Contribution of MEK Inhibition to BRAF/MEK Inhibitor Combination Treatment of BRAF-Mutant Melanoma: Part 2 of the Randomized, Open-Label, Phase III COLUMBUS Trial

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Abstract: PURPOSE In COLUMBUS part 1, patients with advanced $BRAF^{V600}$-mutant melanoma were randomly assigned 1:1:1 to encorafenib 450 mg once daily plus binimetinib 45 mg twice a day (COMBO450), vemurafenib 960 mg twice a day, or encorafenib 300 mg once daily (ENCO300). As previously reported, COMBO450 improved progression-free survival (PFS) versus vemurafenib (part 1 primary end point) and ENCO300 (part 1 key secondary end point; not statistically significant). Part 2, requested by the US Food and Drug Administration, evaluated the contribution of binimetinib by maintaining the same encorafenib dosage in the combination (encorafenib 300 mg once daily plus binimetinib 45 mg twice daily [COMBO300]) and ENCO300 arms. METHODS In part 2, patients were randomly assigned 3:1 to COMBO300 or ENCO300. ENCO300 (parts 1 and 2) data were combined, per protocol, for PFS analysis (key secondary end point) by a blinded independent review committee (BIRC). Other analyses included overall response rate (ORR), overall survival, and safety. RESULTS Two hundred fifty-eight patients received COMBO300, and 86 received ENCO300. Per protocol, ENCO300 arms (parts 1 and 2 combined) were also evaluated (n = 280). The median follow-up for ENCO300 was 40.8 months (part 1) and 57.1 months (part 2). The median PFS (95% CI) was 12.9 months (10.9 to 14.9) for COMBO300 versus 9.2 months (7.4 to 11.1) for ENCO300 (parts 1 and 2) and 7.4 months (5.6 to 9.2) for ENCO300 (part 2). The hazard ratio (95% CI) for COMBO300 was 0.74 (0.60 to 0.92; two-sided P = .003) versus ENCO300 (parts 1 and 2). The ORR by BIRC (95% CI) was 68% (62 to 74) and 51% (45 to 57) for COMBO300 and ENCO300 (parts 1 and 2), respectively. COMBO300 had greater relative dose intensity and fewer grade 3/4 adverse events than ENCO300. CONCLUSION COMBO300 improved PFS, ORR, and tolerability compared with ENCO300, confirming the contribution of binimetinib to efficacy and safety.

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ABSTRACT

PURPOSE In COLUMBUS part 1, patients with advanced *BRAF*^{V600}-mutant melanoma were randomly assigned 1:1:1 to encorafenib 450 mg once daily plus binimetinib 45 mg twice a day (COMBO450), vemurafenib 960 mg twice a day, or encorafenib 300 mg once daily (ENCO300). As previously reported, COMBO450 improved progression-free survival (PFS) versus vemurafenib (part 1 primary end point) and ENCO300 (part 1 key secondary end point; not statistically significant). Part 2, requested by the US Food and Drug Administration, evaluated the contribution of binimetinib by maintaining the same encorafenib dosage in the combination (encorafenib 300 mg once daily plus binimetinib 45 mg twice daily [COMBO300]) and ENCO300 arms.

METHODS In part 2, patients were randomly assigned 3:1 to COMBO300 or ENCO300. ENCO300 (parts 1 and 2) data were combined, per protocol, for PFS analysis (key secondary end point) by a blinded independent review committee (BIRC). Other analyses included overall response rate (ORR), overall survival, and safety.

RESULTS Two hundred fifty-eight patients received COMBO300, and 86 received ENCO300. Per protocol, ENCO300 arms (parts 1 and 2 combined) were also evaluated (n = 280). The median follow-up for ENCO300 was 40.8 months (part 1) and 57.1 months (part 2). The median PFS (95% CI) was 12.9 months (10.9 to 14.9) for COMBO300 versus 9.2 months (7.4 to 11.1) for ENCO300 (parts 1 and 2) and 7.4 months (5.6 to 9.2) for ENCO300 (part 2). The hazard ratio (95% CI) for COMBO300 was 0.74 (0.60 to 0.92; two-sided P = .003) versus ENCO300 (parts 1 and 2). The ORR by BIRC (95% CI) was 68% (62 to 74) and 51% (45 to 57) for COMBO300 and ENCO300 (parts 1 and 2), respectively. COMBO300 had greater relative dose intensity and fewer grade 3/4 adverse events than ENCO300.

CONCLUSION COMBO300 improved PFS, ORR, and tolerability compared with ENCO300, confirming the contribution of binimetinib to efficacy and safety.

ACCOMPANYING CONTENT

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Protocol

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INTRODUCTION

Activating *BRAF*^{V600} mutations occur in approximately 50% of patients with melanoma.[1] Mutations drive constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, resulting in melanoma development and progression.[2] Dual inhibition of the MAPK pathway with BRAF/MEK inhibitor (BRAFi/MEKi) combination therapy is a standard treatment in patients with *BRAF*^{V600}-mutant metastatic melanoma[3] and has demonstrated improved progression-free survival (PFS) and overall survival (OS) with manageable tolerability compared with BRAFi monotherapy.[4-8]

Binimetinib is a potent, selective, allosteric, adenosine triphosphate (ATP)–uncompetitive inhibitor of MEK1/2 with a shorter half-life than other MEK1/2 inhibitors. Earlier studies demonstrated a maximum tolerated dose of binimetinib of 45 mg twice daily and showed that binimetinib may provide a rapid resolution of toxicity on interruption.[9] Via reduction of the MAPK pathway activity, binimetinib has a direct antitumor effect and indirect pharmacologic action at the tumor cell level. Encorafenib is an ATP-competitive BRAFi with unique pharmacology and dose-dependent efficacy.[10] In a phase I study of encorafenib, the recommended phase II dose was 300 mg

CONTEXT

Key Objective

What does binimetinib contribute to the efficacy and safety outcomes observed with encorafenib plus binimetinib combination therapy in patients with *BRAF*^{V600}-mutant melanoma?

Knowledge Generated

The addition of binimetinib to encorafenib (300 mg once daily) improved the efficacy and tolerability profile of the combination compared with encorafenib alone by mitigating BRAF inhibitor (BRAFi)–associated toxicity and allowing patients to receive a higher dose of encorafenib longer than those in the monotherapy arm. These results confirm the contribution of binimetinib to the encorafenib plus binimetinib combination regimen and extend the evidence for the inclusion of MEK inhibitor (MEKi) in BRAFi therapy in patients with *BRAF*^{V600}-mutant melanoma.

Relevance *(G.K. Schwartz)*

This study confirms that a MEKi should be combined with a BRAFi in the treatment of patients with BRAFV600-mutant melanoma.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD, FASCO.

once daily[11]; however, a phase Ib/II study demonstrated that encorafenib could be tolerated at a higher dose (450 mg once daily) when combined with binimetinib.[12,13]

COLUMBUS (ClinicalTrials.gov identifier: NCT01909453) is a two-part, randomized, active-controlled, phase III study evaluating the BRAFi/MEKi combination of encorafenib plus binimetinib.[8,14] In COLUMBUS part 1, 577 eligible patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation were randomly assigned to encorafenib 450 mg once daily plus binimetinib 45 mg twice a day (COMBO450; n = 192), encorafenib 300 mg once daily (ENCO300; n = 194), or vemurafenib 960 mg twice a day (n = 191).[8,14,15] The part 1 primary end point was PFS in the COMBO450 versus vemurafenib groups as assessed by blinded independent central review (BICR), and the part 1 key secondary end point was PFS in the COMBO450 versus ENCO300 groups.[8,14] As previously reported, COMBO450 improved PFS compared with vemurafenib, leading to approval of this dosage globally for the treatment of patients with *BRAF*^{V600}-mutant unresectable or metastatic melanoma.[16,17] PFS was improved for COMBO450 versus ENCO300 but was not statistically significant (P = .051).[8] Favorable safety and tolerability were observed for COMBO450 versus vemurafenib and versus ENCO300 monotherapy.

To isolate the contribution of binimetinib to combination therapy, COLUMBUS part 2 was designed with the same dosage of encorafenib in the combination and comparator arms: ENCO300 plus binimetinib 45 mg twice a day (COMBO300) versus ENCO300. Herein, we report the results of COLUMBUS part 2.

METHODS

Study Design and Patients

Results of part 1 have been published previously.[8,14,15] Part 2 was added by a protocol amendment after the study was initiated. The current analyses included patients randomly assigned to ENCO300 (part 1) and all patients randomly assigned in part 2 through the cutoff date (September 15, 2020). The study Protocol (online only) was approved by independent ethics committees or site institutional review boards. The 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.

Eligible patients were 18 years and older with a histologically confirmed diagnosis of locally advanced, unresectable/metastatic cutaneous melanoma or unknown primary melanoma (American Joint Committee on Cancer [AJCC] stage IIIB, IIIC, or IV) and the presence of *BRAF*^{V600E} and/or *BRAF*^{V600K} mutation in tumor tissue, determined before enrollment; were treatment-naive or had progressed on or after previous first-line immunotherapy for unresectable locally advanced/metastatic melanoma; had evidence of ≥1 measurable lesion as per radiologic or photographic methods according to criteria on the basis of RECIST version 1.1; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and had adequate bone marrow, organ function (including cardiac function), and laboratory parameters. Patients were not eligible if they had CNS lesions, unless the lesions were treated and not progressing; uveal or mucosal melanoma; history of leptomeningeal metastases; history or current evidence of or risk

of retinal vein occlusion; Gilbert's syndrome; previous BRAFi or MEKi treatment; previous systemic chemotherapy, extensive radiotherapy, or an investigational agent other than immunotherapy, or received >1 line of immunotherapy for locally advanced/unresectable or metastatic melanoma; impaired cardiovascular function; uncontrolled arterial hypertension; and neuromuscular disorders associated with elevated creatine kinase.

Random Assignment and Masking

Data collected from patients who received ENCO300 in part 1 were included in the analyses. Patients were not concurrently recruited to the ENCO300 group in part 1 and part 2. In part 1, patients were randomly assigned 1:1:1 via interactive response technology (IRT) to one of the three treatment arms (COMBO450, ENCO300, or vemurafenib).[8] In part 2, patients were randomly assigned 3:1 via IRT to COMBO300 or ENCO300, respectively. For the part 2 PFS analysis timepoint, patients randomly assigned to COMBO300 and ENCO300 (parts 1 and 2) contributed to the main comparisons. The random assignment ratio used in part 2 was designed to achieve similar numbers of patients for analysis of the COMBO300 and ENCO300 arms combined from parts 1 and 2. Random assignment was stratified by AJCC stage (IIIB + IIIC + IVM1a + IVM1b *v* IVM1c), ECOG PS (0 *v* 1), and previous first-line immunotherapy (yes *v* no). Investigators and patients were aware of the treatment assignment.

Procedures

The presence of *BRAF* mutations was determined centrally before enrollment. For patients who did not tolerate initial doses of encorafenib or binimetinib, adjustments, including dose reductions or interruptions, were permitted to allow the patient to continue taking study medication (see the study Protocol [online only] for details).

Baseline imaging was conducted within 21 days before random assignment and included chest, abdomen, and pelvis magnetic resonance imaging (MRI) or computed tomography (CT), and brain MRI or CT scan to assess CNS disease. For suspected bone metastases, whole-body bone scans were performed as indicated, with localized CT, MRI, or x-rays of all skeletal lesions identified. Tumor evaluations were performed every 8 weeks during the first 24 months and every 12 weeks thereafter, using the same baseline imaging modality, until progression as determined by the blinded independent review committee (BIRC). Survival was assessed every 12 weeks after progression.

Safety assessments included collection of all adverse events (AEs), including AE severity assessed via Common Terminology Criteria for Adverse Events v4.03. AEs were coded using Medical Dictionary for Regulatory Activities. AEs of special interest for encorafenib and binimetinib were selected on the basis of safety signals observed in previous studies and from known toxicities associated with other same-class drugs. Other assessments in the study included regular physical, ophthalmic, and dermatologic examinations; cardiac assessments (electrocardiogram, multiple-gated acquisition scan, echocardiogram); ECOG PS; vital signs; body weight; and regular laboratory testing (hematology, chemistry, coagulation, and urine).

Outcomes

Updated analyses were conducted 65 months after the last patient was randomly assigned for PFS, OS, overall response rate (ORR), safety, and tolerability outcomes. A key secondary end point of COLUMBUS was PFS (time from the date of random assignment to the date of first documented progression or death from any cause, whichever occurred first) for COMBO300 versus ENCO300 (parts 1 and 2) by BIRC. Other end points included best overall response, disease control rate (DCR), OS, and duration of response. Tumor response was assessed by BIRC on the basis of RECIST 1.1[18]; data from local assessments of tumors on the basis of RECIST 1.1 were used in supportive analyses. Analyses of other secondary outcomes, including quality of life, comparison of ECOG PS, and pharmacokinetic analysis, were reported previously.[19]

Statistical Analysis

Statistical testing for COLUMBUS part 1 has been previously reported.[8,14] Briefly, the testing strategy in part 1 was a hierarchical testing of PFS for (1) COMBO450 versus vemurafenib (part 1 primary end point) and (2) COMBO450 versus ENCO300 (part 1 key secondary end point). The analysis of ENCO300 versus vemurafenib was a secondary end point. Part 2 did not have a primary end point. The key secondary end point in part 2 was PFS for COMBO300 versus ENCO300 (parts 1 and 2) by BICR. Part 2 key secondary end point testing was hierarchical after the part 1 key secondary end point. As the PFS comparison for COMBO450 versus ENCO300 was not statistically significant, all alpha for the study was spent. As a result, the PFS for COMBO300 versus ENCO300 (parts 1 and 2) was summarized descriptively in part 2, and this initial analysis had no impact on the family-wise error rate of the study. For determination of the sample sizes for COMBO300 and ENCO300 (parts 1 and 2), it was expected that approximately 330 PFS events would provide 80% power to detect a hazard ratio (HR) of 0.73 (one-sided 2.5% significance level; Appendix Fig A1, online only). Efficacy end points were analyzed using the full analysis set (comprising all randomly assigned patients) by treatment arm and stratum as assigned during random assignment. Safety analyses were based on the safety set (all patients who received ≥1 dose of study drug and had ≥1 postbaseline safety evaluation). Relative dose intensity was calculated using the following formula: relative dose intensity (%) = 100 ([cumulative dose/duration of exposure]/planned dose intensity).

Analysis of the key secondary PFS end point used a stratified, log-rank test (one-sided 2.5% cumulative level of significance). Kaplan-Meier curves were used to depict PFS distribution, on the basis of data from the full analysis set according to the treatment arm and stratification by cancer stage and ECOG PS. To calculate the median duration of potential follow-up for PFS, while the PFS times were used, the censoring indicators were reversed (ie, PFS events were considered as censors, and PFS censors were considered as events). Stratified Cox regression with treatment as a covariate was used to estimate HRs and 95% CIs for PFS; nominal *P* values are presented for descriptive purposes only, and no formal statistical comparisons were performed. Sensitivity analyses for PFS were repeated with data from local review (ENCO300 parts 1 and 2) and comparisons of COMBO300 versus ENCO300 (part 2; by BIRC and local review). DCR and ORR were presented by treatment arm with 95% CIs, and duration of response was estimated using Kaplan-Meier methods. SAS version 9.2 or higher (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Patients in part 1 were randomly assigned between December 30, 2013, and April 10, 2015; patients in part 2 were randomly assigned between March 19, 2015, and November 12, 2015. Overall, 116 clinical sites in 24 countries enrolled patients in COLUMBUS part 2 (full patient enrollment and treatment allocation are shown in Fig 1). Demographic and clinical characteristics at baseline are shown in Table 1 for the COMBO300 (n = 258) and ENCO300 arms (parts 1 [n = 194] and 2 [n = 86]). The baseline characteristics were generally similar for ENCO300 parts 1 and 2 (Appendix Table A1, online only). Baseline characteristics were generally similar across treatment arms, except for patients with high levels of lactate dehydrogenase (LDH): 80 (31%) in the COMBO300 arm, 79 (28%) in the ENCO300 arm (parts 1 and 2), and 32 (37%) in the ENCO300 arm (part 2).

Efficacy

The median duration of follow-up for PFS (by reverse Kaplan-Meier analysis) was 54.4 months for COMBO300, 43.5 months for ENCO300 (parts 1 and 2), and 57.1 months for ENCO300 (part 2). PFS for COMBO300 versus ENCO300 (parts 1 and 2) is shown in Figure 2A. Median PFS assessed by BIRC was longer for patients in the COMBO300 arm (12.9 months; 95% CI, 10.9 to 14.9) than for those in the ENCO300 arm (parts 1 and 2; 9.2 months; 95% CI, 7.4 to 11.1), with an estimated 26% risk reduction with COMBO300 (HR, 0.74; 95% CI, 0.60 to 0.92; two-sided $P = .003$ per stratified log-rank test). Similar results were observed for PFS as assessed by local investigator review, with the median (95% CI) PFS of 12.9 (10.9 to 14.8) months with COMBO300 versus 9.1 (7.4 to 11.1) months with ENCO300 (parts 1 and 2); an estimated 29% risk reduction with COMBO300 was shown for local review (HR, 0.71; 95% CI, 0.58 to 0.87; two-sided $P = .0005$ per stratified log-rank test). Findings were consistent for the ENCO300 (part 2) arm; there was an estimated 40% risk reduction with COMBO300 as assessed by BIRC (HR, 0.60; 95% CI, 0.45 to 0.80; two-sided $P < .001$) and local review (HR, 0.60; 95% CI, 0.45 to 0.80; two-sided $P < .001$ per stratified log-rank test; Appendix Fig A2A, online only).

Table 2 summarizes the results for ORR and DCR for COMBO300 and ENCO300 (parts 1 and 2) by central and local review. A confirmed overall response by BIRC occurred in 175 (68%) of 258 patients in the COMBO300 arm compared with 144 (51%) of 280 patients in the ENCO300 arms (parts 1 and 2). The confirmed overall response by local review had a similar pattern but was higher in each arm than in the central review (Table 2). Estimates of median (95% CI) duration of confirmed responses by BIRC were 15.4 (11.8 to 20.6) months in the COMBO300 arm and 14.8 (11.0 to 21.2) months in the ENCO300 arms (parts 1 and 2). The median (95% CI) locally assessed duration of confirmed response was 14.0 (11.2 to 18.9) months in the COMBO300 arm and 13.9 (10.0 to 16.3) months in the ENCO300 arms (parts 1 and 2; Table 2). Appendix Table A2 (online only) summarizes the results for ORR, DCR, and median duration of confirmed response for ENCO300 (part 2) by central and local review.

Results for the OS assessment for COMBO300 and ENCO300 (parts 1 and 2) are shown in Figure 2B. The median duration of follow-up for OS in this study was 60.7 months for COMBO300 and 67.6 months for ENCO300 (parts 1 and 2). The median (95% CI) OS was 27.1 (21.6 to 33.3) months with COMBO300 and 22.7 (19.3 to 29.3) months with ENCO300 (parts 1 and 2). The HR of COMBO300 versus ENCO300 in parts 1 and 2 was 0.90 (95% CI, 0.73 to 1.11; two-sided $P = .17$ per stratified log-rank test). Appendix Figure A2B (online only) shows OS for ENCO300 (part 2); there was an estimated 24% risk reduction with COMBO300 versus ENCO300 (part 2; HR, 0.76; 95% CI, 0.57 to 1.02; two-sided $P = .03$ per stratified log-rank test).

Safety

Safety was evaluated in 257 patients in the COMBO300 arm, 276 patients in the combined ENCO300 arms (parts 1 and 2), and 84 patients from ENCO300 part 2. The median daily dose of encorafenib was similar between the COMBO300 and ENCO300 arms (parts 1 and 2, and part 2 alone; Appendix Table A3, online only). The median duration of exposure was longer in the COMBO300 arm than in the ENCO300 arms (parts 1 and 2, and part 2 alone). The relative dose intensity of ≥80% was 87.5% and 80.6% for encorafenib and binimetinib in the COMBO300 arm, respectively, 51.8% for encorafenib in the ENCO300 arm (parts 1 and 2), and 57.1% in the ENCO300 arm (part 2; Appendix Table A3).

Table 3 summarizes the most commonly reported AEs of all grades (occurring in >10% of patients in either treatment arm) and the frequency of grade 3 and 4 AEs for the COMBO300 and ENCO300 arms (parts 1 and 2). The most frequently reported (≥25%) AEs (all grades) for patients in

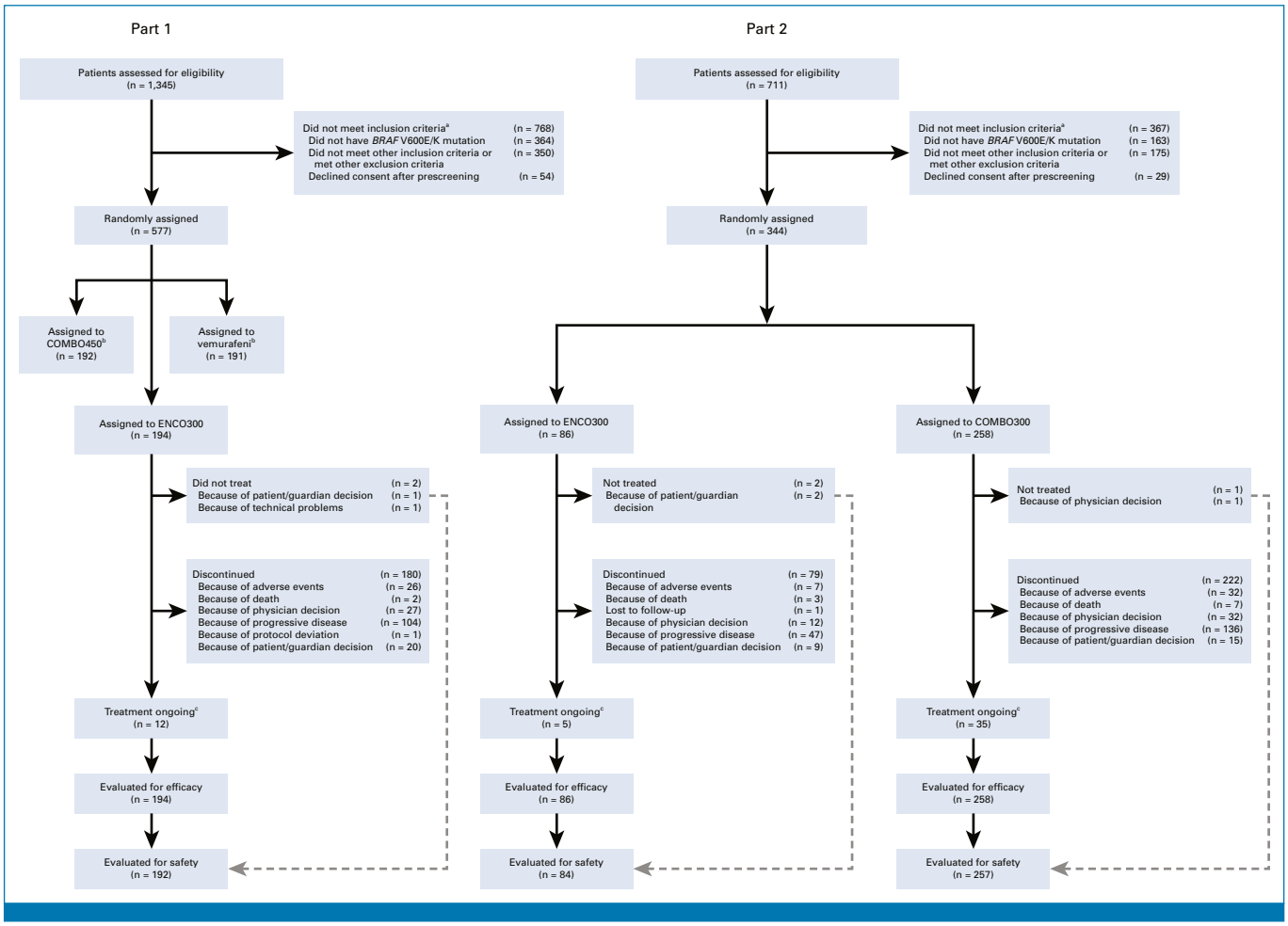

FIG 1. CONSORT diagram. [a]Some patients were ineligible for more than one reason. [b]The detailed CONSORT diagram for part 1 has been previously reported.[15] This diagram focuses on information pertinent to part 2. [c]Ongoing at the time of data cutoff (September 15, 2020). Adapted from Dummer et al.[15]

the COMBO300 arm were diarrhea, arthralgia, nausea, fatigue, and blood creatine phosphokinase (CPK) increased; for patients in the ENCO300 arm (parts 1 and 2), these were alopecia, arthralgia, palmar-plantar erythrodysesthesia (PPE) syndrome, hyperkeratosis, nausea, headache, myalgia, pruritus, fatigue, dry skin, rash, and vomiting (Table 3). The AEs (all grades) reported more frequently with COMBO300 than with ENCO300 (parts 1 and 2), with a difference in proportion of patients of 10% or higher, were diarrhea and blood CPK increase. The AEs (all grades) reported more frequently with ENCO300 (parts 1 and 2) than with COMBO300, with a difference in proportion of patients of 10% or higher, were toxic effects to the skin (ie, hyperkeratosis, palmoplantar keratoderma, PPE syndrome, pruritus, keratosis pilaris, dry skin, rash, alopecia), arthralgia, myalgia, headache, and insomnia (Table 3). The most common (≥25%) AEs (all grades) in the ENCO300 arm (part 2) were arthralgia, hyperkeratosis, PPE syndrome, alopecia, rash, nausea, fatigue, headache, and myalgia (Appendix Table A4, online only).

AE-related study drug discontinuation for all grades occurred in 30 (12%) patients in the COMBO300 arm, 29 (11%) patients in the ENCO300 arms (parts 1 and 2), and 7 (8%) patients in the ENCO300 (part 2) arm; AE-related study drug interruption or modification for all grades occurred in 98 (38%), 173 (63%), and 48 (57%) patients, respectively (Appendix Table A5, online only). A total of 96 (37%) patients in the COMBO300 arm, 100 (36%) in the ENCO300 arm (parts 1 and 2), and 30 (36%) in the ENCO300 (part 2) arm experienced serious AEs (all grades). Study drug–related serious AEs occurred in 25 (10%) patients in the COMBO300 arm, 47 (17.0%) in the ENCO300 arm (parts 1 and 2), and 12 (14%) in the ENCO arm (part 2; data not shown).

DISCUSSION

COLUMBUS consists of two parts; part 1 compared the COMBO450, ENCO300, and 960-mg vemurafenib arms, and part 2 compared the COMBO300 and ENCO300 arms. As previously reported,[8] results from part 1 demonstrated that COMBO450 improved PFS versus vemurafenib, leading to approval of this dosage in countries globally for the treatment of patients with $BRAF^{V600}$-mutatant unresectable or metastatic melanoma.[16,17] PFS was also improved for

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	COMBO300 (n = 258)	ENCO300 (parts 1 and 2; n = 280)
Age, years, median (range)	58 (20-94)	55 (19-88)
Sex, No. (%)		
Female	107 (41.5)	128 (45.7)
Male	151 (58.5)	152 (54.3)
ECOG PS 0, No. (%)	189 (73.3)	202 (72.1)
LDH at baseline, No. (%)		
Normal	178 (69.0)	201 (71.8)
High	80 (31.0)	79 (28.2)
Tumor stage at study entry, No. (%)		
IIIB/IIIC	8 (3.1)	11 (3.9)
IVM1a	31 (12.0)	42 (15.0)
IVM1b	47 (18.2)	49 (17.5)
IVM1c	172 (66.7)	178 (63.6)
No. of organs involved at baseline, No. (%)		
1	78 (30.2)	79 (28.2)
2	65 (25.1)	74 (26.4)
≥3	115 (44.6)	127 (45.4)
Previous checkpoint inhibitor, No. (%)		
Ipilimumab	17 (6.6)	14 (5.0)
Adjuvant	0	1 (0.4)
Therapeutic/metastatic	17 (6.6)	13 (4.6)
Anti–PD-1/anti–PD-L1	2 (0.8)	4 (1.4)
Primary cancer site, No. (%)		
Cutaneous melanoma	239 (92.6)	271 (96.8)
Unknown	19 (7.4)	9 (3.2)

Abbreviations: COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; ECOG, Eastern Cooperative Oncology Group; ENCO300, encorafenib 300 mg once daily; LDH, lactate dehydrogenase; PS, performance status.

COMBO450 (14.9 months; 95% CI, 11.0 to 18.5) versus ENCO300 (9.6 months; 95% CI, 7.5 to 14.8) but was not statistically significant (P = .051).[8] Favorable safety and tolerability were observed for COMBO450 versus vemurafenib and versus ENCO300 monotherapy.

The purpose of part 2, which resulted from a study amendment requested by the US Food and Drug Administration, was to delineate the contribution of binimetinib to the efficacy and safety of encorafenib plus binimetinib combination therapy by keeping the same dosage of encorafenib in both study arms. Efficacy results from COLUMBUS part 2 demonstrated the direct contribution of binimetinib to the treatment combination. The median PFS assessed by BIRC was longer for patients in the COMBO300 arm (12.9 months; 95% CI, 10.9 to 14.9) than for those in the ENCO300 arm (parts 1 and 2; 9.2 months; 95% CI, 7.4 to 11.1). Per BIRC, PFS with COMBO300 showed a significant estimated 26% risk reduction versus ENCO300 (parts 1 and 2; HR, 0.74; P = .003). A limitation of the study is that patients were not concurrently recruited to the ENCO300 group in parts 1 and 2. Population differences in patients randomly assigned to ENCO300 in part 1[8] versus part 2 (ie, higher percentage of patients with high LDH levels at baseline in the ENCO300 [part 2] arm, indicating worse prognosis) are therefore likely responsible for the difference in PFS between the ENCO300 arms (median PFS by BIRC, 9.6 months in part 1 *v* 7.4 months in part 2) and the higher estimated risk reduction for COMBO300 versus ENCO300 (part 2). Median OS was numerically longer for COMBO300 versus ENCO300; OS from this study will continue to be assessed, and future updates with longer follow-up will be reported.

The results reported here are consistent with previous studies and confirm the contribution of MEKi when added to BRAFi monotherapy reported in other pivotal trials such as COMBI-d (dabrafenib plus trametinib *v* dabrafenib plus placebo; ClinicalTrials.gov identifier: NCT01584648), COMBI-v (dabrafenib plus trametinib *v* vemurafenib; ClinicalTrials.gov identifier: NCT01597908), and coBRIM (vemurafenib plus cobimetinib *v* vemurafenib plus placebo; ClinicalTrials.gov identifier: NCT01689519).[20-23] Indeed, the median PFS achieved in our study with COMBO300 (12.9 months [95% CI, 10.9 to 14.8]) is similar to that reported in the COMBI-d/COMBI-v pooled 5-year

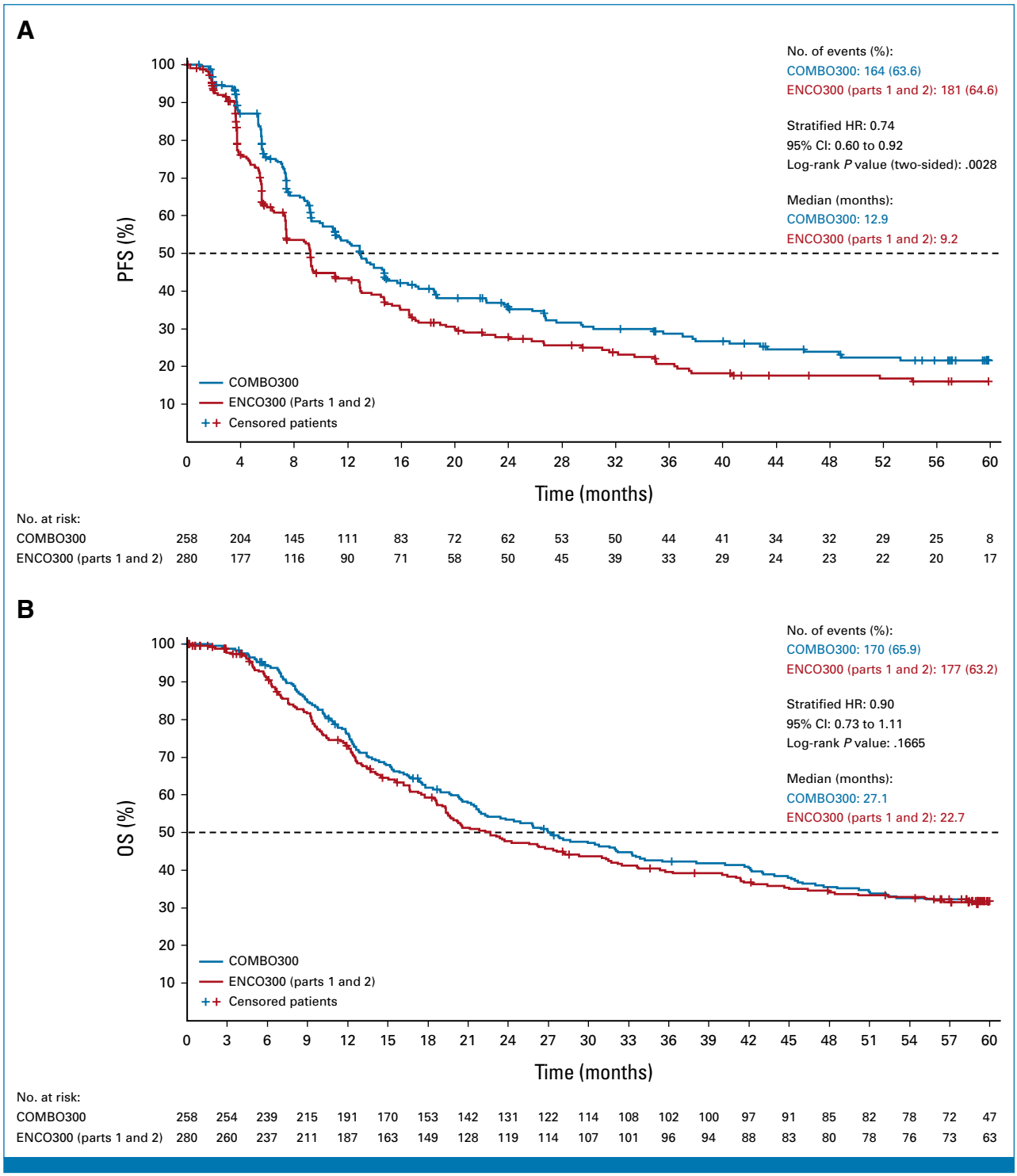

FIG 2. Kaplan-Meier curves of (A) PFS by BIRC and (B) OS for COMBO300 versus ENCO300 (parts 1 and 2). BIRC, blinded independent review committee; COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; ENCO300, encorafenib 300 mg once daily; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

analysis (11.1 months [95% CI, 9.5 to 12.8]) and the coBRIM study (12.6 months [95% CI, 9.5 to 14.8]).[20,22] Furthermore, 3-year PFS rates achieved with BRAFi/MEKi combinations were comparable across all studies: 27% in COLUMBUS part 2, 24% in COMBI-d/COMBI-v, and 30% in coBRIM. All PFS rates were superior to those reached with BRAFi comparator arms.[20–23] Similar trends were also observed for OS.[20,22]

Our safety analysis demonstrates that COMBO300 was better tolerated than ENCO300, resulting in greater relative dose intensity, fewer skin and musculoskeletal toxicities, and

TABLE 2. Confirmed Response Rates

	COMBO300 (n = 258)		ENCO300 (parts 1 and 2; n = 280)	
Confirmed Response	BIRC	Local Review	BIRC	Local Review
ORR,[a] No. (%; 95% CI)	175 (67.8; 61.8 to 73.5)	195 (75.6; 69.9 to 80.7)	144 (51.4; 45.4 to 57.4)	160 (57.1; 51.1 to 63.0)
Complete response, No. (%)	31 (12.0)	45 (17.4)	22 (7.9)	28 (10.0)
Partial response, No. (%)	144 (55.8)	150 (58.1)	122 (43.6)	132 (47.1)
Stable disease,[b] No. (%)	59 (22.9)	51 (19.8)	87 (31.1)	79 (28.2)
Progressive disease,[c] No. (%)	24 (9.3)	12 (4.7)	49 (17.5)	41 (14.6)
DCR,[d] No. (%; 95% CI)	234 (90.7; 86.5 to 93.9)	246 (95.3; 92.0 to 97.6)	231 (82.5; 77.5 to 86.8)	239 (85.4; 80.7 to 89.3)
Duration of confirmed responses, months, median (95% CI)	15.4 (11.8 to 20.6)	14.0 (11.2 to 18.9)	14.8 (11.0 to 21.2)	13.9 (10.0 to 16.3)

Abbreviations: BIRC, blinded independent review committee; COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; DCR, disease control rate; ENCO300, encorafenib 300 mg once daily; ORR, overall response rate.

[a]ORR was defined as complete response plus partial response.

[b]Includes patients with only nontarget lesions with best response of noncomplete response/nonprogressive disease.

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

[d]DCR was defined as the proportion of patients with a best overall response of complete response, partial response, stable disease, or noncomplete response/nonprogressive disease.

TABLE 3. Common Adverse Events Occurring in >10% of Patients in the COMBO300 and ENCO300 Arms (parts 1 and 2)

	COMBO300 (n = 257)		ENCO300 (part 1 + 2; n = 276)	
Preferred Term	All Grades, No. (%)	Grade 3/4, No. (%)	All Grades, No. (%)	Grade 3/4, No. (%)
Total	253 (98.4)	151 (58.8)	273 (98.9)	186 (67.4)
Diarrhea	91 (35.4)	4 (1.6)	36 (13.0)	4 (1.4)
Arthralgia	76 (29.6)	6 (2.3)	136 (49.3)	25 (9.1)
Nausea	74 (28.8)	4 (1.6)	101 (36.6)	9 (3.3)
Fatigue	68 (26.5)	3 (1.2)	77 (27.9)	3 (1.1)
Blood CPK increased	65 (25.3)	19 (7.4)	3 (1.1)	1 (0.4)
Back pain	52 (20.2)	4 (1.6)	43 (15.6)	6 (2.2)
Constipation	52 (20.2)	0	44 (15.9)	1 (0.4)
Vomiting	52 (20.2)	1 (0.4)	74 (26.8)	11 (4.0)
Pyrexia	49 (19.1)	0	45 (16.3)	2 (0.7)
Headache	48 (18.7)	2 (0.8)	81 (29.3)	8 (2.9)
Asthenia	44 (17.1)	3 (1.2)	59 (21.4)	7 (2.5)
GGT increased	43 (16.7)	15 (5.8)	30 (10.9)	12 (4.3)
Myalgia	39 (15.2)	1 (0.4)	78 (28.3)	23 (8.3)
Abdominal pain upper	39 (15.2)	1 (0.4)	24 (8.7)	2 (0.7)
Pain in extremity	37 (14.4)	1 (0.4)	60 (21.7)	5 (1.8)
Hypertension	36 (14.0)	17 (6.6)	17 (6.2)	10 (3.6)
Alopecia	36 (14.0)	0	137 (49.6)	0
Edema peripheral	36 (14.0)	0	23 (8.3)	0
Nasopharyngitis	35 (13.6)	0	23 (8.3)	0
Anemia	34 (13.2)	11 (4.3)	21 (7.6)	9 (3.3)
Abdominal pain	33 (12.8)	4 (1.6)	23 (8.3)	7 (2.5)
ALT increased	33 (12.8)	13 (5.1)	12 (4.3)	2 (0.7)
Decreased appetite	30 (11.7)	1 (0.4)	53 (19.2)	1 (0.4)
Hyperkeratosis	30 (11.7)	0	112 (40.6)	8 (2.9)
Rash	30 (11.7)	5 (1.9)	77 (27.9)	8 (2.9)
Vision blurred	29 (11.3)	1 (0.4)	6 (2.2)	0
Pruritus	28 (10.9)	0	78 (28.3)	1 (0.4)
Dizziness	27 (10.5)	1 (0.4)	16 (5.8)	0
Dry skin	26 (10.1)	0	77 (27.9)	1 (0.4)
Palmoplantar keratoderma	20 (7.8)	1 (0.4)	68 (24.6)	5 (1.8)
Cough	20 (7.8)	0	29 (10.5)	1 (0.4)
Insomnia	19 (7.4)	1 (0.4)	51 (18.5)	7 (2.5)
Erythema	18 (7.0)	0	45 (16.3)	3 (1.1)
Skin papilloma	18 (7.0)	0	34 (12.3)	0
PPE syndrome	13 (5.1)	1 (0.4)	131 (47.5)	31 (11.2)
Decreased weight	10 (3.9)	0	38 (13.8)	2 (0.7)
Dysgeusia	10 (3.9)	0	28 (10.1)	0
Keratosis pilaris	8 (3.1)	0	43 (15.6)	0

NOTE. Some sites adopted amendment 6 before the data cutoff of September 15, 2020. Amendment 6 allows for patients still on treatment to be monitored in a manner that is consistent with local standard-of-care practice for patients with unresectable or metastatic *BRAF*^{V600}-mutant melanoma because of the approval of COMBO450.[15] After the adoption date, only grade 3 and 4 AEs and all serious AEs were recorded at those sites.

Abbreviations: AAT, aspartate aminotransferase; AEs, adverse events; COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; CPK, creatine phosphokinase; ENCO300, encorafenib 300 mg once daily; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia.

fewer grade 3/4 AEs. Ocular toxicities (ocular discomfort, ocular hypertension, and ocular hyperemia) of binimetinib were observed during the trial but were mild (grade 1/2). There were no new safety signals or concerns for the combination or encorafenib monotherapy.

In conclusion, the efficacy, safety, and tolerability of COMBO300 were improved compared with ENCO300. Together with part 1 results, these data confirm and extend the evidence for the contribution of binimetinib for the treatment of *BRAF*-mutant, advanced, unresectable melanoma. These results suggest that maximizing BRAF inhibition in BRAFi/MEKi combinations improves efficacy and that COMBO450, the approved dosage, should be used on the basis of available evidence from COLUMBUS.

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Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Contribution of MEK Inhibition to BRAF/MEK Inhibitor Combination Treatment of *BRAF*-Mutant Melanoma: Part 2 of the Randomized, Open-Label, Phase III COLUMBUS Trial

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APPENDIX

TABLE A1. Baseline Demographic and Clinical Characteristics for ENCO300

Characteristic	ENCO300 (part 1; n = 194)	ENCO300 (part 2; n = 86)
Age, years, median (range)	54 (23-88)	57 (19-81)
Sex, No. (%)		
Female	86 (44.3)	42 (48.8)
Male	108 (55.7)	44 (51.2)
ECOG PS 0, No. (%)	140 (72.2)	62 (72.1)
LDH at baseline, No. (%)		
Normal	147 (75.8)	54 (62.8)
High	47 (24.2)	32 (37.2)
Tumor stage at study entry, No. (%)		
IIIB/IIIC	6 (3.1)	5 (5.8)
IVM1a	29 (14.9)	13 (15.1)
IVM1b	39 (20.1)	10 (11.6)
IVM1c	120 (61.9)	58 (67.4)
No. of organs involved at baseline, No. (%)		
1	56 (28.9)	23 (26.7)
2	52 (26.8)	22 (25.6)
≥3	86 (44.3)	41 (47.7)
Previous checkpoint inhibitor, No. (%)		
Ipilimumab	10 (5.2)	4 (4.7)
Adjuvant	1 (0.5)	0
Therapeutic/metastatic	9 (4.6)	4 (4.7)
Anti–PD-1/anti–PD-L1	2 (1.0)	2 (2.3)
Primary cancer site, No. (%)		
Cutaneous melanoma	192 (99.0)	79 (91.9)
Unknown	2 (1.0)	7 (8.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ENCO300, encorafenib 300 mg once daily; LDH, lactate dehydrogenase; PS, performance status.

TABLE A2. Confirmed Response Rates for ENCO300 (part 2)

	ENCO300 (part 2; n = 86)	
Confirmed Response	BIRC	Local Review
ORR,[a] No. (%; 95% CI)	44 (51.2; 40.1 to 62.1)	47 (54.7; 43.5 to 65.4)
Complete response, No. (%)	7 (8.1)	7 (8.1)
Partial response, No. (%)	37 (43.0)	40 (46.5)
Stable disease,[b] No. %	24 (27.9)	23 (26.7)
Progressive disease,[c] No. (%)	18 (20.9)	16 (18.6)
DCR,[d] No. (%; 95% CI)	68 (79.1; 69.0 to 87.1)	70 (81.4; 71.6 to 89.0)
Duration of confirmed responses, months, median (95% CI)	11.0 (7.3 to 17.1)	10.0 (7.4 to 18.3)

Abbreviations: BIRC, blinded independent review committee; DCR, disease control rate; ENCO300, encorafenib 300 mg once daily; ORR, overall response rate.

[a]ORR was defined as complete response plus partial response.

[b]Includes patients with only nontarget lesions with best response of noncomplete response/nonprogressive disease.

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

[d]DCR was defined as the proportion of patients with a best overall response of complete response, partial response, stable disease, or noncomplete response/nonprogressive disease.

TABLE A3. Dose Intensity and Dose Exposure in the COMBO300 and ENCO300 Arms

	COMBO300 (n = 257)		ENCO300 (parts 1 and 2; n = 276)	ENCO300 (part 2; n = 84)
Dose Intensity and Exposure	Encorafenib	Binimetinib	Encorafenib	Encorafenib
Daily dose, mg/d, median (min-max)	300.0 (115.1-301.3)	90.0 (31.8-90.0)	281.4 (54.9-300.3)	300.0 (54.9-300.0)
Dose intensity, mg/d, median (min-max)	299.3 (102.7-300.0)	89.4 (28.2-90.0)	262.4 (44.4-300.0)	283.4 (53.5-300.0)
Relative dose intensity ≥80%, No. (%)	225 (87.5)	207 (80.5)	143 (51.8)	48 (57.1)
Duration of exposure, weeks, median (min-max)	52.1 (2.7-286.0)	50.1 (2.7-286.0)	31.5 (0.1-339.0)	31.5 (0.4-283.0)

Abbreviations: COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; ENCO300, encorafenib 300 mg once daily; max, maximum; min, minimum.

TABLE A4. Common AEs Occurring in >10% of Patients in the ENCO300 Arm (part 2)

	ENCO300 (part 2; n = 84)	
Preferred Term	All Grades, No. (%)	Grade 3/4, No. (%)
Total	82 (97.6)	52 (61.9)
Arthralgia	39 (46.4)	4 (4.8)
Hyperkeratosis	36 (42.9)	1 (1.2)
PPE syndrome	32 (38.1)	5 (6.0)
Alopecia	29 (34.5)	0
Rash	27 (32.1)	3 (3.6)
Nausea	27 (32.1)	1 (1.2)
Fatigue	26 (31.0)	2 (2.4)
Headache	24 (28.6)	2 (2.4)
Myalgia	22 (26.2)	4 (4.8)
Pruritus	19 (22.6)	0
Dry skin	19 (22.6)	0
Vomiting	18 (21.4)	2 (2.4)
Palmoplantar keratoderma	17 (20.2)	1 (1.2)
Asthenia	16 (19.0)	2 (2.4)
Pain in extremity	15 (17.9)	3 (3.6)
Insomnia	14 (16.7)	2 (2.4)
Erythema	13 (15.5)	1 (1.2)
Skin papilloma	13 (15.5)	0
Constipation	12 (14.3)	1 (1.2)
Pyrexia	12 (14.3)	0
Decreased appetite	12 (14.3)	0
Keratosis pilaris	10 (11.9)	0
Keratoacanthoma	10 (11.9)	1 (1.2)

NOTE. Some sites adopted amendment 6 before the data cutoff of September 15, 2020. Amendment 6 allows for patients still on treatment to be monitored in a manner that is consistent with local standard-of-care practice for patients with unresectable or metastatic *BRAF*^{V600}-mutant melanoma because of the approval of COMBO450.[15] After the adoption date, only grade 3 and 4 AEs and all serious AEs were recorded at those sites.

Abbreviations: AEs, adverse events; COMBO450, encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ENCO300, encorafenib 300 mg once daily; PPE, palmar-plantar erythrodysesthesia.

TABLE A5. AEs Leading to Dose Modification, Reduction, and Interruption in the COMBO300 and ENCO300 Arms

Incidence of AE Leading to Dose Modification, Reduction, and Interruption	COMBO300 (n = 257)		ENCO300 (parts 1 and 2; n = 276)		ENCO300 (part 2; n = 84)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
AEs requiring dose interruption and/or change, No. (%)	127 (49.4)	73 (28.4)	193 (69.9)	127 (46.0)	54 (64.3)	36 (42.9)
Suspected to be drug related	98 (38.1)	49 (19.1)	173 (62.7)	108 (39.1)	48 (57.1)	29 (34.5)
AEs leading to discontinuation, No. (%)	44 (17.1)	34 (13.2)	42 (15.2)	30 (10.9)	11 (13.1)	6 (7.1)
Suspected to be drug related	30 (11.7)	21 (8.2)	29 (10.5)	19 (6.9)	7 (8.3)	2 (2.4)
AEs leading to additional therapy, No. (%)	226 (87.9)	104 (40.5)	259 (93.8)	153 (55.4)	77 (91.7)	42 (50.0)
Suspected to be drug related	151 (58.8)	39 (15.2)	246 (89.1)	106 (38.4)	73 (86.9)	25 (29.8)

Abbreviations: AE, adverse event; COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; ENCO300, encorafenib 300 mg once daily.

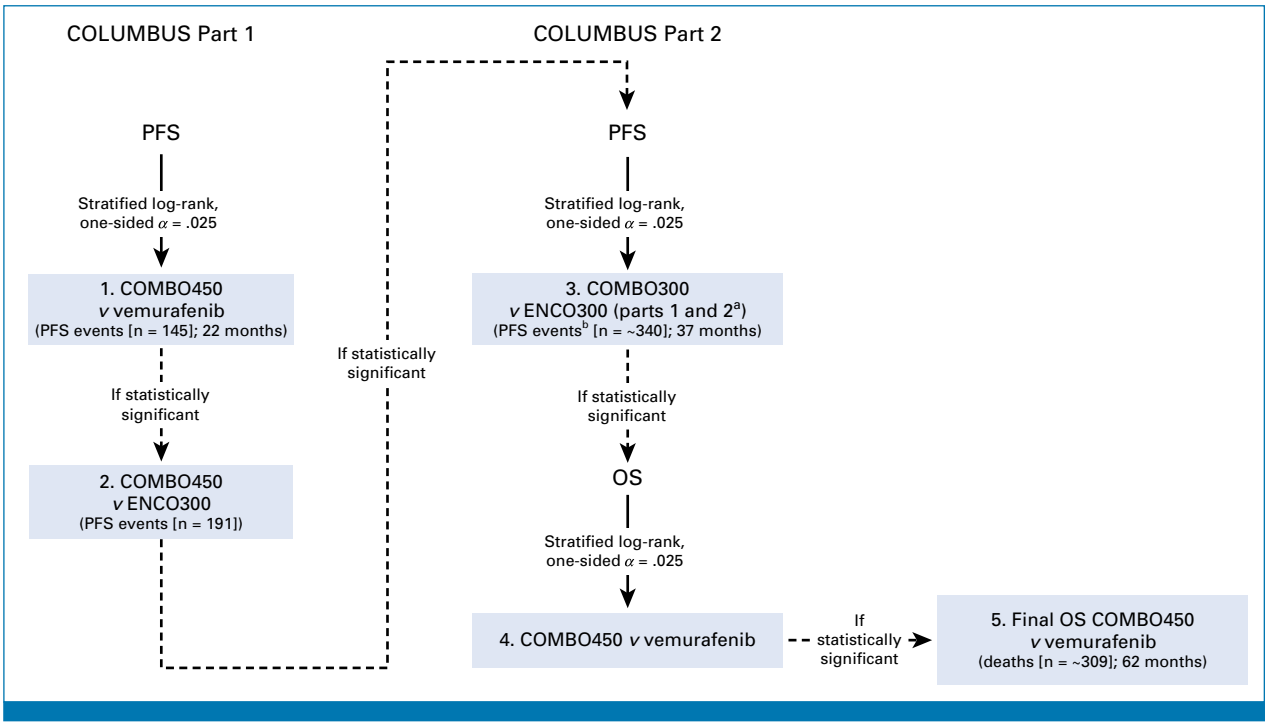

FIG A1. Overview of statistical testing hierarchy. [a]For the part 2 PFS analysis timepoint, patients randomly assigned to COMBO300 and ENCO300 (irrespective of the study part) contributed to the main comparisons. [b]On the basis of the differential follow-up and expected median PFS times, it is expected that approximately 330 PFS events will contribute to the hazard ratio estimate and log-rank test and will result in approximately 80% power to detect a hazard ratio of 0.727 (8 of 11) at a one-sided 2.5% level of significance. COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; COMBO450, encorafenib 450 mg once daily plus binimetinib 45 mg twice a day; ENCO300, encorafenib 300 mg once daily; OS, overall survival; PFS, progression-free survival.

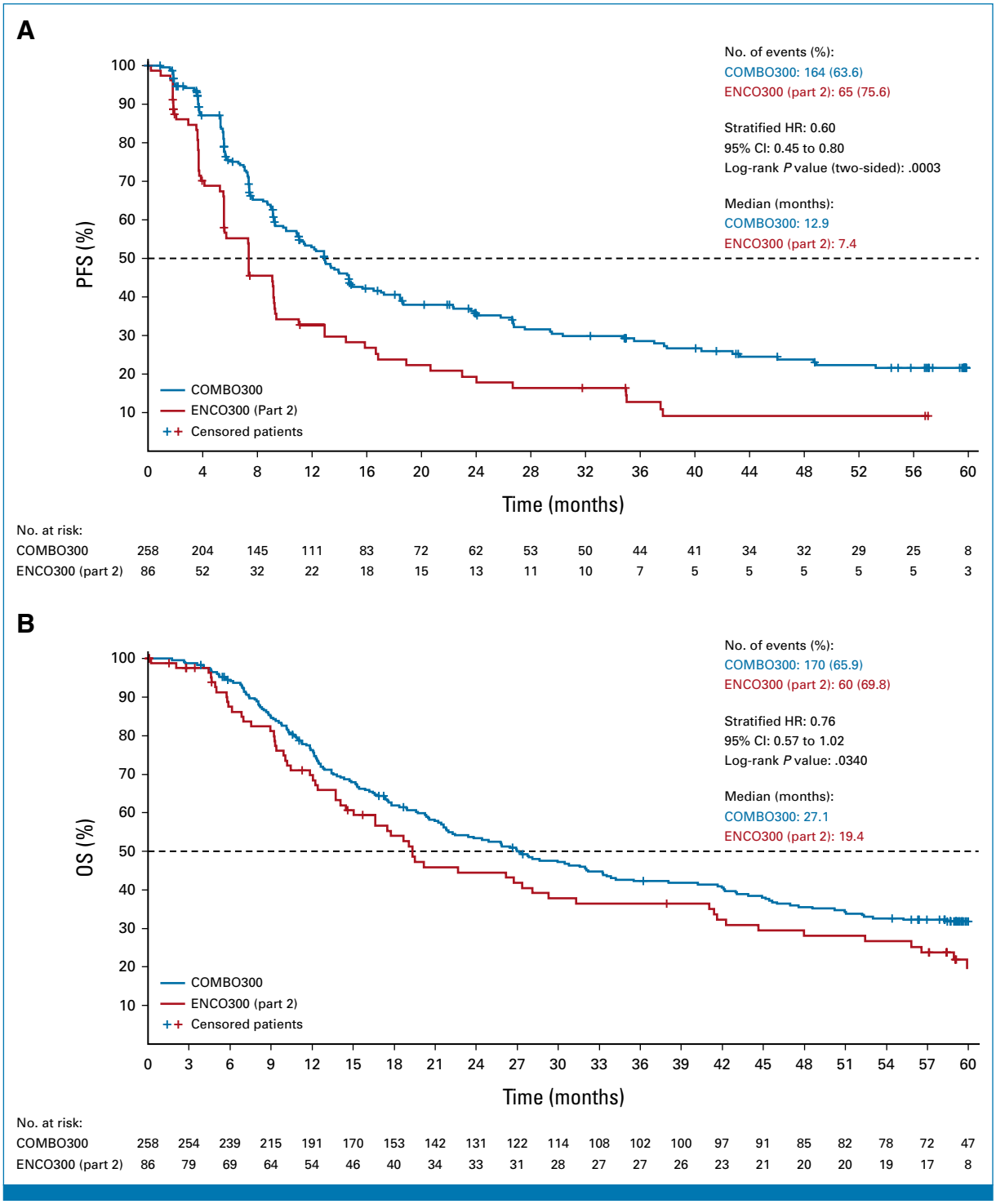

FIG A2. Kaplan-Meier curves of (A) PFS by BIRC and (B) OS for COMBO300 versus ENCO300 (part 2). BIRC, blinded independent review committee; COMBO300, encorafenib 300 mg once daily plus binimetinib 45 mg twice daily; ENCO300, encorafenib 300 mg once daily; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.