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BEACON CRC Study Safety Lead-in (SLI) in Patients With *BRAF*^{V600E} Metastatic Colorectal Cancer (mCRC): Efficacy and Tumor Markers

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INTRODUCTION

- *BRAF* mutations are detected in 10%–15% of metastatic colorectal cancer (mCRC) cases[1,2] and confer a poor prognosis, with a progression-free survival (PFS) of approximately 2 months, objective response rates (ORRs) generally <10%, and an overall survival (OS) of less than 6 months after failure of first-line therapy **(Table 1)**.[1,3-10]
  - In a recent prospective trial in patients with *BRAF*^{V600E} mCRC, among those receiving standard-of-care treatment with irinotecan plus cetuximab (CETUX) after 1 or 2 previous regimens in the metastatic setting, only 21% experienced tumor shrinkage and 60% of patients had unequivocal increases of ≥100% in tumor volume.[5]

Table 1. Clinical Efficacy of Treatments in Patients With *BRAF*-mutant mCRC After ≥1 Prior Line of Treatment

Regimen	ORR, %	PFS, mo	OS, mo	Reference
Irinotecan + CETUX (N=50)	4[7]	2.0	5.9	Kopetz et al, 2017[6]
Chemotherapy (N=51)	7	2.5	6.2	Mitani et al, 2017[5]
FOLFIRI (N=23)	N/A	1.8	5.7	Peeters et al, 2014[7]
FOLFIRI + PAN (N=22)	N/A	2.5	4.7	Peeters et al, 2014[7]
Chemotherapy 2nd line (N=58) 3rd line (N=31)	 N/A N/A	 2.5 2.6	 N/A N/A	Morris et al, 2014[8]
Chemotherapy + CETUX (N=22)	N/A	2.2	4.3	Saridaki et al, 2013[9]
Irinotecan + PAN (N=37)	11	N/A	N/A	Seymour et al, 2013[9]
Irinotecan (N=31)	6	N/A	N/A	Seymour et al, 2013[9]
Chemotherapy + CETUX (N=12)	8.3	2.8	5.8	Ulivi et al, 2012[10]
Chemotherapy + CETUX (N=24)	8	1.8	6.0	De Roock et al, 2010[3]
Irinotecan + CETUX (N=13)	N/A	N/A	4.1	Loupakis et al, 2009[1]

CETUX=cetuximab; FOLFIRI=folinic acid/5-fluorouracil/irinotecan; mCRC=metastatic colorectal cancer; N/A=not available; ORR=objective response rate; OS=overall survival; PAN=panitumumab; PFS=progression-free survival.
[7]Confirmed + unconfirmed responses; other sources cited in this table did not specify whether ORR required confirmation.

- In a phase 2 study in patients with *BRAF*^{V600E} mCRC, treatment with the anti–epidermal growth factor receptor (EGFR) antibody CETUX + the BRAF inhibitor encorafenib (ENCO) led to a median PFS of 4.2 months, an ORR of 22%, and a median OS >1 year, substantially improving outcomes relative to historical data for this population.[11]
  - Results from the phase 2 study led to the initiation of the BEACON CRC phase 3 study.
    - Addition of a MEK inhibitor to BRAF inhibitor has demonstrated improved efficacy and tolerability over BRAF inhibition alone in several tumor settings, including mCRC.[12-14]
- BEACON CRC (NCT02928224) is a 3 arm multicenter, randomized, phase 3 study evaluating the triplet combination of binimetinib (BINI, a MEK inhibitor) + ENCO + CETUX compared with investigator's choice of irinotecan standard biweekly dose + CETUX or folinic acid/5-fluorouracil/irinotecan (FOLFIRI) + CETUX and to the doublet combination of ENCO + CETUX in patients with *BRAF*^{V600E} mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting **(Figure 1)**.

Figure 1. BEACON CRC Trial Schema

mCRC=metastatic colorectal cancer; FOLFIRI=folinic acid/5-fluorouracil/irinotecan; OS=overall survival.

- As the triplet combination of BINI + ENCO + CETUX had not been studied previously, a safety lead-in (SLI) for the study was designed to determine the safety of the triplet combination and provide an initial assessment of activity before the phase 3 portion of the study.
- Preliminary analysis showed that in addition to the 41% of patients with *BRAF*^{V600E} tumors who responded (confirmed ORR, 12/29; 41%), an additional 9/29 (31%) had extended SD (≥6 months).[15]
- Carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9) are tumor markers widely used to monitor the effectiveness of systemic therapies for mCRC.[16-17]
- Here we report updated results from the SLI with approximately 3 months of additional follow-up as well as analyses exploring the association of CEA and CA19-9 changes while on treatment with clinical outcomes.

OBJECTIVES (SLI)

- Primary: to assess safety/tolerability of the triplet combination
- Secondary: to assess the activity of the triplet combination as measured by investigator-determined response per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1
- Exploratory: to assess changes in biomarkers CEA and CA19-9 in relation to radiographic responses to treatment

METHODS

- Key inclusion and exclusion criteria are described in **Table 2**.

Table 2. Key Patient Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
≥18 years of age Histologically or cytologically confirmed mCRC with disease progression after 1 or 2 prior regimens in the metastatic setting Measurable or evaluable nonmeasurable disease per RECIST, version 1.1 Presence of *BRAF*^{V600E} in tumor tissue as detected by PCR or NGS per local* or central testing Eligible to receive cetuximab per local label ECOG PS of 0 or 1	Prior treatment with any RAF inhibitor, MEK inhibitor, cetuximab, panitumumab, or other anti-EGFR inhibitor(s) Prior irinotecan hypersensitivity or contraindication to receive 5-fluorouracil, cetuximab, folinic acid, or irinotecan Symptomatic brain metastasis or leptomeningeal disease

*Tumor samples must also be submitted to the central laboratory for confirmation of presence of *BRAF*^{V600E} mutation.
ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; mCRC=metastatic colorectal cancer; NGS=next-generation sequencing; PCR=polymerase chain reaction; RECIST=Response Evaluation Criteria in Solid Tumors.

- All patients were treated with the single starting dose of ENCO 300 mg once daily (QD) + BINI 45 mg twice daily (BID) + CETUX at the standard weekly dose (400 mg/m^2 [initial dose], then 250 mg/m^2 once weekly [QW]) administered in 28-day cycles.
- Safety data were periodically reviewed by an independent data monitoring committee (DMC) before proceeding to dose expansion and following the completion of dose expansion (after enrollment of a total of 30 patients in the SLI). Efficacy was assessed based on radiologic imaging (eg, computed tomography, magnetic resonance imaging, x-ray, different methods of whole-body bone scans) and tumor response determined by the investigator according to RECIST, version 1.1.
  - Tumor assessments were performed every 6 weeks from the first dose in the SLI for the first 24 weeks, then every 12 weeks until disease progression, withdrawal of consent for treatment, initiation of subsequent anticancer therapy, patient being lost to follow-up, or death.
- Changes in tumor markers CEA and CA19-9 were assessed by the central laboratory based on blood samples collected on cycle 1 day 1 and day 1 of subsequent cycles, and at end of treatment.

RESULTS

- Enrollment in the SLI portion of BEACON CRC was completed in April 2017.
- 30 patients were treated in the SLI **(Table 3)**.

Table 3. Baseline Patient and Disease Characteristics

Characteristic	Patients (N=30)
BRAF^{V600E} mutation,* n (%)	29 (97)
Male, n (%)	13 (43)
Age, median (range), y	59 (38–77)
ECOG PS, n (%) 0 1	 17 (57) 13 (43)
Location of primary tumor, n (%) Right side Left side Unknown	 17 (57) 10 (33) 3 (10)
No. of organs with metastases, n (%) 1 >1	 8 (27) 22 (73)
Metastatic site locations, n (%) Liver Lymph nodes Peritoneum Lung Other	 20 (67) 15 (50) 11 (37) 9 (30) 16 (53)
No. of prior systemic therapies,† n (%) 1 2	 17 (57) 13 (43)
Received prior irinotecan, n (%)	13 (43)
MSI-H, n (%)	1 (3)
CEA at baseline, mean (range), µg/L	220.0 (1.4–3434.2)
CA19-9 at baseline, mean (range), U/mL	7840.5 (1.0–42,500.0)

CA19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; ECOG PS=Eastern Cooperative Oncology Group performance status; MSI-H=microsatellite high.
*Based on local or central lab assessment.
†Includes prior systemic therapies in only the metastatic setting.

RESULTS (CONTINUED)

Patient Disposition

- Of the 30 patients treated, 10 (33%) patients were still on treatment and 20 (67%) had discontinued treatment. The median time on study treatment was 7.8 months (range .5–11.9 months) **(Table 4)**.
- One patient (without the *BRAF*^{V600E} mutation) died while on treatment and 4 additional patients died within 30 days of the last dose of study drug, all due to progression of disease.

Table 4. Patient Disposition

Event, n (%)	Patients (N=30)
Continue on treatment	10 (33)
Discontinued treatment	20 (67)
Disease progression	17 (57)*
Adverse event unrelated to study treatment	1 (3)†
Adverse event related to study treatment	1 (3)‡
Death	1 (3)§

*Includes 2 patients with clinical progression.
†Grade 1 cholangitis.
‡Grade 2 fatigue.
§Due to disease progression in a patient with non-V600E *BRAF* mutation.

Safety Profile

- A summary of the safety data from the SLI portion of BEACON CRC is presented in **Table 5**.

Table 5. AEs of Any Grade Occurring in ≥15% of Patients, Regardless of Causality (N=30)

Event, n (%)	Any Grade	Grade 3/4
Any AE	30 (100)	19 (63.3)
Diarrhea	23 (76.7)	1 (3.3)
Dermatitis acneiform	20 (66.7)	0
Fatigue	19 (63.3)	4 (13.3)
Nausea	19 (63.3)	2 (6.7)
Vomiting	15 (50.0)	2 (6.7)
Dry skin	14 (46.7)	0
Anemia	11 (36.7)	2 (6.7)
Blood creatine phosphokinase increased	11 (36.7)	3 (10.0)
Decreased appetite	11 (36.7)	2 (6.7)
Abdominal pain	10 (33.3)	1 (3.3)
Dyspnea	10 (33.3)	2 (6.7)
Constipation	9 (30.0)	0
Pyrexia	9 (30.0)	0
Arthralgia	8 (26.7)	0
Blood creatinine increased	8 (26.7)	0
Vision blurred	8 (26.7)	0
Skin fissures	7 (23.3)	0
Aspartate aminotransferase increased	6 (20.0)	3 (10.0)
Asthenia	6 (20.0)	0
Palmar-plantar erythrodysesthesia syndrome	6 (20.0)	0
Rash maculopapular	6 (20.0)	0
Dizziness	5 (16.7)	0
Malaise	5 (16.7)	1 (3.3)
Myalgia	5 (16.7)	0
Edema peripheral	5 (16.7)	0
Peripheral sensory neuropathy	5 (16.7)	0
Urinary tract infection	5 (16.7)	3 (10.0)

AE=adverse event.

- Grade 3/4 adverse events (AEs) reported in ≥10% of patients were fatigue (4 patients), urinary tract infection (3 patients), increased aspartate aminotransferase (AST; 3 patients), and increased blood creatine phosphokinase (3 patients); of these, all were grade 3 except for a grade 4 AST increase in 1 patient.
- Observed AEs were consistent with known BRAF, MEK, and EGFR inhibitor toxicities.
- The only grade 3/4 skin-related AE reported was rash (grade 3) in 1 patient (3%).
  - The rate of severe skin toxicities (grade 3/4) was lower than generally observed for CETUX alone or in combination with standard chemotherapy for mCRC.[18]

Efficacy

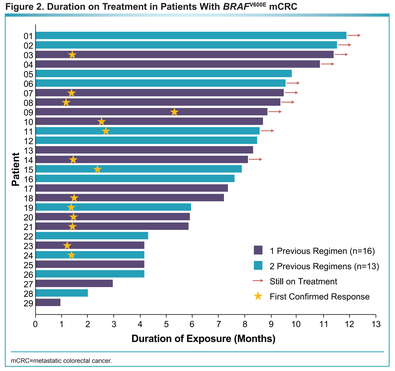
- A *BRAF*^{V600E} mutation was identified in 29 patients; 1 treated patient was determined to have a non-V600 *BRAF* mutation (*BRAF*^{D446V}).
- Of the 29 patients with a *BRAF*^{V600E} mutation, the median time on study treatment was 7.9 months (range, 1.0–11.9 months), and 10 (33%) patients remained on study treatment at the time of data cutoff.
- In patients with *BRAF*^{V600E} mCRC, confirmed ORR (complete response + partial response) was seen in 14/29 (48%) of patients **(Table 6)**, including a complete response in 3/29 patients.
  - The ORR in patients with 1 previous line of therapy was 62% (10/16) including 8 PR and 2 CR, and in patients with 2 previous lines of therapy, it was 31% (4/13) including 3 PR and 1 CR.

Table 6. Summary of Confirmed Best Response

Best Overall Response, n (%)	Patients (N=29)*
ORR (CR + PR)	14 (48)
CR	3 (10)
PR	11 (38)
SD	13 (45)
PD	0
Not evaluable for response†	2 (7)

CR=complete response; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.
*Patients with *BRAF*^{V600E} mutations.
†Nonresponders per intent-to-treat analysis.

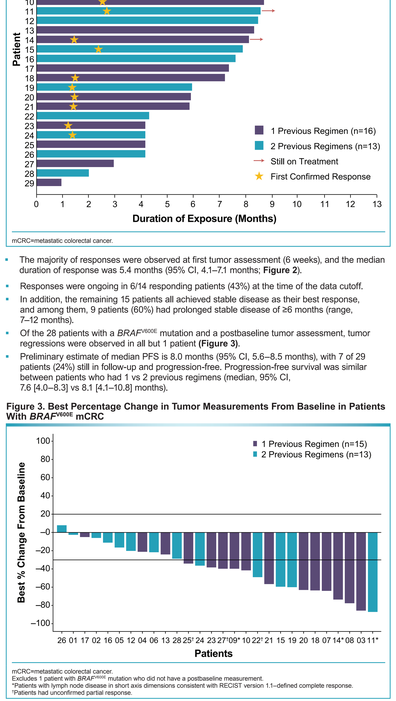
Figure 2. Duration on Treatment in Patients With *BRAF*^{V600E} mCRC



mCRC=metastatic colorectal cancer.

- The majority of responses were observed at first tumor assessment (6 weeks), and the median duration of response was 5.4 months (95% CI, 4.1–7.1 months; **Figure 2**).
- Responses were ongoing in 6/14 responding patients (43%) at the time of the data cutoff.
- In addition, the remaining 15 patients all achieved stable disease as their best response, and among them, 9 patients (60%) had prolonged stable disease of ≥6 months (range, 7–12 months).
- Of the 28 patients with a *BRAF*^{V600E} mutation and a postbaseline tumor assessment, tumor regressions were observed in all but 1 patient **(Figure 3)**.
- Preliminary estimate of median PFS is 8.0 months (95% CI, 5.6–8.5 months), with 7 of 29 patients (24%) still in follow-up and progression-free. Progression-free survival was similar between patients who had 1 vs 2 previous regimens (median, 95% CI, 7.6 [4.0–8.3] vs 8.1 [4.1–10.8] months).

Figure 3. Best Percentage Change in Tumor Measurements From Baseline in Patients With *BRAF*^{V600E} mCRC

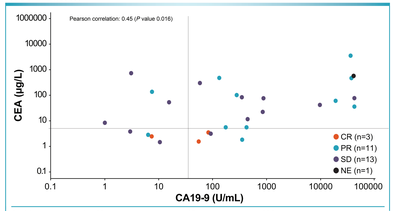


mCRC=metastatic colorectal cancer.
Excludes 1 patient with *BRAF*^{V600E} mutation who did not have a postbaseline measurement.
*Patients with lymph node disease in short axis dimensions consistent with RECIST version 1.1—defined complete response.
†Patients had unconfirmed partial response.

Tumor Markers

- CEA and CA19-9 were analyzed in 28 patients.
- CEA and CA19-9 at baseline were not well correlated, with the majority of patients having elevation of at least 1 marker **(Figure 4)**.
  - At baseline, 20 patients had CEA ≥ upper limit of normal (ULN), 20 patients had CA19-9 ≥ULN, and 16 patients had both ≥ULN.

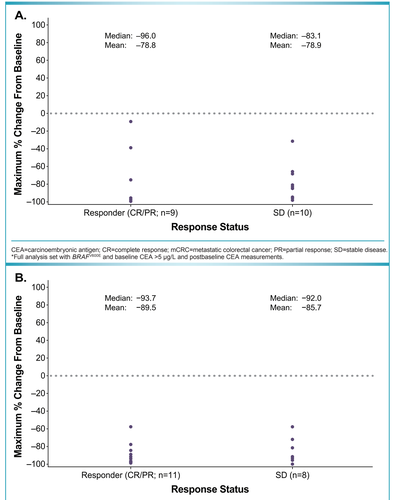
Figure 4. Scatter Plot of Baseline CEA vs Baseline CA19-9 Levels in Patients With *BRAF*^{V600E} mCRC



CA19-9=cancer antigen 19-9; CEA=carcinoembryonic antigen; CR=complete response; mCRC=metastatic colorectal cancer; NE=not evaluable; PR=partial response; SD=stable disease.
The horizontal line within the graph represents the upper limit of normal for CEA and the vertical line within the graph represents the upper limit of normal for CA19-9.

- Among patients with elevated baseline values (≥ULN), CEA and CA19-9 decreased in all patients.
- There were no notable differences in percentage change in either CEA or CA19-9 from baseline to nadir between patients with confirmed response and those with prolonged SD **(Figure 5)**.

Figure 5. Maximum CEA* (A) and CA19-9† (B) Percentage Change From Baseline in Patients With *BRAF*^{V600E} mCRC



CEA=carcinoembryonic antigen; CR=complete response; mCRC=metastatic colorectal cancer; PR=partial response; SD=stable disease.
*Full analysis set with *BRAF*^{V600E} and baseline CEA >5 µg/L and postbaseline CEA measurements.

CA19-9=cancer antigen 19-9;CR=complete response; mCRC=metastatic colorectal cancer; PR=partial response; SD=stable disease.
†Full analysis set with *BRAF*^{V600E} and baseline CA19-9 >35 U/mL and postbaseline CA19-9 measurements.

CONCLUSIONS

- In the BEACON CRC SLI, triple-combination ENCO 300 mg QD + BINI 45 mg BID + standard weekly CETUX continues to be generally well tolerated with additional follow-up.
  - Only 1 patient discontinued because of a treatment-related AE (grade 2 fatigue).
  - Common AEs were those associated with BRAF, MEK, and EGFR inhibitors and included gastrointestinal and skin toxicities.
  - Severe skin AEs were observed less frequently in the combination than reported rates for CETUX monotherapy.
- The triplet combination continues to show promising antitumor activity, with additional responses, as well as additional CRs with further follow-up.
  - In patients with *BRAF*^{V600E} mCRC, the ORR is 48% including 3 complete responses. The ORR among 16 patients treated in the 2nd-line setting was 62%.
  - Preliminary estimated median PFS was 8 months. Progression-free survival was similar between patients who had 1 vs 2 previous regimens.
  - Both ORR and PFS were substantially improved over historical standards of care, which generally have an ORR of <10% and a median PFS of approximately 2 months.
- Reduction in tumor markers CEA and CA19-9 were similar between patients with prolonged SD and objective response. Changes in tumor markers indicate a biological effect on the disease and support a treatment effect leading to the observed clinical benefit in patients with prolonged SD.
- Prolonged SD (≥6 months) was observed in 9 of 15 (60%) patients without a confirmed objective response.
  - There was evidence of tumor regression in all but 1 evaluable patient.
- Safety and preliminary efficacy data supported the initiation of the phase 3 portion of the BEACON CRC trial, and enrollment is currently ongoing.

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