



Original Research

Impact of radiation, systemic therapy and treatment sequencing on survival of patients with melanoma brain metastases



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Abbreviations: anti-CTLA-4, cytotoxic T-lymphocyte-associated protein 4 antibody/antibodies; anti-PD-1, programmed cell death protein 1 antibody/antibodies; BRAF, v-Raf murine sarcoma viral oncogene homolog B; BRAFi, BRAF inhibitor/s; BRAFmut, BRAF mutation / mutated; BRAFwt: BRAF wild type, CTCAE; Common Terminology Criteria for Adverse Events, ECOG PS; Eastern Cooperative Oncology Group performance status, IT; immunotherapy, LDH; lactate dehydrogenase, LINAC; linear accelerator, MBMs; melanoma brain metastases, MEK; mitogen activated protein kinase, MEKi; MEK inhibitor/s, OS; overall survival, OS_{RT}: overall survival from beginning of radiotherapy; PD-1, programmed cell death protein 1; RT, radiotherapy; SRS, stereotactic radiosurgery; ST, systemic therapy; TT, targeted therapy; WBRT, whole brain radiation therapy.

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Abstract Background: Combining stereotactic radiosurgery (SRS) and active systemic therapies (STs) achieved favourable survival outcomes in patients with melanoma brain metastases (MBMs) in retrospective analyses. However, several aspects of this treatment strategy remain poorly understood. We report on the overall survival (OS) of patients with MBM treated with a combination of radiotherapy (RT) and ST as well as the impact of the v-Raf murine sarcoma viral oncogene homolog B (BRAF)-V600 mutation (BRAFMut) status, types of RT and ST and their sequence.

Patients and methods: Data of 208 patients treated with SRS or whole brain radiation therapy (WBRT) and either immunotherapy (IT) or targeted therapy (TT) within a 6-week interval to RT were analysed retrospectively. OS was calculated from RT to death or last follow-up. Univariate and multivariate Cox proportional hazard analyses were performed to determine prognostic features associated with OS.

Results: The median follow-up was 7.3 months. 139 patients received IT, 67 received TT and 2 received IT and TT within 6 weeks to RT (WBRT 45%; SRS 55%). One-year Kaplan-Meier OS rates were 69%, 65%, 33% and 18% ($P < .001$) for SRS with IT, SRS with TT, WBRT with IT and WBRT with TT, respectively. Patients with a BRAFMut receiving IT combined with RT experienced higher OS rates (88%, 65%, 50% and 18%). TT following RT or started before and continued thereafter was associated with improved median OS compared with TT solely before RT (12.2 [95% confidence interval {CI} 9.3–15.1]; 9.8 [95% CI 6.9–12.6] versus 5.1 [95% CI 2.7–7.5]; $P = .03$).

Conclusion: SRS and IT achieved the highest OS rates. A BRAFMut appears to be a favourable prognostic factor for OS. For the combination of RT and TT, the sequence appears to be crucial. Combinations of WBRT and ST achieved unprecedentedly high OS rates and warrant further studies.

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1. Introduction

Considering a median overall survival (OS) of roughly 2 months with best supportive care only, the prognosis for patients with melanoma brain metastases (MBMs) is grim [1]. Until 2011, local therapies (e. g. neurosurgery and radiotherapy [RT]) were the only treatment options

for MBM and remain recommended standard treatments for selected patients [2,3]. Clinical studies on chemotherapies have failed to show any survival benefit [4,5]. Recently, the v-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor (BRAFi) dabrafenib combined with the mitogen activated protein kinase (MEK) inhibitor (MEKi) trametinib and the immune

checkpoint inhibitors anti-cytotoxic T-lymphocyte-associated protein 4 antibody (CTLA-4) ipilimumab combined with anti-programmed cell death protein 1 (PD)-1 nivolumab demonstrated activity against MBM with response rates of 50–60%—comparable to those outside the brain [6–8]. Nevertheless, most patients progress and die from MBM [9].

Preclinical and clinical data suggest that combining RT with immune checkpoint inhibitors augments the immunogenic cell death induced by RT [10–14] and that BRAFi increases radiosensitivity by a G1 cell cycle arrest [15,16]. However, there are concerns regarding toxicity when combining RT with immunotherapy (IT) or targeted therapy (TT), in particular skin toxicity, oedema, haemorrhage and radionecrosis [17–19].

Retrospective analyses suggest that combining stereotactic radiosurgery (SRS) with active systemic therapies (STs) improves MBM control and prolongs survival without increasing toxicity [20–23].

Here, we report on the OS and toxicity of more than 200 patients with MBM treated with radiation and new systemic agents in Germany. Furthermore, we explored the impact of the BRAF-V600 mutation (BRAFmut) status, types of RT and ST and their sequence on OS.

2. Methods

2.1. Patient characteristics and treatment regimens

Following ethics board approval, a retrospective analysis of patients having received SRS or whole brain radiation therapy (WBRT) for at least one MBM and additionally either IT (either anti-PD-1 or anti-CTLA-4 alone or combined) or TT (BRAF_i or BRAF_i + MEK_i) within a 6-week interval to RT (before, after or started before and continued after RT) was conducted. Fourteen German Skin Cancer Centres participated and provided data of patients treated between March 2014 and August 2016.

Prior to treatment, the patients had undergone magnetic resonance imaging of the brain and a total-body computer tomography for the assessment of intracerebral and extracerebral disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. MBM were treated with SRS in a single session or fractionated, using either a linear accelerator-based or a Gamma-knife approach. Radiosurgery was delivered according to local standards. WBRT was delivered either alone or with an additional boost.

2.2. End-points and statistical analysis

The primary end-point of this study was overall survival from beginning of radiotherapy (OS_{RT}), defined as interval from the beginning of RT to death. OS_{RT} rates were calculated applying the Kaplan-Meier method with

the log-rank test used to determine differences between treatment regimens. Patients who did not experience the outcome were censored at their last follow-up date. Univariate and multivariate Cox proportional hazard regression analyses were performed on prognostic factors associated with OS_{RT} (applying the entrance method), and the following variables were included age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), BRAFmut status, number and symptoms of MBM, presence of extracerebral metastases, type of RT and ST. Variables with $P \leq .01$ on univariate analysis were included in the multivariate analysis. To determine baseline cohort differences the Pearson's χ^2 , Fisher's exact and Mann-Whitney U test were used when appropriate. Continuous variables are expressed as median with range (min and max) and categorical variables as count (N) and percentages. Statistical analysis was performed using IBM SPSS Statistics, version 23.

Results are reported as two-sided P values with 95% confidence intervals (95% CI). Statistical significance was set at $P < .05$. Numeral discrepancies to the total number or subgroup number of patients represent missing data.

Toxicity is reported according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

3. Results

3.1. Patient characteristics and treatment regimens

A total of 208 patients were included in this study. The median follow-up was 7.3 (range: 0–40.5) months. Patient and disease characteristics are summarised in [supplementary Table S1](#). The median age at initial MBM diagnosis was 60.1 (range 26.6–92.7) years. Neuroimaging before RT indicated a single MBM in 55 patients, 2–3 MBM in 49 patients and >3 MBM in 99 patients, respectively. Besides, 174 (84%) patients had extracerebral metastases.

In total, 128 (62%) patients had melanoma with a BRAFmut. They tended to have a higher frequency of >3 MBM (54% versus 39%; $P = .07$) and of neurological symptoms (36% versus 22%; $P = .06$) than patients without a BRAF mutation (BRAF wild type, BRAFwt) ([supplementary Table S2a](#)). ECOG PS, S100 and lactate dehydrogenase (LDH) levels did not differ significantly between both subgroups.

Altogether, 114 (55%) patients received SRS ([supplementary Table S2b](#)). In this group, the median number of irradiated MBM was 1 (range 1–7), the median number of fractions 1 (range 1–13) and the resulting median total dose 20Gy (range 9–60Gy) delivered in fractions of 20Gy (range 2.4–25Gy). Those 94 (45%) patients who received WBRT had a median

number of 5 (range 1–100) MBM and were treated with median 10 (range 2–22) fractions of 3Gy (1.64–7.6Gy) to a median total dose of 30Gy (range 7.5–54Gy).

Regarding ST, 139 (66%) patients received IT, and 67 patients (33%) received TT (28% BRAFi, 72% BRAFi + MEKi). In addition to 77 BRAFwt patients (58% anti-PD-1, 33% anti-CTLA-4 and 8% anti-PD-1+anti-CTLA-4), 59 BRAFmut patients were treated with IT (49% anti-PD-1, 36% anti-CTLA-4 and 15% anti-PD1+anti-CTLA-4) (supplementary Table S2c).

4. Overall survival

4.1. All patients

At the last follow-up, 119 (57%) patients had died, and 88 (42%) patients were alive. The median OS_{RT} was 11.7 (95% CI 8.9–14.4) months, and 1-year and 2-year OS_{RT} rates were 49% and 32% (Table 1), respectively. There was a median OS_{RT} benefit for patients treated with SRS compared with patients treated with WBRT (19.7 versus 7.1 months, $P < .001$), considering that patients receiving SRS had significantly less MBM. Furthermore, there was a median OS_{RT} benefit for patients treated with IT versus TT (14.8 versus 9.8 months, $P = .03$). In particular, favourable OS_{RT} rates were observed for anti-CTLA-4 + anti-PD-1 combined with SRS (Table 1; supplementary Figure S1).

The univariate analysis of baseline characteristics for OS_{RT} (Table 2) revealed age < 60 years, ECOG PS of 0–1, ≤ 3 MBM, absence of neurological symptoms and presence of extracerebral metastases to be significantly associated with a better OS_{RT}.

In the multivariate analysis, age, ECOG PS, BRAFmut and presence of extracerebral metastases proved to be associated with a prolonged OS_{RT} (Table 2).

4.2. BRAFmut patients

Supplementary Table 2d compares pretreatment characteristics of the BRAFmut patients treated with IT or TT. Subanalysis of BRAFmut patients stratified by the type of ST combined with RT revealed a difference of median OS_{RT} between IT and TT (not yet reached versus 9.8 months; $P < .001$). The 1-year and 2-year OS_{RT} rates were 71% and 61%, if treated with IT compared with 38% and 21%, respectively, if treated with TT ($P < .001$) (supplementary Table S3). The superiority of IT over TT was demonstrated for SRS and WBRT (supplementary Figure S2).

4.3. Sequencing of radiation and systemic therapy

Compared with administration of TT solely before RT, we observed a significant median OS_{RT} benefit for patients who received TT after RT or who started TT

Table 1

Median overall survival, 6-months and 1- and 2-year survival rates from beginning of radiotherapy of 206* patients stratified according to radiotherapy, systemic therapy and the combinations received.

Treatment modalities	N	Median OS _{RT} (95% CI) (months)	6-months (1-year; 2-year) survival rate	P-value
All	206	11.7 (8.9–14.4)	72% (49%; 32%)	
SRS	114	19.7 (13.9–25.5)	81% (68%; 43%)	<0.001
WBRT	92	7.1 (5.9–8.3)	61% (25%; 18%)	
Immunotherapy	137	14.8 (9.9–19.7)	73% (56%; 38%)	.03
Targeted therapy	68	9.8 (7.8–11.7)	71% (38%; 21%)	
SRS + Immunotherapy	87	21.0 (12.9–29.1)	81% (69%; 46%)	.23
SRS + Targeted therapy	27	12.9 (9.1–16.7)	82% (65%; 34%)	
WBRT + Immunotherapy	51	7.1 (5.1–9.1)	59% (33%; 24%)	.55
WBRT + Targeted therapy	40	7.0 (3.5–10.4)	63% (18%; 13%)	
anti-CTLA-4	47	11.2 (7.7–14.6)	70% (45%; 33%)	.23
anti-PD-1	75	17.6 (14.1–21.2)	73% (60%; 34%)	
anti-CTLA-4 + anti-PD-1	15	not yet reached	79% (79%; 79%)	
BRAFi mono	19	8.9 (5.4–12.4)	74% (24%; 6%)	.30
BRAFi + MEKi	48	9.8 (6.3–13.2)	70% (42%; 28%)	
SRS + anti-PD1	52	21.0 (–)	77% (70%; 38%)	.11
SRS + anti-CTLA	30	20.5 (–)	87% (65%; 47%)	
SRS + anti-PD1 + anti-CTLA	5	Not yet reached	100% (100%; not reached)	
SRS + BRAFi mono	6	8.9 (–)	83% (50%; not reached)	
SRS + BRAFi + MEKi	21	19.7 (–)	81% (70%; 44%)	
WBRT + anti-PD1	24	7.1 (–)	66% (38%; 22%)	.07
WBRT + anti-CTLA	17	4.5	41% (8%; 8%)	
WBRT + anti-PD1 + anti-CTLA	10	Not yet reached	70% (70%; 70%)	
WBRT + BRAFi mono	13	7.4 (–)	69% (15%; 8%)	
WBRT + BRAFi + MEKi	27	6.7	61% (19%; not reached)	

SRS stereotactic radiosurgery; WBRT whole-brain radiation therapy; CI, confidence interval; OS_{RT}, overall survival from beginning of radiotherapy; BRAF, v-Raf murine sarcoma viral oncogene homolog B; BRAFi, BRAF inhibitor; MEKi, mitogen activated protein kinase inhibitor; CTLA, cytotoxic T-lymphocyte-associated protein; PD1, programmed cell death protein 1.

*Numerical discrepancies to the total number of patients represent missing data.

Table 2

Impact of baseline patient and disease characteristics on overall survival (from beginning of radiotherapy): Univariate and multivariate* Cox regression analyses.

Baseline characteristics	Univariate			Multivariate		
	N	HR (death) (95% CI)	P-value	N	HR (death) (95% CI)	P-value
Age at diagnosis (years)						
<60	103	1		85	1	
≥60	103	1.6 (1.1–2.3)	.01	75	1.8 (1.1–2.9)	.01
Gender						
Female	74	1				
Male	132	1.3 (0.9–2.0)	.14	–		
ECOG PS						
0–1	166	1		148	1	
2–4	20	4.5 (2.8–7.5)	< .001	12	2.5 (1.02–6.0)	.04
BRAF status						
Wild type	76	1		61	1	
Mutation	127	0.7 (0.5–1.1)	.10	99	0.3 (0.2–0.6)	.001
Number of MBM						
1	55	1		49	1	
2–3	49	1.8 (1.0–3.2)	.049	39	1.8 (0.9–3.7)	.09
>3	97	3.0 (1.8–5.0)	< .001	72	1.5 (0.7–3.2)	.31
Symptoms from MBM						
No	134	1		117	1	
Yes	60	1.9 (1.3–2.8)	.001	43	1.5 (0.8–2.5)	.19
Extracerebral MTS						
No	19	1		12	1	
Yes	172	0.1 (0.1–0.2)	< .001	148	0.1 (0.01–0.35)	< .001
Radiotherapy						
WBRT	92	2.7 (1.8–3.9)	< .001	67	2.5 (1.3–4.7)	.006
SRS	114	1		93	1	
Type of systemic therapy						
Immunotherapy	137	1		110	1	
Targeted therapy	68	1.5 (1.0–2.2)	.03	50	3.2 (1.7–6.3)	.001

Variables with $P \leq .01$ on univariate analysis were included in the multivariate analysis.

SRS stereotactic radiosurgery; WBRT whole-brain radiation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; 95% CI, 95% confidence interval; MBM, melanoma brain metastasis; MTS, metastases; BRAF, v-Raf murine sarcoma viral oncogene homolog B.

Bold values indicate statistically significant data ($P < .05$).

*Entrance method; Numeral discrepancies to the total number of patients represent missing data.

before RT and continued thereafter (5.1 versus 9.8 and 12.2 months, respectively; $P = .03$) irrespective of SRS and WBRT (supplementary Table S4; Fig. 1). No clear trend was found for the sequence of IT and RT.

4.4. Toxicity

Toxicities following ST were documented in 54 (26%) patients (supplementary Table S5–S6). The most frequent toxicities were hepatitis, pruritus and colitis. CTCAE grade 3/4 toxicities occurred in 12 (5.7%) of these patients, including hepatitis ($N = 4$) and colitis ($N = 4$).

Intracerebral oedema was documented in 13 (6%) patients (4 after SRS and 9 after WBRT) and intracerebral bleeding in 19 (9%) patients (8 after SRS and 11 after WBRT). Radionecrosis was observed in 4 (2%) patients treated with SRS and IT. Following WBRT, 9 patients treated with IT and 4 patients treated with TT developed skin toxicity, including dermatitis ($N = 13$) and alopecia ($N = 10$). CTCAE grade 3/4 neurological symptoms were not observed (supplementary Table S7).

5. Discussion

This retrospective study represents a real-life cohort of patients with MBM treated in German Skin Cancer Centres with a median age of 60 years, 70% of patients with more than one MBM, 80% of patients in ECOG PS 0–1, 90% of patients with extracerebral metastases and one-third of patients with increased tumour markers (S100 and LDH) before radiation.

Consistent with other retrospective studies on the efficacy and safety of combining RT and ST, the majority of patients were male, and the frequency of BRAFmut (62%) was within the expected range (45%–66%) [20–22,24,25]. Known prognostic factors for OS such as age, performance status, number of MBM, neurological symptoms, extracerebral metastases as well as BRAFmut were confirmed by our analyses with the exception that the presence of extracerebral metastases was associated with superior OS [20–23]. The conflicting data may be explained by generally small numbers of patients without extracerebral metastases [20,21,23,26]. Furthermore, brain MRI monitoring may be more

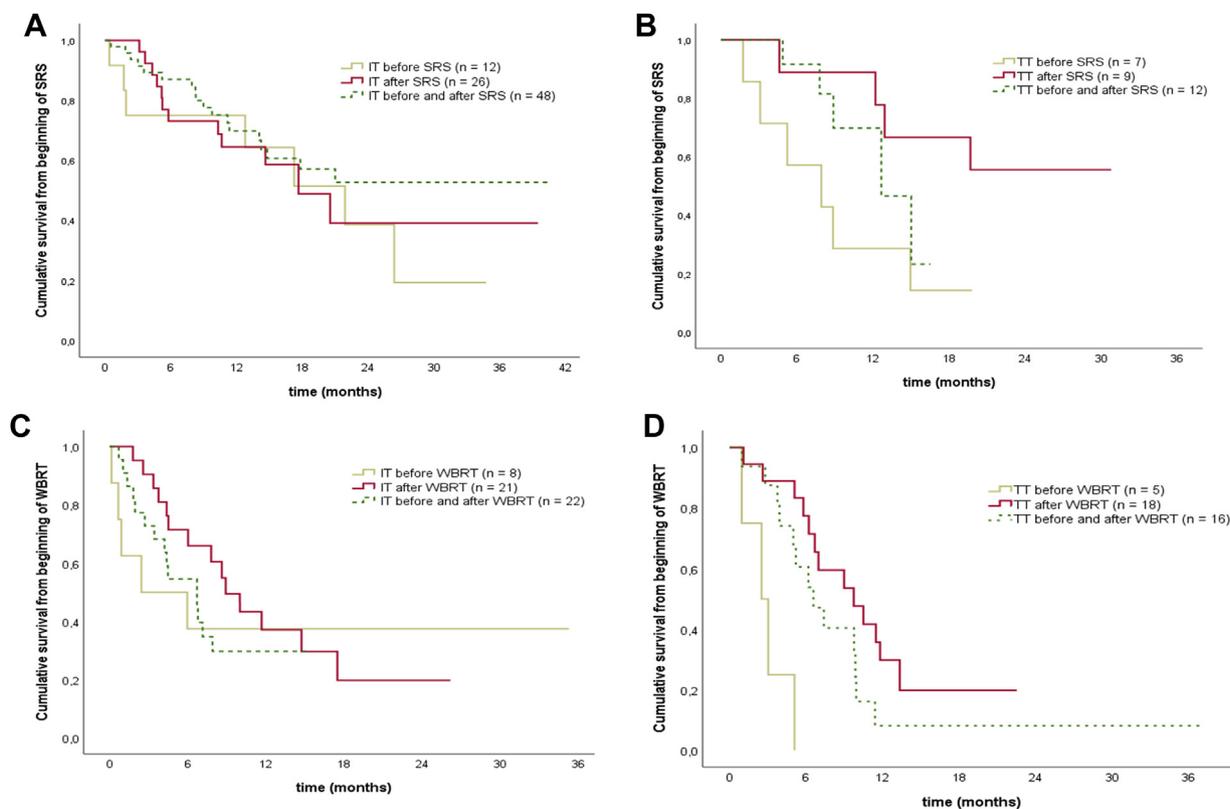


Fig. 1. Overall survival of 202 patients treated with A: IT and SRS (N = 86); B: TT and SRS (N = 26); C: IT and WBRT (N = 51); D: TT and WBRT (N = 39). IT, immunotherapy; TT, targeted therapy; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

frequent in patients with extracerebral metastases, i.e. MBM may be detected earlier. Of particular interest in this context is the recent preclinical study in a melanoma tumour transplantation model with intracranial plus extracranial tumour, mimicking the clinically observed coexistence of metastases inside and outside the brain [27]. The data indicate that in the context of extracranial disease, anti-PD-1/anti-CTLA-4 treatment increases intratumoural CD8⁺ T cells in the brain through peripheral expansion of effector CD8⁺ T cells and potentiation of their trafficking to intracranial tumours via up-regulation of T cell entry receptors on the tumour vasculature. Therefore, the coexistence of metastases inside and outside the brain may be a survival advantage which probably depends on the tumour burden and localisation [28]. In our study, this phenomenon was also observed in MBM treated with TT suggesting immunologic effects of BRAFi ± MEKi as well (supplementary Table S8).

Previous retrospective series varied in terms of endpoints, patient characteristics, medications, radiation protocols, sequencing and timing of RT plus ST making a direct comparison difficult. Besides, their findings referred mainly to patients treated with SRS. However, WBRT combined with ST, in particular with IT, is a considerable option for patients with multiple MBM

having a poor prognosis [29]. Therefore, we also included 94 patients treated with a combination of WBRT and ST, with the majority having >3 MBM. Their median OS_{RT} was 7.1 months, and the 1-year and 2-year survival rates were 25% and 18%, respectively. Taking into account a historical median OS of 2–4 months for WBRT alone [1,30], the combination of WBRT and ST appears to be a beneficial treatment strategy. In this context, protection against neurocognitive dysfunction associated with WBRT is gaining relevance [31]. Moreover, alternative approaches such as SRS for multiple brain metastases should be taken into account [32]. Interestingly, data of a recent retrospective study suggest that combining an upfront and repeated direct control of MBM by SRS and a ST with TT or IT is a way to keep MBM under control and prevent neurocognitive decline [21].

Patients treated with SRS and ST in our study experienced a median OS_{RT} of 19.7 months. The majority had ≤3 MBM. Based on a median OS of 5 months for SRS alone [33], the combination SRS plus ST results in a significant prolongation of survival. Patients treated with IT appeared to benefit most, in particular in combination with SRS (median OS_{RT} of 21.0 months). This observation affirms other retrospective findings. Considering anti-PD-1 combined with SRS, median OS

rates of 20.4 months ($N = 11$), 11.8 months ($N = 19$) and 12.3 months ($N = 11$), respectively, have been published for small cohorts [20–22]. Reasons for data discrepancies may be different SRS and IT protocols, different timing of RT and ST and low patient numbers.

In our study, the best survival was seen in patients treated with anti-PD-1 plus anti-CTLA-4 or anti-PD-1 alone combined with SRS with 6-month survival rates of 100% and 77%, respectively, and 12-month survival rates of 100% and 70%, respectively (Table 1). In a recently published phase II trial [34], treatment of patients with asymptomatic MBM with anti-PD-1 nivolumab plus anti-CTLA-4 ipilimumab or with nivolumab alone achieved a 6-month survival rate of 78% and 68%, respectively. In a second phase II study [8], patients with at least one asymptomatic MBM received nivolumab plus ipilimumab. Fifty-two percent of patients had one target lesion. In an initial assessment of OS, the 6-month and 9-month survival rates were 92.3% and 82.8%, respectively, and the estimated 12-month survival rate was 81.5%. These data suggest that the survival of patients treated with IT in combination with SRS may exceed the survival of patients treated with IT alone. However, we have to bear in mind that the populations in these studies differ in several aspects. Furthermore, a limited number of patients treated with anti-PD-1 plus anti-CTLA-4 combined with SRS were included in our study because of its approval in Europe 2016. Prospective studies investigating anti-PD-1 plus anti-CTLA-4 or anti-PD-1 alone combined with SRS are warranted. Indeed, NRG Oncology is planning a study that will investigate early SRS in the setting of immune checkpoint inhibitors versus salvage SRS for non-responders [3].

In our study, patients treated with SRS and TT had a median OS_{RT} of 12.9 months, with BRAFi + MEKi achieving the best results (19.7 months). In previous studies on combining SRS and TT, the median OS ranged from 7.2 to 17.8 months [20,35–37]. For this combination, the sequence of treatment modalities appears to play a crucial role. A significant OS_{RT} benefit was observed for patients who received BRAFi-/ +MEKi after RT or who started BRAFi-/ +MEKi before radiation and continued thereafter compared with patients who received BRAFi-/ +MEKi solely before RT (10.5 versus 5.1 months). Further evidence is provided by recent studies showing a better outcome in patients receiving BRAFi-/ +MEKi after SRS [21,36,38]. Hecht *et al.* [39] reported that interrupting treatment with the BRAFi vemurafenib before radiation was associated with a longer survival compared with concurrent treatment.

The sequence of IT and SRS or WBRT did not appear to play a relevant role. This is in line with Qian *et al.* [24] who found a superiority of IT within 4 weeks of SRS, whereas the sequence did not have any influence on OS. However, IT following SRS was significantly

superior in terms of OS in a case series including 56 patients [21]. Given the current inconsistent data, sequencing of IT and RT should be the subject of future investigations.

Our findings also demonstrate a prolonged survival for BRAFmut patients. One may speculate that patients with BRAFmut MBM have more treatment options with IT and TT. The literature provides conflicting data on the significance of the BRAF status as a prognostic factor [25,35,36]. Sperto *et al.* [40] reported higher median OS rates for BRAFmut patients compared with BRAFwt patients in contrast to Ly *et al.* [35].

Our subgroup analysis showed a significant OS_{RT} advantage for BRAFmut patients receiving RT combined with IT (1-year and 2-year OS_{RT} rates of 71% and 61%) compared with RT combined with TT (1-year and 2-year OS_{RT} rates of 38% and 21%). One may attribute this result to a poorer outcome by BRAFi administration or/and the emergence of BRAFi resistance prior to radiation. However, a reliable comparison of anti-PD-1/ +anti-CTLA-4 versus BRAF-/ +MEKi following radiation is not feasible because of small or unequal patient numbers. The question of the optimal therapy sequence, in particular when combining BRAFi-/ +MEKi with RT, should be the subject of prospective clinical studies.

Of importance, our data demonstrate that the combination of IT or TT with SRS or WBRT is associated with favourable survival outcomes without increased toxicity within the considered follow-up time which is supported by the majority of previous studies [20,22,23]. Unexpected toxicity was not found. Severe adverse drug reactions were documented in 5.7% of patients and mainly affected the liver and colon. Overall, the frequency of adverse events following ST appears to be low, and toxicity following RT was within reported limits [20–22,41]. Neurocognitive dysfunction was not recorded. However, taking into account the prolonged OS after WBRT, monitoring and preservation of neurocognitive function will be mandatory. Oedema and haemorrhage of MBM following RT were documented in 6% and 9% of patients, respectively. Gaudy-Marqueste *et al.* [42] found an increase in preexisting oedema in 4.7% and haemorrhage in 6.3% of patients. The incidence of haemorrhage associated with SRS alone was 2% in a study by Minniti *et al.* [43]. Taking into account the high propensity for spontaneous haemorrhage in MBM [44], the haemorrhage rates in our study appear to be low.

Patients receiving ST concurrent with RT may have an increased risk of radionecrosis [18,19]. However, the majority of retrospective analyses suggest that combining SRS with ST does not increase toxicity including radionecrosis [20–22]. In our study, radionecrosis after SRS and ST was documented in 2% of patients. It is known that radionecrosis may occur several months or years after SRS [45]. After a median follow-up of 17.2 months, Kohutek *et al.* found radionecrosis in 25.8% of brain

metastases of different tumour types (including 22.9% MBM) treated with SRS alone [41]. Considering a median follow-up of 7.3 months from the start of radiation in our study, the incidence of radionecrosis may increase with time. A detailed radiological investigation is ongoing, with a longer follow-up, in particular in anti-PD-1-treated patients [21].

Our results are limited by the retrospective design of the study. Data were contributed by 14 Skin Cancer Centres with different imaging techniques and non-uniform RT protocols. Current tumour markers (S100 and LDH) were not provided in about 30% of patients. Patients were included regardless of received systemic or local therapies prior to or after the study interval. Altogether, these aspects caused pretreatment, treatment and posttreatment heterogeneity and may have introduced a recall or selection bias and potentially confounded the measured survival outcomes. Given the limitations of this retrospective study, future prospective studies are warranted.

However, this study supports previous findings on synergistic effects of SRS and active systemic agents. It also reports on the efficacy and safety of combining WBRT with ST. In addition, it provides clinically relevant data on the impact of the BRAFmut status, types of RT and ST and their sequence on survival. For patients with MBM, active systemic agents have only recently been established, and many questions currently remain unanswered. However, our results provide approaches for future investigations. Altogether, MBM still present a substantial unmet medical need that should be addressed by further preclinical research and prospective clinical studies focussing on brain-specific resistance mechanisms and new treatment strategies.

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Conflict of interest statement

R. R. received Honoraria from Novartis and Amgen, reimbursement of travel/accommodations expenses from Bristol-Myers Squibb and Amgen.

A.F. serves as consultant to Roche, Novartis, MSD, received travel grants from Roche, Novartis, BMS and speaker fees from Roche, Novartis, BMS, MSD.

C.B. has received speaker's fees and/or advisor's honoraria and/or travel support by Amgen, AstraZeneca, BMS, Merck, MSD, Novartis, Pierre Fabre, Regeneron, Sanofi-Aventis and Roche.

J.U. is on the advisory board or has received honoraria and travel support from Amgen, BMS, GSK, LeoPharma, MSD, Novartis, Pierre Fabre and Roche.

R.G. received Honoraria from Almirall Hermal, Amgen, AstraZeneca, Bristol-Myers Squibb, Incyte, Leo Pharma, Merck Serono, MSD, Novartis, Pierre Fabre, Pfizer, Roche and SUN, research funding from Johnson & Johnson, Novartis and Pfizer and travel & accommodations support from Bristol-Myers Squibb, Merck Serono, Pierre Fabre and Roche.

P.T. has received speaker's honoraria from BMS, Novartis and Roche, consultant's honoraria from BMS, Merck, Novartis and Roche and travel support from BMS and Roche.

D.D. has received speaker's fees and/or advisor's honoraria and/or travel support by Amgen, BMS, MSD, Novartis, Pierre Fabre, Sanofi-Aventis and Roche.

M.G. has received travel support and/or speaker's fees and/or advisor's honoraria by Roche, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, MSD and Amgen.

S.B. is on the advisory board of Amgen.

F.M. 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2018.12.023>.

References

- [1] Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol* 2004;22:1293–300. <https://doi.org/10.1200/JCO.2004.08.140>.
- [2] Kuske M, Rauschenberg R, Garzarolli M, Meredyth-Stewart M, Beissert S, Troost EGC, et al. Melanoma brain metastases: local therapies, targeted therapies, immune checkpoint inhibitors and their combinations—chances and challenges. *Am J Clin Dermatol* 2018;1–13. <https://doi.org/10.1007/s40257-018-0346-9>.
- [3] Kruser TJ, Gondi V, Sperduto PW, Brown PD, Mehta MP. Omitting radiosurgery in melanoma brain metastases: a drastic and dangerous de-escalation. *Lancet Oncol* 2018;19:e366. [https://doi.org/10.1016/S1470-2045\(18\)30439-X](https://doi.org/10.1016/S1470-2045(18)30439-X).
- [4] Mornex F, Thomas L, Mohr P, Hauschild A, Delaunay MM, Lesimple T, et al. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res* 2003;13:97–103. <https://doi.org/10.1097/01.cmr.0000043161.28051.2d>.
- [5] Schild SE, Behl D, Markovic SN, Brown PD, Sande JR, Deming RL, et al. Brain metastases from melanoma: is there a role for concurrent temozolomide in addition to whole brain radiation therapy? *Am J Clin Oncol* 2010;33:633–6. <https://doi.org/10.1097/COC.0b013e3181c4c54b>.
- [6] Davies MA, Saiag P, Robert C, Grob J-J, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 2017;18:863–73. [https://doi.org/10.1016/S1470-2045\(17\)30429-1](https://doi.org/10.1016/S1470-2045(17)30429-1).
- [7] Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre

- randomised phase 2 study. *Lancet Oncol* 2018;19:672–81. [https://doi.org/10.1016/S1470-2045\(18\)30139-6](https://doi.org/10.1016/S1470-2045(18)30139-6).
- [8] Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 2018;379:722–30. <https://doi.org/10.1056/NEJMoa1805453>.
- [9] Peuvrel L, Saint-Jean M, Quéreux G, Brocard A, Khammari A, Knol AC, et al. Incidence and characteristics of melanoma brain metastases developing during treatment with vemurafenib. *J Neuro Oncol* 2014;120:147–54. <https://doi.org/10.1007/s11060-014-1533-z>.
- [10] Rekers NH, Troost EGC, Zegers CML, Germeraad WTV, Dubois LJ, Lambin P. Stereotactic ablative body radiotherapy combined with immunotherapy: present status and future perspectives. *Cancer Radiother* 2014;18:391–5. <https://doi.org/10.1016/j.canrad.2014.06.012>.
- [11] Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* 2005;11:728–34.
- [12] Stamell EF, Wolchok JD, Gnjatich S, Lee NY, Brownell I. The abscopal effect associated with a systemic anti-melanoma immune response. *Int J Radiat Oncol Biol Phys* 2013;85:293–5. <https://doi.org/10.1016/j.ijrobp.2012.03.017>.
- [13] Chicas-Sett R, Morales-Orue I, Rodriguez-Abreu D, Lara-Jimenez P. Combining radiotherapy and ipilimumab induces clinically relevant radiation-induced abscopal effects in metastatic melanoma patients: a systematic review. *Clin Transl Radiat Oncol* 2018;9:5–11. <https://doi.org/10.1016/j.ctro.2017.12.004>.
- [14] Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys* 2004;58:862–70. <https://doi.org/10.1016/j.ijrobp.2003.09.012>.
- [15] Hecht M, Zimmer L, Loquai C, Weishaupt C, Gutzmer R, Schuster B, et al. Radiosensitization by BRAF inhibitor therapy-mechanism and frequency of toxicity in melanoma patients. *Ann Oncol Off J Eur Soc Med Oncol* 2015;26:1238–44. <https://doi.org/10.1093/annonc/mdv139>.
- [16] Sambade MJ, Peters EC, Thomas NE, Kaufmann WK, Kimple RJ, Shields JM. Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032. *Radiother Oncol* 2011;98:394–9. <https://doi.org/10.1016/j.radonc.2010.12.017>.
- [17] Satzger I, Degen A, Asper H, Kapp A, Hauschild A, Gutzmer R. Serious skin toxicity with the combination of BRAF inhibitors and radiotherapy. *J Clin Oncol* 2013;31:e220–2. <https://doi.org/10.1200/JCO.2012.44.4265>.
- [18] Kim JM, Miller JA, Kotecha R, Xiao R, Juloori A, Ward MC, et al. The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies. *J Neuro Oncol* 2017;133:357–68. <https://doi.org/10.1007/s11060-017-2442-8>.
- [19] Fang P, Jiang W, Allen P, Glitza I, Guha N, Hwu P, et al. Radiation necrosis with stereotactic radiosurgery combined with CTLA-4 blockade and PD-1 inhibition for treatment of intracranial disease in metastatic melanoma. *J Neuro Oncol* 2017;133:595–602. <https://doi.org/10.1007/s11060-017-2470-4>.
- [20] Choong ES, Lo S, Drummond M, Fogarty GB, Menzies AM, Guminski A, et al. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. *Eur J Cancer* 2017;75:169–78. <https://doi.org/10.1016/j.ejca.2017.01.007>.
- [21] Gaudy-Marqueste C, Dussouil AS, Carron R, Troin L, Malissen N, Loundou A, et al. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. *Eur J Cancer* 2017;84:44–54. <https://doi.org/10.1016/j.ejca.2017.07.017>.
- [22] Ahmed KA, Abuodeh YA, Echevarria MI, Arrington JA, Stallworth DG, Hogue C, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. *Ann Oncol* 2016;27:2288–94. <https://doi.org/10.1093/annonc/mdw417>.
- [23] Tio M, Wang X, Carlino MS, Shivalingam B, Fogarty GB, Guminski AD, et al. Survival and prognostic factors for patients with melanoma brain metastases in the era of modern systemic therapy. *Pigment Cell Melanoma Res* 2018;31:509–15. <https://doi.org/10.1111/pcmr.12682>.
- [24] Qian JM, Yu JB, Kluger HM, Chiang VLS. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. *Cancer* 2016;122:3051–8. <https://doi.org/10.1002/cncr.30138>.
- [25] Fang P, Boehling NS, Koay EJ, Bucheit AD, Jakob JA, Settle SH, et al. Melanoma brain metastases harboring BRAF V600K or NRAS mutations are associated with an increased local failure rate following conventional therapy. *J Neuro Oncol* 2018;137:67–75. <https://doi.org/10.1007/s11060-017-2695-2>.
- [26] Ahmed KA, Stallworth DG, Kim Y, Johnstone PAS, Harrison LB, Caudell JJ, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. *Ann Oncol* 2016;27:434–41. <https://doi.org/10.1093/annonc/mdv622>.
- [27] Taggart D, Andreou T, Scott KJ, Williams J, Rippaus N, Brownlie RJ, et al. Anti-PD-1/anti-CTLA-4 efficacy in melanoma brain metastases depends on extracranial disease and augmentation of CD8+ T cell trafficking. *Proc Natl Acad Sci U S A* 2018;115:E1540–9. <https://doi.org/10.1073/pnas.1714089115>.
- [28] Staudt M, Lasithiotakis K, Leiter U, Meier F, Eigentler T, Bamberg M, et al. Determinants of survival in patients with brain metastases from cutaneous melanoma. *Br J Cancer* 2010;102:1213–8. <https://doi.org/10.1038/sj.bjc.6605622>.
- [29] Schmieder K, Keilholz U, Combs S. The interdisciplinary management of brain metastases. *Dtsch Aertzblatt Online* 2016. <https://doi.org/10.3238/arztebl.2016.0415>.
- [30] Broadbent AM, Hruba G, Tin MM, Jackson M, Firth I. Survival following whole brain radiation treatment for cerebral metastases: an audit of 474 patients. *Radiother Oncol* 2004;71:259–65. <https://doi.org/10.1016/j.radonc.2004.02.019>.
- [31] Oehlke O, Wucherpfennig D, Fels F, Frings L, Egger K, Weyerbrock A, et al. Whole brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: local tumour control and survival. *Strahlenther Onkol* 2015;191:461–9. <https://doi.org/10.1007/s00066-014-0808-9>.
- [32] Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLKG0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387–95. [https://doi.org/10.1016/S1470-2045\(14\)70061-0](https://doi.org/10.1016/S1470-2045(14)70061-0).
- [33] Gaudy-Marqueste C, Regis J-M, Muracciole X, Laurans R, Richard M-A, Bonerandi J-J, et al. Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65:809–16. <https://doi.org/10.1016/j.ijrobp.2006.01.024>.
- [34] Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol* 2018;19:672–81. [https://doi.org/10.1016/S1470-2045\(18\)30139-6](https://doi.org/10.1016/S1470-2045(18)30139-6).
- [35] Ly D, Bagshaw HP, Anker CJ, Tward JD, Grossmann KF, Jensen RL, et al. Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment. *J Neurosurg* 2015;123:395–401. <https://doi.org/10.3171/2014.9.JNS141425>.
- [36] Wolf A, Zia S, Verma R, Pavlick A, Wilson M, Golfinos JG, et al. Impact on overall survival of the combination of BRAF inhibitors and stereotactic radiosurgery in patients with melanoma brain

- metastases. *J Neuro Oncol* 2016;127:607–15. <https://doi.org/10.1007/s11060-016-2072-6>.
- [37] Ahmed KA, Freilich JM, Sloot S, Figura N, Gibney GT, Weber JS, et al. LINAC-based stereotactic radiosurgery to the brain with concurrent vemurafenib for melanoma metastases. *J Neuro Oncol* 2015;122:121–6. <https://doi.org/10.1007/s11060-014-1685-x>.
- [38] Shannan B, Matschke J, Chauvistre H, Vogel F, Klein D, Meier F, et al. PO-332 Sequence-dependent cross-resistance of combined radiotherapy plus BRAFv600e-inhibition in melanoma. *Tumour Heterog. – Evol.*, vol. 3. BMJ Publishing Group Ltd; 2018. p. A358.1–358. <https://doi.org/10.1136/esmooopen-2018-EACR25.844>.
- [39] Hecht M, Meier F, Zimmer L, Polat B, Loquai C, Weishaupt C, et al. Clinical outcome of concomitant vs interrupted BRAF inhibitor therapy during radiotherapy in melanoma patients. *Br J Cancer* 2018;118:785–92. <https://doi.org/10.1038/bjc.2017.489>.
- [40] Sperduto PW, Jiang W, Brown PD, Braunstein S, Sneed P, Wattson DA, et al. The prognostic value of BRAF, C-KIT, and NRAS mutations in melanoma patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2017;98:1069–77. <https://doi.org/10.1016/j.ijrobp.2017.03.030>.
- [41] Kohutek ZA, Yamada Y, Chan TA, Brennan CW, Tabar V, Gutin PH, et al. Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases. *J Neuro Oncol* 2015;125:149–56. <https://doi.org/10.1007/s11060-015-1881-3>.
- [42] Gaudy Marqueste C, Carron R, Amatore F, Malissen N, Muracciole, Xavier Loundou A. Safety and results of anti-PD1 combined with radiosurgery for the treatment of melanoma brain metastases. *J Clin Oncol* 2017;35(abstr):9552. <https://doi.org/10.1200/JCO.2017.35>.
- [43] Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol* 2011;6:48. <https://doi.org/10.1186/1748-717X-6-48>.
- [44] Donato J, Campigotto F, Uhlmann EJ, Coletti E, Neuberger D, Weber GM, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. *Blood* 2015;126:494–9. <https://doi.org/10.1182/blood-2015-02-626788>.
- [45] Le Rhun E, Dhermain F, Vogin G, Reyns N, Metellus P. Radionecrosis after stereotactic radiotherapy for brain metastases. *Expert Rev Neurother* 2016;16:903–14. <https://doi.org/10.1080/14737175.2016.1184572>.