Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial

Reinhard Dummer, Paolo A Ascierto*, Helen J Gogas, Ana Arance, Mario Mandala, Gabriella Liszkay, Claus Garbe, Dirk Schadendorf, Ivana Krajsova, Ralf Gutzmer, Vanna Chiarion Sileni, Caroline Dutriaux, Jan Willem B de Groot, Naoya Yamazaki, Carmen Loquai, Laure A Moutouh-de Parseval, Michael D Pickard, Victor Sandor, Caroline Robert†, Keith T Flaherty†*

Summary

Background Encorafenib plus binimetinib and encorafenib alone improved progression-free survival compared with vemurafenib in patients with *BRAF*^{V600}-mutant melanoma in the COLUMBUS trial. Here, we report the results of the secondary endpoint of overall survival.

Methods COLUMBUS was a two-part, randomised, open-label, phase 3 study done at 162 hospitals in 28 countries. Eligible patients were aged at least 18 years with histologically confirmed, locally advanced, unresectable, or metastatic cutaneous melanoma, or unknown primary melanoma, *BRAF*^{V600E} or *BRAF*^{V600K} mutation, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and were treatment naive or had progressed on or after first-line immunotherapy. In part 1 of the study, patients were randomly assigned (1:1:1) by use of interactive response technology to receive oral encorafenib 450 mg once daily plus oral binimetinib 45 mg twice daily (encorafenib plus binimetinib group), oral encorafenib 300 mg once daily (encorafenib group), or oral vemurafenib 960 mg twice daily (vemurafenib group). Randomisation was stratified by the American Joint Committee on Cancer stage, ECOG performance status, and *BRAF* mutation status. The primary outcome of the trial, progression-free survival with encorafenib plus binimetinib versus vemurafenib, was reported previously. Here we present the prespecified interim overall survival analysis. Efficacy analyses were by intent to treat. Safety was analysed in patients who received at least one dose of study drug. Part 2 of the study was initiated at the request of the US Food and Drug Administration to better understand the contribution of binimetinib to the combination therapy by comparing encorafenib 300 mg once daily plus binimetinib 45 mg twice daily with encorafenib 300 mg once daily alone. Results of part 2 will be published separately. This trial is ongoing and is registered with ClinicalTrials.gov, number NCT01909453, and EudraCT, number 2013-001176-38.

Findings Between Dec 30, 2013, and April 10, 2015, 577 of 1345 screened patients were randomly assigned to receive encorafenib plus binimetinib (n=192), encorafenib (n=194), or vemurafenib (n=191). Median follow-up for overall survival was 36·8 months (95% CI 35·9–37·5). Median overall survival was 33·6 months (95% CI 24·4–39·2) with encorafenib plus binimetinib and 16·9 months (14·0–24·5) with vemurafenib (hazard ratio 0·61 [95% CI 0·47–0·79]; two-sided p<0·0001). The most common grade 3 or 4 adverse events did not change substantially from the first report; those seen in more than 5% of patients treated with encorafenib plus binimetinib were increased γ-glutamyltransferase (18 [9%] of 192 patients), increased blood creatine phosphokinase (14 [7%]), and hypertension (12 [6%]); those seen with encorafenib alone were palmar-plantar erythrodysaesthesia syndrome (26 [14%] of 192 patients), myalgia (19 [10%]), and arthralgia (18 [9%]); and with vemurafenib the most common grade 3 or 4 adverse event was arthralgia (11 [6%] of 186 patients). One death in the combination treatment group was considered by the investigator to be possibly related to treatment.

Interpretation The combination of encorafenib plus binimetinib provided clinically meaningful efficacy with good tolerability as shown by improvements in both progression-free survival and overall survival compared with vemurafenib. These data suggest that the combination of encorafenib plus binimetinib is likely to become an important therapeutic option in patients with *BRAF*^{V600}-mutant melanoma.

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*Joint first authors

†Joint last authors

Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland (Prof R Dummer MD); **Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy** (P A Ascierto MD); **Department of Internal Medicine, National and Kapodistrian University of Athens, Laikon Hospital, Athens, Greece** (H J Gogas MD); **Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain** (A Arance MD); **Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy** (M Mandala MD); **Department of Dermatology, National Institute of Oncology, Budapest, Hungary** (Prof G Liszkay MD); **Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany** (Prof C Garbe MD); **Department of Dermatology, University Hospital Essen, Essen, Germany** (Prof D Schadendorf MD); **German Cancer Consortium, Heidelberg, Germany** (Prof D Schadendorf); **Department of Dermato-oncology, University Hospital Prague and Charles University First Medical Faculty, Prague, Czech Republic** (I Krajsova MD); **Department of Dermatology and Allergy, Skin**

Introduction

Approximately 50% of patients with metastatic melanoma have point mutations in *BRAF*, predominantly in the Val600 codon (*BRAF*^{V600} mutations), which promote melanoma progression through constitutive activation of the MAPK pathway.[1–3] Small-molecule BRAF inhibitors,

Cancer Center Hannover, Hannover Medical School, Hannover, Germany (Prof R Gutzmer MD); **Melanoma Cancer Unit, Oncology Institute of Veneto IRCCS, Padua, Italy** (V Chiarion Sileni MD); **Department of Oncologic Dermatology, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux Cédex, France** (C Dutriaux MD); **Department of Medical Oncology, Isala, Zwolle, Netherlands** (J W B de Groot MD); **Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan** (N Yamazaki MD); **Department of Dermatology, University Medical Center Mainz, Mainz, Germany** (C Loquai MD); **Translational Clinical Oncology, Novartis Pharma AG, Basel, Switzerland** (L A Moutouh-de Parseval MD); **Array BioPharma, Boulder, CO, USA** (M D Pickard PhD, V Sandor MD); **Service of Dermatology, Department of Medicine and Paris-Sud University, Gustave Roussy, Villejuif Cedex, France** (Prof C Robert MD); **and Cancer Center, Massachusetts General Hospital, Boston, MA, USA** (K T Flaherty MD)

Correspondence to:
Prof Reinhard Dummer, Department of Dermatology, University Hospital Zürich Skin Cancer Center, 8091, Zürich, Switzerland
reinhard.dummer@usz.ch

Research in context

Evidence before this study

BRAF–MEK inhibitor combinations have a central role in the targeted treatment of *BRAF*^{V600}-mutant melanoma. We searched for articles and abstracts published in PubMed and Embase between Jan 1, 2014, and Mar 30, 2018, including the search terms "melanoma" AND "treatment" AND "phase" AND "encorafenib," "BRAF inhibition" AND "melanoma". The most relevant articles selected were phase 3 clinical trials. We found that the established BRAF–MEK inhibitor combinations provided a median progression-free survival of approximately 12 months and median overall survival of approximately 24 months, and both of the established combinations were associated with unique treatment-limiting and dose-limiting toxicities. The phase 3 COLUMBUS study was designed to compare a third BRAF–MEK inhibitor combination, encorafenib plus binimetinib versus vemurafenib or encorafenib alone. The initial report of COLUMBUS, published in March, 2018, showed that median progression-free survival was improved with encorafenib plus binimetinib, compared with vemurafenib. Here, we provide an efficacy and safety update based on an additional 18 months of follow-up, including an analysis of overall survival.

Added value of this study

We present further data from the COLUMBUS study that characterise the safety and efficacy of the combination with an additional 18 months of follow-up and analysis of overall survival relative to vemurafenib alone. Data also include a head-to-head comparison of encorafenib monotherapy versus vemurafenib, providing clinical evidence that the unique pharmacological characteristics of encorafenib might be, in part, responsible for the efficacy results observed in the combination arm. The new combination of encorafenib plus binimetinib showed favourable results in terms of the low rates of pyrexia and photosensitivity observed in COLUMBUS. These data suggest that there are inherent differences in the pharmacological characteristics of the drugs used in BRAF–MEK inhibitor therapy and that some combinations might provide additional clinical benefits to patients.

Implications of all the available evidence

BRAF–MEK inhibitor combinations have improved progression-free and overall survival in patients with *BRAF*-mutant melanoma but with treatment-limiting and dose-limiting toxicities. The combination of encorafenib plus binimetinib might be an important addition to the treatment options available to patients with *BRAF*^{V600}-mutant melanoma. The favourable tolerability of encorafenib plus binimetinib could benefit patients in first-line treatment, as an option for those with poor tolerance to other BRAF–MEK inhibitor combinations, and for subsequent treatment after progression on immunotherapy. Trials are underway to assess the use of encorafenib plus binimetinib as adjuvant treatment or in combination with immunotherapy.

initially introduced as monotherapy treatment for patients with *BRAF*^{V600}-mutant melanoma, showed improved efficacy compared with standard therapy, including improved response rates and progression-free and overall survival.[4] However, response durations were short and BRAF inhibitor treatment was associated with the development of squamous cell skin cancer and other skin toxicities related to paradoxical MAPK pathway activation.[4–7]

Dual MAPK pathway inhibition with the addition of a MEK inhibitor to a BRAF inhibitor showed promising initial results[8,9] that were substantiated in three phase 3 studies.[10–12] BRAF–MEK inhibitor combination therapy for *BRAF*-mutant melanoma improved clinical outcomes, delayed development of resistance, and reduced toxicities associated with BRAF inhibitors resulting from paradoxical MAPK pathway activation.[10,12]

Consequently, BRAF–MEK inhibitor combinations are recommended as first-line or second-line therapies for advanced *BRAF*-mutant melanoma.[13] All BRAF–MEK inhibitor therapies are associated with characteristic adverse events, but both of the established combinations (dabrafenib plus trametinib and vemurafenib plus cobimetinib) have distinct safety profiles with unique toxicities that affect overall tolerability and might affect the ability to deliver optimal treatment.[11,12,14,15] Although the available combinations are effective, resulting in a median progression-free survival of approximately 12 months and overall survival of approximately 24 months, further improvements in treatment are needed.[6,10,12,14,16–20]

An additional combination, the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib, was introduced into late-stage clinical trials in 2013. Preliminary clinical data suggested activity and safety profiles distinct from those of available BRAF–MEK inhibitor combinations, including low rates of pyrexia and photosensitivity.[21] Additionally, the improved tolerability with encorafenib plus binimetinib resulted in a higher tolerated dose of encorafenib in the combination (450 mg once daily) than the recommended phase 2 monotherapy dose (300 mg once daily), thereby allowing increased dose intensity of encorafenib when used in combination with binimetinib.[21,22]

COLUMBUS was a three-arm, two-part, phase 3 study in patients with advanced *BRAF*^{V600}-mutant melanoma. Part 1 assessed encorafenib 450 mg once daily plus binimetinib 45 mg twice daily compared with encorafenib 300 mg once daily or vemurafenib 960 mg twice daily. The primary endpoint of progression-free survival comparing the combination therapy with vemurafenib was met; median progression-free survival was 14·9 months (95% CI 11·0–18·5) with encorafenib plus binimetinib versus 7·3 months (5·6–8·2) with vemurafenib.[23] Here, we report the results of overall survival, a secondary endpoint of the study, and update efficacy and safety results on the basis of additional follow-up data at 18 months.

Methods

Study design and participants

COLUMBUS was a two-part, multicentre, randomised, open-label, phase 3 study. Primary results of part 1 have been published.[23] Part 2, which was added to the study protocol via amendment 3 (dated Nov 4, 2014), was a request by the US Food and Drug Administration (FDA) to understand the contribution of binimetinib to the combination. Part 2 enrolled further patients to investigate an encorafenib dose of 300 mg once daily in combination with binimetinib 45 mg twice daily compared with encorafenib 300 mg once daily alone. Follow-up results for part 1 are reported here; part 2 results will be reported separately.

In part 1, patients were recruited from 162 hospitals in 28 countries (20 sites in North America, 124 sites in Europe, and 18 sites in other countries; appendix pp 3–5). Eligible patients were aged at least 18 years with a histologically confirmed diagnosis of locally advanced, unresectable, or metastatic cutaneous melanoma or unknown primary melanoma classified as American Joint Committee on Cancer (AJCC) stage IIIB, IIIC, or IV; were treatment naive or had progressed on or after previous first-line immunotherapy; had a *BRAF*^{V600E} or *BRAF*^{V600K} mutation or both in tumour tissue as ascertained by central genetic mutation analysis with the bioMérieux THxID BRAF diagnostic test (bioMérieux, Marcy l'Etoile, France) before enrolment (appendix p 6); an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate bone marrow, organ function, and laboratory parameters (ie, absolute neutrophil count, haemoglobin concentration, platelet count, aspartate aminotransferase or alanine aminotransferase concentrations, and total bilirubin, creatinine, or calculated creatinine clearance [acceptable test limits for laboratory parameters are in the appendix p 6]); and at least one measurable lesion, according to guidelines based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[24] Patients were ineligible if they had untreated CNS lesions; uveal or mucosal melanoma; a history of leptomeningeal metastases; Gilbert's syndrome; history, current evidence, or risk of retinal vein occlusion; previous BRAF inhibitor or MEK inhibitor treatment; previous use of systemic chemotherapy (as per protocol amendment 2 [Dec 20, 2013] and clarified in amendment 3 [Nov 4, 2014]), extensive radiotherapy as evaluated by local investigators, or an investigational agent other than previous immunotherapy for locally advanced, unresectable, or metastatic melanoma (immunotherapy must have ended ≥6 weeks before randomisation). Complete eligibility criteria are in the protocol (appendix pp 101–04). Part 2 enrolment followed the same criteria.

The study protocol and amendments were approved by independent ethics committees or review boards at each study site. Study conduct conformed to Good Clinical Practice guidelines and ethical requirements outlined in the Declaration of Helsinki. All study participants provided written informed consent before screening procedures were initiated.

Randomisation and masking

All eligible patients were randomly assigned (1:1:1) according to a permuted block design (block size nine) by use of validated interactive response technology and a treatment allocation sequence provided by Parexel International (Billerica, MA, USA) to receive encorafenib plus binimetinib, encorafenib, or vemurafenib. Patients were enrolled by local clinicians in the participating hospitals (appendix pp 3–5). Randomisation was stratified by AJCC stage (IIIB, IIIC, IVM1a, IVM1b, or IVM1c), ECOG performance status (0 or 1), and *BRAF* mutation status (*BRAF*^{V600E} or *BRAF*^{V600K}). After protocol amendment 2 (Dec 20, 2013), use of previous first-line immunotherapy (yes or no) replaced *BRAF* mutation status as a stratification factor. Neither investigators nor patients were masked to treatment assignment.

See Online for appendix

Procedures

As previously described,[23] patients received encorafenib 450 mg once daily orally plus binimetinib 45 mg twice daily orally, encorafenib 300 mg once daily orally, or vemurafenib 960 mg twice daily orally, until progression of disease as assessed by central review, death, unacceptable toxic effects, or withdrawal of consent. Dose modifications, including treatment interruptions and dose reductions, were permitted for each drug on the basis of tolerability and adverse events. For patients receiving encorafenib 450 mg once daily plus binimetinib 45 mg twice daily, dose modifications for encorafenib were permitted to 300 mg and subsequently to 200 mg, 100 mg, and 50 mg once daily; patients who could not tolerate 50 mg discontinued the combination treatment of encorafenib plus binimetinib. For binimetinib, a dose modification to 30 mg and subsequently to 15 mg twice daily was permitted; if 15 mg twice daily was not tolerated, binimetinib was discontinued. However, the binimetinib dose could be re-escalated to 45 mg if the toxicity that had caused the dose reduction improved to baseline levels and remained stable without occurrence of other concomitant binimetinib-related toxicities. For patients receiving encorafenib alone, dose reductions to 200 mg, 100 mg, and 50 mg once daily were permitted. For patients receiving vemurafenib 960 mg twice daily, the dose could be reduced to 720 mg and then to 480 mg twice daily. No further dose reductions were allowed. Details about drug manufacture are in the appendix (p 6).

Relative dose intensity (%) was defined as 100 multiplied by the total cumulative dose a patient actually received during the study divided by the total cumulative dose a patient was scheduled to receive (ie, had they not had any dose adjustments or interruptions) during the study. For the primary and secondary endpoints and analyses of best overall response, duration of response, and disease control we used tumour assessment data analysed by

masked independent central review. Supportive analyses used data based on local review by use of RECIST version 1.1 to assess response or progression as done at individual investigative sites.

Progression and tumour responses were assessed centrally by masked independent committee review and locally according to guidelines based on RECIST version 1.1.[24] Tumour evaluations were done via imaging at baseline (within 21 days of randomisation), every 8 weeks during the first 24 months, and every 12 weeks thereafter. Baseline assessments included MRI or CT scans of the chest, abdomen, pelvis, and brain. Whole-body bone scans were done if bone metastases were suspected. Subsequent assessments included MRI or CT scan of the chest, abdomen, and pelvic and other areas of disease (eg, neck) documented at baseline. Subsequent brain MRI or CT scans were required in patients with brain metastases documented at baseline. On-study tumour assessments were to be done with the same imaging method that was used at baseline. Colour photography was required to document skin lesions at baseline and on-study. Survival status and use of subsequent systemic therapy was ascertained every 12 weeks for all patients who discontinued treatment until death, loss to follow-up, withdrawal of consent, or study closure. This information was collected at clinic visits or via phone calls or letters, and documented in source documents and survival electronic case report forms. Safety assessments included collection of adverse events, physical examinations (a full list of all safety assessments is included in the appendix pp 118, 150), and clinical laboratory assessments. Safety assessments were done continuously until 30 days after the last dose of the study drug; patients could report adverse events at any time throughout their course of treatment and were also queried about any adverse event occurrence at each visit. Laboratory assessments were done on day 1 of each cycle (a full schedule of all assessments is available in the appendix pp 134–53).

Adverse events were monitored during the study and for at least 30 days after the last dose of study drug. Adverse event severity was assessed by use of Common Terminology Criteria for Adverse Events, version 4.03.[25] Safety data were reviewed by a data monitoring committee approximately every 6 months.

Outcomes

The primary endpoint for this study was progression-free survival by masked independent central review for encorafenib plus binimetinib compared with vemurafenib (previously reported).[23] An analysis of overall survival and an update of efficacy and safety results for part 1 of the study based on additional follow-up are reported here. The key secondary endpoint was progression-free survival for encorafenib plus binimetinib compared with encorafenib. Progression-free survival was defined as the time from randomisation to first documented progression or death from any cause (whichever occurred first). Overall survival (time from randomisation to death from any cause) for encorafenib plus binimetinib compared with vemurafenib was a secondary endpoint for which the type I error rate was controlled with a hierarchical testing procedure. Other secondary endpoints included the remaining comparisons of overall survival (encorafenib plus binimetinib compared with encorafenib and encorafenib compared with vemurafenib) and all comparisons of best overall response (proportion of patients with a complete response, partial response, stable disease, progressive disease, or unknown, derived from RECIST version 1.1[24]); overall response (proportion of patients with a best overall response of confirmed complete or partial response); disease control (proportion of patients with a best overall response of confirmed complete response, partial response, or stable disease, including patients with non-measurable disease by masked independent central review); duration of response (time from the first documented confirmed complete or partial response to the first documented progression or death from melanoma); and time to response (time from randomisation to first documented complete or partial response).

Additional secondary outcomes, including quality of life, comparison of ECOG performance status, and pharmacokinetic analysis, will be reported elsewhere, as will resource utilisation, which was an exploratory endpoint.

Statistical analysis

The statistical analysis for the primary endpoint has been reported.[23] Previously, we estimated that 145 progression-free survival events would provide 90% or greater power to detect a hazard ratio (HR) of 0·58 (for encorafenib plus binimetinib *vs* vemurafenib) by log-rank test at a one-sided 2·5% level of significance. Here, we report an analysis of overall survival, which was prespecified as an interim analysis to be done after 232 events had occurred in the encorafenib plus binimetinib and vemurafenib groups combined. The data cutoff date for this analysis was Nov 7, 2017. A final analysis would occur after 309 events if interim analysis results fail to reject the null hypothesis. Updated analyses of COLUMBUS will be published separately. The type I error rate for the analysis was to be maintained with a gamma-family spending function with parameter value 1 to define the stopping boundaries for each analysis.[26] We calculated that 232 events would allow for detection of a minimum HR for death of 0·765. A hierarchical testing procedure was used to control the overall type I error rate for the study. Included in the formal testing sequence were the primary endpoint and key secondary endpoints, as well as the overall survival endpoint for encorafenib plus binimetinib versus vemurafenib. Although formal testing was discontinued before analysis of overall survival, the study team remained masked to the overall survival results until the predefined number of required events had been

observed in order to preserve the integrity of the analysis. The analysis of overall survival for binimetinib and encorafenib compared with encorafenib, and for encorafenib compared with vemurafenib, was not formally powered.

Efficacy endpoints were assessed in the intent-to-treat population (defined as all randomly assigned patients). All patients who received one or more doses of study drug and had one or more post-baseline safety assessments were analysed for safety according to the treatment they actually received. The data were subjected to as little imputation as possible for missing values (appendix p 7).

Median durations of follow-up for overall and progression-free survival were estimated by reverse Kaplan-Meier analysis, for which median values are reported and reflect the potential follow-up in the absence of progressive disease or death.

The Kaplan-Meier method was used to estimate rates of overall and progression-free survival; the log-rank test, stratified by AJCC stage (IIIB, IIIC, IVM1a, and IVM1b, *vs* IVM1c) and ECOG performance status (0 *vs* 1), was used to compare distributions. Prespecified sensitivity analyses included unstratified analyses, analyses of the per-protocol population, analyses of progression-free survival based on local tumour assessments, and different censoring rules for progression-free survival. Subgroup analyses of baseline variables and potential prognostic factors, including previous immunotherapy, were also specified. HRs were estimated by use of stratified Cox regression models, with 95% CIs based on the Wald test. We present the data for overall response and disease control by treatment group with exact 95% CIs; p values are two-sided and included for descriptive purposes.

All analyses were done with SAS version 9.2 or higher. This study is registered with ClinicalTrials.gov (NCT01909453) and EudraCT (2013-001176-38).

Role of the funding source

The study was designed by Novartis, with input from the steering committee (RD, PAA, and KTF), and was funded and sponsored by Novartis until September 2015, when sponsorship was transfered to Array BioPharma. The sponsors had a role in data collection, analysis, and interpretation. RD, PAA, and KTF wrote the first draft of the manuscript, had full access to all study data, and had final responsibility for the decision to submit for publication.

Results

Between Dec 30, 2013, and April 10, 2015, 1345 patients were screened; of these, 768 were excluded (364 did not have the *BRAF*^{V600E} or *BRAF*^{V600K} mutation, 350 did not meet other inclusion criteria or met other exclusion criteria, and 54 declined consent after pre-screening). 577 patients were enrolled and randomly assigned to receive encorafenib plus binimetinib (n=192), encorafenib (n=194), or vemurafenib (n=191). At the data cutoff date of Nov 7, 2017, 43 (22%) of 192 patients in the encorafenib plus binimetinib group, 24 (12%) of 194 in the encorafenib group, and 13 (7%) of 191 in the vemurafenib group continued to receive study treatment (appendix p 24).

Baseline characteristics, including key prognostic factors at baseline, were similar among treatment groups (table 1).

105 events contributed to the overall survival analysis in the encorafenib plus binimetinib group, 106 events in the encorafenib group, and 127 in the vemurafenib group. Median follow-up for overall survival was

	Encorafenib 450 mg plus binimetinib 45 mg group (n=192)	Encorafenib 300 mg group (n=194)	Vemurafenib 960 mg group (n=191)
Median age (range; IQR), years	57 (20–89; 48–66)	54 (23–88; 46–63)	56 (21–82; 45–65)
Sex			
Men	115 (60%)	108 (56%)	111 (58%)
Women	77 (40%)	86 (44%)	80 (42%)
ECOG performance status			
0	136 (71%)	140 (72%)	140 (73%)
1	56 (29%)	54 (28%)	51 (27%)
LDH concentration			
≥Upper limit of normal	55 (29%)	47 (24%)	52 (27%)
<Upper limit of normal	137 (71%)	147 (76%)	139 (73%)
BRAF mutation status			
BRAF^{V600E}	170 (89%)	173 (89%)*	168 (88%)
BRAF^{V600K}	22 (11%)	19 (10%)*	23 (12%)
AJCC tumour stage at study entry			
IIIB/IIIC	9 (5%)	6 (3%)	11 (6%)
IVM1a	26 (14%)	29 (15%)	24 (13%)
IVM1b	34 (18%)	39 (20%)	31 (16%)
IVM1c	123 (64%)	120 (62%)	125 (65%)
Number of organs involved			
1	47 (24%)	56 (29%)	45 (24%)
2	58 (30%)	52 (27%)	59 (31%)
≥3	87 (45%)	86 (44%)	87 (46%)
Previous immunotherapy	57 (30%)	58 (30%)	57 (30%)
Ipilimumab†	7 (4%)	10 (5%)	7 (4%)
Adjuvant	2 (1%)	1 (1%)	2 (1%)
Advanced or metastatic	5 (3%)	9 (5%)	5 (3%)
Anti-PD-1 or anti-PD-L1†‡	1 (1%)	2 (1%)	0
Advanced or metastatic	1 (1%)	2 (1%)	0
Interferons or interleukins	51 (27%)	51 (26%)	52 (27%)
Adjuvant§	47 (24%)	46 (24%)	46 (24%)
Neoadjuvant¶	0	1 (1%)	1 (1%)
Advanced or metastatic‖	4 (2%)	4 (2%)	5 (3%)

Data are median (range; IQR) or n (%), and include all randomised patients. ECOG=Eastern Cooperative Oncology Group. AJCC=American Joint Committee on Cancer. LDH=lactate dehydrogenase. PD-1=programmed death 1. PD-L1=programmed death ligand 1. *Two observations were indeterminate. †A patient might have received ipilimumab or combinations including PD-1 or PD-L1 inhibitors. ‡Nivolumab. §Including interferon, interferon alfa, interferon alfa-2a, interferon alfa-2b, and interferon β. ¶Interferon. ‖Including interferon, interferon alfa-2b, and interleukin 2.

Table 1: **Baseline demographics and clinical characteristics**

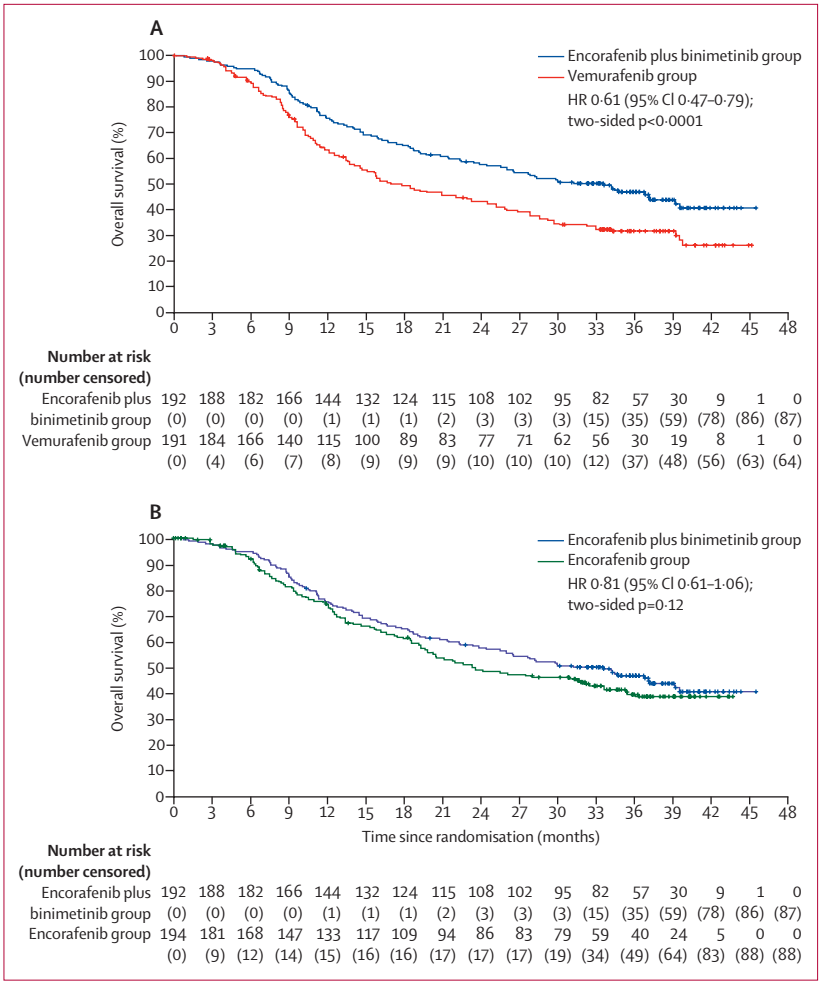

Figure 1: **Kaplan-Meier curves of overall survival**
(A) Encorafenib 450 mg once daily plus binimetinib 45 mg twice daily compared with vemurafenib 960 mg twice daily. (B) Encorafenib 450 mg once daily plus binimetinib 45 mg twice daily compared with encorafenib 300 mg once daily. HR=hazard ratio.

36·8 months (95% CI 35·9–37·5; appendix p 11). Median overall survival was 33·6 months (95% CI 24·4–39·2) in the encorafenib plus binimetinib group, 23·5 months (19·6–33·6) in the encorafenib group, and 16·9 months (14·0–24·5) in the vemurafenib group.

Overall survival was longer in the encorafenib plus binimetinib group than in the vemurafenib group (HR 0·61 [95% CI 0·47–0·79]; p<0·0001; figure 1A). When the encorafenib plus binimetinib group was compared with the encorafenib group, overall survival did not differ significantly (HR 0·81 [95% CI 0·61–1·06]; two-sided p=0·12; figure 1B). Overall survival was longer in the encorafenib group than in the vemurafenib group (HR 0·76; 95% CI 0·58–0·98; two-sided p=0·033; appendix p 26).

1-year overall survival was 75·5% (95% CI 68·8–81·0) in the encorafenib plus binimetinib group, 74·6% (67·6–80·3) in the encorafenib group, and 63·1% (55·7–69·6) in the vemurafenib group. 2-year overall survival was 57·6% (95% CI 50·3–64·3) in the encorafenib plus binimetinib group, 49·1% (41·5–56·2) in the encorafenib group, and 43·2% (35·9–50·2) in the vemurafenib group. Additional timepoints are provided in the appendix (p 11). Overall survival analyses in the encorafenib plus binimetinib and vemurafenib subgroups indicated that all point estimates favoured the encorafenib plus binimetinib group, except for the subgroup of 12 patients with brain metastases (nine in the encorafenib plus binimetinib group and three in the vemurafenib group; figure 2).

At the time of data cutoff, 113 events contributed to the updated progression-free survival analysis in the encorafenib plus binimetinib group, 112 in the encorafenib group, and 118 in the vemurafenib group. Median follow-up was 32·1 months (95% CI 29·5–32·3). Median progression-free survival was 14·9 months (95% CI 11·0–20·2) in the encorafenib plus binimetinib group, 9·6 months (7·4–14·8) in the encorafenib group, and 7·3 months (5·6–7·9) in the vemurafenib group. Progression-free survival was longer in the encorafenib plus binimetinib group than in the vemurafenib group (HR 0·51 [95% CI 0·39–0·67]; two-sided p<0·0001; appendix p 26). The HR for progression-free survival in the encorafenib plus binimetinib group compared with the encorafenib group was 0·77 (95% CI 0·59–1·00; two-sided p=0·050; appendix p 26). Progression-free survival was also longer in the encorafenib group than in the vemurafenib group (HR 0·68 [95% CI 0·52–0·88]; two-sided p=0·0038; appendix p 27).

Confirmed overall response by masked independent central review was observed in 122 (64%) of 192 patients in the encorafenib plus binimetinib group, 100 (52%) of 194 patients in the encorafenib group, and 78 (41%) of 191 patients in the vemurafenib group; by local review, a confirmed overall response was observed in 145 (76%) patients in the encorafenib plus binimetinib group, in 112 (58%) in the encorafenib group, and in 94 (49%) in the vemurafenib group (appendix p 13). By masked independent central review, the proportion of patients achieving a complete response increased compared with the initial analysis,[23] to 22 (11%) patients in the encorafenib plus binimetinib group, 14 (7%) in the encorafenib group, and 16 (8%) in the vemurafenib group. By local review, the proportion of patients achieving a complete response was 37 (19%) in the encorafenib plus binimetinib group, 19 (10%) in the encorafenib group, and 16 (8%) in the vemurafenib group. Duration of response was analysed by central and local reviews. By central review, it was 18·6 months (95% CI 12·7–24·1) in the encorafenib plus binimetinib group, 15·2 months (11·1–27·6) in the encorafenib group, and 12·3 months (6·9–14·5) in the vemurafenib group (appendix p 13).

After study drug discontinuation, systemic treatments were received by 80 (42%) of 192 patients in the encorafenib plus binimetinib group, 108 (56%) of 194 in the encorafenib group, and 119 (62%) of 191 in the vemurafenib group (table 2). The most common

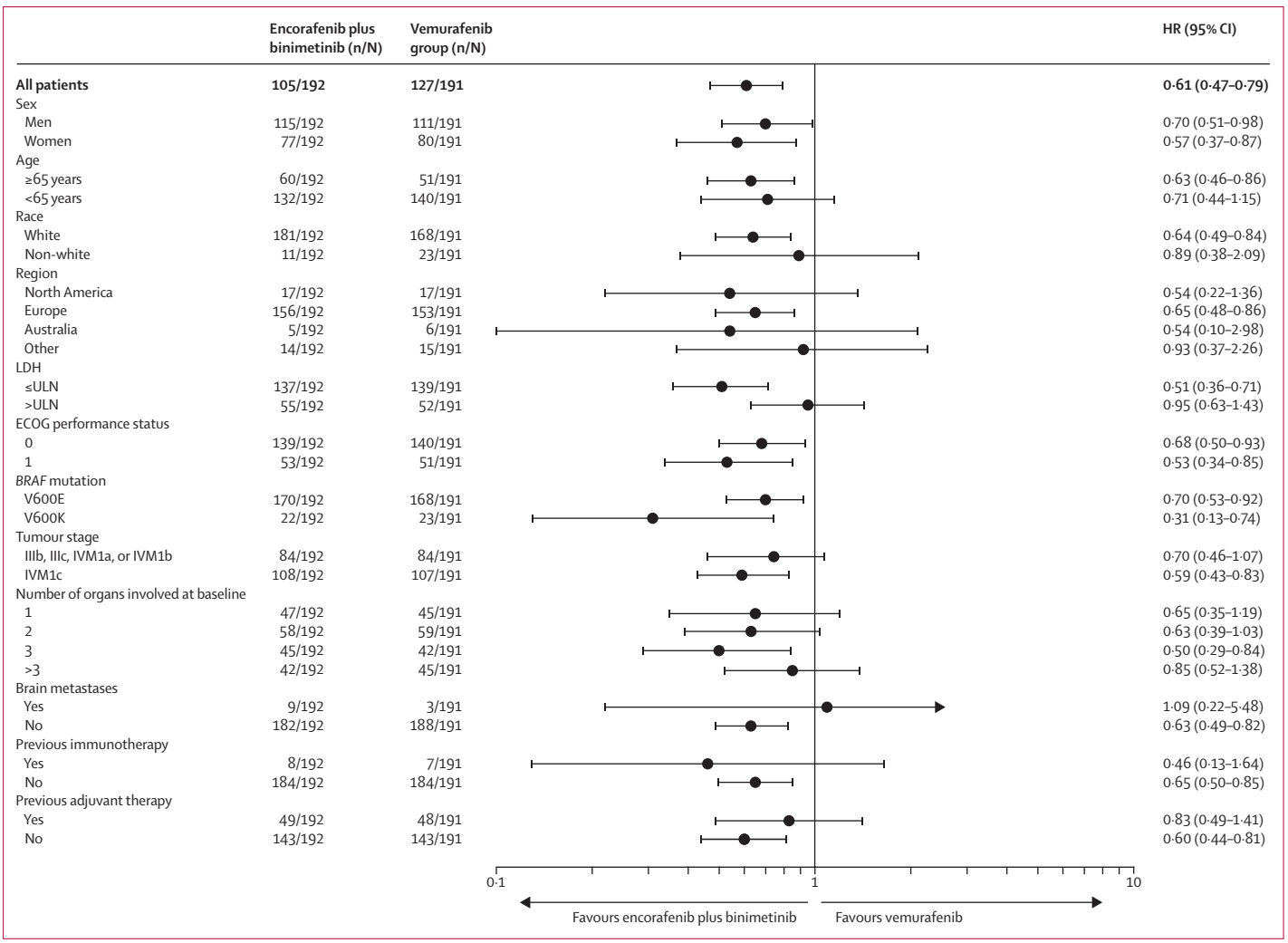

Figure 2: **Overall survival by prespecified subgroups according to baseline characteristics for the encorafenib plus binimetinib group versus the vemurafenib group**
HR=hazard ratio. LDH=lactate dehydrogenase. ULN=upper limit of normal. ECOG=Eastern Cooperative Oncology Group.

regimens involved an anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1), with 20–25% of patients receiving anti-PD-1 or anti-PD-L1 monotherapy and 2–3% receiving anti-PD-1 or anti-PD-L1 in combination with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) across treatment groups (table 2). Anti-CTLA-4 and anti-PD-1 or anti-PD-L1 immunotherapies were the most frequent first and second subsequent regimens (appendix p 14).

570 patients (192 in both the encorafenib plus binimetinib and encorafenib groups and 186 in the vemurafenib group) were included in the safety analysis. The median duration of exposure was 51·2 weeks (IQR 27·1–139·1) in the encorafenib plus binimetinib group, 31·4 weeks (16·6–78·0) in the encorafenib group, and 26·3 weeks (15·1–48·3) in the vemurafenib group. Relative dose intensities representing the total cumulative dose received relative to the planned cumulative dose were highest in the encorafenib plus binimetinib group (appendix p 28). The higher dose intensity in the encorafenib plus binimetinib group was because of lower frequencies of treatment interruption and dose modification in this group compared with the other groups. Study drug discontinuations related to adverse events occurred in 29 (15%) of 192 patients in the encorafenib plus binimetinib group, in 29 (15%) of 192 in the encorafenib group, and in 32 (17%) of 186 in the vemurafenib group. Adverse events requiring dose adjustment or study drug interruption were reported in 102 (53%) of 192 patients in the encorafenib plus binimetinib group, in 137 (71%) of 192 in the encorafenib group, and in 115 (62%) of 186 in the vemurafenib group. The most common reasons for dose adjustment or study drug interruption were nausea in 17 (9%) of 192 patients in the encorafenib plus binimetinib group, palmar-plantar erythrodysaesthesia syndrome in 48 (25%) of 192 patients in the encorafenib group, and arthralgia in

	Encorafenib 450 mg plus binimetinib 45 mg group (n=192)	Encorafenib 300 mg group (n=194)	Vemurafenib 960 mg group (n=191)
Any treatment	80 (42%)	108 (56%)	119 (62%)
Anti-PD-1 or anti-PD-L1*	39 (20%)	40 (21%)	48 (25%)
Anti-CTLA-4†	33 (17%)	32 (16%)	36 (19%)
Anti-CTLA-4 plus anti-PD-1 or anti-PD-L1‡	6 (3%)	4 (2%)	3 (2%)
BRAF inhibitor plus MEK inhibitor§	10 (5%)	28 (14%)	39 (20%)
BRAF inhibitor¶	11 (6%)	15 (8%)	24 (13%)
Chemotherapy	14 (7%)	24 (12%)	23 (12%)
MEK inhibitor** or other††	5 (3%)	4 (2%)	13 (7%)

Data are n (%). Multiple uses of a therapy in a single patient were only counted once in the frequency for that category of therapy; patients who received multiple categories of therapy are counted in each respective row. CTLA-4=cytotoxic T-lymphocyte-associated protein 4. PD-1=programmed death 1. PD-L1=programmed death ligand 1. *Nivolumab, pembrolizumab, or unidentified PD-1 inhibitor. †Ipilimumab. ‡Ipilimumab plus nivolumab or ipilimumab plus pembrolizumab. §Dabrafenib plus trametinib; dabrafenib plus cobimetinib plus trametinib; encorafenib plus binimetinib; vemurafenib plus cobimetinib; vemurafenib plus protein kinase inhibitors. ¶Dabrafenib or vemurafenib. Abemaciclib; bleomycin; bleomycin plus dacarbazine plus lomustine plus vincristine; carboplatin plus dacarbazine plus vinblastine; carboplatin plus paclitaxel; carmustine plus cisplatin plus dacarbazine; carmustine plus dacarbazine plus hydroxycarbamide; cisplatin plus dacarbazine; cisplatin plus dacarbazine plus vinblastine/vinblastine; cisplatin plus temozolomide; cisplatin plus vinblastine; dacarbazine; fotemustine; gemcitabine plus treosulfan plus trofosfamide; melphalan plus norfloxacin; temozolomide; or vinblastine. **Cobimetinib or trametinib; received by two patients in the vemurafenib group. ††Antineoplastic and immunomodulating agents; antineoplastic and immunomodulating agents plus monoclonal antibodies; bevacizumab; bevacizumab plus ipilimumab plus nivolumab; binimetinib plus buparlisib plus encorafenib; binimetinib plus capmatinib plus encorafenib; binimetinib plus encorafenib plus ribociclib; dabrafenib plus pembrolizumab; dabrafenib plus pembrolizumab plus trametinib; interferon; investigational drug; investigational drug plus pembrolizumab; ipilimumab plus vemurafenib; monoclonal antibodies; paclitaxel; radiotherapy; or talimogene laherparepvec.

Table 2: **Systemic treatment following study drug discontinuation**

18 (10%) of 186 patients in the vemurafenib group. Additional details are in the appendix (p 8).

Grade 1 or 2 adverse events that occurred in at least 10% of patients and grade 3 or 4 adverse events occurring in at least 2% of patients in any study group are shown in table 3. As per the protocol, adverse events that were life threatening were graded as grade 4, and data about deaths were collected and reported separately and therefore do not appear in the table. A list of at least 10% grade 1 or 2 and all grade 3 or 4 adverse events in the study groups is shown in the appendix (pp 16–22).

Selected adverse reactions associated with BRAF inhibitors and MEK inhibitors were further characterised by grouping together individual adverse events that represented similar clinical entities (appendix pp 29,30). Skin toxicities, including skin papilloma, rash, acneiform dermatitis, and cutaneous squamous cell carcinoma, occurred less frequently in the encorafenib plus binimetinib group than in the encorafenib or vemurafenib group. Frequencies of all-grade events (in the encorafenib plus binimetinib group *vs* encorafenib group *vs* vemurafenib group) were as follows: skin papilloma (in 17 [9%] of 192 patients *vs* 23 [12%] of 192 *vs* 36 [19%] of 186), rash (in 48 [25%] *vs* 80 [42%] *vs* 100 [54%]), acneiform dermatitis (in six [3%] *vs* 16 [8%] *vs* 12 [6%]), and cutaneous squamous cell carcinoma (in seven [4%] *vs* 16 [8%] *vs* 32 [17%]). Increased aminotransferase concentrations, serous retinopathy (or retinal pigment epithelial detachment), and left ventricular dysfunction occurred more frequently in the encorafenib plus binimetinib group than in either the encorafenib or vemurafenib group. Frequencies of all-grade events (in the encorafenib plus binimetinib group *vs* encorafenib group *vs* vemurafenib group) were as follows: increased aminotransferase concentrations (in 26 [14%] of 192 patients *vs* 14 [7%] of 192 *vs* 19 [10%] of 186), serous retinopathy (in 45 [23%] *vs* five [3%] *vs* four [2%]), and left ventricular dysfunction (in 15 [8%] *vs* four [2%] *vs* two [1%]). Among the 45 patients who had serous retinopathy in the encorafenib plus binimetinib group, seven had the event during the additional follow-up period. 27 (60%) of these 45 patients had a maximum grade of grade 1, and 12 (27%) had a maximum grade of grade 2. With 18 months of additional follow-up, pyrexia was observed in 39 (20%) patients and photosensitivity in eight (4%) patients in the encorafenib plus binimetinib group.

Deaths occurred during treatment or within 30 days of the last dose in 23 (12%) of 192 patients in the encorafenib plus binimetinib group, in 16 (8%) of 192 in the encorafenib group, and in 20 (11%) of 186 in the vemurafenib group. Most on-treatment deaths were from melanoma, occurring in 15 (8%) of 192 patients in the encorafenib plus binimetinib group, in 14 (7%) of 192 in the encorafenib group, and in 19 (10%) of 186 in the vemurafenib group. Deaths considered to be due to events other than disease progression in the encorafenib plus binimetinib group were multiple organ dysfunction syndrome, cerebral haemorrhage, suicide, euthanasia, and cerebral ischaemia, each of which occurred in one patient; for three patients in the encorafenib plus binimetinib group, the cause of death was unknown (appendix p 23). In the encorafenib group, one death was due to acute myocardial infarction and one cause of death was unknown. In the vemurafenib group, one death was due to intestinal sepsis and a second death, attributed to lung infection in the previous report, was attributed to malignant melanoma on the basis of updated information. One death in the combination group was considered by the investigator to be possibly related to treatment. This patient died by suicide on day 24, which was 15 days after the last dose of study drug.

Discussion

We present overall survival and updated efficacy data from the COLUMBUS study, extending the findings of the initial report on the primary efficacy endpoint.[23] The observed median overall survival with encorafenib plus binimetinib was 33·6 months (95% CI 24·4–39·2). Together with a mature median progression-free survival of 14·9 months (95% CI 11·0–20·2), these data represent a new benchmark for BRAF–MEK inhibitor therapy for *BRAF*-mutant melanoma.

Encorafenib plus binimetinib is the third BRAF–MEK inhibitor combination to be tested in a phase 3 trial for

the treatment of patients with *BRAF*-mutant melanoma. Preclinical data showed a longer dissociation half-life for encorafenib (>30 h) than for dabrafenib (2 h) or vemurafenib (0·5 h) and increased antitumour activity in *BRAF*^{V600}-mutant cell lines.[22,27] Early clinical data suggested that the activity of encorafenib could be enhanced by increasing its dose in combination with binimetinib, while improving tolerability.[21] Both encorafenib plus

	Encorafenib 450 mg plus binimetinib 45 mg group (n=192)			Encorafenib 300 mg group (n=192)			Vemurafenib 960 mg group (n=186)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Nausea	80 (42%)	4 (2%)	0	66 (34%)	8 (4%)	0	62 (33%)	3 (2%)	0
Diarrhoea	67 (35%)	4 (2%)	1 (1%)	24 (13%)	4 (2%)	0	60 (32%)	4 (2%)	0
Vomiting	58 (30%)	3 (2%)	0	46 (24%)	9 (5%)	0	28 (15%)	2 (1%)	0
Fatigue	52 (27%)	4 (2%)	0	48 (25%)	1 (1%)	0	53 (28%)	4 (2%)	0
Arthralgia	52 (27%)	2 (1%)	0	67 (35%)	18 (9%)	0	74 (40%)	11 (6%)	0
Blood creatine phosphokinase increased	35 (18%)	11 (6%)	3 (2%)	2 (1%)	0	0	4 (2%)	0	0
Headache	45 (23%)	3 (2%)	0	48 (25%)	6 (3%)	0	35 (19%)	1 (1%)	0
Constipation	47 (24%)	0	0	30 (16%)	0	0	11 (6%)	0	1 (1%)
Asthenia	37 (19%)	2 (1%)	1 (1%)	36 (19%)	5 (3%)	0	27 (15%)	8 (4%)	0
Pyrexia	31 (16%)	7 (4%)	0	29 (15%)	2 (1%)	0	52 (28%)	0	0
Abdominal pain	28 (15%)	5 (3%)	0	10 (5%)	4 (2%)	0	12 (6%)	2 (1%)	0
Anaemia	22 (11%)	8 (4%)	1 (1%)	8 (4%)	5 (3%)	0	12 (6%)	4 (2%)	1 (1%)
Dry skin	31 (16%)	0	0	58 (30%)	0	0	42 (23%)	0	0
Myalgia	31 (16%)	0	0	36 (19%)	19 (10%)	0	33 (18%)	1 (1%)	0
Blurred vision	31 (16%)	0	0	4 (2%)	0	0	4 (2%)	0	0
Dizziness	26 (14%)	4 (2%)	0	11 (6%)	0	0	8 (4%)	0	0
Increased GGT	11 (6%)	18 (9%)	0	13 (7%)	9 (5%)	1 (1%)	15 (8%)	5 (3%)	1 (1%)
Hyperkeratosis	28 (15%)	1 (1%)	0	68 (35%)	7 (4%)	0	54 (29%)	0	0
Rash	26 (14%)	2 (1%)	1 (1%)	36 (19%)	4 (2%)	0	49 (26%)	6 (3%)	0
Hypertension	16 (8%)	12 (6%)	0	5 (3%)	6 (3%)	0	17 (9%)	6 (3%)	0
Alopecia	27 (14%)	0	0	108 (56%)	0	0	68 (37%)	0	0
Back pain	24 (13%)	2 (1%)	0	25 (13%)	5 (3%)	0	9 (5%)	3 (2%)	1 (1%)
Muscle spasms	24 (13%)	1 (1%)	0	6 (3%)	0	0	3 (2%)	1 (1%)	0
Upper abdominal pain	22 (11%)	2 (1%)	0	18 (9%)	2 (1%)	0	17 (9%)	2 (1%)	0
Cough	23 (12%)	1 (1%)	0	20 (10%)	1 (1%)	0	14 (8%)	1 (1%)	0
Nasopharyngitis	24 (13%)	0	0	14 (7%)	0	0	20 (11%)	0	0
Pruritus	23 (12%)	0	1 (1%)	41 (21%)	1 (1%)	0	20 (11%)	0	0
Peripheral oedema	19 (10%)	3 (2%)	0	16 (8%)	0	0	18 (10%)	2 (1%)	0
Pain in extremity	20 (10%)	2 (1%)	0	41 (21%)	2 (1%)	0	25 (13%)	2 (1%)	0
Increased ALT	11 (6%)	10 (5%)	0	9 (5%)	2 (1%)	0	11 (6%)	3 (2%)	0
Insomnia	19 (10%)	0	0	31 (16%)	5 (3%)	0	15 (8%)	0	0
Decreased appetite	18 (9%)	0	0	39 (20%)	1 (1%)	0	34 (18%)	2 (1%)	0
Palmoplantar keratoderma	18 (9%)	0	0	47 (24%)	3 (2%)	0	29 (16%)	2 (1%)	0
Increased aspartate aminotransferase	13 (7%)	4 (2%)	0	7 (4%)	1 (1%)	0	12 (6%)	3 (2%)	0
Erythema	15 (8%)	0	0	24 (13%)	1 (1%)	0	30 (16%)	1 (1%)	0
Musculoskeletal pain	15 (8%)	0	0	28 (15%)	6 (3%)	0	10 (5%)	2 (1%)	0
Skin papilloma	15 (8%)	0	0	20 (10%)	0	0	31 (17%)	0	0
Hyperglycaemia	9 (5%)	5 (3%)	0	4 (2%)	3 (2%)	1 (1%)	0	1 (1%)	0
PPE syndrome	14 (7%)	0	0	72 (38%)	26 (14%)	0	24 (13%)	2 (1%)	0
Dysgeusia	11 (6%)	0	0	23 (12%)	0	0	18 (10%)	0	0
Keratosis pilaris	9 (5%)	0	0	33 (17%)	0	0	43 (23%)	0	0
Photosensitivity reaction	6 (3%)	1 (1%)	0	7 (4%)	0	0	44 (24%)	2 (1%)	0
Metastases to CNS	2 (1%)	3 (2%)	1 (1%)	1 (1%)	1 (1%)	3 (2%)	0	4 (2%)	0

(Table 3 continues on next page)

	Encorafenib 450 mg plus binimetinib 45 mg group (n=192)			Encorafenib 300 mg group (n=192)			Vemurafenib 960 mg group (n=186)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
(Continued from previous page)									
Generalised pruritus	6 (3%)	0	0	18 (9%)	0	0	18 (10%)	2 (1%)	0
Generalised rash	6 (3%)	0	0	12 (6%)	1 (1%)	0	9 (5%)	8 (4%)	0
Decreased weight	6 (3%)	0	0	27 (14%)	2 (1%)	0	20 (11%)	0	0
General physical health deterioration	1 (1%)	3 (2%)	1 (1%)	1 (1%)	3 (2%)	0	1 (1%)	6 (3%)	2 (1%)
Keratoacanthoma	4 (2%)	1 (1%)	0	13 (7%)	0	0	15 (8%)	6 (3%)	0
Pain	3 (2%)	2 (1%)	0	5 (3%)	7 (4%)	0	3 (2%)	0	0
Pleural effusion	0	4 (2%)	0	2 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0
Maculopapular rash	4 (2%)	0	0	17 (9%)	1 (1%)	0	19 (10%)	8 (4%)	0
Squamous cell carcinoma	2 (1%)	0	0	3 (2%)	0	0	4 (2%)	8 (4%)	0

Data are n (%). Data shown for at least 10% (grade 1 or 2) or at least 2% (grade 3 or 4) of patients in any treatment group. Complete data are found in the appendix on pp 16–22. As per the study protocol, deaths were not graded and therefore are not included in this table. One instance of acute myocardial infarction leading to death in the encorafenib group is presented as a death in the appendix (p 24). ALT=alanine aminotransferase. GGT=γ-glutamyltransferase. PPE=palmar-plantar erythrodysaesthesia.

Table 3: **Common adverse events by treatment group**

binimetinib and encorafenib monotherapy improved progression-free survival compared with vemurafenib,[23] consistent with preclinical observations that increased encorafenib potency could translate into enhanced clinical efficacy.[22,27]

However, some differences between the patient population in COLUMBUS and the pivotal trials for other BRAF–MEK inhibitor combination therapies should be kept in mind when assessing the efficacy of encorafenib plus binimetinib. The proportion of patients with elevated lactate dehydrogenase concentrations, a negative prognostic factor, was lower in the combination treatment group in COLUMBUS (29%) than in the trials investigating dabrafenib plus trametinib (COMBI-v [34%] and COMBI-d [37%]) or vemurafenib plus cobimetinib (coBRIM [46%]).[10–12] Other prognostic factors (eg, proportion of patients in each study with late-stage disease, performance status, and degree of organ involvement) were similar.[10–12]

Although the COLUMBUS trial was not designed to compare encorafenib plus binimetinib with established BRAF–MEK inhibitor combinations, vemurafenib results observed across multiple trials, including COLUMBUS, COMBI-v, and coBRIM, were similar across multiple endpoints. This indicates that the patient populations across these trials had a similar prognosis and expected response to treatment despite small differences in individual patient characteristics (eg, baseline lactate dehydrogenase concentrations). Median progression-free survival for vemurafenib was 7·3 months (95% CI 5·6–8·2) in COLUMBUS and COMBI-v and 7·2 months (5·6–7·5) in coBRIM.[14,23,28] Median overall survival in the vemurafenib groups in these studies was also similar: 16·9 months (95% CI 14·0–24·5) in COLUMBUS, 18·0 months (15·6–20·7) in COMBI-v, and 17·4 months (15·0–19·8) in coBRIM.[14,28] These data suggest that differences in the prognostic characteristics across trials did not affect outcomes.

The use of newly available immunotherapies among patients in COLUMBUS after they had discontinued the study drug must also be considered when assessing the efficacy results observed with encorafenib plus binimetinib. The types of systemic treatment received after study drug discontinuation—including immunotherapy with ipilimumab, nivolumab, and pembrolizumab—were generally similar in all three groups, with slightly higher use of BRAF–MEK inhibitor regimens in the encorafenib and vemurafenib groups, as expected in patients who progress on monotherapy.

COLUMBUS was done more recently than other pivotal trials of BRAF–MEK inhibitors for *BRAF*-mutant melanoma, by which time other effective therapies for *BRAF*-mutant melanoma had become available in some countries for post-progression treatment. However, the use of such subsequent therapies was generally similar in COLUMBUS and other major trials of BRAF–MEK inhibitor therapies (appendix p 15) because most patients who participated in these trials were enrolled from EU countries, where anti-PD-1 immunotherapies were not approved until 2015. For many patients, access to these approved therapies occurred later because of the time required for national payer reimbursement assessments. Therefore, use of subsequent immunotherapy is unlikely to underlie the observed differences in overall survival between COLUMBUS and the main trials of other BRAF–MEK inhibitor combinations.[14,20] Vemurafenib showed a similar overall survival across trials, including COMBI-d, coBRIM, and COLUMBUS, implying that differences in subsequent therapies are unlikely to have affected relative overall survival outcomes.

Without a direct randomised comparison, a definitive assessment of the relative efficacy of BRAF–MEK

inhibitor regimens is not possible. However, assessment of the data suggests that neither differences in patient populations nor use of subsequent therapy had a major influence on the overall and progression-free survival outcomes in COLUMBUS, so the efficacy of encorafenib plus binimetinib is likely to be related to the specific molecular properties of encorafenib or binimetinib.

One limitation of this report is that we were not able to include quality-of-life data, which put progression-free and overall survival in the context of patient experience and are an important component of the overall assessment of a therapy. These data will be reported separately.

During an additional 18 months of follow-up, we noted minor increases in treatment discontinuations related to adverse events and dose modifications among all treatment groups with longer follow-up. Increases in the frequency of adverse events were small, and most additional adverse events were grade 1 or 2. The relative incidence of individual adverse events was consistent with that in the earlier report,[23] and the most frequent adverse events in the binimetinib plus encorafenib group continued to be gastrointestinal (eg, nausea, diarrhoea, and vomiting); few additional adverse events associated with BRAF inhibitors or MEK inhibitors were noted. No additional events of left ventricular dysfunction or increased liver aminotransferase concentrations associated with MEK inhibitors occurred during longer-term treatment with encorafenib plus binimetinib. Serous retinopathy, a known class effect of MEK inhibitors, occurred at a similar frequency in the encorafenib plus binimetinib group to that observed in other trials of BRAF–MEK inhibitor combination therapy that monitored intensively for ocular toxicities; reported incidence correlates strongly with monitoring frequency.[14,29] Serous retinopathy is typically asymptomatic (grade 1) or minimally symptomatic (grade 2)[29] and is generally self-limiting and not associated with treatment interruption, functional deficits, or changes in the structural integrity of the eye even after years of therapy.[29] The incidence of pyrexia and photosensitivity with encorafenib plus binimetinib appeared to be better than that shown in trials of established BRAF–MEK inhibitor combinations.[12,14] Again, we could not make a direct comparison, but long-wave UVA-dependent photosensitivity—a common occurrence with vemurafenib, which necessitates UVA-optimised photoprotection—and the pyrexia that is regularly observed during treatment with dabrafenib plus trametinib, occurred less frequently in the encorafenib plus binimetinib group in COLUMBUS than has been reported in studies of these other treatments.[6,30]

Overall survival was not the primary endpoint of the study, although the comparison of the encorafenib plus binimetinib group with the vemurafenib group was included in the testing hierarchy in COLUMBUS. Testing within the hierarchy was stopped when patients treated with encorafenib plus binimetinib showed a greater than 5-month improvement in median progression-free survival compared with those treated with encorafenib, although the difference in progression-free survival at the time of the initial analysis did not reach significance (p=0·051).[23] Despite this outcome, the study sponsor remained masked to overall survival data until the analysis, and the analysis was done when the prespecified number of events had occurred. Nonetheless, the observed effect of encorafenib plus binimetinib compared with vemurafenib was clinically meaningful and reached nominal significance (ie, p<0·0001). Analyses of overall survival for the combination of binimetinib and encorafenib compared with encorafenib, and for encorafenib compared with vemurafenib, were not powered. However, results for overall survival from the comparison of the combination group versus encorafenib (HR 0·81 [95% CI 0·61–1·06]) and the comparison of encorafenib versus vemurafenib (0·76 [0·58–0·98]) were consistent with results for the primary endpoint of progression-free survival. Further follow-up will be required to better characterise these comparisons.

In conclusion, patients treated with encorafenib plus binimetinib had longer progression-free and overall survival than those treated with vemurafenib. These data provide a new benchmark against which new BRAF–MEK inhibitor therapies for *BRAF*-mutant melanoma can be measured. Together with a favourable tolerability profile, encorafenib plus binimetinib could become an important new treatment option for patients with *BRAF*-mutant melanoma. Trials are planned and underway to assess the use of encorafenib and binimetinib as adjuvant treatment or in combination with immunotherapy.

Contributors

RD was on the steering committee and contributed to protocol development, development of algorithms for adverse event management, trial management, analysis of the data, and writing. PAA was on the steering committee and contributed to study design, recruitment of patients, data collection, data analysis, data interpretation, and writing. HJG contributed to the literature search, recruitment of patients, data collection, and data interpretation. AA contributed to recruitment of patients and interpretation of data. MM contributed to recruitment of patients and collection of data. GL contributed to recruitment of patients and collection of data. CG contributed to recruitment of patients, data collection, data analysis, data interpretation, and writing. DS contributed to recruitment of patients, study design, data collection, data analysis, and writing. IK contributed to recruitment of patients and collection of data. RG contributed to recruitment of patients, data collection, data interpretation, and writing. VCS contributed to recruitment of patients, data collection, and data interpretation, and writing. CD was a study investigator and contributed to recruitment of patients. JWBdG contributed to patient recruitment, data collection, and data interpretation. NY contributed to recruitment of patients and collection of data. CL contributed to recruitment of patients and collection of data. LAM-dP contributed to the study design, data collection, data analysis, and data interpretation. MDP contributed to data analysis and data interpretation. VS contributed to data interpretation and writing. CR was on the steering committee and contributed to study design, data collection, data analysis, data interpretation, and writing. KTF was on the steering committee and contributed to the study design, data collection, data analysis, data interpretation, and writing. All authors contributed to the final review of the manuscript.

Declaration of interests

RD has had intermittent, project-focused consulting or advisory relationships, or both, with Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Amgen, Takeda, and Pierre Fabre outside the submitted work. RD works at the University of Zurich, which receives research funding for translational research projects from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, and Roche outside the submitted work. PAA has received consulting fees from Bristol-Myers Squibb, Roche Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array BioPharma, Merck Serono, Pierre Fabre, Incyte, NewLink Genetics, Genmab, MedImmune, Syndax, and AstraZeneca. PAA has received research funding from Bristol-Myers Squibb, Roche Genentech, and Array BioPharma outside the submitted work. HJG has received consulting fees from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Amgen, and research funding from Bristol-Myers Squibb and Merck Sharp & Dohme outside the submitted work. AA has received honoraria from, had a consulting or advisory role with, or been a member of the speakers bureau for Novartis, Roche, Merck Sharp & Dohme, and Bristol-Myers Squibb outside the submitted work, and has received travel expenses from Roche and Bristol-Myers Squibb. MM has received personal fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, and Pierre Fabre outside the submitted work. GL has received consulting fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, and Novartis outside the submitted work. CG has received personal fees and research funding from Novartis and Pierre Fabre during the conduct of the study. CG has received personal fees for presentations and consulting or advisory roles from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Philogen, and Roche and research funding from Bristol-Myers Squibb and Roche outside the submitted work. DS has received personal fees and patients' fees from Pierre Fabre during the conduct of the study. DS has received honoraria and travel expenses from, has a consulting or advisory role with, been a member of the speakers bureau for, and received personal fees from, Amgen, Boehringer Ingelheim, LEO Pharma, Roche, Merck Sharp & Dohme, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, Pierre Fabre, Merck-EMD, Pfizer, Philogen, and Array BioPharma. DS has received patients' fees from Roche, Merck Sharp & Dohme, Regeneron, Bristol-Myers Squibb, Merck-EMD, and Philogen outside the submitted work. IK is an advisory board member for and has received travel expenses from Bristol-Myers Squibb, Novartis, and Merck Sharp & Dohme during the conduct of the study. RG has received personal fees from Novartis and Pierre Fabre, patients' fees from Novartis and Array BioPharma, and research funding from Novartis during the conduct of the study. RG has received honoraria for lectures and consulting fees from Roche, Bristol-Myers Squibb, Novartis, Almirall, LEO Pharma, Amgen, Incyte, Boehringer Ingelheim, Regeneron, 4SC, AstraZeneca, Merck-EMD, Philogen, Johnson & Johnson, and Pfizer. RG has received research funding from Novartis, Pfizer, and Johnson & Johnson, non-financial support from Roche and Bristol-Myers Squibb, and patients' fees from Roche, Novartis, Regeneron, Philogen, and Bristol-Myers Squibb outside the submitted work. VCS has received consulting fees from Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, and Pierre Fabre outside the submitted work. JWBdG reports personal fees from Roche, Bristol-Myers Squibb, and Merck Sharp & Dohme outside the submitted work. NY reports research funding from Bristol-Myers Squibb during the conduct of the study. NY has received personal fees from Bristol-Myers Squibb and personal fees and research funding from Ono Pharmaceutical, Merck Sharp & Dohme, and Novartis outside the submitted work. CL reports personal fees from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, LEO Pharma, and Amgen outside the submitted work. MDP and VS were employees and shareholders of Array BioPharma during the conduct of the study. CR participated in advisory boards for Pierre Fabre, Roche, Novartis, Bristol-Myers Squibb, Merck, Array BioPharma, and Amgen outside the submitted work. KTF received consulting fees from Array BioPharma, Novartis, and Roche and received research funding from Novartis during the conduct of the study. CD and LAM-dP declare no competing interests.

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