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Dabrafenib in *BRAF* V600E–Mutant Advanced Non-Small Cell Lung Cancer: an Open-label, Single arm, Multicenter, Phase 2 Trial

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Provision of study material or patients: EFS and HJMG

Declaration of interests

DP reports advisory role for Novartis, Pfizer, Roche, Boehinger, Lilly, Bristol-Myers Squibb, AstraZeneca, MSD and Pierre Fabre. GR reports grants from GlaxoSmithKline and Novartis; consulting with Novartis; and employer receives research funding from Pfizer, Chugai/Roche and Millennium for support of research led by him. FB reports personal fees from GlaxoSmithKline and Novartis. P-J Souquet reports clinical trial for GlaxoSmithKline. HJMG reports payments to his institution from Roche, MSD, Pfizer and GlaxoSmithKline. LP at the time of the study, was an employee of GlaxoSmithKline. CN reports employment at GlaxoSmithKline at the time the study was conducted, former employment at Novartis and current employment at GlaxoSmithKline. B. Ma reports employment at GlaxoSmithKline at the time the study was conducted. AD, at the time of the study, was an employee of GlaxoSmithKline, is now an employee of Novartis. B Mookerjee, at the time of the study, was an employee of GlaxoSmithKline, is now an employee of Novartis; and owns stock in GlaxoSmithKline and Novartis. CMC was an employee of Novartis and GlaxoSmithKline. BEJ reports personal fees from AstraZeneca, Clovis Oncology, Novartis, Merck, Genentech; honoraria from Chugai Pharmaceuticals; received shares of post-market revenue for EGFR Genotyping patent. TMK, JM, EQ, EFS, RJK, BCC, and MAS report nothing to disclose.

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Abstract

Background—Activating *BRAF* V600E mutations are found in approximately 1–2% of adenocarcinomas of the lung offering an opportunity to test targeted therapy for this disease. Dabrafenib is an oral selective inhibitor of the *BRAF* kinase. The aim of this study was to assess the clinical activity of dabrafenib in patients with advanced *BRAF* V600E-mutant non-small cell lung cancer (NSCLC).

Methods—In this phase 2, multicenter, nonrandomized, open-label study of previously treated and untreated patients with stage IV, metastatic NSCLC and *BRAF* V600E mutation, we evaluated the antitumor activity and safety of oral dabrafenib (150 mg twice daily). The primary endpoint was investigator-assessed overall response rate (ORR) in patients receiving ≥ 1 dose of study drug. Safety analysis was performed on the all-treated population (all previously treated and untreated patients receiving ≥ 1 dose of study drug). The study is ongoing but not enrolling participants in this cohort. This trial is registered with ClinicalTrials.gov, number NCT01336634.

Findings—Between August 2011 and February 2014 a total of 84 previously treated and untreated patients were enrolled. Investigator-assessed ORR for 78 pretreated patients was 33% (95% confidence interval [CI], 23·1 to 44·9). Independent review committee assessment of ORR was consistent with investigator-based assessment. Four of the six previously untreated patients had an objective response. One patient died on study due to intracranial hemorrhage that was considered by the investigator to be due to study drug. Serious adverse events were reported in 35 (42%) of 84 patients. The most frequent grade 3 or higher adverse events were cutaneous squamous cell carcinoma (10 [12%] of 84 patients), asthenia (4 [5%] of 84 patients), and basal cell carcinoma (4 [5%] of 84 patients).

Interpretation—This is, to our knowledge, the first prospective trial focusing on *BRAF* V600E-mutant NSCLC to show clinical activity of a BRAF inhibitor. The results presented here suggest that dabrafenib may represent a future treatment option for patients with *BRAF* V600E-mutant NSCLC, a population with limited therapeutic options.

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers and remains a major cause of cancer-related deaths globally.[1] In the past few decades, significant strides have been made in defining the molecular pathogenesis of lung cancers—particularly in detection of critical oncogenic drivers—leading to accelerated development of specific targeted agents. Constitutively activating mutations in the *BRAF* gene, first described in lung cancers in 2002,[2,3] drive growth and survival of cancer cells that harbor them and are extremely sensitive to selective BRAF inhibitor therapy across multiple tumor types.[4] Moreover, *BRAF* V600E behaves as an oncogenic driver in a transgenic murine lung cancer model.[5]

BRAF mutations are present in approximately 2–4% of lung adenocarcinomas, and approximately one-half are V600E mutations.[2,6–8] The clinical outcome in patients with *BRAF* V600E mutations is associated with shorter overall survival (OS) and lower response rates to platinum-based chemotherapy than in patients with wild-type *BRAF*.[9,10] A high unmet need remains for novel therapeutic strategies in this population with limited treatment options and poor prognosis. Importantly, *BRAF* mutations and other oncogenic drivers, including epidermal growth factor receptor (*EGFR*) and *RAS* mutations as well as anaplastic lymphoma kinase (*ALK*) rearrangements, are typically mutually exclusive; this is consistent with the notion that *BRAF* mutation defines a unique molecular subset of patients with NSCLC who may benefit from treatment with a BRAF inhibitor.

To date, the clinical experience with BRAF inhibitors in *BRAF* V600E-mutant NSCLC has been primarily limited to isolated cases and a retrospective case series.[11–14] A recent basket study examining the activity of vemurafenib in patients with a variety of solid tumors and hematologic malignancies, enrolled a cohort of 19 patients with *BRAF* V600E NSCLC and demonstrated a promising overall response rate (ORR) of 42%.[15] Here we report the first prospective trial examining the clinical activity and safety of a BRAF inhibitor for the treatment of patients with *BRAF* V600E-mutant NSCLC. Dabrafenib, a potent adenosine triphosphate–competitive inhibitor of BRAF kinase selective for the *BRAF* V600E mutant in kinase panel screening, cell lines, and xenografts[16] is approved globally for the treatment of unresectable or metastatic *BRAF* V600–mutated melanoma. This study investigated the therapeutic effects of dabrafenib administered at the approved dose for melanoma (150 mg twice daily)[13] to patients with previously treated advanced or metastatic NSCLC whose tumors carry a *BRAF* V600E mutation.

Methods

Study design and participants

In this phase 2, multicenter, nonrandomized, open-label study, patients were recruited from 34 centers in 10 countries within North America, Europe, and Asia (appendix pp 3–4). Eligible patients, ≥ 18 years of age, had histologically confirmed stage IV NSCLC that had progressed after receiving ≥ one systemic treatment for metastatic disease. *BRAF* V600E mutational status was required based on local testing in Clinical Laboratory Improvement Amendments–approved (or equivalent) laboratories as well as measurable disease per

Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. The authors and sponsor believe that an FDA approved next-generation sequencing platform will improve patient identification, however, as this platform is not yet clinically validated, central screening has not yet been carried out. Other key eligibility criteria included an Eastern Cooperative Oncology Group performance status of ≤ 2, a tumor sample adequate for central confirmation of *BRAF* V600E mutation, and an anticipated life expectancy > 3 months. Adequate amount of tumor tissue for central *BRAF* V600E confirmation testing was defined as at least 10–15 unstained slides with no less than 50% tumor content per slide. All enrolled subjects were required to either provide archival tumor tissue or, if archival sample was not available, a pre-dose biopsy was required to collect an adequate amount of fresh tumor tissue. The central *BRAF* V600E confirmation has not yet been completed at the time of the submission. Patients with inadequate tumor sample after enrollment were permitted to stay on study; additional patients were enrolled to ensure an adequate number with centrally confirmed mutation for the analysis of clinical activity. Laboratory assessments for eligibility included hematology (ANC ≥ 1.5×10^9/L; hemoglobin ≥ 9 g/dL; platelet count ≥ 100×10^9/L), chemistry (total bilirubin ≤ 1.5 × upper limit of normal [ULN]; alanine aminotransferase and aspartate aminotransferase ≤ 2.5 × ULN; serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min), and coagulation (prothrombin time/ international normalized ratio and partial thromboplastin time ≤ 1.5 × ULN). Patients with *EGFR* mutations or *ALK* rearrangement were eligible if they had previously received EGFR or ALK inhibitors, respectively. Key exclusion criteria were previous therapy with a BRAF or MEK inhibitor and symptomatic or unstable brain metastases. Patients were excluded if they had received anticancer therapy (including chemotherapy, radiation therapy, immunotherapy, biological therapy, or major surgery) within 14 days of the start of therapy or if they had received an investigational anticancer drug within 14 days or 5 half-lives of start of therapy (minimum 14 days). Women who are pregnant, patients with known hepatitis B or C virus, or those with a history or signs of cardiovascular risk (left ventricular ejection fraction ≥ lower limit of normal by ECHO) were excluded. Patients with asymptomatic, untreated brain metastases < 1 cm were allowed to enroll. The rate and duration of response for dabrafenib in ≥ second-line patients at the interim analysis and the preferential safety profile supported the use of dabrafenib prior to chemotherapy in first-line patients. Therefore, patients with no prior systemic anticancer therapy for metastatic disease were enrolled in the expansion cohort under a protocol amendment in April 2013. Following discussions with regulatory agencies, a decision was made to delay further enrollment for first-line patients until the enrollment of the dabrafenib plus trametinib combination cohort due to an expectation of increased response rates with combination therapy. Therefore, first-line enrollment in this cohort was stopped at 6 patients. This study was conducted 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 (Tafinlar; Novartis AG) 150 mg orally twice daily until disease progression (PD), unacceptable adverse events (AEs), withdrawal of consent, or death. Study treatment could also be discontinued for any of the following reasons: protocol

deviation, patient request, investigator discretion, patient is lost to follow-up, or in the event that the study is closed or terminated. Dose interruptions and/or modifications were used to manage intolerable ≥ grade 2 AEs. Doses were sequentially reduced to 100, 75, or 50 mg twice daily, depending on event severity. Treatment was discontinued in patients not tolerating 50 mg twice daily. Patients with PD were permitted to continue dabrafenib if they had a confirmed response (complete response [CR] or partial response [PR]) or stable disease (SD) lasting ≥ 12 weeks while taking dabrafenib and the investigator believed that the patient was clinically benefiting from therapy. Baseline disease assessment included computed tomography (CT) with contrast material of the chest and abdomen and clinical disease assessment for palpable lesions. In patients with known brain metastases, contrast-enhanced brain magnetic resonance imaging or head CT was conducted at baseline and repeated during each disease assessment. All baseline medical history, physical examination, laboratory, demographic, cardiac, and radiological tumor assessments were performed within 28 days before the first dose of dabrafenib. Patients were evaluated for safety at least once every three weeks. AEs, laboratory values (hematology and clinical chemistry), and vital signs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Cardiac echocardiograms and electrocardiograms were performed at baseline, week 6, week 15, and every 9 weeks thereafter. Radiological disease assessments by CT using RECIST 1.1 were performed every 6 weeks until week 36, then every 12 weeks, with any responses confirmed by repeat assessment ≥ 28 days after the initial response. RECIST scans to determine the primary endpoint, and all time-to-event endpoints, except for OS, were reviewed by an independent review committee as a sensitivity analysis. All patients who discontinued study medication were followed for subsequent treatment(s) and survival every 12 weeks, until death or study completion. Safety data were evaluated three times per year by an independent data monitoring committee.

Outcomes

The primary endpoint was investigator-assessed overall response rate (ORR) which is defined as the percentage of subjects with a confirmed CR or PR by investigator assessment as per RECIST v1.1 criteria. Tumor response was also assessed by independent review. Secondary endpoints included PFS (defined as the interval between first dose and the earliest date of disease progression or death due to any cause), duration of response (DOR; defined as the time from first documented evidence of CR or PR until time of first documented disease progression or death due to any cause, whichever occurs earlier), disease control rate (DCR; defined as the percentage of patients with ≥ SD) for > 12 weeks, OS (defined as the time from first dose until death due to any cause), pharmacokinetic assessment and safety and tolerability of dabrafenib.

Statistical analysis

The anticipated ORR based on prior literature in patients with advanced unselected NSCLC receiving single-agent chemotherapy or erlotinib in the second- or third-line setting was estimated to be 7–10%.[17,18] The null hypothesis was that the ORR was not clinically meaningful (≤ 10%). The alternative hypothesis was that the ORR was clinically meaningful (≥ 30%) and therefore, the compound warrants further development. To allow early termination of the trial due to lack of activity, ORR was assessed at an interim time point

based on a 2-stage Green-Dahlberg[19] design for phase 2 cancer trials with a planned enrollment of 40 patients (20 patients in each stage; criteria for study continuation are provided in the Appendix p. 5). The above design corresponded to a type I error of 0·038 and power of 92·6%. To further refine the 95% confidence interval for ORR in this treatment setting and to allow treatment-naive patients, an expansion cohort was added with a planned enrollment of 20 patients in the ≥ second line therapy and first-line patients.

Primary analyses of clinical activity were performed in patients who received ≥ 1 dose of dabrafenib and had prior systemic therapy for metastatic NSCLC (≥ second-line patients). The DOR, PFS, and OS were estimated by medians calculated using the Kaplan-Meier method, with corresponding two-sided 95% confidence intervals calculated using the Brookmeyer-Crowley method.[20] Two-sided 95% confidence intervals for ORR were determined using the Clopper-Pearson method.[21] Six patients who did not have prior systemic therapy for metastatic disease were included in an exploratory activity analysis population (first-line all-treated population). All patients (both pretreated and previously untreated) who received ≥ 1 dose of study drug were included in the safety analysis. Exploratory analyses utilized the same methodology as primary and secondary analyses. A protocol-mandated analysis was performed when the investigators and sponsor believed that enrollment was sufficient to include 60 previously treated patients with measurable disease by independent reviewer assessment and is presented in the appendix (p 5, 8, 10). An updated analysis was performed to obtain more mature DOR data and is presented in the main text of the manuscript. SAS version 9.4 was used for statistical analyses. This study is registered with ClinicalTrials.gov, number NCT01336634.

Role of the funding source

This study was sponsored by GlaxoSmithKline; dabrafenib is an asset of Novartis AG as of March 2, 2015. The study was designed by the academic authors in conjunction with representatives of the sponsor. The data were collected by the sponsor and analyzed in collaboration with the authors. LP, CN, B Ma, AD, BM, and MC had access to the raw data. The first and last authors wrote the initial draft of the manuscript, and all authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. The authors vouch for the accuracy of the data and the fidelity of the study to the protocol. Editorial support that did not involve writing was provided by Articulate Science and funded by the sponsor.

Results

Patients

Between 3 August, 2011 and 25 February, 2014, 84 patients (44 female), with a median age of 66 years were enrolled. A total of 78 patients received dabrafenib after ≥ one prior chemotherapy regimen for metastatic disease due to over-recruitment designed to offset any potential issues with central confirmation of mutation status and central review of responses, and six patients received dabrafenib as first-line treatment for metastatic disease. Central confirmation of *BRAF* mutation status has not yet been completed. The median duration of

exposure to dabrafenib monotherapy was 4·6 months (IQR, 1·79 to 11·07 months; appendix p 11).

Baseline characteristics of the 78 ≥ second-line patients are provided in Table 1. One-half of the patients were women; a large majority of patients had adenocarcinoma of the lung and were former (46 [59%] of 78) or current (3 [4%] of 78) smokers. As of November 21, 2014, nine (12%) of 78 patients remain on therapy, 69 (88%) discontinued therapy, and 46 (59%) died (Fig. 1).

Clinical Activity

Analyses based on data generated from independent review of disease assessment scans were performed to validate response data based on the investigator's assessments. For the ≥ second-line population, this consisted of 64 patients with measurable disease at baseline as determined by an independent review committee (IRC). At the time of the protocol-mandated activity analysis, results for DOR were immature and thus an updated, mature activity analysis, was performed and is presented in this section (protocol-mandated activity results are presented the appendix, p 5, 8, 10).

With a median follow-up of 10·7 months (IQR, 4·5–16·2 months), 26 of 78 ≥ second-line patients receiving dabrafenib monotherapy (33%; 95% CI, 23 to 45; Fig. 1 and Table 2) had a confirmed ORR by the investigator. Most initial objective responses were observed at first postbaseline disease assessment (19 patients with PR). Seven patients had a PR after the first postbaseline assessment (three at week 12; two at week 18; one at week 24; and one at week 36). The DCR (≥ SD) was 58% (45 of 78 patients [95% CI, 46 to 67]; Fig. 2, Table 2). Of the 78 ≥ second-line patients, 23 (29%) had PD as best response. Ten (13%) of 78 patients were not evaluable for response due to lack of post-baseline assessment or discontinuation prior to 12-weeks without PD according to RECIST (n=6 had SD < 12 weeks [< 2 planned post-baseline assessments] without PD; n=4 had no post-baseline assessment [n=3 due to AEs; n=1 due to patient or proxy decision to transfer to palliative care]). The IRC ORR and DCR were 33% (21 of 64 patients [95% CI, 22 to 46]; PR, 20 [31%] of 64 patients; SD, 13 [20%] of 64 patients; PD, 23 [36%] of 64 patients) and 53% (34 of 64 patients [95% CI, 40 to 66]), respectively. A post-hoc analysis demonstrated an ORR of 38% (≥ PR in 15 of 40 patients) and DCR of 65% (≥ SD in 26 of 40 patients) in patients with one prior line of therapy compared with an ORR of 29% (≥ PR in 11 of 38 patients) and DCR of 50% (≥ SD in 19 of 38 patients) in patients who had received ≥ 2 prior lines of therapy (appendix p 6). In a post-hoc analysis of response based upon prior smoking history, the ORR of patients with no prior history of smoking was 52% (≥ PR in 15 of 29 patients) vs 24% (≥ PR in 6 of 25 patients) in patients with a history of < 30 pack-years and 21% (≥ PR in 5 of 24 patients) among patients with a history of ≥ 30 pack-years (appendix p 7).

Investigator-assessed median DOR for ≥ second-line patients was 9·6 months (95% CI, 5·4 to 15·2; Fig. 3). DOR was > 6 months in 16 patients, > 9 months in 12 patients, and > 12 months in 9 patients. Median PFS was 5·5 months (95% CI, 3·4 to 7·3); 59 (76%) of 78 patients progressed or died at the time of updated analyses (Table 2; appendix pp 12–13). Based on IRC assessment, median DOR was 9·9 months (95% CI, 4·2 to not defined) and PFS was 5·5 months (95% CI, 2·8 to 6·9). The preliminary median OS was 12·7 months

(95% CI, 7·3 to 16·9; appendix p 14); 46 (59%) of 78 patients had died at the time of the analysis. Results of a protocol-mandated clinical activity analysis performed prior to full maturation of DOR data were similar and are included in the appendix p 5, 8, & 10.

Four of six patients in first-line treatment had a PR by investigator assessment. The four patients with PR had PFS of 4·5, 8·6, 11·0, and 16·6 months, corresponding to DORs of 3·2, 7·2, 9·6, and 12·5 months, respectively. The two patients without a response had PFS of 4·0 and 8·1 months.

Safety and adverse events

As of April 30, 2014, almost all patients had ≥ one AE (83 of 84 patients [99%]), with 45 (54%) of 84 patients having maximum-grade AEs ≤ grade 2 (appendix p 9). Maximum AE grades of 3, 4, and 5 were reported in 33 (39%), 4 (5%), and 1 (1%) of the 84 patients, respectively. Seventy-seven (92%) of 84 patients had AEs related to study treatment. Five (6%) of 84 patients had AEs that led to dabrafenib discontinuation (blister, general health deterioration, intracranial hemorrhage, malaise, and palmar-plantar erythrodysaesthesia syndrome; n=1 each). Thirty-six (43%) and 15 (18%) of the 84 patients had AEs that led to dose interruptions and reductions, respectively. The most common AEs leading to dose interruption were pyrexia (9 [11%] of 84 patients), chills (5 [6%] of 84 patients), and vomiting (4 [5%] of 84 patients). The most common AEs leading to dose reduction included palmar-plantar erythrodysaesthesia (3 [4%] of 84 patients) and pyrexia (3 [4%] of 84 patients). Patients were exposed to a median dose of 296·2 mg per day, representing 98·7% of the intended dose of 300 mg per day. The most common AEs (all grades, > 20%) were pyrexia (36% [30 of 84 patients]), asthenia (30% [25 of 84 patients])), hyperkeratosis (30% [25 of 84 patients]), decreased appetite (29% [24 of 84 patients]), nausea (27% [23 of 84 patients]), cough (26% [22 of 84 patients]), fatigue (26% [22 of 84 patients]), skin papillomas (26% [22 of 84 patients]), dry skin (23% [19 of 84 patients]), and alopecia (21% [18 of 84 patients]; Table 3). Ten (12%) of 84 patients had cutaneous squamous cell carcinomas (SCCs) and four (5%) had basal cell carcinomas (all grade 3). The median time to development of cutaneous SCC was 13·1 weeks, and dose modification/interruption was not required. No SCCs at other organ sites were observed. One patient with asymptomatic brain metastasis at baseline did not have visible brain lesion on 6-week or 12-week tumor assessment prior to study discontinuation due to non-compliance. A total of 4 patients developed new brain metastases during the course of the study. One patient died on study due to intracranial hemorrhage that was reported within 2 weeks of starting dabrafenib and was considered related to study treatment. Serious AEs were pyrexia (five of 84 patients [6%]) and ejection fraction decrease and pneumonias (two of 84 patients each [2%]).

PK assessment is a secondary outcome. The assessments are ongoing so we do not yet have the full dataset. Therefore, the investigators have not yet analyzed the PK data and are not yet able to report it.

Discussion

This phase 2 study demonstrates antitumor activity of dabrafenib monotherapy in patients with *BRAF* V600–mutated NSCLC. We report a confirmed ORR of 33% with a DCR of

58% for dabrafenib monotherapy in 78 previously treated metastatic *BRAF* V600–mutated NSCLC. Median PFS and DOR were 5·5 and 9·6 months, respectively. The responses were durable and had rapid onset, with 73% of responses initially observed at first postbaseline assessment at week 6. Results from an independent review of clinical activity data were consistent with investigator-assessed responses. The preliminary survival data for these patients with one to three previous lines of therapy shows a median OS of 12·7 months. Targeted treatment options for patients with advanced NSCLC are limited thus far except for the subset of patients with cancers harboring activating mutations in the *EGFR* gene or ALK rearrangements.[22,23] The antitumor activity with BRAF inhibitors in metastatic *BRAF* V600E–mutant lung cancers has been primarily reported in isolated clinical cases, one retrospective case series of 35 patients, and a basket trial of 19 patients.[11–14] In the recently reported phase 2 basket study, a cohort of 19 patients with *BRAF* V600–mutant NSCLC treated with the BRAF inhibitor vemurafenib had an ORR of 42% and a median PFS of 7·3 months, similar to the clinical activity observed here in a much larger cohort.[15] The current results also compare favorably with those observed in *BRAF* V600E metastatic melanoma (median PFS and DOR of 5·1 and 5·5 months, respectively).[24] However, cross-trial comparison should be interpreted with caution. The *BRAF* V600E mutant kinase is considered a promising therapeutic target for different cancers, and targeting the mutant kinase is a standard approach in malignant BRAF V600-mutated melanoma.[2,25]

Although comparison between trials should be viewed cautiously, in the current study, dabrafenib demonstrated clinically evident antitumor activity with increased response rates and prolonged PFS and OS compared with previously used treatments in unselected patients (10% response rate, 2- to 3-month PFS, and OS of 7 to 10.5 months in patients with *EGFR* and *ALK* wild-type tumors treated with docetaxel and EGFR-TKI).[17,18,26,26] The AEs are also tolerable for those patients treated with dabrafenib when compared with approved therapies for second- and third-line NSCLC. Thirty-five of the patients treated with dabrafenib (42%) had a SAE compared to 42% of those treated with docetaxel and 37% for erlotinib.[17,27] Therefore, the increased response rates, longer PFS, and promising survival with acceptable toxicity makes this a reasonable treatment option for patients with *BRAF* V600E NSCLC. However, the response rates for the patients with *BRAF* V600E mutations treated with dabrafenib were indeed lower when compared with the > 50% response rates observed with other targeted therapies in oncogene-driven NSCLCs including responses to EGFR-TKIs in patients with *EGFR* activating mutations[28,29] and responses to ALK inhibitors in patients with *ALK* rearrangement.[30]

AEs in this study were common but generally not severe or life-threatening. While being treated with dabrafenib, one patient on a factor Xa inhibitor died from an intracranial hemorrhage that was considered by the investigator to be related to dabrafenib treatment. Although some patients required dose interruptions or reductions, most patients were treated with their intended daily dose. AEs were largely related to the skin (hyperkeratosis, skin papilloma, dry skin); other common AEs included pyrexia, asthenia, decreased appetite, nausea, cough, fatigue, and alopecia. Dabrafenib, as with other BRAF inhibitors, was associated with development of cutaneous SCC (12%) or keratoacanthoma (8%), which was similar to that observed in the treatment of melanoma.[13,31,32] Lesions usually appeared in the first months of therapy and were effectively managed with simple resection without

discontinuation of dabrafenib. No further prospective information was collected on SCC and KAs because the protocol mandated that they be removed surgically by the institution according to institutional (not protocol mandated) practices. The AE profile appears comparable to that in melanoma studies except for rates of asthenia, decreased appetite, dry skin, and cough, which were higher in this study.[13,24,33]

The need for more systematic profiling of gene mutations to ensure that patients receive the most appropriate treatments in NSCLC is well-accepted but this remains a challenge for rare genomic changes (those less than 1–2%). The ability to molecularly prescreen large numbers of patients with NSCLC was crucial in this study given the low frequency of *BRAF* V600E in NSCLC (1·5%).[6,8] Studies have shown that *BRAF*-mutated melanomas harbor a V600E mutation in > 80% of cases in contrast to *BRAF*-mutated NSCLCs which harbor a V600E mutation in only approximately 50% of cases.[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 demonstrate the importance of screening all patients for oncogenic drivers and not selecting them solely by using clinical characteristics (non-smoking women) for multiplex genomic testing. The frequency of *BRAF* mutations in former and current smokers is striking when compared with patients with *EGFR* mutations and *ALK* rearrangements, in whom never smokers are more frequent, however these alterations are almost exclusively present in adenocarcinomas. Selection of patients on the basis of clinicopathological characteristics (aside from adenocarcinoma histology) is probably limited in the subset of *BRAF* V600E NSCLC indicating that molecular genetic identification is critical to guide the selection of patients and should include patients with a history of smoking.

In conclusion, this study is, to our knowledge, the first trial of BRAF inhibition to focus on *BRAF* V600E–mutant NSCLC. Dabrafenib induced durable clinical responses in a significant number of patients and had an acceptable safety profile. This study defines a new molecular subgroup of metastatic NSCLC in which dabrafenib demonstrates substantial antitumor activity. These results highlight the importance of screening for *BRAF* genetic alteration in patients with advanced NSCLC, notably in *EGFR* and *ALK* negative patients. Potential limitations of the current study are the inclusion of only *BRAF* V600E-mutant patients precluding the analysis of dabrafenib activity in other *BRAF*-mutant and wild-type NSCLC and the lack of systematic tumor biopsy upon progression to assess mechanisms of resistance to BRAF inhibition. Another potential limitation with regard to BRAF inhibitor therapy is the lower response rate in comparison to targeted therapies in patients harboring mutations in *EGFR* or *ALK* rearrangements. However, upfront inhibition of both MEK and mutant BRAF kinases may be a strategy for obtaining a higher number of and more durable responses than BRAF inhibition alone, as observed in melanoma studies.[33,35] Two additional cohorts in this study involving combination of dabrafenib and trametinib are ongoing. The first combination cohort enrolled second- to fourth-line patients with metastatic *BRAF* V600E–mutant NSCLC,[36] and the second cohort is enrolling first-line patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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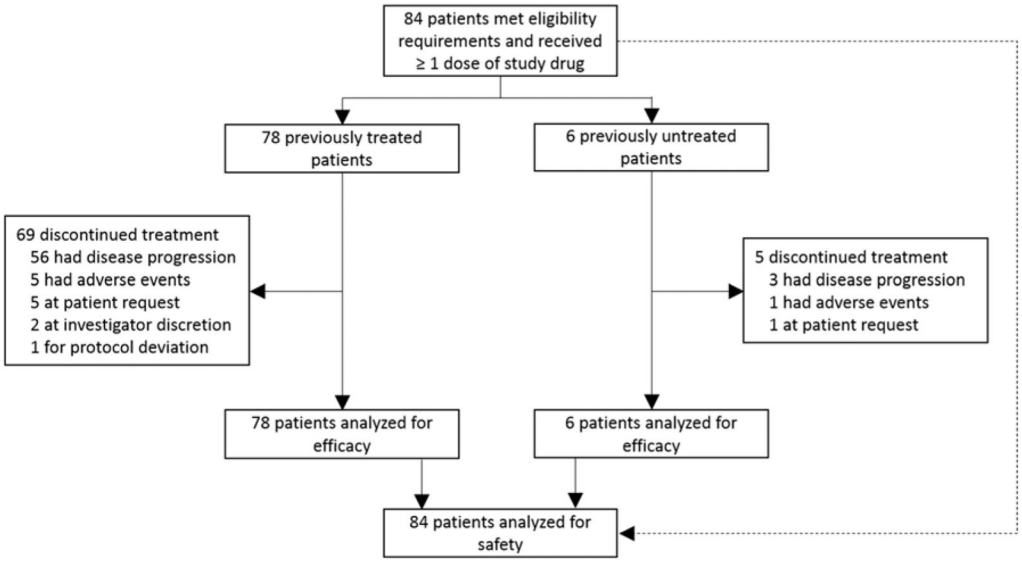

Figure 1.
Trial profile

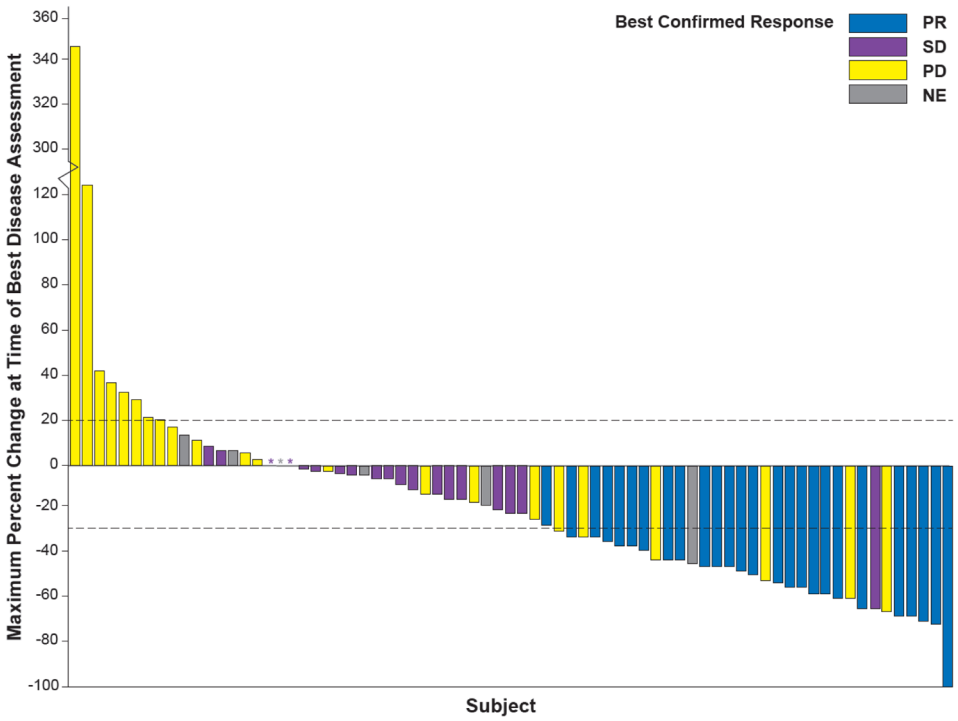

Figure 2. Response to dabrafenib in *BRAF* V600E–mutant NSCLC

Maximum change in the sum of lesion diameters by best confirmed response in ≥ second-line patients treated with dabrafenib (N = 78) at the time of the clinical activity analyses. The dashed line at 20 represents the RECIST 1.1 definition for progressive disease, while the dashed line at −30 represents the definition for partial response. Asterisks represent patients with no change from baseline at the time of assessment. NE denotes not estimable, NSCLC non-small cell lung cancer, PD progressive disease, PR partial response, RECIST Response Evaluation Criteria In Solid Tumors, SD stable disease.

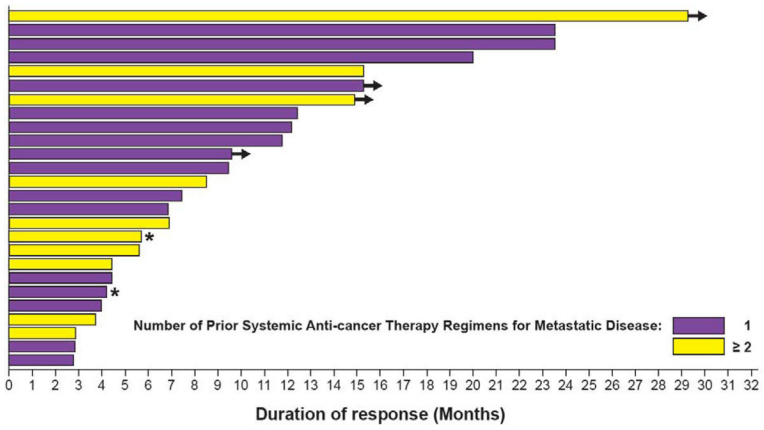

Figure 3. Duration of investigator-assessed response in ≥ second-line patients at time of mature activity analyses

Duration of response in patients with one prior therapy (purple bars) or ≥ two prior therapies (yellow bars). Arrows indicate patients remaining on therapy. Asterisks represent patients censored/lost to follow-up.

Table 1

Baseline demographic and clinical characteristics of the 78 ≥ second-line patients

Characteristic	Classification	≥ Second-Line Patients (N = 78)
Age, years	Median (range)	66 (28–85)
Sex, n (%)	Female/male	39 (50)/39 (50)
Race, n (%)	White	59 (76)
	Asian	17 (22)
	African American	2 (3)
ECOG PS at baseline, n (%)	0	16 (21)
	1	50 (64)
	2	12 (15)
Smoking history, n (%)	Never smoker[a]	29 (37)
	Smoker ≤ 30 pack-years[b]	25 (32)
	Smoker > 30 pack-years[b]	24 (31)
Histology at initial diagnosis, n (%)	Adenocarcinoma	75 (96)
	Other[c]	3 (4)
Number of prior systemic regimens for metastatic disease, n (%)	1	40 (51)
	2	14 (18)
	3	24 (31)
Time since last progression, months (n = 71)	Median (IQR)	1·1 (0·7–2·1)

ECOG denotes Eastern Cooperative Oncology Group, PS performance status.

[a]The definition of never-smokers was at the discretion of the local sites.

[b]Among 49 smokers, 3 current smokers, and 46 former smokers.

[c]"Other" includes 1 patient with adenosquamous carcinoma, predominately squamous cell carcinoma; 1 patient with bronchioalveolar carcinoma, mucinous type; and 1 patient with large cell carcinoma, adenocarcinoma.

Table 2

Clinical activity endpoints as assessed in patients with measurable disease at baseline (≥ second-line patients) at the time of mature activity analyses

Clinical Activity Endpoint:	Investigator assessment (N= 78)	Independent review committee (n = 64)
Best Response		
Response rate, n (%), ≥ confirmed PR [95% CI]	26 (33) [23–45]	21 (33) [22–46][d]
Stable disease, n (%), confirmed SD [95% CI][a]	19 (24) [15–35]	13 (20) [11–32]
Disease control rate, n (%), CR + PR + SD [95% CI][b]	45 (58) [46–67]	34 (53) [40–66]
PD, n (%)	23 (29)	23 (36)
Not evaluable, n (%)[c]	10 (13)	7 (11)
Progression-free survival, median (95% CI), months	5·5 (3.4–7.3)	5.5 (2.8 – 6.9)
Duration of response, median (95% CI)	9·6 (5.4–15.2)	9.9 (4.2 – ND)

CR, complete response; ND, not defined; PD, progressive disease; PR, partial response; SD stable disease.

[a] Defined as SD ≥ 12 weeks (planned time for the second postbaseline disease assessment).

[b] Disease control rate was the percentage of patients with a confirmed response or stable disease for at least 12 weeks after initiation of therapy.

[c] Not evaluable patients were those lacking post-baseline assessment or discontinuing prior to 12-weeks without PD according to RECIST (n=6 had SD < 12 weeks [planned 2 post-baseline assessments]; n=4 had no post-baseline assessment [n=3 due to AEs; n=1 due to patient or proxy decision to transfer to palliative care])

[d] One patient reviewed by independent review committee had a best response of complete response

Table 3

Adverse events in the 84 dabrafenib-treated patients

Common adverse events (preferred term)	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
Dyspnea	14 (17)	2 (2)	0	0
Headache	13 (15)	2 (2)	0	0
Arthralgia	13 (15)	1 (1)	0	0
Diarrhea	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
Anemia	7 (8)	2 (2)	0	0
Constipation	8 (10)	1 (1)	0	0
Melanocytic naevus	9 (11)	0	0	0
Seborrheic 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
Hypophosphatemia	2 (2)	3 (4)	0	0
Hypotension	4 (5)	1 (1)	0	0
Anxiety	2 (2)	2 (2)	0	0
Basal cell carcinoma	0	4 (5)	0	0

Common adverse events (preferred term)	Grade 1–2	Grade 3	Grade 4	Grade 5
Hyperglycemia	3 (4)	0	1 (1)	0
Hypokalemia	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
Hyponatremia	1 (1)	2 (2)	0	0
Leukopenia	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
Ischemic colitis	0	1 (1)	0	0
Intracranial hemorrhage	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

Data are n (%). Adverse events (preferred terms) of grades 1–2 occurring in at least 10% of patients and all grade 3 or higher events are listed