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

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Abstract: BACKGROUND Combined BRAF-MEK inhibitor therapy is the standard of care for BRAF-mutant advanced melanoma. We investigated encorafenib, a BRAF inhibitor with unique target-binding properties, alone or in combination with the MEK inhibitor binimetinib, versus vemurafenib in patients with advanced BRAF-mutant melanoma. METHODS COLUMBUS was conducted as a two-part, randomised, open-label phase 3 study at 162 hospitals in 28 countries. Eligible patients were aged 18 years or older and had histologically confirmed locally advanced (American Joint Committee on Cancer [AJCC] stage IIIB, IIIC, or IV), unresectable or metastatic cutaneous melanoma, or unknown primary melanoma; a BRAF or BRAF mutation; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and were treatment naive or had progressed on or after previous first-line immunotherapy. In part 1 of the study, patients were randomly assigned (1:1:1) via interactive response technology to receive either 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). The primary endpoint was progression-free survival by blinded independent central review for encorafenib plus binimetinib versus vemurafenib. Efficacy analyses were by intention-to-treat. Safety was analysed in patients who received at least one dose of study drug and one postbaseline safety assessment. The results of part 2 will be published separately. This study 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 either the encorafenib plus binimetinib group (n=192), the encorafenib group (n=194), or the vemurafenib group (n=191). With a median follow-up of 16 · 6 months (95% CI 14 · 8-16 · 9), median progression-free survival was 14 · 9 months (95% CI 11 · 0-18 · 5) in the encorafenib plus binimetinib group and 7 · 3 months (5 · 6-8 · 2) in the vemurafenib group (hazard ratio [HR] 0 · 54, 95% CI 0 · 41-0 · 71; two-sided p<0 · 0001). The most common grade 3-4 adverse events seen in more than 5% of patients in the encorafenib plus binimetinib group were increased -glutamyltransferase (18 [9%] of 192 patients), increased creatine phosphokinase (13 [7%]), and hypertension (11 [6%]); in the encorafenib group they were palmoplantar erythrodysaesthesia syndrome (26 [14%] of 192 patients), myalgia (19 [10%]), and arthralgia (18 [9%]); and in the vemurafenib group it was arthralgia (11 [6%] of 186 patients). There were no treatment-related deaths except for one death in the combination group, which was considered possibly related to treatment by the investigator. INTERPRETATION Encorafenib plus binimetinib and encorafenib monotherapy showed favourable efficacy compared with vemurafenib. Overall, encorafenib plus binimetinib appears to have an improved tolerability profile compared with encorafenib or vemurafenib. Encorafenib plus binimetinib could represent a new treatment option for patients with BRAF-mutant melanoma. FUNDING Array BioPharma, Novartis.

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Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With *BRAF*-Mutant Melanoma: A Multicentre, Open-Label, Randomised Phase 3 Trial

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Summary

Background: BRAF/MEK inhibitor combination therapy is standard-of-care in *BRAFV600*-mutant advanced melanoma. We investigated encorafenib, a BRAF inhibitor with unique pharmacology, alone or in combination with the MEK inhibitor binimetinib, *vs* vemurafenib in advanced *BRAFV600*-mutant melanoma.

Methods: COLUMBUS (**CO**mbined **L**GX818 **U**sed with **M**EK162 in ***B****RAF*-mutant **U**nresectable **S**kin cancer) is a 2-part randomised phase 3 study conducted at 162 centres in 28 countries. In Part 1, patients with American Joint Committee on Cancer unresectable stage IIIB/C or IV *BRAFV600*-mutant melanoma were randomised via interactive response technology (1:1:1) to oral encorafenib 450 mg once daily plus binimetinib 45 mg twice daily (COMBO450), encorafenib 300 mg once daily (ENCO300), or vemurafenib 960 mg twice daily (VEM). Progression-free survival for COMBO450 *vs* VEM (primary endpoint) was analysed in the intention-to-treat population by blinded independent central review. Safety was analysed in patients who received at least one dose of study drug and one postbaseline safety assessment. Results of Part 2 will be published separately(NCT01909453/EudraCT 2013-001176-38).

Findings: Between December 30, 2013, and April 10, 2015, 577 patients were randomised (COMBO450, n=192; ENCO300, n=194; VEM, n=191) in Part 1. With a median follow-up of 16·6 (95% CI 14·8–16·9) months, risk of progression or death with COMBO450 compared with VEM was reduced by 46% (HR 0·54 [95% CI 0·41–0·71], 2-sided p<0·001). Median progression-free survival was 14·9 months (95% CI 11·0–18·5) with COMBO450, 9·6 months (95% CI 7·5–14·8) with ENCO300, and 7·3 months (95% CI 5·6–8·2) with VEM. The most common grade 3/4 adverse events seen in more than 5% of patients were increased gamma-glutamyl transferase (18 [9%]), increased creatine phosphokinase (13 [7%]), and hypertension

(11 [6%]) with COMBO450; palmoplantar erythrodysaesthesia syndrome (26 [14%]) and myalgia (19 [10%]) with ENCO300; and arthralgia (11 [6%]) with VEM.

Interpretation: COMBO450 and ENCO300 demonstrated favourable efficacy compared with VEM. Overall, COMBO450 displayed better tolerability than either comparator arm.

Funding: Array BioPharma and Novartis Pharmaceuticals Corporation.

Introduction

Genetic alterations resulting in an activated mitogen-activated protein kinase (MAPK) pathway occur in almost all melanomas. The most frequent is the *BRAFV600* mutation, occurring in 35–50% of patients.[1] Activating *BRAF* mutations drive constitutive MAPK pathway activation, with subsequent proliferation and enhanced cellular survival, making it a promising therapeutic target.[1] In vitro investigations demonstrated that growth of *BRAF*-mutated melanoma cells can be inhibited by BRAF or MEK inhibitors.[2]

A crystallography-guided drug design approach produced multiple ATP-competitive BRAF kinase inhibitors entering clinical trials, with vemurafenib the first to demonstrate efficacy in *BRAF*-mutant melanoma,[3,4] followed by dabrafenib.[5] MAPK pathway reactivation is implicated in BRAF inhibitor monotherapy resistance.[6] In addition, toxicities associated with BRAF inhibition, notably secondary squamous cell skin cancer and other skin toxicities, are caused by BRAF inhibitors paradoxically activating the wild-type BRAF kinase, promoting dimerization that triggers RAS-independent transactivation and activation of the MAPK pathway in normal tissues.[7] Subsequent clinical trials in patients with *BRAFV600*-mutant melanoma demonstrated that dual MAPK pathway targeting with a BRAF inhibitor and a MEK inhibitor improves efficacy and ameliorates paradoxical MAPK activation–related toxicities associated with BRAF inhibitor monotherapy.[8-11] Two BRAF/MEK inhibitor combinations (dabrafenib/trametinib and vemurafenib/cobimetinib) are considered options for the treatment of metastatic or unresectable *BRAFV600*-mutant melanoma in current treatment guidelines.[12,13] These BRAF/MEK inhibitor combinations are highly effective. However, both are associated with disease progression at a median of approximately 12 months, and each combination presents distinct tolerability

challenges to patients, highlighting the need for more effective and better tolerated therapies.[8-10,14-17]

Encorafenib is an ATP-competitive BRAF inhibitor that suppresses the MAPK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D, and K), with more than a 10-fold longer dissociation half-life (>30 hours) than either dabrafenib or vemurafenib, which enables sustained target inhibition.[18] Preclinical studies suggest that this property may enhance antitumour activity while reducing paradoxical activation of MAPK in normal tissues.[18,19] Binimetinib is an orally available, non-ATP competitive, allosteric inhibitor of MEK1 and MEK2.[20]

Promising clinical activity and tolerability of the combination of encorafenib and binimetinib were observed in patients with *BRAFV600*-mutated melanoma in a phase 1b/2 and a phase 2 study.[21,22] Further, the maximum tolerated dose of encorafenib, when combined with binimetinib, was higher than the maximum tolerated dose of encorafenib monotherapy, thus allowing the use of a higher encorafenib dose when combined with binimetinib in subsequent trials.[22] Here, we describe the results of the Part 1 of COLUMBUS trial, a phase 3 study of encorafenib plus binimetinib *vs* vemurafenib or encorafenib monotherapy in patients with advanced *BRAFV600*-mutant melanoma.

Methods

Study design and patients

COLUMBUS is a 2-part, multicentre, randomised, open-label, phase 3 study of the efficacy and safety of encorafenib and binimetinib combination therapy *vs* vemurafenib or encorafenib

monotherapy in patients with locally advanced unresectable or metastatic *BRAFV600*-mutant melanoma. In Part 1, patients were randomised at 162 centres in 28 countries, including 20 sites in North America, 124 sites in Europe, and 18 sites in other selected countries (see **Supplementary Materials**). After completion of Part 1 enrolment, patients were recruited into Part 2 of the study, and the combination of encorafenib at its monotherapy maximum dose plus binimetinib was compared with encorafenib monotherapy at the same dose. It was conducted to better characterize the contribution of binimetinib to the combination. Results of Part 2 will be published separately.

Eligible patients were 18 years of age or older; had a histologically confirmed diagnosis of locally advanced, unresectable/metastatic cutaneous melanoma or unknown primary melanoma with American Joint Committee on Cancer (AJCC) stage IIIB, IIIC, or IV; had presence of *BRAF* V600E and/or V600K mutation in tumour tissue; and were treatment-naive or had progressed on or after previous first-line immunotherapy (see **Supplementary Material** for detailed inclusion/exclusion criteria).

Independent ethics committees or review boards at each study site approved the study protocol and all amendments. Conduct of the study conformed with Good Clinical Practice guidelines and the ethical requirements outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before screening procedures were initiated.

Randomisation and masking

Patients were randomised (1:1:1) using validated interactive response technology (Parexel International, Billerica, MA, USA) to encorafenib 450 mg orally once daily plus binimetinib 45

mg orally twice daily (COMBO450), encorafenib 300 mg orally once daily (ENCO300), or vemurafenib 960 mg orally twice daily (VEM). Randomisation was stratified by AJCC stage (IIIB, IIIC, IVM1a, IVM1b, or IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0 or 1), and *BRAF* mutation status (*V600E vs V600K*). After protocol amendment 2 (December 20, 2013), prior first-line immunotherapy (yes *vs* no) replaced *BRAF* mutation status as a stratification factor. Investigators and patients were not masked to treatment assignment.

Procedures

Central genetic mutation analysis to determine the presence of *BRAF* mutations was conducted before enrolment using the bioMérieux THxID® BRAF diagnostic test (bioMérieux, Marcy l'Etoile, France), which identifies both *BRAF V600E* and *V600K* gene mutations. Patients received COMBO450, ENCO300, or VEM according to randomised treatment assignment and continued until progression of disease per central review, death, unacceptable toxicity or withdrawal of consent. Dose modifications, including treatment interruptions and dose reductions, were permitted for each of the agents based on tolerability and adverse events. Details regarding drug manufacture and permitted dose modifications are provided in the **Supplementary Materials**.

Baseline imaging was conducted within 21 days of randomisation and included chest, abdomen, and pelvis magnetic resonance imaging (MRI) or computed tomography (CT) and brain MRI or CT scan to assess central nervous system (CNS) disease. In the case of suspected bone metastases, a whole-body bone scan was performed; localized CT, MRI, or radiograph was performed for all skeletal lesions identified via the bone scan if not visible on the chest,

abdomen, and pelvis CT/MRI. If clinically indicated, a CT/MRI scan of other areas of disease, as appropriate, was performed. Color photography for all skin lesions, including a metric ruler to estimate the size, was performed. Tumour evaluations were performed every 8 weeks during the first 24 months and every 12 weeks thereafter using the same imaging modality as used at baseline. Additional tumour assessments were conducted if progression was clinically suspected. Tumour response was assessed centrally by blinded independent committee review (BICR) and by local review according to guidelines based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1·1.[23]

Safety assessments included collection of all adverse events; physical examinations included specific ophthalmic and dermatologic examination, cardiac assessments (electrocardiograms and multigated acquisition scans/echocardiograms), and clinical laboratory assessments. All patients in the COMBO450 arm had routine ophthalmic testing at each regularly scheduled visit during the treatment period. For patients in the ENCO300 and VEM arms, ophthalmic testing at each regularly scheduled visit was only required if retinal abnormalities were present at baseline. Details on the ophthalmological examinations are included in the **Supplementary Materials.** Adverse event severity was assessed according to the Common Terminology Criteria for Adverse Events version 4·03. Adverse events were monitored during the study and for at least 30 days after the last dose of study drug.

Outcomes

The primary endpoint was comparison of progression-free survival in the COMBO450 *vs* VEM groups as assessed by BICR. Secondary endpoints included comparison of progression-free survival in the COMBO450 *vs* ENCO300 groups; progression-free survival of patients in the

ENCO300 *vs* VEM groups; and best overall response, disease control rate, duration of response, and time to response. Detailed endpoint definitions are found in the **Supplementary Materials**. Data from tumour assessments read by BICR were used for the primary and secondary endpoints and analysis of best overall response, duration of response, and disease control; data from local assessments were used in supportive analyses. Analyses of other secondary outcomes, including overall survival (for which the number of events needed to trigger analyses has not yet been reached), quality of life, comparison of ECOG PS, and pharmacokinetic analysis, will be reported in a separate manuscript.

Statistical analysis

Sample size calculations were based on assumptions for progression-free survival medians derived from results of a phase 1b/2 study (NCT01543698) for COMBO450, a phase 1 study for ENCO300, and updated results from BRIM-3 and BRIM-2/COMBI-v, and coBRIM for VEM.[9,14,18,22,24-26]

Analyses of the primary and key (type 1 error controlled) secondary endpoints for Part 1 were event-driven and were performed when enrolment in Part 1 was complete and the prespecified number of progression-free survival events for both the final primary and Part 1 key secondary comparison were available. A hierarchical testing procedure was adopted to control type 1 error for the primary and key secondary endpoints. The Part 1 key secondary endpoint, progression-free survival of COMBO450 *vs* ENCO300, was to be tested if the primary efficacy endpoint, progression-free survival of COMBO450 *vs* VEM, was statistically significant. The driver of sample size was the key secondary endpoint of progression-free survival with COMBO450 *vs* ENCO300; for this comparison, 191 progression-free survival events were required to detect a

hazard ratio (HR) of 0·667 with 80% power using a log-rank test at a 1-sided 2·5% level of significance. For the primary comparisons of COMBO450 *vs* VEM, 145 progression-free survival events were required to detect an HR of 0·58 with 90% power using a log-rank test at a 1-sided 2·5% level of significance. Assuming that 15% of patients would be lost to follow-up, it was estimated that 576 patients (192 in each group) would need to be recruited.

Efficacy endpoints were analysed in the intention-to-treat population, which comprised all randomised patients. Patients were analysed by treatment group and strata as assigned during randomisation. Safety was analysed in all patients who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation; patients were analysed according to treatment actually received. All available data were used to the greatest extent possible without imputations for missing data. Details are included in **Supplementary Materials.**

Median duration of follow-up for progression-free survival was estimated in two ways: 1) by summarising the observed follow-up for each patient (ie, the duration from date of randomisation to date of progression-free survival event or censoring), and 2) by conducting reverse Kaplan-Meier analysis; the latter values are reported and reflect the potential follow-up in the absence of progressive disease or death. Progression-free survival was analysed according to the treatment group and 2 of the stratification factors (AJCC stage and ECOG PS) in which patients were randomised. Owing to the relatively low expected prevalence of patients with prior immunotherapy (~15%), it was prespecified that the 2 prior immunotherapy strata (yes *vs* no) were to be combined to avoid small or empty strata. Comparison of the distribution of progression-free survival used a stratified log-rank test; for the purposes of this summary, 2-sided p-values are reported. The distribution of progression-free survival was described using

Kaplan-Meier methodology. Stratified Cox regression models were used to estimate the HRs for progression-free survival, along with 95% CIs based on the Wald test. The same methods were used for the key secondary comparison and for the supportive analyses based on local tumour assessments. Overall response and disease control were presented by treatment group with exact 95% CIs; duration of response was estimated using the Kaplan-Meier methodology. For selected safety parameters, the time to first event was summarized using Kaplan-Meier methodology. Median time to onset and 95% CIs were summarised. Other median values were described using 95% CIs or interquartile ranges (IQRs).

The data cutoff date for analyses presented here was May 19, 2016. SAS version 9·2 (SAS Institute, Cary, NC, USA) or higher was used for all analyses. This study is registered with ClinicalTrials.gov, number NCT01909453, and with EudraCT, number 2013-001176-38.

Role of the funding source

The study was sponsored and designed with input from the steering committee (PAA, RD, CR, and KTF) by Novartis Pharmaceuticals Corporation until September 2015, when sponsorship was transferred to Array BioPharma Inc. The steering committee contributed to the creation of adverse event management guidelines and supervised patient recruitment. Data were collected by Novartis and Array BioPharma during their respective sponsorships. Data analysis was conducted by Array BioPharma's statistical team and interpreted by Array, in collaboration with the study authors. RD, PAA, CR, and KTF wrote the first draft of the manuscript with editorial support funded by the study sponsors, had full access to all study data, and held final responsibility for the decision to submit for publication.

Results

Between December 30, 2013, and April 10, 2015, 577 patients were enrolled and were randomised to receive COMBO450 (n=192), ENCO300 (n=194), or VEM (n=191). Among 1345 patients screened, 768 did not meet inclusion criteria; the most common reason for ineligibility was lack of the required *BRAFV600E/V600K* mutation in 364 of excluded patients (**Figure 1**). As of the data cutoff date of May 19, 2016, treatment was ongoing in 68, 46, and 27 patients in the COMBO450, ENCO300, and VEM groups, respectively. Demographic and clinical characteristics, including key prognostic factors at baseline, were similar across treatment groups (**Table 1**). Lactate dehydrogenase was above the upper limit of normal in 55 (29%), 47 (24%), and 52 patients (27%) randomised to COMBO450, ENCO300, and VEM, respectively. Patients had extensive disease, with 368 (64%) overall having stage IV M1c disease and 260 (45%) having 3 or more organs involved. A total of 172 patients (30%) overall had received prior immunotherapy; 26 patients (5%) had received prior checkpoint inhibitor therapy.

At the time of the data cutoff, 98, 96, and 106 events contributed to the analysis of progression-free survival in the COMBO450, ENCO300, and VEM groups, respectively. Median duration of follow-up was 16·7 months (95% CI 16·3–18·4) for the COMBO450 group, 14·4 months (95% CI 10·1–16·6) for the VEM group, and 16·6 months (95% CI 14·8–18·1) for the ENCO300 group. **Supplementary Table 1** provides the duration of progression-free survival by summary of the observed follow-for each patient and by reverse Kaplan-Meier analysis

Median progression-free survival assessed by BICR was longer for patients in the COMBO450 group (14·9 months [95% CI 11·0–18·5]) compared with either the VEM (7·3 months [95% CI 5·6–8·2]) or ENCO300 (9.6 months [95% CI 7·5–14·8]) groups.

The primary comparison of progression-free survival by BICR of the COMBO450 *vs* VEM groups showed a statistically significant 46% reduction in the risk of progression or death (HR 0·54 [95% CI 0·41–0·71]; 2-sided p<0·001; **Figure 2A**). Median progression-free survival by local assessment was similar: 14·8 months (95% CI 10·4–18·4), 7·3 months (95% CI 5·7–8·5), and 9·2 months (95% CI 7·4–12·9) in the COMBO450, VEM, and ENCO300 groups, respectively. Progression-free survival by local review was similarly improved with COMBO450 *vs* VEM (HR 0·49 [95% CI 0·37–0·64]; 2-sided nominal p<0·001; **Supplementary Figure 1**). All subgroup analyses for the comparison of COMBO450 with VEM demonstrated point estimates in favor of the COMBO450 group, except for the presence of brain metastases at baseline, but this analysis included only 9 patients in the COMBO450 group and 3 in the VEM group (**Figure 3**).

The secondary comparison of progression-free survival by BICR of the COMBO450 group with the ENCO300 group showed a 25% reduction in risk of progression or death in favour of the combination arm that did not reach statistical significance (HR 0·75 [95% CI 0·56–1·00] 2-sided p=0·051; **Figure 2B**). Progression-free survival by local assessment showed a slightly larger treatment effect in favour of COMBO450 compared with ENCO300 (HR 0·68 [95% CI 0·52–0·90]; 2-sided nominal p=0·006; **Supplementary Figure 1B**). Comparison of progression-free survival by BICR favoured the ENCO300 group over the VEM group (HR 0·68 [95% CI 0·52–0·90]; 2-sided nominal p=0·007); similar results were obtained by local assessment (**Supplementary Figure 2).**

A confirmed overall response by BICR occurred in 121 patients (63%) in the COMBO450 group compared with 98 (51%) in the ENCO300 group and 77 (40%) in the VEM group **(Table 2)**. The confirmed overall response by local review had a similar pattern but was higher in each group (COMBO450 group: 144 [75%]; ENCO300 group: 112 [58%]; VEM group: 94 [49%]). Median duration of confirmed objective response by BICR was 16·6 months (95% CI 12·2–20·4) for COMBO450, 14·9 months (95% CI 11·1–not estimable) for ENCO300, and 12·3 months (95% CI 6·9–16·9) for VEM. A confirmed complete response by BICR was achieved by 15 (8%), 10 (5%), and 11 patients (6%) in the COMBO450, ENCO300, and VEM groups, respectively. By local review, confirmed complete response occurred in 31 (16%), 17 (9%), and 14 patients (7%) in the COMBO450, ENCO300, and VEM groups, respectively.

In the COMBO450 group, the median duration of exposure for each component of the combination was similar, 51·2 weeks (IQR 27·1–79·7) for encorafenib and 50·6 weeks (IQR 26·1–79·7) for binimetinib. Median duration of exposure was 31·4 weeks (IQR 16·6–69·1) in the ENCO300 group and 27·1 weeks (IQR 15·1–48·3) in the VEM group. The median dose intensities in COMBO450 for encorafenib and binimetinib were 100% (IQR 93–100%) and 99·6% (IQR 80–100%) of planned doses, respectively. Median dose intensity was 86% (IQR 55–100%) of the planned dose for ENCO300 and 94% (IQR 74–100%) for VEM. The distribution of dose intensity for each treatment group is presented in **Supplementary Figure 3.** Most patients in the COMBO450 arm were able to achieve a dose intensity between 80% and 100% (152 [79%] for encorafenib and 144 [75%] for binimetinib), and few patients receiving the combination received less than 50% dose intensity (5 [3%] for encorafenib and 11 [6%] for binimetinib). In contrast, 98 patients (51%) and 116 patients (62%) in the ENCO300 and VEM

arms, respectively, achieved a dose intensity between 80% and 100%, and 42 (22%) and 13 (7%), respectively, achieved less than 50% dose intensity.

A total of 192 patients were evaluable for safety in both the COMB450 and ENCO300 groups; 186 patients were evaluable in the VEM group. Adverse events of grade 1 or 2 occurring in at least 10% of patients and grade 3 or 4 occurring in at least 2% of patients in any treatment group are summarized in **Table 3**. Common adverse events reported more frequently (at a rate of at least 10% higher) with COMBO450 than with ENCO300 or VEM included gastrointestinal toxicities (diarrhea, constipation, vomiting, and abdominal pain), predominantly asymptomatic increases in creatine phosphokinase, and blurred vision. Common adverse events reported at a lower frequency (at a rate of at least 10% lower) with COMBO450 than with ENCO300 or VEM were skin toxicities (including pruritus, hyperkeratosis, rash, keratosis pilaris, palmoplantar keratoderma, palmoplantar erythrodysaesthesia syndrome, dry skin, skin papilloma, macropapular rash, and sunburn), alopecia, photosensitivity reaction, arthralgia, myalgia, pain in the extremity, decreased appetite, musculoskeletal pain, and decreased weight. Grade 3/4 adverse events were reported in fewer patients with COMBO450 (111 [58%]) than with either ENCO300 (127 [66%]) or VEM (118 [63%]).

The median time to first grade 3 or 4 toxicity in all patients evaluable for safety was longer with COMBO450 (8·4 months [95% CI 6·1–11·8]) compared with ENCO300 (2.8 months [95% CI 1·2–5·8]) or VEM (3·7 months [95% CI 2·4–6·5]; **Supplementary Figure 4A**). Similarly, adverse events leading to treatment discontinuation and leading to dose reduction or interruption were lower with COMBO450 than with either ENCO300 or VEM; time to adverse event–related

treatment discontinuation was longer with COMBO450 than with ENCO300 or VEM (**Supplementary Table 1 and Supplementary Figure 4B**).

Toxicities known to be associated with available BRAF and MEK inhibitors were further explored by grouping individually reported adverse events representing similar clinical entities or pathophysiologic processes. These included pyrexia, rash, photosensitivity, secondary nonmelanoma skin cancers (including squamous cell cancer and basal cell carcinoma), serous retinopathy (including retinal pigment epithelial detachment), left ventricular dysfunction, and liver function test abnormalities (**Supplementary Table 2**). A toxicity associated with dabrafenib,[9,17] pyrexia (including increased body temperature, hyperpyrexia, and hyperthermia), occurred in 35 patients (18%) with COMBO450, 30 (16%) with ENCO300, and 55 (30%) with VEM. Pyrexia was grade 1 or 2 in 27 patients (14%), 28 patients (15%), and 55 patients (30%) in the COMBO450, ENCO300, VEM groups, respectively. Generally, skin toxicities, including rash, acneiform dermatitis, and palmoplantar erythrodysaesthesia syndrome, occurred less frequently with COMBO450 than with ENCO300 or VEM. Photosensitivity, a toxicity associated with vemurafenib,[10,14] was seen in 56 patients (30%) with VEM, 9 (5%) with COMBO450, and 8 (4%) with ENCO300. Secondary nonmelanoma skin cancers occurred infrequently. The most common were squamous cell cancers, in 5 patients (3%) with COMBO450, 15 (8%) with ENCO300 and 32 (17%) with VEM. Specific MEK inhibitor toxicities, including serous retinopathy and left ventricular dysfunction, were seen more frequently in the COMBO450 group than either the ENCO300 or VEM groups. Serous retinopathy occurred in 38 (20%), 4 (2%), and 3 patients (2%) treated with COMBO450, ENCO300, and VEM, respectively. The majority of events in the COMBO450 group were grade 1 (23 [12%]) or grade 2 (10 [5%]) and resulted in dose interruption/adjustment in 11 patients

(6%) but did not result in treatment discontinuations. Left ventricular dysfunction occurred in 15 (8%), 4 (2%), and 1 patient (1%) with COMBO450, ENCO300, and VEM treatment, respectively. In the COMBO450 group, the majority of left ventricular dysfunction was grade 1 (4 [2%]) or 2 (8 [4%]), led to dose interruption/adjustment in 12 patients (6%), was generally reversible, and did not result in treatment discontinuations. Elevated aspartate aminotransferase or alanine aminotransferase of grade 3 were reported in 13 (7%), 3 (2%), and 3 patients (2%) treated with COMBO450, ENCO300, and VEM, respectively. No grade 3 or 4 bilirubin elevations occurred in any treatment group.

Despite the longer duration of exposure in the COMBO450 group, the number of deaths that occurred during treatment or within 30 days of the last dose was similar among the 3 treatment groups: 17 (9%), 14 (7%), and 19 patients (10%) in the COMBO450, ENCO300, and VEM groups, respectively. On-treatment deaths were due to disease progression in 11 (6%), 12 (6%), and 17 patients (9%) in the COMBO450, ENCO300, and VEM groups, respectively. None of the deaths due to adverse events were considered likely to be related to study treatment (**Supplementary Table 3**).

Discussion

COMBO450 demonstrated a favourable efficacy and safety profile compared with VEM monotherapy in this phase 3, randomised trial in patients with *BRAF*-mutant melanoma. Progression-free survival with COMBO450 treatment was significantly longer than with VEM, which had progression-free survival consistent with that demonstrated in previous trials using VEM as the control in patients with *BRAF*-mutant melanoma.[9,10] COMBO450 improved median progression-free survival versus ENCO300, although results by blinded independent assessment

did not meet statistical significance (p=0·051). Overall response, complete response, and duration of response also were improved with COMBO450 relative to VEM and ENCO300. In addition, the tolerability profile of COMBO450 was favourable compared with VEM or ENCO300 monotherapy, as reflected in the higher dose intensity achieved and the longer median exposure to treatment in the COMBO450 group. The adverse event profile was also favourable, with fewer grade 3 or 4 toxicities, fewer toxicities requiring dose interruption or modification, a later time to onset of grade 3 or 4 adverse events, and fewer adverse event–related treatment discontinuations.

The mechanistic underpinnings of efficacy and safety for the various BRAF/MEK inhibitor combinations likely rest on the particular characteristics of the individual agents. Encorafenib inhibits BRAF V600E kinase activity in a biochemical assay at similar concentrations as dabrafenib and vemurafenib but with a dissociation half-life of more than 30 hours versus 2 hours with dabrafenib and 0·5 hours with vemurafenib, resulting in improved pharmacodynamics with prolonged pERK inhibition.[18] Further, in *BRAFV600*-mutant cell lines, encorafenib was more potent at inhibiting proliferation compared with dabrafenib or vemurafenib.[18]

Previous studies suggest that the maximum monotherapy dose of encorafenib was defined as 300 mg/d.[18] In combination with the MEK inhibitor binimetinib, however, the toxicities and overall tolerability of encorafenib when administered as a monotherapy are substantially ameliorated. This allows the use of the higher 450-mg dose of encorafenib in the combination, thus potentially providing greater and more prolonged pathway inhibition.[18] Consistent with these earlier results, this study confirmed the ability to safely increase the dose intensity of encorafenib in the combination.

In the phase 3 COMBI-d trial and COMBI-v trials, median progression-free survival for dabrafenib/trametinib was 11·0 months (95% CI 8·0–13·9) and 11·4 months (95% CI 9·9–14·9), respectively.[8,9,27] Median progression-free survival for vemurafenib/cobimetinib in the phase 3 coBRIM study was 12·3 months (95% CI 9·5–13·4).[10] In the current study, COMBO450 was associated with a median progression-free survival of 14·9 months (95% CI 11·0–18·5), the longest median progression-free survival observed to date with any BRAF/MEK inhibitor combination. Although cross-trial comparisons may be confounded by differences in patient populations, vemurafenib has served as a common control group across trials for all available BRAF/MEK inhibitor combinations, and its performance across those trials and in this study were nearly identical. In the COMBI-v and coBRIM studies, median progression-free survival was 7·3 months (95% CI 5·8–7·8) and 7·2 months (95% CI 5·6–7·5), respectively,[9,10,27] compared with 7·3 months (95% CI 5·6–8·2) by BICR and 7·3 months (95% CI 5·7–8·5) by local review in this study. This suggests that despite differences in individual baseline prognostic factors, such as the proportion of patients with elevated lactate dehydrogenase, the populations across these trials are similar overall with respect to their expected response to treatment. In addition, the improved efficacy of ENCO300 compared with VEM within this trial supports the hypothesis that prolonged pathway inhibition can lead to improved clinical outcomes. A direct comparison of COMBO450 with other BRAF/MEK inhibitor combinations would be needed for confirmation.

Although these currently available BRAF/MEK inhibitor combinations present largely overlapping toxicity profiles, each is associated with a specific toxicity: pyrexia with dabrafenib/trametinib and photosensitivity with vemurafenib/cobimetinib.[28,29] Both of these

toxicities are infrequent with COMBO450. Pyrexia is the most frequent adverse event with the dabrafenib and trametinib combination (in more than 50% of patients) and a leading cause of discontinuation, dose interruption, and dose reduction.[9,17] Some patients experienced multiple episodes of pyrexia, with episodes having a median duration of 3 days and, in some cases, requiring prophylactic treatment with glucocorticoids.[17] Photosensitivity reactions (47%) are common with the combination of vemurafenib and cobimetinib.[10,14,30] Photosensitivity is noted as requiring patient education and prospective and ongoing management by patients and clinical staff to mitigate effects.[10] In the current study, COMBO450 was associated with all-grade adverse events of interest of pyrexia in 35 patients (18%) and photosensitivity in 9 patients (5%). Pyrexia was qualitatively different from that observed with dabrafenib and trametinib; it generally was low grade, not recurrent, and most often associated with intercurrent illness or progressive disease.

This study has several limitations. Few patients had received prior immunotherapy; the ongoing SECOMBIT (NCT02631447), EORTC 1612 (NCT03235245), and IMMU-TARGET (NCT02902042) studies are formally testing the optimal approach for sequencing immunotherapy with ipilimumab/nivolumab or pembrolizumab with encorafenib/binimetinib. It is anticipated that these and other studies will determine the optimal combinations and sequences that will further improve outcomes for patients with *BRAF*-mutant melanoma.

In addition, this study did not have comparator arms for the available BRAF/MEK inhibitor combinations, limiting the ability to make direct comparisons. The comparator, vemurafenib, however, was used across all combinations and performed similarly across the trials, providing a common benchmark.[9,10] The benefit of COMBO450 will be further defined with longer follow-

up for progression-free survival. In prior *BRAF*-mutant melanoma trials, progression-free survival at first readout was 9·3 to 11·4 months, whereas more mature progression-free survival, reported about 1 year later, was about 2 months longer at 11·0 to 12·6 months.[8-10,14-16] Further follow-up of this study will determine whether a similar pattern will be observed. Finally, overall survival data, when it becomes available, will provide additional insights into the efficacy of COMBO450.

In conclusion, results of the COLUMBUS study demonstrate that COMBO450 improved progression-free survival compared with VEM and showed improvements in response and other secondary endpoints compared with ENCO300. Overall, COMBO450 had better tolerability compared with ENCO300 or VEM. COMBO450 represents a new treatment option for patients with *BRAF*-mutant melanoma.

Contributors

RD: steering committee, protocol development, development of algorithms for adverse event management, trial management, analysis of the data, manuscript writing and approval

PAA: steering committee, study design, data collection, data analysis, data interpretation, writing, final review, patient recruitment

HJG: literature search, data collection, data interpretation, final review, patient recruitment

AA: data interpretation, final review, patient recruitment

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Declaration of interests

RD: intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, and Pierre Fabre outside of the submitted work. The University of Zurich receives research funding for translational research projects from Novartis, MSD, BMS, and Roche.

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HJG: consultant for Roche, BMS, MSD, Novartis, and Amgen

AA: honoraria from and consulting/advisory role and speakers bureau for Novartis, Roche, MSD, and BMS; travel expenses from Roche and BMS

MM: honoraria from Novartis, GSK, BMS, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and BMS; advisory board member for Novartis, Amgen, MSD, and BMS; research funding from Roche

GL: none

CG: honoraria and travel expenses from and served in a consulting/advisory role and speakers bureau member for Amgen, BMS, MSD, Novartis, Roche, and Philogen; has received research funding for University Hospital Tübingen from BMS, Novartis, and Roche

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Panel: Research in context

Evidence before this study

We carefully reviewed articles and abstracts during the development of this manuscript identified via PubMed and Embase searches published between January 1, 2014, and December 20, 2017. Search terms were comprehensive (melanoma + treatment + phase [all fields]; encorafenib, BRAF inhibition + melanoma [all fields]). Selected abstracts were not limited to the English language and focused on phase 3 clinical trial data. Our search results indicate that combined the BRAF (dabrafenib and vemurafenib) and MEK (cobimetinib and trametinib) pathway inhibitors generate benefit in advanced melanoma in comparison to monotherapy. Preclinical and early clinical phase I and II data suggest that encorafenib in combination with binimetinib could be a new promising treatment option for patients with *BRAF*-mutant melanoma.

Added value of this study

In this prospective, randomised trial in patients with *BRAF*-mutant melanoma, treatment with the combination of encorafenib 450 mg and binimetinib 45 mg improved progression-free survival

and overall response compared with encorafenib 300 mg or vemurafenib, with better tolerability. For the first time, the head-to-head comparison of encorafenib 300 mg or vemurafenib showed a progression-free survival advantage for encorafenib supporting preclinical observations and a more profound pathway inhibition results in improved tumor control

Implications of all the available evidence

Encorafenib 450 mg in combination with binimetinib is a well-tolerated and efficacious treatment option for *BRAF*-mutant metastatic melanoma.

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Table 1: Baseline Demographics and Clinical Characteristics

Characteristic	COMBO450 n=192	ENCO300 n=194	VEM n=191
Mean age (SD), y	56 (14)	55 (13)	55 (14)
Male sex, n (%)	115 (60%)	108 (56%)	111 (58%)
ECOG performance status 0,* n (%)	136 (71%)	140 (72%)	140 (73%)
LDH ≥ULN, n (%)	55 (29%)	47 (24%)	52 (27%)
BRAF mutation status (*V600E*/*V600K*), n (%)	170 (89%)/22 (11%)	173 (89%)/19 (10%)†	168 (88%)/23 (12%)
Tumour stage at study entry, n (%)			
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, n (%)			
1	47 (24%)	56 (29%)	45 (24%)
2	58 (30%)	52 (27%)	59 (31%)
≥3	87 (45%)	86 (44%)	87 (46%)
Prior immunotherapy, n (%)	57 (30%)	58 (30%)	57 (30%)
Ipilimumab	7 (4%)	10 (5%)	7 (4%)
Prior anti–PD-1 or anti–PD-L1	1 (1%)	2 (1%)	0
Interferons/interleukins	51 (27%)	51 (26%)	52 (27%)

COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ECOG=Eastern Cooperative Oncology Group; ENCO300=encorafenib 300 mg once daily; LDH=lactate dehydrogenase; PD-1=programmed death 1; PD-L1=programmed death ligand 1; ULN=upper limit of normal; VEM=vemurafenib.

*All other patients had ECOG performance status of 1.

†Two observations were indeterminate.

Table 2: Best Overall Response by Central Blinded Independent and Local Review

	COMBO450		ENCO300		VEM	
Confirmed Response	**n=192**		**n=194**		**n=191**	
	Central Review	**Local Review**	**Central Review**	**Local Review**	**Central Review**	**Local Review**
Best overall response, n (%)						
Complete response	15 (8%)	31 (16%)	10 (5%)	17 (9%)	11 (6%)	14 (7%)
Partial response	106 (55%)	113 (59%)	88 (45%)	95 (49%)	66 (35%)	80 (42%)
Stable disease*	56 (29%)	35 (18%)	65 (34%)	56 (29%)	79 (41%)	66 (35%)
Progressive disease[†]	15 (8%)	13 (7%)	31 (16%)	26 (13%)	35 (18%)	31 (16%)
Overall response,[‡] n (%) [95% CI]	121 (63%) [56–70]	144 (75%) [68–81]	98 (51%) [43–58]	112 (58%) [50–65]	77 (40%) [33–48]	94 (49%) [42–57]
Disease control[§] n (%) [95% CI]	177 (92%) [87–96]	179 (93%) [89–96]	163 (84%) [78–89]	168 (87%) [81–91]	156 (82%) [75–87]	160 (84%) [78–89]

COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ENCO300=encorafenib 300 mg once daily; VEM=vemurafenib.

*Includes patients with nonmeasurable disease and a status of non-complete response/non-progressive disease.

[†]Includes patients with best response of unknown or no assessment.

[‡]Overall response was defined as complete response plus partial response.

[§]Disease control defined as the proportion of patients with a best overall response of complete response, partial response, stable disease, or non-complete response/non-progressive disease.

Table 3: Adverse Events Irrespective of Causality in at Least 10% (Grade 1 or 2) or at Least 2% (Grade 3 or 4) of Patients in Any Treatment Group

	COMBO450 n=192			ENCO300 n=192			VEM n=186		
Preferred Term, n (%)	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**
Nausea	76 (40%)	3 (2%)	0	66 (34%)	8 (4%)	0	60 (32%)	3 (2%)	0
Diarrhoea	65 (34%)	4 (2%)	1 (1%)	23 (12%)	3 (2%)	0	59 (32%)	4 (2%)	0
Vomiting	54 (28%)	3 (2%)	0	43 (22%)	9 (5%)	0	26 (14%)	2 (1%)	0
Fatigue	51 (27%)	4 (2%)	0	47 (24%)	1 (1%)	0	53 (28%)	4 (2%)	0
Arthralgia	48 (25%)	1 (1%)	0	66 (34%)	18 (9%)	0	72 (39%)	11 (6%)	0
Blood CK increased	31 (16%)	11 (6%)	2 (1%)	2 (1%)	0	0	4 (2%)	0	0
Constipation	42 (22%)	0	0	27 (14%)	0	0	11 (6%)	0	1 (1%)
Headache	39 (20%)	3 (2%)	0	46 (24%)	6 (3%)	0	34 (18%)	1 (1%)	0
Asthenia	32 (17%)	2 (1%)	1 (1%)	32 (17%)	5 (3%)	0	26 (14%)	8 (4%)	0
Pyrexia	28 (15%)	7 (4%)	0	27 (14%)	2 (1%)	0	52 (28%)	0	0

Abdominal pain	27 (14%)	5 (3%)	0	9 (5%)	4 (2%)	0	11 (6%)	1 (1%)	0
Vision blurred	30 (16%)	0	0	4 (2%)	0	0	4 (2%)	0	0
Anaemia	21 (11%)	7 (4%)	1 (1%)	6 (3%)	5 (3%)	0	10 (5%)	3 (2%)	1 (1%)
GGT increased	11 (6%)	18 (9%)	0	12 (6%)	8 (4%)	1 (1%)	15 (8%)	5 (3%)	1 (1%)
Dry skin	27 (14%)	0	0	58 (30%)	0	0	42 (23%)	0	0
Hyperkeratosis	26 (14%)	1 (1%)	0	65 (34%)	7 (4%)	0	54 (29%)	0	0
Rash	25 (13%)	1 (1%)	1 (1%)	37 (19%)	4 (2%)	0	48 (26%)	6 (3)	0
Alopecia	26 (14%)	0	0	107 (56%)	0	0	68 (37%)	0	0
Myalgia	26 (14%)	0	0	35 (18%)	19 (10%)	0	33 (18%)	1 (1%)	0
Dizziness	21 (11%)	3 (2%)	0	9 (5%)	0	0	5 (3%)	0	0
ALT increased	11 (6%)	10 (5%)	0	8 (4%)	2 (1%)	0	11 (6%)	3 (2%)	0
Hypertension	10 (5%)	11 (6%)	0	5 (3%)	6 (3%)	0	15 (8%)	6 (3%)	0
Pain in extremity	19 (10%)	2 (1%)	0	40 (21%)	2 (1%)	0	23 (12%)	2 (1%)	0
Pruritus	20 (10%)	0	1 (1%)	41 (21%)	1 (1%)	0	20 (11%)	0	0
Back pain	17 (9%)	1 (1%)	0	24 (13%)	5 (3%)	0	8 (4%)	2 (1%)	1 (1%)
Insomnia	18 (9%)	0	0	30 (16%)	5 (3%)	0	15 (8%)	0	0

Palmoplantar keratoderma	17 (9%)	0	0	46 (24%)	3 (2%)	0	27 (15%)	2 (1%)	0
Decreased appetite	16 (8%)	0	0	39 (20%)	1 (1%)	0	34 (18%)	2 (1%)	0
Erythema	13 (7%)	0	0	23 (12%)	1 (1%)	0	30 (16%)	1 (1%)	0
PPE syndrome	13 (7%)	0	0	72 (38%)	26 (14%)	0	24 (13%)	2 (1%)	0
Skin papilloma	12 (6%)	0	0	18 (9%)	0	0	31 (17%)	0	0
Musculoskeletal pain	11 (6%)	0	0	26 (14%)	6 (3%)	0	9 (5%)	2 (1%)	0
Keratosis pilaris	9 (5%)	0	0	33 (17%)	0	0	43 (23%)	0	0
Photosensitivity reaction	7 (4%)	1 (1%)	0	7 (4%)	0	0	43 (23%)	2 (1%)	0
Keratoacanthoma	4 (2%)	0	0	12 (6%)	0	0	15 (8%)	6 (3%)	0
Rash maculo-papular	3 (2%)	0	0	17 (9%)	1 (1%)	0	19 (10%)	8 (4%)	0

ALT=alanine aminotransferase; CK=creatine phosphokinase; COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ENCO300=encorafenib 300 mg once daily; GGT=gamma-glutamyl transferase; PPE=palmoplantar erythrodysaesthesia; VEM=vemurafenib.

FIGURE LEGENDS

Figure 1: CONSORT Diagram.

BID=twice daily; QD=once daily. *Patient/guardian decision. †Primary reason. ‡Ongoing at the time of data cutoff of May 19, 2016.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival – Response Assessed by Blinded Independent Review. (A) COMBO450 versus VEM. (B) COMBO450 versus ENCO300.

COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ENCO300=encorafenib 300 mg once daily; HR=hazard ratio; VEM=vemurafenib.

Figure 3: Progression-Free Survival by BICR of Patients in the COMBO450 versus VEM Treatment Groups by Prespecified Subgroups According to Baseline Characteristics.

AJCC=American Joint Committee on Cancer; BICR=Blinded Independent Committee Review; COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactate dehydrogenase; PS=performance status; ULN=upper limit of normal; VEM=vemurafenib.

Figure 1.

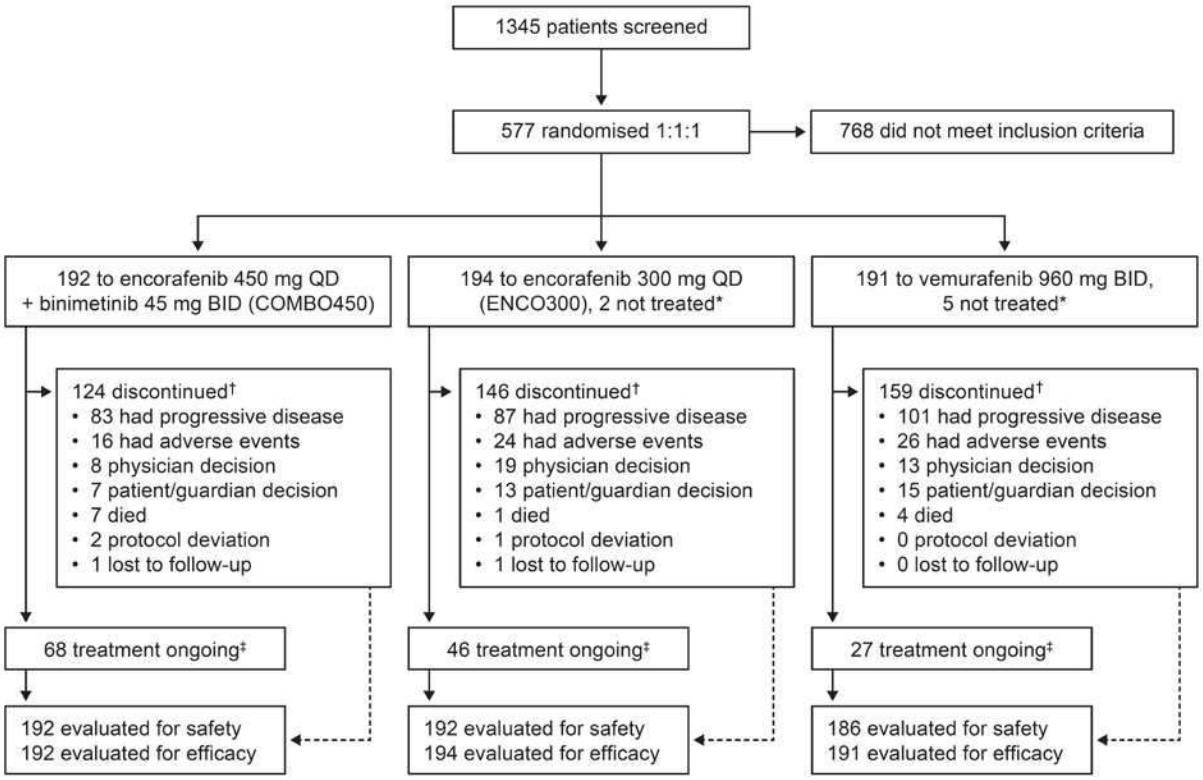
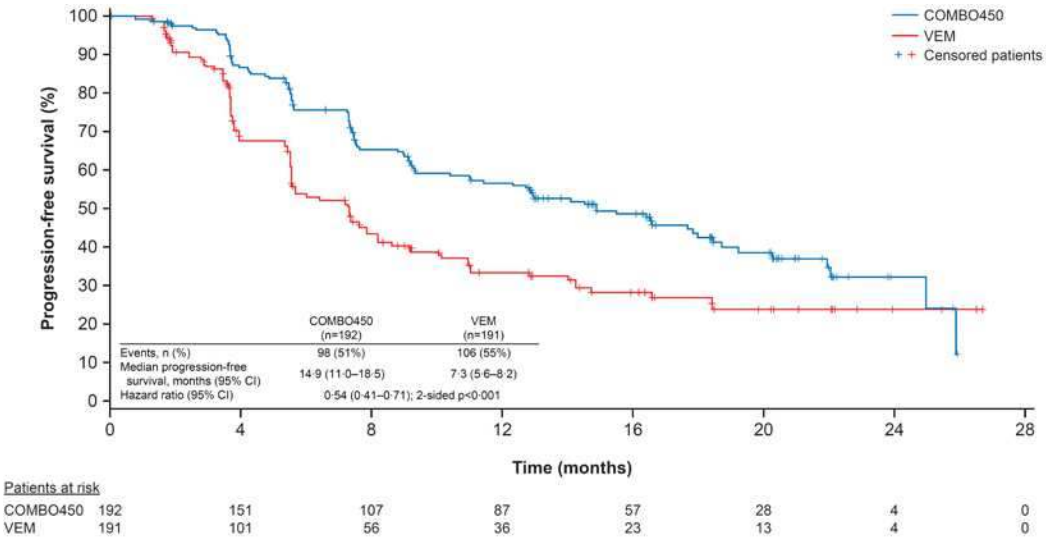

1345 patients screened
577 randomised 1:1:1
768 did not meet inclusion criteria
192 to encorafenib 450 mg QD + binimetinib 45 mg BID (COMBO450)
194 to encorafenib 300 mg QD (ENCO300), 2 not treated*
191 to vemurafenib 960 mg BID, 5 not treated*
124 discontinued†
• 83 had progressive disease
• 16 had adverse events
• 8 physician decision
• 7 patient/guardian decision
• 7 died
• 2 protocol deviation
• 1 lost to follow-up
146 discontinued†
• 87 had progressive disease
• 24 had adverse events
• 19 physician decision
• 13 patient/guardian decision
• 1 died
• 1 protocol deviation
• 1 lost to follow-up
159 discontinued†
• 101 had progressive disease
• 26 had adverse events
• 13 physician decision
• 15 patient/guardian decision
• 4 died
• 0 protocol deviation
• 0 lost to follow-up
68 treatment ongoing‡
46 treatment ongoing‡
27 treatment ongoing‡
192 evaluated for safety
192 evaluated for efficacy
192 evaluated for safety
194 evaluated for efficacy
186 evaluated for safety
191 evaluated for efficacy

Figure 2.

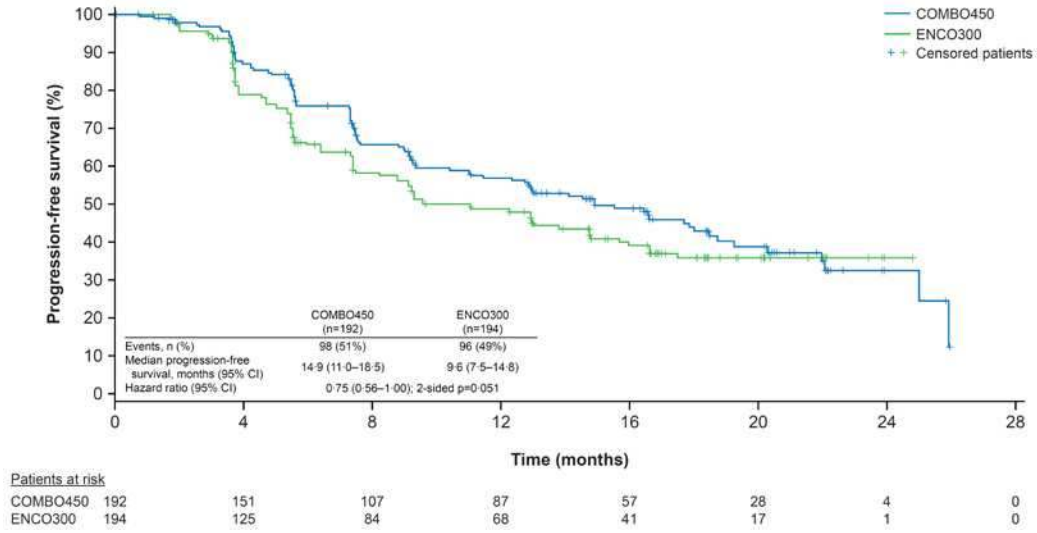
A



Patients at risk

COMBO450	192	151	107	87	57	28	4	0
VEM	191	101	56	36	23	13	4	0

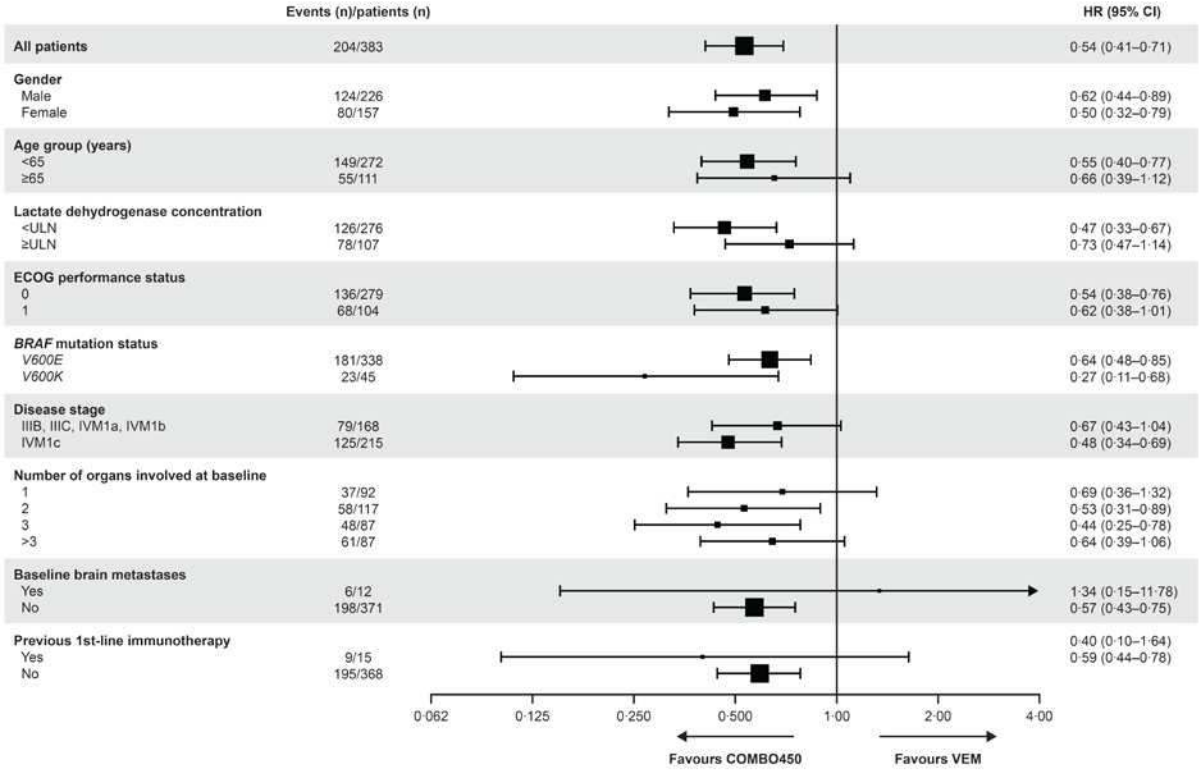
B



Patients at risk

COMBO450	192	151	107	87	57	28	4	0
ENCO300	194	125	84	68	41	17	1	0

Figure 3.


Events (n)/patients (n)
HR (95% CI)
All patients
204/383
0·54 (0·41–0·71)
Gender
Male
124/226
0·62 (0·44–0·89)
Female
80/157
0·50 (0·32–0·79)
Age group (years)
<65
149/272
0·55 (0·40–0·77)
≥65
55/111
0·66 (0·39–1·12)
Lactate dehydrogenase concentration
<ULN
126/276
0·47 (0·33–0·67)
≥ULN
78/107
0·73 (0·47–1·14)
ECOG performance status
0
136/279
0·54 (0·38–0·76)
1
68/104
0·62 (0·38–1·01)
BRAF mutation status
V600E
181/338
0·64 (0·48–0·85)
V600K
23/45
0·27 (0·11–0·68)
Disease stage
IIIB, IIIC, IVM1a, IVM1b
79/168
0·67 (0·43–1·04)
IVM1c
125/215
0·48 (0·34–0·69)
Number of organs involved at baseline
1
37/92
0·69 (0·36–1·32)
2
58/117
0·53 (0·31–0·89)
3
48/87
0·44 (0·25–0·78)
>3
61/87
0·64 (0·39–1·06)
Baseline brain metastases
Yes
6/12
1·34 (0·15–11·78)
No
198/371
0·57 (0·43–0·75)
Previous 1st-line immunotherapy
0·40 (0·10–1·64)
Yes
9/15
0·59 (0·44–0·78)
No
195/368
0·062
0·125
0·250
0·500
1·00
2·00
4·00
Favours COMBO450
Favours VEM