Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial

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Summary

Background Brain metastases are common in patients with metastatic melanoma and median overall survival from their diagnosis is typically 17–22 weeks. We assessed dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain.

Methods We undertook a multicentre, open-label, phase 2 trial in 24 centres in six countries. We enrolled patients with histologically confirmed Val600Glu or Val600Lys BRAF-mutant melanoma and at least one asymptomatic brain metastasis (≥5 mm and ≤40 mm in diameter). Eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had adequate organ function. Patients were split into two cohorts: those in cohort A had not received previous local treatment for brain metastases and those in cohort B had progressive brain metastases after previous local treatments. Patients received 150 mg oral dabrafenib twice a day until disease progression, death, or unacceptable adverse events. The primary endpoint was the proportion of patients with Val600Glu BRAF-mutant melanoma who achieved an overall intracranial response, which was defined as a complete response or partial response assessed with a modified form of Response Evaluation Criteria in Solid Tumors (RECIST 1.1). We included patients who received at least one dose of dabrafenib in efficacy and safety analyses. This study is registered with ClinicalTrials.gov, number NCT01266967.

Findings Between Feb 2, 2011, and Aug 5, 2011, we enrolled 172 patients: 89 (52%) in cohort A and 83 (48%) in cohort B. 139 (81%) had Val600Glu BRAF-mutant melanoma. 29 (39·2%, 95% CI 28·0–51·2) of 74 patients with Val600Glu BRAF-mutant melanoma in cohort A achieved an overall intracranial response, as did 20 (30·8%, 19·9–43·4) of 65 in cohort B. One (6·7%, 0·2–31·9) of 15 patients with Val600Lys BRAF-mutant melanoma achieved an overall intracranial response in cohort A, as did four (22·2%, 6·4–47·6) of 18 such patients in cohort B. Treatment-related adverse events of grade 3 or worse occurred in 38 (22%) patients. Eleven (6%) patients developed squamous-cell carcinoma (five [6%] patients in cohort A, of whom one also had keratoacanthoma; six [7%] in cohort B). Four grade 4 treatment-related adverse events occurred in cohort A: one blood amylase increase, one convulsion, one lipase increase, and one neutropenia. Two grade 4 events occurred in cohort B: one agranulocytosis and one intracranial haemorrhage. 51 (30%) patients had a serious adverse event. The three most frequent serious adverse events were pyrexia (ten [6%] patients), intracranial haemorrhage (ten [6%]; one treatment-related), and squamous-cell carcinoma (11 [6%]).

Interpretation Dabrafenib has activity and an acceptable safety profile in patients with Val600Glu BRAF-mutant melanoma and brain metastases irrespective of whether they are untreated or have been previously treated but have progressed.

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Introduction

Brain metastases are common in cutaneous melanoma and are associated with a poor prognosis, which has been compounded by lack of effective treatments. 20% of patients have brain metastases at diagnosis of metastatic melanoma[1,2] and nearly half develop brain metastases in the course of the disease.[1,3] Median overall survival from diagnosis of brain metastases is 17–22 weeks.[3–5] In some patients with few brain metastases, surgery and stereotactic radiosurgery might provide local control;[6] however, systemic treatments have been ineffective, with at most 10% of patients having a response.[7–9]

BRAF is mutated in about 50% of patients with metastatic melanoma.[2,10,11] Of these individuals, substitution of valine with glutamate at position 600 (Val600Glu BRAF) occurs in 70–95% and substitution with lysine (Val600Lys BRAF) in 5–30%.[2,10–13] Brain metastases might be more common in patients with a BRAF mutation than in those with wild-type BRAF and NRAS.[2]

BRAF inhibitors are a standard of care for patients with Val600Glu BRAF-mutant metastatic melanoma.[14–18] Dabrafenib is a potent ATP-competitive inhibitor of BRAF kinase.[19] A phase 1 study showed that dabrafenib has activity in patients with Val600Glu and Val600Lys

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BRAF-mutant melanoma and untreated, asymptomatic brain metastases.[15] A reduction in the size of brain metastases was reported in nine of ten patients, including four complete remissions.[15] To confirm the activity of dabrafenib in brain metastases, we assessed dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma and at least one brain metastasis who were either previously untreated for brain metastases or who had progressive metastases after previous local treatments.

Methods

Study design and participants

BREAK-MB is a multicentre, open-label, phase 2 trial done in 24 centres in six countries (Australia, Canada, France, Germany, Italy, and the USA). We enrolled patients with histologically confirmed Val600Glu or Val600Lys BRAF-mutant melanoma and asymptomatic brain metastases. Tumour BRAF-mutation status was identified by Response Genetics (Los Angeles, CA, USA) by use of an allele-specific, investigational-use-only PCR assay. Eligible patients had at least one measurable brain metastasis between 5 mm and 40 mm in diameter, were aged at least 18 years, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function. We excluded patients who had leptomeningeal disease, primary dural metastases, or a history of other clinically significant malignancies in the 5 years before screening (appendix).

See Online for appendix

Eligible patients were split into two cohorts: cohort A and cohort B. Patients in cohort A had not received any previous local treatment for brain metastases and those in cohort B had disease progression in the brain after surgery, whole-brain radiotherapy, or stereotactic radiosurgery.

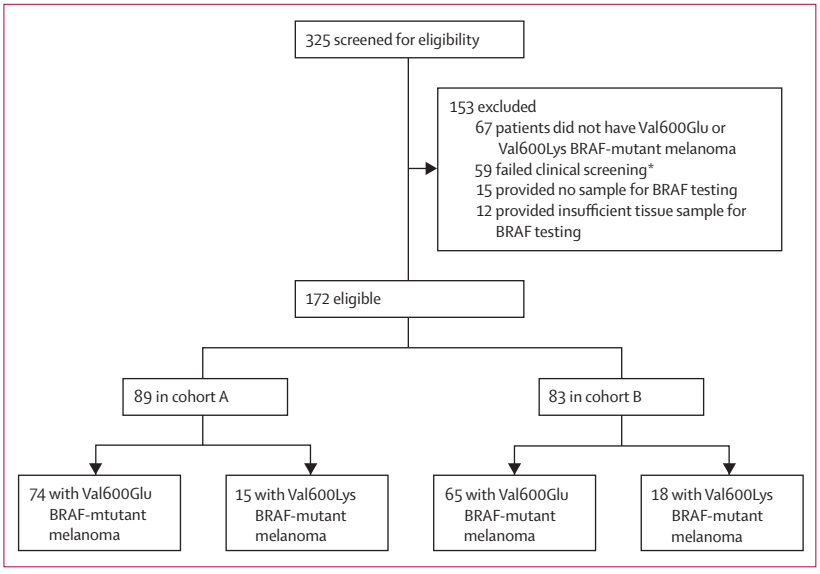

Figure 1: **Trial profile**
*Reasons for clinical screen failure include absence of intracranial lesion progression, echocardiogram findings, leptomeningial disease, and Eastern Cooperative Oncology Group performance status too high.

Patients could receive stable or decreasing doses of corticosteroids, and those in cohort B were allowed prophylactic antiepileptic treatment. Patients could have received up to two previous treatment regimens for extracranial metastatic melanoma, excluding BRAF or MEK inhibitors. Patients in cohort B could have had any number of previous local treatments.

The study protocol was approved by institutional review boards or human research ethics committees of participating centres and complied with country-specific regulatory requirements. Furthermore, the study was done in accordance with both the Declaration of Helsinki and International Conference of Harmonisation Good Clinical Practice. All patients provided written informed consent at screening.

Procedures

Patients were given 150 mg oral dabrafenib twice a day until disease progression, death, or unacceptable adverse events. Patients with radiologically confirmed disease progression who continued to have clinical benefit as assessed by the treating investigators were allowed to remain on treatment.

We recorded demographic and disease characteristics at baseline. All patients underwent a physical examination, electrocardiogram, echocardiogram, dermatological skin assessment, and assessment of vital signs and ECOG performance status. Baseline documentation of intracranial and extracranial lesions was done within 28 days before dabrafenib treatment.

Disease progression and response assessments for intracranial and extracranial metastatic lesions were assessed by the centre's investigator and an independent review committee with a modified form of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[20] We extended RECIST to include up to five intracranial target lesions and up to five extracranial target lesions; we allowed intracranial target lesions of between 5 mm and 40 mm in diameter; intracranial disease assessment could be done only by gadolinium-enhanced MRI; and MRI scan slices of 1 mm were necessary for brain metastases 5 mm or larger but less than 10 mm.

We did disease assessment scans at baseline, weeks 4 and 8, then every 8 weeks until week 40, and then every 3 months until discontinuation of study treatment. Response confirmation occurred at least 4 weeks after the initial response. Disease assessments deemed to be non-assessable were included in the denominator of all reported response rates. We assessed toxic effects with the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).

The primary endpoint was the proportion of patients with Val600Glu BRAF-mutant melanoma with investigator-assessed overall intracranial response. An overall intracranial response was defined as a best intracranial response of complete response (CR) or partial response (PR). Secondary efficacy endpoints

were the proportion of patients with Val600Lys BRAF-mutant melanoma with an overall intracranial response, overall response, duration of overall intracranial response and overall response, progression-free survival, and overall survival in patients with Val600Glu or Val600Lys BRAF-mutant melanoma. An overall response was defined as a best response of CR or PR when all disease (both extracranial and intracranial) was assessed. We measured progression-free survival and overall survival from the first dose of study treatment; time of first progression (extracranial or intracranial) was used to calculate progression-free survival. We calculated duration of response in patients with a CR or PR. These investigator-assessed endpoints were analysed separately for cohorts A and B. All responses were confirmed by a second scan. The effect of known metastatic melanoma prognostic factors (performance status, lactate dehydrogenase concentrations, and age)[21] on response to dabrafenib and clinical outcome were analysed for patients with Val600Glu BRAF-mutant melanoma in cohorts A and B (appendix).

Third-party adjudication was undertaken when investigator and review committee assessments were discordant. The adjudicator was masked to both investigator and committee target and non-target lesion selections, but able to view the images and see both case-report forms and response assessments. The adjudicator assessed all images from all timepoints, including all image series within each timepoint for every patient. The adjudicator selected the one of the two readers' response assessments that most accurately represented the patient's disease status and provided rationale for each case.

Dose modifications and interruptions of dabrafenib were recommended for treatment-related toxic effects of grade 2 or worse, according to the severity of the event. When dose modification was recommended, dabrafenib treatment was suspended until the toxic effects resolved to grade 1; treatment was resumed at the previous dose after grade 2 toxic effects, or reduced by one dose level for grade 3 adverse events. Dabrafenib was permanently discontinued for treatment-related grade 4 toxic effects.

Statistical analysis

Our study was designed to test the hypothesis that the proportion of patients with Val600Glu BRAF-mutant melanoma who achieved an overall intracranial response with dabrafenib would be 30% or more in each cohort versus the null hypothesis that the proportion would be 10% or less. For each cohort, we needed at least 11 (18·3%) of 60 patients with Val600Glu BRAF-mutant melanoma to achieve an overall intracranial response to reject the null hypothesis. The study was designed with 98·2% power and a one-sided α of 0·025 to assess cohorts A and B separately, but did not necessitate rejection of the null hypothesis in both to be successful. Therefore we did not adjust for type I error.

We report the proportion of patients achieving an overall intracranial response with exact two-sided 95% CIs, secondary endpoints with Kaplan-Meier estimates and two-sided 95% CIs, and proportions of patients responding with exact two-sided 95% CIs. All safety measures were analysed separately for patients with Val600Glu BRAF-mutant melanoma and those with Val600Lys BRAF-mutant melanoma in each cohort, and also in aggregate.

We included patients who received at least one dose of dabrafenib in the efficacy and safety analyses. We did the primary analysis on Nov 28, 2011, when all patients in both cohorts had at least 4 months of follow-up. We used SAS (version 9.1) for all analyses.

This study is registered with ClinicalTrials.gov, number NCT01266967.

Role of the funding source

This study was funded, administered, and sponsored by GlaxoSmithKline. The study was designed by some of the investigators in collaboration with the sponsor. Data were obtained by the sponsor and authors had access to study data. GVL, JMK, and DS developed the report in collaboration with the sponsor. All authors reviewed the report and are responsible for the decision to submit it for publication.

	Cohort A (n=89)	Cohort B (n=83)
Age (years)	52 (43–63)	53 (44–62)
Sex		
Male	65 (73%)	55 (66%)
Female	24 (27%)	28 (34%)
Eastern Cooperative Oncology Group performance status		
0	48 (54%)	51 (61%)
1	41 (46%)	32 (39%)
Concentrations of lactate dehydrogenase higher than the upper limit of normal	49 (55%)*	44 (53%)
BRAF mutation		
Val600Glu	74 (83%)	65 (78%)
Val600Lys	15 (17%)	18 (22%)
Target brain metastases		
1	41 (46%)	30 (36%)
2–4	40 (45%)	39 (47%)
>4	8 (9%)	14 (17%)
Previous systemic treatment for metastatic melanoma		
Chemotherapy (cytotoxics, non-cytotoxics)	23 (26%)	35 (42%)
Immunotherapy	5 (6%)	14 (17%)
Small-molecule targeted treatment	1 (1%)	2 (2%)
Biological treatment (monoclonal antibodies, vaccines)	1 (1%)	1 (1%)
Hormonal treatment	0	1 (1%)
Previous adjuvant systemic treatment		
Immunotherapy	18 (20%)	22 (27%)
Chemotherapy (cytotoxics, non-cytotoxics)	6 (7%)	5 (6%)
Biological treatment (monoclonal antibodies, vaccines)	1 (1%)	1 (1%)

Data are median (IQR) or n (%). *Lactate dehydrogenase data are missing for four patients in cohort A.

Table 1: **Baseline characteristics**

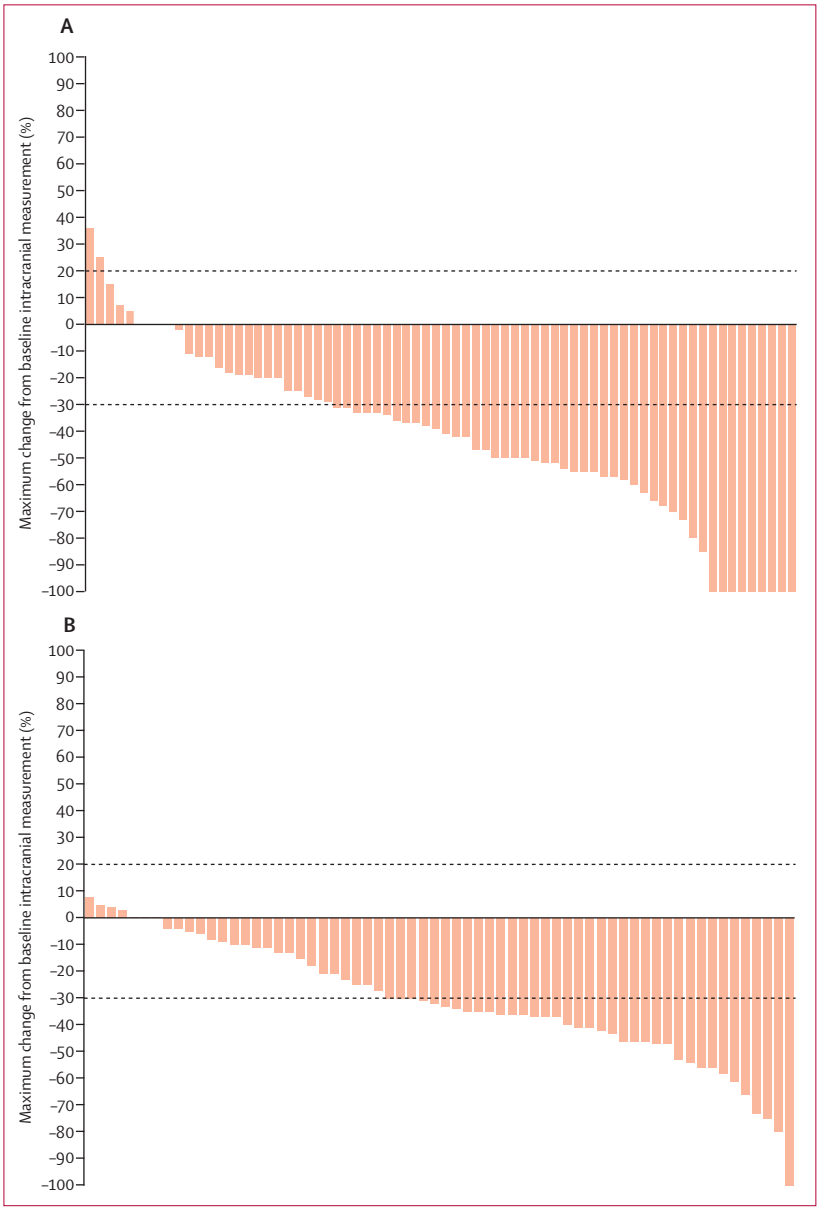

Figure 2: **Confirmed maximum reduction in intracranial target lesion for patients with Val600Glu BRAF-mutant melanoma and brain metastases in (A) cohort A and (B) cohort B**

Dotted line at 20% represents cutoff for progressive disease; dotted line at –30% represents cutoff for partial response. Similar waterfall plots for patients with Val600Lys BRAF-mutant melanoma can be found in the appendix.

	Cohort A	Cohort B
Val600Glu BRAF mutant	74	65
Overall intracranial response (CR+PR)	29 (39·2%, 28·0–51·2%)	20 (30·8%, 19·9–43·4%)
Intracranial disease control (CR+PR+SD)*	60 (81·1%, 70·3–89·3%)	58 (89·2%, 79·1–95·6%)
Intracranial CR	2 (3%)	0
Intracranial PR	27 (36%)	20 (31%)
Intracranial SD	31 (42%)	38 (58%)
Intracranial PD	9 (12%)	5 (8%)
Not assessable	5 (7%)†	2 (3%)‡
Overall response (CR+PR)§	28 (37·8%, 26·8–49·9%)	20 (30·8%, 19·9–43·5%)
Overall disease control (CR+PR+SD)	59 (79·7%, 68·8–88·2%)	54 (83·1%, 71·7–91·2%)
6-month survival estimate (%)	61% (46·7–73·2%)	61% (46·3–72·7%)
Val600Lys BRAF mutant	15	18
Overall intracranial response (CR+PR)	1 (6·7%, 0–31·9%)	4 (22·2%, 6·4–47·6%)
Intracranial disease control (CR+PR+SD)*	5 (33·3%, 11·8–61·6%)	9 (50·0%, 26·0–74·0%)
Intracranial CR	0	0
Intracranial PR	1 (7%)	4 (22%)
Intracranial SD	4 (27%)	5 (28%)
Intracranial PD	6 (40%)	6 (33%)
Not assessable	4 (27%)¶	3 (17%)‖
Overall response (CR+PR)§	0 (0%, 0–21·8%)	5 (27·8%, 9·7–53·5)
Overall disease control (CR+PR+SD)	7 (46·7%, 21·3–73·4%)	9 (50·0%, 26·0–74·0%)
6-month survival estimate (%)	27% (8·3–49·6%)	41% (16·5–64·0%)

Data are n, n (%, 95% CI), or n (%). CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. *SD as best response at or after week 8 assessment. †Two patients with no disease assessments after baseline, two patients with only week 4 assessments of SD, and one patient with only a week 4 assessment of PR. ‡One patient started new anticancer treatment 2 days after first dose of study treatment, and one patient with only a week 4 assessment of PR. §Overall response was defined as the proportion of patients with a best response of CR or PR when all disease (both extracranial and intracranial) was assessed. ¶Four patients with no disease assessments after baseline. ‖One patient with clinical progression at week 1, two with only week 4 assessments of SD.

Table 2: **Disease response**

Results

Between Feb 2, 2011, and Aug 5, 2011, we enrolled 172 patients (figure 1). Overall, 139 patients (81%) had Val600Glu BRAF-mutant melanoma and 33 (19%) had Val600Lys BRAF-mutant disease (table 1). More than half of patients in both cohorts had increased lactate dehydrogenase concentrations, and most had more than two target brain lesions (table 1).

29 (39·2%, 95% CI 28·0–51·2) patients with Val600Glu BRAF-mutant melanoma in cohort A achieved an overall intracranial response, as did 20 (30·8%, 95% CI 19·9–43·4) in cohort B (figure 2). Two CRs were recorded in cohort A (table 2). Fewer patients with Val600Lys BRAF-mutant melanoma achieved an overall intracranial response than did those with Val600Glu BRAF-mutant disease: one (6·7%, 0·2–31·9) of 15 patients with Val600Lys BRAF-mutant melanoma achieved an overall intracranial response in cohort A, as did four (22·2%, 6·4–47·6) of 18 such patients in cohort B. Durations of response are shown in table 3.

The best overall response (table 2), progression-free survival (figure 3, table 3), and overall survival (figure 3, table 3) were assessed by cohort and BRAF mutation. At the time of the primary analyses (Nov 28, 2011),

86 (62%) of 139 patients with Val600Glu BRAF-mutant disease and 16 (48%) of 33 with Val600Lys BRAF-mutant melanoma had experienced disease progression, which included new brain lesions in 33 (24%) and five (15%) individuals, respectively. Patients with Val600Lys BRAF-mutant metastatic melanoma had a shorter median overall survival and 6-month overall survival than did individuals with Val600Glu BRAF-mutant disease (tables 2, 3). Median progression-free survival for patients with Val600Glu BRAF-mutant tumours was longer than 16 weeks in both cohorts, and overall survival was greater than 31 weeks (table 3).

The most discriminating prognostic factor was serum lactate dehydrogenase concentration at study entry: increased concentrations predicted lower response (both overall intracranial response and overall response) and shorter median progression-free survival and overall survival in both cohorts (appendix). ECOG performance status at study entry of 0 versus 1 predicted median progression-free survival in cohort A only, and did not predict response or median overall survival in either cohort (appendix). Age younger than 54 versus 54 years or older did not predict response, median progression-free survival, or overall survival in either cohort (appendix).

Investigator and review committee assessments were discordant in 72 (42%) patients. The committee identified 15 (20%) of 74 individuals with Val600Glu BRAF-mutant melanoma in cohort A and 12 (19%) of 65 in cohort B who achieved an objective intracranial response. It found that no patients with Val600Lys BRAF-mutant disease in cohort A and two (11%) of 18 in cohort B achieved an overall intracranial response. In these further assessments, 21 (28%) of patients with Val600Glu BRAF-mutant tumours achieved an overall response in cohort A, as did 15 (23%) in cohort B. No patients with Val600Lys BRAF-mutant tumours in cohort A and two (11%) in cohort B achieved an overall response. Median progression-free survival was consistent with investigator results (Val600Glu: cohort A 16·1 weeks, 95% CI 15·7–21·9; cohort B 16·6, 15·9–23·7; Val600Lys: cohort A 8·1, 3·1–16·1; cohort B 15·9, 7·9–22·4). Third-party adjudications affirmed investigator assessments in 49 (68%) patients and the review committee in 23 (32%). Haemorrhagic, oedematous, and necrotic lesions, heterogeneous responses for differing lesions, and imaging variability were cited by the adjudicator as probable reasons for discordance.

141 (82%) patients had at least one adverse event related to study treatment (table 4) and 38 (22%) had treatment-related adverse events of grade 3 or worse. The incidence of adverse events was similar in both cohorts. Overall, 44 (26%) patients had pyrexia of any grade and 11 (6%) had cutaneous squamous-cell carcinoma. No squamous-cell carcinoma was reported in any organ other than skin. Median time to onset of first squamous-cell carcinoma was 8·4 weeks (IQR 4·6–12·1). Keratoacanthoma occurred in one (1%) patient in cohort A and actinic keratosis in nine

	Cohort A	Cohort B
Val600Glu BRAF mutant		
Intracranial duration of response*	20·1 (12·1–NR)	28·1 (20·1–28·1)
Progression-free survival	16·1 (15·7–21·9)	16·6 (15·9–23·7)
Overall survival	33·1 (25·6–NR)	31·4 (25·7–NR)
Val600Lys BRAF mutant		
Intracranial duration of response*	12·4 (NR–NR)	16·6 (NR–NR)
Progression-free survival	8·1 (3·1–16·1)	15·9 (7·9–22·4)
Overall survival	16·3 (6·9–22·4)	21·9 (15·3–NR)

Data are median number of weeks (95% CI). NR=not reached. *Duration of response in those with an intracranial partial or complete response.

Table 3: **Duration of response**

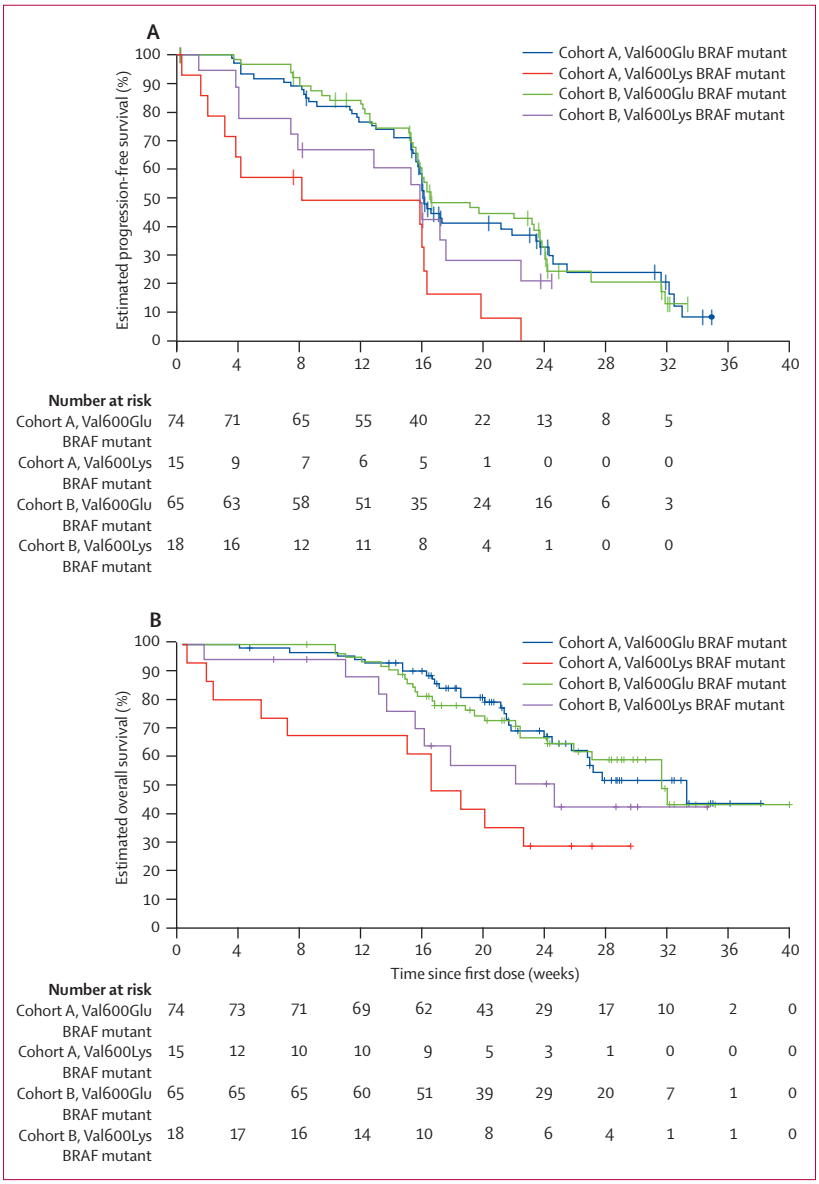

Figure 3: **Confirmed progression-free survival (A) and overall survival (B) by cohort and BRAF mutation subtype**

	Cohort A (n=89)	Cohort B (n=83)
Any event	73 (82%)	68 (82%)
Hyperkeratosis*		
Grade 2	7 (8%)	7 (8%)
Grade 3	0	1 (1%)
Rash		
Grade 2	5 (6%)	1 (1%)
Fatigue		
Grade 2	6 (7%)	4 (5%)
Grade 3	0	1 (1%)
Pyrexia		
Grade 2	6 (7%)	9 (11%)
Grade 3	0	1 (1%)
Palmar-plantar erythrodysaesthesia or plantar-palmar hyperkeratosis		
Grade 2	5 (6%)	4 (5%)
Grade 3	3 (3%)	0
Alopecia		
Grade 2	1 (1%)	1 (1%)
Arthralgia		
Grade 2	2 (2%)	1 (1%)
Nausea		
Grade 2	1 (1%)	2 (2%)
Grade 3	1 (1%)	0
Chills		
Grade 2	2 (2%)	2 (2%)
Grade 3	0	1 (1%)
Headache		
Grade 2	6 (7%)	1 (1%)
Grade 3	1 (1%)	0
Myalgia		
Grade 2	3 (3%)	1 (1%)
Decreased appetite		
Grade 2	3 (3%)	0
Grade 3	2 (2%)	0
Vomiting		
Grade 2	3 (3%)	2 (2%)
Diarrhoea		
Grade 2	1 (1%)	1 (1%)
Grade 3	0	1 (1%)
Squamous-cell carcinoma or keratoacanthoma†		
Grade 3	5 (6%)	6 (7%)
Melanocytic naevus		
Grade 2	1 (1%)	0
Pain in extremity		
Grade 2	1 (1%)	1 (1%)
Increased concentrations of alanine aminotransferase		
Grade 2	1 (1%)	3 (4%)
Grade 3	1 (1%)	1 (1%)

Graded with Common Terminology Criteria for Adverse Events (version 4.0). No grade 4 events were noted in more than 5% of patients. *Includes actinic keratosis, acrochordon, hyperkeratosis, seborrhoeic keratosis, and skin papilloma. †Keratoacanthoma was recorded as grade 1 in one patient; all cases of squamous-cell carcinoma were graded as grade 3.

Table 4: **Treatment-related adverse events of grade 2 or worse experienced by at least 5% of patients**

(5%) patients. Cutaneous basal-cell carcinoma occurred in three (2%) patients. We noted four grade 4 treatment-related events in cohort A: one blood amylase increase, one convulsion, one lipase increase, and one case of neutropenia. We recorded two grade 4 events in cohort B: one case of agranulocytosis and one intracranial haemorrhage. 51 (30%) patients had any serious adverse event. The three most frequent serious adverse events were pyrexia (ten [6%] patients), intracranial haemorrhage (ten [6%]; one treatment-related), and squamous-cell carcinoma (11 [6%]). No treatment-related deaths occurred.

Dose interruptions and reductions due to adverse events were necessary in 33 (37%) patients in cohort A and 46 (55%) in cohort B. The most common reason for dose interruption was pyrexia (18 [10%] patients) and the most common reason for dose reductions was pyrexia (seven [4%]). Discontinuation of study treatment because of adverse events occurred in four (2%) patients due to intracranial haemorrhage (two [1%] individuals), lymphopenia (one [1%]), and pancytopenia (one [1%]). Both lymphopenia and pancytopenia were assessed as treatment-related. Intracranial haemorrhage occurred in ten (6%) patients: five (3%) in cohort A and five (3%) in cohort B. Nine were deemed to be unrelated to study treatment; one patient in cohort B was judged to have had a treatment-related haemorrhage, but the lesion was haemorrhagic before enrolment. In patients with complete compliance data at time of analysis, median percentage compliance in cohort A was 91·8% and in cohort B 96·6%.

Discussion

To our knowledge, our trial is the largest prospective study undertaken in patients with melanoma and brain metastases (panel). Our results show that the BRAF inhibitor dabrafenib is active and has an acceptable safety profile in melanoma metastatic to the brain. In patients with the most prevalent BRAF mutation, intracranial disease control was recorded in many patients who had and had not received previous local brain treatment. The proportion of patients who achieved a CR is consistent with rates reported in large phase 3 studies of vemurafenib and dabrafenib in patients with Val600Glu BRAF-mutant melanoma and no brain metastases.[14,17] Extracranial response and progression were not predefined endpoints of the trial, and therefore we assessed only overall and intracranial responses.

In a study of temozolomide in patients with melanoma and brain metastases who were not BRAF genotyped,[7] median overall survival was 15·6 weeks for patients who had not received previous treatment for brain lesions and 9·5 weeks in those who had progressed after previous treatment. Our results (33 weeks of survival in patients who had not been treated for brain metastases and 31 weeks in those with progressive brain metastases after local treatment) are roughly three times longer than these values. Our results for dabrafenib, Margolin and

colleagues' phase 2 trial of ipilimumab,[8] findings for ipilimumab plus fotemustine in 20 patients with brain metastases,[24] and the pilot study of vemurafenib in five assessable patients with heavily pretreated brain metastases[22] support the inclusion of patients with brain metastases in investigations of new agents for melanoma.[25]

In our trial, dabrafenib was active in patients irrespective of whether or not they had had previous local treatment for brain metastases. Therefore, dabrafenib could be considered as initial treatment or after progression following local brain treatment (stereotactic or surgical). Dabrafenib was well tolerated, with adverse events and dose interruptions or reductions consistent with previous studies.[15,17,26] Only 2% of patients discontinued dabrafenib because of adverse events. The number of intracranial haemorrhages was lower than the reported 14–30% for spontaneous haemorrhage of melanoma brain metastases.[27,28] Compliance was also high.

Cutaneous squamous-cell carcinoma or keratoacanthoma occurred in 6% of patients in this study, which is consistent with proportions reported in other studies of dabrafenib in individuals with metastatic melanoma.[15,17,26] All lesions were excised and the diagnosis determined by histopathology, but there was no central histopathological review. BRAF-inhibitor induced cutaneous squamous-cell carcinoma occurs because of paradoxical activation of the MAPK pathway in BRAF wild-type cells that have upstream molecular aberrations.[29–31] The frequency of cutaneous squamous-cell carcinoma in this study is lower than that reported for vemurafenib[14,16,18] and may be due to different levels of paradoxical activation of the MAPK pathway by each of the drugs because of one of two reasons: differences in selectivity and inhibition of BRAF and CRAF between the two drugs or the fact that vemurafenib was dosed to maximum tolerated dose and dabrafenib was not. Another explanation could be that the classification and histopathological diagnosis of hyperkeratotic lesions differs between pathologists.

We modified RECIST 1.1 to ensure that dabrafenib efficacy was assessed in patients with multiple small brain metastases who are representative of the metastatic melanoma population.[1] The discordance between the investigator and review committee response assessment, particularly for intracranial disease, led to a blinded adjudication, in which investigator assessments were upheld in two-thirds of cases. Several factors could have affected the reproducibility of lesion measurements and therefore contributed to the discordance, such as measure variability, image quality, presence of several target lesions or small-volume disease, cystic nature of brain metastases, and haemorrhagic lesions or lesions that became necrotic with dabrafenib treatment. Discordance of 24–29% between investigator and review committee assessments of median progression-free survival has been reported previously.[32] In our study, median progression-free survival and number of events were consistent. No such benchmark has been established for discordant response rates. Our study draws attention to the difficulties of intracranial disease assessment, which has been a long-standing challenge in the specialty of neuro-oncology.[33] Such assessment is increasingly important for metastatic solid tumours because targeted drugs often show activity in brain metastases. We did not do a secondary validation method with alternate metrics of response and progression, including volume and measurements of necrosis, because it might have introduced further variability into the study.

The decreased activity of dabrafenib in patients with Val600Lys BRAF-mutant metastatic melanoma compared with Val600Glu BRAF-mutant disease was expected, in view of the results of the phase 2 study of dabrafenib (BREAK-2) in patients without active brain metastases.[26] Disease response and survival were particularly poor for patients with Val600Lys BRAF-mutant melanoma in cohort A, although the smaller numbers of patients in this group qualify interpretation of these results. Patients with Val600Lys BRAF-mutant melanoma have a shorter disease-free interval than do those with Val600Glu BRAF-mutant disease from diagnosis of first melanoma to stage IV, and the Val600Lys BRAF mutation has been linked to high cumulative ultraviolet-exposure disease.[11] Studies using enzyme panels suggest dabrafenib is equally active against Val600Glu and Val600Lys BRAF-mutant disease (unpublished) and further studies are needed to establish why activity between the genotypes differs in people.

Panel: Research in context

Systematic review

We searched PubMed for reports published before July 24, 2012, with the search terms "cerebral metastases", "melanoma", "clinical trial", and "drug". We used no language restrictions. We excluded all reviews. Of 109 reports identified, 20 were clinical trials of systemic treatments in patients with active melanoma brain metastases, including the phase 1 study of dabrafenib.[15] We also identified a conference abstract reporting a pilot study of vemurafenib in brain metastases.[22]

Activity of dabrafenib was first tested in a prospective cohort of ten asymptomatic patients.[15] Eight patients had a response, including four complete remissions in the brain, which led to the development of this study. None of the phase 1, 2, or 3 trials of vemurafenib[14,16,18] included patients with active or untreated brain metastases. Similarly, the expanded-access programme of vemurafenib[23] specifically excluded patients with active brain metastases unless no other treatment options were available, and no formal assessment of intracranial response was done. However, in a pilot study of vemurafenib,[22] one of five assessable patients with Val600Glu BRAF-mutant melanoma and progressing brain metastases after several lines of treatment (including local brain-directed treatments) had a partial response and four had stable disease. A phase 2 trial (NCT01378975) is underway to investigate the activity of vemurafenib in patients with previously treated and untreated brain metastases.

Interpretation

Dabrafenib is well tolerated and active in patients with BRAF-mutant melanoma with brain metastases, irrespective of whether or not the brain metastases have been previously treated, and so could be considered as initial treatment or after progression after local brain treatment. These individuals are traditionally excluded from clinical trials of new drugs, but our results support their inclusion.

Nevertheless, the proportions of patients with intracranial disease control support the use of dabrafenib in Val600Lys BRAF-mutant melanoma involving the brain.

The mechanism by which dabrafenib penetrates the brain is unknown. Measurement of brain concentrations after repeat dosing in mouse models has shown that dabrafenib or one of its metabolites, or both, might penetrate an intact blood–brain barrier (unpublished). The blood–brain barrier could also be disrupted in radiologically visible brain metastases.[34] A multicentre translational study is planned to clarify the mechanism of brain penetration.

In conclusion, our study has shown that dabrafenib has activity and an acceptable safety profile in patients with Val600Glu and Val600Lys BRAF-mutant melanoma metastatic to the brain, whether the brain metastases are untreated or previously treated but have progressed. We believe that the high proportion of patients with Val600Glu BRAF-mutant tumours who achieved intracranial disease control and median survival of longer than 31 weeks are promising for patients with Val600Glu or Val600Lys BRAF-mutant melanoma and brain metastases.

Contributors

GVL, JMK, and DS developed the report, with contributions by all authors. GVL, UT, MAD, RFK, PAA, PBC, IP, AH, CR, AA, LM, HT, TW, LZ, JMK, and DS recruited patients. GVL, UT, MAD, RFK, PAA, AH, CR, TW, JS, SS, A-MM, MG, VG, and JMK interpreted data. GVL, MAD, RFK, PBC, SS, MG, VG, MS, JMK, and DS designed the study. JS and MS wrote the protocol. MS was involved in medical monitoring.

Conflicts of interest

GVL is a paid consultant and adviser to GlaxoSmithKline, Bristol-Myers Squibb, and Roche; and receives honoraria, research support, and travel and related expenses from Roche. UT is a consultant and adviser to GlaxoSmithKline, Bristol-Myers Squibb, and Merck Sharp and Dohme; and receives honoraria from GlaxoSmithKline, Roche, Bristol-Myers Squibb, and Merck Sharp and Dohme. MAD is a paid consultant and adviser to GlaxoSmithKline, Novartis, and Genentech; and receives research funding from GlaxoSmithKline, Genentech, AstraZeneca, Merck, and Myriad. RFK is a paid consultant and adviser to GlaxoSmithKline. PAA is a paid consultant and adviser to Bristol-Myers Squibb, Merck Sharp and Dohme, Genentech, GlaxoSmithKline, Amgen, Celgene, Medimmune, and Novartis; and has received honoraria from Bristol-Myers Squibb, Merck Sharp and Dohme, and Genentech. PBC is a consultant and adviser and has received research funding from Genentech and GlaxoSmithKline. AH has received honoraria for advisory board membership, consultancy, and lectures from Amgen, AstraZeneca, Biovex, Bristol-Myers Squibb, Boehinger Ingelheim, Celgene, Eisai, GlaxoSmithKline, IGEA, Lilly, Medac, Melasciences, Merck Sharp and Dohme, Merck, Novartis, Roche, Sobi, Vical, and Jansen. CR is a paid consultant and adviser for Genentech, Bristol-Myers Squibb, and GlaxoSmithKline. AA has received research funding from GlaxoSmithKline. HT is a consultant and adviser for, and has received research funding from, Novartis. LZ has received honoraria from Roche. JS, SS, A-MM, MG, VG, and MS are employees of GlaxoSmithKline and own stock in the company. JMK is a paid consultant and adviser for GlaxoSmithKline, Novartis, and Merck. DS is a paid consultant and adviser and has received honoraria from GlaxoSmithKline, Roche, Novartis, Genentech, and Amgen. The other authors declare that they have no conflicts of interest.

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