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ORIGINAL ARTICLE

Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study

G. A. McArthur[1*], M. Maio[2], A. Arance[3], P. Nathan[4], C. Blank[5], M.-F. Avril[6], C. Garbe[7], A. Hauschild[8], D. Schadendorf[9], O. Hamid[10], M. Fluck[11], M. Thebeau[12], J. Schachter[13], R. Kefford[14], M. Chamberlain[15], M. Makrutzki[16], S. Robson[16], R. Gonzalez[17] & K. Margolin[18]

[1]Department of Medical Oncology, Peter MacCallum Cancer Centre, East Melbourne and University of Melbourne, Parkville, Australia; [2]AOU Senese Policlinico Santa Maria Alle Scotte, Siena, Italy; [3]Department of Medical Oncology, Hospital Clínic Barcelona, Spain; [4]Mount Vernon Hospital, Centre for Cancer Treatment, Northwood, UK; [5]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [6]University Paris Descartes, Hospital Cochin, APHP, Paris, France; [7]Department of Dermatology, University Hospital Tuebingen, Tuebingen; [8]Department of Dermatology, University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel; [9]Department of Dermatology, Comprehensive Cancer Center, University Hospital Essen, Essen, Germany; [10]Angeles Clinic and Research Institute, Los Angeles, USA; [11]Fachklinik Hornheide, Munster, Germany; [12]Moffitt Cancer Center, Tampa, USA; [13]Chaim Sheba Medical Centre, Oncology Institute, Ramat-Gan, Israel; [14]Crown Princess Cancer Centre Westmead Hospital and Department of Clinical Medicine, Macquarie University, Sydney NSW, Australia; [15]Seattle Cancer Care Alliance, Seattle, USA; [16]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [17]University of Colorado Cancer Center, Aurora; [18]City of Hope, Duarte, USA

*Correspondence to: Dr Grant A. McArthur, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne and University of Melbourne, Parkville, Australia. Tel: + 61-3-8559-6680; Fax: +61-3-8559-7379; E-mail: grant.mcarthur@petermac.org

Background: Vemurafenib has shown activity in patients with *BRAF*^{V600} mutated melanoma with brain metastases (BM). This phase 2 study evaluated vemurafenib in patients with/without prior treatment for BM.

Methods: Patients with *BRAF*^{V600} mutated melanoma with BM were enrolled into cohort 1 (previously untreated BM) and cohort 2 (previously treated BM) and received vemurafenib (960 mg BID) until disease progression (PD) or intolerance. Primary endpoint was best overall response rate (BORR) in the brain in cohort 1 that was evaluated using modified RECIST 1.1 criteria using lesions ≥0.5 cm to assess response.

Results: 146 patients were treated (cohort 1 $n = 90$; cohort 2 $n = 56$), 62% of whom were male. Median (range) time since diagnosis of BM: 1.0 (0–9) month in cohort 1 and 4.2 (1–68) months in cohort 2. Median duration of treatment was 4.1 months (range 0.3–34.5) in cohort 1 and 4.1 months (range 0.2–27.6) in cohort 2. Intracranial BORR in cohort 1 by an independent review committee (IRC) was 18% (2 CRs, 14 PRs). Extracranial BORR by IRC was 33% in cohort 1 and 23% in cohort 2. Median PFS (brain only, investigator-assessed) was 3.7 months (range 0.03–33.4; IQR 1.9–5.6) in cohort 1 and 4.0 months (range 0.3–27.4; IQR 2.2–7.4) in cohort 2. Median OS was 8.9 months (range 0.6–34.5; IQR 4.9–17.0) in cohort 1 and 9.6 months (range 0.7–34.3; IQR 4.5–18.4) in cohort 2. Adverse events (AEs) were similar in type, grade and frequency to other studies of single-agent vemurafenib. Grade 3/4 AEs occurred in 59 (66%) patients in cohort 1 and 36 (64%) in cohort 2. Overall, 84% of patients died during the study (86% in cohort 1 and 80% in cohort 2), mainly due to disease progression.

Conclusions: The study demonstrates clinically meaningful response rates of melanoma BM to vemurafenib, which was well tolerated and without significant CNS toxicity.

Key words: vemurafenib, *BRAF*^{V600} mutated melanoma, brain metastases, phase 2 study

Introduction

Over 40% of patients with advanced melanoma develop brain metastases (BM) detected after symptoms develop or by surveillance imaging [1] in which median overall survival (OS) is only 3.8–5.0 months [1–3]. Single BM can be resected or irradiated using stereotactic methods (SRT) [4], but multiple BM are poorly controlled with current local and/or systemic therapies [4–7].

Both targeted therapies and immune checkpoint inhibitors improve OS in patients with advanced melanoma (median

13.6–18.7 months) and for targeted therapies even longer survival (22.3–25.1 months) is obtained with combinations of BRAF and MEK inhibitors in patients with $BRAF^{V600}$ mutations [8–10]. The outcome of patients with BM treated with these novel agents is less well defined. The BREAK-MB study showed that patients with BM treated with dabrafenib had a median OS of 3.7–7.5 months [11]. Ipilimumab has also been evaluated in patients with BM with reported median OS of 3.7–7.0 months [12]. The activity of these classes of therapy against BM provided proof-of-concept for the potential effectiveness of treating BM with targeted and/or immunomodulatory agents.

The BRAF inhibitor vemurafenib is less well studied in patients with BM. One pilot study indicated activity in patients with $BRAF^{V600}$ mutated melanoma and symptomatic BM [13]. A phase 2 clinical trial was performed to estimate the overall response rate (ORR) of vemurafenib in patients with previously treated BM or with no prior treatment for BM. Secondary endpoints included intracranial and extracranial duration of response and OS.

Methods

Study design and treatment

An open-label, single-arm, multicentre, international phase 2 study in adults with histologically confirmed metastatic melanoma harbouring $BRAF^{V600}$ mutations with either symptomatic or asymptomatic BM that included two simultaneous cohorts:

Cohort 1: no previous treatment for BM; previous systemic therapy allowed, exclusive of BRAF or MEK inhibitors.

Cohort 2: BM previously treated with SRT, whole-brain radiation therapy (WBRT), or surgery, with measurable disease progression (excluding sites of prior surgery or SRT).

Patients received vemurafenib 960 mg bid continuously as tolerated, with up to two dose reductions (to 720 or 480 mg bid) for toxicity, and no re-escalation.

Primary and secondary objectives

The primary objective was best overall response rate (BORR) in the brain in patients with previously untreated BM, assessed by an independent review committee (IRC), using Response Evaluation Criteria In Solid Tumors (RECIST) with a modification for BM to be at least 0.5 cm in diameter.

Secondary objectives: intracranial BORR in the overall study population, and in each separate cohort; and safety and tolerability of vemurafenib. Additional secondary endpoints: IRC- and investigator-assessed extracranial BORR, intracranial and extracranial duration of response (DOR), progression-free survival (PFS), time to new BM in responding patients, and OS.

Study eligibility

Key inclusion criteria. Histologically confirmed metastatic melanoma with $BRAF^{V600}$ mutation (by Cobas® 4800 $BRAF^{V600}$ Mutation Test, Roche Molecular Systems) on any prior tissue sample. Measurable BM (minimum of one and maximum of five lesions) accurately measurable in one dimension as $\geq$0.5 cm by MRI with contrast.

Other inclusion criteria: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; may or may not have received prior systemic therapy for metastatic melanoma excluding MAPK-pathway inhibitors; received no prior SRT, WBRT, or surgery for BM (cohort 1) or received prior SRT, WBRT, or surgery for BM and progressed (cohort 2); $\geq$6 weeks since any previous monoclonal antibody-based therapy; if receiving corticosteroids, neurologically stable on a stable or a decreasing dose within 7 days prior to study start.

Key exclusion criteria. Leptomeningeal metastasis permitted only in cohort 2; previous malignancy requiring active treatment within the past 2 years (except BCC or SCC of the skin or cervical carcinoma *in situ*); concomitant anticancer therapies (anti-seizure medications were allowed).

Assessments

Efficacy. Tumour response was evaluated with RECIST v1.1. Magnetic resonance imaging (MRI) of the brain was performed at weeks 4, 8, and then every 8 weeks. Leptomeningeal disease was evaluated as nonmeasurable and evaluated qualitatively.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment could continue until the next scheduled assessment. If progression was confirmed, the date of progression was assigned as the earlier date. Computed tomography or MRI of the chest/abdomen/pelvis (using the same imaging method each time) was performed at week 8 and then every 8 weeks.

Safety. Safety evaluations occurred 2–4 weekly until week 28, then every 12 weeks. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) grading system.

Statistical analysis

The sample size was selected to estimate ORRs ±11–12%. If the BORR was 40% then 80 patients in cohort 1 would result in a 95% CI of 29–52%, taking into account a 10% withdrawal rate. Similarly, 120 patients enrolled overall, with a BORR of 30%, would require 132 patients for a 95% confidence interval (CI) of 22–39%. Direct comparisons were not intended between Cohort 1 and 2.

Efficacy endpoints were analysed according to the intention-to-treat (ITT) principle. BORR was presented by cohort and overall with exact two-sided 95% Pearson–Clopper CIs. Time-to-event endpoints (e.g. PFS, OS, time to development of new BM, time to progression, and DOR) were analysed using Kaplan–Meier methods. Safety data were summarized for the individual and overall cohorts.

Results

Between July 2011 and April 2013, 289 patients were screened and 146 (51%) were enrolled and treated (Figure 1). Patients were enrolled in Australia, Canada, France, Germany, Israel, Italy, Netherlands, Spain, UK, and USA. The most common reason for ineligibility was lack of $BRAF^{V600}$ mutation (52%). The cut-off date for information presented in this article is 16 April 2015 (2 years after the last patient was enrolled). All enrolled patients received $\geq$1 dose of study medication, with a median duration of follow-up of 9.6 months (95% CI 7.2–11.5). Baseline patient and disease characteristics are shown in Table 1 and supplementary Appendix Table 4, available at *Annals of Oncology* online.

Efficacy

Intracranial BORR by IRC and investigator is presented in Table 2. The intracranial BORR in cohort 1 by IRC (primary endpoint) was 18% (95% CI 10.5–27.3%): complete response, 2 patients;

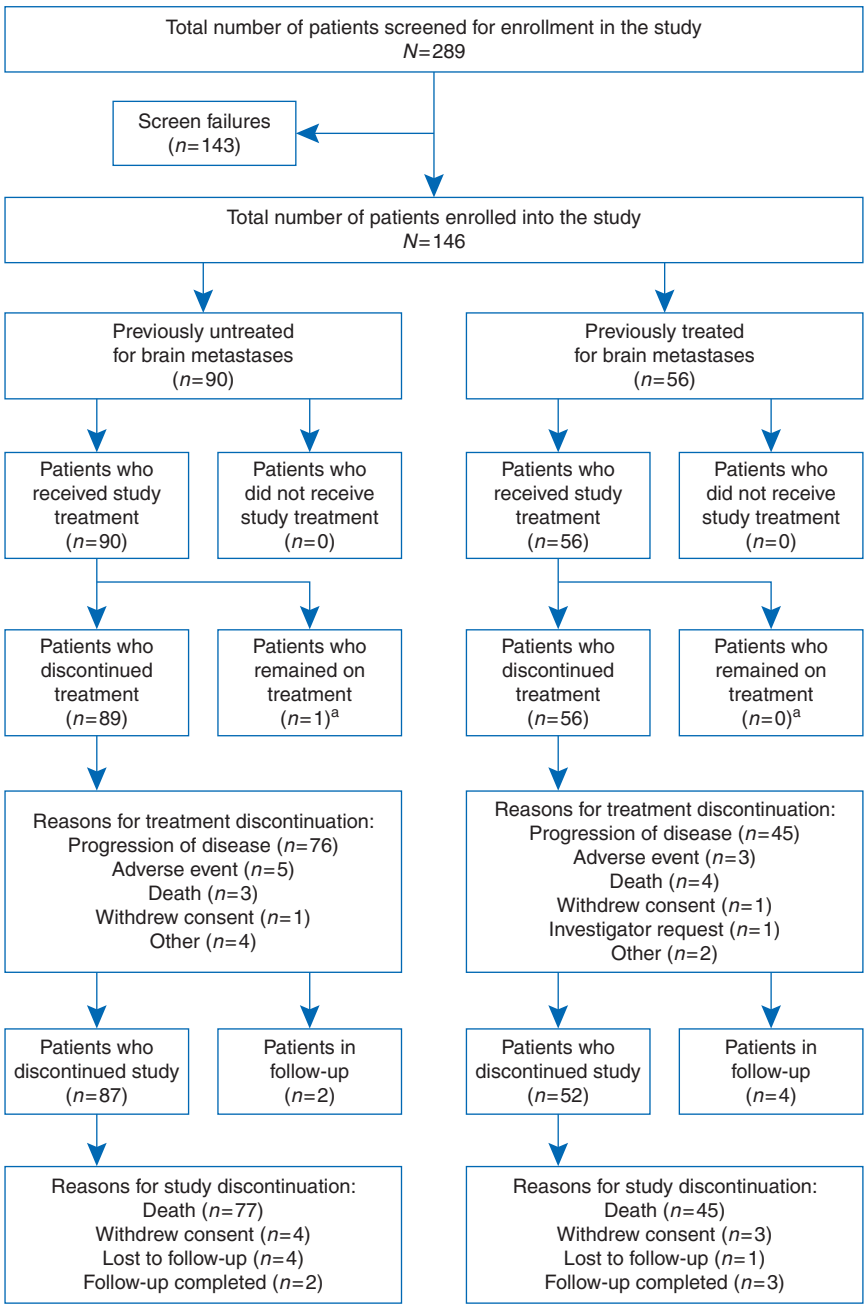

Figure 1. Patient flow and disposition. Reasons for screen failures ($n = 143$): BRAF mutation test negative, $n = 75$ (52%); failed another eligibility criterion, $n = 47$ (33%); clinical deterioration, $n = 9$ (6%); withdrawal of consent by patient, $n = 9$ (6%); screening procedures not followed, $n = 3$ (2%). Primary reasons for death ($n = 122$): Previously untreated group: adverse events in 2 (2%) patients (pneumonia, glioma*); disease progression in 74 (82%) patients; unknown in 1 (1%) patient. Previously treated group: adverse events in 1 (2%) patient (pneumonia); disease progression in 44 (79%) patients. *This patient was classified as having the serious adverse event of progression of glioma on study day 19, which caused discontinuation from the study medication and the study. The patient died on study day 184. The event was reported as not related to study medication. Retrospective assessment concluded that an enrolment error occurred for this patient, who was suffering from glioma (not brain metastasis from melanoma) that worsened and led to death soon after enrolment. This was not reported as a protocol violation because the patient was enrolled in good faith.

partial response, 14 patients. BORR and the percentage change in the sum of diameters of the target lesions from baseline are presented in Figure 2. Investigator-assessed BORR in the four patients who had leptomeningeal involvement was: improved ($n = 1$); stable ($n = 1$); and progressive disease ($n = 2$, brain and body).

The extracranial BORR by IRC was 33% in cohort 1 and 23% in cohort 2 (see supplementary Appendix, available at *Annals of Oncology* online). Investigator-evaluated composite of intracranial and extracranial BORR, considered as the 'global' BORR, was 19% in cohort 1 and 18% in cohort 2.

Table 1. Baseline demographics and disease characteristics

Characteristic	Cohort 1 ($n = 90$)	Cohort 2 ($n = 56$)	Total ($n = 146$)
Median age (range)	55.5 years (26–82)	52.5 years (28–83)	53.5 years (26–83)
Gender			
Male	56 (62%)	34 (61%)	90 (62%)
Female	34 (38%)	22 (39%)	56 (38%)
Race			
Caucasian	80 (89%)	55 (98%)	135 (93%)
Not applicable[a]	10 (11%)	1 (2%)	11 (8%)
ECOG performance status at baseline			
0	42 (47%)	21 (38%)	63 (43%)
1	47 (52%)[b]	35 (63%)	83 (56%)
LDH			
Normal	38 (42%)	24 (43%)	62 (43%)
Elevated	51 (57%)	29 (52%)	80 (55%)
Missing	1 (1%)	3 (5%)	4 (3%)
Leptomeningeal involvement			
Yes	0	4 (7%)	4 (3%)
No	90 (100%)	52 (93%)	142 (97%)
Time since diagnosis of BM, median (range)	1.0 month (0–9)	4.2 months (1–68)	1.7 months (0–68)
Number of brain target lesions at baseline[c]			
1	40 (44%)	11 (20%)	51 (35%)
2–4	37 (41%)	35 (63%)	72 (49%)
>4	13 (14%)	10 (18%)	23 (16%)
Sum of diameters of target lesions at baseline[d], median (range)	19.8 mm (4–109)	37.0 mm (5–95)	28.8 mm (4–109)
Previous surgery for BM at baseline	0	34 (61%)	34 (23%)
Patients with ≥1 previous therapy			
Systemic agent[e]	18 (20%)	22 (39%)	40 (27%)
Radiotherapy to brain	0	41 (73%)	41 (28%)
Whole-brain radiation therapy	0	15 (27%)	15 (10%)
Stereotactic radiation therapy	0	28 (50%)	28 (19%)

Percentages may not add up to 100% in all cases due to rounding.

[a]As per local regulations.

[b]One patient in Cohort 1 had an ECOG PS of 2 at baseline and was excluded from the per protocol population.

[c]Up to five BM could be considered as 'target' lesions. 'Nontarget' Lesions for brain imaging were defined as lesions that were not included as target lesions (including oedema, haemorrhage, mass effect, leptomeningeal disease).

[d]Investigator assessment.

[e]The most common prior systemic therapies in cohort 1 versus cohort 2 were: dacarbazine (8% versus 4%); ipilimumab (6% versus 11%); interferon (6% versus 5%); fotemustine (4% versus 5%); and temozolomide (0 versus 7%).

The median intracranial duration of response as assessed by the IRC were 4.6 months (range 2.7–29.9; interquartile range [IQR] 3.6–6.3) for cohort 1 and 6.6 months (range 1.0–18.4; IQR 4.5–10.7) for cohort 2. The corresponding values for investigator assessed response were 4.7 months (range 2.7–24.2; interquartile range [IQR] 3.9–11.7) in cohort 1 and 6.6 months (range 1.9–22.0; IQR 4.4–11.1) in cohort 2. Median extracranial duration of response assessed by the by the IRC were 7.7 months (range 1.8–21.6; IQR 3.7–14.7) for cohort 1 and 11.1 months (range 1.8–23.1; IQR 3.7–18.4) for cohort 2. The corresponding values for investigator assessed response were 5.6 months (range 1.8–25.6; IQR 3.6–12.7) in cohort 1 and 10.7 months (range 1.8–23.1; IQR 5.6–16.0) in cohort 2.

Median PFS (brain only) as assessed by the investigator was 3.7 months (range 0.03–33.4; IQR 1.9–5.6) in cohort 1 and 4.0 months (range 0.3–27.4; IQR 2.2–7.4) in cohort 2 (Figure 3a). Median OS was 8.9 months (range 0.6–34.5; IQR 4.9–17.0) in cohort 1 and 9.6 months (range 0.7–34.3; IQR 4.5–18.4) in cohort 2 (Figure 3b). The median time to development of new BM in brain responding patients (as assessed by investigator) was 14.9 months (range 3.5–33.4; IQR 5.6–NR) in cohort 1 and 14.5 months (range 2.8–27.4; IQR 7.3–NR) in cohort 2.

Table 2. Intracranial BORR assessed by IRC and investigator

	Cohort 1 (*n*=90)	Cohort 2 (*n*=56)	Total (*n*=146)
IRC assessment			
Complete response	2 (2%)	0	2 (1%)
Partial response	14 (16%)	10 (18%)	24 (16%)
Stable disease	39 (43%)	23 (41%)	62 (43%)
Progressive disease	29 (32%)	19 (34%)	48 (33%)
Not evaluable	6 (7%)	4 (7%)	10 (7%)
Number of responders	16 (18%)	10 (18%)	26 (18%)
[95% CI]	[11–27]	[9–30]	[12–25]
Investigator assessment			
Complete response	2 (2%)	0	2 (1%)
Partial response	24 (27%)	13 (23%)	37 (25%)
Stable disease	36 (40%)	30 (54%)	66 (45%)
Progressive disease	25 (28%)	11 (20%)	36 (25%)
Not evaluable	3 (3%)	2 (4%)	5 (3%)
Number of responders	26 (29%)	13 (23%)	39 (27%)
[95% CI]	[20–39]	[13–36]	[20–35]

Treatment exposure

The median duration of treatment was 4.1 months (range 0.3–34.5) in cohort 1 and 4.1 months (range 0.2–27.6) in cohort 2. 40 patients (44.4%) in cohort 1 and 31 (55.4%) in cohort 2 required dose interruption and/or modification. Details of new anti-cancer therapies used during the follow-up phase are shown in the supplementary Appendix, available at *Annals of Oncology* online.

Safety

Adverse events were similar in type, grade and frequency to other studies of single agent vemurafenib. Grade 3/4 AEs occurred in 59 (66%) patients in cohort 1 and 36 (64%) in cohort 2 (see supplementary Appendix, available at *Annals of Oncology* online).

Serious AEs were reported by 37 (41%) patients in cohort 1 and 27 (48%) patients in cohort 2 (see supplementary Appendix, available at *Annals of Oncology* online). Serious AEs reported in >1 patient (in either cohort) were: squamous skin cancer (12% in cohort 1; 11% in cohort 2); keratoacanthomas (12%

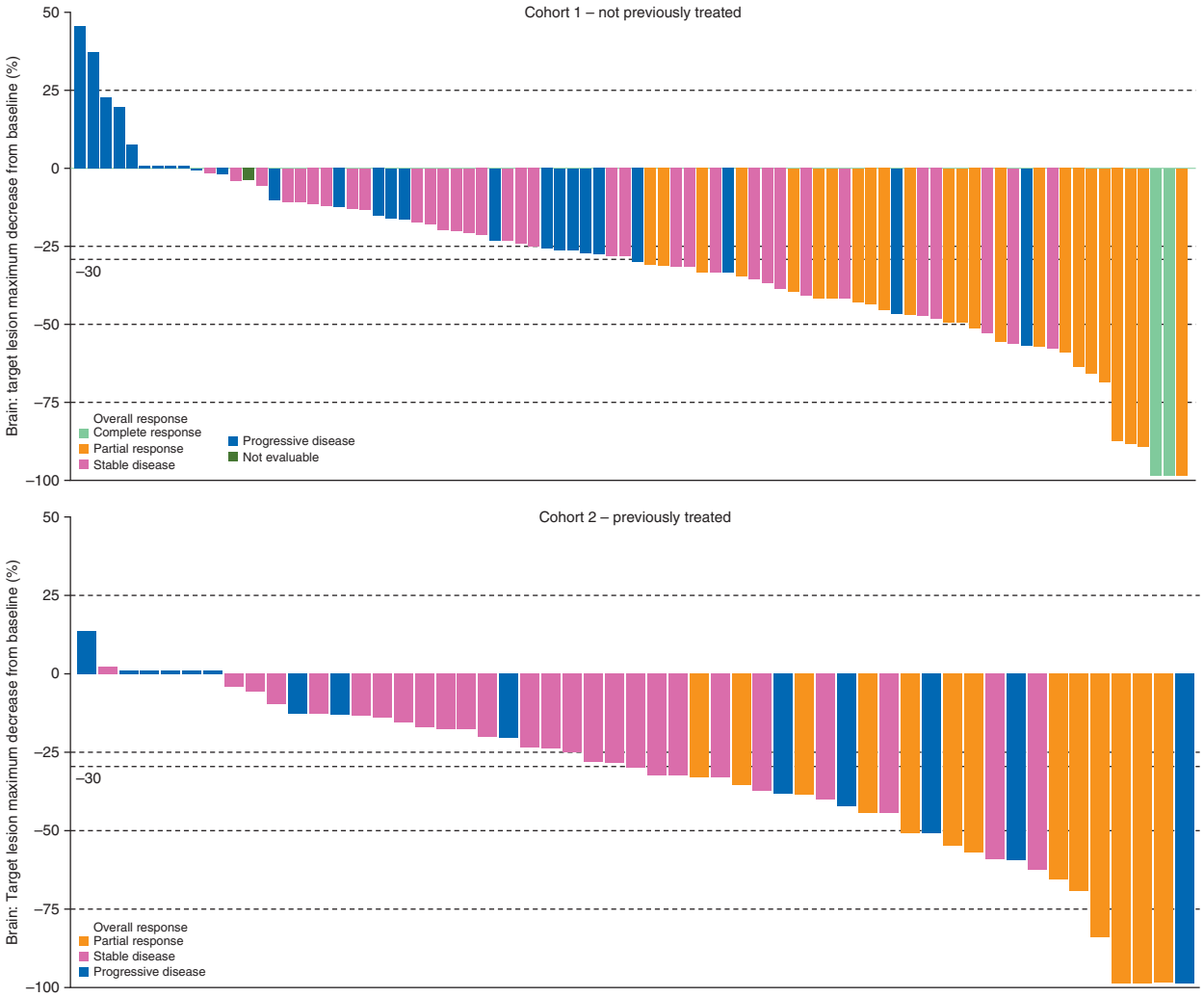

Figure 2. Percentage change in the sum of diameters of target lesions from baseline (investigator assessment). *One patient in cohort 2 had complete disappearance of their target lesion in the brain but appearance of a new lesion. This patient did not have a confirmed response and progressive disease was subsequently assigned as the patients' BORR. Response assessed using modified RECIST 1.1.

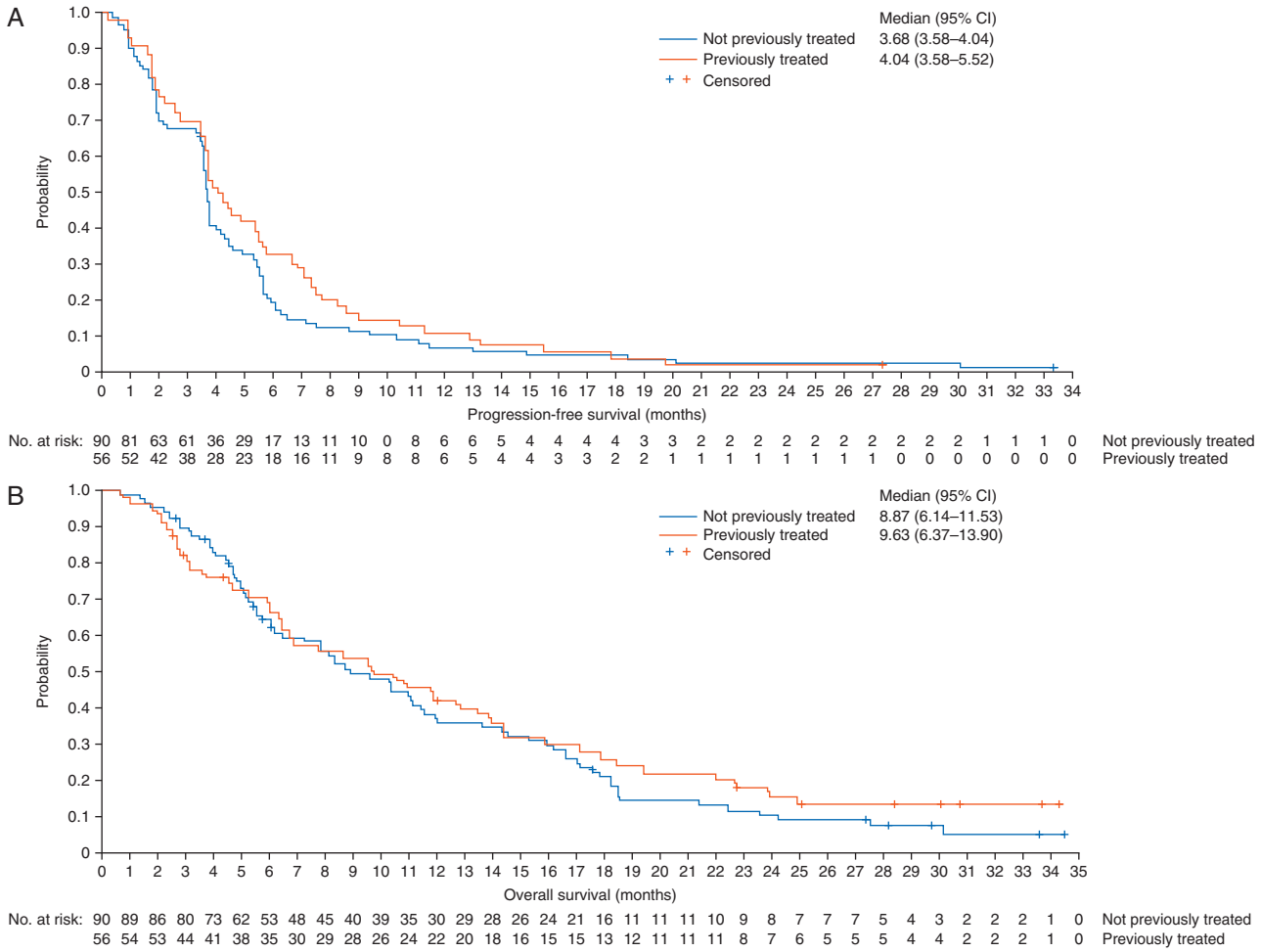

Figure 3. (A) Kaplan–Meier plot of PFS as assessed by the investigator (brain only). (B) Kaplan–Meier plot of OS.

versus 7%); central nervous system haemorrhages (2% versus 5%); new primary melanomas (2% versus 4%); pneumonia (1% versus 4%); seizure (1% versus 2%); confusion (0% versus 4%); upper abdominal pain (2% versus 0%); and pyrexia (2% versus 0%).

AEs required treatment discontinuation in five (6%) patients in cohort 1 (one each of prolonged ECG QT, pericardial effusion, pericarditis, cholestasis, pneumonia, glioma, agitation) and three (5%) in cohort 2 (two with prolonged ECG QT and one intracranial haemorrhage).

Overall, 122 patients (84%) died during the study (77 patients [86%] in cohort 1 and 45 [80%] in cohort 2), mainly due to disease progression (cohort 1, 82%; cohort 2, 79%). AEs led to death in two patients in cohort 1 (pneumonia, glioma) and one in cohort 2 (pneumonia). Another patient in cohort 2 died of an unknown cause.

Exploratory outcomes

The BORR (IRC) across both cohorts for patients with LDH < upper limit of normal (ULN) was 22.6% (95% CI 12.9–35.0) versus 17.6% (95% CI 8.4–30.9) for LDH >ULN but <2×ULN and 6.9% (95% CI 0.8–22.8) for LDH >2×ULN (see supplementary Appendix, available at *Annals of Oncology* online). The BORR across both cohorts was 25.5% (95% CI 14.3–39.6) for patients with a single BM, versus 16.7% (95% CI 8.9–27.3) for 2–4 metastases and 4.3% (95% CI 0.1–21.9) for >4 metastases.

Discussion

The activity of vemurafenib was evaluated in two cohorts of patients, Cohort 1 with no prior therapy for BM, and Cohort 2 with patients who had undergone locoregional and/or systemic therapy. Not unexpectedly, patients in Cohort 2 had a lower performance status and more brain lesions.

The primary endpoint of the study was intracranial response in patients with previously untreated BM as assessed by an IRC. The sample size of the current study was calculated based on intracranial BORR of 40 ± 11–12% in the cohort with previously untreated BM. The BORR of 18% (95% CI 11–27%) was lower than the BORR used to calculate sample size but is nonetheless clinically meaningful in the setting of brain metastases. The BORR as assessed by an IRC was comparable to the BREAK-MB study, which reported an IRC-assessed BORR of 17% (15 responders out of 89) in patients with previously untreated BM [11]. It is important to note the BREAK-MB study used identical modified

RECIST 1.1 criteria for the definition of measurable intracranial lesions (≥0.5 cm). For patients with previously treated BM, the IRC-assessed BORR in BREAK-MB was 17% (14 responders out of 83), which is comparable to the 18% (95% CI 9–30%) we observed in the current study. These results are contrasted with the IRC-determined extracranial response rates of 33% for cohort 1 and 23% for cohort 2. Interestingly, the extracranial response rates were higher at 57% in the BRIM3 study [8] and 45% in the coBRIM study [14], which excluded patients with active brain metastases.

Challenges in accurate measurement of BM were likely responsible for differences between investigators and the IRC determinations. Overall, these data suggest BM in BRAF-mutant melanoma are less responsive to BRAF inhibition due to either different tumour characteristics of the BM, different characteristics of both BM and extracranial metastases in patients with BM, or differences in drug concentrations between intracranial and extracranial metastases. We believe the second explanation is most likely, since the brain and extracranial response rates were lower in our study and BREAK-MB than for the metastases of patients without BM in studies that excluded them. Molecular differences in BRAF mutant melanoma that metastasizes to the brain are under investigation and point to the PTEN pathway as likely mediating important elements of their biology [15]. Clinical studies of inhibiting signalling in the PTEN pathway, such as PI3K, AKT or mTOR-inhibitors either in combination or sequenced with BRAF and MEK inhibitors, should provide data to address this hypothesis.

Cohort 2 patients, despite more unfavourable prognostic features, had similar ORR to Cohort 1 patients, suggesting that the allowed prior treatments did not select for BM with greater resistance to vemurafenib, data that are also consistent with those of BREAK-MB and dabrafenib [11]. Responses occurred rapidly with a median time to response of 1 month, corresponding to the first BM assessment. The waterfall plots indicated that the vast majority of patients achieved some intracranial tumour regression, suggesting possible clinical benefit for a greater proportion of patients than indicated by formal RECIST criteria. The duration of response was somewhat shorter than reported in studies of patients with only extracranial disease, with a median response duration of 4.7 months in Cohort 1 and 6.6 months in Cohort 2, which appears shorter than 6.7 and 7.3 months in the BRIM2 [16], and CoBRIM studies, respectively [14]. The long median time to tumour progression of almost 15 months to detection of new BM, which is significantly longer than the response duration of target lesions, suggesting that micrometastatic disease is well-controlled or that subclinical lesions grow so slowly that they do not become detectable until much later than progression of existing lesions.

The use of BRAF-inhibitors in patients with BM was safe and did not appear to increase intracranial haemorrhage or seizures. The overall safety profile was consistent with previous safety reports of vemurafenib, with cutaneous events, arthralgia, fatigue and low-grade gastrointestinal symptoms predominating. Few patients discontinued therapy because of adverse events.

The median PFS in the brain, 3.7 months in Cohort 1 and 4.2 months in Cohort 2, was substantially shorter than that of the BRIM3 study (6.9 months) or vemurafenib alone in the CoBRIM trial (6 months), and the median OS were also shorter than in BRIM3 and CoBRIM (8.9 versus 13.6 months and 9.6 versus 17.4 months, respectively). Although exploratory and limited by small patient numbers, patients with high LDH, higher burden of intracranial disease, measured by either lesion size or number, appeared to have lower response rate and shorter PFS (supplementary Table 2, available at *Annals of Oncology* online). Taken together, these data highlight the poor prognosis of patients with metastatic melanoma and BM, despite a targetable 'driver' oncogene mutation and evidence of initial drug-responsiveness.

In conclusion, the study demonstrates clinically meaningful response rates of melanoma BM to vemurafenib, which was well tolerated without significant intracranial toxicity. Given the relatively small number and good performance status of participants, we suggest caution in interpretation of the results to all patients with BM. Toxicities were manageable and similar to those in patients without BM. The development of combined BRAF and MEK inhibition as a new standard of care for patients with BRAF-mutant melanoma offers further options for patients with BM, and clinical data on these combination therapies are awaited. Further innovation is still needed for patients with BM, including evaluation of immunotherapies and other approaches in combination with BRAF-pathway inhibition.

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Disclosure

Two of the authors (MM and SR) are in full-time employment with the study sponsor. The other authors have declared no conflicts of interest.

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