BEACON CRC: Safety Lead-In (SLI) for the Combination of Binimetinib (BINI), Encorafenib (ENCO), and Cetuximab in Patients with *BRAF*^{V600E} Metastatic Colorectal Cancer (mCRC)

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INTRODUCTION

- *BRAF* mutations are found in 10%–15% of mCRC cases[1-3] and are generally mutually exclusive with *RAS* mutations.[4]
- Patients with *BRAF*^{V600E} mCRC have a poor prognosis, with progression-free survival (PFS) of 2–3 months, objective response rates (ORRs) of 4%–8%, and overall survival of 4–6 months after failure of first-line therapy.[5-8]
- In a recent randomized phase 2 study of patients with previously treated *BRAF*^{V600E} mCRC, among those who received cetuximab and irinotecan, ORR was 4% and PFS was 2 months.[8]
- In advanced CRC, the overlap of *BRAF* mutations with a defective DNA mismatch repair system, exhibited as microsatellite instable (MSI), is relatively rare.[9]
- Prospectively collected data in *BRAF*-mutant mCRC patients showed the prevalence of MSI-high (MSI-H) to be 14% of 106 patients in a recent phase 1b/2 trial (NCT01719380) (Array, data on file) and 18% of 72 patients in a recent Southwestern Oncology Group (SWOG) randomized phase 2 study.[8]
- Benefits of combination therapies, including dual inhibition of BRAF + epidermal growth factor receptor (EGFR) or triplet combinations consisting of BRAF + EGFR inhibition plus MEK inhibition or chemotherapy, have been demonstrated in clinical studies of patients with mCRC (**Table 1**).

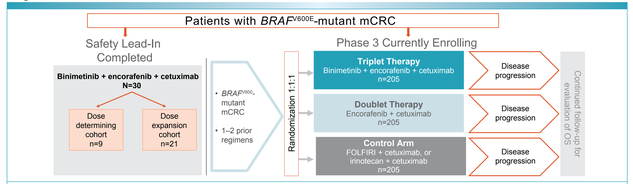
Table 1. Summary of Trial Outcomes with BRAF Inhibitor Combinations

	Doublet Therapy		Triplet Therapy	
	Cetuximab + Encorafenib[10] (n=50)	Panitumumab + Dabrafenib[11] (n=20)	Cetuximab + Vemurafenib + Irinotecan[5] (n=49)	Panitumumab + Dabrafenib + Trametinib[11] (n=91)
No. of prior regimens for advanced disease, n (%)				
0	0	4 (20)	3 (6)*	21 (23)
1	21 (42)	8 (40)	27 (55)	27 (30)
2	20 (40)	7 (35)	19 (39)	33 (36)
≥3	9 (18)	1 (5)	0	10 (11)
ORR (CR + PR), %	22%	10%	16%†	21%
mPFS, months	4.2	3.5	4.3	4.2

*Failed adjuvant within 6 months. †Confirmed and unconfirmed responses.
CR=complete response; mPFS=median progression-free survival; NR=not reported; ORR=objective response rate; PR=partial response.

- In a phase 2 study of cetuximab + ENCO in patients with *BRAF*^{V600E} mCRC, ORR was 22%, median PFS was 4.2 months, and median overall survival exceeded 1 year, which is substantially improved over the historical standard of care for this population.[10] These results led to the initiation of the BEACON CRC phase 3 study.
- BEACON CRC (NCT02928224) is a multicenter, randomized, phase 3 study evaluating BINI (a MEK inhibitor) + ENCO (a selective BRAF inhibitor) + cetuximab (an anti-EGFR antibody) standard once-weekly regimen and ENCO + cetuximab compared with investigator's choice of irinotecan standard biweekly dose + cetuximab or folinic acid/5-fluorouracil/irinotecan (FOLFIRI) + cetuximab 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



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

- In the phase 3 portion of BEACON CRC, the number of patients having received 2 prior regimens is limited to 35% of the total randomized (ie, a maximum of 215 patients across all 3 arms).
- Here we describe results of the BEACON CRC SLI portion, which was designed to determine the safety of the triplet combination and provide an initial assessment of activity prior to the phase 3 portion of the study.

SAFETY LEAD-IN METHODS

Eligibility

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 • 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}.
EGFR=epidermal growth factor receptor; ECOG PS=Eastern Cooperative Oncology Group Performance Status; mCRC=metastatic colorectal cancer; NGS=next-generation sequencing; PCR=polymerase chain reaction; RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

Dose Determining Cohort

- Tolerability was assessed in the first 9 patients dosed with ENCO 300 mg once daily (QD) + BINI 45 mg twice daily (BID) + cetuximab 400 mg/m^2 (initial dose) then 250 mg/m^2 once weekly (QW) administered in 28-day cycles.
- Initiation of dose expansion could occur if <3 patients experienced dose-limiting toxicities (DLTs) as defined in the protocol.
- An independent data monitoring committee (DMC) reviewed safety data prior to proceeding to dose expansion.

Dose Expansion Cohort

- Tolerability was assessed in an additional 21 patients.
- DMC reviewed safety data after the first 6 patients were treated in the dose expansion and following completion of the dose expansion (after enrollment of a total of 30 patients in the SLI).

RESULTS

- Enrollment in the SLI portion of BEACON CRC was completed in April 2017.
- As of the 09 August 2017 cutoff date, 30 patients were treated (**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), years	59 (38–77)
ECOG PS, n (%)	
0	17 (57)
1	13 (43)
Location of primary tumor, n (%)	
Right side	17 (57)
Left side	10 (33)
Unknown	3 (10)
No. of organs with metastases, n (%)	
1	8 (27)
>1	22 (73)
Metastatic site locations, n (%)	
Liver	20 (67)
Lymph nodes	15 (50)
Peritoneum	11 (37)
Lung	9 (30)
Colon/rectum	8 (27)
Other	16 (53)
No. of prior systemic therapies, n (%)†	
1	18 (60)
2	12 (40)
Received prior irinotecan, n (%)	12 (40)
MSI-H, n (%)‡	1 (4)

*1 patient treated with a non-V600E *BRAF* mutation. †Includes prior systemic therapies in the metastatic setting only. ‡Based on immunohistochemical assessment of MLH1 and MSH6 proteins successfully analyzed in 23 patients.
ECOG PS=Eastern Cooperative Oncology Group Performance Status; MSI-H=microsatellite high.

Patient Disposition

- Of the 30 patients treated, 22 (73%) were still on treatment and 8 had discontinued treatment at the data cutoff date (**Table 4**).

Table 4. Reasons for Treatment Discontinuation

Event, n (%)	Patients (n=30)
Disease progression	4 (13)
AE unrelated to study treatment*	2 (7)
AE related to study treatment (grade 2 fatigue)	1 (3)
Death†	1 (3)

*Biliary obstruction (n=1), cholangitis (n=1). †Due to disease progression in patient with non-V600E *BRAF* mutation.
AE=adverse event.

- Four patients (13%) died on study or within 30 days of last dose due to disease progression.

Dose-Limiting Toxicities

- Dose-determining cohort: DLT was reported in 1 of 9 patients:
  - Grade 2 infusion reaction following cetuximab infusion.
    - Patient continued in the study on BINI and ENCO.
- Dose-expansion cohort: DLTs were reported in 4 of 21 patients:
  - Grade 3 infusion reaction following cetuximab infusion (n=1).
    - Patient continued in the study on BINI and ENCO.
  - Grade 2 decreased ejection fraction (n=1).
    - Patient continued in the study on a reduced dose of BINI.
  - Inability to receive ≥75% dose intensity due to grade 2 retinopathy (n=2).
    - Both patients continued in the study following an interruption of BINI dosing.

Safety Profile

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)	18 (60)
Diarrhea	23 (77)	1 (3)
Nausea	17 (57)	3 (10)
Dermatitis acneiform	17 (57)	0
Fatigue	16 (53)	2 (7)
Vomiting	15 (50)	3 (10)
Dry skin	13 (43)	0
Increased blood creatine phosphokinase	10 (33)	3 (10)
Decreased appetite	10 (33)	1 (3)
Constipation	9 (30)	0
Dyspnea	9 (30)	1 (3)
Anemia	8 (27)	2 (7)
Pyrexia	8 (27)	0
Blurred vision	8 (27)	0
Abdominal pain	7 (23)	0
Rash maculo-papular	7 (23)	0
PPE syndrome	6 (20)	0
Asthenia	6 (20)	0
Rash	6 (20)	1 (3)
Arthralgia	5 (17)	0
Increased AST	5 (17)	2 (7)*
Malaise	5 (17)	0
Peripheral sensory neuropathy	5 (17)	0
Skin fissures	5 (17)	0
Urinary tract infection	5 (17)	3 (10)

*All data shown are grade 3, except for 2 patients with grade 4 increased AST.
AE=adverse event; AST=aspartate transaminase; PPE=palmar-plantar erythrodysesthesia.

- Grade 3/4 adverse events (AEs) reported in ≥10% of patients were nausea, vomiting, urinary tract infection, and increased blood creatine kinase (3 patients [10%] each, all grade 3).
- The only grade 3/4 skin-related AE reported was rash (grade 3) in 1 patient (3%).
- Observed AEs were consistent with known BRAF, MEK, and EGFR inhibitor toxicities. The rate of severe skin toxicities (grade 3/4) was lower than generally observed for cetuximab alone or in combination with standard chemotherapy for mCRC.[12]

Efficacy

- A *BRAF*^{V600E} mutation was identified in 29 patients; 1 treated patient was determined to have a non-V600 *BRAF* mutation (*BRAF*^{D465V}).
- In patients with *BRAF*^{V600E} mCRC, confirmed ORR (complete response + partial response) was 41% (**Table 6**).

Table 6. Summary of Confirmed Best Overall Response

Best Overall Response, n (%)	Patients (n=29)*
ORR (CR + PR)	12 (41)
CR	1 (3)
PR	11 (38)
SD	15 (52)
PD	0
Not evaluable for response†	2 (7)

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

- The majority of responses were observed at first tumor assessment (6 weeks).
- Responses were observed across all key subgroups (**Table 7**).

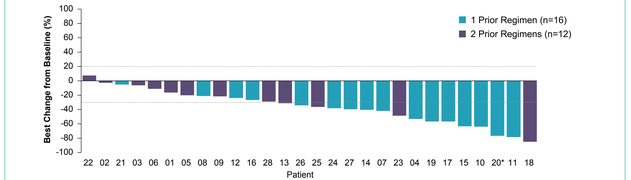
Table 7. Summary of Confirmed Best Overall Response by Baseline Characteristics in Patients with *BRAF*^{V600E} Mutation

Characteristic	Confirmed Response Rate, n (%)
No. of prior systemic therapies	
1 (n=17)	10 (59)
2 (n=12)	2 (17)
Primary tumor location*	
Left-side (n=10)	5 (50)
Right-side (n=16)	7 (44)
No. of metastatic sites	
1 (n=7)	3 (43)
>1 (n=22)	9 (41)
Received prior irinotecan	
No (n=17)	8 (47)
Yes (n=12)	4 (33)

*n=26 patients had available data on tumor location.

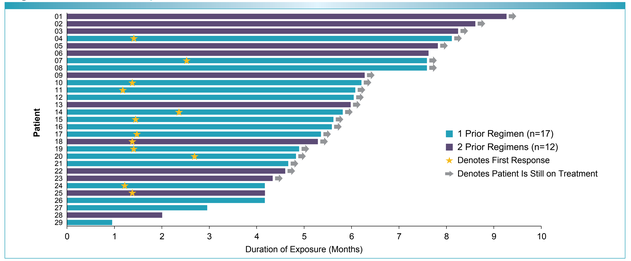
- Of the 28 patients with a *BRAF*^{V600E} mutation and a postbaseline tumor assessment, tumor regressions were observed in all except 1 patient (**Figure 2**).
- Of the 29 patients with a *BRAF*^{V600E} mutation, the median time on study treatment was 5.6 months (range, 1.0–9.3 months), and 22 (76%) remained on study treatment at the time of data cutoff (**Figure 3**).

Figure 2. Best Percent Change from Baseline



Excludes 1 patient with *BRAF*^{V600E} mutation who did not have a postbaseline measurement. *Patient with lymph node disease with decreases in short axis dimensions consistent with Response Evaluation Criteria In Solid Tumors version 1.1 defined complete response.

Figure 3. Duration of Exposure



CONCLUSIONS

- **In the BEACON CRC SLI, triple combination ENCO 300 mg QD + BINI 45 mg BID + cetuximab 400 mg/m^2 (initial dose) then 250 mg/m^2 QW was generally well tolerated.**
- **The triplet combination showed promising antitumor activity in patients with *BRAF*^{V600E} mCRC, with evidence of tumor regression in all evaluable patients except 1.**
- **Confirmed ORR of 41% with BINI + ENCO + cetuximab exceeds standard-of-care benchmarks and exceeds the ORR of 22% in a phase 2 trial of the doublet of ENCO + cetuximab.[10]**
- **Confirmed ORR was consistent regardless of primary tumor location (left side or right side), number of metastatic sites, and previous irinotecan exposure. The observed ORR was higher in patients with 1 prior therapy (59%) than in those with 2 prior therapies (17%); the randomized portion of the study restricts the proportion of patients with 2 prior lines of therapy to 35% of the total.**
- **Of the 29 patients with a *BRAF*^{V600E} mutation, the median time on study treatment was 5.6 months (range, 1.0–9.3 months), and 22 (76%) remained on study treatment at the time of data cutoff.**
- **Safety and preliminary efficacy data supported the initiation of the phase 3 portion of the BEACON CRC trial, and enrollment is currently ongoing.**

References

1. Loupakis et al. *Br J Cancer.* 2009;101:715-21.
2. Vecchione et al. *Cell.* 2016;165:317-30.
3. Sanidas et al. *PLoS One.* 2013;8:e84604.
4. Sahin IH et al. *J Cancer.* 2013;4:320-22.
5. De Roock et al. *Lancet Oncol.* 2010;11:753-62.
6. Ulivi et al. *J Transl Med.* 2012;10:87-95.
7. Peeters et al. *J Clin Oncol.* 2014;32:abstr 3568.
8. Kopetz et al. *J Clin Oncol.* 2017;35:abst 3505.
9. Gelsomino et al. *Cancer Treat Rev.* 2016;51:19-26.
10. Tabernero et al. *J Clin Oncol.* 2016;34:abstr 3544.
11. Corcoran et al. *Ann Oncol.* 2016;27:abstr 455O.
12. ERBITUX (cetuximab) injection, for intravenous infusion. Indianapolis, IN: Eli Lilly and Company; 2016.

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