth Klinik Oberhausen, University Witten-Herdecke, Herdecke, Germany
[18]Department of Dermatology, Klinikum Bremerhaven Reinkenheide, Bremerhaven, Germany
[19]Department of Dermatology and Allergology, University Hospital Augsburg, Augsburg, Germany
[20]Department of Dermatology and Allergology, Ludwig-Maximilian University, München, Germany
[21]Department of Dermatology and Venereology, Medical Center, University of Freiburg, Freiburg im Breisgau, Germany
[22]Department of Dermatology, University Hospital of Münster, Münster, Germany
[23]Department of Dermatology, Ruhr University Bochum, Bochum, Germany
[24]Department of Dermatology and Allergology, Hospital Bayreuth, Bayreuth, Germany
[25]Department of Dermatology, Ludwigshafen Medical Center, Ludwigshafen, Germany
[26]Department of Dermatology, Heinrich Heine University, Düsseldorf, Germany
[27]Department of Radiation Oncology and Cyberknife Center, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[28]Department of Dermatology, Venereology and Allergology, University Hospital Essen, Essen, Germany and German Cancer Consortium (DKTK) partner site Essen/Düsseldorf, Essen, Germany
[29]Rudolf-Schönheimer-Institute of Biochemistry, Medical Faculty of the University Leipzig, Leipzig, Germany

Acknowledgements We would like to thank all investigators and patients participating in the ADOREG registry.

Contributors Guarantor: CF and SU. Conceptualization: CF and SU. Data collection: all authors. Analysis of data: CF, SU and SH. Writing of manuscript: all authors.

Funding CF was funded by the Köln Fortune Program, Faculty of Medicine, University of Cologne. IH and DS were supported by the German Cancer Aid (DKH, no. 70112507). This research did otherwise not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests The authors declare no competing interests in reference to this work. For conflicts of interest outside the submitted work see list: CF has been on the advisory board or has received honoraria from Bristol Myers Squibb, Immunocore and Novartis and received travel grants from Bristol Myers Squibb, Novartis and Pierre Fabre. PM declares research support from Bristol Myers Squibb, Novartis and Merck Sharp & Dome; speakers and advisory board honoraria from Almirall Hermal, Beiersdorf, Bristol Myers Squibb, Merck Sharp & Dome, Immunocore, Merck Serono, Medac, Novartis, Pierre Fabre, Sanofi Genzyme, Sun Pharma and Roche, and travel support from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis and Pierre Fabre. LB received honoraria from Amgen, Bristol Myers Squibb and Sun Pharma. IG declares speakers and advisory board honoraria from Almirall Hermal, Bristol Myers Squibb, Merck Sharp & Dome, Novartis, Pierre Fabre, Sanofi Genzyme, Sun Pharma and Roche. FM has received travel support or/and speaker's fees or/and advisor's honoraria by Novartis, Roche, BMS, MSD and Pierre Fabre and research funding from Novartis and Roche. RH reports speakers and advisory board honoraria from Bristol Myers Squibb (BMS), Immunocore, Novartis, Pierre-Fabre, Roche and SUN pharma. CP received honoraria (speaker honoraria or honoraria as a consultant) and travel support from: Novartis, BMS, Roche, Merck Serono, MSD, Celgene, AbbVie, SUNPHARMA, UCB, Allergy Therapeutics, Pierre Fabre, Kyowa Kirin and LEO. JUl has received research support from Novartis; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Pierre Fabre, and travel support from Bristol Myers Squibb and medac. PT declares speakers and advisory board honoraria from Almirall, Bristol Myers Squibb, Novartis, Merck Sharp & Dohme, Pierre-Fabre, CureVac, Merck Serono, Sanofi, Roche, Kyowa Kirin, Biofrontera and 4SC; travel support from Bristol Myers Squibb and Pierre-Fabre. DN has received advisory and speaker honoraria from Merck Sharp & Dome, Bristol Myers Squibb, Novartis, Almirall and Sanofi. AF Advisory Board: Roche, Novartis, MSD, BMS, Pierre-Fabre; support for congress participation: Roche, Novartis, BMS, Pierre-Fabre; speaker honoraria: Roche, Novartis, BMS, MSD, CeGaT; institutional research support BMS Stiftung Immunonkologie. JUt is on the advisory board or has received honoraria and travel support from Amgen, Bristol Myers Squibb, GSK, Immunocore, LeoPharma, Merck Sharp and Dohme, Novartis, Pierre Fabre, Roche and Sanofi. TG has received speakers and/or advisory board honoraria and travel support from BMS, Sanofi-Genzyme, MSD, Novartis Pharma, Roche, Abbvie, Almirall, Janssen, Lilly, Pfizer, Pierre Fabre, and Merck-Serono. FM served as consultant and/or has received honoraria from Novartis, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Sanofi Genzyme and travel support from Novartis, Sunpharma and Bristol Myers Squibb. JW received honoraria from Pierre Fabre, Novartis and Merck Sharp & Dohme. KS has been on the advisory board or has received honoraria from Bristol Myers Squibb, Roche, Merck Sharp & Dome, Pierre Fabre, Novartis and received travel grants from Bristol Myers Squibb, Novartis and Pierre Fabre. IH has been on the advisory board of Ymmunobio. AR reported grants from Novartis, Bristol Myers Squibb, and Adtec; personal fees from Merck Sharp & Dohme; and non-financial support from Amgen, Roche, Merck Sharp & Dohme, Novartis, Bristol Myers Squibb, and Teva. LZ served as consultant and/or has received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre-Fabre, Sunpharma and Sanofi; research funding to institution: Novartis; travel support from Merck Sharp & Dohme, Bristol Myers Squibb, Amgen, Pierre-Fabre, Sunpharma, Sanofi and Novartis. EL served as consultant and/or has received honoraria from Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Medac, Sanofi, Sunpharma and travel support from Medac, Bristol Myers Squibb, Pierre Fabre, Sunpharma and Novartis. DS: relevant financial activities (Roche, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Sanofi, Regeneron, Array, Pierre Fabre, 4SC, Helsinn, Philogen, InFlarX, Merck-Serono, SunPharma, Ultimovacs, and Sandoz). SU declares research support from Bristol Myers Squibb and Merck Serona; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dome, Merck Serono, Novartis and Roche, and travel support from Bristol Myers Squibb, Merck Sharp & Dohme and Pierre Fabre. All other authors have no conflict of interest to declare.

Patient consent for publication Not applicable.

Ethics approval The ADOREG registry was approved by the ethics committee of the University Duisburg-Essen (14-5921-BO); informed consent was obtained from all patients. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Cindy Franklin http://orcid.org/0000-0001-9142-5423
Michael Weichenthal http://orcid.org/0000-0002-9060-4961
Patrick Terheyden http://orcid.org/0000-0002-5894-1677
Andrea Forschner http://orcid.org/0000-0002-6185-4945
Alexander Kreuter http://orcid.org/0000-0003-2275-499X
Thilo Gambichler http://orcid.org/0000-0001-7862-3695
Maike Trommer http://orcid.org/0000-0003-2864-4273
Selma Ugurel http://orcid.org/0000-0002-9384-6704

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