O-026

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Combination of Encorafenib and Cetuximab With or Without Alpelisib in Patients With Advanced *BRAF*-Mutant (*BRAF*m) Colorectal Cancer: Phase 2 Results

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INTRODUCTION

- Patients with relapsed *BRAF*m colorectal cancer (CRC) have a poor prognosis vs those with wild-type *BRAF* CRC.
  - Treatment nonresponse[1-3]
  - Shorter progression-free survival (PFS; ~2 vs ~6 months)[2]
  - Reduced overall survival (OS; ~5 vs ~17 months)[2]
- 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[6-8]
- Preclinical study results show synergistic antitumor activity with combination of:[6-9]
  - BRAF and EGFR inhibitors
  - BRAF, EGFR, and PI3K inhibitors

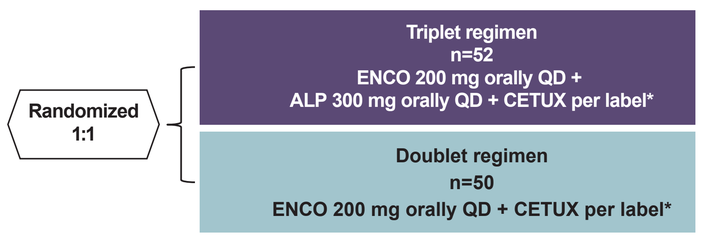
OBJECTIVE

- To describe efficacy and safety from the randomized phase 2 portion of an ongoing phase 1b/2 study evaluating the 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 (ClinicalTrials.gov: NCT01719380)

METHODS

- The phase 1b portion of the study established the recommended phase 2 doses for encorafenib and alpelisib in the combination regimens.
- The phase 2 portion of the study included 102 patients with *BRAF*m CRC failing ≥1 prior therapy.
- Evaluated efficacy and safety of the triplet vs doublet regimen **(Figure 1)**
  - Primary endpoint: PFS
  - Secondary endpoints: confirmed overall response rate (ORR), OS, and safety and tolerability

Figure 1. Phase 2 Study Design



ALP=alpelisib; CETUX=cetuximab; ENCO=encorafenib; QD=once daily.
*Intravenously dosed at 400 mg/m² for the first dose and 250 mg/m² for subsequent weekly doses.[10]

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)
Colon as the primary site of cancer, n (%)	44 (85)	46 (92)
ECOG performance status, n (%)		
0	20 (38)	21 (42)
1	29 (56)	28 (56)
2	3 (6)	1 (2)
LDH >ULN,* n (%)	15 (29)	15 (30)
Prior treatment regimen		
Median number (range)	2 (1–4)	2 (1–6)
Prior regimens, 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.
*LDH information missing in 23% of patients in the triplet and 18% of patients in the doublet regimen groups.

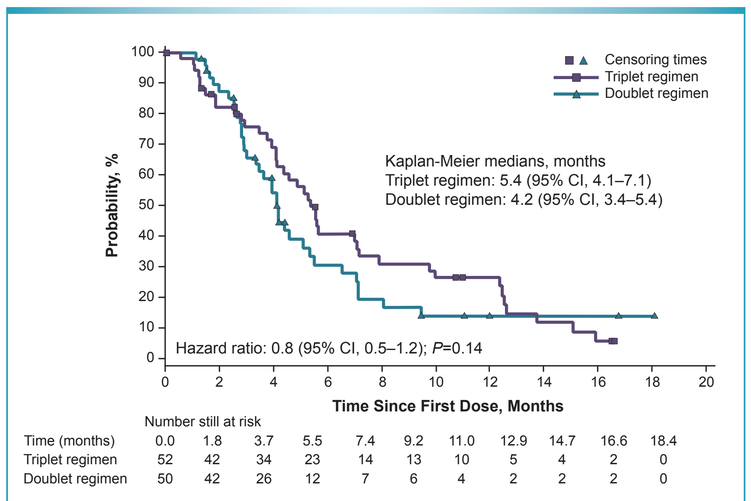
- As of February 15, 2016, treatment was ongoing in 5 patients (10%) in the triplet regimen arm and 4 patients (8%) in the doublet regimen arm.

RESULTS (CONTINUED)

Efficacy

- A PFS analysis comparing the triplet with the doublet regimen was performed after 77 events **(Figure 2)**.

Figure 2. 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.
†Complete response + partial response + stable disease.

- Interim OS analysis was determined with 44 events **(Figure 3)**.
  - Median OS was improved with the triplet and doublet regimens relative to historical controls in patients with *BRAF*m CRC **(Figure 4)**.

Figure 3. Overall Survival

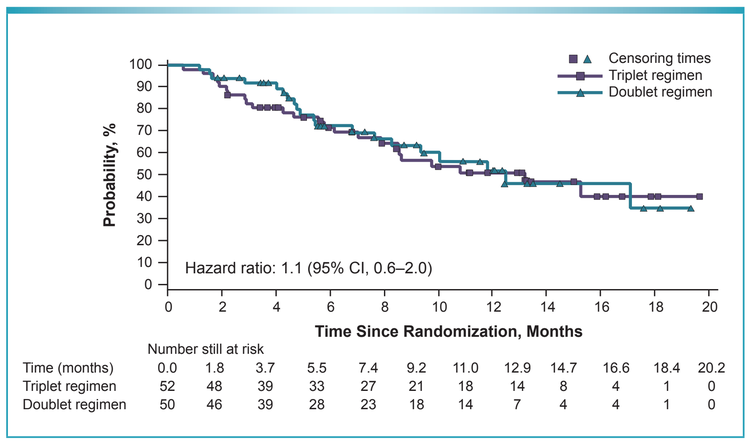
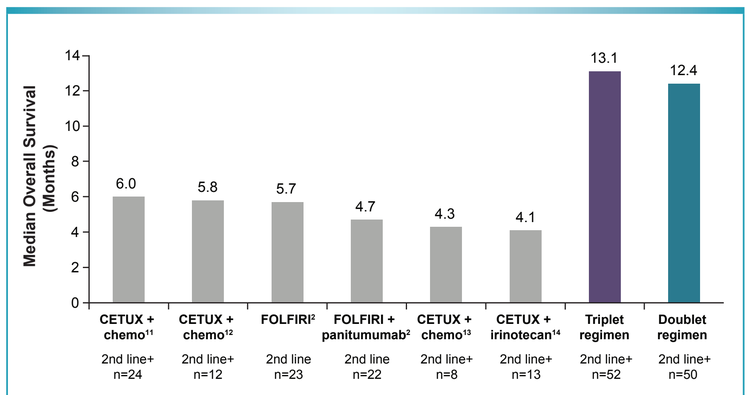


Figure 4. Median Overall Survival in *BRAF*m CRC With the Triplet and Doublet Regimens Compared With Historical Controls*



*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.

Safety

- The most frequent all-cause AEs and grade 3/4 AEs are listed in **Table 3**.

Table 3. 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.

CONCLUSIONS

- Encorafenib and cetuximab combinations ± alpelisib show promising clinical activity in patients with advanced *BRAF*m CRC.
  - PFS and OS with the triplet and doublet regimens were improved compared with historical data.[2,11-15]
  - Compared with the encorafenib + cetuximab regimen, addition of alpelisib may increase PFS benefit for patients with advanced *BRAF*m CRC.
- Both regimens were generally well tolerated.
  - Additional toxicities were seen with the triplet regimen.
  - Grade 3/4 dermatologic AEs were infrequent in either treatment arm.
    - Cetuximab monotherapy studies have reported 12%–18% grade 3/4 skin-related AEs.[16,17]
- Results of pharmacokinetic, pharmacodynamic, and biomarker analyses (not yet available) may be informative for interpretation of efficacy and safety data.

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DISCLOSURES

JT has received consulting fees from Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, and Takeda.
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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.
EE has received consulting fees from Array BioPharma.
RMJMvG, TKG, AS, YY, JCB, H-JL, and JHMS have nothing to disclose.

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