

A Phase Ib/II Study of the BRAF Inhibitor Encorafenib Plus the MEK Inhibitor Binimetinib in Patients with *BRAF*^{V600E/K}-mutant Solid Tumors

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ABSTRACT

Purpose: This open-label, dose-finding phase Ib/II study reports the safety and activity of the first combination use with BRAF inhibitor (BRAFi) encorafenib plus MEK inhibitor (MEKi) binimetinib in patients with *BRAF* V600E-mutant solid tumors.

Patients and Methods: In phase I, the recommended phase 2 doses (RP2D) were established (primary objective). In phase II, the clinical activity of the combination at the RP2D was assessed (primary objective) in patients with *BRAF*-mutant metastatic colorectal cancer (mCRC), BRAFi-treated *BRAF*-mutant melanoma, and BRAFi-naïve *BRAF*-mutant melanoma.

Results: A total of 126 patients with *BRAF*-mutant solid tumors were enrolled (phase I: 47 patients; phase II: 79 patients). The RP2D was encorafenib 450 mg once daily plus binimetinib 45 mg twice daily and pharmacokinetic data suggest that drug

exposures of each agent were similar in combination compared with single-agent studies. In the phase II cohorts, confirmed responses were seen in two of 11 (18%) evaluable patients with mCRC, 11 of 26 (42%) evaluable patients with BRAFi-pretreated melanoma, and 28 of 42 (67%) BRAFi-naïve patients with melanoma. The most common grade 3/4 adverse event in phase II was increased alanine aminotransferase.

Conclusions: The combination of encorafenib (450 mg) plus binimetinib (45 mg) showed acceptable tolerability and encouraging activity in patients with *BRAF* V600-mutant tumors, which led to the dose selection for the melanoma COLUMBUS study. The safety profile of the combination was consistent with other approved BRAFi plus MEKi regimens, with several differences, including lower rates of dose-limiting pyrexia, arthralgia, and photosensitivity.

Introduction

The MAPK signaling pathway (i.e., RAS-RAF-MEK-ERK pathway) regulates cellular proliferation, survival, and differentiation and plays an important role in melanoma pathogenesis (1). This pathway can become constitutively activated through several mechanisms, includ-

ing *BRAF* or *RAS* mutations, which are the most frequently altered MAPK pathway components in cancer (2).

BRAF V600E mutation is found in approximately 8% to 15% of patients with metastatic colorectal cancer (mCRC) and approximately 50% of primary cutaneous melanomas (3, 4). Dual inhibition of MAPK signaling with inhibitors to BRAF (BRAFi) and MEK (MEKi), which is downstream of BRAF in the MAPK pathway, is standard treatment in patients with *BRAF*V600-mutant metastatic melanoma (5–10) and is recommended therapy with an EGFR inhibitor for *BRAF*V600E-mutant mCRC (11). Compared with BRAFi monotherapy in melanoma, BRAFi/MEKi combination therapy improves survival while reducing BRAFi-associated toxicities resulting from paradoxical MAPK pathway activation (5, 7–9, 12–14). The more durable responses observed with BRAFi/MEKi combination therapy than with BRAF inhibition alone are consistent with multiple genetic mechanisms of resistance and provide a rationale for dual MEK and BRAF inhibition (15–20).

The combination of BRAFi plus MEKi has demonstrated improved efficacy versus single-agent BRAFi in four randomized controlled phase III trials in patients with *BRAF* V600-mutated metastatic melanoma (5, 7, 8, 12, 13). Combination regimens with dabrafenib plus trametinib and vemurafenib plus cobimetinib were generally well tolerated, although patients receiving combination therapy required more dose modifications than those receiving monotherapy (7, 8). The vemurafenib plus cobimetinib combination was associated with more frequent gastrointestinal events, photosensitivity, and elevated aminotransferase levels compared with vemurafenib monotherapy (8, 9). In the dabrafenib plus trametinib studies, 11% (21) and 16% (22) discontinuation rates were documented, with pyrexia being the most common reason for treatment discontinuation. On the basis of phase III trials, dabrafenib plus trametinib and vemurafenib plus

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Translational Relevance

This phase Ib/II study showed encouraging activity for the encorafenib plus binimetinib combination with predictable toxicity. The tolerable dose and exposure of encorafenib are higher in combination than as a single agent. Relative to other BRAFi plus MEKi regimens, the safety profile of the combination consistent, with several key differences, including lower rates of dose-limiting pyrexia, arthralgia, and photosensitivity. Data presented here formed the foundation for encorafenib plus binimetinib phase III studies in melanoma (COLUMBUS) and colorectal cancer (BEACON CRC) in patients with *BRAF* V600E mutations, which have both now reported positive results.

cobimetinib combination therapies received regulatory approval from the FDA and the European Commission for *BRAF*-mutant metastatic melanoma.

More recently, the combination of encorafenib plus binimetinib has demonstrated clinical activity and tolerability in the phase III COLUMBUS study in patients with *BRAF* V600-mutated melanoma (12, 13, 23). This combination is distinct in that encorafenib is an ATP-competitive BRAFi that suppresses the MAPK pathway in tumor cells that express several mutated forms of *BRAF* kinase (e.g., V600E, V600D, and V600K mutations), with a dissociation half-life that is more than 10 times longer (>30 hours) than either dabrafenib or vemurafenib (24). Preclinical studies suggest that this property could allow for sustained target inhibition and enhance antitumor activity, while reducing paradoxical activation of MAPK pathways in normal tissues (22, 25). Binimetinib is an orally available, nonATP competitive, allosteric inhibitor of MEK1 and MEK2 (26). Results from the COLUMBUS study demonstrated that the encorafenib plus binimetinib combination provides favorable efficacy and tolerability profile versus vemurafenib monotherapy, as evidenced by higher median dose intensities and longer median treatment exposure observed (13). Furthermore, encorafenib demonstrated improved efficacy relative to vemurafenib monotherapy in this study (12, 13). These data led to regulatory approvals of the combination starting in 2018 (25). In addition, the combination of encorafenib, binimetinib, and cetuximab has shown promising results for previously treated *BRAF* V600E-mutant mCRC in the BEACON study (27, 28).

In this study, we report the initial safety and therapeutic activity of encorafenib plus binimetinib from a phase Ib/II dose escalation study in patients with *BRAF* V600-dependent advanced solid tumors, including phase II cohorts with BRAFi-naïve and previously BRAFi-treated *BRAF*-mutant metastatic melanoma, as well as patients with *BRAF* V600-mutant mCRC.

Patients and Methods

Study design and participants

In this multicenter, open-label, phase Ib/II, dose-finding study of encorafenib plus binimetinib, adults with *BRAF*-mutant malignancies were enrolled initially to dose-escalation cohorts and subsequently to phase II cohorts at the RP2D (NCT01543698). Three arms were enrolled at the RP2D: (i) BRAFi-naïve patients with *BRAF* V600-mutant mCRC; (ii) patients with *BRAF* V600-mutant melanoma following progression on a selective BRAFi (e.g., vemurafenib or dabrafenib); and (iii) BRAFi-naïve patients with *BRAF* V600-mutant

melanoma. A total of 17 centers from Canada, the United States, Europe, and Australia participated in the study. Eligible patients were ages ≥ 18 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had adequate organ function [creatinine $< 1.5 \times$ upper limit of normal (ULN), bilirubin $\leq 1.5 \times$ ULN, hepatic transaminases $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN in the setting of preexisting liver metastases, and left ventricular ejection fraction $> 45\%$]. Previous cancer therapy was permitted, except BRAFi as previously noted for specific cohorts. Patients with symptomatic brain metastases were excluded; however, patients with asymptomatic untreated brain metastasis were eligible. Malignancy other than non-melanoma skin cancer, active systemic infection, evidence of or risk factor for retinal disease, and patients with a life expectancy < 3 months were excluded. Patients were treated until disease progression, unacceptable toxicity, or withdrawal of informed consent.

All patients provided written informed consent. An institutional review board or independent ethics committee approved the protocol at all study sites. This study was conducted in accordance with the requirements of each country's regulatory authorities as well as in accordance with Good Clinical Practice guidelines, as defined by the International Council for Harmonisation.

Procedures

Patients received open-label encorafenib once daily and binimetinib 45 mg twice daily. During the phase I dose escalation, patients with *BRAF*-mutant solid tumor malignancies, independent of prior BRAFi therapy, were enrolled in cohorts of increasing daily encorafenib doses (50, 100, 200, 400, 450, 600, and 800 mg) plus binimetinib. Following recommended phase 2 doses (RP2D) determination, patients were enrolled in one of three phase II cohorts described previously.

For the purpose of scheduling and evaluations, a treatment cycle was defined as 28 days. Radiological assessment was performed by the investigator prior to cycle 2, cycle 3, and before every subsequent odd numbered cycle; clinical response was classified according to RECIST version 1.1 (RECIST v1.1).

Safety parameters were regularly assessed, and included hematology, blood chemistry, urinalysis, vital signs, physical examination, and body weight. Echocardiography was performed at baseline and every third cycle. Dermatology assessments were performed at baseline and every other cycle to monitor for the appearance of squamous cell carcinoma or keratoacanthomas. Extensive ocular toxicity monitoring was performed with full ophthalmologic examinations at screening, cycle 1 day 15, cycle 2 day 1, cycle 2 day 15, day 1 of all subsequent cycles, and at the end of the trial. These examinations included slit-lamp examination, visual acuity testing, visual field testing (intraocular pressure), optical coherence tomography, and indirect funduscopy (with dilation) with attention to retinal abnormalities (especially central serous retinopathy and retinal vein occlusion). For patients with clinical suspicion of retinal changes, additional fluorescein angiography and/or focal electroretinogram (when feasible) assessments were recommended at the treating physician's discretion. Adverse events (AEs) were monitored until 30 days after the last dose of study drug.

Archived tissue was provided for every patient. Expanded genotyping was performed centrally on all patients in collaboration with Foundation Medicine. Correlation between mutation status and response per RECIST v1.1 was reported.

Outcomes

The primary objective of the phase Ib part of the study was to estimate the MTD) and/or RP2D in patients with solid tumors

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harboring a *BRAF* V600 mutation. Objective response rate (ORR) was assessed as per RECIST v1.1 as a secondary endpoint. Primary endpoints for the phase II part of the study were disease control rate [DCR; defined as best overall response of either a complete response (CR), partial response (PR), or stable disease (SD)] for arm 1 (patients with mCRC) and ORR for arm 2 and arm 3 (all assessments utilized RECIST v1.1). Secondary endpoints for the phase II part of the study included progression-free survival (PFS), time to response, duration of response (all assessed as per RECIST v1.1) and overall survival (OS). Safety and tolerability of the combination were assessed in both the phase Ib and phase II parts of the study. AEs were described using the NCI Common Terminology Criteria for Adverse Events version 4.0. For the safety and therapeutic activity analyses, data from patients receiving encorafenib 400 mg once daily plus binimetinib 45 mg twice daily were pooled with those receiving encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; analyses on the data from patients in the encorafenib 600 mg once daily plus binimetinib 45 mg twice daily group included patients who both were and were not deescalated to 450 mg.

Pharmacokinetics

For phase Ib and a subset of patients in phase II, the single and multiple dose plasma concentration-time profiles of encorafenib, binimetinib, and a metabolite of binimetinib were assessed on days 1 and 15, respectively. On both days, samples in the phase Ib portion were collected predose, 0.5, 1.5, 2.5, 4, 6, 8, and 24 hours postdose.

Similar sampling in the phase II was conducted, relative to the phase Ib, with the exception of a 5-hour postdose sample being collected in lieu of the 4 and 6 hours postdose samples.

Analysis of the samples for binimetinib and encorafenib was performed by QPS and Novartis, respectively, and were validated under good laboratory practice conditions. Plasma samples for binimetinib were spiked with internal standard and extracted from plasma using solid-phase extraction cartridges. Samples for binimetinib were subsequently eluted, evaporated to dryness and reconstituted. Plasma samples for encorafenib were spiked with internal standard and precipitated. Samples for encorafenib were subsequently eluted from solid-phase extraction cartridges, evaporated to dryness and reconstituted. Both binimetinib and encorafenib concentrations in reconstituted samples were determined by reverse-phase high-performance liquid chromatography with MS/MS. The lower limit of quantitation for binimetinib and encorafenib was 5 ng/mL and 1 ng/mL, respectively. The upper limit of quantitation for binimetinib and encorafenib was 1,000 ng/mL and 5,000 ng/mL, respectively.

Pharmacokinetic (PK) parameter estimates were generated using standard noncompartmental approaches. Results were summarized using descriptive statistics. Encorafenib dose proportionality and accumulation across all cohorts (including intraindividual variability) was assessed using a mixed-effects analysis of log-transformed exposures (AUC_{tau} and C_{max}).

Table 1. Baseline patient and disease characteristics for phase Ib portion of study.

	Encorafenib 50 mg qd plus binimetinib 45 mg b.i.d. (n = 6)	Encorafenib 100 mg qd plus binimetinib 45 mg b.i.d. (n = 5)	Encorafenib 200 mg qd plus binimetinib 45 mg b.i.d. (n = 4)	Encorafenib 400 mg qd plus binimetinib 45 mg b.i.d. (n = 5)	Encorafenib 450 mg qd plus binimetinib 45 mg b.i.d. (n = 13)	Encorafenib 600 mg qd plus binimetinib 45 mg b.i.d. (n = 8)	Encorafenib 800 mg qd plus binimetinib 45 mg b.i.d. (n = 6)	All patients (N = 47)
Age (years)								
Median	60.5	54.0	44.0	40.0	49.0	52.5	61.0	54.0
Minimum	33	48	30	33	24	25	26	24
Maximum	75	66	58	70	89	74	65	89
Sex, n (%)								
Female	2 (33)	3 (60)	4 (100)	1 (20)	5 (39)	3 (38)	4 (67)	22 (47)
Male	4 (67)	2 (40)	0	4 (80)	8 (62)	5 (63)	2 (33)	25 (53)
Predominant race, n (%)								
Caucasian	4 (67)	5 (100)	2 (50)	5 (100)	12 (92)	8 (100)	6 (100)	42 (89)
Black	0	0	0	0	0	0	0	0
Asian	2 (33)	0	2 (50)	0	1 (8)	0	0	5 (11)
Ethnicity, n (%)								
Hispanic/Latino	0	0	0	0	0	0	0	0
Not Hispanic or Latino	6 (100)	5 (100)	4 (100)	5 (100)	13 (100)	8 (100)	6 (100)	47 (100)
ECOG performance status, n (%)								
0	4 (67)	2 (40)	1 (25)	1 (20)	7 (54)	4 (50)	6 (100)	25 (53)
1	2 (33)	3 (60)	3 (75)	4 (80)	6 (46)	4 (50)	0	22 (47)
Primary site of cancer, n (%)								
Chest wall	0	0	0	0	1 (8)	0	0	1 (2)
Choroid plexus	0	1 (20)	0	0	0	0	0	1 (2)
Colon	0	0	1 (25)	1 (20)	2 (15)	2 (25)	0	6 (13)
Lung	0	0	0	0	1 (8)	0	1 (17)	2 (4)
Melanoma unknown primary	0	1 (20)	0	0	0	1 (13)	0	2 (4)
Skin	4 (67)	3 (60)	3 (75)	4 (80)	9 (69)	4 (50)	5 (83)	32 (68)
Thyroid gland	2 (33)	0	0	0	0	1 (13)	0	3 (6)

Abbreviations: b.i.d., twice daily; qd, once daily.

Table 2. Most common treatment-related AEs occurring in >15% of all patients in phase Ib safety set.

All grades/ grade 3/4 n (%)	Encorafenib 50 mg qd plus binimetinib 45 mg b.i.d. (n = 6)		Encorafenib 100 mg qd plus binimetinib 45 mg b.i.d. (n = 5)		Encorafenib 200 mg qd plus binimetinib 45 mg b.i.d. (n = 4)		Encorafenib 400 mg qd plus binimetinib 45 mg b.i.d. (n = 5)		Encorafenib 450 mg qd plus binimetinib 45 mg b.i.d. (n = 13)		Encorafenib 600 mg qd plus binimetinib 45 mg b.i.d. (n = 8)		Encorafenib 800 mg qd plus binimetinib 45 mg b.i.d. (n = 6)		All patients (N = 47)	
	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
Total	6 (100)	3 (50)	4 (80)	1 (20)	3 (75)	2 (50)	4 (80)	2 (40)	13 (100)	5 (39)	8 (100)	2 (25)	6 (100)	3 (50)	44 (94)	18 (38)
Nausea	1 (17)	0	4 (80)	0	2 (50)	0	2 (40)	0	6 (46)	0	5 (63)	0	2 (33)	0	22 (47)	0
Diarrhea	3 (50)	0	0	0	0	0	2 (40)	0	7 (54)	0	5 (63)	0	3 (50)	0	20 (43)	0
Fatigue	3 (50)	0	0	0	0	0	2 (40)	0	5 (39)	0	3 (38)	0	3 (50)	1 (17)	16 (34)	1 (2)
Abdominal pain	2 (33)	0	1 (20)	0	0	0	1 (20)	0	4 (31)	0	1 (13)	0	2 (33)	1 (17)	11 (23)	1 (2)
Constipation	1 (17)	0	2 (40)	0	1 (25)	0	0	0	3 (23)	0	1 (13)	0	2 (33)	0	10 (21)	0
ALT increased	0	0	0	0	1 (25)	1 (25)	1 (20)	1 (20)	2 (15)	0	2 (25)	1 (13)	2 (33)	0	8 (17)	3 (6)
Blood CPK increased	3 (50)	2 (33)	2 (40)	0	0	0	1 (20)	0	0	0	1 (13)	0	1 (13)	0	8 (17)	2 (4)
Headache	2 (33)	0	0	0	1 (25)	0	2 (40)	0	0	0	1 (13)	0	2 (33)	0	8 (17)	0
Pain in extremity	0	0	1 (20)	0	2 (50)	0	1 (20)	0	1 (8)	0	1 (13)	0	2 (33)	0	8 (17)	0

Abbreviations: ALT, alanine aminotransferase; b.i.d., twice daily; CPK, creatine phosphokinase; qd, once daily.

Statistical analysis

For demographic and baseline characteristics as well as activity and safety observations, continuous variables are summarized as medians and ranges, while categorical variables are expressed as frequencies and percentages. An adaptive Bayesian logistic regression model guided by the escalation with overdose control principle was used to guide dose escalation and estimate the MTD. The dose-escalation phase was continued until the MTD and/or RP2D was determined. The best overall response, ORR, and DCR are provided. Median PFS values were estimated using the Kaplan–Meier method and reported with corresponding 95% confidence intervals (CIs).

For phase Ib, at least 18 patients were expected to be treated in the dual combination dose-escalation part of the study for the model to have reasonable operating characteristics relating to its MTD recommendation. For phase II, the sample size was based on the probability of correctly declaring the activity. For arm 1 in phase II, a sample size of 28 patients was estimated to provide an 85.2% probability to correctly declare activity if the true DCR is 40%, and a 9% probability of wrongly declaring activity if the true DCR is 20%. A sample size of 41 patients was estimated for arm 2 to provide a 73.9% probability to correctly declare activity if the true ORR is 20%, and a 11% probability of wrongly declaring activity if the true ORR is 10%. For arm 3, a sample size of 40 patients was estimated to provide a 92.3% probability to correctly declare activity if the true ORR is 50%, and a 11.5% probability of wrongly declaring activity if the true ORR is 30%.

Results

Patients characteristics

Between May 30, 2012 and February 11, 2014 (data cut-off August 31, 2015), 47 patients were enrolled to seven dose-escalation cohorts. The majority of the patients in phase Ib had melanoma [36 patients (77%)] and had received prior antineoplastic therapy [41 patients (87%)], including 28 patients who received a BRAFi. Baseline characteristics of patients in the phase Ib portion of the study are summarized in **Table 1**.

In the phase II portion of the study, a total of 79 patients received dual combination therapy and were grouped as follows: arm 1 [patients with mCRC (N = 11)], arm 2 [prior BRAFi-treated patients with melanoma (N = 26)], and arm 3 [BRAFi-naïve patients with melanoma (N = 42)]. Across patient populations, a total of 64 patients received 600 mg once daily as the starting encorafenib dose and 15 patients received 450 mg once daily as the starting encorafenib dose. Baseline characteristics of patients in the phase II portion of the study are summarized in Supplementary Table S1. In addition, the baseline characteristics for the 55 patients with BRAFi-naïve BRAF-mutant melanoma enrolled overall in both study phases are provided in the Supplementary Information (Supplementary Table S2).

MTD and RP2D Determination

Only one patient (2%) across all cohorts investigated experienced a DLT, which occurred in a patient receiving 800-mg encorafenib and 45-mg binimetinib (nonserious AE of grade 3 arthritis). The MTD was defined as 600-mg encorafenib daily plus 45-mg twice daily of binimetinib. Following the phase Ib part of the trial, two RP2Ds for the phase II part were established: encorafenib 600 mg once daily plus binimetinib 45 mg twice daily, and encorafenib 450 mg once daily plus binimetinib 45 mg twice daily. A total of 64 patients received 600 mg once daily as the starting encorafenib dose and 15 patients received 450 mg once daily as the starting encorafenib dose. Early-onset renal insufficiency (grade 3 creatinine increase) was observed in three

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Table 3. Phase Ib steady-state PK estimates for encorafenib and binimetinib (cycle 1, day 15).

N	Dose (mg once daily)	Encorafenib					Binimetinib (fixed: 45 mg twice daily)				
		C _{max} (μg/mL)	T _{max} (h)	AUC _{tau} (h·μg/mL)	C _{trough} (ng/mL)	t _{1/2} (h)	C _{max} (μg/mL)	T _{max} (h)	AUC _{tau} (h·μg/mL)	C _{trough} (ng/mL)	t _{1/2} (h)
6	50	0.5 (76)	1.5 (0.5, 1.5)	2.3 (59)	6.1 (81)	4.6 (25)	0.6 (41)	1.5 (0.5, 2.5)	2.7 (50)	88.8 (38)	4.6 (31)
5	100	1.1 (34)	2.5 (1.5, 2.7)	5.4 (27)	11.8 (36)	4.5 (9)	0.5 (49)	1.5 (0.5, 1.6)	2.5 (38)	92.2 (55)	4.7 (30)
4	200	1.1 (19)	2.0 (1.5, 2.5)	4.5 (38)	11.7 (18)	4.2 (30)	0.5 (92)	2.0 (1.5, 2.5)	2.3 (92)	59.1 (76)	3.3 (NE)
5	400	3.6 (35)	1.5 (1.5, 1.7)	10.1 (21)	15.4 (35)	4.2 (17)	0.5 (85)	1.5 (1.5, 1.7)	1.9 (59)	42.3 (49)	4.0 (39)
13	450	3.8 (63)	1.5 (0.5, 2.6)	13.9 (59)	13.9 (82)	3.5 (17)	0.6 (39)	1.6 (0.5, 2.6)	2.4 (34)	51.4 (42)	3.5 (29)
8	600	7.0 (123)	2.0 (0.5, 2.5)	23.2 (69)	20.4 (76)	3.4 (7)	0.7 (52)	1.5 (0.5, 2.7)	2.2 (68)	35.9 (123)	NE (NE)
6	800	6.1 (47)	1.5 (0.5, 4.0)	23.8 (28)	13.0 (74)	3.2 (15)	0.7 (28)	2.1 (0.5, 2.5)	2.5 (20)	41.8 (42)	2.9 (5)

Note: Geo-mean (CV% geo-mean) values were reported for the parameters. Median (minimum, maximum) presented for T_{max}. Abbreviations: h, hours; NE, not estimable.

patients with melanoma (two with preexisting conditions that could be associated with renal insufficiency) at the higher encorafenib dose level (600 mg once daily), leading to a decision to no longer treat patients at this dose. All subsequent patients in phase II were started at 450 mg once daily, and all ongoing patients on the higher encorafenib dose were reduced to 450 mg once daily in combination with their current binimetinib dose. A summary of the most common treatment-related AEs across phase Ib cohorts is summarized in **Table 2**.

PK

Cycle 1, day 15 steady-state PK results for encorafenib and binimetinib across phase Ib cohorts are summarized in **Table 3**. Encorafenib was rapidly absorbed with a median T_{max} that ranged from 1.5 to 2.5 hours across cohorts at day 15. Plasma AUCs and C_{max} of encorafenib increased in a slightly less than dose-proportional manner as the encorafenib dose increased from 50 to 800 mg on day 15.

Variability of PK exposure parameters for encorafenib was moderate to high with coefficient of variation (%CV) geometric values for AUC over the dosing interval (AUC_{tau}) of approximately 59% for the 450-mg encorafenib plus 45-mg binimetinib cohort (N = 13). Variability of C_{max} was similar to each cohort's steady-state AUC_{tau}. Across all cohorts, intrasubject CV for encorafenib was 36% for AUC_{tau}. After reaching C_{max}, encorafenib concentrations rapidly declined and the geometric mean half-life was similar across different encorafenib doses, ranging from 2.88 hours on day 1 to 4.63 hours on day 15. The geometric mean accumulation ratio ranged from 0.294 to 0.811 across dose levels, indicating a decrease in exposure of encorafenib after multiple doses, likely due to metabolic autoinduction of encorafenib.

There were no distinct trends for increasing or decreasing binimetinib C_{max} or AUC values with increasing doses of encorafenib over the entire encorafenib dose range, suggesting no drug interaction effect by encorafenib on the PK of binimetinib. These

Table 4. Efficacy in phase Ib as defined by RECIST v1.1.

	Phase Ib						
	Encorafenib 50 mg qd plus binimetinib 45 mg b.i.d. (n = 6)	Encorafenib 100 mg qd plus binimetinib 45 mg b.i.d. (n = 5)	Encorafenib 200 mg qd plus binimetinib 45 mg b.i.d. (n = 4)	Encorafenib 400 mg qd plus binimetinib 45 mg b.i.d. (n = 5)	Encorafenib 450 mg qd plus binimetinib 45 mg b.i.d. (n = 13)	Encorafenib 600 mg qd plus binimetinib 45 mg b.i.d. (n = 8)	Encorafenib 800 mg qd plus binimetinib 45 mg b.i.d. (n = 6)
CR ^a , n (%)	1 (17)	1 (20)	0	0	1 (8)	0	1 (17)
PR ^a , n (%)	3 (50)	1 (20)	1 (25)	2 (40)	6 (46)	3 (38)	2 (33)
CR ^b , n (%)	1 (17)	1 (20)	0	0	1 (8)	0	1 (17)
PR ^b , n (%)	3 (50)	1 (20)	1 (25)	2 (40)	6 (46)	2 (25)	2 (33)
SD, n (%)	2 (33)	3 (60)	0	1 (20)	5 (39)	3 (38)	2 (33)
PD, n (%)	0	0	2 (50)	1 (20)	1 (8)	3 (38)	1 (17)
Unknown, n (%)	0	0	1 (25)	1 (20)	0	0	0
ORR, n (%)	4 (67)	2 (40)	1 (25)	2 (40)	7 (54)	2 (25)	3 (50)
(95% CI) ^{b,c}	(22–96)	(5–85)	(1–81)	(5–85)	(25–81)	(3–65)	(12–88)
DCR, n (%)	6 (100)	5 (100)	1 (25)	3 (60)	12 (92)	5 (63)	5 (83)
(95% CI) ^{b,c}	(54–100)	(48–100)	(1–81)	(15–95)	(64–100)	(25–92)	(36–100)

Abbreviations: b.i.d., twice daily; CIs, confidence intervals; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; qd, once daily; SD, stable disease.

^aResponse confirmation is not required.

^bResponse confirmation is required.

^cEstimate (95% CI) for ORR and DCR were obtained using exact binomial CIs.

results indicate that binimetinib exposure is likely unaffected by coadministration with encorafenib. The variability in exposure was moderate (34% CV for AUC_{tau} in the 450-mg encorafenib cohort) as observed in previous single-agent binimetinib studies. Across all cohorts, intrasubject CV for binimetinib was 28% for AUC_{tau} . The terminal half-life ($t_{1/2}$) of binimetinib ranged from 2.9 to 4.7 hours across encorafenib dose groups. In addition, little to no binimetinib accumulation was observed, a result that is consistent with that observed following single-agent binimetinib administration (29).

Therapeutic activity

In the phase Ib study, the confirmed ORR was 54% (seven of 13 patients; 95% CI, 25–81) for patients in the encorafenib 450-mg plus binimetinib 45-mg group and 25% (two of eight patients; 95% CI, 3–65) for patients in the encorafenib 600-mg plus binimetinib 45-mg group. Confirmed responses were observed in every dose cohort below the RP2D, with ORR ranging from 25% (encorafenib 200-mg plus binimetinib 45-mg cohort; $n = 4$; 95% CI, 1–81) to 67% (encorafenib 50-mg plus binimetinib 45-mg cohort; $n = 6$; 95% CI, 22–96). A summary of the efficacy results from phase Ib can be found in **Table 4**.

A summary of the efficacy results for the phase II cohorts, as well as the pooled BRAFi-naïve melanoma patient population from the phase Ib and phase II parts of the study can be found in Supplementary Table S3.

BRAFi previously treated, BRAF-mutant melanoma cohort

A total of 26 patients were enrolled into the BRAFi previously treated, BRAF-mutant melanoma cohort. Confirmed best response, per RECIST v1.1 was as follows: one patient had a CR, 10 had a confirmed PR, eight had SD, four had progression of disease (PD), and three patients' best response was unknown. The ORR was 42% (95% CI, 23–63) and DCR, defined as best response of CR, PR, and SD, was 73% (95% CI, 52–88).

BRAF-mutant CRC cohort

Eleven patients were enrolled in the BRAF-mutant CRC cohort. Best response, per RECIST was as follows: two had a confirmed PR, five had SD, three had PD, and one was unknown. The overall response rate was 18% (95% CI, 2–52) and DCR was 64% (95% CI, 31–89).

BRAFi-naïve BRAF-mutant melanoma phase Ib and II patients

A total of 55 patients with BRAFi-naïve, BRAF-mutant melanoma were enrolled overall in both study phases (Supplementary Table S2). At the time of data cut-off, 11/55 (20%) patients were still ongoing. Forty of 55 patients (73%; 95% CI, 59–84) achieved an objective response (Supplementary Table S3). The maximal tumor volume reduction shows that all but one patient had initial disease regression on imaging (**Fig. 1**). Response was observed across all doses (**Fig. 1A**) and in patients with both visceral and untreated brain metastases (**Fig. 1B and C**). Per RECIST v1.1, the numbers of patients with confirmed CR and PR by investigator assessment were 6/55 (11%) and 34/55 (62%), respectively. The DCR was 53/55 (96%; 95% CI, 88–100). Two patients had a best response defined as progressive disease (Supplementary Table S3).

The median PFS was 11.0 months (95% CI, 6.8–14.6). In patients with lactate dehydrogenase (LDH) levels \leq ULN, the median PFS was 20.4 months (95% CI, 11.0–not estimable), whereas the median PFS in patients with LDH levels $>$ ULN was 6.8 months (95% CI, 4.4–11.3).

Figure 2 shows the Kaplan–Meier curves for all patients (**Fig. 1D**) and according to LDH stratification (**Fig. 2E**).

Phase II safety

The median exposure to the dual combination for phase II part of the study was 5.5 months (range, 0.2–20.4 months) in the mCRC population, 4.3 months (range, 0.2–23.2 months) in the prior BRAFi melanoma population, and 11.1 months (range, 0.8–26.4 months) in the BRAFi-naïve melanoma population. More than half of all patients in phase II [44 patients (56%)] had an exposure of greater than 6 months. The median relative dose intensity for all patients in phase II was 94% for 400 encorafenib and 98% for binimetinib and was proportional to the dose administered across the assigned treatment groups, ranging from 38 to 102 mg/day for encorafenib and 14 to 100 mg/day for binimetinib. The relative dose intensity for majority of patients was \geq 90% [43 patients (54%) for the encorafenib part of the dose and 51 patients (65%) for the binimetinib part of the dose].

All 79 (100%) patients in phase II reported at least one AE and 77 patients (98%) reported at least one treatment-related AE. **Table 5** reports the most common AEs in each of the phase II cohorts. Diarrhea was the most frequently reported AE in the mCRC population [eight patients (73%)] and the prior BRAFi melanoma population [14 patients (54%)] while nausea was the most frequently reported AE in the BRAFi-naïve melanoma population [20 patients (48%)], with a similar proportion of patients reporting nausea in the other patient populations. Vomiting was also a frequently reported event for all populations with six patients (55%) reporting the event in the mCRC population, nine patients (35%) in the prior BRAFi melanoma population and 14 patients (33%) in the BRAFi-naïve melanoma population. During phase II for all patients, the most frequently reported grade 3 or 4 AEs were ALT increased for seven patients (9%) and the following AEs for six patients (8%) each: anemia, aspartate aminotransferase (AST) increased, blood CPK increased, and lipase increased. In general, the frequency of grade 3 or 4 AEs was lower in the mCRC population.

All 79 patients in phase II experienced at least one AE of special interest (AESI) of any grade (i.e., AEs that are specific clinical interest in connection with binimetinib and/or encorafenib, based on the mechanism of action). The most frequently reported AESIs ($>$ 20% of patients) regardless of grade were fatigue in 24 patients (30%), diarrhea in 41 patients (52%), nausea in 37 patients (47%), vomiting in 29 patients (37%), constipation in 20 patients (25%), increased AST in 20 patients (25%), increased ALT in 18 patients (23%), increased blood CPK in 19 patients (24%), blurred vision in 16 patients (20%), and retinopathy in 17 patients (22%). Most of the AESIs were reported with a severity of grade 1 or 2.

Seven patients (9%) experienced AEs that resulted in permanent discontinuation of study treatment during the phase II part of the study. AEs leading to discontinuation were acute kidney injury and hypercreatininemia [two patients (3%)], blood CPK increased and hypercreatininemia [two patients (3%)], ALT increased, AST increased, myocardial infarction, pain in extremity, and peripheral neuropathy [all others: one patient (1%) each]. Thirty-nine patients (49%) experienced AEs that resulted in a dose adjustment or interruption during the phase II part of the study. The proportion of AEs reported for patients in the BRAFi-naïve melanoma population [23 (55%) patients] was comparable with that reported for patients in the prior BRAFi melanoma population [11 (42%) patients] and mCRC population [five (46%) patients]. The most common AEs (reported by $>$ 2 patients across all patient populations) leading to dose adjustment or interruption were ALT increased, amylase increased, anemia, AST increased,

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blood alkaline phosphatase increased, blood CPK increased, diarrhea, fatigue, hypercreatininemia, lipase increased, nausea, vomiting, pyrexia, and retinopathy. Notably, there appears to be higher rate of total and grade 3 toxicities in the dose-expansion cohorts than was seen in dose escalation (Table 2).

Discussion

We present the dose-escalation data from the phase Ib study of encorafenib and binimetinib that includes toxicity, therapeutic

activity, and pharmacokinetic data. In addition, we provide the first description of the therapeutic activity data from the phase II cohorts of patients with *BRAF*-mutant mCRC and patients with *BRAF*-mutant metastatic melanoma, for both patients treated and not previously treated with BRAFi. Following the completion of this study, the COLUMBUS trial in patients with *BRAF*V600-mutant melanoma and BEACON CRC study in patients with *BRAF* V600E mCRC were launched and completed, building on the foundation of safety data from this trial and establishing efficacy with encorafenib and binimetinib regimens.

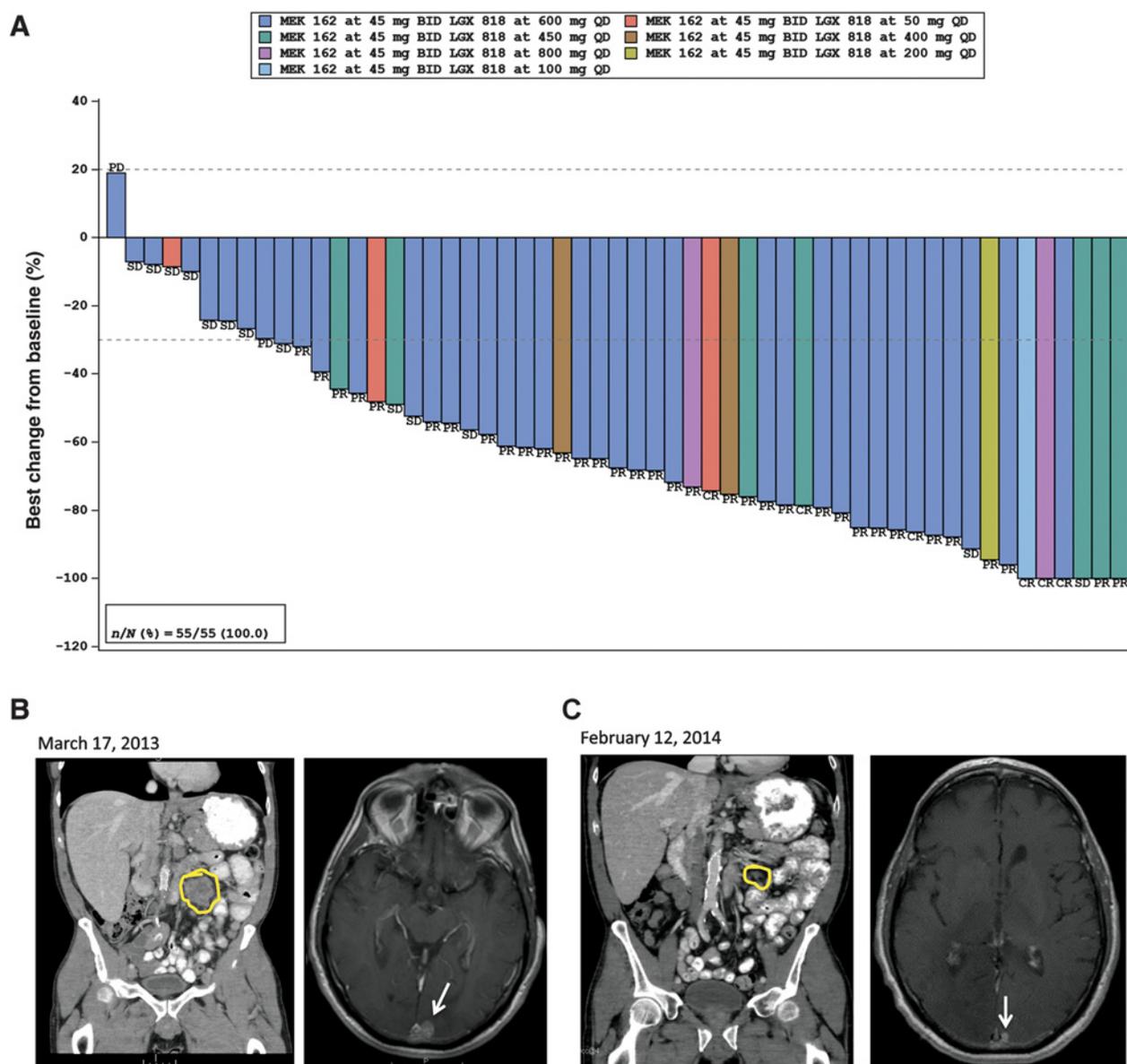


Figure 1.

A, Waterfall plot of best percentage change from baseline in the analysis set for response for patients with BRAFi-naive, *BRAF*-mutant melanoma. **B**, Scan of previously untreated 70-year-old patient with recurrent and metastatic melanoma before treatment (March 17, 2013). **C**, Scan of same patient after 11 months of treatment with encorafenib 450 mg once daily plus binimetinib 45 mg twice daily (February 12, 2014). (Continued on the following page.)

Encorafenib+binimetinib in BRAF-mutant Solid Tumors

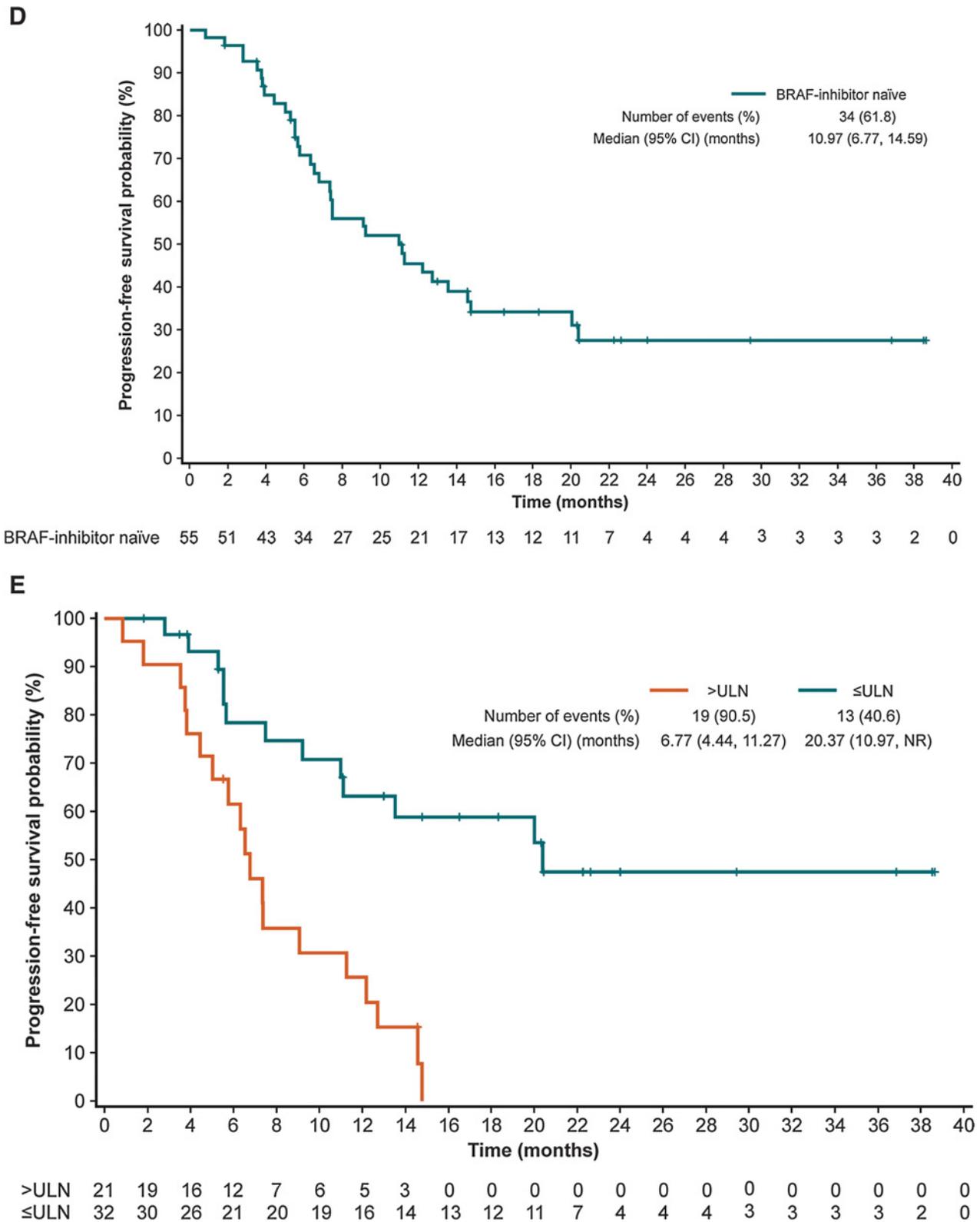


Figure 1. (Continued.) Kaplan-Meier estimates of PFS in all patients with BRAFi-naïve, BRAF-mutant melanoma (D) and according to LDH stratification (E). b.i.d., twice daily; CR, complete response; PD, progressive disease; PR, partial response; qd, once daily; SD, stable disease; LDH, lactate dehydrogenase; NE, not estimable; PFS, progression-free survival; ULN, upper limit of normal.

Table 5. Summary of most common ($\geq 25\%$) adverse events in phase II per NCI Common Terminology Criteria for Adverse Events version 4.1, regardless of study drug relationship^a.

	BRAF V600-mutant mCRC (n = 11)		BRAF-mutant melanoma progressed post BRAF inhibitor (n = 26)		BRAF-mutant melanoma no prior BRAF inhibitor (n = 42)	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	11 (100)	4 (36)	26 (100)	15 (58)	42 (100)	25 (60)
Diarrhea	8 (73)	2 (18)	14 (54)	1 (4)	19 (45)	1 (2)
Nausea	6 (55)	0	11 (42)	3 (12)	20 (48)	2 (5)
Vomiting	6 (55)	0	9 (35)	3 (12)	14 (33)	2 (5)
Pyrexia	6 (55)	0	6 (23)	0	14 (33)	2 (5)
Arthralgia	4 (36)	0	7 (27)	0	13 (31)	0
Fatigue	2 (18)	0	10 (39)	1 (4)	12 (29)	0
AST increased	1 (9)	0	6 (23)	1 (4)	13 (31)	5 (12)
Constipation	4 (36)	0	5 (19)	0	11 (26)	0

Abbreviation: AST, aspartate aminotransferase.

^aAdverse events occurring in $\geq 25\%$ in all patients in phase II.

A number of important observations are presented. The first is that the combination of encorafenib and binimetinib has a safety profile that is consistent with other BRAF-MEK inhibitor combinations, but with several key differences. General toxicities such as nausea, diarrhea, and fatigue were common, and BRAFi- and MEKi-related AEs, such as secondary malignancies (BRAFi), hand-foot syndrome (BRAFi; ref. 5), retinopathy (MEKi; ref. 30), and decreased ejection fraction (MEKi; ref. 31) were observed at expected rates. As has been observed previously (12, 13), the rates of pyrexia and photosensitivity were lower than expected on the basis of previous studies for dabrafenib plus trametinib and vemurafenib plus cobimetinib, respectively (20, 32).

At the completion of the dose-escalation portion of the study, two dose levels, encorafenib 600 mg once daily and 450 mg once daily (both in combination with binimetinib 45 mg twice daily), were identified as tolerable and included an encorafenib dose that was higher than the MTD of single-agent encorafenib. For this reason, both were considered to be possible RP2D, although the initial enrollment of the dose-expansion cohorts was at the encorafenib 600-mg dose level until the 3 patients developed otherwise unexplained acute kidney injury, which subsequently was not seen at the lower dose levels in the dose-expansion cohorts. Importantly, the efficacy and safety data from this phase Ib/II study informed the dose and regimen for two phase III studies evaluating encorafenib plus binimetinib regimens utilizing the encorafenib 450-mg dose. In the COLUMBUS study, the combination of encorafenib plus binimetinib has demonstrated clinical activity and tolerability in patients with BRAF V600-mutated metastatic melanoma (12, 13, 22), leading to regulatory approvals starting in 2018. In addition, the BEACON CRC study demonstrated that the combination of the EGFR inhibitor cetuximab with encorafenib and binimetinib improved OS relative to the current standard-of-care in patients with BRAF V600-mutated mCRC (27).

In conclusion, this phase Ib/II study showed encouraging activity for the encorafenib plus binimetinib combination with expected toxicity. The tolerable dose and exposure of encorafenib are higher in combination than as a single agent in previous studies. Lower rates of dose-limiting pyrexia, arthralgia, and photosensitivity relative to published data from other BRAFi plus MEKi regimens, is another distinguishing feature of the encorafenib plus binimetinib combination.

Disclosure of Potential Conflicts of Interest

R.J. Sullivan reports personal fees from Array, Asana, Compugen, Novartis, Syndax, Replimmune, Bristol-Myers Squibb, and Roche-Genentech, and grants and personal fees from Amgen and Merck outside the submitted work. J.S. Weber reports personal fees from Array (less than 5,000 dollars per year for Ad Boards) outside the submitted work. S.P. Patel reports other from Novartis (institution received support for clinical trial) during the conduct of the study; personal fees from Merck (nonpromotional speaker and bureau), Immunocore (data safety monitoring board), and Reata (data safety monitoring board); and other from Castle Biosciences (honorarium for advisory board) and Incyte (honorarium for advisory board) outside the submitted work. R. Dummer reports personal fees from intermittent, project-focused consulting and/or advisory relationships from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, and Alligator outside the submitted work. M.S. Carlino reports personal fees from Bristol-Myers Squibb (advisory board member and honoraria), MSD (advisory board member and honoraria), Novartis (advisory board member and honoraria), Roche (advisory board member), Amgen (advisory board member), Pierre Fabre (advisory board member), Eisai (advisory board member), Sanofi (advisory board member), Merck Serono (advisory board member), Nektar (advisory board member), Ideay (advisory board member), and Q Biotics (advisory board member) outside the submitted work. D.S. Tan reports grants from Pfizer, GlaxoSmithKline, AstraZeneca, and Novartis, and personal fees from Boehringer Ingelheim, Pfizer, MSD, Roche, Novartis, AstraZeneca, and Bayer outside the submitted work. C. Lebbe reports personal fees from Novartis (honoraria, consultancy, speakers bureau, advisory role, serving on an advisory board) during the conduct of the study; grants and personal fees from Bristol-Myers Squibb (honoraria, consultancy, speakers bureau, travel accommodations-meetings, advisory role, serving on an advisory board) and Roche (honoraria, consultancy, speakers bureau, advisory role, serving on an advisory board); personal fees from MSD (honoraria, consultancy, speakers bureau, advisory role, serving on an advisory board, travel accommodations-meetings), Novartis (honoraria, consultancy, speakers bureau, advisory role, serving on an advisory board), Amgen (honoraria, consultancy, speakers bureau, serving on an advisory board), Avantis Medical Systems (board), Pierre Fabre (honoraria), Pfizer (honoraria), Incyte (honoraria), Merck Serono (consulting or advisory role), and Sanofi (consulting or advisory role) outside the submitted work. S. Siena reports other from Amgen (advisory board member), Bayer (advisory board member), Bristol-Myers Squibb (advisory board member), CheckmAb (advisory board member), Daiichi-Sankyo (advisory board member), Merck (advisory board member), Roche-Genentech (advisory board member), and Seattle Genetics (advisory board member) during the conduct of the study. E. Elez reports other from Hoffman La-Roche (institution received honoraria due to investigator contribution in clinical trials), Sanofi Aventis (institution received honoraria due to investigator contribution in clinical trials), Amgen (institution received honoraria due to investigator contribution in clinical trials), Merck Serono (institution received honoraria due to investigator contribution in clinical trials), MSD (institution received honoraria due to investigator contribution in clinical

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advisory role) outside the submitted work. No other potential conflicts of interest were disclosed.

Authors' Contributions

R.J. Sullivan: Conceptualization, writing-original draft, writing-review and editing. **J. Weber:** Data curation, writing-review and editing. **S. Patel:** Data curation, writing-review and editing. **R. Dummer:** Conceptualization, data curation, writing-review and editing. **M.S. Carlino:** Data curation, writing-review and editing. **D.S.W. Tan:** Data curation, writing-review and editing. **C. Lebbé:** Data curation, writing-review and editing. **S. Siena:** Data curation, writing-review and editing. **E. Elez:** Data curation, writing-review and editing. **L. Wollenberg:** Conceptualization, data curation, formal analysis, methodology, writing-review and editing. **M.D. Pickard:** Conceptualization, methodology, writing-original draft, writing-review and editing. **V. Sandor:** Conceptualization, writing-review and editing. **P.A. Ascierto:** Conceptualization, data curation, writing-original draft, writing-review and editing.

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References

- Vennepureddy A, Thumallapally N, Nehru VM, Atallah J-P, Terjanian T. Novel drugs and combination therapies for the treatment of metastatic melanoma. *J Clin Med Res* 2016;8:63-75.
- Chappell WH, Steelman LS, Long JM, Kempf RC, Abrams SL, Franklin RA, et al. Ras/Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR inhibitors: rationale and importance to inhibiting these pathways in human health. *Oncotarget* 2011; 2:135-64.
- Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. *Nature* 2002;417:949-54.
- Tie J, Gibbs P, Lipton L, Christie M, Jorissen RN, Burgess AW, et al. Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the BRAF(V600E) mutation. *Int J Cancer* 2011;128: 2075-84.
- Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507-16.
- Hauschild A, Grob J-J, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012;380:358-65.
- Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30-9.
- Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014;371:1877-88.
- Larkin J, Ascierto PA, Dréno B, Atkinson V, Liskay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014; 371:1867-6.
- Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liskay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016;17: 1248-60.
- National Comprehensive Cancer Network. Clinical practice guidelines in oncology, colon cancer version 1; 2019. Fort Washington, PA: National Comprehensive Cancer Network, 2019. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx.
- Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature* 2010;467:596-99.
- Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liskay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2018;19: 1315-27.
- Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liskay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma: a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:603-15.
- Johannessen CM, Boehm JS, Kim SY, Thomas SR, Wardwell L, Johnson LA, et al. COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. *Nature* 2010;468:968-72.
- Poulikakos PI, Persaud Y, Janakiraman M, Kong X, Ng C, Moriceau G, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF (V600E). *Nature* 2011;480:387-90.
- Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, et al. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* 2012;487:500-4.
- Corcoran RB, Dias-Santagata D, Bergethon K, Iafrate J, Settleman J, Egelman JA. BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation. *Sci Signal* 2010;3:ra84.
- Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, et al. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov* 2012;2:227-35.

Sullivan et al.

20. Kakadia S, Yarlagadda N, Awad R, Kundranda M, Niu J, Naraev B, et al. Mechanisms of resistance to BRAF and MEK inhibitors and clinical update of US Food and Drug Administration-approved targeted therapy in advanced melanoma. *Onco Targets Ther* 2018;11:7095–107.
21. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015;386:444–51.
22. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma [abstract]. *Ann Oncol* 2016;27:LBA40.
23. Ascierto PA, Dummer R, Gogas HJ, Flaherty KT, Arance A, Mandala M, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. *Eur J Cancer* 2020; 126:33–44.
24. Delord JP, Robert C, Nyakas M, McArthur GA, Kudchakar R, Mahipal A, et al. Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF-mutant melanoma. *Clin Cancer Res* 2017;23: 5339–48.
25. Adelman CH, Ching G, Du L, Saporito RC, Bansal V, Pence LJ, et al. Comparative profiles of BRAF inhibitors: the paradox index as a predictor of clinical toxicity. *Oncotarget* 2016;7:30453–60.
26. Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CM, Queirolo P, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. *Lancet Oncol* 2013;14:249–56.
27. Van Cutsem E, Huijberts S, Grothey A, Yaeger R, Cuyle P-J, Elez E, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-mutant metastatic colorectal cancer: safety lead-in results from the phase III BEACON colorectal cancer study. *J Clin Oncol* 2019;37:1460–9.
28. Kopetz S, Grothey A, Van Cutsem E, Yaeger R, Wasan H, Yoshino T, et al. BEACON CRC: a randomized, 3-arm, phase 3 study of encorafenib and cetuximab with or without binimetinib vs. choice of either irinotecan or FOLFIRI plus cetuximab in BRAF V600E-mutant metastatic colorectal cancer [abstract]. In: Proceedings of the ESMO 21st World Congress on Gastrointestinal Cancer; July 3–6, 2019, Barcelona, Spain. Lugano, Switzerland: ESMO; 2019. Abstract nr LBA-006.
29. Bendell JC, Javle M, Bekaii-Saab TS, Finn RS, Wainberg ZA, Laheru DA, et al. A phase 1 dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor. *Br J Cancer* 2017;116:575–83.
30. Wang D, Boerner SA, Winkler JD, LoRusso PM. Clinical experience of MEK inhibitors in cancer therapy. *Biochim Biophys Acta* 2007;1773:1248–55.
31. Britten CD. PI3K and MEK inhibitor combinations: examining the evidence in selected tumor types. *Cancer Chemother Pharmacol* 2013;71:1395–409.
32. COTELLIC® (cobimetinib) tablets [package insert]. South San Francisco, CA 94080–4990. Genentech USA, Inc. Available from: <http://labeling.pfizer.com/ShowLabeling.aspx?id=12988>.

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