Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

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Summary

Background Dabrafenib, an inhibitor of mutated BRAF, has clinical activity with a manageable safety profile in studies of phase 1 and 2 in patients with $BRAF^{V600}$-mutated metastatic melanoma. We studied the efficacy of dabrafenib in patients with $BRAF^{V600E}$-mutated metastatic melanoma.

Methods We enrolled patients in this open-label phase 3 trial between Dec 23, 2010, and Sept 1, 2011. This report is based on a data cutoff date of Dec 19, 2011. Patients aged 18 years or older with previously untreated, stage IV or unresectable stage III $BRAF^{V600E}$ mutation-positive melanoma were randomly assigned (3:1) to receive dabrafenib (150 mg twice daily, orally) or dacarbazine (1000 mg/m² intravenously every 3 weeks). Patients were stratified according to American Joint Committee on Cancer stage (unresectable III+IVM1a+IVM1b *vs* IVM1c). The primary endpoint was investigator-assessed progression-free survival and was analysed by intention to treat; safety was assessed per protocol. This study is registered with ClinicalTrials.gov, number NCT01227889.

Findings Of the 733 patients screened, 250 were randomly assigned to receive either dabrafenib (187 patients) or dacarbazine (63 patients). Median progression-free survival was 5·1 months for dabrafenib and 2·7 months for dacarbazine, with a hazard ratio (HR) of 0·30 (95% CI 0·18–0·51; p<0·0001). At data cutoff, 107 (57%) patients in the dabrafenib group and 14 (22%) in the dacarbazine group remained on randomised treatment. Treatment-related adverse events (grade 2 or higher) occurred in 100 (53%) of the 187 patients who received dabrafenib and in 26 (44%) of the 59 patients who received dacarbazine. The most common adverse events with dabrafenib were skin-related toxic effects, fever, fatigue, arthralgia, and headache.The most common adverse events with dacarbazine were nausea, vomiting, neutropenia, fatigue, and asthenia. Grade 3–4 adverse events were uncommon in both groups.

Interpretation Dabrafenib significantly improved progression-free survival compared with dacarbazine.

Funding GlaxoSmithKline.

Introduction

In 2008, about 46 000 people died from melanoma in the world.[1,2] When we initiated this clinical trial, standard therapy for metastatic melanoma was either chemotherapy (ie, dacarbazine) or high-dose interleukin 2 (in USA). About 50% of melanomas have an activating mutation in the *BRAF* gene.[3–5] 80–90% of BRAF-mutated melanomas have a V600E mutation and 10–20% have a V600K mutation. Other V600 mutations are rare.[5] Melanomas with *BRAF* mutations seem to be dependent on mutated BRAF, which is constitutively active and drives cell proliferation in many cases of melanoma. In vitro and preclinical data show that inhibitors of mutated BRAF induce clear antiproliferative effects in $BRAF^{V600E}$-mutated melanomas, but not in melanomas with wild-type BRAF. Substantial clinical effects were noted in patients with BRAF-mutated melanoma treated with vemurafenib, the first BRAF inhibitor brought to the clinic. Vemurafenib induced objective responses in 48% of patients and was associated with improvement in overall survival and progression-free survival.[6] Since completion of accrual to the trial we report here, vemurafenib was approved by the US Food and Drug Administration and the European Medicines Agency.

Dabrafenib is a reversible, ATP-competitive inhibitor that selectively inhibits $BRAF^{V600E}$ kinase with a concentration required for 50% inhibition of the kinase activity (IC_{50}) five times lower than the IC_{50} for wild-type BRAF or CRAF.[7] Preclinical data show that dabrafenib inhibits the MAPK pathway in $BRAF^{V600E}$-mutated melanoma cells leading to decreased proliferation and regression in xenograft mouse models. In a phase 2 trial,[8] dabrafenib showed a confirmed response rate (complete response+partial respone) of 59%. To assess whether dabrafenib was better than standard dacarbazine chemotherapy, we did a phase 3, multicentre, randomised trial in previously untreated melanoma patients whose tumours harboured a $BRAF^{V600E}$ mutation.

Methods

Study design and patients

We enrolled patients from 70 sites (hospitals, outpatient clinics, academic institutions) in 12 countries. Patients with histologically confirmed, measurable metastatic melanoma (stage IV or unresectable stage III) shown to

have a *BRAF*^{V600E} mutation by central testing using an investigational-use-only assay, were eligible for the study.

No previous antitumour therapy for unresectable or metastatic melanoma was allowed other than interleukin 2. Other eligibility criteria included age of 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active and able to carry on all performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), and adequate haematological, hepatic, renal, and cardiac function. Exclusion criteria included surgery, radiotherapy, or immunotherapy within 4 weeks; history of HIV infection; glucose-6-dehydrogenase deficiency; and previous malignancy within the past 5 years. Patients with CNS metastases were excluded unless they were without evidence of active CNS metastases for more than 3 months after surgery or stereotactic radiosurgery. Other exclusion criteria were corrected QT interval of 480 ms or more; acute coronary syndrome, coronary angioplasty, placement of stents, or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks; abnormal cardiac valve morphology grade 2 or higher on ECHO cardiography, or known cardiac metastases.

The protocol (appendix) was approved by the independent review board at each participating institution. All patients signed written informed voluntary consent before enrolment and an independent data monitoring committee assessed benefit risk and monitored safety measures.

Randomisation and masking

In this open-label trial, eligible patients were randomly assigned (ratio 3:1) to receive either oral dabrafenib 150 mg twice-daily or intravenous dacarbazine 1000 mg/m² every 3 weeks. We chose a ratio of 3:1 because it allowed better characterisation of the efficacy and safety of dabrafenib given the small sample size dictated by the hypothesised effect size. We stratified patients according to American Joint Committee on Cancer stage (unresectable III+IVM1a+IVM1b *vs* IVM1c). A centrally located, computerised, interactive, voice activated response system controlled assignment of patient treatment. Although investigators were aware of treatment group when assessing progression-free survival, a masked independent review committee (IRC) reviewed all scans and, per protocol, had to confirm progression before patients crossed over from dacarbazine to dabrafenib.

Procedures

Tumour *BRAF* mutation status was centrally identified with an allele-specific PCR assay for investigational use only (Response Genetics Inc, Los Angeles, CA, USA). This assay specifically differentiated between V600E, V600K, and wild-type forms of the *BRAF* gene.

The hypothesised progression-free survival hazard ratio (HR) of 0·33 (67% reduction in the risk of progression or death), meant that conventional error rates would lead to a smaller trial but would not necessarily produce a convincing body of evidence. Therefore, we selected a one-sided 0·02 type-I error rate with high statistical power to provide rigorous evidence of the hypothesised difference.

Treatment continued until disease progression, death, study treatment discontinuation, or withdrawal. Patients in the dacarbazine group were allowed to cross over to receive dabrafenib after progression was confirmed by independent review. Patients who permanently discontinued dacarbazine because of an adverse event, withdrawal of consent, or for any reason other than progression of disease, were not eligible for crossover.

Dose reductions for both dabrafenib and dacarbazine were pre-specified for adverse events of grade 2 or higher. Treatment with dabrafenib was interrupted until the

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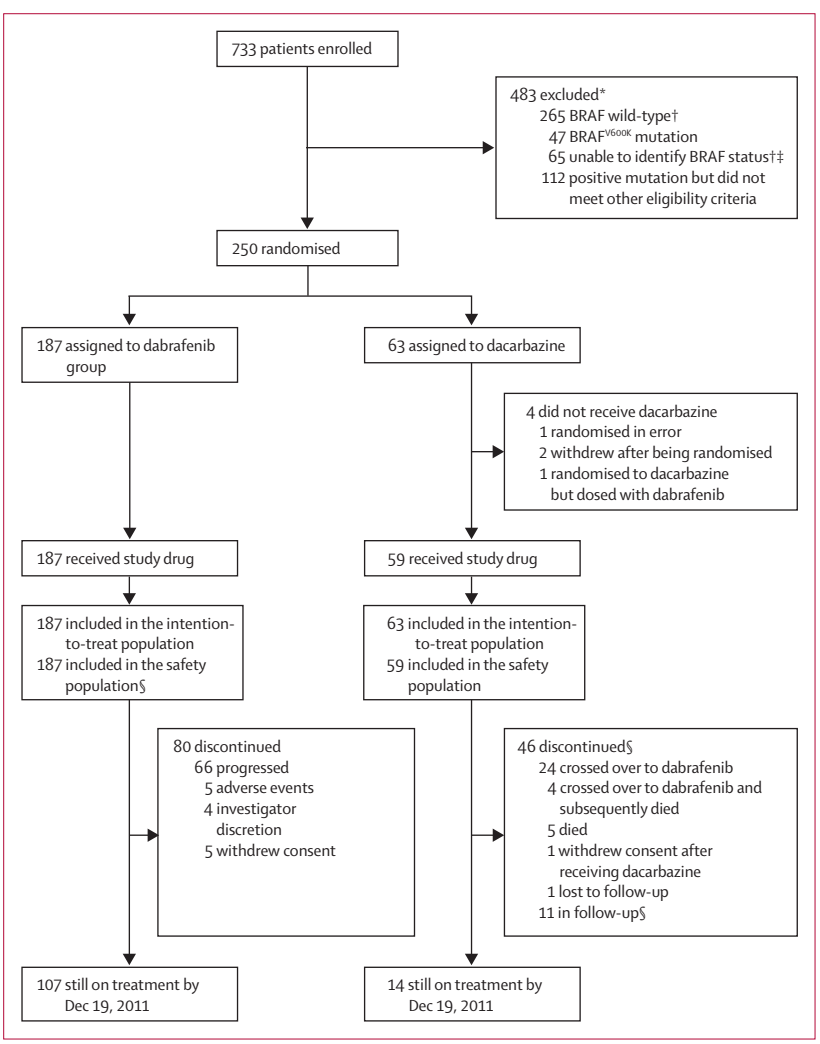

Figure 1: **Trial profile**

*Some patients had multiple tests. †330 (45%) of 733 screened for eligibility had wild-type *BRAF* (n=265) or indeterminate BRAF results (n=65); this proportion is consistent with population estimates of melanomas with an activating mutation in the *BRAF* gene. ‡45 because samples were insufficient 20 because of technical reasons. §Includes patient randomised to dacarbazine but who only received dabrafenib, who was in follow-up at data cutoff date.

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See Online for appendix

adverse event resolved or reduced to grade 1. Treatment was restarted at the current dose for an adverse event of grade 2 or reduced by one dose level for an adverse event of grade 3 unless the adverse event was deemed unrelated to dabrafenib by the investigator. Dabrafenib was discontinued for drug-related grade 4 toxic effects and the patient was monitored and supportive care provided; if in the investigator's opinion, the event was not likely to be treatment-related and was therefore unlikely to recur, dabrafenib was restarted at one dose level lower. For fevers of grade 3 or higher, or of any grade with signs and symptoms including rigors, dehydration, hypotension, dizziness, or weakness, dabrafenib treatment was interrupted until fever resolved to less than 38°C and symptoms resolved; treatment was restarted at one dose level lower. For fevers of grade 2 or lower, treatment was interrupted until fever resolved to less than 38°C and then restarted at the original dose level.

For dacarbazine-related toxic effects of grades 3 or 4, treatment was interrupted until the adverse event returned to grade 1 or lower, and then restarted with a dose reduction of 20%. Treatment with dacarbazine was discontinued if the adverse event did not resolve to grade 2 or lower within 4 weeks, or if a haematological adverse event of grade 4 recurred after dose reduction.

	Dabrafenib (n=187)	Dacarbazine (n=63)
Age, median (range)	53·0 (22–93)	50·0 (21–82)
Sex		
Male	112 (60%)	37 (59%)
Ethnic origin		
White	187 (100%)	63 (100%)
ECOG performance status at baseline		
0	124 (66%)	44 (70%)
≥1	62 (33%)	16 (25%)
Unknown	1 (<1%)	3 (5%)
M-status at screening		
M0	6 (3%)	1 (2%)
M1a	23 (12%)	10 (16%)
M1b	34 (18%)	12 (19%)
M1c	124 (66%)	40 (63%)
Lactate dehydrogenase level at baseline		
Elevated (>upper limit of the normal range)	67 (36%)	19 (30%)
Normal (≤upper limit of the normal range)	119 (64%)	43 (68%)
Unknown	1 (<1%)	1 (2%)
Previous treatment		
No previous therapy	6 (3%)	1 (2%)
Previous therapy	181 (97%)	62 (98%)
Immunotherapy	52 (28%)	15 (24%)
Radiotherapy	37 (20%)	10 (16%)
Adjuvant biologic therapy (monoclonal antibody, vaccines)	3 (2%)	3 (5%)
Adjuvant chemotherapy	1 (<1%)	4 (6%)

Data are number of patients (%), unless otherwise stated. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Patient demographics and baseline characteristics**

Patients underwent baseline physical examination and assessment of disease history, radiographic tumour assessment by CT or MRI of brain, chest, abdomen, and pelvis, ECHO cardiogram, electrocardiogram, blood counts, and biochemical screen. Physical examinations, blood counts, and biochemical screens were repeated at 3-week intervals. Tumour assessments were repeated at weeks 6 and 12, and every 9 weeks afterwards. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and were assessed while patients were on study and for 28 days afterwards. This report is based on a data cutoff date of Dec 19, 2011.

Statistical analysis

The primary endpoint was progression-free survival as assessed by the individual investigator from randomisation. Secondary endpoints included progression-free survival as assessed by an IRC, overall survival, objective response rate according to Response Evaluation Criteria in Solid Tumors, version 1.1[9] assessed by the investigator and the IRC, progression-free survival after crossover, duration of response, quality of life, safety and tolerability, and support of a *BRAF* mutation assay validation.

All randomised patients were included in efficacy analyses; safety analyses included all randomised patients who received at least one dose of study medication.

The trial was designed to enrol 200 patients to observe 102 progression-free survival events with statistical power of 99·7% to detect a HR of 0·33 (median progression-free survival of 2 months in patients who received dacarbazine and 6 months in patients who received dabrafenib). The trial design used a one-sided log-rank test with α=0·02. We did no interim efficacy analyses for this study. We did prespecified subgroup analyses for sex, age, baseline concentrations of lactate dehydrogenase, and ECOG performance status, visceral disease (yes or no), and number of disease sites.

We defined progression-free survival as the time from randomisation to the earliest date of radiographic or photographic disease progression or death due to any cause. We estimated the HR using the Pike method with a two-sided 95% CI. We also used the Pike estimate of the HR for overall survival. We compared overall survival and overall response rate between treatment groups. We reported all secondary efficacy endpoints with two-sided, 95% CIs. Patients randomly assigned to dacarbazine who progressed during the study were permitted to enter a crossover group to receive dabrafenib. We followed up these patients for response, progression, survival, and additional anticancer therapy. We analysed these results using α=0·05 and two-sided 95% CIs. This study is registered with ClinicalTrials.gov, number NCT01227889.

Role of the funding source

This study was funded, administrated, and sponsored by GlaxoSmithKline. The study was designed by the senior authors and the sponsor. Data were collected by the sponsor and all authors had full access to all data in the study. All authors had final responsibility for the decision to submit for publication.

Results

Between Dec 23, 2010, and Sept 1, 2011, patients were screened at 70 institutions. The most common reason for screening failure was absence of *BRAF*^{V600E} mutation or failure to meet other eligibility requirements (figure 1). Of the 733 patients screened, 250 patients were randomly assigned to receive dabrafenib (187 patients) or dacarbazine (63 patients; figure 1, table 1). Treatment groups were well balanced for age, sex, race and disease status (table 1). As of Dec 19, 2011, the date of the most recent analysis, 107 (57%) of the 187 patients given dabrafenib were still on treatment. Of the 80 patients who discontinued study treatment, 66 had progressed, five stopped treatment because of adverse events, four by investigator discretion (including one who had a complete response), and five withdrew consent. Of the dacarbazine patients, 14 (22%) were still on treatment and 28 (44%) had crossed over to dabrafenib. Three patients stopped treatment and did not cross over to dabrafenib, two due to having had a complete response and one because of withdrawal of consent. Median time on study was 4·9 months (range 0–9·9 months).

The estimated median progression-free survival for the dabrafenib group was 5·1 months and 2·7 months for the dacarbazine group (figure 2A). The progression-free survival curves separated early and remained separated. The HR for progression was 0·30 (95% CI 0·18–0·51; p<0·0001). The progression-free survival as estimated by independent review confirmed the investigator-assessed results, with a median for dabrafenib of 6·7 months versus 2·9 months for dacarbazine (HR 0·35; 95% CI 0·20–0·61; figure 2B). The benefit in progression-free survival was observed in all subgroups analysed (appendix).

30 patients died (21 [11%] patients in the dabrafenib group and 9 [14%] patients in the dacarbazine group). The overall survival HR was 0·61 (95% CI 0·25–1·48) in favour of dabrafenib; additional follow-up is ongoing. Confirmed objective responses (table 2) were reported by the IRC in 93 (50%, 95% CI 42·4–57·1) of 187 patients randomly assigned to dabrafenib (6 [3%] had a complete response and 87 [47%] had a partial response), with a median time to response of 6·3 weeks (95% CI 6·1–6·3). Confirmed objective responses were reported by the investigator in 99 (53%, 95% CI 45·5–60·3) of the 187 patients (6 [3%] had a complete response and 93 [50%] had a partial response) with a median time to response of 6·2 weeks (95% CI 6·1–6·3). The estimated median duration of response was 5·5 months for IRC and 5·6 months for investigator assessment. Most patients randomly assigned to dabrafenib experienced some degree of reduction in target lesion size. This effect was noted across all baseline disease stage, including M1c, which is predictive of poorer prognosis

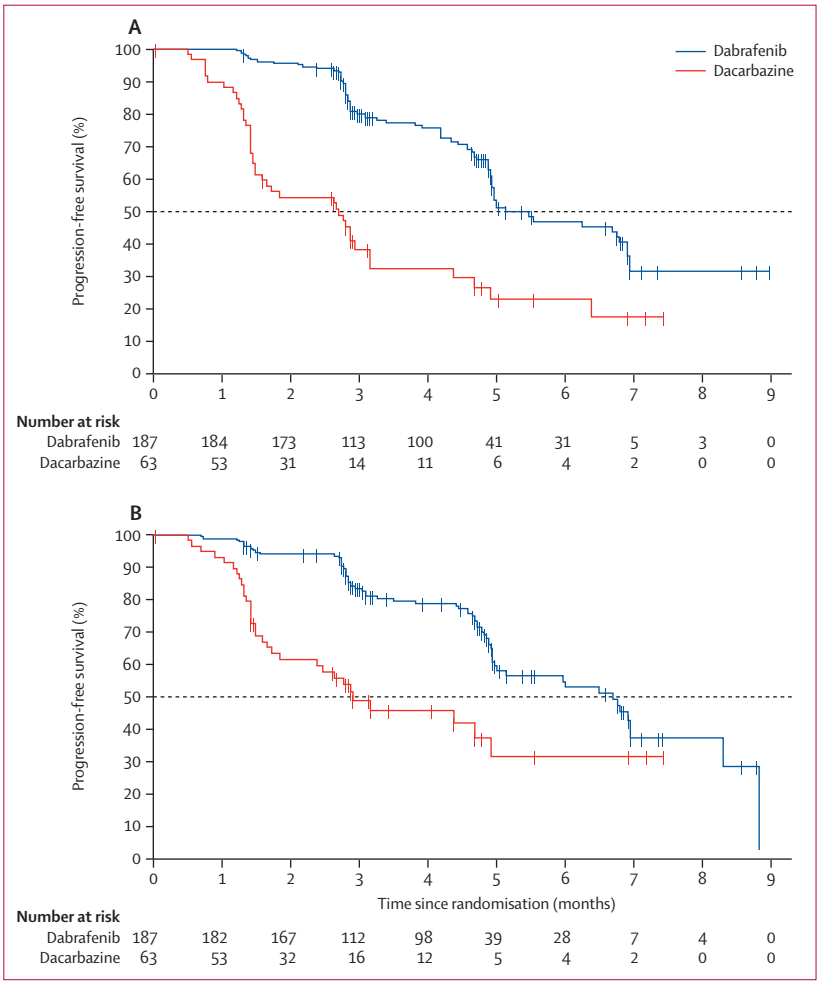

Figure 2: **Progression-free survival by investigator assessment (A) and independent review (B)**
Progression-free survival (PFS) as assessed by the investigator (A) and by the independent review committee (B). Patients randomised to dabrafenib are shown in blue, patients randomised to dacarbazine in red. Tick marks indicate censored patients.

	Dabrafenib (n=187)	Dacarbazine (n=63)
Complete response	6 (3%)	1 (2%)
Partial response	87 (47%)	3 (5%)
Stable disease*	78 (42%)	30 (48%)
Progressive disease	10 (5%)	23 (37%)
Not evaluable†	6 (3%)	6 (10%)
Response rate (complete+partial response, n [%, 95% CI])	93 (50%, 42·4–57·1)	4 (6%, 1·8–15·5)

Data are number of patients (%), unless otherwise stated. *Includes cases determined to have non-target disease only by independent review. †Includes two cases determined to have no disease at baseline or post-baseline assessment by independent review.

Table 2: **Best confirmed response to treatment, by independent review**

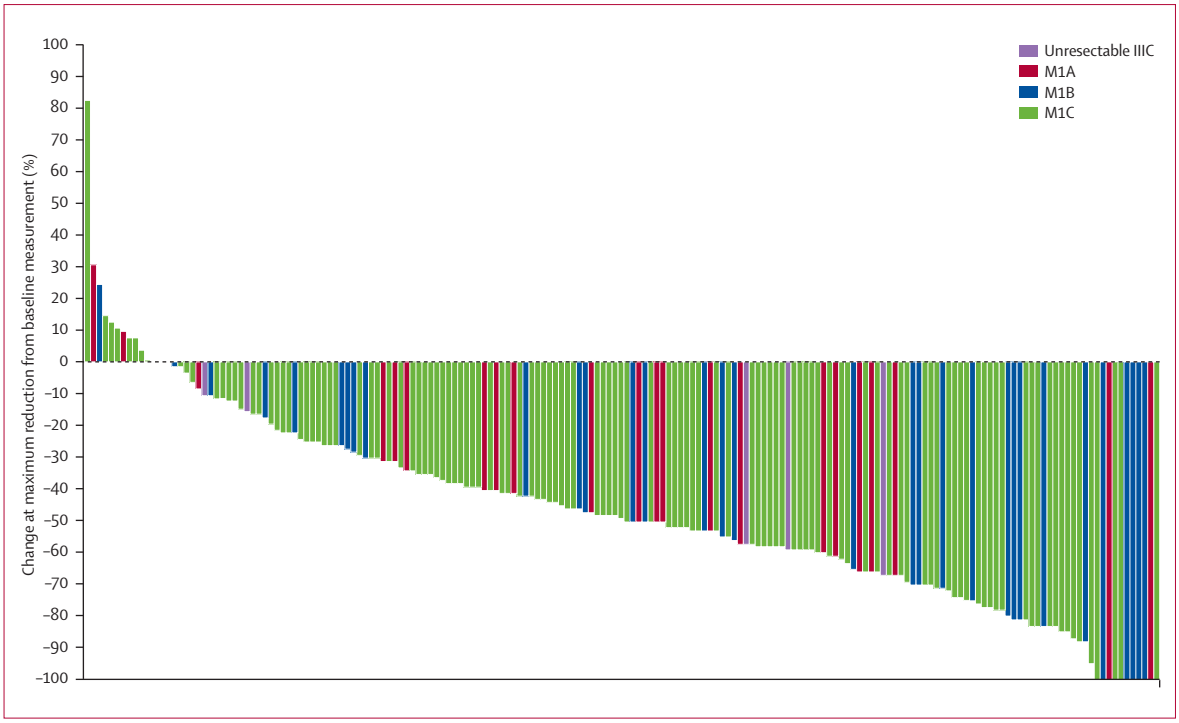

Figure 3: **Maximum tumour percent change from baseline in patients treated with dabrafenib**
Maximum reduction from baseline measurement is shown for patients in the dabrafenib group (n=187). Individual patients are indicated by each bar, with colour indicating the baseline disease stage.

(figure 3). Of the patients in the dacarbazine group, confirmed responses were seen by the IRC in four (6%, 95% CI 1·8–15·5) of 63 patients (table 2). Confirmed responses were reported by the investigator in 12 (19%, 10·2–30·9) patients (all 12 patients had a partial response). The estimated median duration of response to dacarbazine has not yet been reached. 28 patients randomly assigned to dacarbazine have crossed over to dabrafenib; at data cutoff, 13 (46%) patients have had partial responses but, among these patients, no complete responses have been noted. Quality of life analyses are ongoing and will be reported separately.

Table 3 shows drug-related adverse events of grade 2 or higher that occurred in more than 5% of patients. In patients receiving dabrafenib, the most common adverse events were cutaneous (hyperkeratosis, papillomas, palmar-plantar erythrodysaesthesia), pyrexia, fatigue, headache, and arthralgia (table 3). Toxic effects of grade 3–4 were uncommon. 12 patients had either keratoacanthoma or squamous-cell carcinoma of the skin, which did not require dose modification or interruption. Table 3 does not show four basal-cell carcinomas of the skin, one grade 1 mycosis fungoides, and two new primary malignant melanomas deemed related to dabrafenib because these events occurred in less than 5% of patients. In the dacarbazine group, four (7%) of patients experienced phototoxic reactions, all of which were grade 1. In the dabrafenib group, five (3%) of patients experienced phototoxic reactions; three (2%) were grade 1, and two (<1%) were grade 2. Dose reduction of dabrafenib was needed in 52 (28%) patients, and five (3%) patients discontinued drug because of adverse events. In patients receiving dacarbazine, nausea, vomiting, fatigue, and neutropenia were the most common toxic effects. Dose reduction was needed in 10 (17%) of patients receiving dacarbazine and two (3%) patients discontinued drug because of adverse events.

Discussion

These results show that most patients have a substantial response to dabrafenib and an improvement in progression-free survival compared with dacarbazine. Overall, 733 patients were screened to determine *BRAF* mutation status. Of those, 362 patients were found to have a $BRAF^{V600E}$ mutation; 112 of these patients did not meet other entry criteria. The reasons why these patients did not meet eligibility criteria were failing to meet the biochemical criteria, presence of baseline brain metastases, and absence of measureable disease. Of the 250 eligible patients, 187 were randomised to receive dabrafenib and 63 to receive dacarbazine. These patients are representative of previously untreated patients with $BRAF^{V600E}$–mutated stage IV melanoma with good performance status. The patient population selected for this trial was consistent with those of previously reported dacarbazine comparative phase 3 trials, and the treatment groups were well balanced. Because we did not include patients who had received previous therapy, had

significant organ dysfunction, poor performance status, or active CNS metastases, the generalisability to these patients is unknown. Although some limitations for enrolment existed, the patient age range, sex, and disease status can be generalised for this disease population.

As the first-in-class phase 3 trial (panel), the vemurafenib trial was powered to show that this degree of anti-melanoma activity can be associated with improvement in overall survival. The primary endpoint of our trial was progression-free survival; which allowed dacarbazine patients to crossover at the time of progression. Further interpretation of overall survival data is limited because the median duration of follow-up for patients receiving dabrafenib was 5 months at the time of the primary analysis, and because patients given dacarbazine could cross over to dabrafenib in cases of disease progression. Progression-free survival has not been widely acknowledged as a surrogate endpoint for overall survival in advanced or metastatic melanoma, probably because systemic therapies are generally ineffective in this disease setting and have failed to provide improvements in either endpoint. However, data[6] suggest that for molecular targeted agents against $BRAF^{V600}$-mutated melanoma, a large benefit in progression-free survival is likely to correlate with improved survival.

The most common toxic effects associated with dabrafenib in our trial were related to skin. However, phototoxic reactions were rarely seen with dabrafenib in this clinical trial. Grade 2 or higher skin papilloma, palmar–plantar erythrodysaesthesia, and keratoacanthoma/squamous cell cancer of the skin were seen in less than 10% of patients treated. Three new primary malignant melanomas were also observed with dabrafenib, two of which were attributed to dabrafenib by the investigator, although it is unclear at this time whether these were due to dabrafenib treatment.

Although precise comparisons are not possible across trials, the incidence of epithelial skin lesions seemed to be lower in this trial than in the phase 2 and phase 3 trials with vemurafenib.[6,10] The low incidence reported for this current trial is also consistent with previous studies for dabrafenib[8,11] and might be due to dabrafenib's relative specificity for mutated BRAF compared with wild-type BRAF and CRAF. We speculate that, because of the low specificity of dabrafenib for wild-type BRAF and CRAF, dabrafenib concentrations attained in this study were less efficient in activating wild-type RAF dimers, leading to fewer cutaneous adverse events. Additional possibilities for this differ-

	Dabrafenib	Dacarbazine
Any event	100 (53%)	26 (44%)
Skin		
Hyperkeratosis*		
Grade 2	23 (12%)	0
Grade 3	1 (<1%)	0
Grade 4	1 (<1%)	0
PPE/palmar-plantar hyperkeratosis†		
Grade 2	12 (6%)	0
Grade 3	4 (2%)	0
Squamous cell carcinoma/keratoacanthoma‡		
Grade 2	4 (2%)	0
Grade 3	8 (4%)	0
Gastrointestinal		
Nausea		
Grade 2	2 (1%)	8 (14%)
Grade 3	0	0
Vomiting		
Grade 2	2 (1%)	3 (5%)
Grade 3	0	0
Haematological		
Neutropenia		
Grade 2	0	2 (3%)
Grade 3	1 (<1%)	3 (5%)
Grade 4	0	4 (7%)
Thrombocytopenia		
Grade 2	0	0
Grade 3	1 (<1%)	1 (2%)
Grade 4	0	2 (3%)
Leukopenia		
Grade 2	0	2 (3%)
Grade 3	0	1 (2%)
(Continued from previous column)		
Other		
Arthralgia		
Grade 2	9 (5%)	0
Grade 3	1 (<1%)	0
Asthenia		
Grade 2	6 (3%)	3 (5%)
Grade 3	0	0
Fatigue		
Grade 2	10 (5%)	3 (5%)
Grade 3	2 (1%)	0
Headache		
Grade 2	9 (5%)	0
Grade 3	0	0
Pyrexia		
Grade 2	15 (8%)	0
Grade 3	5 (3%)	0

Data are number of patients (%). PPE=palmar-plantar erythrodysaesthesia. *Hyperkeratosis includes acanthoma, acrochordon, actinic keratosis, hyperkeratosis, keratosis pilaris, lichenoid keratosis, papilloma, seborrhoeic keratosis and skin papilloma. †PPE/palmar-plantar hyperkeratosis includes hyperkeratosis palmaris and plantaris, and palmar–plantar erythrodysaesthesia syndrome. ‡Includes squamous cell carcinoma of skin, squamous cell carcinoma, and keratoacanthoma (grade 2).

Table 3: **Treatment-related adverse events grade 2 or higher, experienced by at least 5% of patients on either group**

Panel: Research in context

Systematic review

We did an extensive search of Medline from January, 2008, until present, using the search terms "BRAF" and "metastatic melanoma" for full papers reporting results from any randomised clinical trial of BRAF inhibitors in BRAF-mutated metastatic melanoma. We identified one relevant phase 3 study of vemurafenib, which was enriched for $BRAF^{V600E}$-mutated metastatic melanoma (BRIM-3).[6] This study,[6] comparing first-line vemurafenib with dacarbazine chemotherapy in patients with metastatic melanoma, showed an improvement in the rates of overall survival and progression-free survival. Vemurafenib was associated with a 63% reduction in the risk of death and a 74% reduction in the risk of either death or disease progression.[6] Common adverse events associated with vemurafenib were arthralgia, rash, fatigue, alopecia, squamous cell carcinoma or keratoacanthoma (SCC/KA), photosensitivity, nausea, and diarrhoea; 38% of patients required dose modification because of toxic effects. No other published phase 3 randomised clinical trials in $BRAF^{V600E}$-mutated metastatic melanoma were identified. The phase 1 and 2 clinical studies using dabrafenib in BRAF-mutated melanoma patients are either about to be published or have only been presented at congresses. As such, they did not appear as results of the Medline search. The phase 1 study of dabrafenib[11] reported a confirmed response rate of 50% and a median progression-free survival of 5·5 months. In the phase 2 study,[8] the confirmed response rate was 59% (investigator-assessed) and the median progression-free survival was 6·3 months. No other published clinical trials for dabrafenib were identified from the Medline search.

Interpretation

In this clinical trial, dabrafenib showed a statistically significant improvement in progression-free survival, which was the primary endpoint. These results relative to the vemurafenib trial are consistent, with a significant treatment effect compared with dacarbazine in $BRAF^{V600E}$-mutated metastatic melanoma. However, there were too few deaths to make any conclusions about overall survival, which was a secondary endpoint in this study. The most common toxic effects associated with dabrafenib were also related to skin. Phototoxic reactions were rarely seen with dabrafenib in this clinical trial and grade 2 or higher proliferative epidermal skin lesions were observed in less than 10% of patients treated, specifically SCC/KA were observed in 6% of patients; 28% of patients required dose modifications. These results demonstrate the role of dabrafenib in the treatment of metastatic melanoma and further corroborate the importance of BRAF inhibition in melanoma patients with $BRAF^{V600}$ mutation.

ence could include distinct pharmacological properties of the two BRAF inhibitors, which include dabrafenib being given at a therapeutic level lower than a maximum tolerated dose and the potential contribution of three active metabolites.[11]

Changes in quality of life and health status were assessed from baseline in all patients. These assessments include measures of functioning (eg, emotional and cognitive), overall health, and symptoms such as fatigue and nausea (EORTC Quality of Life Questionnaire Core 30 and EuroQoL-5D). These might provide useful assessments of health-related quality of life benefits for patients with metastatic disease.

Despite the encouraging response rate and improvement in progression-free survival, the median progression-free survival was 5·1 months, which shows that melanoma cells become resistant quite quickly. This finding has been reported with vemurafenib as well.[6,10] The mechanism of resistance is being actively investigated by many investigators and seems to involve reactivation of the MAPK pathway upstream of MEK.[12–15] Gatekeeper mutations, in which secondary mutations in $BRAF^{V600E}$ would prevent dabrafenib or other drugs from binding, have not been reported so far. Results from these studies show that resistant tumours have reactivated the MAPK pathway rather than a parallel, bypass pathway. This directs future strategies towards trying to overcome, or prevent, this reactivation, perhaps by the addition of a MEK inhibitor. Combination trials with dabrafenib and the MEK inhibitor trametinib are currently underway (ClinicalTrials.gov NCT01584648).

Contributors

All authors participated in critical review of the report. AH, MEG, and SS designed the study. PBC, RG, EK, AH, J-JG, and CUB participated in patient recruitment. MM, PBC, PR, SS, CUB, VCS, LD, J-JG, MEG, AH, EK, A-MM, and RG were involved in data collection and data analysis. PH, AH, A-MM, CUB, MEG, MM, PBC, PR, and SS wrote the report. SS did the statistical analyses. All authors reviewed and commented on the report at all stages and approved the final version.

Conflicts of interest

SM-A has participated in advisory boards for Roche, GlaxoSmithKline, and BMS. CUB has received payment from Roche for teaching, has participated in advisory boards for Roche and BMS, has participated in conferences for Roche and Novartis, and has received study or research funding from Roche, BMS, and MedImmune. VCS has received reimbursement for participation in advisory boards and for research protocols from BMS, Roche, MSD, and GlaxoSmithKline. LD has had consultancies with Merck, Roche, and GlaxoSmithKline; has received honoraria from HemOncToday Melanoma 2012; and has been involved in clinical trials with Roche, GlaxoSmithKline, Pfizer, and BMS. VLG is an employee of GlaxoSmithKline and has stock ownership. J-JG has participated in advisory boards for GlaxoSmithKline. MEG is an employee of GlaxoSmithKline. PH is an employee of GlaxoSmithKline and has stock ownership. AH has received study grants, compensation for presentations and consultancy honoraria for advisory boards from AstraZeneca, Biovex, BMS, Boehringer Ingelheim, Celgene, Eisai, GlaxoSmithKline, IGEA, Lilly, Medac, MelaSciences, MSD/Merck, Novartis, Roche Pharma, SOBI, Vical, and Janssen. A-MM is an employee of GlaxoSmithKline and holds stock as a GSK employee. RG has cooperated in clinical studies with Roche Pharma, BMS, GlaxoSmithKline, Novartis, MSD/Essex, Celgene, Lilly, Eisai, AstraZeneca, Vicla, Cytavis, Centocor, Genta, SwedishOrphan, and Philogen; has received research support from Roche Pharma, Novartis, and MSD/Essex; has received honoraria for lectures from Roche Pharma, BMS, GlaxoSmithKline, Novartis, Merck Serono, MSD/Essex, Almirall-Hermal, and Amgen; and has received support for participating in meetings from Roche Pharma, BMS, and MSD/Essex. WHM has received fees to his institution (Jewish General Hospital), has been a paid consultant to BMS, GlaxoSmithKline, Roche, Ziopharm, and Merck; has received grants from Merck; and has received travel, accommodation, or meetings expenses from BMS and Pfizer. MM has participated in advisory boards for GlaxoSmithKline. PBC has received consultancy fees from and participated in advisory boards with GlaxoSmithKline and Genentech/Roche. PR has received travel grants and honoraria for lectures from Novartis, Pfizer, BMS, MSD, and Roche; and has participated in advisory boards for Novartis, MSD, and BMS. SS is an employee of GlaxoSmithKline, including salary and stock ownership. MDJ, and EK declare that they have no conflicts of interest.

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