Search for Gamma-Ray Emission from the Sun during Solar Minimum with the ARGO-YBJ Experiment

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Summary

Background

BRAF mutations act as an oncogenic driver via the mitogen-activated protein kinase (MAPK) pathway in non-small cell lung cancer (NSCLC). BRAF inhibition has shown antitumour activity in patients with *BRAF*^{V600E}-mutant NSCLC. Dual MAPK pathway inhibition with BRAF and MEK inhibitors in *BRAF*^{V600E}-mutant NSCLC might improve efficacy over BRAF inhibitor monotherapy based on observations in *BRAF*^{V600}-mutant melanoma. We aimed to assess the antitumour activity and safety of dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutant NSCLC.

Methods

In this phase 2, multicentre, non-randomised, open-label study, we enrolled adult patients (aged ≥18 years) with pretreated metastatic stage IV *BRAF*^{V600E}-mutant NSCLC who had documented tumour progression after at least one previous platinum-based chemotherapy and had had no more than three previous systemic anticancer therapies. Patients with previous BRAF or MEK inhibitor treatment were ineligible. Patients with brain metastases were allowed to enrol only if the lesions were asymptomatic, untreated (or stable more than 3 weeks after local therapy if treated), and measured less than 1 cm. Enrolled patients received oral dabrafenib (150 mg twice daily) plus oral trametinib (2 mg once daily) in continuous 21-day cycles until disease progression, unacceptable adverse events, withdrawal of consent, or death. The primary endpoint was investigator-assessed overall response, which was assessed by intention to treat in the protocol-defined population (patients who received second-line or later treatment); safety was also assessed in this population and was assessed at least once every 3 weeks, with adverse events, laboratory values, and vital signs graded according to the Common Terminology Criteria for Adverse Events version 4.0. The study is ongoing but no longer recruiting patients. This trial is registered with ClinicalTrials.gov, number NCT01336634.

Findings

Between Dec 20, 2013, and Jan 14, 2015, 59 patients from 30 centres in nine countries across North America, Europe, and Asia met eligibility criteria. Two patients who had previously been untreated due to protocol deviation were excluded; thus, 57 eligible patients were enrolled. 36 patients (63·2% [95% CI 49·3–75·6]) achieved an investigator-assessed overall response. Serious adverse events were reported in 32 (56%) of 57 patients and included pyrexia in nine (16%), anaemia in three (5%), confusional state in two (4%), decreased appetite in two (4%), haemoptysis in two (4%), hypercalcaemia in two (4%), nausea in two (4%), and cutaneous squamous cell carcinoma in two (4%). The most

common grade 3–4 adverse events were neutropenia in five patients (9%), hyponatraemia in four (7%), and anaemia in three (5%). Four patients died during the study from fatal adverse events judged to be unrelated to treatment (one retroperitoneal haemorrhage, one subarachnoid haemorrhage, one respiratory distress, and one from disease progression that was more severe than typical progression, as assessed by the investigator).

Interpretation

Dabrafenib plus trametinib could represent a new targeted therapy with robust antitumour activity and a manageable safety profile in patients with *BRAF*^{V600E}-mutant NSCLC.

Funding

GlaxoSmithKline.

Introduction

Non-small cell lung cancer (NSCLC), which constitutes about 85% of all lung cancers, remains a leading cause of cancer-related deaths worldwide.[1] Recently, progress has been made in characterising the oncogenic driver mutations that contribute to the molecular pathogenesis of lung cancers, including activating mutations in *EGFR* and *ALK* rearrangements. This progress has led to rapid development of targeted therapeutics and a more personalised approach to NSCLC treatment. [2 and 3]

Activating mutations in the *BRAF* gene, which are generally mutually exclusive from *EGFR* mutations or *ALK* rearrangements, act as an alternative oncogenic driver in NSCLC. The most common of these mutations, *BRAF*^{V600E}, is observed in 1–2% of lung adenocarcinomas. [4, 5, 6 and 7] Although the prognostic implications of *BRAF*^{V600E} mutation are unclear, several studies have associated *BRAF*^{V600E} with poor outcomes and with a lower proportion of patients achieving a response to platinum-based chemotherapy in patients with NSCLC compared with patients with NSCLC without *BRAF* mutations. [8 and 9] Furthermore, in a recent analysis, half of 106 patients with *BRAF*-mutant NSCLC received only best supportive care in a real-world second-line treatment setting. [5] Therefore, more effective targeted therapies are needed for these patients with limited therapeutic options.

Research in context

Evidence before this study

Mutations in the *BRAF* gene, which encodes for a serine/threonine kinase at the top of the MAPK pathway, act as an oncogenic driver in non-small cell lung cancer (NSCLC). The most common *BRAF* mutation, *BRAF*^{V600E}, has been associated with more aggressive tumours, providing a strong rationale for targeting this pathway in patients with *BRAF*^{V600E}-mutant NSCLC. BRAF inhibitors have shown clinical activity in patients treated with dabrafenib monotherapy

in cohort A of the current phase 2 trial. Combined BRAF and MEK inhibition has shown superior efficacy compared with BRAF inhibitor monotherapy in patients with *BRAF*-mutant metastatic melanoma, potentially contributing to sustained pathway inhibition and delay or prevention of resistance. Moreover, the addition of the MEK inhibitor trametinib to dabrafenib led to synergistic antitumour activity in a *BRAF*-mutant human lung cancer cell line, suggesting that combined BRAF and MEK inhibition could potentially provide increased benefit over BRAF inhibitor monotherapy in patients with $BRAF^{V600E}$-mutant NSCLC. We searched PubMed for studies of combined BRAF and MEK inhibition for the treatment of patients with $BRAF^{V600E}$-mutant NSCLC, without date limitations or language or study type restrictions. We used the search terms "dabrafenib AND trametinib" and "vemurafenib AND cobimetinib" both with "non-small cell lung cancer" OR "NSCLC." No clinical studies were identified that used combined BRAF and MEK inhibition in patients with $BRAF^{V600E}$-mutant NSCLC.

Added value of this study

We noted that combination dabrafenib plus trametinib had substantial antitumour activity (proportion of patients with overall response 63%) in patients with $BRAF^{V600E}$-mutant NSCLC. Furthermore, responses were durable, with a median progression-free survival of 9·7 months, and the safety profile was tolerable.

Implications of all the available evidence

To the best of our knowledge, this trial is the first to assess combination BRAF and MEK inhibition in patients with $BRAF^{V600E}$-mutant NSCLC. Notably, the overall response and median progression-free survival recorded with combination dabrafenib plus trametinib were higher when compared indirectly with dabrafenib monotherapy, used in cohort A of this study. Although cross-trial comparisons should be undertaken with caution, the clinical activity recorded in this study seems similar to that shown for other targeted therapies, including EGFR tyrosine kinase inhibitors and ALK inhibitors in selected patient populations. Moreover, the rarity of this patient population renders the potential conduct of a randomised trial extremely challenging. Therefore, these results have a strong potential to change the management of patients with $BRAF^{V600E}$-mutant NSCLC—a population with an unmet medical need.

In a preclinical study, dabrafenib plus trametinib synergistically inhibited cell growth in a $BRAF^{V600E}$-mutant lung carcinoma cell line (MV522; Mookerjee B, unpublished). Clinically, BRAF plus MEK inhibition has shown an increased proportion of patients achieving an overall response, progression-free survival, and overall survival compared with BRAF inhibitor monotherapy in patients with $BRAF^{V600}$-mutant metastatic melanoma. [10, 11 and 12]

This phase 2 study reports on the second (cohort B) of three sequentially enrolled cohorts. In cohort A, the antitumour activity of a selective BRAF inhibitor, dabrafenib, was assessed exclusively in previously treated patients with $BRAF^{V600E}$-mutant NSCLC.[13] Dabrafenib showed clinical activity with an overall confirmed response of 33% (95% CI 23–45) and median progression-free survival of 5·5 months (3·4–7·3) in patients with previously treated NSCLC.[13] In cohort B, reported here, we aimed to assess the clinical activity and safety of the combination BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib in patients with previously treated metastatic $BRAF^{V600E}$-mutant NSCLC,

at doses that have been successfully used to treat melanoma.[10] An additional cohort of this study (cohort C) has enrolled treatment-naive patients with *BRAF*^{V600E}-mutant NSCLC treated with dabrafenib plus trametinib, and the patients are now being followed up for response and progression-free survival.

Methods

Study design and participants

This study was part of an ongoing phase 2, multicentre, non-randomised, open-label study. We enrolled adult patients (aged ≥18 years) with histologically or cytologically confirmed stage IV *BRAF*^{V600E}-mutant NSCLC, documented tumour progression after at least one platinum-based chemotherapy regimen (based on medical history), and no more than three previous systemic treatments for metastatic NSCLC. *BRAF*^{V600E} mutational status was ascertained based on local testing in Clinical Laboratory Improvement Amendments-approved (or its equivalent outside the USA) laboratories. Patients had to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower, adequate organ function, and an estimated life expectancy of 3 months or longer. Patients who had previously been treated with a BRAF inhibitor or MEK inhibitor, those who had received anticancer treatment (including chemotherapy, radiation therapy, immunotherapy, biological therapy, or major surgery) within 14 days before the start of study treatment, those who had received an investigational anticancer drug within 14 days or 5 half-lives of start of therapy (minimum 14 days), those with active gastrointestinal disease, and those with hepatitis B or C virus infection were ineligible. Patients with brain metastases were ineligible unless they were asymptomatic, were untreated, and measured less than 1 cm, or, if treated, were clinically and radiographically stable 3 weeks after local therapy. For the full inclusion and exclusion criteria see appendix p 4.

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 institution. All patients provided written informed consent.

Procedures

Patients were treated with oral dabrafenib (150 mg twice daily) plus oral trametinib (2 mg once daily) in continuous 21-day cycles until disease progression, unacceptable adverse events, withdrawal of consent, or death. Patients with progressive disease according to RECIST version 1.1 were allowed to continue treatment if they had a confirmed partial or complete response according to RECIST version 1.1 or had stable disease lasting for 12 weeks or longer during study treatment, had no clinical signs or symptoms of disease progression, no grade 4 or serious adverse events during the past 4 weeks of treatment, and the investigator believed the patient was clinically benefiting from therapy. The decision to continue treatment had to be approved by the GlaxoSmithKline Medical Monitor. Dose modifications or interruptions were used to manage intolerable grade 2 or worse adverse events. Dose modification guidelines are included in appendix p 4.

Radiological disease assessments by CT scans based on RECIST version 1.1 were done at baseline, at week 6, every 6 weeks until week 36, and then every 12 weeks, and the responses were confirmed by repeat assessment 4–7 weeks after initial response. RECIST scans were reviewed by an independent review committee. All patients who discontinued study drug were followed up for subsequent treatments and survival every 12 weeks, until death or study completion. Patients were assessed for safety at least once every 3 weeks. Adverse events, laboratory values (haematology and clinical chemistry), and vital signs were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Development of cutaneous squamous carcinoma was required to be reported as at least grade 3 in accordance with the clinical study team practice and is consistent throughout studies in the dabrafenib plus trametinib development programme. The protocol also required certain events (grade 2 or worse pyrexia with symptoms, left ventricular ejection fraction decrease, and others) to be reported as protocol specified serious adverse events, irrespective of whether or not they met the standard definition of serious adverse events. Full details of the study assessment are in the appendix (p 4). The cutoff date for safety and efficacy data was Oct 7, 2015, which was the date of database lock.

Optional biopsy samples could be collected at week 6 and at the end of study per protocol. The method of optional biopsy collection was not mandated in the protocol and any clinically available tumour or cytological specimen could be accepted.

Outcomes

The primary endpoint was investigator-assessed overall response, which was defined as the proportion of patients with a confirmed complete response or partial response according to RECIST version 1.1. This event could occur at any point during the study. If the response was documented at week 6, confirmation could occur at the week 12 scan. Initial responses occurring at week 12 or after must be confirmed 4–7 weeks later. Secondary endpoints (defined in appendix p 4) were progression-free survival based on investigator-assessed disease response, duration of response based on investigator-assessed confirmed response, overall survival, safety and tolerability, and pharmacokinetic assessment. Predefined exploratory outcomes were examination of the molecular mechanisms of sensitivity and resistance to dabrafenib plus trametinib, assessment of the relationship between exposure and response, assessment of cell free DNA to identify *BRAF* mutation, and investigation of the relationship genetic variations and efficacy, safety, and pharmacokinetics. Independent review committee assessment was done as a sensitivity analysis.

Statistical analysis

A two-stage Green-Dahlberg[14] design was used to monitor patients for clinical response during the study to enable early stopping for futility if sufficient clinical activity was not shown. An interim analysis was planned after 20 patients had at least two post-baseline scans or withdrew from the study before response was assessed. The null hypothesis was that the overall response was not clinically meaningful (≤30%), and the alternative hypothesis was that 55% or more of second-line to fourth-line patients with *BRAF*^{V600E}-mutant NSCLC would achieve an overall response with dabrafenib plus trametinib. The trial could be terminated for futility after enrolment of 20 patients if a confirmed

response was not noted in six or more of 20 patients after stage 1 and 18 or more of 40 patients after both stages. Enrolment of additional patients was allowed per protocol to ensure an adequate number of assessable patients with central confirmation of response assessments and *BRAF* mutation status. The statistical analyses were based on the planned enrolment of 40 patients (20 in each stage) and corresponded to a type I error of 0·032 and a power of 92·2%. These statistical assumptions were not changed by the enrolment of additional patients. Efficacy and safety were assessed by intention to treat in the protocol-defined population (those patients who received second-line or later treatment). Patients defined as not assessable either had no post-baseline CT scan or discontinued before 12 weeks without documented progression. For overall response, we used the Clopper-Pearson method to calculate 95% CIs. The duration of response, progression-free survival, and overall survival were estimated by medians calculated using the Kaplan-Meier method with corresponding two-sided CIs calculated with the Brookmeyer-Crowley method. [15] A sensitivity analysis for these endpoints was done by an independent review committee using the same methods. An additional prespecified sensitivity analysis was done for progression-free survival with the inclusion of clinical progression as an event and the same methods.

SAS version 9.4 was used for statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT01336634.

Role of the funding source

This study was funded by GlaxoSmithKline; dabrafenib and trametinib are assets of Novartis AG as of March 2, 2015. The study was designed by the academic authors in conjunction with representatives of the funder. Data were collected by the funder and analysed in collaboration with the authors. AMD'A, PZ, BM, and AU had full access to the raw data. The funder was involved in writing of the report. The first and last authors wrote the initial draft; all authors contributed to subsequent drafts and made the decision to submit for publication. The authors affirm accuracy of the data and fidelity of the study to the protocol. Editorial support was provided by ArticulateScience and funded by Novartis Pharmaceuticals. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

Between Dec 20, 2013, and Jan 14, 2015, 59 patients were enrolled from 30 centres in nine countries across North America, Europe, and Asia. Because this study enrolled patients who had *BRAF*^{V600E} mutation based on testing in local laboratories, the exact number of patients with NSCLC who were screened at the participating institutions for *BRAF*^{V600E} mutation was not recorded.

Of the 59 enrolled patients, two were excluded (figure 1); thus, 57 patients previously treated for metastatic disease (one previous regimen [n=38]; two to three previous regimens [n=19]) received dabrafenib plus trametinib and were included in the efficacy and safety analyses (figure 1). Two treatment-naive patients were enrolled due to accidental protocol deviation and are reported separately.

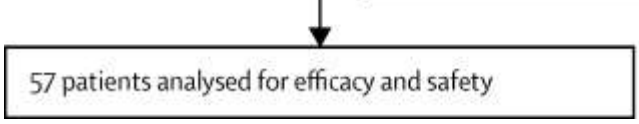

Figure 1.

Trial profile

Table 1 shows the baseline characteristics for the 57 patients receiving dabrafenib plus trametinib as second-line or later treatment. One patient (2%) had a non-measurable brain metastasis at enrolment and the lesion was asymptomatic. At the cutoff date of Oct 7, 2015, 21 patients (37%) remained on treatment. 28 patients (49%) discontinued due to disease progression, seven (12%) due to adverse events, and one (2%) at the patient's request (figure 1). Chemotherapy was the most commonly used post-progression therapy (15 patients [26%]).

Table 1.

Baseline characteristics

	Patients receiving dabrafenib plus trametinib as second-line or later treatment (n=57)
Age (years)	64 (58–71)
Sex	
Male	29 (51%)
Female	28 (49%)
Ethnic origin	
White	49 (86%)
Black	2 (4%)
Asian	4 (7%)
Mixed	1 (2%)
Missing	1 (2%)
ECOG performance status	
0	17 (30%)

	Patients receiving dabrafenib plus trametinib as second-line or later treatment (n=57)
1	35 (61%)
2	5 (9%)
Histology at initial diagnosis	
Adenocarcinoma*	56 (98%)
Large cell	1 (2%)
History of tobacco use	
Never smoker	16 (28%)
Current smoker	6 (11%)
Former smoker	35 (61%)
Smoking history†	
≤30 pack-years	22 (54%)
>30 pack-years	19 (46%)
Number of previous systemic regimens for metastatic disease	
1	38 (67%)
≥2	19 (33%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

*Includes one patient with adenosquamous carcinoma—predominantly adenocarcinoma histology—and two patients with lepidic predominant or invasive mucinous adenocarcinoma (formerly known as bronchioalveolar carcinoma). All histology was determined by local pathological report.

†Data available for 41 patients.

With a median follow-up of 11·6 months (IQR 8·8–15·2), the investigator-assessed confirmed overall response was achieved by 36 (63·2% [95% CI 49·3–75·6]) of 57 patients, including two patients (4%) with complete responses and 34

(60%) with partial responses. The investigator-assessed disease control (complete response + partial response + stable disease) was achieved by 45 patients (78·9% [95% CI 66·1–88·6]; table 2, figure 2). The independent review committee-assessed overall response and disease control were similar to the investigator-assessed results (table 2). Two patients with confirmed complete response by investigator assessment did not have a confirmed complete response by independent review. The patient with non-measurable brain metastasis at baseline had a non-complete response and non-progressive disease response in the brain lesion. No patients had documented new brain metastases as part of their progression.

Table 2.

Antitumour activity in patients receiving dabrafenib plus trametinib as second-line or later treatment

	Investigator assessment (n=57)	**Independent assessment (n=57)**
Best response		
Complete response	2 (4%)	0
Partial response	34 (60%)	36 (63%)
Stable disease	9 (16%)	4 (7%)
Progressive disease	7 (12%)	8 (14%)
Non-complete response/non-progressive disease	0	3 (5%)
Not assessable	5 (9%)	6 (11%)
Overall response (complete response + partial response)	36 (63·2%; 49·3–75·6)	36 (63·2%; 49·3–75·6)
Disease control (complete response + partial response + stable disease)	45 (78·9%; 66·1–88·6)	43 (75·4%; 62·2–85·9)
Progression-free survival (months)	9·7 (6·9–19·6)	8·6 (5·2–19·1)
Duration of response (months)	9·0 (6·9–18·3)	9·0 (5·8–17·6)

Data are n (%), n (%; 95% CI), or median (95% CI).

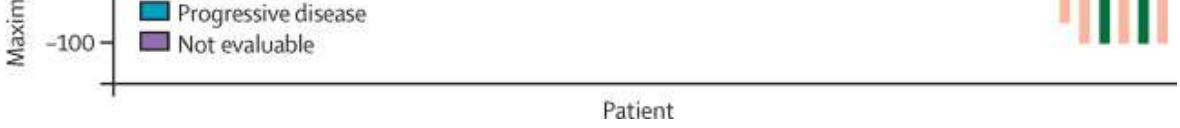

Figure 2.

Tumour responses to dabrafenib and trametinib in *BRAF*^{V600E}-mutant non-small cell lung cancer

Maximum percentage reduction from baseline sum of lesion diameters by best investigator-assessed confirmed response in 57 patients receiving second-line or later treatment. The grey line at 20 represents the

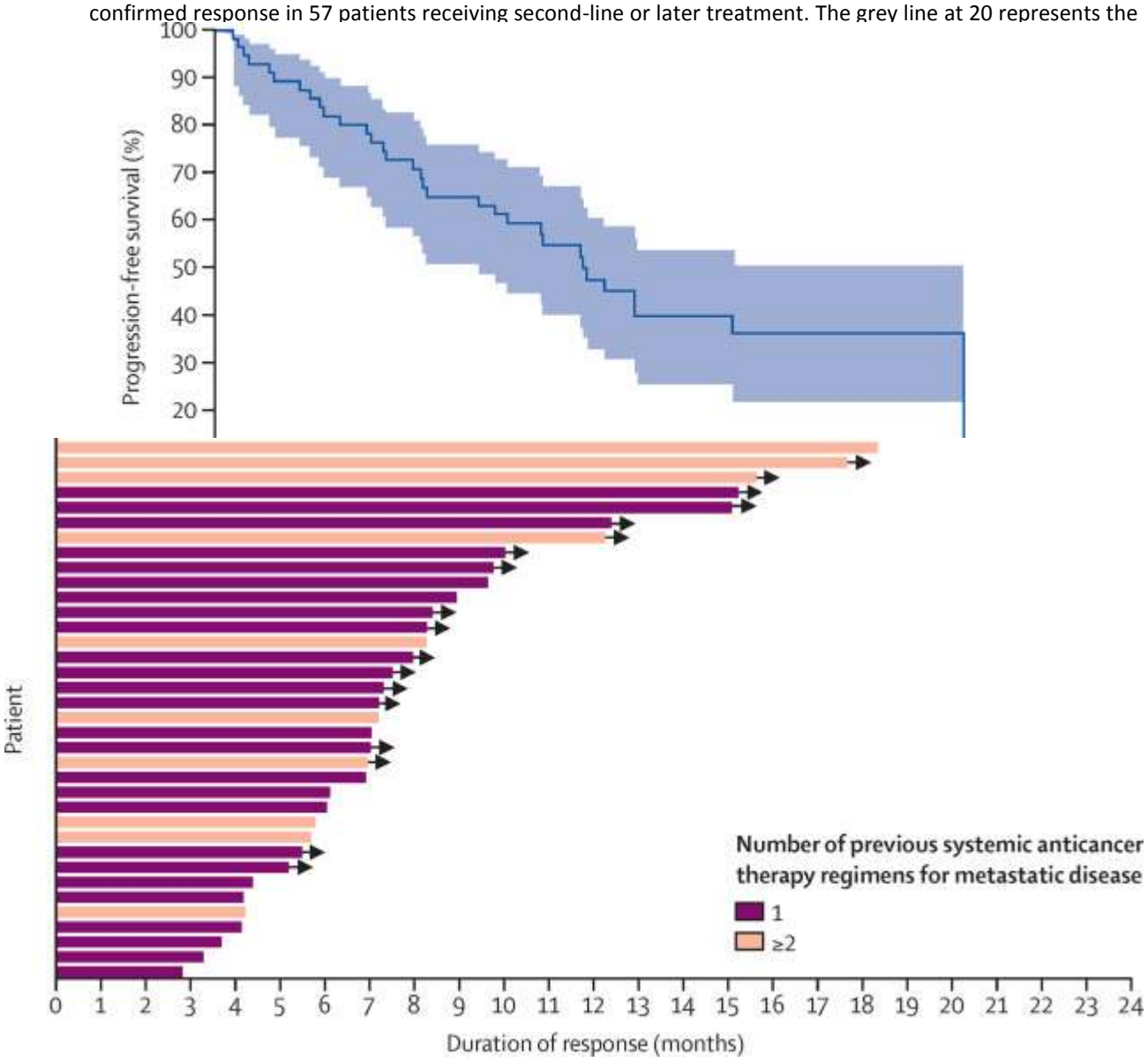

Figure 4.

Duration of response in the 36 patients receiving second-line or later treatment who achieved an investigator-assessed overall response

Duration of response by number of previous systemic anticancer therapies for metastatic disease. Arrows denote ongoing response at the time of data cutoff. Note that half (n=18) of the patients had an ongoing response at the time of data cutoff.

Two patients without previous systemic treatment for metastatic disease were enrolled due to protocol deviation and these patients were excluded from analyses. One patient achieved a complete response and remained progression-free at data cutoff (received study drug for >16 months). The other patient achieved a partial response and progressed after 9·7 months of treatment.

The median duration of treatment for both dabrafenib and trametinib was 10·6 months (IQR 4·2–12·2); 17 (30%) of 57 patients received more than 12 months of treatment (appendix p 7). Adverse events led to permanent discontinuation in seven patients (12%), dose interruption or delay in 35 (61%), and dose reduction in 20 (35%). 33 patients (58%) received at least 80% of the planned dose of dabrafenib and 43 (75%) patients received at least 80% of the planned dose of trametinib. Nearly all patients had at least one adverse event (56 [98%] of 57), and nearly half (28 [49%] of 57) had at least one grade 3–4 event. Common adverse events of any grade (≥30%) included pyrexia in 26 patients (46%), nausea in 23 (40%), vomiting in 20 (35%), diarrhoea in 19 (33%), asthenia in 18 (32%), and decreased appetite in 17 (30%; table 3). Common grade 3–4 adverse events (occurring in ≥5% of patients) were neutropenia in five patients (9%), hyponatraemia in four (7%), and anaemia in three (5%). Serious adverse events were reported in 32 (56%) of 57 patients; the most common were pyrexia in nine patients (16%), anaemia in three (5%), confusional state in two (4%), decreased appetite in two (4%), haemoptysis in two (4%), hypercalcaemia in two (4%), nausea in two (4%), and squamous cell carcinoma of the skin in two (4%) (appendix pp 8, 9). For the 32 patients with recorded serious adverse events, 19 had recovered from all serious adverse events (one of those 19 recovered with sequelae) and two patients were recovering/resolving from all serious adverse events by the time of data cutoff. Seven patients had serious adverse events which were not recovered/not resolved at time of data cutoff. Two (4%) of 57 patients died from fatal serious adverse events considered to be unrelated to study treatment by the investigators. One patient with a history of mitral valve replacement and receiving anticoagulative therapy had an episode of ventricular fibrillation, was admitted to hospital, and developed retroperitoneal haemorrhage, and one patient with a history of cranial artery aneurysm had a subarachnoid haemorrhage. Two patients died from disease-related causes that were unrelated to study treatment: one from respiratory distress and one from neoplasm progression that was judged by the investigator to be more severe than typical progression and was thus recorded as an adverse event.

Table 3.

Adverse events

	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**
Pyrexia	25 (44%)	1 (2%)	0	0
Nausea	23 (40%)	0	0	0
Vomiting	20 (35%)	0	0	0

	Grade 1–2	Grade 3	Grade 4	Grade 5
Diarrhoea	18 (32%)	1 (2%)	0	0
Decreased appetite	17 (30%)	0	0	0
Asthenia	16 (28%)	2 (4%)	0	0
Dry skin	14 (25%)	1 (2%)	0	0
Peripheral oedema	13 (23%)	0	0	0
Chills	12 (21%)	1 (2%)	0	0
Cough	12 (21%)	0	0	0
Rash	11 (19%)	1 (2%)	0	0
Arthralgia	11 (19%)	0	0	0
Constipation	10 (18%)	0	0	0
Fatigue	9 (16%)	1 (2%)	0	0
Blood alkaline phosphatase increased	9 (16%)	0	0	0
Dyspnoea	8 (14%)	2 (4%)	0	0
Pruritus	8 (14%)	1 (2%)	0	0
Dizziness	8 (14%)	0	0	0
Anaemia	7 (12%)	2 (4%)	1 (2%)	0
Weight decreased	7 (12%)	1 (2%)	0	0
Upper abdominal pain	7 (12%)	0	0	0
Hypotension	7 (12%)	0	0	0
Neutropenia	6 (11%)	5 (9%)	0	0
Chest pain	6 (11%)	0	0	0

	Grade 1–2	Grade 3	Grade 4	Grade 5
Dysgeusia	6 (11%)	0	0	0
Headache	6 (11%)	0	0	0
Muscle spasms	6 (11%)	0	0	0
Myalgia	6 (11%)	0	0	0
Productive cough	6 (11%)	0	0	0
Vertigo	6 (11%)	0	0	0
Hyperkeratosis	5 (9%)	1 (2%)	0	0
Weight increased	5 (9%)	1 (2%)	0	0
Back pain	4 (7%)	0	1 (2%)	0
Haemoptysis	4 (7%)	1 (2%)	0	0
Aspartate aminotransferase increased	3 (5%)	1 (2%)	0	0
Blood creatinine increased	3 (5%)	1 (2%)	0	0
Hypophosphataemia	3 (5%)	1 (2%)	0	0
Thrombocytopenia	3 (5%)	1 (2%)	0	0
Hyponatraemia	2 (4%)	3 (5%)	1 (2%)	0
Leucopenia	2 (4%)	2 (4%)	0	0
Alanine aminotransferase increased	2 (4%)	1 (2%)	0	0
Dehydration	1 (2%)	2 (4%)	0	0
Hypertension	1 (2%)	2 (4%)	0	0
Serum amylase increased	1 (2%)	1 (2%)	0	0
Basal cell carcinoma	1 (2%)	1 (2%)	0	0

	Grade 1–2	Grade 3	Grade 4	Grade 5
Erythema nodosum	1 (2%)	1 (2%)	0	0
Haematuria	1 (2%)	1 (2%)	0	0
Peripheral neuropathy	1 (2%)	1 (2%)	0	0
Pain	1 (2%)	1 (2%)	0	0
Pulmonary embolism	1 (2%)	1 (2%)	0	0
Tubulointerstitial nephritis	1 (2%)	1 (2%)	0	0
Visual impairment	1 (2%)	1 (2%)	0	0
γ-glutamyltransferase increased	0	1 (2%)	1 (2%)	0
Hypercalcaemia	0	2 (4%)	0	0
Respiratory distress	0	1 (2%)	0	1 (2%)
Squamous cell carcinoma of skin	0	2 (4%)	0	0
C-reactive protein increased	0	1 (2%)	0	0
Cholecystitis acute	0	1 (2%)	0	0
Coronary artery stenosis	0	1 (2%)	0	0
Febrile neutropenia	0	1 (2%)	0	0
Hepatocellular carcinoma	0	1 (2%)	0	0
Hip fracture	0	1 (2%)	0	0
Incisional hernia	0	1 (2%)	0	0
Intestinal obstruction	0	1 (2%)	0	0
Legionella infection	0	0	1 (2%)	0
Lung neoplasm malignant[*]	0	1 (2%)	0	0

	Grade 1–2	Grade 3	Grade 4	Grade 5
Neoplasm progression[‡]	0	0	0	1 (2%)
Pancytopenia	0	1 (2%)	0	0
Pleural effusion	0	1 (2%)	0	0
Pyelonephritis	0	1 (2%)	0	0
Quadriplegia	0	1 (2%)	0	0
Renal failure	0	1 (2%)	0	0
Retroperitoneal haemorrhage	0	0	0	1 (2%)
Subarachnoid haemorrhage	0	0	0	1 (2%)
Ventricular fibrillation	0	0	1 (2%)	0

Data are n (%). All treated patients (n=57). Grade 1–2 adverse events occurring in ≥10% patients and all grade 3–5 events are reported. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

*One patient had a lung metastasis that did not respond to therapy, had a biopsy sample done, and was determined to have a *KRAS* mutation. This was reported as an adverse event by the investigator.

†One patient was established by the investigator to have progression that was more severe than typical progression; according to the study protocol, this can be documented as an adverse event.

In a post-hoc analysis of response by previous lines of systemic therapy, investigator-assessed response was noted in 26 (68% [95% CI 51·3–82·5]) of 38 patients with one previous line versus ten (53% [28·9–75·6]) of 19 patients with two to three previous lines of therapy. Post-hoc analysis of investigator-assessed response by smoking history showed an overall response was achieved by ten (63% [95% CI 35·4–84·8]) of 16 patients with no previous smoking history, 24 (69% [50·7–83·1]) of 35 former smokers, and two (33% [4·3-77·7]) of six current smokers. Of the five patients who had an ECOG performance status of 2 at baseline, four (80%) of five had a best response of partial response and one (20%) had a best response of stable disease. Of the 52 patients with an ECOG performance status of 0 or 1 at baseline 32 (62%) had a confirmed response (two complete response + 30 partial response) and an additional eight had a best response of stable disease. One of the five patients remains on treatment with a progression-free survival of about 25 months at the time of writing (based on 16·6 month progression-free survival at data cutoff in August, 2015); the remaining four patients discontinued due to progressive disease with progression-free survival ranging from 3·5

months to 13·0 months. One of the five patients had a fatal serious adverse event of respiratory distress that was associated with the disease under study and was judged to be unrelated to study treatment.

Pharmacokinetic analysis has not been completed and these data will be reported elsewhere.

Across all cohorts, only two optional post-progression biopsy samples have been obtained so far, and further sample acquisition is ongoing.

Discussion

This trial is, to our knowledge, the first assessment of combined BRAF and MEK inhibition in NSCLC. The results show the substantial clinical activity of dabrafenib plus trametinib therapy in patients with previously treated *BRAF*^{V600E}-mutant metastatic NSCLC. The protocol-defined primary objective was met, with 63% of patients achieving a confirmed overall response. Responses were durable, with half of confirmed responses ongoing at data cutoff, and toxicity was manageable.

These results are particularly noteworthy because of the scarce data and clear unmet need of effective targeted therapy for patients with *BRAF*-mutant NSCLC. In patients with NSCLC with *BRAF* mutations, half of the mutations are *BRAF*^{V600E}, which activate BRAF in its monomeric state and are sensitive to *BRAF* mutant-specific inhibitors. Other *BRAF* mutations are either activating constitutive or RAS-dependent dimer formation or do not activate BRAF, and their relevance to the disease is undefined; thus, BRAF inhibitors are not effective in patients with these mutations. [8] and [16]

A previous analysis of patients with *BRAF*-mutant NSCLC who received standard-of-care chemotherapy as second-line treatment in a real-world setting showed poor outcomes: overall response was achieved by 59 (9%) of patients with available data and median progression-free survival was 3·1 months (1·4–6·1) for 71 patients with available data. [5] BRAF inhibitor monotherapy has been shown to have clinical activity in *BRAF*^{V600E}-mutant NSCLC in several studies, in cohort A of this study (dabrafenib monotherapy), 26 (33%) of 78 patients achieved an overall response and progression-free survival was 5·5 months (3·4–7·3);[13] in a trial of vemurafenib monotherapy, eight (42%) of 19 achieved an overall response (although unconfirmed by repeat imaging) and progression-free survival was 7·3 months (3·5–10·8);[17] and in a retrospective analysis of patients treated with dabrafenib, vemurafenib, or sorafenib,[18] progression-free survival was 5 months (3·0–10·3). However, the overall response and progression-free survival outcomes need further improvement. The increased efficacy of the combination of BRAF and MEK inhibition in NSCLC versus BRAF inhibitor alone (dabrafenib) is similar to observations in a trial of this treatment combination in *BRAF*^{V600}-mutant melanoma.[12] Acquired resistance to BRAF and MEK inhibitors can occur in patients with melanoma and seems to be mainly linked to reactivation of the MAPK pathway and adaptations in the PI3K–PTEN–AKT pathway.[19] Whether or not these mechanisms of acquired resistance occur in patients with *BRAF*^{V600E}-mutant NSCLC treated with BRAF or MEK inhibitors, or combined therapy, is unknown, and further investigation is warranted and ongoing. In this study, optional biopsy samples could be collected at week 6 and at the end of study per protocol. So far, only two post-

progression biopsy samples have been acquired across all cohorts of this trial, and further sample acquisition and follow-up is ongoing.

Targeted therapeutics have proven to be a successful strategy in patients with NSCLC harbouring oncogenic driver mutations. For example, in previously untreated patients with activating mutations in *EGFR*, EGFR tyrosine kinase inhibitors induce a durable overall response in a high proportion of patients. [2, 20 and 21] Similarly, in previously treated patients with *ALK* rearrangements, ALK inhibitors show substantial efficacy. [3] Moreover, inhibition of ROS1 with crizotinib has shown clinical activity in patients with *ROS1* rearranged NSCLC. [22] Additional personalised therapies targeting oncogenic drivers could also be on the horizon, including the use of crizotinib in patients with MET exon 14 skipping mutation. [23, 24 and 25]

As shown in this study, dabrafenib plus trametinib seems to have similar clinical activity in a selected patient population. Although the prognostic implications of *BRAF*^{V600E} mutations in NSCLC remain unclear, [5, 8, 9 and 26] our data indicate a 6-month overall survival of 82% with a more mature overall survival assessment planned in a future analysis. Longer-term overall survival data will help to ascertain whether targeted agents can change the natural history of NSCLC, similar to results reported in melanoma.[27] Such a finding could change NSCLC treatment by placing increased emphasis on determination of *BRAF* mutation status at diagnosis to help to inform personalised therapeutic decisions.

In view of the rarity of the *BRAF*^{V600E} mutation rate (1%)[5] to do a randomised trial is infeasible, since it would have been necessary to screen 6000 patients to identify the 59 patients enrolled in this cohort. The potential for advances in liquid biopsy methods to detect oncogenic driver mutations has been tested in NSCLC for more common mutations and in melanoma for *BRAF*^{V600E} mutations and could provide enhanced screening capabilities once the technique has been optimised and validated.[28] Furthermore, the future inclusion of rare mutations such as *BRAF*^{V600E} in umbrella trials in patients with NSCLC could help to enhance enrolment and allow for larger trials. Upcoming discussions regarding revisions to the European and US guidelines for molecular testing in NSCLC could potentially recommend assessment of *EGFR, ALK, ROS1*, and *BRAF*^{V600E} for all patients with lung adenocarcinoma. In addition to the non-randomised nature of the trial and the absence of post-progression biopsies to this point, other limitations of this study are the inclusion of only patients with *BRAF*^{V600E}-mutant NSCLC, which precludes the examination of the regimen in patients with other activating *BRAF* mutations, and the exclusion of patients without previous treatment.

Studies suggest that the ALK inhibitor crizotinib might show better efficacy in treatment-naive than in previously treated patients with *ALK* rearrangements, yielding a slightly higher proportion of patients achieving an overall response and a longer median progression-free survival. [3 and 29] Cohort C of this trial (treatment-naive patients with *BRAF*^{V600E}-mutant NSCLC treated with dabrafenib and trametinib) had completed enrolment at the time of preparation of this report, and patients are being followed for response and progression-free survival. These data will help to confirm whether clinical activity of the combination is increased in earlier lines of therapy in *BRAF*^{V600E}-mutant NSCLC.

The immune checkpoint inhibitors, nivolumab and pembrolizumab, are a new second-line treatment option for patients with NSCLC: nivolumab without biomarker selection and pembrolizumab in PDL-1-positive patients. Trials done in 2015 showed that patients with previously treated metastatic primarily non-squamous NSCLC who were treated with nivolumab or pembrolizumab had a median overall survival of 10·4–12·7 months.[30, 31 and 32] However, a response was noted in only a small subset (about 20%) of patients, and no data exist regarding the efficacy of these checkpoint inhibitors in patients with *BRAF*^{V600E}-mutant NSCLC. In view of the high overall response noted with dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant NSCLC and the success of other targeted therapies in early lines of treatment, future research will determine the position of dabrafenib plus trametinib as an early treatment option compared with platinum-based chemotherapy or immunotherapy options.

The safety profile recorded in this study was manageable and similar to that for dabrafenib plus trametinib in patients with unresectable or metastatic melanoma.[12 and 33] Dabrafenib plus trametinib provides a clear clinical benefit in patients with *BRAF*^{V600E}-mutant NSCLC, but grade 3–4 adverse events were noted in nearly half of patients in this study. Notably, experience with the treatment combination in patients with *BRAF*^{V600}-mutant melanoma has shown that most grade 3–4 adverse events can be managed through dose modification, providing a framework for physicians to manage patients and mitigate risk of unacceptable toxicity. In our trial, four (80%) of five patients with ECOG performance status of 2 at baseline had a confirmed response and none discontinued due to adverse events. Although the sample is small, this suggests that combination of dabrafenib plus trametinib could be safely given to patients with a baseline ECOG performance status of 2. Similar to previous experiences in melanoma, pyrexia was noted in 30 (36%) of 84 patients with dabrafenib monotherapy in cohort A of this trial[13] and in 26 (46%) of 57 patients with dabrafenib plus trametinib in the current report. Analysis of pyrexia in melanoma showed an association between dabrafenib and hydroxydabrafenib concentrations and pyrexia, although the cause of the reported increase in incidence with dabrafenib plus trametinib remains unclear.[34] Conversely, cutaneous squamous cell carcinoma was noted in ten (12%) of 84 patients with dabrafenib monotherapy and in only two (4%) of 57 patients treated with dabrafenib plus trametinib. Similarly, in previous melanoma studies, combination of MEK and BRAF inhibitors substantially reduced the risk of cutaneous squamous cell carcinoma compared with BRAF inhibitor monotherapy (1–3% *vs* 9–18%). [11, 12 and 33] This finding supports the hypothesis that the addition of MEK inhibitor to BRAF inhibitor therapy can block paradoxical activation of MAPK signalling in *BRAF* wild-type cells and reduce the incidence of cutaneous squamous cell carcinoma. [10 and 35] Haemoptysis was reported as a serious adverse event in two (4%) of 57 patients in this study, which is consistent with other studies in patients with previously treated lung cancer.[36] Haemorrhage has also been noted in patients with metastatic melanoma treated with combination dabrafenib plus trametinib, but the rate of grade 3–4 events was modest and similar between patients treated with the combination and patients receiving dabrafenib monotherapy.[37]

Overall, dabrafenib plus trametinib is a promising new therapy for patients with *BRAF*^{V600E}-mutant NSCLC, with high overall response, a prolonged duration of response, and manageable toxicity. To the best of our knowledge, this report is the first to show a highly effective targeted therapy combination strategy in this patient population, which has few treatment options that can achieve more than 50% overall response and median progression-free survival of

longer than 9 months. The emergence of optimised sequencing strategies and targeted agents including dabrafenib plus trametinib will continue to broaden personalised therapy in NSCLC and improve patient outcomes.

Contributors

PZ did the literature search. DP, BB, JM, JRR, AMD'A, BM, and BEJ conceived and designed the study. DP, BB, P-JS, EQ, FB, TMK, JM, SN, AU, PZ, BM, and BEJ gathered and assembled the data. DP, BB, HJMG, P-JS, CSB, FB, TMK, JM, SN, JRR, AU, AMD'A, PZ, BM, and BEJ analysed and interpreted the data. JRR and AMD'A developed the figures and tables. DP, BB, HJMG, P-JS, EQ, CSB, FB, JM, SN, JRR, AU, AMD'A, PZ, BM, and BEJ wrote the report. DP, BB, HJMG, P-JS, EQ, CSB, FB, TMK, JM, SN, JRR, AU, AMD'A, PZ, BM, and BEJ approved the final report. P-JS and CSB provided study materials or patients.

Declaration of interests

DP acts as an adviser for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Sanofi and has received research funding from Novartis unrelated to this study. BB's institution received a grant from Novartis for this study. HJMG's institution has received payments from Eli Lilly, Merck Sharp & Dohme, and Roche. P-JS has been involved in clinical trials for GlaxoSmithKline and Novartis. EQ has received personal fees from AbbVie, Bristol-Myers Squibb, Clovis, Lilly, Pfizer, and Roche, has received grants from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck Sharp & Dohme, Mundipharma, and Roche, and has received non-financial support from Boehringer Ingelheim. CSB's institution received a grant for this study from Novartis and CSB has received personal fees from Novartis. FB has received personal fees from Novartis. SN has received personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, and Roche. AU, PZ, AMD'A, and BM are currently employees of Novartis. AMD'A and BM were employees of GlaxoSmithKline during a portion of the study. AMD'A and BM own stock in GlaxoSmithKline and Novartis and BM owns stock in Incyte and AstraZeneca. BEJ has received personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceuticals, Clovis, Genentech, KEW Group, Merck, and Novartis, and shares of post-market revenue for an EGFR genotyping patent. All other authors declare no competing interests.

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