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Vemurafenib in patients with $BRAF^{V600}$ mutation-positive melanoma with symptomatic brain metastases: Final results of an open-label pilot study

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Abstract ***Background & Aim:*** Brain metastases are frequent in patients with metastatic melanoma, indicating poor prognosis. We investigated the BRAF kinase inhibitor vemurafenib in patients with advanced melanoma with symptomatic brain metastases.
Methods: This open-label trial assessed vemurafenib (960 mg twice a day) in patients with $BRAF^{V600}$ mutation-positive metastatic melanoma with non-resectable, previously treated brain metastases. The primary end-point was safety. Secondary end-points included best overall response rate, and progression-free and overall survival.
Results: Twenty-four patients received vemurafenib for a median treatment duration of 3.8 (0.1–11.3) months. The majority of discontinuations were due to disease progression ($n = 22$). Twenty-three of 24 patients reported at least one adverse event (AE). Grade 3 AEs were reported in four (17%; 95% confidence interval [CI], 4.7–37.4%) patients and included cutaneous squamous cell carcinoma in four patients. Median progression-free survival was 3.9 (95% CI, 3.0–5.5) months, and median survival was 5.3 (95% CI, 3.9–6.6) months. An overall partial response (PR) at both intracranial and extracranial sites was achieved in 10 of 24 (42%; 95% CI, 22.1–63.4) evaluable patients, with stable disease in nine

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(38%; 95% CI, 18.8–59.4) patients. Of 19 patients with measurable intracranial disease, seven (37%) achieved >30% intracranial tumour regression, and three (16%; 95% CI, 3.4–39.6%) achieved a confirmed PR. Other signs of improvement included reduced need for corticosteroids and enhanced performance status.

Conclusions: Vemurafenib can be safely used in patients with advanced symptomatic melanoma that has metastasised to the brain and can result in meaningful tumour regression.

1. Introduction

Brain metastases are diagnosed in up to 50% of melanoma patients with metastatic disease and are found in most of those who die [1–7]. Cerebral metastases indicate poor prognosis (median survival is less than 6 months [3,4,8,9]) and are associated with a wide spectrum of neurological symptoms that impact patient quality of life. Brain metastases frequently contribute to death in most patients [3,4,8–10].

Vemurafenib and dabrafenib have demonstrated efficacy in metastatic melanoma [11–19]. Efficacy data including progression-free survival (PFS) and overall survival (OS) led to the approval of both compounds in the United States and in Europe. While patients with active brain metastases were excluded from these trials, dabrafenib has demonstrated activity in patients with asymptomatic $BRAF^{V600E}$ mutation-positive melanoma brain metastases [14].

Driven by the need for a therapy for patients with advanced melanoma and symptomatic brain metastases, a study was initiated in Switzerland to study the safety, tolerability and efficacy of vemurafenib in this population [20]

2. Patients and methods

2.1. Study design

This was an open-label, single-arm, two-centre, study designed to evaluate the safety and efficacy of vemurafenib in patients with $BRAF^{V600}$ mutation-positive metastatic melanoma and unresectable brain metastases for whom at least one treatment for brain metastases had failed and who required corticosteroids for symptom control. Tumours were evaluated for the $BRAF^{V600}$ mutation using a polymerase chain reaction-based test (cobas® 4800 $BRAF^{V600}$ Mutation Test; Roche Molecular Systems, Branchburg, NJ). Eligible patients were treated with continuous, oral twice-daily dosing of vemurafenib (960 mg) until disease progression (investigator assessment), unacceptable toxicity, withdrawal of consent, death or investigator decision.

Patients experiencing disease progression who, in the investigator's opinion, would benefit from continuing vemurafenib treatment were permitted to continue after discussion with the study sponsor. With the exception of patients who withdrew consent, were lost to follow-up, or died, all patients discontinuing vemurafenib were followed for survival for 6 months. An independent ethics committee at each study centre approved the study protocol. The study was performed in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before enrolment. The trial is registered with ClinicalTrials.gov, number NCT01253564.

2.2. Eligibility criteria

Eligible patients were older than 18 years and had histologically confirmed stage IV (American Joint Committee on Cancer staging criteria) metastatic melanoma that was $BRAF^{V600}$ mutation positive; confirmed brain metastases for which surgical resection was not a treatment option; and at least one previous failed treatment for brain metastases and required treatment with corticosteroids for symptom control (either a stable or a decreasing dose within 1 week of study entry). Patients could have measurable or non-measurable disease according to Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1). They were to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, have recovered from the side-effects of their most recent treatment for metastatic melanoma, and have adequate haematological, renal and hepatic function. Evidence of progression of brain metastases by magnetic resonance imaging (MRI) was not required prior to study entry.

Patients were excluded if they were taking concurrent chemotherapy, targeted therapy or experimental drugs. Other exclusion criteria included malignancy within the past 2 years (except basal or cutaneous squamous cell carcinoma [cuSCC] or carcinoma *in situ* of the cervix) or any of the following within 6 months before the first vemurafenib administration: myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischaemic attack, pulmonary embolism or hypertension not adequately controlled by current medication. Patients with a history of congenital long QT syndrome, a history or presence of clinically significant ventricular or atrial dysrhythmias of grade 2 or higher, or corrected QT interval $\geqslant$450 ms at baseline were also excluded, as were pregnant and lactating women.

2.3. Study assessments

The primary objective was to evaluate the safety and tolerability of vemurafenib. Adverse events (AEs) were assessed throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Other safety assessments included routine laboratory values, vital signs, electrocardiography, dermatology and head and neck evaluations and chest computed tomography (CT) for SCC surveillance, and physical examination.

The secondary objective was to evaluate the efficacy of vemurafenib through the determination of best overall response rate (BORR), defined as the number of patients who had a best objective response of complete response (CR) or partial response (PR) divided by the total number of treated patients evaluable for response. Other secondary efficacy measures included duration of response, PFS and OS. Overall tumour responses were assessed by the investigator using RECIST 1.1 criteria. BORRs were calculated separately for the intracranial, extracranial and whole body tumour sites. Duration of response was defined as the time between the date of the earliest qualifying response and the date of progressive disease or death from any cause. Brain MRI and CT or MRI of the chest, abdomen and pelvis were conducted at baseline, weeks 4 and 8, and every 8 weeks thereafter to assess the extent of disease. Brain MRI was used to assess disease in the brain.

PS was assessed using the ECOG five-point scale and the Physician's Assessment of Global PS seven-point scale at each clinical visit. Total daily dose of corticosteroids and total daily dose and frequency of narcotic pain analgesics as documented in patient diaries were assessed as measures of improvement in physical symptoms. A visual analogue scale (VAS) was used to evaluate pain at baseline and at day 1 of every visit.

2.4. Statistical analysis

All analyses were carried out on the safety population (all patients who received at least one dose of vemurafenib). The intent-to-treat population was identical to the safety population.

BORRs were summarised separately for intracranial and extracranial sites and all tumour sites. A responder was defined as a patient experiencing best objective response of a CR or PR by these criteria, whereas BORR was defined by the number of responders divided by the total number of patients with measurable disease at baseline and was presented with associated Clopper–Pearson exact confidence intervals (CP exact CIs). All CIs quoted for proportions were CP exact CIs. For time-to-event, CIs

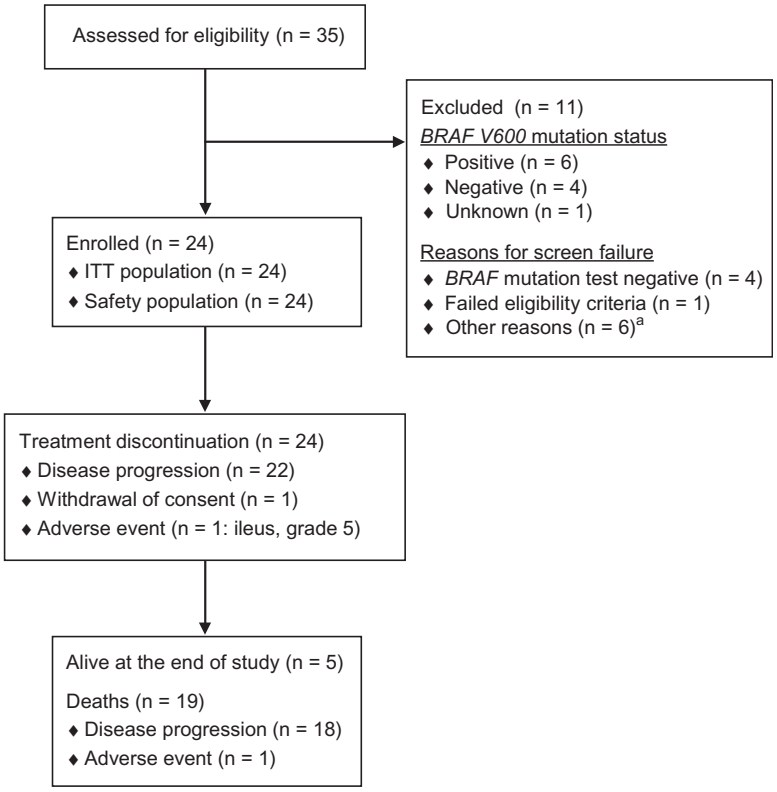

Fig. 1. Patient flow for all patients included in the study. Twenty-four eligible patients with $BRAF^{V600}$ mutation-positive metastatic melanoma and brain metastases who had failed at least one prior treatment and required corticosteroids for symptom relief were enrolled. [a]Died (one patient); died because of disease progression (three patients); withdrew consent (one patient); insufficient amount of tumour tissue for BRAF analysis (one patient). ITT = intent-to-treat.

quoted were 95% median CIs. Waterfall plots were used to demonstrate maximum tumour shrinkage during the study compared with baseline. Kaplan–Meier methods were used to estimate PFS and OS.

3. Results

3.1. Patient disposition

In total, 35 patients with metastatic melanoma were screened for the trial at two study centres in Switzerland. Main reasons for screening failure included negative $BRAF^{V600}$ mutation test result and death because of disease progression. Twenty-four patients were enrolled between November 2010 and November 2011 (Fig. 1).

3.2. Baseline characteristics

Baseline patient demographics and disease characteristics are summarised in Table 1. All patients were white, and the median age was 47 (range, 24–70) years. Fifteen (63%) patients had nervous system symptoms at baseline, including headache (eight patients), dysgeusia (five patients) and dizziness and seizure (three patients each). Median time since diagnosis of brain metastases was 3.2 (range, 0–19) months. Patients had a median number of four (range, 1–20) brain metastases at study entry. Other lesion sites at study entry included lung (16 patients), lymph nodes (nine patients), liver (eight patients), skin (seven patients), peritoneum (five patients) and adrenal (five patients). At baseline, all 24 patients were receiving corticosteroids, and 14 (58%) were dependent on narcotic pain medication. Nineteen (79%) patients had received previous radiotherapy, and four (17%) had previously undergone surgery for brain metastases. Four patients had previously received ipilimumab.

Table 1
Baseline demographic and clinical characteristics.

Characteristic	Vemurafenib[c] ($n = 24$)
Age, years	
Median (range)	47 (24–70)
Race, *n* (%)	
White	24 (100)
Sex, *n* (%)	
Male	13 (54)
Female	11 (46)
ECOG performance status, *n* (%)[a]	
0–1	18 (75)
2	6 (25)
Months since first diagnosis of malignant melanoma, median (range)	26.5 (1–320)
Months since first diagnosis of brain metastases, median (range)	3.2 (0–19)
Brain metastases on entry to study, *n*, median (range)	4.0 (1–20)
Brain metastases at study entry, *n* (%)	
1	2 (8)
2–3	9 (38)
>3	13 (54)
Involved organ sites outside brain, *n* (%)	
1	10 (42)
2	14 (58)
Previous surgery or radiotherapy for brain metastases, *n* (%)	
Whole-brain radiotherapy	14 (58)
Stereotactic radiotherapy	6 (25)
Surgery for brain metastases	4 (17)
Previous surgery and previous radiotherapy	4 (17)
At least one systemic therapy for metastatic melanoma, *n* (%)[b]	20 (83)

[a] ECOG = Eastern Cooperative Oncology Group; ECOG performance status 0 = patient is fully active, performance status 1 = patient is restricted in physically strenuous activity but is able to walk and perform work that is light or of a sedentary nature, status 2 = patient able to walk and capable of self-care, unable to work but is up and about for more than 50% waking hours.

[b] Including alkylating agents, cytokines, antineoplastic agents, monoclonal antibodies (ipilimumab), platinum compounds, *Vinca* alkaloids, antimetabolites, immunostimulants and tyrosine inhibitors (sorafenib).

[c] Results may not total 100 because of rounding.

3.3. Treatment exposure

The median duration of vemurafenib treatment was 3.8 (range, 0.1–11.3) months and the median total dose was 1920 mg (range, 1559–1920 mg) per day. One patient had a dose reduction (lowest dose received of 480 mg twice a day), and the same patient also had a dose interruption that lasted $\geqslant$1 week. By study end, all 24 (100%) patients had discontinued vemurafenib treatment: 22 (92%; 95% CI, 73.0–99.0%) as a result of first disease progression and one (4%; 95% CI, 0.1–21.1%) each because of an AE (ileus) or withdrawal of consent.

3.4. Safety and tolerability

Twenty-three (96%; 95% CI, 78.9–99.9%) patients reported at least one AE, most commonly including arthralgia (nine patients), seizure (six patients) and alopecia, diarrhoea, dizziness, muscular weakness, maculopapular rash, paraesthesia, solar dermatitis or vomiting (five patients each) (Table 2). Most AEs reported were mild or moderate (grade 1 or 2) and most (88%) resolved without sequelae. One AE (ileus occlusion) led to death in one patient. Grade 3 AEs were reported by four patients, including cuSCC (four patients) and elevated amylase and gamma-glutamyltransferase (one patient each). No one experienced a grade 4 AE. AEs judged to be related to treatment were reported by 20 (83%; 95% CI, 62.6–95.3%) patients and included arthralgia (six patients) and alopecia, maculopapular rash or solar dermatitis

Table 2
Adverse events by preferred term reported in 10% or more of patients.

Adverse event[a]	Incidence, *n* (%)		
	Any grade	Grade 1 or 2	Grade 3
Total	23 (96)	22 (92)	4 (17)
Arthralgia	9 (38)	9 (38)	0
Seizure	6 (25)	6 (25)	0
Alopecia	5 (21)	5 (21)	0
Diarrhoea	5 (21)	5 (21)	0
Dizziness	5 (21)	5 (21)	0
Muscular weakness	5 (21)	5 (21)	0
Maculopapular rash	5 (21)	5 (21)	0
Paraesthesia	5 (21)	5 (21)	0
Solar dermatitis	5 (21)	5 (21)	0
Vomiting	5 (21)	5 (21)	0
Squamous cell carcinoma of the skin	4 (17)	0	4 (17)
Fatigue	4 (17)	4 (17)	0
Hyperkeratosis	4 (17)	4 (17)	0
Oral candidiasis	4 (17)	4 (17)	0
Peripheral oedema	4 (17)	4 (17)	0
Cough	3 (13)	3 (13)	0
Dysgeusia	3 (13)	3 (13)	0
Headache	3 (13)	3 (13)	0
Oral herpes	3 (13)	3 (13)	0
Papilloma	3 (13)	3 (13)	0
Skin papilloma	3 (13)	3 (13)	0
Sleep disorder	3 (13)	3 (13)	0
Constipation	3 (13)[b]	2 (8)	0
Haematoma	3 (13)	3 (13)	0

[a] Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[b] Includes one adverse event of constipation with unknown most extreme Common Toxicity Criteria grade.

(five patients each). AEs led to the withdrawal of vemurafenib in one (4%; 95% CI, 0.1–21.1%) patient. There were no other dose modifications or interruptions because of AEs. Fourteen (58%; 95% CI, 36.7–77.9%) patients experienced a serious AE (SAE), including seizure (five patients) and cuSCC (four patients); four patients (17%; 95% CI, 4.7–37.4%) reported SAEs that were judged to be related to treatment. One SAE (occlusion of the ileus) led to death and was judged by the investigator not to be related to vemurafenib.

3.5. Efficacy

Vemurafenib demonstrated antitumour activity in both intracranial and extracranial sites (Fig. 2). Overall, a PR was reported in 10 (42%; 95% CI, 22.1–63.4%) patients and stable disease (SD) was reported in nine (38%; 95% CI, 18.8–59.4%) patients. Of 19 patients with measurable intracranial disease at baseline, seven (37%) achieved >30% intracranial tumour regression (Fig. 2), three (16%; 95% CI, 3.4–39.6%) achieved intracranial PR and 13 (68%; 95% CI, 43.4–87.4%) achieved intracranial SD (Table 3, Fig. 3). Of the 21 patients with measurable extracranial disease at baseline, PR at extracranial disease sites was reported in 13 (62%; 95% CI, 38.4–81.9%) patients, and SD was reported in six (29%; 95% CI, 11.3–52.2%) patients (Table 3). Times to response and progression in the brain and extracranial regions are presented in Fig. 4. Median duration of response in the brain was 4.4 (95% CI, 2.1–4.6) months and 3.8 (95% CI, 2.7–5.3) months at extracranial sites. Median PFS was 3.9 (95% CI, 3.0–5.5) months (Fig. 5). Of the 24 patients enrolled in the study, five (21%; 95% CI, 7.1–42.2%) were alive at the end of the study. Median OS was 5.3 (95% CI, 3.9–6.6) months (Fig. 6).

3.6. Assessments of physical symptoms

All patients reported corticosteroid use (average dose of 6.1 mg/day). Corticosteroid use improved in 16 of 24 (67%) patients (95% CI, 45–84%), as defined by a decrease of at least 33% from baseline or a complete discontinuation (reduction maintained for at least 28 days). Median time to first improvement in corticosteroid use was 1.5 (95% CI, 1.1–4.4) months. Fourteen (58%; 95% CI, 36.7–77.9%) patients reported use of narcotic pain analgesics. However, the interpretation of changes was limited by the multiplicity of drugs used. Six of the 24 (25%; 95% CI: 9.8–46.7%) patients had >20 mm improvement in VAS assessment of pain at any visit compared with baseline. Most patients (83%; 15 of 18 evaluable patients; 95% CI, 58.6–96.4%) were judged to have improvement from baseline in the Physician's

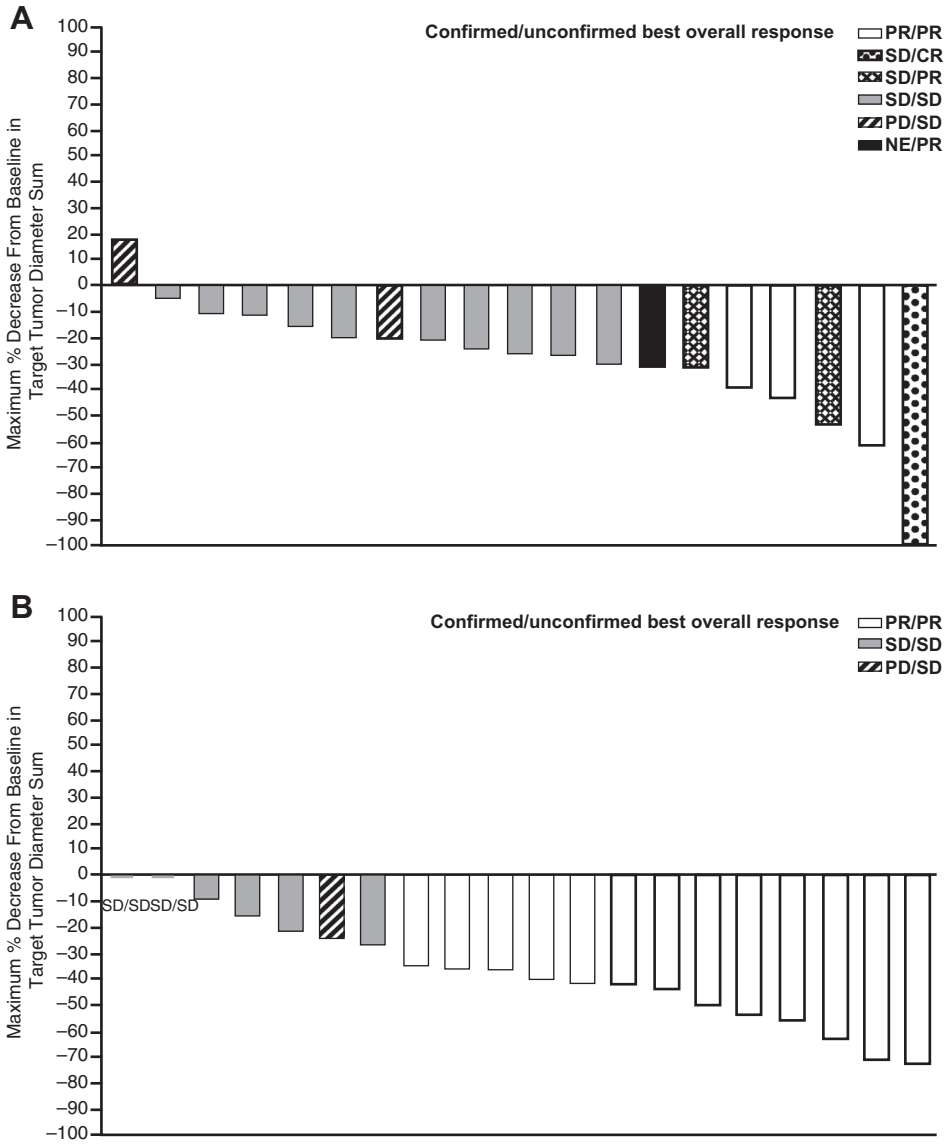

Fig. 2. Waterfall plots of maximum tumour shrinkage compared with baseline in patients with measurable disease at baseline in (A) intracranial disease ($n = 19$) and (B) extracranial disease ($n = 20$). In (B), one patient with measurable disease at baseline but no post-baseline tumour assessments was not included in the waterfall plot. Objective tumour responses were defined on the basis of the Response Evaluation Criteria in Solid Tumours, version 1.1. CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Assessment of Global PS at any post-baseline visit (improvement defined as a decrease from baseline of at least one-point). Eleven of 24 patients (46%; 95% CI, 25.6–67.2%) were judged to have improvement at any visit in ECOG PS (defined as a decrease of at least one point).

4. Discussion

This clinical trial evaluated vemurafenib in melanoma patients with previously treated symptomatic brain metastases who would not have previously been eligible for a clinical trial [21]. The most frequent AEs included arthralgia, seizures, alopecia, diarrhoea, dizziness, muscular weakness, maculopapular rash, paraesthesia, solar dermatitis and vomiting. This safety profile was similar to that reported in earlier studies and supports the feasibility of vemurafenib therapy in patients with advanced melanoma with symptomatic brain metastases. Importantly, vemurafenib treatment was associated with tumour regression in the brain in addition to extracranial sites of involvement (Figs. 2 and 3), with PR achieved at intracranial sites in three patients and extracranial sites in 13 patients. Median OS was 5.3 (95% CI, 3.9–6.6) months, as expected in this population. In addition, vemurafenib was associated

Table 3
Best overall response rate in brain metastases and other sites in patients with measurable disease at baseline.

	Intracranial ($n = 19$)		Extracranial ($n = 21$)		Both intracranial and extracranial ($n = 24$)	
	n (%)	95% confidence interval (CI)[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Complete response	0		0		0	
Partial response	3 (16)	3–40	13 (62)	38–82	10 (42)	22–63
Stable disease	13 (68)	43–87	6 (29)	11–52	9 (38)	19–59
Progressive disease	2 (11)	1–33	1 (5)	0–24	3 (13)	3–32
Not evaluable	1 (5)	0–26	1 (5)	0–24	2 (8)	1–27

[a] Clopper–Pearson method.

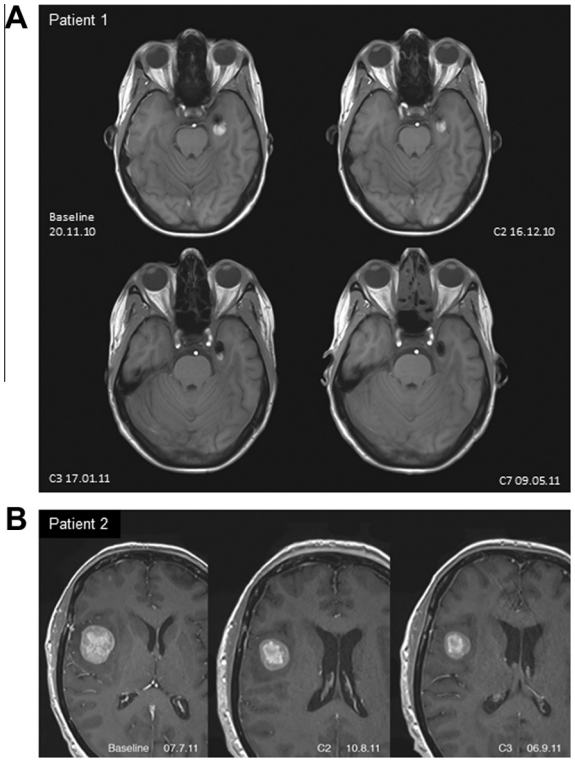

Fig. 3. Magnetic resonance imaging of two patients with brain metastases showing partial responses after treatment with vemurafenib. Patient 1 (A) at baseline and after 1, 2 and 6 months of treatment with vemurafenib. Patient 2 (B) at baseline and after 2 and 3 months of treatment with vemurafenib.

with additional clinically meaningful benefit in some patients, including alleviation of pain and improved PS and use of corticosteroids.

Clinical activity was reported with dabrafenib in asymptomatic patients with *BRAF*-mutated melanoma and at least one measurable brain metastasis between 5 and 40 mm in diameter [14]. In patients who had not received previous local treatment for brain metastases, investigator-assessed overall intracranial response (CR + PR) was 39% in patients with the $BRAF^{V600E}$ mutation (substitution of valine by glutamate) ($n = 74$) and 7% in patients with the $BRAF^{V600K}$ mutation (substitution of valine by lysine) ($n = 15$). In patients who had received previous local treatment for brain metastases, the investigator-assessed overall intracranial response was 31% ($BRAF^{V600E}$ mutation) ($n = 65$) and 22% ($BRAF^{V600K}$ mutation) ($n = 18$). In contrast, overall intracranial response by independent radiology review committee was 18% in both cohorts of patients with the $BRAF^{V600E}$ mutation (i.e. patients who had and had not received previous local treatment for brain metastases). PFS for dabrafenib was 4 months (16 weeks) and OS was approximately 8 months (32 weeks) for $BRAF^{V600E}$ mutation-positive patients. Both PFS and OS appear to be shorter in $BRAF^{V600K}$ mutation-positive patients [14]. In our study, intracranial and extracranial tumour regression was observed in most patients; the overall response rate was 42% (10/24 patients). Data for the breakdown of the BRAF genotype are not available in this study. However, these results might indicate that the selective available BRAF inhibitors have similar efficacy in the treatment of brain metastases.

Recent data are also available for ipilimumab in melanoma patients with brain metastases. A response rate of 16% was reported in patients without neurological symptoms, with responses achieved in 1 of 21 (5%) patients with symptoms who were receiving systemic corticosteroids [22]. Although the duration of PFS was less than 2 months in both groups, the authors did not report neurological deterioration. The OS rate of patients with symptoms who were receiving systemic corticosteroids was 38% (range, 17–59%) and 19% (range, 2–36%) at 6 and 12 months, respectively. This appears comparable to our survival data.

Patients with brain metastases may experience neurocognitive impairment. Although it is suggested that whole-brain radiotherapy should remain the standard of care in brain metastasis [23], this approach can negatively impact patient quality of life [24]. Moreover, the combination of stereotactic radiosurgery and whole-brain radiotherapy can lead to significant declines in learning and memory function [25]. Frequently administered co-medication in cancer patients, including corticosteroids, analgesic medication (e.g. opioids) and sedatives, are also known to cause neurocognitive dysfunction [26,27]. Our data suggest that vemurafenib therapy in patients with advanced melanoma and brain metastases reduces corticosteroid use and improves global PS. These results, together with other publications [14,22], support a change in the treatment

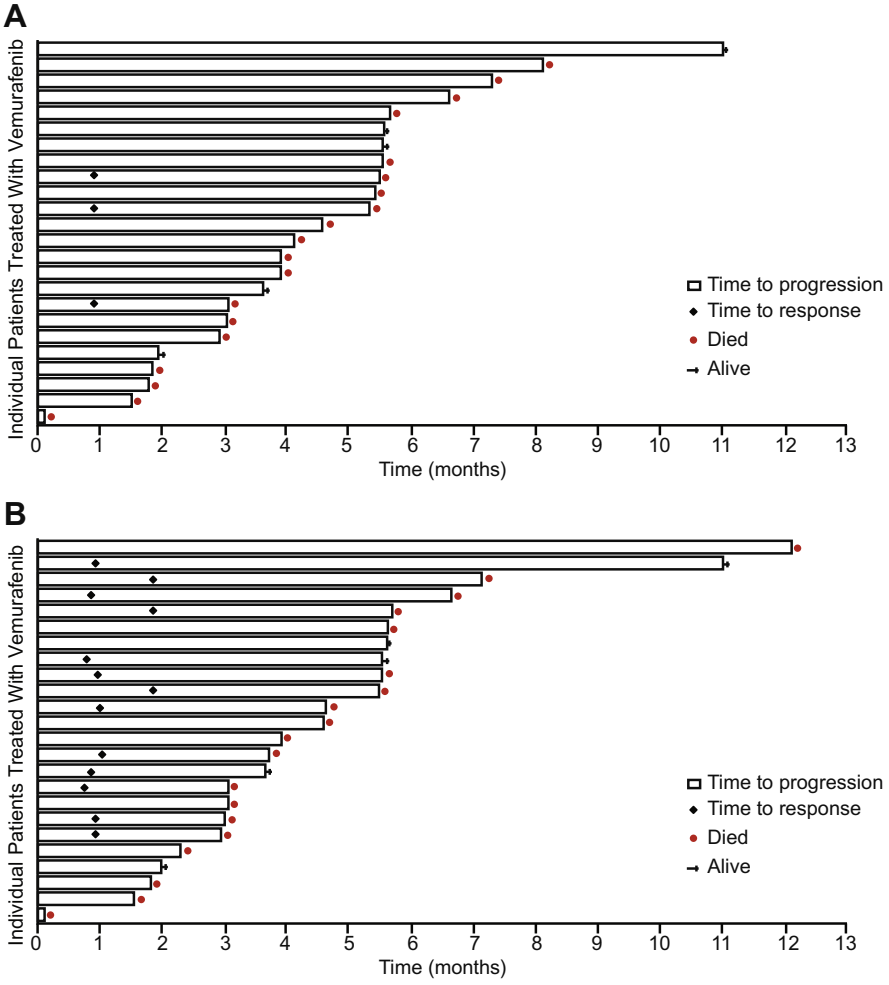

Fig. 4. Time to progression and response for (A) intracranial disease ($n = 24$) and (B) extracranial disease ($n = 24$).

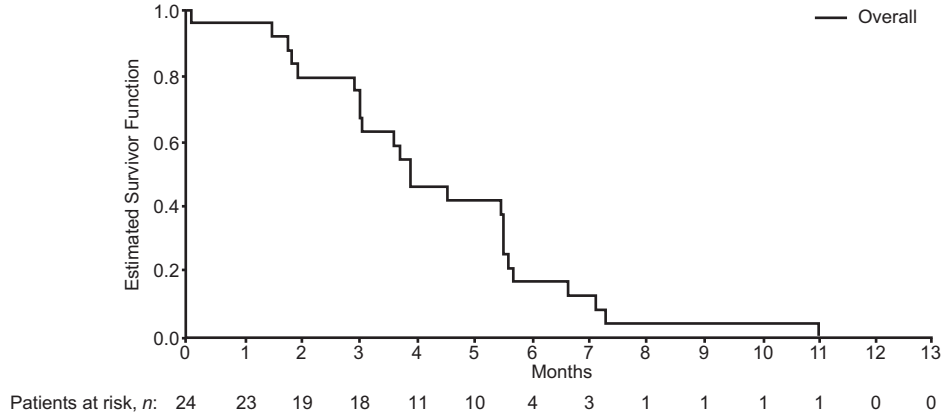

Fig. 5. Kaplan–Meier plot of progression-free survival after the use of vemurafenib (both intracranial and extracranial). Median duration of progression-free survival was 3.9 (95% CI, 3.0–5.5) months. CI = confidence interval.

paradigm for patients with *BRAF* mutation-positive advanced melanoma with brain metastases and are in accordance with the European Society for Medical Oncology clinical practice recommendations [10,28].

In conclusion, vemurafenib can be used safely and effectively in patients with brain metastases. These data encourage investigations of vemurafenib—including as part of combination regimens—in this population.

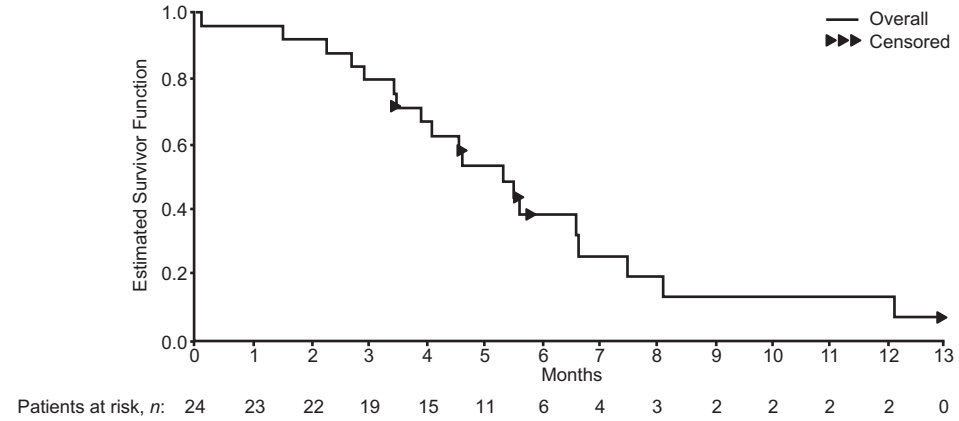

Fig. 6. Kaplan–Meier plot of overall survival after the use of vemurafenib. Median duration of overall survival was 5.3 (95% CI, 3.9–6.6) months. CI = confidence interval.

Contributors

Reinhard Dummer conducted the literature search, designed the study, collected data, analysed and interpreted the data, drafted and revised the manuscript and figures and approved the final version of the manuscript.

Simone M. Goldinger conducted the literature search, designed the study, collected data, analysed and interpreted the data, drafted and revised the manuscript and figures and approved the final version of the manuscript.

Christian P. Turtschi was responsible for informing potential patients about the study; checking for eligibility and organising screening and performing screening if informed consent was given; performing the clinical visits and organising evaluation of response (e.g. computed tomography); evaluating clinical response (e.g. skin examination/computed tomography evaluation to see tumour response; data entry in CRF; adverse event reporting; data analysis to evaluate tumour response (e.g. stable disease, partial response, complete response); follow-up of patients who were excluded because of tumour progression; and drug account. Also, Dr. Turtschi was the contact person for patients treated in the study, for patients' family doctors, for the patients in case of questions and approved the final version of the manuscript.

Nina B. Eggmann designed the study, collected data, analysed and interpreted the data, drafted and revised the manuscript and approved the final version of the manuscript.

Olivier Michielin enrolled patients in the study, drafted and revised the manuscript, and approved the final version of the manuscript.

Lada Mitchell designed the study, wrote the statistical portion of the protocol and the protocol synopsis, designed the CRF and its implementation, was responsible for the statistical analysis plan, helped monitor data quality during the study and data cleaning at the end of the study (for the final database lock), supervised all statistical analysis (e.g. tables/listings and outputs) and reviewed and signed the clinical study report for this study. The database was stored and data were analysed by Chiltern CRO, after the database lock after the final data sets were transferred to F. Hoffmann-La Roche, double checked with a senior programmer (F. Hoffmann-La Roche GMA Biometrics) the main outputs and results. Lada Mitchell approved the final version of the manuscript.

Luisa Veronese is the physician responsible for the study (Senior International Medical Leader, F. Hoffmann-La Roche). She significantly contributed to the study design, preparation of the study synopsis and protocol, preparation of case report forms and statistical plan; oversaw the overall conduct of the study; was significantly involved in cleaning of the data and in review and analysis of the data; drafted and revised the manuscript and approved the final version of the manuscript.

Paul René Hilfiker collected and analysed the imaging data, performed RECIST analysis, and approved the final version of the manuscript.

Lea Felderer designed the study, collected data, analysed and interpreted the data, drafted and revised the manuscript and approved the final version of the manuscript.

Jeannine D. Rinderknecht designed the study, collected data, analysed and interpreted the data, drafted and revised the manuscript and approved the final version of the manuscript.

Role of the funding source

This study was sponsored by F. Hoffmann-La Roche Ltd and was designed by the academic investigators and representatives of the sponsor. Data were collected with the use of the Chiltern data management systems and were analysed by the Chiltern and sponsor's statistical and programming teams. All authors contributed to the interpretation of data and the subsequent writing,

reviewing and finalisation of the manuscript. Medical writing support for the methods and results sections was provided by David Gibson, PhD, CMPP (ApotheCom) and was funded by the sponsor. All authors vouch for the completeness and veracity of the data and data analyses and had final responsibility for the decision to submit this publication.

Conflict of interest statement

Reinhard Dummer receives research funding from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche and has a consultant or an advisory board relationship with Novartis, Cephalon, Merck Sharp & Dohme, Roche, Bristol-Myers Squibb, Glaxo-SmithKline and Spirig.

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