Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

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Summary

Background Activating *BRAF*^{V600E} (Val600Glu) mutations are found in about 1–2% of lung adenocarcinomas, which might provide an opportunity for targeted treatment in these patients. Dabrafenib is an oral selective inhibitor of BRAF kinase. We did a trial to assess the clinical activity of dabrafenib in patients with advanced non-small-cell lung cancer (NSCLC) positive for the *BRAF*^{V600E} mutation.

Methods In this phase 2, multicentre, non-randomised, open-label study, we enrolled previously treated and untreated patients with stage IV metastatic *BRAF*^{V600E}-positive NSCLC. Patients received oral dabrafenib 150 mg twice daily. The primary endpoint was investigator-assessed overall response, which was assessed in patients who had received at least one dose of dabrafenib; safety was also assessed in this population. The study is ongoing but not enrolling patients in this cohort. This trial is registered with ClinicalTrials.gov, number NCT01336634.

Findings Between Aug 3, 2011, and Feb 25, 2014, 84 patients were enrolled, six of whom had not previously received systemic treatment for NSCLC. 26 of the 78 previously treated patients achieved an investigator-assessed overall response (33% [95% CI 23–45]). Four of the six previously untreated patients had an objective response. One patient died from an intracranial haemorrhage that was judged by the investigator to be due to the study drug. Serious adverse events were reported in 35 (42%) of 84 patients. The most frequent grade 3 or worse adverse events were cutaneous squamous-cell carcinoma in ten (12%), asthenia in four (5%), and basal-cell carcinoma in four (5%).

Interpretation Dabrafenib showed clinical activity in *BRAF*^{V600E}-positive NSCLC. Our findings suggest that dabrafenib could represent a treatment option for a population of patients with limited therapeutic options.

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Introduction

Non-small-cell lung cancer (NSCLC) accounts for around 85% of all lung cancers and remains a major cause of cancer-related deaths worldwide.[1] In the past few decades, important advances have been made in defining the molecular pathogenesis of lung cancers—particularly detection of crucial oncogenic drivers—that have accelerated development of targeted agents. Constitutively activating mutations in the *BRAF* gene, which were first described in lung cancer,[2,3] drive growth and survival of the cancer cells that harbour them, and are extremely sensitive to selective BRAF-inhibitor therapy across multiple tumour types.[4] In a transgenic murine lung cancer model, *BRAF*^{V600E} (Val600Glu) mutations behaved as oncogenic drivers.[5]

BRAF mutations are present in about 2–4% of lung adenocarcinomas, and roughly 50% of those are *BRAF*^{V600E} mutations.[2,6–8] Patients with *BRAF*^{V600E} mutations have shorter overall survival and smaller proportions of patients respond to platinum-based chemotherapy than patients with wild-type *BRAF*.[9,10] Treatment options for patients with *BRAF*^{V600E} mutations are limited and outlook is poor; therefore, novel therapeutic strategies are needed. Of note, *BRAF* mutations and other oncogenic drivers, including *EGFR* and *RAS* mutations and *ALK* rearrangements, are typically mutually exclusive. This finding is consistent with the notion that the *BRAF* mutation defines a unique molecular subset of patients with NSCLC who might benefit from treatment with BRAF inhibitors.

Much of the clinical experience with BRAF inhibitors in *BRAF*^{V600E}-positive NSCLC has been limited to isolated cases and a retrospective case series.[11–14] The activity of the *BRAF*^{V600E} inhibitor vemurafenib was assessed in patients with various solid tumours and haematological malignancies in a basket study that included 19 patients with *BRAF*^{V600E}-positive NSCLC, of whom 42% achieved an overall response.[15] Dabrafenib is a potent adenosine-triphosphate-competitive inhibitor of BRAF kinase selective for the *BRAF*^{V600E} mutation in kinase panel screening, cell lines, and xenografts.[16] This drug is approved in the USA and Europe for the treatment of unresectable or metastatic *BRAF*^{V600E}-positive melanoma. We aimed to investigate the clinical activity and safety of dabrafenib for the treatment of patients with advanced or metastatic *BRAF*^{V600E}-positive NSCLC.

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See Online for appendix

Research in context

Evidence before this study

For most patients with advanced non-small-cell lung cancer (NSCLC), conventional cytotoxic chemotherapy, with or without bevacizumab, is the standard treatment, but it offers only a small survival benefit. Oncogenic drivers of NSCLC have been identified, which has led to the development of targeted agents, particularly small-molecule tyrosine-kinase inhibitors targeting EGFR and ALK. Oncogenic mutations of BRAF, a serine-threonine protein kinase in the RAF/MEK/ERK pathway, are rare in NSCLC (around 2% of tumours). Importantly, most cancer cells harbouring *BRAF*^{V600E} (Val600Glu) mutations are dependent on the activity of this oncogene for growth and survival, and are exquisitely sensitive to selective BRAF and MEK inhibitors. In melanoma, two selective BRAF inhibitors, vemurafenib and dabrafenib, have gained regulatory approval in the USA and Europe for the treatment of patients with unresectable or metastatic *BRAF*^{V600}-positive disease. Importantly, *BRAF*^{V600E} mutations are thought to correlate with more aggressive tumours, which implicates the *BRAF*^{V600E} mutation as an oncogenic driver and provides a robust rationale for the use of dabrafenib in genotype-selected patients.

We searched PubMed for studies of BRAF inhibitors in the treatment of *BRAF*^{V600}-positive NSCLC, without date limitations. We used the search terms "dabrafenib", "vemurafenib", "GSK2118436", and "PLX4032", all with "non-small cell lung cancer OR NSCLC". We identified a prospective basket study of vemurafenib used to treat non-melanoma cancers, including 19 patients with *BRAF*^{V600}-positive NSCLC. Other reports were case studies and a retrospective case series that involved 35 patients in total. We found no studies of targeted BRAF-inhibitor therapy exclusively in patients with *BRAF*^{V600E}-positive NSCLC.

Added value of this study

We found that dabrafenib had substantial antitumour activity (proportion with overall response 33%) in patients with *BRAF*^{V600E}-positive advanced NSCLC. The clinical responses were durable in a substantial proportion of patients in our study and the safety profile was tolerable.

Implications of all the available evidence

In this prospective trial assessing targeted BRAF-inhibitor treatment exclusively in patients with *BRAF*^{V600E}-positive NSCLC, our results highlight the importance of screening for specific genetic alterations before treatment in patients with advanced NSCLC. The clinical benefit of dabrafenib seems to be better than that associated with unselected treatments in NSCLC, including docetaxel and EGFR tyrosine-kinase inhibitors, although cross-trial comparisons must be done with caution. Because *BRAF*^{V600} mutations are rare in NSCLC, which limits the possibility of doing randomised trials, and because benefits derived from second-line chemotherapy are small, our results could potentially change management strategies in this cancer.

Methods

Study design and participants

This study was part of a continuing phase 2, multicentre, non-randomised, open-label study and recruited patients from 34 centres in ten countries within North America, Europe, and Asia (appendix pp 3–4). Enrolment for the cohort reported here has been completed. In two other cohorts, clinical activity and safety of the combination of dabrafenib plus trametinib is being assessed in patients with previously treated advanced or metastatic *BRAF*^{V600E}-positive NSCLC and in treatment-naive patients. The three cohorts were enrolled sequentially. The results for the other two cohorts will be reported elsewhere. Eligible patients were aged 18 years or older and had histologically confirmed stage IV *BRAF*^{V600E}-mutated NSCLC that had progressed after at least one systemic treatment for metastatic disease. Patients who had received no previous systemic anticancer therapy for metastatic disease could be enrolled after a protocol amendment in April, 2013, an interim analysis showed that overall response, duration of response, and the safety profile in patients receiving second-line or later therapy supported the use of dabrafenib before chemotherapy in first-line patients. However, after discussions with regulatory agencies, enrolment of first-line patients was delayed until after that of the cohort assigned dabrafenib plus trametinib, because an increased proportion of patients achieving a response was expected with combination therapy. *BRAF*^{V600E} mutation status was established by local test results in laboratories certified by Clinical Laboratory Improvement Amendments (or equivalent), and disease was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 2 or lower, a tumour sample adequate for central confirmation of *BRAF*^{V600E} mutation (ten to 15 unstained slides with 50% or more tumour content), and an anticipated life expectancy longer than 3 months. All enrolled patients were asked to provide archival tumour tissue or, if no sample was available, to undergo a biopsy before the first treatment dose. Patients with inadequate tumour samples after enrolment were allowed to stay in the study, and we amended the protocol in April, 2013, to allow enrolment of additional patients to ensure the number with centrally confirmed *BRAF*^{V600E} mutations would be adequate for the analysis of clinical activity. Laboratory assessments for eligibility were as follows: haematology (absolute neutrophil count $\geq 1{\cdot}5 \times 10^9$ cells per L, haemoglobin ≥90 g/L, and platelet count $\geq 100 \times 10^9$ cells per L), chemistry (total bilirubin up to 1·5×the upper limit of normal [ULN], alanine aminotransferase and aspartate aminotransferase up to 2·5×ULN, and serum creatinine ≤1·5 mg/dL [132·6 μmol/L] or creatinine clearance ≥50 mL/min

[≥0·8 mL/s per m²]), and coagulation (prothrombin time or international normalised ratio and partial thromboplastin time up to 1·5×ULN). Patients with *EGFR* mutations or *ALK* rearrangements were eligible if they had previously received, respectively, EGFR or ALK inhibitors.

Patients were excluded if they had previously been treated with a BRAF or MEK inhibitor or had symptomatic or unstable brain metastases, had anticancer treatment (including chemotherapy, radiation therapy, immunotherapy, biological therapy, or major surgery) within 14 days of starting dabrafenib or treatment with an investigational anticancer drug within 14 days or five half-lives of starting dabrafenib, known infection with hepatitis B or C virus, history or signs of cardiovascular risk (left ventricular ejection fraction at or above the lower limit of normal on echocardiography), and pregnancy. Patients with asymptomatic, untreated brain metastases smaller than 1 cm could be enrolled.

This study was done in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board at each participating institution. All patients gave written informed consent.

Procedures

Patients were treated with dabrafenib 150 mg orally twice daily until disease progression or unacceptable adverse events, withdrawal of consent, or death. Study treatment could also be discontinued for any of the following reasons: protocol deviation, request by the patient, decision by the investigator, loss to follow-up, or study closure or termination. Dose interruptions and modifications were used to manage intolerable grade 2 or worse adverse events. Doses were sequentially reduced to 100, 75, or 50 mg twice daily, dependent on event severity, and could be re-escalated when the adverse event had resolved. Treatment was discontinued in patients who could not tolerate 50 mg twice daily. Patients with progressive disease were permitted to continue dabrafenib if they had a confirmed response (complete response or partial response) or stable disease lasting at least 12 weeks during treatment and the investigator believed that the patient was clinically benefiting from therapy.

Baseline disease assessment included contrast-enhanced CT of the chest and abdomen and clinical assessment for palpable lesions. In patients with known brain metastases, contrast-enhanced brain MRI or head CT was done at baseline and repeated during each disease assessment. Baseline medical history, physical examination, laboratory tests, collection of demographic data, and cardiac and radiological tumour assessments were done within 28 days before the first dose of dabrafenib.

Safety was assessed at least once every 3 weeks. Adverse events, haematology and clinical chemistry laboratory values, and vital signs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Cardiac assessments with echocardiography and electrocardiography were done at baseline, week 6, week 15, and every 9 weeks thereafter. Radiological disease assessments with CT based on RECIST 1.1 were done every 6 weeks until week 36, then every 12 weeks, with any responses confirmed by repeat assessment 28 days or later after the initial response. Scans used to assess the primary endpoint and all time-to-event endpoints except for overall survival were also reviewed by an independent review committee as well. All patients who discontinued study medication were followed up, with subsequent treatments and survival being recorded every 12 weeks, until death or study completion. Safety data were analysed three times per year by an independent data monitoring committee.

Outcomes

The primary endpoint was investigator-assessed overall response, which was defined as the proportion of patients

	Patients receiving dabrafenib as second-line or later treatment (n=78)
Age (years)	66 (28–85)
Sex	
Female	39 (50%)
Male	39 (50%)
Ethnic origin	
White	59 (76%)
Asian	17 (22%)
African American	2 (3%)
ECOG performance status	
0	16 (21%)
1	50 (64%)
2	12 (15%)
Smoking history	
Never smoker*	29 (37%)
Smoker ≤30 pack-years†	25 (32%)
Smoker >30 pack-years†	24 (31%)
Histology at diagnosis	
Adenocarcinoma	75 (96%)
Other‡	3 (4%)
Number of previous systemic regimens	
1	40 (51%)
2	14 (18%)
3	24 (31%)
Median (IQR) time since previous progression (months)§	1·1 (0·7–2·1)

Data are median (range) or number (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. *Local definitions used. †Total three current smokers and 46 former smokers. ‡Includes one patient with adenosquamous carcinoma, predominately squamous-cell carcinoma, one patient with bronchioalveolar carcinoma, mucinous type, and one patient with large-cell carcinoma (adenocarcinoma). §n=71 with specific data available to calculate median time from previous progression.

Table 1: **Baseline characteristics of patients receiving second-line or later therapy**

with a confirmed complete response or partial response. Secondary endpoints were progression-free survival (defined as the time between the first dose of dabrafenib and the earliest documentation of disease progression or death from any cause), duration of response (time from first documented evidence of complete response or partial response to the earlier of first documented disease progression or death from any cause), disease control (defined as the proportion of patients with an overall response or stable disease) for longer than 12 weeks, overall survival (defined as the time from first dose to death from any cause), pharmacokinetic assessment, and safety and tolerability of dabrafenib.

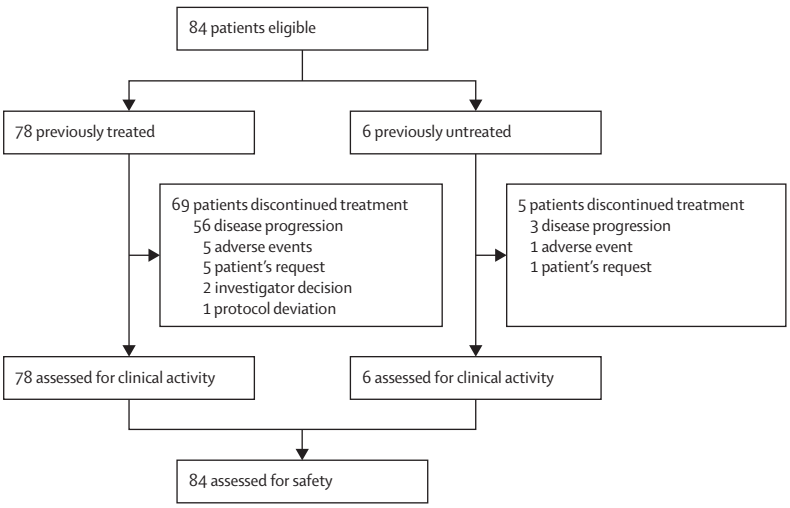

Figure 1: **Trial profile**

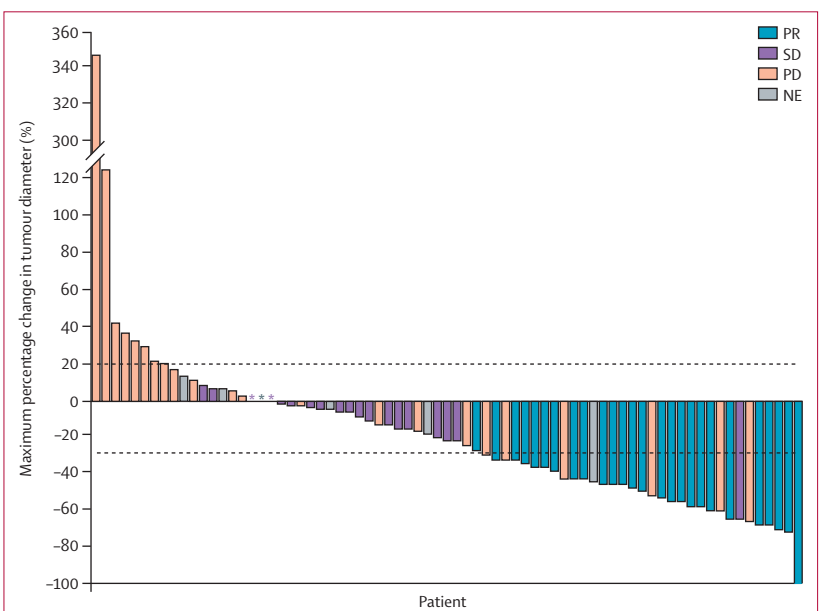

Figure 2: **Maximum change in target lesion by best investigator-assessed confirmed response in patients receiving dabrafenib as second-line or later treatment**

Maximum change in the sum of lesion diameters by best confirmed response in 78 patients receiving dabrafenib as second-line treatment or later at the time of the updated clinical activity analysis (Nov 21, 2014). The data are omitted for one patient with PD who developed a new unequivocal lesion in the first week of treatment and had no post-baseline assessment of the target lesion. The dashed line at 20 represents the Response Evaluation Criteria in Solid Tumors 1.1 definition for progressive disease, and the one at −30 represents the definition for partial response. *No change from baseline. PR=partial response. SD=stable disease. PD=progressive disease. NE=not estimable.

Statistical analysis

On the basis of previous reports in patients with advanced unselected NSCLC receiving second-line or third-line single-agent chemotherapy or erlotinib, we anticipated that an overall response would be achieved in 7–10% of patients.[17,18] The null hypothesis was that the overall response would not be clinically meaningful (10% or less) and the alternative hypothesis was that it would be clinically meaningful (30% or greater) and, therefore, the drug would warrant further development. To allow early termination of the trial due to lack of activity, we assessed overall response at an interim timepoint, in line with a two-stage Green-Dahlberg design for phase 2 cancer trials,[19] with planned enrolment of 20 patients in each stage (appendix p 5). This design corresponded to a type I error of 0·038 and power of 92·6%. To further refine the 95% CI for overall response, the number of patients was increased by planned enrolment of 20 additional patients who had received at least one previous treatment (second-line patients) and treatment-naive patients could be enrolled.

The primary analyses of clinical activity were done in patients who received at least one dose of dabrafenib as a second-line or later treatment (previously treated patients). We estimated median duration of response, progression-free survival, and overall survival with the Kaplan-Meier method, and used the Brookmeyer-Crowley method to calculate corresponding two-sided 95% CIs.[20] For overall response we used the Clopper-Pearson method to calculate 95% CIs.[21] Sensitivity analyses for these endpoints were done with data from the independent review committee and the same statistical methods. Patients who had not received previous systemic therapy for metastatic disease were included in an exploratory analysis of activity and progression-free survival. Exploratory analyses used the same methods as those used for the primary and secondary endpoints. Post-hoc subgroup analyses of clinical activity used the same methods as those used for the primary analysis. All patients who received at least one dose of study drug were included in the safety analysis.

A protocol-mandated analysis of clinical activity was done in April 30, 2014, when the investigators and sponsor believed that enrolment was sufficient to include 60 previously treated patients with measurable disease (appendix pp 5, 8, 10). In this analysis the data on duration of response were immature and, therefore, here we report data from an updated analysis that was done on Nov 21, 2014. Because this updated analysis was intended only to provide updated clinical activity, safety analyses reported here are from the protocol-mandated

analysis on April 30, 2014. All analyses were done with SAS version 9.4. This study is registered with ClinicalTrials.gov, number NCT01336634.

Role of the funding source

The funder was involved in the design of the study, data collection, data analysis, data interpretation, and writing of the report. Editorial support that did not involve writing was provided by ArticulateScience and funded by the sponsor. LP, CN, BMa, AD'A, BMo, and CMC had access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Aug 3, 2011, and Feb 25, 2014, 84 patients were enrolled, 78 of whom had received at least one previous chemotherapy regimen (table 1) and six patients who were receiving dabrafenib as first-line treatment (figure 1). Central confirmation of *BRAF*^{V600E} mutation status has not yet been completed.

Baseline characteristics of the 78 patients receiving dabrafenib as a second-line or later treatment (previously treated patients) are shown in table 1. Baseline characteristics for the six patients who had received no previous systemic anticancer therapy for metastatic disease are presented in the appendix (p 5). As of Nov 21, 2014, nine (12%) of 78 previously treated patients were still being treated with dabrafenib, 69 (88%) had discontinued therapy, and 46 (59%) had died.

The median duration of exposure to dabrafenib for all patients was 4·6 months (IQR 1·8–11·1; appendix p 11). With a median follow-up of 10·7 months (IQR 4·5–16·2), investigator-confirmed overall response was reported in 26 (33%; 95% CI 23–45) of 78 previously treated patients (all partial responses). 19 (73%) initial objective responses were recorded at the first disease assessment 6 weeks from baseline, three at week 12, two at week 18, one at week 24, and one at week 36. Among the 78 previously treated patients, the independent review committee judged that 64 (82%) had measurable disease at baseline. As a sensitivity analysis, the proportion of patients with an overall response according to independent review was 21 (33%; 95% CI 22–46) of 64 patients: one patient had a complete response and 20 had a partial response. Best confirmed response based on investigator assessment is shown in figure 2 and disease control is shown in table 2. Investigator-assessed and independently assessed duration of response is shown in table 2 and figure 3. The overall response results at the time of the protocol-mandated analysis were similar to those of the updated analysis (appendix pp 5, 8, 10).

59 (76%) of 78 patients had disease progression or had died at the time of the updated analyses. Investigator-assessed survival was similar to independently assessed progression-free survival (table 2, appendix pp 12–13). 46 (59%) of 78 patients had died by the time of the analysis and median overall survival was 12·7 months (95% CI 7·3–16·9; appendix p 14).

Four of the six patients receiving first-line treatment with dabrafenib (previously untreated patients) were deemed by investigators to have achieved a partial response. Progression-free survival in these patients was 4·5, 8·6, 11·0, and 16·6 months, and the corresponding durations of response were 3·2, 7·2, 9·6, and 12·5 months. The two patients without a response had progression-free survival of 4·0 and 8·1 months.

Patients received a median dose of dabrafenib of 296·2 mg per day (IQR 269·1–300·0), which represents 98·7% of the intended dose of 300 mg per day. As of April 30, 2014, 83 (99%) of 84 patients had had at least one adverse event, with 45 (54%) of 84 patients having had adverse events of grade 2 or worse (table 3; appendix p 9). The most frequent grade 3 or worse adverse events were the development of cutaneous squamous-cell carcinoma (10 [12%]) and basal-cell carcinoma (4 [5%]) and asthenia (4 [5%]). The median time to development of cutaneous squamous-cell carcinoma was 13·1 weeks (IQR 5·1–21·7)

	Investigator assessment (n=78)	Independent review committee assessment (n=64)
Confirmed SD*	19 (24%, 15–35)	13 (20%, 11–32)
Disease control†	45 (58%, 46–67)	34 (53%, 40–66)
Disease progression	23 (29%)	23 (36%)
Not assessable	10 (13%)‡	7 (11%)
Duration of response (months)	9·6 (5·4–15·2)	9·9 (4·2–ND)
Progression-free survival (months)	5·5 (3·4–7·3)	5·5 (2·8–6·9)

Data are n (%), n (%, 95% CI), or median (95% CI). SD=stable disease. *SD for ≥12 weeks from baseline. †Confirmed response or SD for ≥12 weeks after start of treatment. ‡Four because of no assessment after baseline (three due to adverse events and one decision to transfer to palliative care) and six because of discontinuation before 12 weeks without disease progression (all SD <12 weeks).

Table 2: **Clinical activity endpoints in patients with measurable disease at baseline receiving dabrafenib as second-line or later treatment**

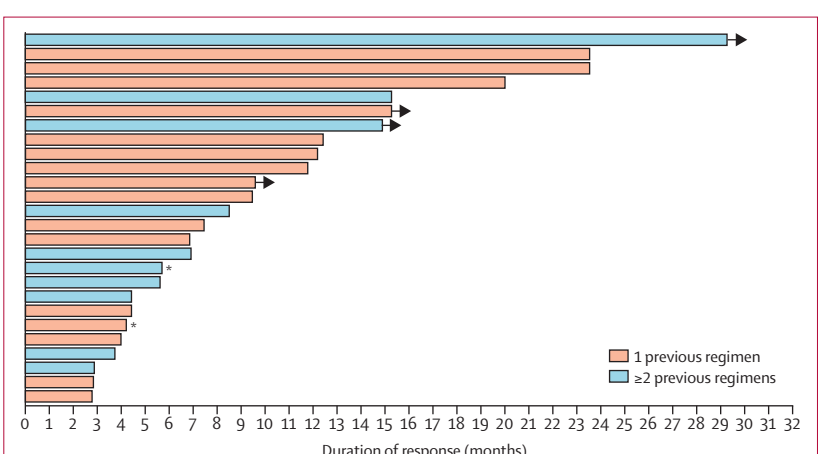

Figure 3: **Duration of investigator-assessed response in patients receiving dabrafenib as second-line or later treatment**

Some patients continued taking treatment after the assessment (arrows).*Censored or lost to follow-up.

and none of these patients needed a dose modification or interruption. No squamous-cell carcinomas were seen in other organs. In 77 (92%) of 84 patients, adverse events were judged to be related to the study treatment. Five (6%) patients had adverse events that led to dabrafenib discontinuation (blistering, deterioration of general health, intracranial haemorrhage, malaise, and palmar–plantar erythrodysaesthesia syndrome [all n=1]). 36 (43%) patients had a treatment-related dose interruption; the most common adverse events leading to dose interruption were pyrexia in nine (11%) patients, chills in five (6%), and vomiting in four (5%). 15 (18%) patients had a treatment-related dose reduction; the most common adverse events leading to dose reductions were palmar–plantar erythrodysaesthesia in three (4%) patients and pyrexia in three (4%). Serious adverse events were reported in 35 (42%) of 84 patients; the most frequent serious adverse events were pyrexia in five (6%) of 84 patients, decreased ejection fraction in two (2%), and pneumonia in two (2%; appendix p 9). One patient, who was taking a factor Xa inhibitor, died during the study from an intracranial haemorrhage that was reported within 2 weeks of starting dabrafenib and was judged to be related to the study treatment. One patient with asymptomatic brain metastasis at baseline had no visible brain lesion at the 6 week and 12 week tumour assessments, but the patient

	Grade 1–2	Grade 3	Grade 4	Grade 5
Pyrexia	28 (33%)	2 (2%)	0	0
Asthenia	21 (25%)	3 (4%)	1 (1%)	0
Hyperkeratosis	24 (29%)	1 (1%)	0	0
Decreased appetite	23 (27%)	1 (1%)	0	0
Nausea	22 (26%)	1 (1%)	0	0
Cough	22 (26%)	0	0	0
Fatigue	21 (25%)	1 (1%)	0	0
Skin papilloma	22 (26%)	0	0	0
Dry skin	19 (23%)	0	0	0
Alopecia	18 (21%)	0	0	0
Palmar–plantar erythrodysaesthesia syndrome	15 (18%)	2 (2%)	0	0
Rash	16 (19%)	1 (1%)	0	0
Vomiting	16 (19%)	1 (1%)	0	0
Dyspnoea	14 (17%)	2 (2%)	0	0
Headache	13 (15%)	2 (2%)	0	0
Arthralgia	13 (15%)	1 (1%)	0	0
Diarrhoea	13 (15%)	1 (1%)	0	0
Pain in extremity	14 (17%)	0	0	0
Chills	12 (14%)	1 (1%)	0	0
Weight decreased	13 (15%)	0	0	0
Pruritus	12 (14%)	0	0	0
Myalgia	11 (13%)	0	0	0
Papule	11 (13%)	0	0	0
Squamous-cell carcinoma	0	10 (12%)	0	0
Back pain	10 (12%)	0	0	0
Anaemia	7 (8%)	2 (2%)	0	0
Constipation	8 (10%)	1 (1%)	0	0
Melanocytic naevus	9 (11%)	0	0	0
Seborrhoeic keratosis	9 (11%)	0	0	0
Actinic keratosis	8 (10%)	0	0	0
Dysphonia	8 (10%)	0	0	0
Nasopharyngitis	8 (10%)	0	0	0
Muscular weakness	5 (6%)	1 (1%)	0	0
Hypophosphataemia	2 (2%)	3 (4%)	0	0
Hypotension	4 (5%)	1 (1%)	0	0
Anxiety	2 (2%)	2 (2%)	0	0

(Table 3 continues in next column)

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous column)				
Basal-cell carcinoma	0	4 (5%)	0	0
Hyperglycaemia	3 (4%)	0	1 (1%)	0
Hypokalaemia	3 (4%)	1 (1%)	0	0
Lymphopenia	3 (4%)	1 (1%)	0	0
White blood cell count increased	2 (2%)	2 (2%)	0	0
Confusional state	2 (2%)	1 (1%)	0	0
Depression	2 (2%)	1 (1%)	0	0
Hypertension	2 (2%)	1 (1%)	0	0
Hyponatraemia	1 (1%)	2 (2%)	0	0
Leucopenia	2 (2%)	0	1 (1%)	0
Thrombocytopenia	2 (2%)	1 (1%)	0	0
Blood creatinine increased	1 (1%)	1 (1%)	0	0
Gastritis	1 (1%)	1 (1%)	0	0
Pericardial effusion	1 (1%)	1 (1%)	0	0
Respiratory tract infection	1 (1%)	1 (1%)	0	0
Cardiac ventricular thrombosis	0	1 (1%)	0	0
Colitis	0	1 (1%)	0	0
Ischaemic colitis	0	1 (1%)	0	0
Intracranial haemorrhage	0	0	0	1 (1%)
Lip squamous-cell carcinoma	0	1 (1%)	0	0
Malnutrition	0	1 (1%)	0	0
Bacterial peritonitis	0	0	1 (1%)	0
Pleuritic pain	0	1 (1%)	0	0
Pneumonia aspiration	0	1 (1%)	0	0
Prostatic obstruction	0	1 (1%)	0	0
Radiation injury	0	1 (1%)	0	0
Uveitis	0	1 (1%)	0	0

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Grade 1–2 events occurring in at least 10% of patients and all grade 3 or worse events are listed. Patients with multiple events in the same category are counted only once in that category. Those with events in more than one category are counted once in each of those categories. Seven patients developed keratochanthoma (five grade 1, two grade 2).

Table 3: **Adverse events in all treated patients**

left the study because of non-adherence. Four patients developed new brain metastases during the study.

A post-hoc analysis of response based on number of previous treatments showed an overall response in 15 (38%) and disease control in 26 (65%) of 40 patients who had previously received one line of therapy, compared with 11 (29%) and 19 (50%) of 38 patients who had received two or more previous lines of therapy (appendix p 6). In a post-hoc analysis of response based on smoking history, 15 (52%) of 29 patients with no smoking history had an overall response, compared with six (24%) of 25 patients with a history of less than 30 pack-years and five (21%) of 24 patients with a history of 30 pack-years or more (appendix p 7).

Pharmacokinetic assessment is not complete and no analysis has been done. These data will be reported elsewhere.

Discussion

This phase 2 study showed antitumour activity of dabrafenib in patients with *BRAF*^{V600E}-positive NSCLC. The confirmed overall response was 33% and disease control was achieved in 58% of 78 patients who had previously received treatment for metastatic disease. Additionally, response was rapid, with 73% of patients having a partial response noted at the first assessment 6 weeks from baseline. Results from an independent review of clinical activity data were consistent with those from the investigator assessments.

Targeted treatment options for patients with advanced NSCLC have so far been limited except for patients with cancers that harbour activating mutations in the *EGFR* gene or *ALK* rearrangements.[22,23] The antitumour activity of BRAF inhibitors in patients with metastatic *BRAF*^{V600E}-positive lung cancers has been primarily reported in isolated clinical cases, one retrospective case series of 35 patients, and a phase 2 basket trial of 19 patients.[11–15] The phase 2 basket trial assessed the BRAF inhibitor vemurafenib in patients with NSCLC and unspecified *BRAF*^{V600} mutations, and reported an overall response of 42% (95% CI 20–67) and median progression-free survival of 7·3 months (95% CI 3·5–10·8).[15] Cross-trial comparisons should be interpreted with caution, however, these values are similar to those noted in our larger cohort. Our results also compare favourably with those seen in patients with *BRAF*^{V600E}-positive metastatic melanoma (median progression-free survival 5·1 months and duration of survival 5·5 months).[24] Moreover, dabrafenib in this study showed better results than docetaxel and EGFR tyrosine-kinase inhibitors in unselected patients with *EGFR* and *ALK* wild-type tumours, where the proportion of patients achieving a response was 10% for each drug, progression-free survival was 2 months and 3 months, respectively, and overall survival was 7·0 months and 10·5 months, respectively.[17,18,25]

The *BRAF*^{V600E} mutant kinase is thought to be a promising therapeutic target for different cancers, and inhibiting it is already a standard approach in malignant BRAF^{V600}-positive melanoma.[2,26] Of note, though, the proportion of patients with a response in this study was lower than that seen with other targeted therapies in oncogene-driven NSCLC, including responses to EGFR tyrosine-kinase inhibitors in patients with *EGFR* activating mutations[27,28] and responses to ALK inhibitors in patients with *ALK* rearrangements (usually responses are seen in >50% of patients).[29]

The adverse events seen in our study were tolerable when compared with those reported for approved second-line and third-line therapies for NSCLC. 35 (42%) of the 84 patients treated with dabrafenib in this study had a serious adverse event, compared with 281 (45%) of 618 treated with docetaxel and 191 (37%) of 517 treated with erlotinib in previous studies.[25,30] One patient in our study died from intracranial haemorrhage while being treated with dabrafenib and taking a factor Xa inhibitor. This death was judged by the investigator to be related to dabrafenib treatment. Some patients required dose interruptions or reductions, although patients generally received the intended daily dose. Adverse events were largely related to the skin (hyperkeratosis, skin papilloma, and dry skin). Dabrafenib, as with other BRAF inhibitors, was associated with development of cutaneous squamous-cell carcinoma in ten (12%) patients or keratoacanthoma in seven (8%). The frequency of these adverse events is similar to that seen in patients receiving dabrafenib to treat melanoma.[13,31,32] Lesions generally appeared in the first months of treatment and were effectively managed with simple resection without discontinuation of dabrafenib. No further prospective information was collected on these cancers because the study protocol mandated that they be removed surgically according to institutional practices. The adverse event profile seems similar to that for treatment of melanoma except for higher frequencies of asthenia, decreased appetite, dry skin, and cough in this study.[13,24,33]

Of note, we were unable to centrally confirm *BRAF* mutational status at the time of this analysis. Although next-generation sequencing might improve genotyping of patients, we have not yet used this platform for central screening as no platform approved by the US Food and Drug Administration has yet been clinically validated. The need for more systematic profiling of gene mutations to ensure that patients receive the most appropriate treatments in NSCLC is well accepted, but remains challenging for rare genomic changes (present in <1–2% of tumours). The ability to molecularly screen large numbers of patients with NSCLC was crucial in this study because of the low frequency of *BRAF*^{V600E} mutations in this cancer (1·5%).[6,8] Studies have shown that among *BRAF*-mutated melanomas, more than 80% harbour the *BRAF*^{V600E} mutation, whereas only 50% of *BRAF*-mutant NSCLCs harbour this mutation.[7,9,10,34] As *BRAF* screening is widely available for melanomas in most molecular platforms, local testing should be

available in real time and should be reproducible in most oncology settings. The clinical characteristics of the patients reported in this study support the importance of screening all patients for oncogenic drivers rather than selecting them on the basis of clinicopathological characteristics (eg, non-smoking women) for multiplex genomic testing. *BRAF* mutations are seen in patients irrespective of smoking history, as opposed to *EGFR* mutations and *ALK* rearrangements, which are most frequent in never smokers (although *BRAF* mutations are seen almost exclusively in adenocarcinomas). Thus, molecular genetic identification is crucial to optimise selection of patients with *BRAF*^{V600E}-positive NSCLC for dabrafenib therapy and should include patients regardless of smoking history.

This study has some potential limitations. We included only patients with *BRAF*^{V600E} mutations, which precluded the analysis of dabrafenib activity in wild-type NSCLC and in NSCLC harbouring other *BRAF* mutations, and we did not use systematic tumour biopsy upon progression to assess mechanisms of resistance to BRAF inhibition. Another potential limitation is the lower proportion of responses with BRAF inhibition than those seen with therapies targeted against *EGFR* mutations or *ALK* rearrangements. Upfront combined inhibition of MEK and mutant BRAF kinases may be a strategy to increase the number and duration of responses compared with BRAF inhibition alone, as has been seen in melanoma studies.[33,35] In two other cohorts in this continuing study, combinations of dabrafenib and trametinib are being assessed: one cohort of patients receiving second-line to fourth-line treatment[36] and one cohort of patients receiving first-line treatment.

Dabrafenib showed substantial antitumour activity leading to durable clinical responses in a substantial proportion of patients with *BRAF*^{V600E}-positive NSCLC and had an acceptable safety profile. Our results highlight the importance of screening for *BRAF* genetic alterations in patients with advanced NSCLC, particularly in patients with tumours negative for *EGFR* mutations and *ALK* rearrangements.

Contributors

DP, JM, GR, P-JS, MAS, LP, CN, BMa, AD'A, BMo, CMC, and BEJ conceived and designed the study. DP, TMK, JM, EQ, GR, FB, RJK, BCC, MAS, LP, BMo, and BEJ collected and assembled the data. DP, TMK, JM, GR, FB, P-JS, EFS, HJMG, RJK, BCC, MAS, LP, CN, BMa, AD'A, BMo, CMC, and BEJ analysed and interpreted the data. DP, JM, EQ, FB, EFS, HJMG, RJK, MAS, LP, AD'A, BMo, CMC, and BEJ wrote the report and DP, TMK, JM, EQ, GR, FB, P-JS, EFS, HJMG, RJK, BCC, MAS, LP, CN, BMa, AD'A, BMo, CMC, and BEJ provided final approval. EFS and HJMG provided study materials and patients.

Declaration of interests

DP acts as an adviser for AstraZeneca, Boerhinger Ingelheim, Bristol-Myers Squibb, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, and Roche. GR has received grants from GlaxoSmithKline and Novartis, acts as a consultant to Novartis and has received funding for research via his employer from Chugai/Roche, Millennium, and Pfizer. FB has received personal fees from GlaxoSmithKline and Novartis. P-JS has been involved in a clinical trial for GlaxoSmithKline. HJMG's institution has received payments from GlaxoSmithKline, MSD, Pfizer, and Roche. LP, CN, BMa, AD'A, BMo, and CMC were employees of GlaxoSmithKline during the study. CN, AD'A, and BMo have been or are currently employees of Novartis, and BMo owns stock in GlaxoSmithKline and Novartis. BEJ has received personal fees from AstraZeneca, Clovis Oncology, Genentech, Merck, and Novartis, honoraria from Chugai, and shares of post-market revenue for an EGFR genotyping patent. The other authors declare no competing interests.

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