**Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study**

Eric Van Cutsem, MD, PhD; Sanne Huijberts, MD; Axel Grothey, MD; Rona Yaeger, MD; Pieter-Jan Cuyle, MD; Elena Elez, MD, PhD; Marwan Fakhri, MD; Clara Montagut, MD; Marc Peeters, MD, PhD; Takayuki Yoshino, MD; Harpreet Wasan, MD; Jayesh Desai, MBBS; Fortunato Ciardiello, MD, PhD; Ashwin Gollerkeri, MD; Janna Christy-Bittel, MSN; Kati Maharry, PhD; Victor Sandor, MD; Jan H.M. Scheliers, MD, PhD; Scott Kopetz, MD, PhD; and Josep Tabernero, MD, PhD

**PURPOSE** To determine the safety and preliminary efficacy of selective combination targeted therapy for BRAF V600E–mutant metastatic colorectal cancer (mCRC) in the safety lead-in phase of the open-label, randomized, three-arm, phase III BEACON Colorectal Cancer trial (ClinicalTrials.gov identifier: NCT02928224; European Union Clinical Trials Register identifier: EudraCT2015-005805-35).

**PATIENTS AND METHODS** Before initiation of the randomized portion of the BEACON Colorectal Cancer trial, 30 patients with BRAFV600E–mutant mCRC who had experienced treatment failure with one or two prior regimens were to be recruited to a safety lead-in of encorafenib 300 mg daily, binimetinib 45 mg twice daily, plus standard weekly cetuximab. The primary end point was safety, including the incidence of dose-limiting toxicities. Efficacy end points included overall response rate, progression-free survival, and overall survival.

**RESULTS** Among the 30 treated patients, dose-limiting toxicities occurred in five patients and included serous retinopathy (n = 2), reversible decreased left ventricular ejection fraction (n = 1), and cetuximab-related infusion reactions (n = 2). The most common grade 3 or 4 adverse events were fatigue (13%), anemia (10%), increased creatine phosphokinase (10%), increased AST (10%), and urinary tract infections (10%). In 29 patients with BRAF V600E–mutant tumors (one patient had a non-BRAF V600E–mutant tumor and was not included in the efficacy analysis), the confirmed overall response rate was 48% (95% CI, 29.4% to 67.5%), median progression-free survival was 8.0 months (95% CI, 5.6 to 9.3 months), and median overall survival was 15.3 months (95% CI, 9.6 months to not reached), with median duration of follow-up of 18.2 months (range, 16.6 to 19.8 months).

**CONCLUSION** In the safety lead-in, the safety and tolerability of the encorafenib, binimetinib, and cetuximab regimen is manageable and acceptable for initiation of the randomized portion of the study. The observed efficacy is promising compared with available therapies and, if confirmed in the randomized portion of the trial, could establish this regimen as a new standard of care for previously treated BRAF V600E–mutant mCRC.

**CONFLICTS OF INTEREST** Complete disclosure is available on ASCO's website.
Unlike in other tumor histologies with \(BRAF\) V600 mutations such as melanoma and non–small-cell lung cancer, where \(BRAF\) inhibition is clinically highly active,\textsuperscript{25–36} \(BRAF\) inhibition in \(BRAF\) V600E–mutant mCRC produced only marginal clinical activity.\textsuperscript{35,37–39} In vitro studies later demonstrated that in \(BRAF\) V600E–mutant colorectal cancer (CRC) cells, \(BRAF\) inhibition results in rapid feedback activation of epidermal growth factor receptor (EGFR), permitting sustained MAPK activation and continued cell proliferation; however, combined inhibition of \(BRAF\) and EGFR resulted in synergistic inhibition of tumor growth in \(BRAF\) V600E–mutant CRC xenograft models.\textsuperscript{40,41} Subsequent clinical studies of EGFR-targeted monoclonal antibodies combined with \(BRAF\) inhibition using the \(BRAF\) inhibitors vemurafenib or dabrafenib confirmed that addition of an EGFR-targeted therapy can improve the activity of \(BRAF\) inhibition in \(BRAF\) V600E–mutant CRC.\textsuperscript{42–44} In addition, preclinical studies indicated that profound inhibition of the MAPK pathway and greater antitumor activity could be achieved with the addition of a MEK inhibitor to \(BRAF\) inhibition, and this was also validated clinically.\textsuperscript{45,46} Despite improvements in the activity of these regimens, to date, triplet combinations of \(BRAF\) inhibition with EGFR-targeted therapy and either a MEK inhibitor or irinotecan have demonstrated response rates of approximately 20%, in contrast to response rates of 60% to 70% for combined dual \(BRAF/MEK\) inhibition alone in melanoma and non–small-cell lung cancer.\textsuperscript{19,34,36,44,47}

The combination of encorafenib, a \(BRAF\) inhibitor, and binimetinib, a MEK inhibitor, has recently been approved in the United States and Europe for the first-line treatment of patients with \(BRAF\) V600–mutant melanoma.\textsuperscript{48,49} Results from a recent phase II study in patients with \(BRAF\) V600E–mutant mCRC who received at least one prior regimen showed that the doublet of encorafenib plus cetuximab resulted in a confirmed ORR of 24%, a PFS of 4.2 months, and an OS of 9.3 months with a tolerable safety profile.\textsuperscript{50} Relative to the standard of care and to other \(BRAF\), MEK, and EGFR-inhibitor triplet combinations, the promising results with the encorafenib and cetuximab doublet supported the initiation of the phase III BEACON CRC study (ClinicalTrials.gov identifier: NCT02928224; European Union Clinical Trials Register identifier: EudraCT2015-005805-35).

BEACON CRC is an open-label, randomized, three-arm, phase III study evaluating the efficacy and safety of encorafenib plus cetuximab with or without binimetinib versus investigators’ choice of cetuximab combined with either irinotecan or fluorouracil, folinic acid, and irinotecan in patients with \(BRAFV600E\)–mutant mCRC whose disease has progressed after one or two prior regimens. At the time BEACON CRC was initiated, the triplet combination of binimetinib, encorafenib, and cetuximab had not been clinically evaluated. Therefore, a 30-patient safety lead-in (SLI) was conducted to determine the safety, tolerability, and preliminary efficacy of the triplet combination at the doses planned for the randomized portion of the trial. Here, we describe results of the BEACON CRC SLI. At the time of this analysis, the randomized portion of the trial was ongoing.

**PATIENTS AND METHODS**

Patients were required to be 18 years of age or older with histologically or cytologically confirmed mCRC, with the presence of \(BRAFV600E\) mutation in tumor tissue. Patients could enroll based on local determination of \(BRAFV600E\) mutation; however, confirmation by a central laboratory was required for all patients within 30 days of starting treatment. Patients must have had progression of disease on at least one but no more than two prior treatment regimens in the metastatic setting; have had evidence of measurable or evaluable, nonmeasurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; have had an Eastern Cooperative Oncology Group performance status of 0 or 1; have been eligible to receive cetuximab per their local label; and have had adequate bone marrow, renal, hepatic, and cardiac function. Patients were excluded if they had previous treatment with any RAF or MEK inhibitor, cetuximab, panitumumab, or other EGFR inhibitor or had symptomatic brain metastasis or leptomeningeal disease. Additional details regarding inclusion and exclusion criteria are provided in the Data Supplement.

The SLI was performed at seven sites in four countries (two in Belgium, one in the Netherlands, two in Spain, and two in the United States). The study was approved by the ethics

![FIG 1. Patient disposition. (*) One treated patient had a non-V600 BRAF mutation (BRAF G466V). (1) Includes two patients with changes in condition or development of an intercurrent illness. (2) Dose interruption for more than 28 consecutive days. (§) As of the data cutoff date of September 2, 2018. AE, adverse event.](image-url)
committee for each study site. All clinical work was conducted in compliance with current Good Clinical Practices as referenced in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. All patients enrolled in the study provided written, informed consent before their participation.

Study Procedures
The first nine patients were enrolled in the SLI on a rolling basis. These patients received encorafenib 300 mg every day plus binimetinib 45 mg twice a day plus cetuximab 400 mg/m² followed by 250 mg/m² intravenously weekly in 28-day cycles. The cohort was to be expanded to a total of 30 patients in the dose-expansion cohort based on assessments of the safety data in the first nine patients by the data monitoring committee.

Outcome Measures
Safety was evaluated by ongoing monitoring of adverse events, clinical laboratory tests, vital signs, physical examinations, ophthalmic examinations, dermatologic examinations, ECGs, and echocardiography or multigated acquisition scans. Tumors were assessed using radiologic imaging (eg, computed tomography, magnetic resonance imaging, x-ray, whole-body bone scans), with tumor response determined locally by the investigator and by blinded independent central review according to RECIST, response determined locally by the investigator. Blinded central review of radiographically determined tumor response and progression was also conducted retrospectively and reported. Pharmacokinetic end points were also evaluated and will be presented elsewhere.

TABLE 1. Baseline Patient and Tumor Characteristics (safety population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients* (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF V600E mutation†</strong></td>
<td>29 (97)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>29 (97)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>59 (38-77)</td>
</tr>
<tr>
<td><strong>ECOG PS of 0</strong></td>
<td>17 (57)</td>
</tr>
<tr>
<td><strong>Location of primary tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Right side</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>No. of organs with metastases ≥ 2</strong></td>
<td>22 (73)</td>
</tr>
<tr>
<td><strong>Metastatic site locations</strong></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15 (50)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Lung</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (50)</td>
</tr>
<tr>
<td><strong>Resection of primary tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (70)</td>
</tr>
<tr>
<td>No</td>
<td>9 (30)</td>
</tr>
<tr>
<td><strong>No. of prior systemic therapies‡</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18 (60)</td>
</tr>
<tr>
<td>2</td>
<td>12 (40)</td>
</tr>
<tr>
<td><strong>Received prior irinotecan</strong></td>
<td>13 (43)</td>
</tr>
<tr>
<td><strong>MSI-H§</strong></td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Median CEA at baseline, μg/mL (range)</strong></td>
<td>28 (1-3,434)</td>
</tr>
</tbody>
</table>

Abbreviations: CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability high.

*Values are numbers and percentages, unless otherwise noted.
†One patient treated had a non-BRAF V600E mutation.
‡Includes prior systemic therapies in the metastatic setting only.
§Based on immunohistochemical assessment of MLH1 and MSH6.
from any cause. The survival status of all patients was assessed as of the cutoff date based on ongoing survival follow-up and public records where permitted. Data for patients who did not die by the data cutoff date were censored for OS at their last contact date. DOR was defined as time from first radiographic evidence of response to the earliest documented disease progression or death. Time to response was defined as time from first dose of study treatment to first radiographic evidence of response. The Kaplan-Meier method was used to estimate PFS and OS rates. This was also used to assess DOR.

RESULTS

Thirty patients were enrolled in the SLI of BEACON CRC between November 1, 2016, and April 24, 2017; as of September 2, 2018, treatment remained ongoing for six patients (20%; Fig 1). A total of 24 patients (80%) discontinued from the study, with the primary reason for study discontinuation being disease progression (n = 21; 70%).

Patient Disposition and Characteristics

Patient demographic and baseline tumor characteristics are listed in Table 1. Patients were characteristic of a population of patients with BRAF V600E–mutant mCRC, with predominantly right-sided disease and high frequency of nodal and peritoneal metastasis, although the liver was the most frequent site of metastasis. One patient had a non-V600 mutation of BRAF (G466V) and was included in the safety analysis but excluded from the efficacy analysis.

Safety

DLTs. DLTs were reported in five of 30 patients and included two patients with cetuximab-related drug hypersensitivity (grade 2 and grade 3; both patients remained in the study on binimetinib and encorafenib), two patients with grade 2 serous retinopathy (both patients remained in the study after an interruption of binimetinib dosing), and one patient with decreased left ventricular ejection fraction (grade 2) that resolved with the interruption of binimetinib dosing (the patient continued in the study on a reduced dose of binimetinib).

AEs. Two patients (6.7%) experienced grade 1 toxicities; seven (23.3%) experienced grade 2 toxicities; 16 (53.3%) experienced grade 3 toxicities; and five (16.7%) experienced grade 4 toxicities. No grade 5 toxicities were reported. The most frequently reported treatment-emergent AEs (any grade) included diarrhea (77%), dermatitis acniform (67%), fatigue (63%), and nausea (63%). The most frequently reported grade 3 or 4 treatment-emergent AEs included fatigue (13%; all grade 3), anemia (10%; two grade 3 and one grade 4), increased AST (10%; one grade 3 and two grade 4), increased creatine phosphokinase (10%; all grade 3), and urinary tract infections (10%; all grade 3; Tables 2 and 3).

Drug discontinuations as a result of AEs. A total of six patients (20%) had at least one study drug discontinued as a result of AEs. Among these, one patient (3.3%) discontinued all three drugs as a result of grade 2 fatigue; two patients (6.7%) discontinued binimetinib alone as a result of increased blood creatinine (n = 1) and retinal detachment (n = 1); two patients (6.7%) discontinued

<table>
<thead>
<tr>
<th>TABLE 2. Adverse Events, Regardless of Causality, Reported in Five or More Patients (safety population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
</tr>
<tr>
<td>Total patients with any adverse event†</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Dermatitis acniform</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td>Skin fissures</td>
</tr>
<tr>
<td>Vision blurred</td>
</tr>
<tr>
<td>AST increased</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Rash maculopapular</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
</tr>
<tr>
<td>Edema peripheral</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Rash pustular</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>

NOTE. Grade is based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

*Any single patient may have experienced adverse events under multiple terms (ie, not mutually exclusive).
†Reported using standard Medical Dictionary for Regulatory Activities dictionary coding.
cetuximab alone as a result of an allergic reaction; and one patient (3.3%) discontinued both encorafenib and binimetinib as a result of increased blood bilirubin. At the time of the increased blood bilirubin, there was radiographic evidence of extrinsic obstruction of the gallbladder. The patient received a dose of cetuximab 2 weeks after discontinuation of encorafenib and binimetinib and then discontinued study treatment completely 2 weeks later as a result of clinical progression. There were five on-treatment deaths (17%), all a result of disease progression.

**Efficacy**

Efficacy was assessed in the 29 patients with *BRAF* V600E mutation–containing tumors. The median time on study drug was 7.9 months (range, 1.0 to 21.4 months), and median follow-up time for survival was 18.2 months (range, 16.6 to 19.8 months).

**Overall response.** Confirmed best overall responses are listed in Table 4. The ORR per local assessment was 48% (95% CI, 29.4% to 67.5%). Fourteen patients had a confirmed response; three patients (10%) had complete responses, and 11 patients (38%) had partial responses. The ORR, as determined by retrospective central assessment, was 41% (95% CI, 23.5% to 61.1%), with two complete responses (7%) and 10 partial responses (34%). Changes in tumor measurements from baseline are presented in Figure 2.

Among the 17 patients treated with one prior therapy, ORRs per local and central assessment were 59% (95% CI, 32.9% to 81.6%) and 53% (95% CI, 27.8% to 77.0%), respectively. Among the 12 patients treated with two prior therapies, the local ORR was 33% (95% CI, 9.9% to 65.1%), with corresponding rates from central assessment of 25% (95% CI, 5.5% to 57.2%).

**Time to response.** Per local assessment, 78.6% of responding patients achieved a response within 2 months, 92.9% within 4 months, and all patients within 6 months of treatment initiation. On the basis of central assessment, 75.0% of responding patients achieved response within 2 months, 91.7% within 4 months, and all patients within 12 months of treatment initiation.

**DOR.** Among responders (n = 14), the median DOR per local assessment was 8.1 months (95% CI, 2.8 months to NR); 73% of patients achieved a DOR of 6 months or longer (Data Supplement). Median DOR among the 12 responders confirmed by central assessment was 8.1 months (95% CI, 2.8 months to NR); 73% of patients achieved a DOR of 6 months or longer (Data Supplement).

**PFS and OS.** Median PFS was 8.0 months (95% CI, 5.6 to 9.3 months; Fig 3A) per local assessment and 5.5 months (95% CI, 4.2 to 9.3 months) per central assessment. Median PFS (by local assessment) by number of prior therapies is presented in Table 2.
regimens was similar: 8.0 months (95% CI, 5.6 to 9.7 months) for patients who received one prior regimen compared with 7.7 months (95% CI, 4.1 to 10.8 months) for patients who received two prior regimens. The median OS time was 15.3 months (95% CI, 9.6 months to NR; Fig 3B), with median duration of follow-up of 18.2 months (range, 16.6 to 19.8 months). The 12-month OS rate was 62% (95% CI, 42.1% to 76.9%).

**DISCUSSION**

On the basis of the safety and efficacy results of the SLI phase of the BEACON CRC study, the randomized phase of the study was initiated and is ongoing. The safety profile of the triplet combination regimen of binimetinib, encorafenib, and cetuximab was similar to that previously reported for the individual agents and included predominantly GI and skin toxicities. Higher grade (grade 3 or 4) skin toxicities were rare and were less common than the 12% rate of grade 3 or 4 rash reported for cetuximab monotherapy, suggesting that BRAF inhibition may ameliorate this cetuximab-related AE. Although the overall rates of grade 3 and grade 4 toxicity were 53.3% and 16.7%, respectively, there was no single predominant toxicity driving these rates, with only the event of fatigue (13%) reported at a rate higher than 10%. The regimen appeared to be well tolerated and the safety profile manageable; a few patients (six patients [20%]) required dose discontinuation of at least one of the study drugs as a result of an AE and only one patient discontinued treatment with all three agents as a result of a drug-related AE. Patients requiring dose discontinuation included two patients who required discontinuation of cetuximab as a result of infusion reactions, a rate consistent with prior reports for cetuximab infusion reactions. The addition of the MEK inhibitor binimetinib did result in some patients experiencing MEK

---

**FIG 2.** Best percent change from baseline in sum of tumor diameters based on (A) local assessment and (B) central assessment. One patient was without postbaseline sum of diameters (not presented). Colors represent best response (confirmed) of partial response (PR) or complete response (CR). The category other represents stable disease (SD) or not evaluable (NE). Patients with CR, defined as the disappearance of all target lesions, could have pathologic lymph node metastases present; target or nontarget lymph node metastases must have had reduction in short axis to less than 10 mm. The other category includes stable disease or patient not evaluable.
inhibitor class–related AEs including serous retinopathy, increased creatine phosphokinase, and decreases in left ventricular ejection fraction. Serous retinopathy (also referred to as retinal pigment epithelial detachment) is a known MEK inhibitor–associated toxicity and was observed as a grade 2 DLT in two patients. It was documented to reverse in all patients who underwent repeat ophthalmologic examination; in one patient, ophthalmologic examination was not repeated but the patient continued on study treatment without loss of visual acuity. Serous retinopathy is most often asymptomatic, and reported rates depend on the frequency of monitoring. Symptomatic serous retinopathy is generally reversible and manageable with dose interruption, with or without subsequent dose reduction. Increased creatine phosphokinase was also observed (37%) but is rarely associated with significant myopathy, and it led to dose modification in only one patient. Clinically significant MEK inhibitor–associated left ventricular dysfunction is uncommon and is generally reversible with interruption and dose modification. Grade 2 left ventricular dysfunction was reported as a DLT in one patient, was reversed with binimetinib interruption, and did not lead to treatment discontinuation.

Benchmarked against both prior standards of care for RAS wild-type metastatic CRC as well as more recent experience with other BRAF inhibitor combinations, including triplet combinations with cetuximab and either irinotecan or the MEK inhibitor trametinib, the efficacy findings from the SLI are promising. The confirmed ORR was 48%, with 43% of responses lasting for more than 6 months. The median PFS time was 8 months and median OS time was 15.3 months, with a median duration of follow-up of 18.2 months. Results by central review were, in general, consistent with local review findings. By comparison, expected outcomes for historical second- and third-line standards of care, similar to the control arm of the randomized portion of the trial, included an ORR of less than 10%, median PFS of 2 to 3 months, and median OS of 4 to 6 months. Similarly, other triplet therapy regimens incorporating a BRAF inhibitor and an EGFR-targeted monoclonal antibody (dabrafenib, trametinib, and panitumumab and vemurafenib, irinotecan, and cetuximab) have shown improved but limited efficacy, with ORRs of 16% to 21%, median PFS of approximately 4.2 to 5.6 months, and median OS of 9.1 to 9.6 months. Although the mechanisms underlying the outcomes associated with encorafenib and binimetinib combined with cetuximab remain to be fully characterized, preclinical data suggest that encorafenib has target binding characteristics that differ from both vemurafenib and dabrafenib, with a prolonged target dissociation half-life and higher potency. Clinically, although never compared head-to-head with other BRAF/MEK inhibitor combinations, in the COLUMBUS trial patients with advanced BRAF V600K or V600E melanoma, the combination of binimetinib and encorafenib produced new benchmarks for efficacy as measured by PFS (median, 14.9 months; 95% CI, 11.0 to 18.5 months) and OS (median, 33.6 months; 95% CI, 24.4 to 39.2 months). Vemurafenib monotherapy, the control arm in the COLUMBUS study, performed almost identically to its activity in pivotal trials of other BRAF/MEK inhibitor combinations. In addition, the COLUMBUS trial did include a head-to-head comparison of encorafenib monotherapy at 300 mg daily and vemurafenib monotherapy and demonstrated improved PFS (hazard ratio, 0.68; 95% CI, 0.52 to 0.88) and OS (hazard ratio, 0.76; 95% CI, 0.58 to 0.98) for encorafenib relative to vemurafenib in patients with BRAF V600E– or BRAF V600K–mutated advanced melanoma. Thus, the data suggest that the differences between encorafenib and other BRAF inhibitors in terms of target binding may underlie the observed differences clinically, including efficacy in BRAF V600E–mutated CRC, which in terms of the ability to modulate the MAPK pathway is inherently less sensitive to BRAF inhibition than melanoma. The randomized portion of the BEACON CRC study is ongoing, and if results approximate those from the SLI, the

FIG 3. Kaplan-Meier plots of (A) progression-free survival (PFS; local assessment) and (B) overall survival (OS). NR, not reached.
combination of binimetinib, encorafenib, and cetuximab may become a new standard of care for patients with previously treated \textit{BRAF} V600E–mutated CRC. To maximize the potential for benefit to patients, results warrant additional investigation of this regimen in the first-line and potentially the adjuvant settings. A trial to investigate the regimen in the first-line setting (ANCHOR-CRC [Encorafenib, Binimetinib, and Cetuximab in Subjects With Previously Untreated \textit{BRAF}-Mutant Colorectal Cancer]; ClinicalTrials.gov identifier: NCT03693170) was recently initiated.

\textbf{REFERENCES}


\textbf{AFFILIATIONS}

1. University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium
2. Netherlands Cancer Institute, Amsterdam, the Netherlands
3. West Cancer Center, Germantown, TN
4. Memorial Sloan Kettering Cancer Center, New York, NY
5. Imelda General Hospital, Bonheiden, Belgium; University Hospitals Gasthuisberg, Leuven, Belgium
6. Vall d’Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain
7. City of Hope Comprehensive Cancer Center, Duarte, CA
8. Hospital del Mar–Institut d’Investigacions Mèdiques, Universitat Pompeu Fabra, Barcelona, Spain
9. Antwerp University Hospital, Edegem, Belgium
10. National Cancer Center Hospital East, Kashiwa, Japan
11. Hammersmith Hospital, Imperial College London, London, United Kingdom
12. Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
13. University of Campania ‘Luigi Vanvitelli,’’ Naples, Italy
15. Utrecht University, Utrecht, the Netherlands
16. The University of Texas MD Anderson Cancer Center, Houston, TX

\textbf{CORRESPONDING AUTHOR}

Scott Kopetz, MD, PhD, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 426, Houston, TX 77030; e-mail: skopetz@mdanderson.org.

\textbf{EQUAL CONTRIBUTION}

J.H.M.S., S.K., and J.T. contributed equally to article development and share senior authorship.

\textbf{PRIOR PRESENTATION}


\textbf{REFERENCES}


\textbf{AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT}

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.02459.

\textbf{AUTHOR CONTRIBUTIONS}

Conception and design: Eric Van Cutsem, Axel Grothey, Pieter-Jan Cuyle, Elena Elez, Harpreet Wasan, Fortunato Ciardiello, Ashwin Gollerkeri, Janna Christy-Bittel, Kati Maharry, Victor Sandor, Jan H.M. Schellens, Scott Kopetz, Josep Tabernero
Administrative support: Harpreet Wasan
Provision of study materials or patients: Eric Van Cutsem, Sanne Huijberts, Pieter-Jan Cuyle, Elena Elez, Harpreet Wasan, Fortunato Ciardiello, Ashwin Gollerkeri, Josep Tabernero
Collection and assembly of data: Eric Van Cutsem, Sanne Huijberts, Axel Grothey, Rona Yaeger, Pieter-Jan Cuyle, Elena Elez, Marwan Fakih, Marc Peeters, Ashwin Gollerkeri, Janna Christy-Bittel, Kati Maharry, Victor Sandor, Jan H.M. Schellens, Scott Kopetz, Josep Tabernero
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

\textbf{ACKNOWLEDGMENT}

We thank the patients, their families, and the sites that participated in this study. For editorial support, funded by Array BioPharma, we thank Philip Sjostedt from The Medicine Group LLC, a Division of Bespoke Communications.


46. Robert C, Karaszewska B, Schachter J, et al: Two year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. Eur J Cancer 51:S663, 2015 (abstr 3301)


ASCt University Essentials Subscription Package Is Now Available

The ASCO University Essentials subscription includes access to over 100 online courses covering all major tumor types including lung, breast, genitourinary, gastrointestinal, hematologic cancers, and more. ABIM MOC points and CME, nursing, and pharmacy credit available.

Stay up-to-date on your learning needs without having to purchase courses individually. Also included is ASCO University’s Personalized Learning Dashboard, a self-evaluation tool that helps you find content recommendations tailored to your knowledge gaps and media preferences.

Start your 2-week free trial today at university. asco.org/essentials
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E-Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rcw or ascopubs.org/jco/site/ifc.

Van Cutsem et al

Eric Van Cutsem
Consulting or Advisory Role: Bayer, Eli Lilly, Roche, Servier, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca
Research Funding: Amgen (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Eli Lilly (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Ipsen (Inst), Merck (Inst), Merck KGaA (Inst), Servier (Inst), Bristol-Myers Squibb (Inst)

Axel Grothey
Honoraria: Elsevier, Aptitude Health
Consulting or Advisory Role: Genentech (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Eli Lilly (Inst), Boston Biomedical (Inst), Amgen (Inst), Array BioPharma (Inst), Guardant Health (Inst), Daiichi Sankyo (Inst)
Research Funding: Genentech (Inst), Bayer (Inst), Pfizer (Inst), Eisai (Inst), Eli Lilly (Inst), Boston Biomedical (Inst), Daiichi Sankyo (Inst), Array BioPharma (Inst)
Travel, Accommodations, Expenses: Genentech, Bayer, Bristol-Myers Squibb, Boston Biomedical, Amgen, Boehringer Ingelheim, Merck Sharp & Dohme

Rona Yaeger
Research Funding: Array BioPharma, GlaxoSmithKline, Novartis
Travel, Accommodations, Expenses: Array BioPharma

Pieter-Jan Cuylen
Consulting or Advisory Role: Eli Lilly, Genentech, Amgen, Novartis, Merck, Genzyme, BMS

Elena Elez
Consulting or Advisory Role: Amgen, Roche, Merck Serono, Sanofi, Servier, Bayer
Research Funding: Merck Serono
Travel, Accommodations, Expenses: Roche, Merck Serono, Sanofi, Amgen

Marwan Fakhri
Consulting or Advisory Role: Amgen, Array BioPharma, Genentech
Speakers’ Bureau: Amgen, Taiho Pharmaceutical
Research Funding: Novartis (Inst), Amgen (Inst), AstraZeneca (Inst)

Clara Montagut
Consulting or Advisory Role: Amgen, Merck Serono, Sanofi, Guardant Health
Speakers’ Bureau: Sysmex
Research Funding: Symphogen

Marc Peeters
Honoraria: Amgen, Bayer, Celgene, Merck Serono, Roche, Sanofi, Servier, Sirtex Medical
Consulting or Advisory Role: Amgen, Bayer, IQVIA, Ipsen, Medac, Sanofi, Servier, Sirtex Medical, Terumo
Speakers’ Bureau: Amgen, Bayer, Celgene, Merck Serono, Roche, Sanofi, Servier, Sirtex Medical
Research Funding: Amgen, Bayer, Ipsen, Novartis, Roche

Takayuki Yoshino
Research Funding: Chugai Pharma (Inst), Sanofi (Inst), Sumitomo Dainippon (Inst), GlaxoSmithKline (Inst)

Harpreet Wasan
Honoraria: Merck KGaA, Celgene, Sirtex Medical, Servier, Array BioPharma, Shire, Genentech, ERYTECH Pharma
Consulting or Advisory Role: Roche Pharma AG, SITEX Medical, ERYTECH Pharma, Shire, Incyte
Speakers’ Bureau: Sirtex Medical, Celgene, Merck KGaA, Servier
Research Funding: Sirtex Medical (Inst), Merck KGaA (Inst), Pfizer (Inst), Merck Sharp & Dohme (Inst)

Jayesh Desai
Consulting or Advisory Role: Biomichem, Eli Lilly, Eisai, BeiGene, Ignyta (Inst)
Research Funding: Roche (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Biomichem (Inst), Medimmune (Inst), BeiGene (Inst), Eli Lilly (Inst), Bristol-Myers Squibb (Inst)

Fortunato Ciardiello
Consulting or Advisory Role: Genentech, Merck KGaA, Bayer, Amgen, Pfizer
Research Funding: Merck KGaA (Inst), Genentech (Inst), Servier (Inst), Symphogen (Inst), Amgen (Inst), Bayer (Inst), Merck Sharp & Dohme (Inst), Bristol-Myers Squibb (Inst), Ipsen (Inst)

Ashwin Gollerkeri
Employment: Array BioPharma, Alnylam (I), Bluebird Bio (I)
Stock and Other Ownership Interests: Array BioPharma, Alnylam (I)
Honorary: Bluebird Bio (I)
Patents, Royalties, Other Intellectual Property: Receives royalties from Yale University on an antibody used in nephrology basic research (I)

Janna Christy-Bittel
Employment: Array Biopharma
Stock and Other Ownership Interests: Array Biopharma, Gilead Sciences

Kati Maharry
Employment: Array Biopharma
Stock and Other Ownership Interests: Array Biopharma
Travel, Accommodations, Expenses: Array Biopharma

Victor Sandor
Employment: Array Biopharma
Leadership: Array Biopharma
Stock and Other Ownership Interests: Array Biopharma

Jan H.M. Schellens
Employment: Modra Pharmaceuticals
Stock and Other Ownership Interests: Modra Pharmaceuticals
Honorary: Debiopharm Group
Consulting or Advisory Role: Debiopharm Group
Research Funding: Dutch Cancer Society
Patents, Royalties, Other Intellectual Property: Patent on oral taxanes

Scott Kopetz
Stock and Other Ownership Interests: MolecularMatch, Navire
Consulting or Advisory Role: Roche, Genentech, EMD Serono, Merck, KaroPharm Therapeutics, Amal Therapeutics, Navire Pharma, Symphogen, Holy Stone, Biocartis, Amal Therapeutics, Amgen, Novartis, Eli Lilly, Boehringer Ingelheim
Research Funding: Amgen (Inst), Sanofi (Inst), Biocartis (Inst), Guardant Health (Inst), Array Biopharma (Inst), Genentech (Inst), EMD Serono (Inst), Medimmune (Inst), Novartis (Inst)

Josep Tabernero
Consulting or Advisory Role: Bayer, Boehringer Ingelheim, Eli Lilly, MSD, Merck Serono, Novartis, Sandofi, Taiho Pharmaceutical, Merrimack, Peptomic, Rafael Pharmaceuticals, Symphogen, Chugai Pharma, Ipsen, Merus, Pfizer, Seattle Genetics, Array BioPharma, AstraZeneca, BeiGene, Genentech, Genmab, Halozyme, Imugene Limited, Inflection Biosciences Limited, Kura, Menarini, Molecular Partners, Pharmacynics, ProteoDesign SL, Roche, Seattle Genetics, Servier, VCN Biosciences, Biocartis, Foundation Medicine, HaloDI SAS, Roche Diagnostics

No other potential conflicts of interest were reported.