Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Michael A Davies, Philippe Saiag*, Caroline Robert, Jean-Jacques Grob, Keith T Flaherty, Ana Arance, Vanna Chiarion-Sileni, Luc Thomas, Thierry Lesimple, Laurent Mortier, Stergios J Moschos, David Hogg, Iván Márquez-Rodas, Michele Del Vecchio, Céleste Lebbé, Nicolas Meyer, Ying Zhang, Yingjie Huang, Bijoyesh Mookerjee, Georgina V Long*

Summary

Background Dabrafenib plus trametinib improves clinical outcomes in *BRAF*^{V600}-mutant metastatic melanoma without brain metastases; however, the activity of dabrafenib plus trametinib has not been studied in active melanoma brain metastases. Here, we report results from the phase 2 COMBI-MB trial. Our aim was to build on the current body of evidence of targeted therapy in melanoma brain metastases through an evaluation of dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases.

Methods This ongoing, multicentre, multicohort, open-label, phase 2 study evaluated oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) in four patient cohorts with melanoma brain metastases enrolled from 32 hospitals and institutions in Europe, North America, and Australia: (A) *BRAF*^{V600E}-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (B) *BRAF*^{V600E}-positive, asymptomatic melanoma brain metastases, with previous local brain therapy, and an ECOG performance status of 0 or 1; (C) *BRAF*$^{V600D/K/R}$-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0 or 1; and (D) *BRAF*$^{V600D/E/K/R}$-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2. The primary endpoint was investigator-assessed intracranial response in cohort A in the all-treated-patients population. Secondary endpoints included intracranial response in cohorts B, C, and D. This study is registered with ClinicalTrials.gov, number NCT02039947.

Findings Between Feb 28, 2014, and Aug 5, 2016, 125 patients were enrolled in the study: 76 patients in cohort A; 16 patients in cohort B; 16 patients in cohort C; and 17 patients in cohort D. At the data cutoff (Nov 28, 2016) after a median follow-up of 8·5 months (IQR 5·5–14·0), 44 (58%; 95% CI 46–69) of 76 patients in cohort A achieved an intracranial response. Intracranial response by investigator assessment was also achieved in nine (56%; 95% CI 30–80) of 16 patients in cohort B, seven (44%; 20–70) of 16 patients in cohort C, and ten (59%; 33–82) of 17 patients in cohort D. The most common serious adverse events related to study treatment were pyrexia for dabrafenib (eight [6%] of 125 patients) and decreased ejection fraction (five [4%]) for trametinib. The most common grade 3 or worse adverse events, regardless of study drug relationship, were pyrexia (four [3%] of 125) and headache (three [2%]).

Interpretation Dabrafenib plus trametinib was active with a manageable safety profile in this melanoma population that was consistent with previous dabrafenib plus trametinib studies in patients with *BRAF*^{V600}-mutant melanoma without brain metastases, but the median duration of response was relatively short. These results provide evidence of clinical benefit with dabrafenib plus trametinib and support the need for additional research to further improve outcomes in patients with melanoma brain metastases.

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*These authors contributed equally

Melanoma Medical Oncology and Systems Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (M A Davies MD); **Service de Dermatologie Générale et Oncologique, Hôpital A Paré, Assistance Publique-Hôpitaux de Paris, Boulogne Billancourt, France** (Prof P Saiag MD); **EA 4340, Université Versailles Saint-Quentin-en-Yvelines, Boulogne Billancourt, France** (Prof P Saiag); **Gustave Roussy, Département de Médecine Oncologique, Service de Dermatologie et Université Paris-Sud, Faculté de Médecine, Villejuif, France** (Prof C Robert MD); **Service de Dermatologie, Centre Hospitalo-Universitaire Timone, Aix Marseille University, Marseille, France** (Prof J-J Grob MD); **Developmental Therapeutics and Melanoma Programs, Massachusetts General Hospital Cancer Center, Boston, MA, USA** (Prof K T Flaherty MD); **Department of Medical Oncology, Hospital Clinic of Barcelona, Carrer de Villarroel, Barcelona, Spain** (A Arance MD); **Melanoma and Oesophageal Oncology Unit, Veneto Oncology Institute-IRCCS, Padova, Italy** (V Chiarion-Sileni MD); **Service de Dermatologie, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France** (Prof L Thomas MD); **Oncologie Dermatologique, Centre Eugène Marquis, Rennes, France** (T Lesimple MD); **Clinique de Dermatologie,**

Introduction

Among common cancers, metastatic melanoma has the highest risk of spreading to the CNS.[1,2] The development of brain metastases in patients with melanoma has been observed at an incidence of up to 43% in clinical studies and 75% in autopsy studies.[2,3] Historically, brain metastases in patients with metastatic melanoma have been associated with poor overall survival (median 4–5 months), and the poorest outcomes are observed in those presenting with neurological symptoms and leptomeningeal involvement.[4,5] Various targeted therapies (ie, BRAF and MEK inhibitors) and checkpoint inhibitor immunotherapies (ie, anti-CTLA-4 and anti-PD-1 antibodies, alone or combined) available for the treatment of *BRAF*^{V600}-mutant melanoma have significantly improved clinical outcomes in patients with metastatic disease.[6–10] However, patients with active brain metastases have typically been excluded from large trials to date, and treatments specifically indicated for the treatment of melanoma brain metastases remain an unmet need.

In the phase 2 BREAK-MB trial,[11] dabrafenib monotherapy showed clinical activity and had a manageable

Unité d'Onco-Dermatologie, Le Centre Hospitalier Régional Universitaire de Lille, University Lille 2, Lille, France (Prof L Mortier MD); **Melanoma Program, Medical Oncology, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA** (S J Moschos MD); **Clinical Cancer Research Unit, Princess Margaret Cancer Centre, Toronto, ON, Canada** (D Hogg MD); **Servicio de Oncología Médica; Hospital General Universitario Gregorio Marañon, Madrid, Spain** (Prof I Márquez-Rodas MD); **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (Prof M Del Vecchio MD); **APHP Dermatology and CIC Departments, INSERM U976, University Paris Diderot, Hôpital Saint Louis Paris, Paris, France** (Prof C Lebbé MD); **Medical Oncology, Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France** (Prof N Meyer MD); **Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA** (Y Zhang PhD, Y Huang MD, B Mookerjee MD); **and Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia** (Prof G V Long MD)

Correspondence to:
Dr Michael A Davies, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
mdavies@mdanderson.org

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical studies published up to March 7, 2017, with the search terms "BRAF", "melanoma", and "brain metastases", and identified 144 articles, of which four were primary analyses of phase 1 or 2 clinical trials of BRAF inhibitor regimens in patients with *BRAF*^{V600}-mutant melanoma brain metastases. BRAF inhibitor monotherapy has previously been shown to have clinical activity and tolerability in patients with *BRAF*-mutant melanoma who developed metastases in the brain. Although the BRAF and MEK inhibitor combination therapy has been shown to be superior to BRAF inhibitor monotherapy in patients with *BRAF*^{V600}-mutant metastatic melanoma without brain metastases, the clinical effect of this regimen on melanoma brain metastases has not been characterised.

Added value of this study

Intracranial outcomes showed that dabrafenib plus trametinib was active in patients with *BRAF*^{V600}-mutant melanoma brain metastases and the primary study endpoint was met; however, responses did not last as long as those previously observed for the combination in patients with melanoma without brain metastases. No unexpected safety issues were observed with dabrafenib plus trametinib in this setting. Our findings represent the first report, to our knowledge, of a phase 2 trial evaluating BRAF and MEK inhibitor combination therapy in patients with melanoma brain metastases and provide evidence that clinical benefit and tolerability are achievable with dabrafenib plus trametinib in a subset of patients with *BRAF*^{V600}-mutant melanoma that has metastasised to the brain.

Implications of all the available evidence

Continued follow-up in this study is necessary to determine the full effect of dabrafenib plus trametinib on overall survival in this setting; however, these preliminary results support the use of this targeted therapy combination as a treatment option for these patients, in whom effective treatments remain a critical unmet medical need.

safety profile in patients with *BRAF*^{V600E}-mutant melanoma brain metastases (n=139), including patients with or without previous local treatment for brain metastases. In patients with *BRAF*^{V600E}-mutant melanoma without previous local treatment (n=74), 39% of patients achieved an overall intracranial response and 38% achieved an overall response by investigator assessment. In patients with *BRAF*^{V600E}-mutant melanoma with previous local treatment (n=65), 31% of patients achieved both an investigator-assessed overall intracranial response and an overall response. In both *BRAF*^{V600E} groups, 6-month overall survival was 61%. Fewer patients with *BRAF*^{V600K}-mutant disease included in the study (n=33) had a response, regardless of whether they had received previous local treatment (overall intracranial response was achieved in 22% of patients who did not have previous treatment and 7% of patients who had previous treatment). Small cohorts of molecularly unselected patients with asymptomatic brain metastases have also been shown to have a response to ipilimumab (16% of 51 patients achieved a brain metastasis response) and pembrolizumab (22% of 18 patients achieved a brain metastasis response) in prospective clinical trials.[12,13]

The combination of dabrafenib and trametinib has been shown to improve progression-free survival and overall survival compared with that seen for BRAF inhibitor monotherapy, with a manageable safety profile in phase 2 and phase 3 trials of patients with *BRAF*$^{V600E/K}$-mutant stage IIIC unresectable or stage IV metastatic melanoma without brain metastases.[6,7,14–19] However, this combination targeted therapy has not been previously evaluated prospectively in patients with *BRAF*^{V600}-mutant melanoma brain metastases.

Here, we report the primary analysis of the phase 2 COMBI-MB trial evaluating dabrafenib plus trametinib in patients with active *BRAF*^{V600}-mutant melanoma brain metastases.

Methods

Study design and patients

This multicentre, open-label, multicohort, phase 2 trial evaluated the activity and safety of dabrafenib plus trametinib in four patient cohorts enrolled from 32 hospitals and institutions in Europe, North America, and Australia (appendix p 9): cohort A included patients with *BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; cohort B included patients with *BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, and an ECOG performance status of 0 or 1; cohort C included patients with *BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, and an ECOG performance status of 0 or 1; and cohort D included patients with *BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy, and an ECOG performance status of 0, 1, or 2 (appendix p 2).

Patients aged 18 years or older with histologically confirmed stage IV metastatic *BRAF*$^{V600D/E/K/R}$-mutant cutaneous melanoma, diagnosed using the THxID BRAF assay (investigational use only; bioMerieux, Marcy-l'Étoile, France) at a central reference laboratory, were eligible for enrolment. Target lesions could be 0·5–4·0 cm in diameter; we excluded patients with the presence of any leptomeningeal disease or parenchymal brain metastasis measuring more than 4·0 cm in diameter.

Patients with any *RAS*-mutant positive malignancy, history of malignancy other than the disease under study within 3 years (except completely resected non-melanoma skin cancer or patients with indolent malignancies), history of hepatitis B virus or hepatitis C virus without laboratory evidence of clearance, and any other serious or unstable pre-existing medical conditions or psychiatric disorders that could interfere with patient safety, consent, or compliance to study procedures were not eligible. Adequate organ function was also required for eligibility. Patients could have received up to two previous systemic therapies for metastatic melanoma, except for BRAF or MEK inhibitors. Previous temozolomide therapy for brain metastases and adjuvant interferon were permitted and did not count towards the maximum of two previous systemic treatments. Previous systemic anticancer treatment in the 3 weeks preceding the first dose of the combination, and chemotherapy without delayed toxicity in the 2 weeks preceding the first dose of the combination, were not permitted. Previous systemic treatment in the adjuvant setting was permitted; however, ipilimumab treatment must have ended at least 8 weeks before enrolment. In cohorts including patients who had previously received local therapies, previous treatments could have included, but were not limited to, craniotomy, whole-brain radiotherapy, and stereotactic radiosurgery. Treatment with stereotactic radiosurgery must have occurred at least 14 days before the start of study treatment and whole-brain radiotherapy must have occurred at least 28 days before the start of study treatment. Eligible patients with previous local therapy to all brain lesions must have shown progression of pre-existing target lesions per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria. For cohorts A, B, and C (but not D), patients who were receiving concomitant corticosteroids must have been on a stable or decreasing dose for at least 1 month before study treatment initiation, and no prophylactic or preventative antiepileptic therapy was permitted.

The study protocol was approved by the institutional review board or human research ethics committee at each participating institution (appendix p 10). The study was conducted in accordance with both the Declaration of Helsinki and the International Conference of Harmonisation Good Clinical Practice. All participants provided written informed consent.

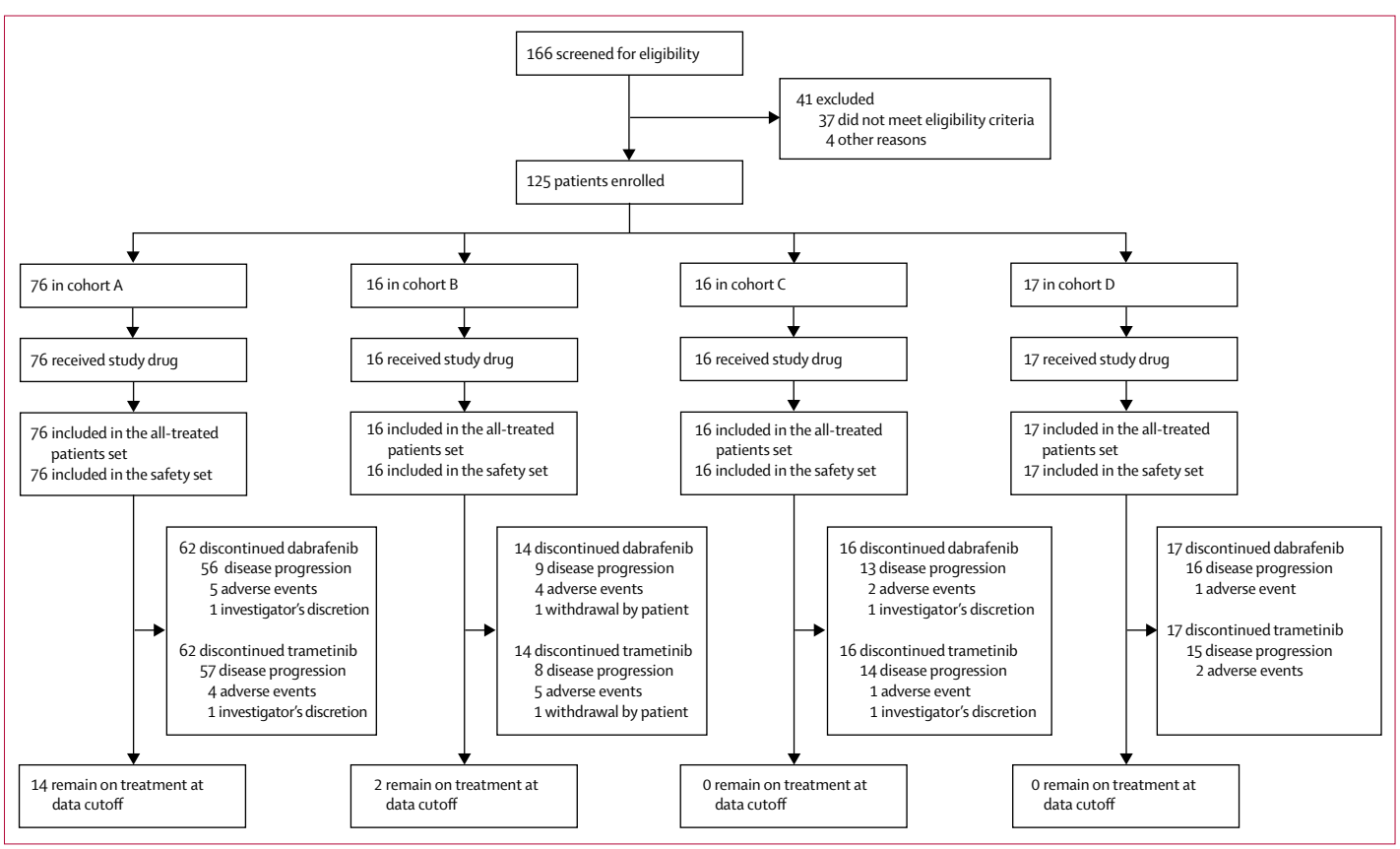

***Figure 1*: Trial profile**

Data cutoff was on Nov 28, 2016. Cohort A=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Cohort B=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, ECOG performance status of 0 or 1. Cohort C=*BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, ECOG performance status of 0 or 1. Cohort D=*BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy ECOG performance status of 0, 1, or 2.

	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
Age (years)				
Median (range)	52·0 (23–84)	54·5 (36–74)	63·0 (44–84)	46·0 (23–68)
<65	60 (79%)	12 (75%)	9 (56%)	16 (94%)
≥65	16 (21%)	4 (25%)	7 (44%)	1 (6%)
Sex				
Male	40 (53%)	10 (63%)	11 (69%)	11 (65%)
Female	36 (47%)	6 (38%)	5 (31%)	6 (35%)
ECOG performance status				
0	50 (66%)	11 (69%)	12 (75%)	9 (53%)
1	25 (33%)	5 (31%)	4 (25%)	6 (35%)
2	1 (1%)*	0	0	2 (12%)
BRAF genotype				
V600E	73 (96%)	16 (100%)	0	15 (88%)
V600K	3 (4%)†	0	14 (88%)	1 (6%)
V600R	0	0	2 (13%)	1 (6%)
V600D	0	0	0	0
Target brain metastases				
1	41 (54%)	7 (44%)	7 (44%)	7 (41%)
2	20 (26%)	7 (44%)	6 (38%)	7 (41%)
3	7 (9%)	2 (13%)	2 (13%)	1 (6%)
4	4 (5%)	0	0	1 (6%)
5	4 (5%)	0	1 (6%)	1 (6%)
SLD of target intracranial lesions (mm)	20 (6–117)	14 (5–40)	20 (5–61)	33 (10–84)
Extracranial metastases				
No	8 (11%)	4 (25%)	0	5 (29%)
Yes	68 (89%)	12 (75%)	16 (100%)	12 (71%)
Lactate dehydrogenase concentration				
Normal (≤ULN)	48 (63%)	13 (81%)	10 (63%)	12 (71%)
Elevated (>ULN)	28 (37%)	3 (19%)	6 (38%)	5 (29%)
Receiving steroid therapy				
Previous treatment	3 (4%)	1 (6%)	0	5 (29%)
On-treatment or post-treatment	38 (50%)	8 (50%)	9 (56%)	15 (88%)
Previous systemic anticancer treatment				
No	59 (78%)	11 (69%)	13 (81%)	10 (59%)
Yes	17 (22%)	5 (31%)	3 (19%)	7 (41%)

Data are median (range) or n (%). Cohort A=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Cohort B=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, ECOG performance status of 0 or 1. Cohort C=*BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, ECOG performance status of 0 or 1. Cohort D=*BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy ECOG performance status of 0, 1, or 2. ECOG=Eastern Cooperative Oncology Group. SLD=sum of lesion diameters. ULN=upper limit of normal. *Patient had ECOG performance status 1 at time of screening and enrolment. †Patients were enrolled on the basis of *BRAF*^{V600E} status, but were found to be *BRAF*^{V600K} on central confirmation.

***Table 1*: Baseline characteristics**

Procedures

Patients in each cohort were given oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) until evidence of disease progression, death, or unacceptable toxicity. Dose interruptions or dose reductions down to 75 mg twice per day for dabrafenib and 1 mg once per day for trametinib were permitted to manage adverse events. If a dose reduction of below 75 mg twice daily for dabrafenib and below 1 mg once daily for trametinib was required, the combination study treatment was discontinued. If a dose reduction below 75 mg twice daily for dabrafenib was required, dabrafenib was permanently discontinued, but trametinib could be continued. If a dose reduction below 1 mg once daily for trametinib was required, trametinib was permanently discontinued, but dabrafenib could be continued.

While patients were on study treatment, palliative radiotherapy was permitted for non-target lesions that were either new or present at baseline; however, patients were censored from progression assessment at the time of initiating a new anticancer therapy (either alone or in combination with dabrafenib plus trametinib).

Intracranial disease was assessed by a neuroradiologist, a trained radiologist, or a neurosurgeon at baseline (up to 28 days before the first study dose), week 4, week 8, and every 8 weeks until week 40, using gadolinium contrast-enhanced MRI—the only method accepted for assigning intracranial lesions. After week 40, disease assessments were to be done every 12 weeks. We assessed extracranial disease at the same timepoints using contrast-enhanced CT or MRI. Intracranial disease could be assessed only by contrast-enhanced MRI, and MRI scan slices of 1 mm were required for brain metastases that were 5 mm to less than 10 mm. RECIST was modified to be extended to include up to five intracranial and up to five extracranial target lesions; intracranial target lesions 5–40 mm in diameter were permitted. Confirmation assessments were done no less than 4 weeks after the criteria for response were initially met. If the criteria for a complete or partial response were not confirmed, then stable disease was considered to be the best response if it was observed for a minimum of 8 weeks. An independent assessment of tumour response and progression was done by Bioclinica (Doylestown, PA, USA). Adverse events were graded throughout the study by the investigator per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), from the first study dose until 30 days after discontinuation of study treatment. Laboratory assessments evaluating chemistry and haematology parameters, were done at screening, on initiating study treatment (baseline), every 4 weeks through week 36, followed by monthly thereafter, and at the time of study discontinuation. An independent data monitoring committee assessed safety periodically until the primary analysis was done.

Outcomes

The primary endpoint was intracranial response in cohort A, defined as the percentage of patients with a confirmed intracranial complete or partial response assessed by the investigator using modified RECIST version 1.1 criteria. Secondary endpoints were intracranial response in cohorts B, C, and D; intracranial disease control, defined as the percentage of patients with

a complete or partial response or stable disease; extracranial response, defined as the percentage of patients with a confirmed extracranial complete or partial response assessed by the investigator using modified RECIST version 1.1 criteria; overall response, defined as the percentage of patients with a confirmed complete or partial response (intracranial or extracranial) by investigator assessment; duration of intracranial, extracranial, and overall response, defined as the time from first documented complete or partial response until the time of disease progression; progression-free survival, defined as the interval between the first dose of study treatment and the earliest date of disease progression or death from any cause; overall survival, defined as the time from first dose until death due to any cause; and safety, measured by the frequency and severity of adverse events per skin, laboratory, vital-sign, cardiac function, and neurological assessment data.

Statistical analysis

This study was designed to assess the null hypothesis of 35% or fewer patients achieving an intracranial response in cohort A and to provide 82% power to detect 50% or more patients in cohort A achieving an intracranial response. Sample sizes were determined to fit the purpose of exploratory analyses and hypothesis generation. We based the sample size of cohort A on the hypothesised improvement in intracranial response. We regarded assessments of intracranial response in other cohorts as exploratory analyses; thus, there were no sample size calculations for cohorts B–D.

We designed the study to have a formal interim analysis for cohort A with a statistical decision rule for futility only, without p-value adjustment. The interim analysis was to take place after 22 patients were treated and had the opportunity for two or more disease assessments. The responses used in this interim analysis did not require confirmation. At least eight of the 22 patients must have had an intracranial response (intracranial complete response or partial response) for the trial to continue. If seven or fewer patients had an intracranial response, this would have been considered as evidence that the null hypothesis was true. Ten of 22 patients had an intracranial response by the time the interim analysis was done (cutoff date Jan 30, 2015); thus, the decision was made to continue the trial. The results presented here are from the primary analysis of activity, which was done when all patients in cohort A had the opportunity for 3 post-baseline disease assessments. The analysis in this Article is regarded as an interim analysis of progression-free survival and overall survival. The final analysis of progression-free survival, overall survival, and safety will occur when 70% of the total enrolled population have died or are lost to follow-up.

We summarised response outcomes using point estimates and two-sided 95% CIs calculated using the unconditional exact method. All analyses were done in the all-treated-patients population (patients who received at least one dose of study drug). We summarised duration of response outcomes, progression-free survival, and overall survival using Kaplan-Meier estimates along with two-sided 95% CIs calculated using the Brookmeyer and Crowley method. Additional endpoint definitions and censoring methods are described in the appendix (p 1). We summarised adverse events by the number and proportion of total patients, and by system organ class and preferred term, with separate summaries provided for all,

	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
Intracranial response				
Overall intracranial response (CR+PR)	44 (58%; 46–69)	9 (56%; 30–80)	7 (44%; 20–70)	10 (59%; 33–82)
Intracranial disease control (CR+PR+SD)	59 (78%)	14 (88%)	12 (75%)	14 (82%)
Intracranial CR	3 (4%)	1 (6%)	0	1 (6%)
Intracranial PR	41 (54%)	8 (50%)	7 (44%)	9 (53%)
Intracranial SD	15 (20%)	5 (31%)	5 (31%)	4 (24%)
Intracranial PD	14 (18%)	1 (6%)	4 (25%)	3 (18%)
Not evaluable	3 (4%)	1 (6%)	0	0
Intracranial duration of response				
Events	29/44 (66%)	6/9 (67%)	4/7 (57%)	8/10 (80%)
Median (95% CI; months)	6·5 (4·9–10·3)	7·3 (3·6–12·6)	8·3 (1·3–15·0)	4·5 (2·8–5·9)
Response at 6 months	63% (45–76)	73% (28–93)	67% (19–90)	13% (1–43)
Extracranial response				
Overall extracranial response (CR+PR)	42 (55%; 43–67)	7 (44%; 20–70)	12 (75%; 48–93)	7 (41%; 18–67)
Extracranial disease control (CR+PR+SD)	60 (79%)	11 (69%)	15 (94%)	11 (65%)
Extracranial CR	3 (4%)	1 (6%)	0	0
Extracranial PR	39 (51%)	6 (38%)	12 (75%)	7 (41%)
Extracranial SD	15 (20%)	2 (13%)	2 (13%)	3 (18%)
Extracranial non-CR, non-PD*	3 (4%)	2 (13%)	1 (6%)	1 (6%)
Extracranial PD	6 (8%)	0	0	1 (6%)
Not evaluable	10 (13%)	5 (31%)	1 (6%)	5 (29%)
Extracranial duration of response				
Events	16/42 (38%)	0/7	6/12 (50%)	4/7 (57%)
Median (95% CI; months)	10·2 (5·8–NE)	NE (NE–NE)	4·9 (3·0–NE)	5·9 (1·8–NE)
Response at 6 months	69% (50–82)	100% (100–100)†	40% (10–70)	48% (8–81)
Overall response				
Overall response (CR+PR)	44 (58%; 46–69)	9 (56%; 30–80)	7 (44%; 20–70)	11 (65%; 38–86)
Overall disease control (CR+PR+SD)	60 (79%)	14 (88%)	12 (75%)	14 (82%)
Overall CR	1 (1%)	0	0	0
Overall PR	43 (57%)	9 (56%)	7 (44%)	11 (65%)
Overall SD	16 (21%)	5 (31%)	5 (31%)	3 (18%)
Overall PD	14 (18%)	1 (6%)	4 (25%)	3 (18%)
Not evaluable	2 (3%)	1 (6%)	0	0
Overall duration of response				
Events	32/44 (73%)	5/9 (56%)	6/7 (86%)	9/11 (82%)
Median (95% CI; months)	6·5 (4·9–10·3)	12·5 (5·3–NE)	6·6 (1·3–16·3)	4·5 (2·8–11·2)
Response at 6 months	57% (41–71)	86% (33–98)	50% (11–80)	23% (3–52)

(Table 2 continues on next page)

	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
(Continued from previous page)				
Progression-free survival (interim)				
Events	58 (76%)	10 (63%)	14 (88%)	15 (88%)
Median (95% CI; months)	5·6 (5·3–7·4)	7·2 (4·7–14·6)	4·2 (1·7–6·5)	5·5 (2·8–7·3)
6-month progression-free survival	44% (32–56)	71% (40–88)	31% (10–55)	46% (21–67)
12-month progression-free survival	19% (10–31)	47% (20–71)	16% (3–39)	8% (1–30)
Overall survival (interim)				
Events	44 (58%)	7 (44%)	13 (81%)	13 (76%)
Median (95% CI; months)	10·8 (8·7–19·6)	24·3 (7·9–NE)	10·1 (4·6–17·6)	11·5 (6·8–22·4)
6-month overall survival	79% (68–87)	81% (52–94)	69% (40–86)	88% (61–97)
12-month overall survival	46% (33–58)	69% (40–86)	44% (20–66)	44% (20–66)

Data are n (%; 95% CI), n (%), % (95% CI), or n/N (%). Overall response was defined as the percentage of patients with a confirmed overall complete or partial response by assessment using the RECIST 1.1 criteria. To determine the overall response, all target and non-target lesions were assessed using modified RECIST 1.1 criteria. Cohort A=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Cohort B=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, ECOG performance status of 0 or 1. Cohort C=*BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, ECOG performance status of 0 or 1. Cohort D=*BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy ECOG performance status of 0, 1, or 2. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. NE=not estimable. *Patients with non-measurable disease at baseline; the response rate relates to the response of the non-target lesion. †No progression event occurred up to the data cutoff date.

***Table 2*: Investigator-assessed disease response and survival outcomes**

drug-related, and serious adverse events and adverse events leading to study treatment discontinuation. The datasets for assessment of all safety endpoints included all safety data collected on patients in the all-treated-patients population. Statistical analyses were done using SAS (version 9.3).

This study is registered with ClinicalTrials.gov, number NCT02039947.

Role of the funding source

The study was designed by the authors and funder. Data were collected by the study site staff and monitored by the funder, and the funder was involved in the data analysis, data interpretation, and writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 28, 2014, and Aug 5, 2016, 125 patients were enrolled, of whom 76 were in cohort A, 16 were in cohort B, 16 were in cohort C, and 17 were in cohort D (figure 1). Lactate dehydrogenase concentrations were elevated (higher than the upper limit of normal) in 28 (37%) of 76 patients in cohort A, three (19%) of 16 patients in cohort B, six (38%) of 16 patients in cohort C, and five (29%) of 17 patients in cohort D, and extracranial metastases were present in 68 (89%) of 76 patients in cohort A, 12 (75%) of 16 patients in cohort B, 16 (100%) of 16 patients in cohort C, and 12 (71%) of 17 patients in cohort D (table 1). At the data analysis cutoff, Nov 28, 2016, 14 (18%) of 76 patients in cohort A and two (13%) of 16 patients in cohort B remained on study treatment, whereas all patients in cohorts C and D had discontinued study treatment (appendix p 2). Median follow-up time at the data cutoff (ie, interval between the date of first study treatment dose to the last patient contact date), which varied across cohorts because of differences in timing of enrolment dates for each cohort, was 8·5 months (IQR 5·5–14·0) in cohort A, 20·0 months (8·5–23·5) in cohort B, 9·5 months (4·5–17·5) in cohort C, and 11·0 months (IQR 6·0–20·0) in cohort D. At the data cutoff, eight (50%) of 16 patients in cohort B were still ongoing (on study treatment or in follow-up), which was higher than those ongoing in cohort A (31 [41%] of 76 patients), cohort C (three [19%] of 16 patients), and cohort D (two [12%] of 17 patients; appendix p 2).

44 (58%; 95% CI 46–69) of 76 patients in cohort A had an investigator-assessed intracranial response, including three (4%) who achieved a complete response and 41 (54%) who achieved a partial response (table 2; figure 2A). Median duration of investigator-assessed intracranial response was 6·5 months (95% CI 4·9–10·3) in cohort A (table 2; figure 3A), which was supported by independent review (appendix p 6). Intracranial response was also observed in nine (56%) of 16 patients in cohort B, seven (44%) of 16 patients in cohort C, and ten (59%) of 17 patients in cohort D (table 2; figure 2B–D). Extracranial responses were observed in 42 (55%; 95% CI 43–67) of 76 patients in cohort A, which lasted a median of 10·2 months (95% CI 5·8 to not estimable), and in seven (44%) of 16 patients in cohort B, 12 (75%) of 16 patients in cohort C, and seven (41%) of 17 patients in cohort D (table 2). Overall responses were achieved by 44 (58%; 95% CI 46–69) of 76 patients in cohort A, which lasted a median of 6·5 months (95% CI 4·9–10·3), and in nine (56%) of 16 patients in cohort B, seven (44%) of 16 patients in cohort C, and 11 (65%) of 17 patients in cohort D (table 2). Disease control in all cohorts, and duration of extracranial, intracranial, and overall responses for cohorts B, C, and D are shown in table 2. Most of the intracranial, extracranial, and overall responses observed in cohort A occurred by week 4 of study treatment, and by week 4 or week 8 in cohorts B, C, and D (appendix p 2).

At the time of analysis, 58 (76%) of 76 patients in cohort A had a progression-free survival event, with an interim median investigator-assessed progression-free survival of 5·6 months (95% CI 5·3–7·4; table 2, figure 3B), which was supported by independent review (appendix p 6); 6-month progression-free survival was 44% (95% CI 32–56) and 12-month progression-free survival was 19% (10–31; table 2). Median progression-free survival in cohorts B, C, and D is shown in table 2 and the appendix (p 7). Most patients in all cohorts had progressive disease in intracranial lesions only (66 [53%] of 125 patients) or in

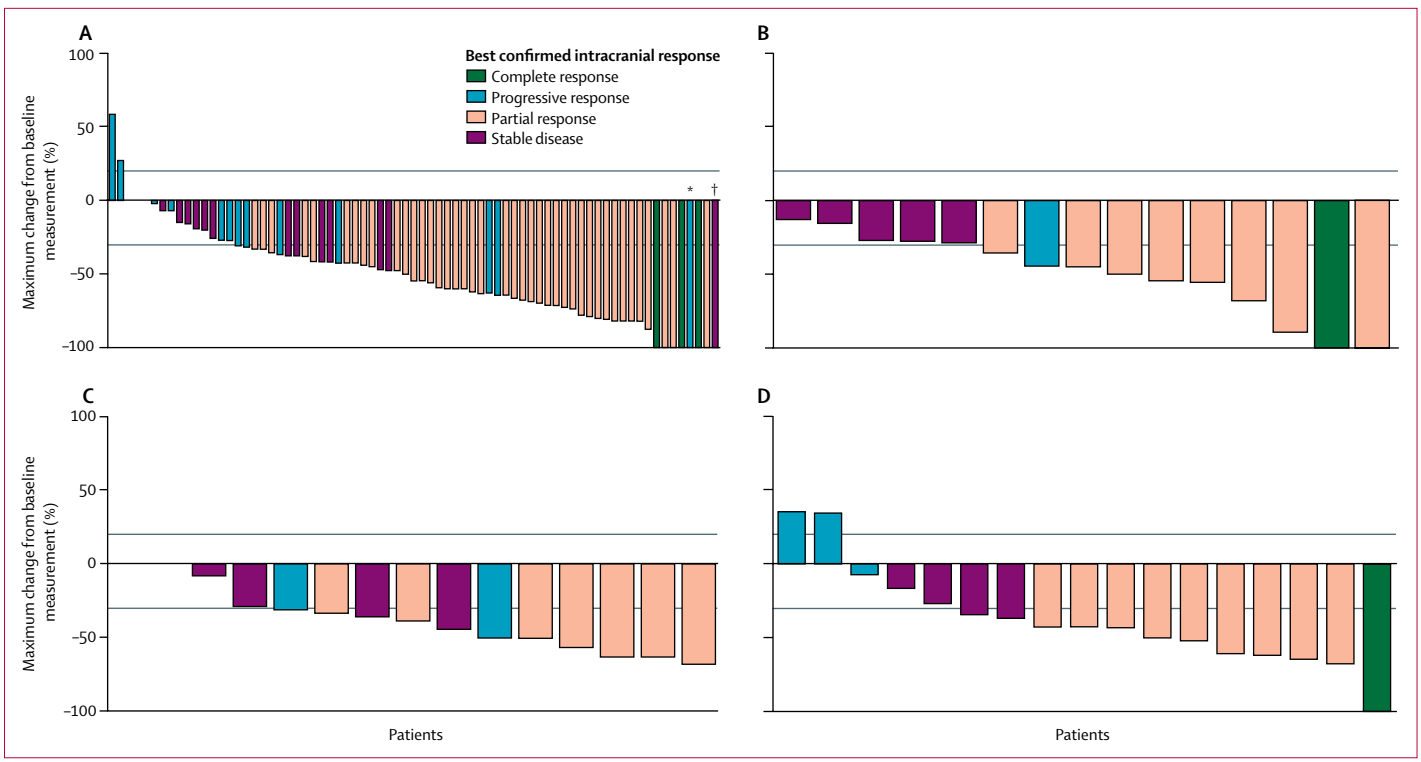

***Figure 2*: Confirmed maxiumum reduction in intracranial target lesion in cohort A (A), cohort B (B), cohort C (C), and cohort D (D)**

Grey lines at 20% represent threshold of progression and grey lines at −30% represent threshold of partial response. Cohort A=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Cohort B=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, ECOG performance status of 0 or 1. Cohort C=*BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, ECOG performance status of 0 or 1. Cohort D=*BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy ECOG performance status of 0, 1, or 2. Three patients in cohort A were not assessable for intracranial response, one patient in cohort B was not assessable for intracranial response, one patient in cohort C was regarded as not assessable for intracranial response at the first visit and was, therefore, not included in the calculations for this figure, according to the study analysis plan. *Patient had a complete response in the target lesion, but the best confirmed response was determined to be progressive disease due to development of an unequivocal new lesion. †Patient had an unconfirmed complete response, but a best confirmed response was stable disease.

both intracranial and extracranial lesions (28 [22%]; appendix p 2). The most common type of subsequent systemic therapy received in patients who progressed in all cohorts was immunotherapy, including anti-PD-1 and anti-CTLA-4 regimens (appendix p 3). Some patients also had on-treatment or post-treatment anticancer surgery or radiotherapy (appendix p 3).

At the time of analysis, median time on study treatment across cohorts was 6·0 months (IQR 3·0–11·0), with 24 (19%) of 125 patients treated with dabrafenib plus trametinib for more than 12 months. With treatment or follow-up ongoing for 44 (35%) of 125 patients at the time of analysis, interim median overall survival was 10·8 months (95% CI 8·7–19·6) in cohort A, with 6-month overall survival of 79% (68–87) and 12-month overall survival of 46% (33–58; table 2, figure 3C, appendix p 8). Overall survival results in cohorts B, C, and D are shown in table 2 and the appendix (p 8).

Adverse events of any grade, regardless of study drug relationship, were observed in 123 (98%) of 125 patients, with 60 (48%) of 125 patients reporting one or more grade 3 or 4 event (table 3), and 44 (35%) of 125 patients reporting serious adverse events (appendix p 4). 108 (86%) of 125 patients had adverse events considered to be related to study treatment (appendix p 4); the most common serious adverse events related to study treatment were pyrexia for dabrafenib (eight [6%] of 125 patients) and decreased ejection fraction (five [4%]) for trametinib (appendix p 5). The most common grade 3 or worse adverse events, regardless of study drug relationship, were pyrexia (four [3%] of 125) and headache (three [2%]). Dose interruptions were recorded for 62 (50%) of 125 patients and reductions due to adverse events were recorded for 28 (22%) patients (appendix p 4). Discontinuations due to adverse events occurred in 12 (10%) of 125 patients (appendix p 4), mostly due to decreased ejection fraction (four [3%] of 125 patients; three [4%] of 76 patients in cohort A and one [6%] of 17 patients in cohort D) and pyrexia (three [2%] of 125 patients; one [1%] of 76 patients in cohort A, two [13%] of 16 patients in cohort B). One patient in cohort A had a fatal serious adverse event of intracranial tumour haemorrhage, which was not deemed to be related to study treatment. The primary cause of death in all cases in all cohorts was deemed to be related to cancer, disease progression, or complications due to melanoma.

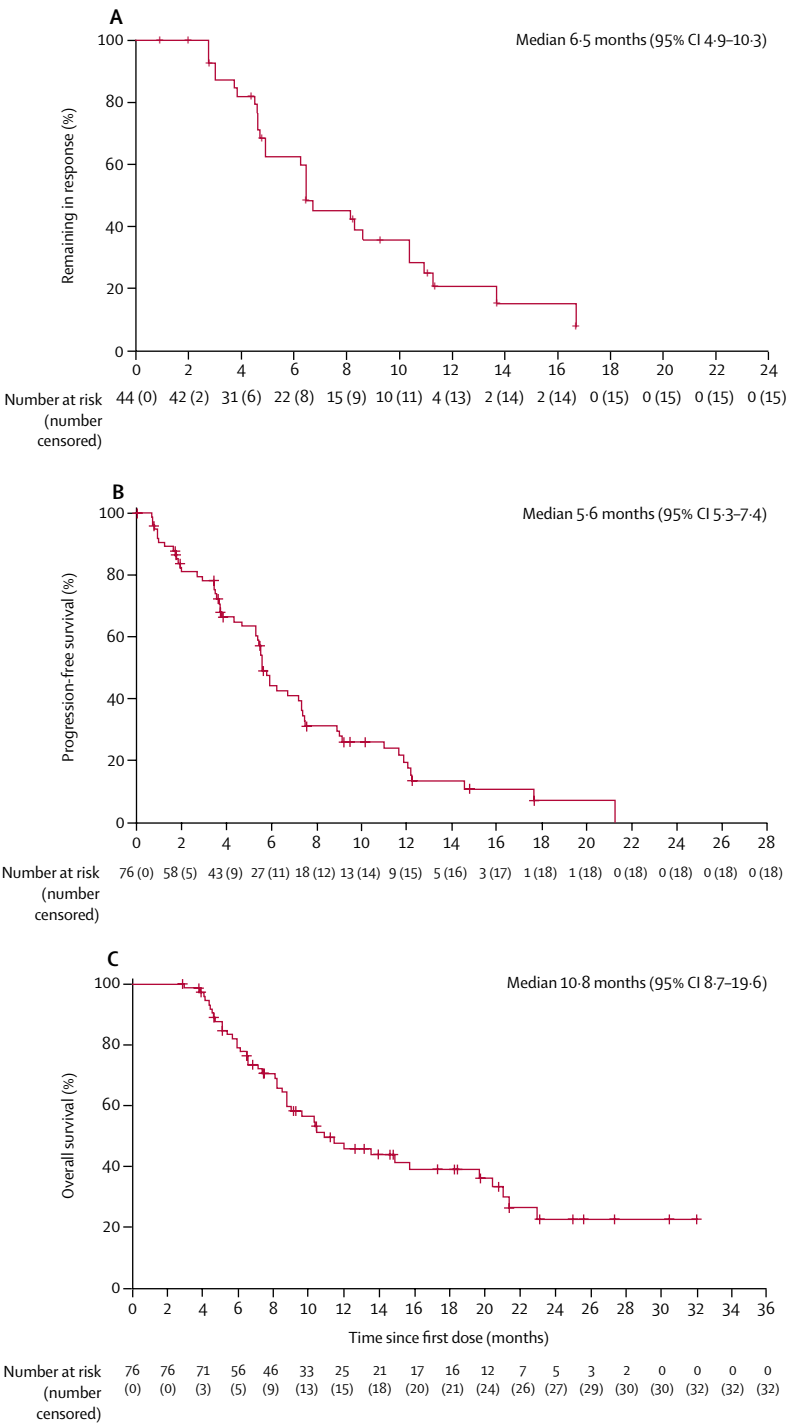

***Figure 3*: Investigator-assessed duration of intracranial response (A), progression-free survival (B), and preliminary overall survival (C) in cohort A**
Crosses denote censored patients.

Discussion

This primary analysis of the COMBI-MB study, representing the first report, to our knowledge, of a phase 2 trial evaluating BRAF and MEK inhibitor combination therapy in patients with *BRAF*^{V600E}-mutant melanoma brain metastases, provides evidence of activity of dabrafenib plus trametinib in patients with active melanoma brain metastases. The primary endpoint of investigator-assessed intracranial response in cohort A was met. Intracranial responses were also observed in cohorts B, C, and D; however, due to the sample sizes of these cohorts, these findings are considered exploratory and hypothesis generating. Furthermore, dabrafenib and trametinib had a manageable safety profile in this population. The clinical benefits experienced by patients treated with dabrafenib plus trametinib in this study were improved over historic outcomes in patients with melanoma brain metastases treated with local therapies (eg, median overall survival of 3·4 months after whole-brain radiotherapy).[20] However, the durability of clinical responses and disease control were relatively short compared with those in previous trials in patients without melanoma brain metastases. For example, median duration of overall response in this study (eg, 6·5 months in cohort A) was generally shorter than that observed in patients without melanoma brain metastases (eg, 12·0 months in the phase 3 study COMBI-d).[17]

The findings of this study suggest that intracranial responses in patients with *BRAF*^{V600}-mutant melanoma brain metastases were improved with dabrafenib and trametinib combination therapy compared with previously reported analyses of BRAF inhibitor monotherapy in this setting. Single-agent vemurafenib was associated with intracranial responses in 16% of patients with symptomatic brain metastases and previous CNS-directed therapy, and single-agent dabrafenib has been associated with intracranial responses in 31% of patients with asymptomatic active brain metastases who had previous local therapy and in 39% of patients with asymptomatic active brain metastases who did not previously have therapy.[11,21]

In a phase 2 study of ipilimumab in patients with melanoma brain metastases, eight (16%) of 51 asymptomatic patients not requiring steroids and one (5%) of 21 symptomatic patients receiving steroids to control neurological symptoms or perilesional oedema achieved a CNS response, with a median overall survival of 7·0 months for asymptomatic patients and 3·7 months for symptomatic patients.[12] In a phase 2 study of pembrolizumab, which excluded patients receiving steroids to control neurological symptoms or perilesional oedema, four (22%) of 18 patients with untreated or progressive melanoma brain metastases had a brain metastasis response lasting at least 4–10 months.[13] In part 4 of the phase 1 CheckMate 038 study,[22] in patients with active melanoma brain metastases, nivolumab led to an objective response (as defined by RECIST version 1.1) in five (50%) of ten patients both when given alone and when given in combination with ipilimumab, with a median

	Cohort A (n=76)				Cohort B (n=16)				Cohort C (n=16)				Cohort D (n=17)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	39 (51%)	30 (39%)	4 (5%)	1 (1%)*	7 (44%)	8 (50%)	1 (6%)	0	7 (44%)	8 (50%)	1 (6%)	0	9 (53%)	7 (41%)	1 (6%)	0
Pyrexia	42 (55%)	2 (3%)	0	0	7 (44%)	0	0	0	7 (44%)	1 (6%)	0	0	7 (41%)	1 (6%)	0	0
Asthenia	27 (36%)	0	0	0	5 (31%)	0	0	0	2 (13%)	1 (6%)	0	0	5 (29%)	0	0	0
Headache	26 (34%)	1 (1%)	0	0	4 (25%)	1 (6%)	0	0	6 (38%)	0	0	0	7 (41%)	1 (6%)	0	0
Nausea	23 (30%)	0	0	0	7 (44%)	0	0	0	4 (25%)	0	0	0	6 (35%)	0	0	0
Diarrhoea	22 (29%)	0	0	0	8 (50%)	0	0	0	3 (19%)	0	0	0	7 (41%)	0	0	0
Vomiting	21 (28%)	1 (1%)	0	0	2 (13%)	0	0	0	2 (13%)	0	0	0	6 (35%)	0	0	0
Chills	16 (21%)	0	0	0	6 (38%)	0	0	0	8 (50%)	0	0	0	5 (29%)	2 (12%)	0	0
Arthralgia	15 (20%)	0	0	0	3 (19%)	0	0	0	2 (13%)	0	0	0	6 (35%)	0	0	0
Myalgia	13 (17%)	0	0	0	5 (31%)	0	0	0	1 (6%)	1 (6%)	0	0	5 (29%)	1 (6%)	0	0
Aspartate aminotransferase increase	11 (14%)	0	0	0	3 (19%)	0	0	0	2 (13%)	0	0	0	3 (18%)	0	0	0
Cough	10 (13%)	0	0	0	2 (13%)	0	0	0	1 (6%)	0	0	0	3 (18%)	0	0	0
Oedema peripheral	10 (13%)	0	0	0	2 (13%)	0	0	0	2 (13%)	0	0	0	3 (18%)	0	0	0
Back pain	9 (12%)	0	0	0	1 (6%)	0	0	0	3 (19%)	0	0	0	2 (12%)	0	0	0
Rash	9 (12%)	0	0	0	6 (38%)	1 (6%)	0	0	3 (19%)	0	0	0	3 (18%)	0	0	0
Constipation	8 (11%)	0	0	0	2 (13%)	0	0	0	4 (25%)	0	0	0	6 (35%)	0	0	0
Decreased appetite	8 (11%)	0	0	0	4 (25%)	0	0	0	7 (44%)	1 (6%)	0	0	3 (18%)	0	0	0
Pain in extremity	8 (11%)	0	0	0	3 (19%)	0	0	0	3 (19%)	0	0	0	2 (12%)	0	0	0
Dizziness	5 (7%)	0	0	0	5 (31%)	0	0	0	0	0	0	0	3 (18%)	0	0	0
Fatigue	7 (9%)	0	0	0	4 (25%)	0	0	0	7 (44%)	1 (6%)	0	0	3 (18%)	0	0	0
Abdominal pain	6 (8%)	0	0	0	2 (13%)	0	0	0	0	0	0	0	5 (29%)	0	0	0
Alanine aminotransferase increased	7 (9%)	0	0	0	2 (13%)	0	0	0	1 (6%)	0	0	0	2 (12%)	1 (6%)	0	0
Dry skin	6 (8%)	0	0	0	2 (13%)	0	0	0	3 (19%)	0	0	0	3 (18%)	0	0	0

Data are n (%). Grade 2 or lower events occurring in 10% or more of patients across cohorts were included. Cohort A=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Cohort B=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, ECOG performance status of 0 or 1. Cohort C=*BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, ECOG performance status of 0 or 1. Cohort D=*BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy ECOG performance status of 0, 1, or 2. *Intracranial tumour haemorrhage, deemed to be unrelated to study treatment.

***Table 3*: Any-cause adverse events**

progression-free survival of 10·8 months for the combination (median not reached with nivolumab monotherapy). Notably, patients enrolled in part 4 of CheckMate 038 generally had more favourable baseline clinical features (eg, 20% had elevated lactate dehydrogenase concentration) than those included in our study. The activity of nivolumab plus ipilimumab continues to be evaluated in phase 2 studies, including the anti-PD-1 Brain Collaboration Trial (NCT02374242) and the CheckMate 204 study of the combination in patients with melanoma brain metastases.[23,24]

The safety profile of dabrafenib plus trametinib in this study was similar to that reported in previous studies, including in patients with metastatic melanoma without brain metastases,[6,7,14–19] in which pyrexia and gastrointestinal issues are common adverse events.[6,7,14–16,18] Thus, the combination also has a manageable safety profile in patients with melanoma brain metastases.

Although the initial response and safety data observed in this population are reassuring, the duration of overall response and progression-free survival in all cohorts in this study were shorter than those observed in randomised trials evaluating dabrafenib and trametinib in patients with metastatic melanoma without brain metastases (overall response duration approximately 12–14 months and progression-free survival 11–12 months in phase 3 trials).[6,17,19] Outcomes for patients treated with the combination in this study were similar to those observed in patients with poor clinical features in previous randomised studies evaluating first-line dabrafenib plus trametinib in patients with metastatic melanoma without brain metastases, such as those who had baseline lactate dehydrogenase concentrations of more than double the upper limit of normal (overall response 51%; median progression-free survival 5·5 months).[25] Findings from other studies support the notion that melanoma brain

metastases might have distinct molecular features, such as increased activation of the phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT) signalling pathway, which has also been associated with resistance to BRAF and MEK inhibitors.[26–28] Altogether, these findings support the need for further research in patients with melanoma brain metastases. Additional clinical trials with dabrafenib and trametinib in these patients are also needed, including combinatorial approaches with brain-directed treatments such as stereotactic radiosurgery with or without other systemic therapies.

We acknowledge that the non-randomised one-arm design of COMBI-MB was a limitation for this study, because our results cannot be compared directly with other current treatments. The small sample sizes for cohorts B, C, and D limited the extent of interpretation of results for these patient subsets. Additionally, because of differences in the prevalence of patients with very different eligibility and enrolment numbers required in each cohort, patients in cohorts B, C, and D were enrolled in the study at an earlier date than patients in cohort A, which resulted in differences in median follow-up time between these patient groups. Analyses incorporating information on patients who received surgery or radiosurgery (eg, gamma knife) during or after study treatment might have provided further insights on the appropriate role of dabrafenib plus trametinib in the current treatment landscape of patients with melanoma brain metastases.

Our preliminary results provide evidence that clinical benefit and tolerability is achievable with dabrafenib plus trametinib in a subset of patients with *BRAF*^{V600}-mutant metastatic melanoma. Continued follow-up is needed to assess the full effect of dabrafenib plus trametinib on overall survival in these cohorts of patients. Nevertheless, these findings serve as a framework for future studies in this setting, in which effective treatments remain a crucial, unmet medical need.

Contributors

MAD, KTF, and GVL contributed to the study design. MAD, PS, CR, J-JG, KTF, AA, VC-S, LT, TL, LM, SJM, DH, IM-R, MDV, CL, NM, YH, and GVL recruited the patients, collected data, or both. YZ did the statistical analyses. All authors analysed and interpreted the data, drafted the manuscript, and approved the final version.

Declaration of interests

MAD has been a principal investigator with grants to his institution from AstraZeneca, Merck, Roche-Genentech, and Sanofi; and has received personal fees from Novartis, Bristol-Myers Squibb, Sanofi, Roche-Genentech, and Merck for advisory board participation. PS has received personal fees from Amgen, Bristol-Myers Squibb, MSD, Merck-Serono, Pfizer, Roche-Genentech, Pierre Fabre, and Novartis; has received non-financial support from Bristol-Myers Squibb, MSD, Roche-Genentech, and Novartis; and has received a funding grant from Roche-Genentech. CR has received personal fees for advisory board participation from Bristol-Myers Squibb, GlaxoSmithKline, Roche, Merck, Amgen, and Novartis. J-JG has received personal fees for participating in advisory boards for Novartis, Roche, GlaxoSmithKline, Bristol-Myers Squibb, Merck, Amgen, and Pierre Fabre. KTF has received personal fees and grant support from Novartis. AA has received personal fees from Novartis, Roche, MSD, and Bristol-Myers Squibb; and financial support for the study from Novartis. VC-S has participated in advisory boards for MSD, Merck-Serono, Roche, Bristol-Myers Squibb, and Novartis. TL has received grants and personal fees for clinical trials and advisory board participation from Roche, Novartis, and MSD; and received grants and personal fees for clinical trials and honoraria from Bristol-Myers Squibb. LM has been a congress invitation investigator for GlaxoSmithKline. SJM has received personal fees for consultancy or travel from Merck, Amgen, Novartis, and Bristol-Myers Squibb; and has received grants from Merck, Amgen, and Pharmacyclics. DH has received personal fees for advisory board participation, lectures, or both from Roche, Bristol-Myers Squibb, EMD Serono, Merck, Amgen, and Novartis. IM-R has received personal fees from Novartis, Roche, MSD, Amgen, Merck-Serono, Pierre Fabre, Bioncotech, GlaxoSmithKline, and Bristol-Myers Squibb. MDV has consulted or had an advisory role for and received honoraria from Bristol-Myers Squibb, Roche, Novartis, and Merck. CL has received grants from Roche and Bristol-Myers Squibb and personal fees for consultancy, advisory roles, speaker's bureaus, or travel or accommodation expenses from Roche, Bristol-Myers Squibb, Novartis, MSD, Amgen, and GlaxoSmithKline. NM has received personal fees from Roche, Bristol-Myers Squibb, MSD, Novartis, and Amgen; and grants from Bristol-Myers Squibb, MSD, and Pierre Fabre. YZ, YH, and BM are employees of Novartis. GVL received personal fees for her role as a consultant adviser to Amgen, Bristol-Myers Squibb, Merck-MSD, Novartis, Pierre Fabre, Array Biopharma, and Roche. LT declares no competing interests.

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