Published OnlineFirst March 31, 2017; DOI: 10.1158/2159-8290.CD-16-0795

RESEARCH ARTICLE

A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab with or without Alpelisib in Metastatic *BRAF*-Mutant Colorectal Cancer

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ABSTRACT Preclinical evidence suggests that concomitant BRAF and EGFR inhibition leads to sustained suppression of MAPK signaling and suppressed tumor growth in *BRAF*^{V600E} colorectal cancer models. Patients with refractory *BRAF*^{V600}-mutant metastatic CRC (mCRC) were treated with a selective RAF kinase inhibitor (encorafenib) plus a monoclonal antibody targeting EGFR (cetuximab), with ($n = 28$) or without ($n = 26$) a PI3Kα inhibitor (alpelisib). The primary objective was to determine the maximum tolerated dose (MTD) or a recommended phase II dose. Dose-limiting toxicities were reported in 3 patients receiving dual treatment and 2 patients receiving triple treatment. The MTD was not reached for either group and the phase II doses were selected as 200 mg encorafenib (both groups) and 300 mg alpelisib. Combinations of cetuximab and encorafenib showed promising clinical activity and tolerability in patients with *BRAF*-mutant mCRC; confirmed overall response rates of 19% and 18% were observed and median progression-free survival was 3.7 and 4.2 months for the dual- and triple-therapy groups, respectively.

SIGNIFICANCE: Herein, we demonstrate that dual- (encorafenib plus cetuximab) and triple- (encorafenib plus cetuximab and alpelisib) combination treatments are tolerable and provide promising clinical activity in the difficult-to-treat patient population with *BRAF*-mutant mCRC. *Cancer Discov; 7(6); 610–9. ©2017 AACR.*

See related commentary by Sundar et al., p. 558.

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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doi: 10.1158/2159-8290.CD-16-0795

Published OnlineFirst March 31, 2017; DOI: 10.1158/2159-8290.CD-16-0795

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer in men and the second in women; 693,900 patients with colorectal cancer died in 2012 (1). The anti-EGFR monoclonal antibody cetuximab is indicated for wild-type *RAS* metastatic colorectal cancer (mCRC), either in combination with cytotoxic chemotherapy or as a single agent.

Investigations of the signaling pathways downstream of EGFR have shown that mutations of *KRAS*, *NRAS*, and *BRAF* play an important role in cancer progression (2). Mutations in the *BRAF* gene at V600 occur in approximately 7% of all cancers, including approximately 8% to 15% of colorectal cancers (3–5). *BRAF*-mutant colorectal cancer is molecularly distinct from *BRAF* wild-type colorectal cancer (6); indeed, a recent publication outlined four distinct consensus molecular subtypes of colorectal cancer and the majority of *BRAF* mutations were found in one of the four subtypes (7). *BRAF*-mutated colorectal cancer is associated with a significantly poorer prognosis and poor response to standard treatments, highlighting the unmet medical need for this group of patients (8, 9).

Two BRAF inhibitors (vemurafenib and dabrafenib) have been approved for the treatment of *BRAF*-mutant melanoma (10, 11). In contrast, BRAF inhibitors have shown limited efficacy in *BRAF*-mutant mCRC (12–17). Preclinical studies of *BRAF*-mutant colorectal cancer and melanoma cell lines treated with selective $BRAF^{V600}$ inhibitors have found that rapid EGFR-mediated reactivation of the MAPK pathway contributed to the unresponsiveness of *BRAF*-mutant colorectal cancer cells (12, 14).

Despite the limited efficacy of EGFR and BRAF inhibitors given as single agents in patients with *BRAF*-mutant colorectal cancer, preclinical evidence suggests that concomitant inhibition leads to sustained suppression of MAPK signaling, resulting in reduced cell proliferation and increased antitumor activity (12, 14, 18).

Activation of the PI3K/AKT pathway has also been identified as a mechanism of resistance to BRAF inhibitors in *BRAF*-mutant colorectal cancer cell lines (13, 19). Combinatorial approaches with BRAF and PI3K inhibitors have been suggested to improve outcomes in patients with *BRAF*-mutant mCRC (13).

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Table 1. Dose-escalation cohorts for dual-combination and triple-combination therapies

ENC + CTX, $n = 26$			ENC + ALP + CTX, $n = 28$			
Patient number, *n*	Dose of encorafenib, mg qd	DLT	Patient number, *n*	Dose of encorafenib, mg qd	Dose of alpelisib, mg qd	DLT
2	100	None	3	200	100	None
7	200	G3 arthralgia ($n = 1$)	8	200	200	None
9	400	G3 vomiting ($n = 1$)	7	300	200	G4 acute renal failure ($n = 1$)
8	450	G3 QT interval prolongation ($n = 1$)	10	200	300	G3 bilateral interstitial pneumonitis ($n = 1$)

Abbreviations: DLT, dose-limiting toxicity; ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab; G3, grade 3; G4, grade 4; qd, daily.

Encorafenib is a potent, selective RAF kinase inhibitor with promising activity in preclinical models, including greater potency compared with vemurafenib and dabrafenib (20). Alpelisib is a class I α-specific PI3K inhibitor with antitumor activity in various cancer cell lines, especially those with documented *PIK3CA* mutations, and in tumor xenograft models with mutated or amplified *PIK3CA* (21).

The synergistic activity of dual inhibition of BRAF, EGFR, or PI3K has been reported in preclinical studies, and preliminary preclinical activity has also been reported for triple inhibition (12–14, 18, 19). These observations led to the initiation of this phase Ib/II study of encorafenib plus cetuximab with or without alpelisib in patients with $BRAF^{V600}$-mutant mCRC. Herein, we report results of the phase Ib portion of this study, which had the primary aim of selecting a dose of encorafenib and alpelisib for phase II by determining the incidence of dose-limiting toxicities (DLT).

RESULTS

Patient Disposition and Characteristics

A total of 54 patients were enrolled into either the dual ($n = 26$) or triple combination ($n = 28$) therapy groups and received escalating doses of encorafenib and/or alpelisib (Table 1). By February 1, 2015, treatment had been discontinued in 24 (92.3%) of the patients in the dual-combination therapy group due to disease progression ($n = 18$; 69.2%), adverse events (AE; $n = 3$; 11.5%), physician decision ($n = 1$; 3.8%), patient decision ($n = 1$; 3.8%), or death ($n = 1$; 3.8%). In the triple-combination therapy group, treatment had been discontinued in 22 (78.6%) patients due to disease progression ($n = 19$; 67.9%), AEs ($n = 2$; 7.1%), or death ($n = 1$; 3.6%).

Patient characteristics in the two groups were similar; however, more patients had a poorer Eastern Cooperative Oncology Group performance status (ECOG PS) in the dual-combination than in the triple-combination group (ECOG PS ≥1: 69.2% vs. 35.7%, respectively; Table 2); comparisons between the two groups should be made with caution. The majority of patients had received two prior lines of therapy, and a considerable proportion had been treated with three or more lines of therapy (23% in the dual-combination and 11% in the triple-combination therapy groups). Fifteen (28%)

Table 2. Patient and disease characteristics at baseline

	ENC + CTX, $n = 26$	ENC + ALP + CTX, $n = 28$
Sex, *n* (%)		
Female	15 (58)	18 (64)
Male	11 (42)	10 (36)
Age, median (range), years	63 (43–80)	59 (40–76)
Primary site of cancer derived, *n* (%)		
Colon	24 (92)	25 (89)
Rectum	2 (8)	3 (11)
ECOG PS, *n* (%)		
0	8 (31)	18 (64)
1	16 (62)	10 (36)
2	2 (8)	0
Visceral involvement at baseline, *n* (%)		
Liver	15 (58)	16 (57)
Peritoneum	5 (19)	8 (29)
Lactate dehydrogenase levels at baseline, *n* (%)		
Normal	9 (35)	10 (36)
>Upper limit of normal	15 (58)	14 (50)
Missing	2 (8)	4 (14)
Number of prior treatment regimens, *n* (%)		
1	7 (27)	10 (36)
2	8 (31)	14 (50)
3	5 (20)	1 (4)
>3	6 (23)	3 (11)
Best response to last prior therapy, *n* (%)		
Partial response	0	2 (7)
Stable disease	10 (39)	12 (43)
Progressive disease	9 (35)	9 (32)
Unknown/not applicable	7 (27)	5 (18)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab.

patients had received prior EGFR-targeted therapy in the form of cetuximab and/or panitumumab [7 patients (27%) in the dual-combination therapy group and 8 patients (29%) in the triple-combination therapy group]. Most patients had *BRAF*^{V600E}; only 2 patients had mutations outside the 600 codon.

Dose Determination

Twenty-one patients in the dual-combination therapy group and 25 patients in the triple-combination therapy group were considered evaluable for dose determination. Three DLTs were identified in the dual-combination therapy group: grade 3 arthralgia, grade 3 vomiting, and grade 3 corrected QT interval prolongation (1 patient each), and two DLTs were identified in the triple-combination therapy group: grade 4 acute renal failure and grade 3 bilateral interstitial pneumonitis (1 patient each; Table 1).

Following assessment of the overall tolerability of treatment, it was decided not to complete dose escalation up to the maximum tolerated dose (MTD) in either of the treatment combinations, and only recommended phase II doses (RP2D) were established. Studies of single-agent alpelisib have suggested that a clinical dose of ≥270 mg is required for efficacy (22). Because one DLT was reported in the triple-combination therapy group at a dose level of 300 mg alpelisib (+ 200 mg encorafenib + cetuximab), it was considered unlikely that a dose of >300 mg alpelisib could be achieved. Hence, 300 mg alpelisib was established as the RP2D in the triple-combination therapy arm. Similarly, among the 7 patients treated at the dose of 300 mg encorafenib (+ 200 mg alpelisib + cetuximab), 1 patient experienced a DLT of grade 4 acute renal failure, suggesting that when combined with alpelisib, encorafenib should be dosed below 300 mg. Although higher encorafenib doses could have been used in the dual-combination arm, the RP2D dose was kept consistent at 200 mg in both the dual and triple combinations in order to allow for the assessment of the safety and efficacy of the addition of alpelisib to the encorafenib plus cetuximab combination. These dose levels fulfilled the protocol criteria for MTD/RP2D: ≥6 patients had been treated at this dose and either the posterior probability of targeted toxicity at this dose exceeded 50% or a minimum of 12 patients had been treated with the dual and triple combinations.

Safety

The overall safety profiles for the two therapy groups are shown in Table 3. AEs occurred in all patients in both treatment groups. Similar proportions of patients in the dual- and triple-combination therapy groups experienced fatigue (n = 13, 50% and n = 12, 43%, respectively) and vomiting (n = 12, 46% and n = 14, 50%, respectively). Higher proportions of patients in the triple-combination than in the dual-combination therapy group experienced nausea (n = 17, 61% vs. n = 8, 31%) and diarrhea (n = 15, 54% vs. n = 5, 19%). Furthermore, dermatologic AEs were more common in the triple-combination than the dual-combination therapy group [rash (n = 10, 36% vs. n = 5, 19%), dermatitis acneiform (n = 8, 29% vs. n = 3, 12%), dry skin (n = 9, 32% vs. n = 5, 19%) and melanocytic nevus (n = 7, 25% vs. n = 1, 4%)]. Eleven (39%) patients in the triple-combination therapy group exhibited hyperglycemia compared with 2 patients (8%) in the dual-combination therapy group. Grade 3/4 AEs were commonly reported in the both the dual- and triple-combination therapy groups (69% and 79%, respectively), with the most common grade 3/4 AEs being hypophosphatemia (n = 5, 19%) in the dual-combination therapy group and dyspnea and hyperglycemia (n = 3, 11% each) in the triple-combination therapy group.

Table 3. Adverse events, regardless of treatment attribution, occurring in >20% of patients

	ENC + CTX, n = 26		ENC + ALP + CTX, n = 28	
Adverse event, n (%)	All grades	Grade 3/4	All grades	Grade 3/4
Fatigue	13 (50.0)	3 (11.5)	12 (42.9)	1 (3.6)
Vomiting	12 (46.2)	2 (7.7)	14 (50.0)	0
Dyspnea	9 (34.6)	1 (3.8)	5 (17.9)	3 (10.7)
Abdominal pain	8 (30.8)	3 (11.5)	7 (25.0)	1 (3.6)
Nausea	8 (30.8)	0	17 (60.7)	1 (3.6)
Hyperglycemia	2 (7.7)	0	11 (39.3)	3 (10.7)
Back pain	7 (26.9)	1 (3.8)	3 (10.7)	1 (3.6)
Constipation	7 (26.9)	1 (3.8)	4 (14.3)	0
Decreased appetite	7 (26.9)	0	8 (28.6)	1 (3.6)
Hypophosphatemia	7 (26.9)	5 (19.2)	4 (14.3)	1 (3.6)
Infusion-related reaction	7 (26.9)	0	1 (3.6)	0
Weight decreased	7 (26.9)	0	10 (35.7)	1 (3.6)
Dysphonia	2 (7.7)	0	7 (25.0)	0
Melanocytic nevus	1 (3.8)	0	7 (25.0)	0
Peripheral edema	2 (7.7)	0	7 (25.0)	0
Cough	6 (23.1)	0	2 (7.1)	1 (3.6)
Headache	6 (23.1)	0	4 (14.3)	0
Myalgia	6 (23.1)	0	4 (14.3)	0
Pain in extremity	6 (23.1)	0	2 (7.1)	0
Stomatitis	6 (23.1)	0	4 (14.3)	1 (3.6)
Dysgeusia	1 (3.8)	0	6 (21.4)	0
Diarrhea	5 (19.2)	1 (3.8)	15 (53.6)	1 (3.6)
Dry skin	5 (19.2)	0	9 (32.1)	0
Rash	5 (19.2)	0	10 (35.7)	0
Hypomagnesemia	4 (15.4)	0	8 (28.6)	1 (3.6)
Dermatitis acneiform	3 (11.5)	0	8 (28.6)	1 (3.6)
Pyrexia	3 (11.5)	0	8 (28.6)	1 (3.6)

NOTE: All patients had at least 1 adverse event.

Abbreviations: ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab.

Efficacy

The dual-combination and triple-combination therapies both demonstrated efficacy in patients with *BRAF*-mutant mCRC (Table 4), with overall response rates of 19% in the

Published OnlineFirst March 31, 2017; DOI: 10.1158/2159-8290.CD-16-0795

Table 4. Best overall response to treatment

Response, *n* (%)	ENC + CTX, *n* = 26	ENC + ALP + CTX, *n* = 28
Complete response (CR)	1 (3.8)	0
Partial response (PR)	4 (15.4)	5 (17.9)
Stable disease[a] (SD)	15 (57.7)	21 (75.0)
Progressive disease (PD)	4 (15.4)	1 (3.6)
Unknown	2 (7.7)	1 (3.6)
Overall response rate (CR + PR)	5 (19.2)	5 (17.9)
Disease control rate (CR + PR + SD)	20 (76.9)	26 (92.8)

Abbreviations: ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab.
[a]In the ENC + CTX group, 1 patient with SD had unconfirmed PR, and 4 patients in the ENC + ALP + CTX group with SD had unconfirmed PR.

dual-combination and 18% in the triple-combination therapy group (Fig. 1). Images of radiologic response are shown in Supplementary Fig. S1A–S1C. The median duration of response was 46 weeks in the dual-combination and 12 weeks in the triple-combination therapy groups for patients with confirmed responses (5 patients in either arm). The duration of exposure to treatment was longer in the dual-combination therapy arm (Supplementary Fig. S2A) than the triple-combination therapy arm (Supplementary Fig. S2B). Median progression-free survival (PFS) for the dual-combination and triple-combination therapy groups was 3.7 and 4.2 months, respectively (Fig. 2). At 50 weeks, 31% of patients in the dual-combination and 11% in the triple-combination therapy group remained on treatment.

Biomarker Analyses

Fresh tumor biopsies were collected before and during treatment for 21 patients (*n* = 13 in dual-combination arm and *n* = 8 in triple-combination arm). Genes from key signaling pathways (MAPK, PI3K, WNT/β-catenin, and EGFR) were investigated over the course of treatment in both treatment combinations (Fig. 3). The majority of mutations were present pre-enrollment in the study. Significant correlations between exploratory genetic analyses and clinical outcomes were not observed in this small sample of patients. However, some interesting trends were noted.

At baseline, *KRAS* gain of copy number was observed in six of 21 patients, and neutral LOH (duplication of one copy and concurrent loss of the other) was observed in 2 patients. *KRAS* gain was seen both in patients with long PFS as well as shorter PFS, suggesting that modest gains of *KRAS* did not preclude response to the encorafenib/cetuximab combination.

Patients with *EGFR* amplification appeared to experience longer PFS. Copy-number gain of the *EGFR* gene was seen in 10 patients; the majority of these patients also had *MET* copy-number gain, most likely due to global amplification of chromosome 7. Six patients treated with the dual combination showed copy-number gain in the *EGFR* gene, and these patients had a median of 248 days of PFS (range, 43–589 days). One patient had a complete response (CR), two had a partial response (PR), two had a stable disease (SD), and one had progressive disease (PD). In contrast, the 7 patients in the dual-combination therapy group without alteration in the *EGFR* gene had a median of 84 days of PFS (range, 1–185 days); 1 patient had a PR. Four patients receiving triple treatment showed gain of copies in the *EGFR* gene and had a median of 130 days of PFS (range, 120–277 days); however, none of the patients had tumor regression meeting RECIST criteria for a radiologic response (all target tumor shrinkage was between 0% and 28%). The 4 patients in this treatment group who did not have any alterations in the *EGFR* gene exhibited prolonged PFS of 66, 126, 176, and 386 days, and 1 patient achieved a PR. However, these patients had alterations in the PI3K pathway, including *PTEN*, *PIK3CA*, or *AKT1*; hence the addition of alpelisib may explain the differences in observation.

Initial observations for patients with PI3K pathway alterations did not reveal clear associations with treatment response. Patients who received dual treatment appeared to have similar

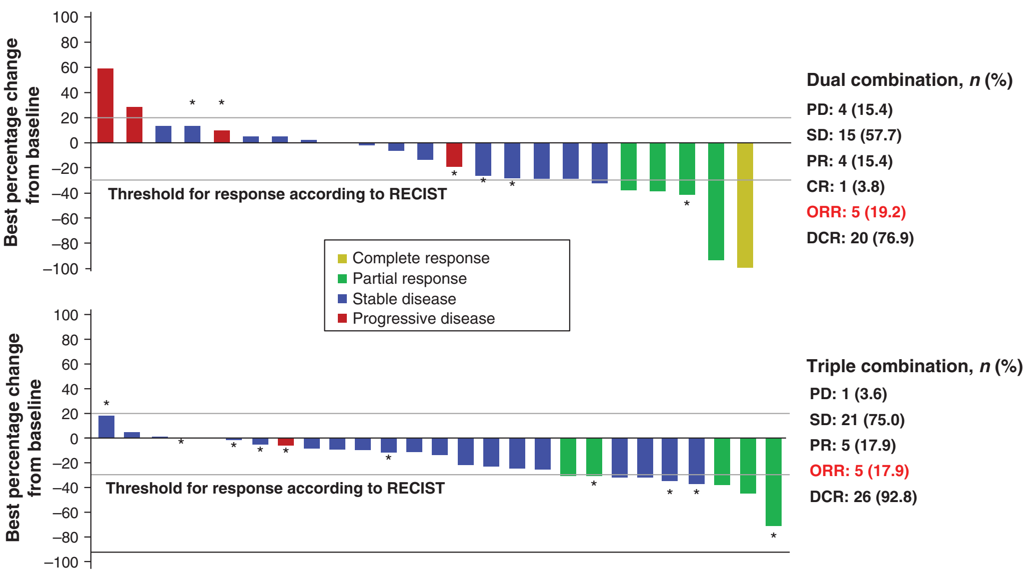

Figure 1. Waterfall plot of best percentage change of tumor size from baseline by best response. Data cutoff date: February 1, 2015. *, Patients treated at the RP2D. CR, complete response; DCR, disease control rate; ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab; ORR, overall response rate; PD, progressive disease; PR, partial response; RP2D, recommended phase II dose; SD, stable disease.

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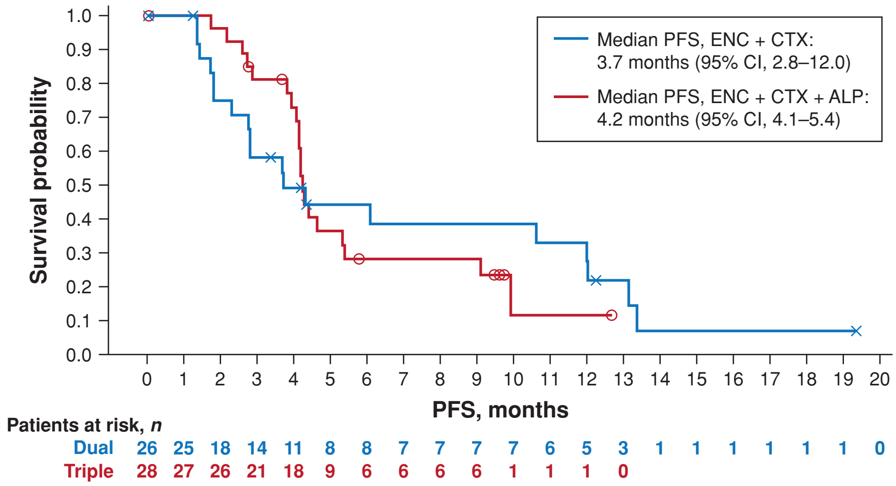

Figure 2. Progression-free survival for all patients. ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab. The two cohorts were recruited sequentially.

responses to patients who received triple treatment. Seven patients in the dual-combination therapy group had *PIK3CA* alterations; this did not appear to preclude benefit, because the median duration of PFS for these patients was 248 days (range, 1–589 days), 1 patient experienced CR, and two had PRs. Only 2 patients in the triple-combination therapy group had *PIK3CA* alterations. One patient had a PFS of 176 days and the other 277 days. Five patients had *PTEN* loss or deletions: the 1 patient in the dual-combination therapy group did not respond and had a PFS of 38 days, and among the 4 patients in the triple-combination therapy group, one had a PR and three did not respond [median PFS of 123 days (66–176 days)].

Alterations in the WNT pathway were also observed. Fourteen patients (67%) had *APC* mutations: nine in the dual-combination and five in the triple-combination therapy group. Patients treated with dual-combination therapy whose tumors harbored *APC* mutations had relatively short PFS, with a median of 70 days (range, 1–589 days). Patients who received triple-combination therapy had a median PFS of 127 days (range, 66–277 days). Seventeen patients (81%) had *RNF43* alterations, and the majority, 11 patients, were treated with the dual combination. These 11 patients had a median of 112 days of PFS (range, 1–589 days), with 3 patients having a PR and one a CR. The 6 patients with *RNF43* alterations who were treated with the triple-combination treatment responded well to treatment and had median PFS of 130 days (120–386 days).

The patient with the best response to dual-combination therapy (CR; 100% best percentage change from the baseline) had alterations in *EGFR*, *AKT1*, *PIK3CA*, *PTEN*, *AKT3*, *MET*, and *RNF43*, whereas the patient with the best response to

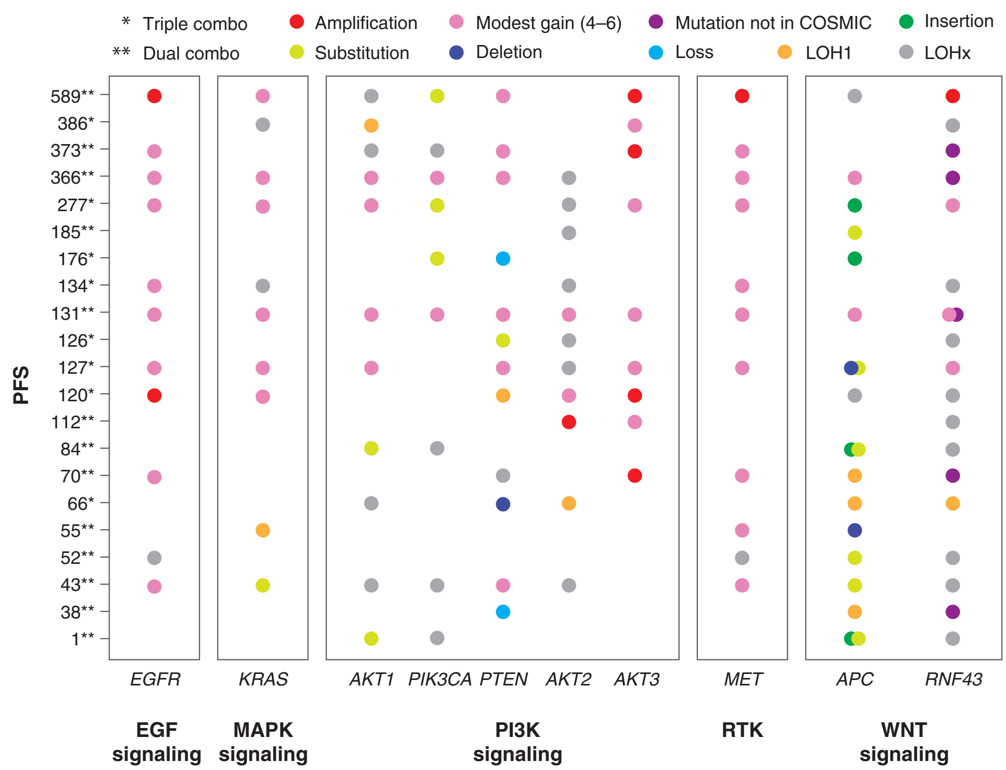

Figure 3. Progression-free survival versus genetic alterations and allele frequency by gene pathways. COSMIC, Catalogue of Somatic Mutations in Cancer; ENC + ALP + CTX, encorafenib combined with alpelisib and cetuximab; ENC + CTX, encorafenib combined with cetuximab.

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triple-combination therapy (PR; 71% best percentage change from baseline) had alterations in *PTEN*, *AKT2*, and *RNF43*.

End-of-treatment biopsies were collected from 6 patients who had responded to study treatment. Interestingly, acquired mutations or amplifications of the *KRAS* gene were noted in four of these patients. *PTEN* loss was observed in 1 patient, and an *AKT1* mutation was seen in the remaining patient.

Pharmacokinetics

Exposure of encorafenib increased with dose in the dual-combination group and had a half-life that ranged from 3 to 4 hours (Supplementary Table S1). Exposure was similar to levels observed in a monotherapy study (K. Litwiler, personal communication; C_{max} [mean ± standard deviation]: 1,427 ± 824 ng/mL, T_{max} [median (range)]: 2 (1−4) hours and AUC_{tau} [mean ± standard deviation]: 7,172 ± 2,888 h·ng/mL with 200 mg encorafenib at steady state in the current study).

For the triple-combination therapy group, the exposure of 200 mg encorafenib in the presence of 100 mg alpelisib was similar to that in the dual-combination therapy group. However, the exposure of 200 mg encorafenib increased by about 2-fold in the presence of 300 mg alpelisib (C_{max} [mean ± standard deviation]: 2,394 ± 2,077 ng/mL, T_{max} [median (range)]: 3 (1−8) hours and AUC_{tau} [mean ± standard deviation]: 12,948 ± 10,649 h·ng/mL at steady state; Supplementary Table S1). Exposure of alpelisib increased with dose and was similar to levels observed in an unpublished monotherapy study (data not shown; C_{max} [mean ± standard deviation]: 2,743 ± 520 ng/mL, T_{max} [median (range)]: 4 (2−6) hours and AUC_{tau} [mean ± standard deviation]: 25,126 ± 3,513 h·ng/mL with 300 mg alpelisib at steady state in the current study).

DISCUSSION

The primary objective of the phase Ib portion of this study was to establish a recommended dose for the dual-combination and triple-combination therapies for use in the phase II section of the study. The selected doses were 200 mg encorafenib daily plus cetuximab in the dual-combination therapy group and 200 mg encorafenib daily plus 300 mg alpelisib daily plus cetuximab in the triple-combination therapy group. Following an overall assessment of tolerability and observation of objective responses in all tested dose cohorts, it was decided not to proceed to the MTD in either the dual-combination or triple-combination therapy arms, and doses for the triple-combination therapy were selected on the basis of the overall tolerability profiles. Although higher encorafenib doses were likely to have been tolerated in the dual combination, the RP2D was selected to be the same in both groups to allow for the assessment of safety and efficacy of additive alpelisib compared with encorafenib plus cetuximab dual-combination therapy.

Both the dual-combination and triple-combination treatments showed clinical efficacy and acceptable safety profiles in patients with *BRAF*-mutant mCRC. Efficacy and safety in the two groups may be compared only with caution: the ECOG PS suggests the health of patients in the dual-combination therapy group was poorer than that of patients in the triple-combination therapy group prior to the start of treatment, and patients in the triple-combination therapy group also showed a better response to the last prior therapy than patients in the dual-combination therapy group. This phase Ib portion of the study was also not powered or designed for comparison purposes, and patient numbers are small.

Previous studies of single-agent BRAF or EGFR inhibitors have shown limited activity in patients with *BRAF*-mutant mCRC (12–14, 23–27). However, clinical studies of combinations of BRAF inhibitors with EGFR inhibitors or MEK inhibitors have shown improved efficacy in this patient population (16, 17, 28, 29). Results from our study compare favorably with combinations of BRAF and EGFR inhibitors in these studies. In our study, overall response rates (ORR) of 19% in the dual-combination group and 18% in the triple-combination therapy group were achieved. In a study of 55 patients treated with dabrafenib plus panitumumab versus dabrafenib plus panitumumab plus trametinib, the dual combination of BRAF and EGFR inhibitors achieved an ORR of 10%, and the triple combination of BRAF, EGFR, and MEK inhibitors achieved an ORR of 26% (28). In another study of 15 patients treated with vemurafenib plus panitumumab, two (13%) achieved a PR (29). Furthermore, a phase II study of vemurafenib in nonmelanoma cancers with *BRAF*^{V600} mutations that enrolled 27 patients with *BRAF*-mutant colorectal cancer showed an ORR of 4% when treated with vemurafenib plus cetuximab (16). Median PFS in our study (3.7 months in the dual-combination and 4.3 months in the triple-combination therapy arm) also compares well with results from these studies: 3.2 months (95% CI, 1.6–5.3 months) for vemurafenib plus panitumumab (29) and 3.7 months (95% CI, 1.8–5.1) for vemurafenib plus cetuximab (16). It should be noted that these studies were small and further follow-up is required. The duration of treatment in our study of patients with previously treated disease was also encouraging.

In our study, the safety profile was acceptable for both combination treatments, and all three drugs were given continuously in the triple therapy, which has been challenging in other targeted combinations. More dermatologic AEs were reported in the triple-combination than the dual-combination therapy group. It should be noted, however, that the incidence of dermatologic AEs was much lower than has been previously reported for single-agent use of BRAF inhibitors (67% of 18 patients had hand–foot skin reaction; ref. 30) or EGFR inhibitors (82% of 116 patients had papulopustular rash; ref. 31), consistent with an opposing effect of encorafenib and cetuximab on ERK signaling in skin. Paradoxical activation of ERK signaling in BRAF wild-type tissues with BRAF inhibitors has been previously reported (32, 33). It is therefore likely that encorafenib opposes cetuximab-mediated inhibition of ERK signaling, which may decrease skin toxicity with the combination. More cases of melanocytic nevi were seen in the triple-combination therapy arm than in the dual-combination therapy arm (25% vs. 4%), possibly secondary to higher effective doses of encorafenib in the triple-combination therapy arm, as encorafenib exposure was increased 2-fold with the addition of 300 mg alpelisib. Hyperglycemia was more common in the triple-combination than the dual-combination therapy group due to the ability of PI3K inhibitors to regulate the insulin-like growth factor receptor. Compared with the incidence of hyperglycemia in patients with solid tumors treated with single-agent alpelisib (47% all grade; 24% grade 3/4; ref. 34), the incidences reported for the triple-therapy group in this trial were lower, albeit at different dose levels.

Alterations in genes associated with the key signaling pathways were assessed and correlated with clinical activity. Due in part to the limited availability of tumor biopsies in the phase I population of the study, no significant correlations could be determined, and further follow-up will be carried out in phase II; however, some preliminary observations were noted. A subgroup of patients with *EGFR* amplifications or gain of copies, especially those patients who received dual-combination therapy, responded well to study treatment, and better than patients without *EGFR* alterations. These results suggest that the presence of *EGFR* alterations may identify tumors more dependent on EGFR signaling (35–37) that are thus more sensitive to combined EGFR- and BRAF-targeted treatment, whereas in patients with no EGFR-mediated pathway activation, other signaling pathways may be activated and may need to be cotargeted with BRAF to lead to tumor regressions.

Patients with WNT pathway alterations, especially those patients with *APC* mutations, had a tendency toward lower PFS rates. This trend was not clear for *RNF43* mutations, suggesting, in agreement with previous theories, that *RNF43* mutations do not activate the WNT pathway in the same manner as *APC* mutations (38). It will be of interest to see whether trials of combination treatments targeting the WNT pathway (e.g., NCT02278133) yield higher response rates.

As has been previously documented for *BRAF*-mutant mCRC, alterations in the PI3K pathway were noted in the limited patient samples (17). Unfortunately, the majority of patients with *PIK3CA* mutations received the dual-combination treatment; however, these patients still responded and remained on treatment for prolonged periods of time, suggesting that such activating mutations may not be a primary source of resistance. Furthermore, some patients with *PTEN* loss responded well to both the triple-combination and dual-combination treatments. Due to the small sample size, however, it is impossible to draw significant correlations. Data from previous studies have reported conflicting information with either no association between response to cetuximab treatment and *PI3KCA* mutation/*PTEN* expression or a correlation with low response to cetuximab (25, 39).

Interestingly, the few samples collected during acquired resistance showed MAPK activation, where patients developed either *KRAS* mutations or amplifications. Similar results have been previously reported for other RAF/EGFR/MEK-targeted treatments (40).

No evidence of drug–drug interaction between encorafenib and cetuximab was observed in the dual-combination therapy group. In the triple-combination therapy group, a mild drug–drug interaction was observed with encorafenib (encorafenib exposure increased 2-fold) in the presence of high alpelisib dose levels, possibly due to alpelisib inhibiting the metabolic enzyme (CYP3A4) of encorafenib. Alpelisib exposure was not affected by encorafenib and cetuximab.

In conclusion, data from this phase Ib study show promising clinical activity and tolerability, warranting further evaluation.

METHODS

Study Design

This multicenter, open-label, phase Ib dose-escalation study enrolled patients with *BRAF*^{V600}-mutant mCRC. The primary objective of phase Ib was to determine the MTD and/or RP2D of encorafenib in combination with cetuximab or with cetuximab and alpelisib.

Adult patients with mCRC were enrolled on the basis of documented wild-type *KRAS* and a *BRAF*^{V600} mutation. Eligibility criteria included ECOG PS of ≤2, either progression after ≥1 prior standard-of-care regimen or intolerance to irinotecan-based regimens, and life expectancy of ≥3 months. All patients gave written informed consent per Declaration of Helsinki recommendations, and the protocol was reviewed and approved by a properly constituted Institutional Review Board prior to study start. The study is registered with ClinicalTrials.gov (NCT01719380).

Study Treatment

Patients were assigned sequentially to either encorafenib and cetuximab (dual) or encorafenib, cetuximab, and alpelisib (triple) combination therapy groups. Treatment cycles were 28 days in length. Cetuximab was dosed intravenously according to the label for patients with mCRC: a 400 mg/m^2 loading dose (cycle 1 day 1) and 250 mg/m^2 for subsequent weekly doses. In the dual combination, the starting dose of encorafenib was chosen as 100 mg daily based on available data from the first-in-human study of encorafenib (41), including a single-agent MTD/RP2D of 450 mg, the estimation of the Bayesian logistic regression model (BLRM), and the escalation with overdose control (EWOC) criteria. The triple combination was not initiated until a minimum of 12 evaluable patients had been treated with the dual combination. The starting dose of encorafenib in the triple-combination therapy group was based on the dual-combination dose, and the starting dose of alpelisib (100 mg) was selected at 25% of the single-agent MTD identified in a phase I clinical study of alpelisib in patients with solid tumors (34). Dose-escalation decisions were based on data from all evaluable patients, including safety information, DLTs, all grade ≥2 toxicity data during cycle 1, and pharmacokinetics (PK). The recommended dose for each level was guided by a BLRM (42, 43). A DLT was defined as an AE or abnormal lab value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurred within the first 28 days of treatment, with the exceptions listed in Supplementary Table S2. In order to be evaluable, patients had to complete a minimum of one cycle of treatment with the minimum safety evaluation and drug exposure (21 of the 28 oral daily doses and the cetuximab loading dose, plus two weekly doses within the 28-day cycle). The MTD was defined as the highest combination drug dosage not causing medically unacceptable DLTs in >35% of treated patients in the first cycle.

Study Assessments

Tumor response was evaluated locally based on RECIST v1.1. assessments, by means of CT scan with intravenous contrast of chest, abdomen, and pelvis, which were performed at screening and every 6 weeks after starting study treatment until disease progression. The best overall response was defined as the best response recorded from the start of the treatment until disease progression/relapse. The study required that for a response of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks and no later than 6 weeks after the criteria for response were first met.

Safety was monitored at screening and throughout the treatment period by physical examination and collection of AEs. Blood samples for plasma PK analysis were collected from all patients during treatment. A full PK profile (pre-dose, 0.5, 1, 2, 4, 6, 8, and 24 hours) was performed on day 1 of cycles 1 and 2. Samples were assayed using validated LC/MS-MS. When feasible, fresh tumor biopsies were collected before and during treatment for the investigation of pharmacodynamics, including comprehensive genomic analysis. Somatic mutations, loss of heterozygosity, and copy-number aberrations were assessed by Foundation Medicine assay analytics. Additional annotations from the Catalogue of Somatic Mutations in Cancer (COSMIC) were used to filter functional mutations.

Statistical Methods

An adaptive BLRM guided by the EWOC principle directed the dose escalation to its MTD/RP2D (42). A 10-parameter BLRM for combination treatment was fitted on the cycle 1 DLT data accumulated throughout the dose escalation to model the dose–toxicity relationship of encorafenib, cetuximab, and alpelisib given in combination. Dose recommendation was based on posterior summaries including the mean, median, standard deviation, 95% credibility interval, and the probability that the true DLT rate for each dose lies in one of the following categories: underdosing (0%–16%), targeted toxicity (16%–35%), or excessive toxicity (35%–100%). The recommended next dose was the one with the highest posterior probability of DLT in the targeted toxicity interval and a less than 25% chance of excessive toxicity.

Initially, cohorts of three to six evaluable patients were enrolled. At least six evaluable patients were treated at MTD/RP2D. PFS was calculated as the time from the start date of study drug until documented disease progression or death due to any cause. Patients who had not progressed or died at the time of the data cutoff were censored at the date of last tumor assessment.

Role of the Funding Source

The trial was planned, initiated, and sponsored by Novartis Pharmaceuticals. The sponsor was responsible for data gathering and pharmacovigilance, shared safety data during the study with the corresponding author, and contributed to preparing and reviewing the report for publication submission. The sponsor and authors were responsible for data analysis and interpretation. The corresponding author had full access to all the study data, and all authors approved the manuscript for publication submission.

Disclosure of Potential Conflicts of Interest

J. Tabernero is a consultant/advisory board member for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, and Takeda. M. Schuler reports receiving commercial research grants from Boehringer Ingelheim, Novartis, and Bristol-Myers Squibb, and is a consultant/advisory board member for Bristol-Myers Squibb, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and Celgene. J.E Faris is Clinical Program Leader at Novartis and a consultant/advisory board member for Merrimack, and has given expert testimony for N-of-One Therapeutics. S. Sharma reports receiving a commercial research grant from Novartis and is a consultant/advisory board member for the same. R. Yaeger is a consultant/advisory board member for GlaxoSmithKline. Z.A. Wainberg is a consultant/advisory board member for Genentech and Sirtex. E. Avsar has ownership interest in Novartis. As reflected in the author affiliations, A. Chatterjee, S. Jaeger, E. Tan, and T. Demuth are employees of Novartis, and K. Maharry is an employee of Array BioPharma. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

Encorafenib (LGX818) is owned by Array BioPharma Inc. Samia Kabi and Nassim Sleiman from Novartis Pharmaceuticals and Jennifer Regensburger from Array BioPharma Inc. are thanked for their assistance with preparing tables, figures, and listings of the study data. Ashwin Gollerkeri and Victor Sandor from Array BioPharma Inc. are thanked for their critical review and editing of the manuscript. Editorial assistance was provided by Zoe Crossman of Articulate Science Ltd. and was funded by Novartis Pharmaceuticals.

Grant Support

M. Schuler was supported by the German Cancer Consortium (DKTK), partner site University Hospital Essen; and an Oncology Center of Excellence grant (no. 110534) of the German Cancer Aid. J. Tabernero and E. Elez were financially supported by the EU Seventh Framework Programme (COLTHERES, grant agreement 259015) and the Cellex Foundation. T. Yoshino was supported by research grants (to institution) from Dainippon Sumitomo Pharma Co. Ltd.

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Received July 18, 2016; revised September 14, 2016; accepted March 30, 2017; published OnlineFirst March 31, 2017.

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Published OnlineFirst March 31, 2017; DOI: 10.1158/2159-8290.CD-16-0795

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CANCER DISCOVERY

A Phase Ib Dose-Escalation Study of Encorafenib and Cetuximab with or without Alpelisib in Metastatic *BRAF*-Mutant Colorectal Cancer

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Cancer Discov 2017;7:610-619. Published OnlineFirst March 31, 2017.