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Phase 2 Results: Encorafenib (ENCO) and Cetuximab (CETUX) With or Without Alpelisib (ALP) in Patients With Advanced *BRAF*-Mutant Colorectal Cancer (*BRAF*m CRC)

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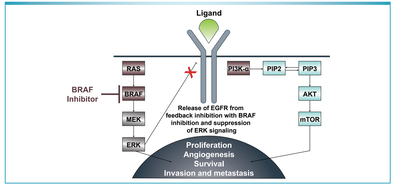
INTRODUCTION

- *BRAF*-mutant colorectal cancer (*BRAF*m CRC) is molecularly distinct from wild-type (WT) *BRAF* CRC and carries a poor prognosis.[1]
  - Relapsed *BRAF*m CRC is associated with nonresponse, shorter progression-free survival (PFS), and reduced overall survival (OS) following cetuximab- or panitumumab-based therapy, relative to WT *BRAF* CRC.[2,3]
- Unlike in melanoma, BRAF inhibitor monotherapy has shown limited efficacy in *BRAF*m CRC.[4,5]
  - Attributed to reactivation of epidermal growth factor receptor (EGFR) signaling with BRAF inhibition and uninhibited phosphatidylinositol 3-kinase (PI3K) signaling (**Figure 1**)[6-8]

Figure 1. Mechanisms of Resistance to BRAF Inhibition in Colorectal Cancer

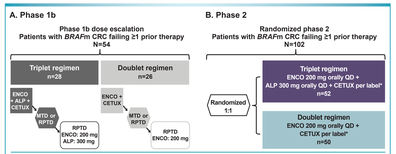


- Preclinical studies in *BRAF*m CRC models have found synergistic antiproliferative effects in vitro and antitumor activity in vivo with combined inhibition of BRAF and EGFR signaling, and with combined inhibition of BRAF, EGFR, and PI3K signaling.[6-10]
- Treatment regimens that combine a BRAF inhibitor with an EGFR inhibitor (dual combination) or a BRAF inhibitor with a PI3K inhibitor and an EGFR inhibitor (triple combination) may have clinical activity in patients with *BRAF*m CRC.[10]
- A phase 1b/randomized phase 2 study was initiated to evaluate a combination of the BRAF inhibitor encorafenib, the PI3K-α inhibitor alpelisib, and the EGFR antibody cetuximab (triplet regimen) and a combination of encorafenib and cetuximab (doublet regimen) in patients with advanced *BRAF*m CRC.
- The phase 1b portion of the study established the recommended phase 2 dose (RPTD) for encorafenib and alpelisib in the combination regimens (**Figure 2A**).

OBJECTIVE

- To describe efficacy and safety from the randomized phase 2 portion of the study (**Figure 2B**)

Figure 2. Study Design



ALP=alpelisib; *BRAF*m CRC=*BRAF*-mutant colorectal cancer; CETUX=cetuximab; ENCO=encorafenib; MTD=maximum tolerated dose; QD=once daily; RPTD=recommended phase 2 dose.
*Intravenously dosed at 400 mg/m² for the first dose and 250 mg/m² for subsequent weekly doses.[11]

METHODS

Study Design and Overview

- In this ongoing phase 1b/randomized phase 2 study (ClinicalTrials.gov: NCT01719380), phase 1b did not identify a maximum tolerated dose for encorafenib for either the triplet or doublet regimen, or for alpelisib in the triplet regimen.
  - Based on general tolerability of the triplet regimen, the chosen RPTD for encorafenib was 200 mg orally once daily (QD) for both arms and the chosen RPTD for alpelisib was 300 mg orally QD.
- In phase 2, patients with advanced *BRAF*m CRC were randomized 1:1 to the triplet regimen of oral encorafenib 200 mg QD, oral alpelisib 300 mg QD, and cetuximab per label,[11] or the doublet regimen of encorafenib and cetuximab (**Figure 2B**).

Key Eligibility Criteria

- Patients ≥18 years of age with metastatic CRC and documented *BRAF*^{V600} mutation
- Progression after ≥1 prior therapy
- Measurable disease
- Eastern Cooperative Oncology Group performance status 0 or 1 (amendment)
- No prior treatment with EGFR, RAF, PI3K, or MEK inhibitors (phase 2 only)

Endpoints

- Primary: PFS based on local assessment per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1
- Secondary endpoints
  - Overall response rate by RECIST version 1.1, OS, and duration of response, based on local assessment. All complete and partial responses were confirmed by a second assessment ≥4–6 weeks later
  - Incidence and severity of adverse events (AEs)

RESULTS

Patients

- A total of 102 patients were randomized (triplet regimen, n=52; doublet regimen, n=50; **Table 1**).

Table 1. Demographic and Clinical Characteristics at Baseline

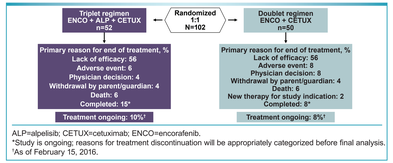
Characteristic	ENCO + ALP + CETUX n=52	ENCO + CETUX n=50
Female sex, n (%)	27 (52)	36 (72)
Age, median (range), y	60 (29–76)	60 (20–79)
Primary site of cancer, n (%)		
Colon	44 (85)	46 (92)
ECOG performance status, n (%)		
0	20 (38)	21 (42)
1	29 (56)	28 (56)
2	3 (6)	1 (2)
LDH level, n (%)		
≤ULN	25 (48)	26 (52)
>ULN	15 (29)	15 (30)
Missing	12 (23)	9 (18)
Prior treatment regimens		
Median number (range)	2 (1–4)	2 (1–6)
n (%)		
1	23 (44)	21 (42)
2	18 (35)	20 (40)
≥3	11 (21)	9 (18)

ALP=alpelisib; CETUX=cetuximab; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; LDH=lactate dehydrogenase; ULN=upper limit of normal.

- As of February 15, 2016, treatment was ongoing in 5 patients (10%) in the triplet regimen arm and 4 patients (8%) in the doublet regimen arm (**Figure 3**).

RESULTS (CONTINUED)

Figure 3. Patient Disposition



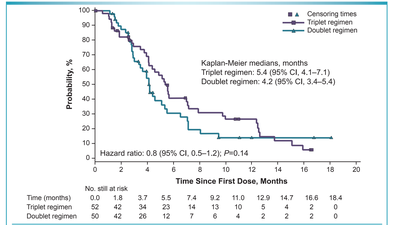
ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib.
*Study is ongoing; reasons for treatment discontinuation will be appropriately categorized before final analysis.
†As of February 15, 2016.

Efficacy

Overall Efficacy

- A PFS analysis comparing the triplet with the doublet regimen was performed after 77 events (**Figure 4**).

Figure 4. Progression-Free Survival



Kaplan-Meier estimates based on local assessment.

- Confirmed response rates are provided in **Table 2**.

Table 2. Confirmed Response Rates as per Local Assessment

Confirmed Response	ENCO + ALP + CETUX n=52	ENCO + CETUX n=50
Best overall response, n (%)		
Complete response	0	0
Partial response	14 (27)	11 (22)
Stable disease	30 (58)	31 (62)
Progressive disease	5 (10)	4 (8)
Unknown	3 (6)	4 (8)
Overall response rate, % (95% CI)*†	27 (16–41)	22 (12–36)
Disease control rate, % (95% CI)*‡	85 (72–93)	84 (71–93)
Median (95% CI) duration of response, mo	9.9 (2.8–11.0)	4.6 (2.0–6.7)

ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib.
*Complete response + partial response.
†The 95% CI for the frequency distribution of each variable was computed using the Clopper-Pearson method.
*Complete response + partial response + stable disease.

- Interim OS analysis was determined with 44 events (**Figure 5**).
  - Median OS was improved with the triplet and doublet regimens relative to historical controls in patients with *BRAF*m CRC (**Figure 6**).

Figure 5. Overall Survival

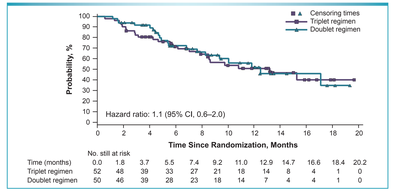
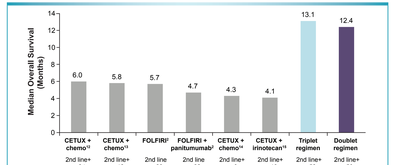


Figure 6. Median Overall Survival in *BRAF*m CRC With the Triplet and Doublet Regimens Compared With Historical Controls*



*BRAF*m CRC=*BRAF*-mutant colorectal cancer; CETUX=cetuximab; chemo=chemotherapy; FOLFIRI=folinic acid, fluorouracil, and irinotecan.
*Data for historical controls derive from retrospective analyses of small subsets of patients with *BRAF*m CRC.

Efficacy by Number of Prior Treatment Regimens

- Confirmed response rates were evaluated by the number of prior treatment regimens received; responses to treatment were observed in all subgroups (**Table 3**).

Table 3. Confirmed Response Rates by Number of Prior Treatment Regimens

Confirmed Response	1 Prior Treatment Regimen		2 Prior Treatment Regimens		≥3 Prior Treatment Regimens	
	ENCO + ALP + CETUX n=23	ENCO + CETUX n=21	ENCO + ALP + CETUX n=18	ENCO + CETUX n=20	ENCO + ALP + CETUX n=11	ENCO + CETUX n=9
Best overall response, n (%)						
Complete response	0	0	0	0	0	0
Partial response	7 (30)	6 (29)	4 (22)	4 (20)	3 (27)	1 (11)
Stable disease	12 (52)	12 (57)	11 (61)	14 (70)	7 (64)	5 (56)
Progressive disease	2 (9)	3 (14)	3 (17)	1 (5)	0	0
Unknown	2 (9)	0	0	1 (5)	1 (9)	3 (33)
Overall response rate, % (95% CI)*†	30 (13–53)	29 (11–52)	22 (6–48)	20 (6–44)	27 (6–61)	11 (0.3–48)
Disease control rate, % (95% CI)*‡	83 (61–95)	86 (64–97)	83 (59–96)	90 (68–99)	91 (59–100)	67 (30–93)

ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib.
*Complete response + partial response.
†The 95% CI for the frequency distribution of each variable was computed using the Clopper-Pearson method.
*Complete response + partial response + stable disease.

Safety

- The most frequent all-cause AEs and grade 3/4 AEs are listed in **Table 4**.
  - Grade 3/4 AEs reported in >10% of patients in either arm for the triplet vs the doublet regimen were anemia (17% vs 6%), hyperglycemia (13% vs 2%), and increased lipase (8% vs 22%).
  - The only grade 3/4 skin-related AE to occur in >1 patient in either study arm was maculopapular rash (n=2 [4%] with the triplet regimen and n=0 with the doublet regimen).

Table 4. All-Cause AEs, Any Grade* and Grade 3/4†

AE, n (%)	ENCO + ALP + CETUX n=52		ENCO + CETUX n=50	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Total	51 (98)	41 (79)	50 (100)	31 (62)
Nausea	29 (56)	3 (6)	23 (46)	0
Diarrhea	28 (54)	4 (8)	14 (28)	2 (4)
Vomiting	27 (52)	1 (2)	16 (32)	0
Fatigue	24 (46)	4 (8)	25 (50)	2 (4)
Abdominal pain	21 (40)	5 (10)	21 (42)	4 (8)
Decreased appetite	19 (37)	3 (6)	17 (34)	1 (2)
Decreased weight	19 (37)	3 (6)	8 (16)	0
Hyperglycemia	19 (37)	7 (13)	5 (10)	1 (2)
Rash	17 (33)	0	7 (14)	0
Stomatitis	16 (31)	2 (4)	5 (10)	0
Dry skin	15 (29)	0	9 (18)	0
Arthralgia	14 (27)	1 (2)	17 (34)	0
Headache	13 (25)	0	16 (32)	0
Pyrexia	12 (23)	0	13 (26)	0
Dermatitis acneiform	12 (23)	0	9 (18)	0
Anemia	12 (23)	9 (17)	8 (16)	3 (6)
Hypomagnesemia	11 (21)	1 (2)	4 (8)	0
Myalgia	11 (21)	0	8 (16)	1 (2)
Back pain	9 (17)	1 (2)	12 (24)	1 (2)
Asthenia	8 (15)	3 (6)	0	0
Increased lipase	7 (13)	4 (8)	15 (30)	11 (22)
Hypophosphatemia	7 (13)	4 (8)	3 (6)	1 (2)
Constipation	6 (12)	0	13 (26)	2 (4)
Malignant melanoma	3 (6)	3 (6)	0	0

AE=adverse event; ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib.
*Occurring in >20% of patients in either treatment group.
†Occurring in >5% of patients in either treatment group.

- 12 patients discontinued study medication because of AEs; of these, only 1 AE (ileus) occurred in >1 patient (n=1 in each study arm).

CONCLUSIONS

- Combinations of encorafenib and cetuximab, with or without alpelisib, show promising clinical activity in patients with advanced *BRAF*m CRC.
- PFS and OS were improved with both combination regimens, relative to historical data.[2,12-16]
- Doublet and triplet regimens were generally well tolerated, but some additional toxicity was observed with the addition of alpelisib to encorafenib and cetuximab.
  - Grade 3/4 dermatologic AEs were rarely observed in either treatment arm, in contrast to cetuximab monotherapy studies, which have reported 12%–18% grade 3/4 skin-related AEs.[17,18]
- This ongoing study includes a wide program of pharmacokinetic, pharmacodynamic, and biomarker analyses; although results are not yet available, these data may be informative for interpretation of efficacy and safety data.
- Compared with the encorafenib and cetuximab doublet regimen, the addition of alpelisib yielded a trend toward an additional PFS benefit for patients with advanced *BRAF*m CRC.

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EA is employed by and owns stock in Novartis Pharmaceuticals.
TD has been employed by Novartis AG and Sandoz AG and owns stock in Novartis AG.
VS is employed by and has a leadership role at Array BioPharma, and owns stock in Array BioPharma and Incyte Corp. VS was previously employed by and had a leadership role at Incyte Corp.
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