Clinical aspects of immunotherapy and targeted therapy of advanced melanoma

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Chapter 4

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

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Melanoma Res. 2018 Apr;28(2)

ABSTRACT

Background

Patients with brain metastases (BM) from melanoma have an overall survival 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.

Methods

We analysed 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 overall survival (OS).

Results

Median OS of patients treated with dabrafenib + trametinib was 11.2 months (n = 30; 95% 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 (HR 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). Sixty-three patients (43%) 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, in 21% they remained stable.

Conclusions

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 symptomatic BM patients treated with TT.

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]. Brain metastases from malignant melanoma carry a poor prognosis with a median survival of less than six 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 CTLA-4 (ipilimumab) and antibodies against Programmed Death Cell Receptor-1 (PD-1; nivolumab and pembrolizumab) were approved for treatment of metastatic melanoma. Moreover, 40-60% of cutaneous melanoma have a mutation in the gene encoding *BRAF*, which leads to constitutive activation of downstream signalling through the mitogen-activated protein kinase (MAPK) 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 to 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 and symptomatic BM (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 melanoma patients 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 versus 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 combination with a MEKi in patients with BRAF-mutated melanoma BM.

METHODS

Patient inclusion criteria

Patients included in the current study are patients with metastatic melanoma and newly diagnosed or progressive BM treated at the Netherlands Cancer Institute. All patients had stage IV melanoma that tested positive for a mutation in the *BRAF* gene (i.e. V600E, V600K). For response analysis, patients were categorized into three groups (vemurafenib, dabrafenib or dabrafenib + trametinib). Patients that switched from one targeted therapy

(TT) to another TT were placed in the group of the drug that they were taking during 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 prior to TT start.

Treatment

Patients received treatment in standard dosages: vemurafenib 960 mg b.i.d., dabrafenib 150 mg b.i.d and trametinib 2 mg q.d.. One cycle equals four weeks of treatment. Patients visited the outpatient clinic every four weeks for physical examination and blood sampling. Every eight weeks extracranial disease was assessed by CT scans of thorax and abdomen and intracranial disease by MRI of the brain. 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 ≥ 5 mm. Assessment of both extra- and intracranial response was done by a (neuro-)radiologist. Intracranial DCR was defined as stable disease (SD) + partial response (PR) + complete response (CR) and was measured at 8 weeks after treatment start 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 four weeks after treatment. They were classified as worsened, stable or improved. Symptomatic patients were patients that had at least one neurological symptom. Progression-free survival was measured from the date of treatment start 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. Overall survival was measured from the date of treatment start until death by any cause, or date of last known follow-up.

Statistics

Kaplan-Meier curves were used to determine the median OS, median intracranial PFS and extracranial PFS. Log-rank, univariate and multivariate Cox regression analysis was used to assess prognostic factors for survival. Data were analyzed using SPSS Statistics software (IBM version 22).

RESULTS

Patient and treatment characteristics

Hundred forty-six 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 fifty-five percent of patients was male (n = 80). Melanoma BRAF mutation status was V600E in 129 patients (88%), V600K in 12 patients (8%), V600R in 2 patients (1%) and K601E, L579R and $V600_{unknown}$ in 1 patient each. Median time from diagnosis of the primary melanoma till BM was 39.4 months (range 0 – 373 months). Thirty-two patients (22%) received systemic therapy (for example DTIC or ipilimumab) for extracranial metastases, but none had been treated with TT. 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 radiotherapy. Eleven patients (8%) had intracranial surgery for BM, with start of TT post-surgery for remaining BM. Forty-nine patients (39%) received RT before start of TT: WBRT (n = 33, 67%), stereotactic RT (n = 13, 27%), or both (n = 3, 6%). Twelve patients had a switch in TT during treatment: 11 cases due 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 between the 3 treatment groups.

Treatment during and after TT

During TT 44 patients (30%) received RT due to progression of BM: twenty-six patients (59%) WBRT and 18 patients stereotactic RT (41%). Twenty-three patients (52%) continued TT as treatment beyond progression. Thirty-eight (26%) patients received systemic therapy after PD on TT, which was immunotherapy in 95% of patients.

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 sBM and asymptomatic BM patients was borderline significantly lower than the extracranial DCR in both groups (sBM: intracranial 65% versus extracranial 70%; p = 0.04, asymptomatic BM: intracranial 70% versus extracranial 77%; p = 0.04; Table 2). Intracranial DCR was 81% (16/42 SD and 18/42 PR) in the group of patients that received prior local RT, compared to 73% (38/89 SD, 20/89 PR, 7/89 CR) in the group of patients that did not receive prior local RT (p = 0.04). There was no statistically significant difference in intracranial DCR in patients that received RT during TT (67%; 17/43 SD, 11/43 PR and 1/43 CR) versus those that did not (80%; 37/88 SD, 27/88 PR and 6/87 CR; p = 0.37).

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)	
Gender *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 (%)					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 (%)					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)	
Symptomatic BM patients 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					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)	

† The World Health Organization (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.
TT; targeted therapy, ULN; upper limit of normal

Table 2. Disease control rate, progression-free survival, clinical response rate and overall survival in patients with BM 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 months (95% CI)	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 months (95% CI)	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 months (95% CI)	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.

Clinical-neurological response

In 29 of 63 sBM patients (46%) neurological symptoms improved after TT; in 13 patients (21%) neurological symptoms remained stable and in 16 patients (25%) symptoms worsened during treatment. Five patients with sBM (8%) were not evaluable. Eleven of 34 sBM patients (32%) treated with vemurafenib showed improvement of neurological symptoms, while this was the case for 12 of 19 patients (63%) treated with dabrafenib and 6 of 10 patients (60%) treated with the combination of dabrafenib + trametinib. Forty-five percent of patients with sBM that used dexamethasone to alleviate neurological symptoms before TT could stop dexamethasone after TT. In the group of patients that had not received prior local RT before TT clinical neurological benefit was 84% (6/31 stable and 20/31 improved), while this was 59% (7/27 stable and 9/27 improved) in the patient group that 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 that 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% CI, 3.2 – 5.0). Median intracranial PFS for vemurafenib was 3.6 months (95% CI, 3.5 – 3.8), for dabrafenib 5.7 months (95% CI, 3.0 – 8.4) and for the combination of dabrafenib + trametinib 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 versus 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). Radiotherapy prior to TT did not significantly impact intracranial PFS (4.3 months with prior RT) versus 4.1 months without (p = 0.47). Radiotherapy during TT did also not significantly influence intracranial PFS (4.8 months with RT during TT versus 4.1 months without RT; p = 0.51). A normal serum S100B level and no use of dexamethasone during TT were significant favourable prognostic factors for intracranial PFS in univariate Cox regression analysis. In multivariate Cox regression analysis a normal serum S100B level remained a significant favourable prognostic factor for intracranial PFS (HR 3.1; 95% CI, 1.6 – 6.1; p < 0.01; Table 3).

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

				Univariate analysis			Multivariate analysis	
Parameter	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†	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

† The World Health Organization (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.
CI; confidence interval, HR; hazard ratio, OS; overall survival, TT; targeted therapy, ULN; upper limit of normal

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 5.8 months (95% CI, 3.3 – 8.3) and for the combination of dabrafenib + trametinib 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 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, ≤ 5 BM and RT during TT were favourable 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).

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

				Univariate analysis			Multivariate analysis	
Parameter	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†	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

† The World Health Organization (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.
CI; confidence interval, HR; hazard ratio, OS; overall survival, TT; targeted therapy, ULN; upper limit of normal

Overall survival

At time of analysis, 117 patients (80%) had died. All but two deaths were due to 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), 8.8 months for patients treated with dabrafenib only (95% CI, 3.9 – 13.7) and 5.7 months for patients treated with vemurafenib (95% CI, 4.6 – 6.8). A significantly longer OS was observed in the dabrafenib + trametinib group as compared to 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; $p = 0.10$) (Figure 1). Moreover, no significant difference was found between the median OS of sBM and asymptomatic BM patients; 6.6 months (95% CI 5.6 – 7.6) and 6.4 months (95% CI 4.2 – 8.5; $p = 0.22$) respectively.

Prognostic factors associated with overall survival

A normal serum LDH level, a normal serum S100B level, ≤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, and no use of dexamethasone during TT and treatment after failing TT remained independent favorable prognostic factors for OS (Table 5). Patients that had 3 or 4 favorable prognostic factors had a median OS of 15.1 months (95% CI, 9.7 – 20.5), compared to 6.0 months (95% CI, 5.2 – 6.7; $p < 0.01$) for patients with 0 – 2 favorable prognostic factor(s) (Figure 2).

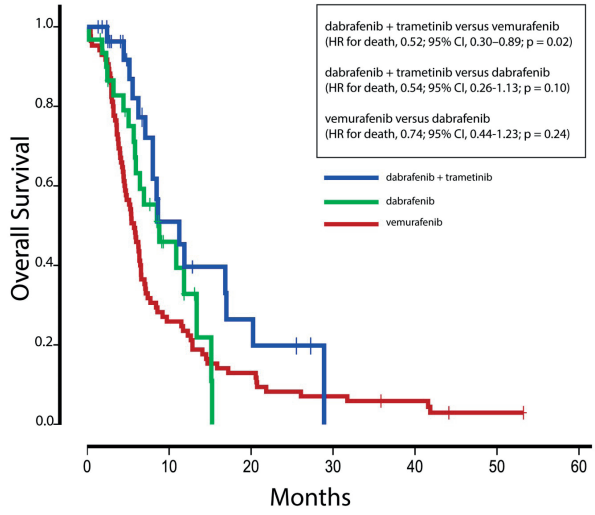

Figure 1. Kaplan-Meier overall survival curve per treatment group
Overall survival curve showing in red patients treated with vemurafenib, in green patients treated with dabrafenib and in blue patients treated with the combination of dabrafenib + trametinib.

Table 5. Univariate and multivariate Cox regression analysis for overall survival

					Univariate analysis		Multivariate analysis	
Parameter	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†	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**

† The World Health Organization (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.
CI; confidence interval, HR; hazard ratio, OS; overall survival, TT; targeted therapy, ULN; upper limit of normal

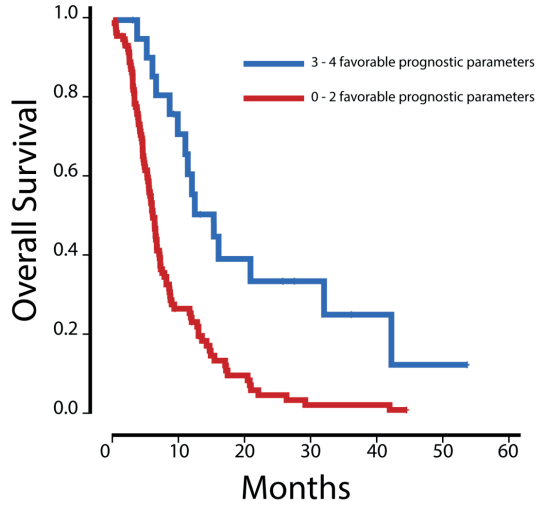

Figure 2. Kaplan-Meier overall survival curve
Kaplan-Meier overall survival curve showing in blue: patients (n = 22) with 3 or 4 favorable prognostic parameters and in red: patients (n = 124) with 0 – 2 favorable prognostic parameters. Median survival for patients with 3 or 4 favorable prognostic factors was 15.1 months (95% CI 9.7 – 20.5) and for patients with 0 – 2 prognostic factors 6.0 months (95% CI 5.2 – 6.7).
Independent favorable prognostic parameters for OS: equal to or less than 5 BM, RT during TT, no dexamethasone during TT and therapy after failing TT.

DISCUSSION

In this retrospective clinical study we analysed 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 of 6.6 months (95% CI 5.7 – 7.4) for all patients with a significant difference in OS between BM patients treated with dabrafenib + trametinib versus 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 BRAF-mutated melanoma patients with BM 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 pre-treated 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 asymptomatic BRAF V600E mutated BM patients was 58% and 56% in patients with, respectively without, previous local RT 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 due 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 dabrafenib + trametinib is the treatment of choice in patients with BRAF-mutated (a) symptomatic melanoma BM. Symptoms due to BM were not an unfavourable prognostic factor for intracranial and extracranial PFS and OS, although the use of dexamethasone was (only for OS). Forty-six percent of all sBM patients showed improvement of neurological symptoms and 45% of sBM patients that were on dexamethasone could stop this after start of TT, which means that TT is an effective palliative treatment. No significant impact 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. (2013) 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 radiotherapy in their study is unknown [21].

Cox regression analysis demonstrated that a normal serum S100B level was an independent favourable prognostic factor both for intracranial PFS and extracranial PFS but not for OS. For OS ≤5 BM, RT during TT, no dexamethasone use during TT and (immune)therapy after tumor progression on TT were independent favourable prognostic factors. Median survival was 15.1 months in patients with 3 or 4 favourable prognostic factors and 6.0 months in patients with 0 – 2 favourable prognostic factors. Recent data showed that normal baseline serum LDH and metastases at < 3 organ sites are factors predictive for durable outcome (≥ 3 years) in patients with metastasized melanoma treated with TT [20]. Overall survival of patients with melanoma BM seems merely dependent on BM characteristics (number of BM, treatment for BM during TT (RT, no dexamethasone)) 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 above-mentioned prognostic factors in larger patient studies.

CONCLUSION

In conclusion, our data support that dabrafenib + trametinib is the treatment of choice in patients with both asymptomatic and symptomatic BRAF-mutated melanoma BM. Favourable prognostic factors for OS were ≤ 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.

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