Clinical and radiological response of BRAF inhibition and MEK inhibition in patients with brain metastases from BRAF-mutated melanoma

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Patients with brain metastases (BM) from melanoma have an overall survival (OS) of 2–6 months after whole-brain radiotherapy. Targeted therapy (TT) is an effective treatment for BRAF-mutated metastatic melanoma. Moreover, recent studies indicate intracranial responses of TT in patients with BM. We analyzed 146 patients with BM from BRAF-mutated melanoma treated with vemurafenib, dabrafenib, or dabrafenib + trametinib between 2010 and 2016. We determined clinical and radiological response, progression-free survival (PFS), and OS. Median OS of patients treated with dabrafenib + trametinib was 11.2 months [*n* = 30; 95% confidence interval (CI): 6.8–15.7], 8.8 months for dabrafenib alone (*n* = 31; 95% CI: 3.9–13.7), and 5.7 months for vemurafenib (*n* = 85; 95% CI: 4.6–6.8). A significantly longer OS was observed in the dabrafenib + trametinib group than in the vemurafenib group (hazard ratio for death, 0.52; 95% CI: 0.30–0.89; *P* = 0.02). Median intracranial PFS of all patients was 4.1 months. Median intracranial PFS for patients treated with dabrafenib + trametinib was 5.8 months (95% CI: 3.2–8.5), 5.7 months (95% CI: 3.0–8.4) for dabrafenib, and 3.6 months (95% CI: 3.5–3.8) for vemurafenib (*P* = 0.54). A total of 63 (43%) patients had symptomatic BM. Intracranial disease control rate at 8 weeks in these patients was 65 versus 70% extracranially. Neurological symptoms improved in 46% of patients with symptomatic BM, whereas in 21%, they remained stable. Median OS in patients with BM from BRAF-mutated melanoma treated with dabrafenib + trametinib was significantly longer than for vemurafenib. Improvement of neurological symptoms was seen in almost half of the patients with symptomatic BM treated with TT. *Melanoma Res* 28:126–133 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

The incidence of metastatic melanoma has steadily increased over the past decades [1]. The incidence of brain metastases (BM) in patients with melanoma ranges from 10 to 73% based on clinical and post-mortem series [2–7]. BM from malignant melanoma carry a poor prognosis, with a median survival of less than 6 months [8]. Before 2011, therapeutic options for BM from melanoma were local therapy such as surgery and/or cranial radiotherapy (RT) and sometimes systemic chemotherapy. Since 2011, antibodies against cytotoxic T-lymphocyte protein 4 (ipilimumab) and antibodies against programmed cell death receptor-1 (nivolumab and pembrolizumab) were approved for treatment of metastatic melanoma. Moreover, 40–60% of cutaneous melanomas have a mutation in the gene encoding *BRAF*, which leads to constitutive activation of downstream signaling through the mitogen-activated protein kinase pathway [9,10]. Vemurafenib and dabrafenib are potent inhibitors of the mutated BRAF protein. Both have shown to improve progression-free survival (PFS) and overall survival (OS) when compared with the chemotherapeutic dacarbazine in randomized phase 3 trials [11,12]. The combination of BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) (e.g. vemurafenib + cobimetinib or dabrafenib + trametinib) has shown to improve OS even further [13–15]. In prospective studies, BRAFi showed intracranial responses in both patients with asymptomatic BM and those with symptomatic brain metastases (sBM) from BRAF-mutated melanoma ranging from 31–40% with a duration of 4–7 months [16,17]. The effect of the combination of BRAFi and MEKi in patients with melanoma with BM has recently been described by Davies *et al.* [18]. In this prospective phase 2 study, the effect of dabrafenib + trametinib in four different patient cohorts with BM from melanoma [based on mutation status (BRAFV600E vs. BRAFV600D/K/R), previous local brain therapy and symptoms of BM] was evaluated. Dabrafenib + trametinib was active in all four groups, with intracranial response rates ranging from 44 to 59%. The aim of our observational study is to compare radiological response, neurological benefit, PFS, and OS of BRAFi as monotherapy, or in

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combination with a MEKi, in patients with BRAF-mutated melanoma BM.

Patients and methods

Patients

This retrospective study included patients with metastatic melanoma and newly diagnosed or progressive BM treated at The Netherlands Cancer Institute between 2010 and 2016 in the Global Safety Study with vemurafenib, or treated with a BRAFi ± MEKi after EMA approval. All patients had stage IV melanoma that tested positive for a mutation in the *BRAF* gene (i.e. V600E, V600K). Other inclusion criteria were age older than 18 years; measurable or nonmeasurable disease (RECIST, version 1.1), and a WHO performance status of 0–3. Patients were also allowed to have received prior systemic therapy for metastatic melanoma. Exclusion criteria were any other form of cancer within the past 2 years, except for basal cell carcinomas, squamous cell carcinoma, or cervical carcinoma *in situ*; concurrent administration of any other anticancer therapies; known hypersensitivity to a BRAFi; pregnant or lactating women; inability to swallow tablets; myocardial infarction, severe angina pectoris, congestive heart failure, or a cerebral vascular accident within 6 months before initiation of therapy; history of congenital long QT syndrome; or unwillingness to practice appropriate birth control. This study was evaluated by the Institutional Review Board (IRB) and was deemed exempt from IRB review, as it is a retrospective study. For response analysis, patients were categorized into three groups (vemurafenib, dabrafenib, or dabrafenib + trametinib). Patients who switched from one targeted therapy (TT) to another TT were placed in the group of the drug that they were taking during computed tomography (CT) thorax/abdomen and MRI brain, if they had used that (combination of) drug(s) for more than 50% of the time. All patients were discussed in a multidisciplinary meeting before starting TT.

Treatment

Patients received treatment in standard dosages: vemurafenib 960 mg twice daily, dabrafenib 150 mg twice daily, and trametinib 2 mg once daily. One cycle equals 4 weeks of treatment. Patients visited the outpatient clinic every 4 weeks for physical examination and blood sampling. Every 8 weeks, extracranial disease was assessed by CT scans of thorax and abdomen and intracranial disease by MRI of the brain. Lactate dehydrogenase (LDH) and S100 serum levels were measured at baseline, at a maximum of 28 days before starting TT.

Response

Extracranial response was determined by RECIST 1.1. For intracranial response, we used a modified RECIST 1.1, which allowed us to include BM of at least 5 mm. Assessment of both extracranial and intracranial responses was done by a (neuro-)radiologist. Intracranial disease control rate (DCR) was defined as stable disease (SD) + partial response (PR) + complete response (CR) and was measured at 8 weeks after treatment started and every 8 weeks thereafter. Clinical response was determined by retrospective analysis of the neurological symptoms in the electronic patient records. Neurological symptoms (i.e. headache, nausea, vomiting, cognitive function disorder, ataxia, and seizures) were scored before treatment and every 4 weeks after treatment. They were classified as worsened, stable, or improved. Symptomatic patients were those who had at least one neurological symptom. PFS was measured from the date of starting treatment until progression of disease (PD) as measured by contrast-enhanced CT thorax/abdomen and contrast-enhanced MRI brain, date of last known follow-up, death, or switch of therapy. OS was measured from the date of starting treatment until death by any cause, or date of last known follow-up.

Statistical analysis

For categorical variables, data are presented as a number (%) and for continuous variables as median with range. Kaplan–Meier curves were used to determine the median OS, median intracranial PFS, and extracranial PFS and compared using log-rank tests. Multivariate Cox regression analysis was used to assess independent prognostic factors for survival. Results are described as hazard ratios (HRs), and *P* values are based on the Wald test. Log-rank tests were used to compare groups. Data were analyzed using SPSS Statistics software (IBM, version 22, Armonk, New York, United States). A *P* value of less than 0.05 was considered statistically significant throughout the entire study.

Results

Patient and treatment characteristics

A total of 146 patients with BM from BRAF-mutated melanoma were treated with TT between January 2010 and March 2016. Median age was 54 years (range: 23–80 years), and 55% of the patients were male ($n = 80$). Melanoma BRAF mutation status was V600E in 129 patients (88%); V600K in 12 (8%) patients; V600R in two (1%) patients; and K601E, L579R, and $V600_{unknown}$ in one patient each. Median time from diagnosis of the primary melanoma till BM was 39.4 months (range: 0–373 months). Thirty-two (22%) patients had received systemic therapy (e.g. dacarbazine or ipilimumab) for extracranial metastases, but none had been treated with TT. Of these 32 patients, 22 (69%) had received immunotherapy before starting TT. All patients who had received systemic therapy before starting TT had PD. Mean time between last cycle of prior systemic therapy and starting TT was 4.1 months (range: 0–37 months).

At study start, BM were either newly diagnosed ($n = 130$, 89%), or TT was given for progressive BM ($n = 16$, 11%). In 74% of patients, TT was given as sole treatment and in 26% as adjuvant treatment directly after RT. Eleven (8%) patients had intracranial surgery for BM, with start

of TT after surgery for remaining BM. Forty-nine (39%) patients received RT before start of TT: whole-brain RT (5×4 Gy) ($n = 33$, 67%), stereotactic RT ($n = 13$, 27%), or both ($n = 3$, 6%). In 46 (32%) patients, BM was larger than 2.0 cm. Thirty-eight (26%) patients had a single BM, 52 (36%) patients 2–5 BM, and 56 (38%) patients had more than 5 BM. Without taking into account intracranial metastases and serum LDH levels, 12 (8%) patients had M1a disease, 16 (11%) patients M1b disease, and 104 (71%) patients M1c disease. Fourteen (10%) patients had no extracranial disease. Twelve patients had a switch in TT during treatment: 11 cases owing to toxicities and one patient because trametinib became available. Patient and treatment characteristics are summarized in Table 1. No significant differences in characteristics were seen among the three treatment groups.

Treatment during and after targeted therapy

During TT, 44 (30%) patients received RT owing to progression of BM: 26 (59%) patients whole-brain RT and 18 (41%) patients stereotactic RT. Twenty-three (52%) patients continued TT as treatment beyond progression. Overall, 38 (26%) patients received systemic therapy after PD on TT, which was immunotherapy in 95% of patients. There were no significant differences in systemic treatment beyond progression among the three patient groups: 19 (22%) patients were treated in the vemurafenib group, whereas this was the case for 13 (42%) patients in the dabrafenib and six (20%) patients in the dabrafenib + trametinib groups, respectively. ($P = 0.07$).

Intracranial and extracranial disease control rate

The mean number of cycles of TT was 6 (range: 1–34). Intracranial DCR at 8 weeks after treatment start of all patients was 68% (37% SD, PR 26%, and CR 5%), whereas extracranial DCR was 74% (32% SD, 40% PR, and 2% CR). Intracranial DCR in both patients with sBM and those with asymptomatic BM was borderline significantly lower than the extracranial DCR in both groups (sBM: intracranial 65% vs. extracranial 70%; $P = 0.04$, asymptomatic BM: intracranial 70% vs. extracranial 77%; $P = 0.04$; Table 2). Intracranial DCR was 81% (16/42 SD and 18/42 PR) in the group of patients who received prior local RT, compared with 73% (38/89 SD, 20/89 PR, and 7/89 CR) in the group of patients who did not receive prior local RT ($P = 0.04$). There was no statistically significant difference in intracranial DCR in patients who received RT during TT (67%; 17/43 SD, 11/43 PR, and 1/43 CR) versus those who did not (80%; 37/88 SD, 27/88 PR, and 6/87 CR; $P = 0.37$).

Clinical–neurological response

In 29 (46%) of 63 patients with sBM, neurological symptoms improved after TT; in 13 (21%) patients, neurological symptoms remained stable; and in 16 (25%) patients, symptoms worsened during treatment. Five (8%) patients with sBM were not evaluable. Eleven (32%) of 34 patients with sBM treated with vemurafenib showed improvement of neurological symptoms, whereas this was the case for 12 (63%) of 19 patients treated with dabrafenib and six (60%) of 10 patients treated with the combination of dabrafenib + trametinib ($P = 0.32$). Overall, 45% of patients with sBM who used dexamethasone to alleviate neurological symptoms before TT could stop dexamethasone after TT. In the group of patients who had not received prior local RT before TT clinical–neurological benefit was 84% (6/31 stable and 20/31 improved), whereas this was 59% (7/27 stable and 9/27 improved) in the patient group who had received prior local RT ($P = 0.04$). No statistical difference was noted in clinical–neurological benefit for patients receiving RT during TT (71%; 5/14 stable and 5/14 improved) and patients who did not (73%; 8/44 stable and 24/44 improved, $P = 0.33$).

Intracranial progression-free survival

The median intracranial PFS of all patients was 4.1 months [95% confidence interval (CI): 3.2–5.0]. Median intracranial PFS for vemurafenib was 3.6 months (95% CI: 3.5–3.8), for dabrafenib was 5.7 months (95% CI: 3.0–8.4) and for the combination of dabrafenib + trametinib was 5.8 months (95% CI: 3.2–8.5). No significant difference in intracranial PFS was observed between dabrafenib + trametinib and vemurafenib (HR for disease progression = 1.23; 95% CI: 0.77–1.96), nor was there a significant difference in intracranial PFS between dabrafenib + trametinib vs. dabrafenib (HR for disease progression = 1.05; 95% CI: 0.56–1.97). Median intracranial PFS in patients with SD ($n = 54$) was not significantly different from patients with PR or CR ($n = 45$), 5.5 months (95% CI: 4.1–6.8) versus 6.1 months (95% CI: 5.1–7.2; $P = 0.11$). RT before TT did not significantly affect intracranial PFS [4.3 months with prior RT versus 4.1 months without ($P = 0.47$)]. RT during TT did also not significantly influence intracranial PFS (4.8 months with RT during TT vs. 4.1 months without RT; $P = 0.51$). A normal serum S100B level and no use of dexamethasone during TT were significant favorable prognostic factors for intracranial PFS in univariate Cox regression analysis. In multivariate Cox regression analysis, a normal serum S100B level remained a significant favorable prognostic factor for intracranial PFS (HR = 3.1; 95% CI: 1.6–6.1; $P < 0.01$; Table 3).

Extracranial progression-free survival

The median extracranial PFS for all patients was 4.6 months (95% CI: 3.4–5.9). Median extracranial PFS for vemurafenib was 4.0 months (95% CI: 3.3–4.7), for dabrafenib was 5.8 months (95% CI: 3.3–8.3), and for the combination of dabrafenib + trametinib was 7.3 months (95% CI: 3.9–10.8). No significant difference in extracranial PFS was observed between dabrafenib + trametinib and vemurafenib (HR = 1.5; 95% CI: 0.95–2.50), nor was there a significant difference in

Table 1 Baseline characteristics of patients with brain metastases from BRAF-mutated malignant melanoma

Characteristics	Vemurafenib ($n=85$)	Dabrafenib ($n=31$)	Dabrafenib + trametinib ($n=30$)	Total ($n=146$)	*P* value
Age (years)					0.15
Median (range)	53 (23–80)	52 (29–78)	58 (37–80)	54 (23–80)	
Sex [*n* (%)]					0.17
Male	43 (51)	16 (52)	21 (70)	80 (55)	
Female	42 (49)	15 (48)	9 (30)	66 (45)	
WHO performance status [*n* (%)][a]					0.53
0	36 (42)	13 (42)	16 (53)	65 (45)	
1	29 (34)	13 (42)	11 (37)	53 (36)	
2	14 (17)	5 (16)	2 (7)	21 (14)	
3	6 (7)	0 (0)	1 (3)	7 (5)	
Lactate dehydrogenase [*n* (%)]					0.39
< ULN	31 (36)	13 (42)	15 (50)	59 (40)	
> ULN	49 (58)	17 (55)	13 (43)	79 (54)	
Unknown	5 (6)	1 (3)	2 (7)	8 (6)	
S100B [*n* (%)]					0.87
≤ ULN	14 (16)	6 (19)	6 (20)	26 (18)	
> ULN	66 (78)	23 (74)	22 (73)	111 (76)	
Unknown	5 (6)	2 (7)	2 (7)	9 (6)	
Brain metastases ≥ 2 cm [*n* (%)]					0.42
Yes	30 (35)	7 (23)	9 (30)	46 (32)	
No	55 (65)	24 (77)	21 (70)	100 (68)	
Number of brain metastases [*n* (%)]					0.86
Single	20 (23)	9 (29)	9 (30)	38 (26)	
2–5	32 (38)	9 (29)	11 (37)	52 (36)	
> 5	33 (39)	13 (42)	10 (33)	56 (38)	
Symptoms of brain metastases [*n* (%)]					0.06
Symptomatic	34 (40)	19 (61)	10 (33)	63 (43)	
Asymptomatic	51 (60)	12 (39)	20 (67)	83 (57)	
Patients with symptomatic BM dependent of corticosteroids [*n* (%)]					0.89
Yes	21 (62)	12 (63)	7 (70)	40 (64)	
No	13 (38)	7 (37)	3 (30)	23 (36)	
Radiotherapy during TT [*n* (%)]					0.96
None	60 (71)	21 (68)	21 (70)	102 (70)	
Stereotactic radiotherapy	7 (8)	7 (22)	4 (13)	18 (12)	
Whole-brain radiotherapy	18 (21)	3 (10)	5 (17)	26 (18)	
Surgery of brain metastases [*n* (%)]					0.48
Yes	9 (11)	3 (10)	1 (3)	13 (9)	
No	76 (89)	28 (90)	29 (97)	133 (91)	
Treatment after progression on TT [*n* (%)]					0.07
Yes	19 (22)	13 (42)	6 (20)	38 (26)	
Anti-CTLA-4 monotherapy	10 (53)	3 (23)	2 (33)	15 (39)	
Anti-PD1 monotherapy	1 (5)	7 (54)	4 (66)	12 (32)	
Anti-CTLA-4 and subsequent anti-PD1	5 (26)	1 (8)	0 (0)	6 (16)	
Concurrent anti-CTLA-4 and anti-PD1	1 (5)	2 (15)	0 (0)	3 (8)	
Temozolomide	2 (11)	0 (0)	0 (0)	2 (5)	
No	66 (78)	18 (58)	24 (80)	108 (74)	

BM, brain metastases; CTLA-4, cytotoxic T-lymphocyte protein 4; PD1, programmed cell death protein 1; TT, targeted therapy; ULN, upper limit of normal.
[a]The WHO performance status of 0 indicates that the patient is asymptomatic and fully active. 1: the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2: ambulatory and capable of all self-care but unable to carry out any work activities, and 3: > 50% in bed, but not bed bound. Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.

extracranial PFS between dabrafenib + trametinib and dabrafenib (HR = 1.71; 95% CI: 0.88–3.31). A normal serum S100B level, a normal serum LDH level, less than or equal to 5 BM, and RT during TT were favorable prognostic factors for extracranial PFS in univariate Cox regression analysis. In multivariate Cox regression analysis, a normal serum S100B level remained an independent favorable prognostic factor (Table 4).

Overall survival

At the time of analysis, 117 (80%) patients had died. All but two deaths were because of metastatic melanoma. Median OS of the entire cohort was 6.6 months (95% CI: 5.7–7.4). Median OS of patients treated with dabrafenib + trametinib was 11.2 months (95% CI: 6.8–15.7), for patients treated with dabrafenib only was 8.8 months (95% CI: 3.9–13.7), and for patients treated with vemurafenib was 5.7 months (95% CI: 4.6–6.8). A significantly longer OS was observed in the dabrafenib + trametinib group as compared with the vemurafenib group (HR for death = 0.52; 95% CI: 0.30–0.89; $P = 0.02$). No significant difference was seen between dabrafenib + trametinib and dabrafenib only (HR for death = 0.54; 95% CI: 0.26–1.1; $P = 0.10$) (Fig. 1a). Moreover, no significant difference was found between the median OS of patients with sBM and those with asymptomatic BM, 6.6 months (95% CI: 5.6–7.6) and 6.4 months (95% CI: 4.2–8.5; $P = 0.22$), respectively.

Table 2 Disease control rate, progression-free survival, clinical response rate, and overall survival in patients with brain metastases from BRAF-mutated malignant melanoma treated with targeted therapy

	Vemurafenib ($n=85$)	Dabrafenib ($n=31$)	Dabrafenib + trametinib ($n=30$)	Total ($n=146$)	*P* value
Intracranial response [*n* (%)]					0.60
CR	3 (3)	1 (3)	3 (10)	7 (5)	
PR	23 (27)	5 (16)	10 (33)	38 (26)	
SD	34 (40)	15 (48)	5 (17)	54 (37)	
PD	16 (19)	7 (23)	9 (30)	32 (22)	
NE	9 (11)	3 (10)	3 (10)	15 (10)	
Intracranial DCR	60 (71)	21 (68)	18 (60)	99 (68)	
Extracranial response [*n* (%)]					0.38
CR	3 (3)	0 (0)	0 (0)	3 (2)	
PR	34 (40)	11 (35)	13 (43)	58 (40)	
SD	27 (32)	12 (39)	8 (27)	47 (32)	
PD	5 (6)	3 (10)	5 (17)	13 (9)	
NE	16 (19)	5 (16)	4 (13)	25 (17)	
Extracranial DCR	64 (75)	23 (74)	21 (70)	108 (74)	
Intracranial PFS (95% CI) (months)	3.6 (3.5–3.8)	5.7 (3.0–8.4)	5.8 (3.2–8.5)	4.1 (3.2–5.0)	0.54
Extracranial PFS (95% CI) (months)	4.0 (3.3–4.7)	5.8 (3.3–8.3)	7.3 (3.9–10.8)	4.6 (3.4–5.9)	0.20
Clinical intracranial response [*n* (%)]					0.32
Improved	11 (32)	12 (63)	6 (60)	29 (46)	
Stable	8 (24)	4 (21)	1 (10)	13 (21)	
Worsened	12 (35)	2 (11)	2 (20)	16 (25)	
NE	3 (9)	1 (5)	1 (10)	5 (8)	
Overall survival (95% CI) (months)	5.7 (4.6–6.8)	8.8 (3.9–13.7)	11.2 (6.8–15.7)	6.6 (5.7–7.4)	**0.04**

CI, confidence interval; CR, complete response; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; ULN, upper limit of normal.
Significant differences are in bold.

Table 3 Univariate and multivariate Cox regression analyses for intracranial progression-free survival

				Univariate analysis			Multivariate analysis	
Parameters	Total (*n*)	Categories	*n* (%)	Median intracranial PFS (months)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment	146	Vemurafenib	85 (31)	3.6	1		1	
		Dabrafenib	30 (58)	5.7	0.8 (0.5–1.3)	0.38	0.7 (0.4–1.2)	0.15
		Dabrafenib + trametinib	21 (21)	5.8	0.8 (0.5–1.3)	0.39	1.0 (0.6–1.6)	0.93
WHO performance status[a]	146	0–1	118 (28)	4.4	1		1	
		2–3	81 (19)	3.2	1.4 (0.9–2.3)	0.19	1.5 (0.9–2.7)	0.14
Lactate dehydrogenase	138	≤ ULN	59 (79)	5.4	1		1	
		> ULN	43 (57)	3.6	1.4 (1.0–2.1)	0.07	1.1 (0.7–1.7)	0.67
S100B	137	≤ ULN	26 (111)	11.3	1		1	
		> ULN	19 (81)	3.6	2.3 (1.4–3.9)	**< 0.01**	3.1 (1.6–6.1)	**< 0.01**
Brain metastases ≥ 2 cm	146	No	100 (46)	4.4	1		1	
		Yes	69 (31)	3.6	1.4 (0.9–2.0)	0.10	1.2 (0.8–1.9)	0.38
Number of brain metastases	146	≤ 5	90 (56)	4.7	1		1	
		> 5	62 (38)	3.6	1.3 (0.9–2.0)	0.13	1.4 (0.9–2.2)	0.11
Symptoms of brain metastases	146	Asymptomatic	83 (63)	5.1	1		1	
		Symptomatic	57 (43)	3.7	1.3 (0.9–1.9)	0.14	1.1 (0.7–1.7)	0.73
Radiotherapy during TT	146	No	102 (44)	4.1	1.1 (0.8–1.7)	0.51	0.7 (0.4–1.1)	0.14
		Yes	70 (30)	4.8	1		1	
Dexamethasone during TT	146	No	52 (94)	5.8	1		1	
		Yes	36 (64)	3.6	1.6 (1.1–2.4)	**0.01**	1.4 (0.9–2.2)	0.15

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TT, targeted therapy; ULN, upper limit of normal.
[a]The WHO performance status of 0 indicates that the patient is asymptomatic and fully active. 1: that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2: ambulatory and capable of all self-care but unable to carry out any work activities and 3: > 50% in bed, but not bed bound. Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.
Significant differences are in bold.

Prognostic factors associated with overall survival

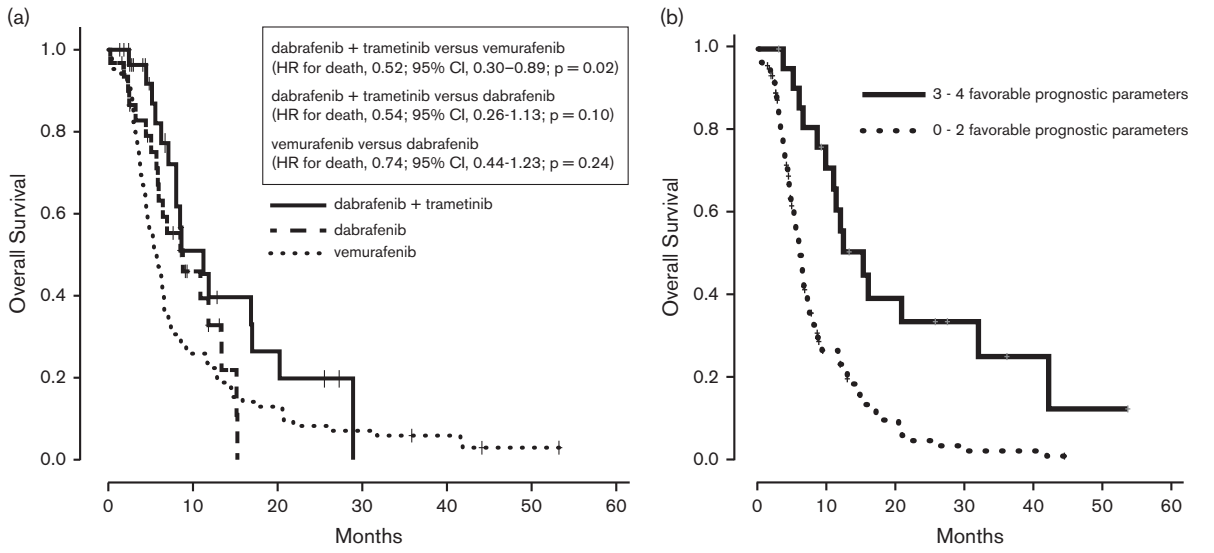
A normal serum LDH level, a normal serum S100B level, less than or equal to 5 BM, RT during TT, no use of dexamethasone during TT, and treatment after failing TT were significant favorable prognostic factors in univariate Cox regression analysis. Equal to or less than 5 BM, RT during TT, no use of dexamethasone during TT, and treatment after failing TT remained independent favorable prognostic factors for OS (Table 5). Patients who had three or four favorable prognostic factors had a median OS of 15.1 months (95% CI: 9.7–20.5), compared with 6.0 months (95% CI: 5.2–6.7; $P < 0.01$) for patients with 0–2 favorable prognostic factor(s) (Fig. 1b).

Table 4 Univariate and multivariate Cox regression analyses for extracranial progression-free survival

				Univariate analysis			Multivariate analysis	
Parameters	Total (*n*)	Categories	*n* (%)	Median extracranial PFS (months)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment	146	Vemurafenib	85 (31)	4.0	1		1	
		Dabrafenib	30 (58)	5.8	1.0 (0.6–1.6)	0.99	1.0 (0.6–1.7)	1.0
		Dabrafenib + trametinib	21 (21)	7.3	0.7 (0.4–1.1)	0.08	0.8 (0.5–1.3)	0.33
WHO performance status[a]	146	0–1	118 (28)	5.5	1		1	
		2–3	81 (19)	3.6	1.5 (0.9–2.3)	0.11	1.6 (0.9–2.9)	0.09
Lactate dehydrogenase	138	≤ ULN	59 (79)	6.0	1		1	
		> ULN	43 (57)	3.6	1.6 (1.1–2.4)	**0.01**	1.2 (0.8–1.8)	0.45
S100B	137	≤ ULN	26 (111)	11.5	1		1	
		> ULN	19 (81)	3.8	2.6 (1.6–4.3)	**< 0.01**	2.3 (1.3–4.3)	**< 0.01**
Brain metastases ≥ 2 cm	146	No	100 (46)	5.7	1		1	
		Yes	69 (31)	3.7	1.2 (0.8–1.7)	0.39	1.3 (0.8–2.0)	0.32
Number of brain metastases	146	≤ 5	90 (56)	5.0	1		1	
		> 5	62 (38)	4.4	1.5 (1.0–2.2)	**0.04**	1.5 (1.0–2.3)	0.08
Symptoms of brain metastases	146	Asymptomatic	83 (63)	5.0	1		1	
		Symptomatic	57 (43)	4.3	1.1 (0.8–1.6)	0.58	0.8 (0.5–1.3)	0.35
Radiotherapy during TT	146	No	102 (44)	4.3	1.5 (1.0–2.3)	**0.03**	1.0 (0.6–1.6)	0.88
		Yes	70 (30)	7.1	1		1	
Dexamethasone during TT	146	No	52 (94)	5.8	1		1	
		Yes	36 (64)	4.4	1.1 (0.8–1.7)	0.50	1.1 (0.7–1.7)	0.66

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TT, targeted therapy; ULN, upper limit of normal.
[a]The WHO performance status of 0 indicates that the patient is asymptomatic and fully active, 1: that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2: ambulatory and capable of all self-care but unable to carry out any work activities and 3: > 50% in bed, but not bed bound. Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.
Significant differences are in bold.

Fig. 1



(a) Kaplan–Meier overall survival curve per treatment group. Overall survival curve showing in dotted line patients treated with vemurafenib, in dashed line patients treated with dabrafenib, and in straight line patients treated with the combination of dabrafenib + trametinib. (b). Kaplan–Meier overall survival curve. Kaplan–Meier overall survival curve showing in straight line, patients ($n = 22$) with three or four favorable prognostic parameters, and in dotted line, patients ($n = 124$) with 0–2 favorable prognostic parameters. Median survival for patients with three or four favorable prognostic factors was 15.1 months (95% CI: 9.7–20.5) and for patients with 0–2 prognostic factors was 6.0 months (95% CI: 5.2–6.7). Independent favorable prognostic parameters for overall survival: equal to or less than 5 brain metastases, radiotherapy during targeted therapy, no dexamethasone during targeted therapy and therapy after failing targeted therapy. CI, confidence interval; HR, hazard ratio.

Discussion

In this retrospective clinical study, we analyzed the effects of TT in patients with (a)symptomatic BM from BRAF-mutated malignant melanoma in three groups: vemurafenib alone, dabrafenib alone, and the combination of dabrafenib + trametinib. We found a median OS

Table 5 Univariate and multivariate Cox regression analyses for overall survival

				Univariate analysis			Multivariate analysis	
Parameters	Total (*n*)	Categories	*n* (%)	Median OS (months)	95% CI	*P* value	HR (95% CI)	*P* value
Treatment	146	Vemurafenib	85 (31)	5.7	1		1	
		Dabrafenib	30 (58)	8.8	0.8 (0.5–1.3)	0.27	0.8 (0.4–1.4)	0.39
		Dabrafenib + trametinib	21 (21)	11.2	0.5 (0.3–0.9)	**0.02**	0.6 (0.3–1.1)	0.09
WHO performance status[a]	146	0–1	118 (28)	7.0	1		1	
		2–3	81 (19)	5.4	1.5 (1.0–2.5)	0.07	1.6 (0.9–2.9)	0.11
Serum lactate dehydrogenase	138	≤ ULN	59 (79)	7.7	1		1	
		> ULN	43 (57)	5.9	1.9 (1.3–2.8)	**< 0.01**	1.3 (0.8–2.1)	0.23
Serum S100B	137	≤ ULN	26 (111)	14.7	1		1	
		> ULN	19 (81)	5.8	2.8 (1.6–4.7)	**< 0.01**	1.8 (0.9–3.4)	0.09
Brain metastases ≥ 2 cm	146	No	100 (46)	7.0	1		1	
		Yes	69 (31)	6.2	1.2 (0.8–1.8)	0.30	1.1 (0.7–1.6)	0.82
Number of brain metastases	146	≤ 5	90 (56)	8.0	1		1	
		> 5	62 (38)	5.9	1.8 (1.2–2.6)	**< 0.01**	1.6 (1.0–2.5)	**0.04**
Symptoms of brain metastases	146	Asymptomatic	83 (63)	6.6	1		1	
		Symptomatic	57 (43)	6.4	1.3 (0.87–1.8)	0.22	1.0 (0.6–1.5)	0.92
Radiotherapy during TT	146	No	102 (44)	5.7	2.2 (1.5–3.4)	**< 0.01**	1.9 (1.1–3.1)	
		Yes	70 (30)	11.5	1		1	**0.02**
Treatment after progression of TT	146	No	108 (73)	5.8	2.2 (1.4–3.4)	**< 0.01**	2.4 (1.4–4.0)	**< 0.01**
		Yes	38 (27)	12.3	1		1	
Dexamethasone during TT	146	No	52 (94)	8.6	1		1	
		Yes	36 (64)	5.9	1.5 (1.0–2.2)	**0.04**	1.6 (1.0–2.5)	**0.04**

CI, confidence interval; HR, hazard ratio; OS, overall survival; TT, targeted therapy; ULN, upper limit of normal.
[a]The WHO performance status of 0 indicates that the patient is asymptomatic and fully active. 1: patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2: ambulatory and capable of all self-care but unable to carry out any work activities and 3: > 50% in bed, but not bed bound. Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.
Significant differences are in bold.

of 6.6 months (95% CI: 5.7–7.4) for all patients with a significant difference in OS between patients with BM treated with dabrafenib + trametinib and those treated with vemurafenib (HR for death = 0.52; 95% CI: 0.30–0.89; $P = 0.02$). The significantly higher OS in patients with BM from melanoma treated with dabrafenib + trametinib versus vemurafenib is an important finding. Our data are in concordance with the large COMBI-V, COMBI-D, and the recently published COMBI-MB trial showing activity of dabrafenib + trametinib in patients with BM from BRAF-mutated melanoma with a manageable safety profile [18–20]. In the COMBI-V and COMBI-D trials, objective response rates, PFS, and OS in patients with metastasized melanoma, including pretreated stable BM, were significantly higher in the dabrafenib + trametinib group versus the vemurafenib group (COMBI-V) or the dabrafenib only group (COMBI-D) [19,20]. The COMBI-MB trial included patients with asymptomatic BM ($n = 108$) and a small group with sBM ($n = 17$). Overall intracranial response (CR + PR) in the patients with asymptomatic BRAF V600E-mutated BM without previous local RT was 58%; in patients with asymptomatic BRAF V600E-mutated BM with previous local RT was 56%, whereas in the sBM group it was 59%. Intracranial response in the dabrafenib + trametinib group in our group is somewhat lower: 47% in asymptomatic BM ($n = 9/19$) and 50% in the sBM ($n = 4/8$), which may be owing to the small patient numbers.

The main limitations of our study are indeed that our patient groups are both small (vemurafenib, $n = 85$; dabrafenib, $n = 31$ and dabrafenib + trametinib, $n = 30$) and heterogeneous, in particular with respect to previous RT treatment and that our data are obtained in a retrospective way. However, our results are in line with the large melanoma trials that state, when choosing for TT, dabrafenib + trametinib is the treatment of choice in patients with BRAF-mutated (a)symptomatic melanoma BM. Other systemic treatment modalities (e.g. immune-checkpoint inhibitors) are currently being evaluated for the treatment of melanoma BM. It remains to be determined which treatment (and under which clinical circumstances) is the best for patients with melanoma BM. Symptoms owing to BM were not an unfavorable prognostic factor for intracranial and extracranial PFS and OS, although the use of dexamethasone during TT was both for intracranial PFS (univariate analysis only) and OS (univariate and multivariate analyses). This latter finding is likely to reflect the absence of intracranial response during TT and the ongoing need for dexamethasone to alleviate neurological symptoms in the nonresponding patients. Overall, 46% of all patients with sBM showed improvement of neurological symptoms, and 45% of patients with sBM who were on dexamethasone could stop this after start of TT, which means that TT is an effective palliative treatment. No significant effect of RT during TT was seen on the improvement of neurological symptoms, but only 30% of patients received RT during TT in our study. Narayana *et al.* [21] showed an improvement of neurological symptoms in 64% of patients with BM from melanoma treated with vemurafenib and radiation, but the contribution of TT and RT in their study is unknown.

Cox regression analysis demonstrated that a normal serum S100B level was an independent favorable prognostic factor for both intracranial PFS and extracranial PFS but not for OS. For OS less than or equal to 5 BM, RT during TT, no dexamethasone use during TT, and (immune)therapy after tumor progression on TT were independent favorable prognostic factors. Median survival was 15.1 months in patients with three or four favorable prognostic factors and 6.0 months in patients with 0–2 favorable prognostic factors. Two other studies report that multiple BM (>3 BM, respectively, >5 BM) are a significant unfavorable prognostic factor for OS in patients with BM from melanoma [22,23]. In our study, RT of BM during TT was a favorable prognostic factor for OS. This may be explained either by a better penetration of TT in BM after RT and/or by a radiosensitizing effect of TT [24,25]. The best timing of RT for BM in combination with TT in BRAF-mutated melanoma (before or during TT or at PD) is unknown and should be determined in future clinical studies. Recent data showed that normal baseline serum LDH and metastases at less than three organ sites are factors predictive for durable outcome (≥3 years) in patients with metastasized melanoma treated with TT [20]. OS of patients with melanoma BM seems merely dependent on BM characteristics (number of BM, treatment for BM during TT (in particular RT) and immunotherapeutic treatment after PD and less on serum S100B level and LDH levels or type of TT treatment, the latter being only significant in univariate Cox regression analysis. Again, our results should be interpreted with caution because of the relatively low patient numbers. Therefore, it will be important to confirm the relevance of the aforementioned prognostic factors in larger patient studies.

Conclusion

Our data support that when choosing TT, BRAFi + MEKi are the treatment of choice in patients with both asymptomatic and symptomatic BRAF-mutated melanoma BM. Favorable prognostic factors for OS were less than or equal to 5 BM, RT during TT, no dexamethasone during TT, and subsequent (immuno)therapy after failing TT. Patients with sBM show high clinical–neurological benefit of TT, with almost 50% showing an improvement of neurological symptoms.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 2008; **44**:1345–1389.

2 Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep* 2012; **14**:48–54.

3 Dasgupta T, Brasfield R. Metastatic melanoma. A clinicopathological study. *Cancer* 1964; **17**:1323–1339.

4 Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. *Am J Surg* 1978; **135**:807–810.

5 De la Monte SM, Moore GW, Hutchins GM. Patterned distribution of metastases from malignant melanoma in humans. *Cancer Res* 1983; **43**:3427–3433.

6 Sampson JH, Carter JH Jr, Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. *J Neurosurg* 1998; **88**:11–20.

7 Zakrzewski J, Geraghty LN, Rose AE, Christos PJ, Mazumdar M, Polsky D, *et al.* Clinical variables and primary tumor characteristics predictive of the development of melanoma brain metastases and post-brain metastases survival. *Cancer* 2011; **117**:1711–1720.

8 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**:1213–1218.

9 Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, *et al.* Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**:949–954.

10 Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, *et al.* Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005; **353**:2135–2147.

11 Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; **364**:2507–2516.

12 Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, *et al.* Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012; **380**:358–365.

13 Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, *et al.* Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014; **371**:1867–1876.

14 Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, *et al.* Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012; **367**:1694–1703.

15 Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, *et al.* Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J Clin Oncol* 2016; **34**:871–878.

16 Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, *et al.* Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13**:1087–1095.

17 Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, *et al.* Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer* 2014; **50**:611–621.

18 Davies MA, Saiag P, Robert C, Grob JJ, 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**:863–873.

19 Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, *et al.* Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015; **372**:30–39.

20 Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, *et al.* Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. *Ann Oncol* 2017; **28**:1631–1639.

21 Narayana A, Mathew M, Tam M, Kannan R, Madden KM, Golfinos JG, *et al.* Vemurafenib and radiation therapy in melanoma brain metastases. *J Neurooncol* 2013; **113**:411–416.

22 Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, *et al.* Prognostic factors for survival in melanoma patients with brain metastases. *Cancer* 2011; **117**:1687–1696.

23 Sloot S, Chen YA, Zhao X, Weber JL, Benedict JJ, Mule JJ, *et al.* Improved survival of patients with melanoma brain metastases in the era of targeted BRAF and immune checkpoint therapies. *Cancer* 2017. [Epub ahead of print].

24 Van Vulpen M, Kal HB, Taphoorn MJ, El-Sharouni SY. Changes in blood–brain barrier permeability induced by radiotherapy: implications for timing of chemotherapy? (review). *Oncol Rep* 2002; **9**:683–688.

25 Zahnreich S, Mayer A, Loquai C, Grabbe S, Schmidberger H. Radiotherapy with BRAF inhibitor therapy for melanoma: progress and possibilities. *Future Oncol* 2016; **12**:95–106.