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

Eric Van Cutsem, MD, PhD\textsuperscript{1}, Sanne Huijberts, MD, PhD\textsuperscript{2}, Axel Grothey, MD\textsuperscript{3}, Rona Yaeger, MD\textsuperscript{4}, Pieter-Jan Cuyle, MD\textsuperscript{1,5}, Elena Elez, MD, PhD\textsuperscript{6}, Marwan Fakih, MD\textsuperscript{7}, Clara Montagut, MD\textsuperscript{8}, Marc Peeters, MD, PhD\textsuperscript{9}, Takayuki Yoshino, MD\textsuperscript{10}, Harpreet Wasan, MD\textsuperscript{11}, Jayesh Desai, MBBS\textsuperscript{12}, Fortunato Ciardiello, MD, PhD\textsuperscript{13}, Ashwin Gollerkeri, MD\textsuperscript{14}, Janna Christy-Bittel, MSN\textsuperscript{14}, Kati Maharry, PhD\textsuperscript{14}, Victor Sandor, MD\textsuperscript{14}, Jan H.M. Schellens, MD, PhD\textsuperscript{15}, Scott Kopetz, MD, PhD\textsuperscript{16}, Josep Tabernero, MD, PhD\textsuperscript{6}  

\textsuperscript{1}University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium  \textsuperscript{2}Netherlands Cancer Institute, Amsterdam, the Netherlands  \textsuperscript{3}West Cancer Center, Germantown, TN  \textsuperscript{4}Memorial Sloan Kettering Cancer Center, New York, NY  \textsuperscript{5}Imelda General Hospital, Bonheiden, Belgium; University Hospitals Gasthuisberg, Leuven, Belgium  \textsuperscript{6}Vall d’Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain  \textsuperscript{7}City of Hope Comprehensive Cancer Center, Duarte, CA  \textsuperscript{8}Hospital del Mar–Institut Hospital del Mar d’Investigacions Mèdiques, Universitat Pompeu Fabra, Barcelona, Spain  \textsuperscript{9}Antwerp University Hospital, Edegem, Belgium  \textsuperscript{10}National Cancer Center Hospital East, Kashiwa, Japan  \textsuperscript{11}Hammersmith Hospital, Imperial

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License http://creativecommons.org/licenses/by-nc-nd/4.0/

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; skopetz@mdanderson.org. J.H.M.S., S.K., and J.T. contributed equally to article development and share senior authorship.

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, Elena Elez, Marwan Fakih, Clara Montagut, Marc Peeters, Ashwin Gollerkeri, Janna Christy-Bittel, Kati Maharry, Victor Sandor, Jan H.M. Schellens, Scott Kopetz, Josep Tabernero
Data analysis and interpretation: Eric Van Cutsem, Sanne Huijberts, Axel Grothey, Rona Yaeger, Pieter-Jan Cuyle, Elena Elez, Marwan Fakih, Marc Peeters, Takayuki Yoshino, Harpreet Wasan, Jayesh Desai, Fortunato Ciardiello, 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

PRIOR PRESENTATION
Presented in part at the 20th Annual Meeting of the European Society for Medical Oncology World Congress on Gastrointestinal Cancer, Barcelona, Spain, June 20-23, 2018, and the 2018 American Society for Clinical Oncology Gastrointestinal Cancers Symposium, San Francisco, CA, January 18-20, 2018.

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.

No other potential conflicts of interest were reported.
Abstract

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 BRAF V600E–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.

INTRODUCTION

BRAFV600E mutation is found in approximately 8% to 15% of patients with metastatic colorectal cancer (mCRC) and is a marker of poor prognosis. Because BRAFV600E and RAS mutations are nearly always mutually exclusive, patients with BRAFV600–mutant mCRC have typically been treated with standard-of-care regimens for RAS wild-type mCRC. Standard first-line therapy, even with intensified regimens, produces poorer results in patients with BRAFV600E–mutant mCRC than in patients with wild-type disease, and after standard first-line therapy, subsequent treatment provides limited benefits.
with reported overall response rates (ORRs) of less than 10%, median progression-free survival (PFS) times of approximately 2 months, and median overall survival (OS) times ranging from 4 to 6 months.\textsuperscript{2,13-19} Immunotherapies such as nivolumab and pembrolizumab are active in patients with microsatellite instability–high or mismatch repair–deficient solid tumors, including mCRC.\textsuperscript{20,21} Although the rate of mismatch repair deficiency is higher in \textit{BRAFV600E}–mutant CRC than in \textit{BRAF} wild-type disease, recent prospective data and a pooled analysis of four clinical trials indicated that less than 20% of patients with \textit{BRAF} V600E–mutant mCRC have microsatellite instability–high or mismatch repair–deficient tumors, thus limiting this option to a minority of patients.\textsuperscript{19,22-24}

Unlike in other tumor histologies with \textit{BRAF}V600 mutations such as melanoma and non–small-cell lung cancer, where BRAF inhibition is clinically highly active,\textsuperscript{25-30} BRAF inhibition in \textit{BRAF}V600E–mutant mCRC produced only marginal clinical activity.\textsuperscript{35,37-39} In vitro studies later demonstrated that in \textit{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 \textit{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 \textit{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{41,45,46} 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 \textit{BRAF}V600–mutant melanoma.\textsuperscript{48,49} Results from a recent phase II study in patients with \textit{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 \textit{BRAF}V600E–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 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, version 1.1. Tumor assessments were performed every 6 weeks for the first 24 weeks, then every 12 weeks until disease progression, withdrawal of consent, or initiation of subsequent anticancer therapy.
**Statistical Methods**

**Study population.**—All patients who received at least one dose of study drug were included in the safety analyses (N = 30). For efficacy analyses, all patients with a *BRAF* V600E mutation (confirmed by local assessment, central assessment, or both) who received at least one dose of study drug were included.

**End points.**—The primary end point of the SLI was the assessment of safety and tolerability, which included dose-limiting toxicities (DLTs; defined as any adverse event [AE] or abnormal laboratory values assessed as unrelated to disease, disease progression, intercurrent illness, or concomitant medications or therapies occurring within the first 28 days of treatment that met criteria that were established before the start of the study; Data Supplement); the incidence and severity of AEs and changes in clinical laboratory parameters, vital signs, ECGs, echocardiography or multigated acquisition scans, and ophthalmic examinations; and the incidence of dose interruptions, dose modifications, and discontinuations.

Efficacy end points included confirmed ORR (per RECIST version 1.1), duration of response (DOR), PFS (per RECIST version 1.1), time to response, and OS. Radiographic assessment of tumor response and progression was 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.

**Statistical analysis.**—Descriptive statistics were used to summarize pretreatment characteristics and to evaluate DLTs, frequency of AEs, and best overall response. PFS was defined as the time from first dose of study drug to the earliest documented date of disease progression, per RECIST version 1.1, or death from any cause. OS was defined as the time from first dose of study drug to death 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 acneiform (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 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 5.5 months (95% CI, 4.1 months to not reached [NR]); 85.7% of patients achieved a DOR of 3 months, 42.9% achieved a DOR of 6 months, and 25.7% achieved a DOR of 15 months. 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 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 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 (ClinicalTrials.gov identifier: NCT01909453) in patients with advanced BRAFV600K 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.\textsuperscript{36} 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.\textsuperscript{40,41}

The randomized portion of the BEACON CRC study is ongoing, and if results approximate those from the SLI, the combination of binimetinib, encorafenib, and cetuximab may become a new standard of care for patients with previously treated $BRAF^{V600E}$-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 $BRAF$-Mutant Colorectal Cancer]; ClinicalTrials.gov identifier: NCT03693170) was recently initiated.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**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.

**REFERENCES**

1. Davies H, Bignell GR, Cox C, et al.: Mutations of the BRAF gene in human cancer. Nature 417:949–954, 2002 [PubMed: 12068308]
2. Loupakis F, Ruzzo A, Creemolini C, et al.: $KRAS$ codon 61, 146 and $BRAF$ mutations predict resistance to cetuximab plus irinotecan in $KRAS$ codon 12 and 13 wild-type metastatic colorectal cancer. Br J Cancer 101:715–721, 2009 [PubMed: 19603018]
3. Tie J, Gibbs P, Lipton L, et al.: Optimizing targeted therapeutic development: Analysis of a colorectal cancer patient population with the $BRAF(V600E)$ mutation. Int J Cancer 128:2075–2084, 2011 [PubMed: 20635392]
4. Clarke CN, Kopetz ES: BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: Clinical characteristics, clinical behavior, and response to targeted therapies. J Gastrointest Oncol 6:660–667, 2015 [PubMed: 26697199]
5. De Roock W, Claes B, Bernasconi D, et al.: Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: A retrospective consortium analysis. Lancet Oncol 11:753–762, 2010 [PubMed: 20619739]
6. Van Cutsem E, Cervantes A, Adam R, et al.: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 27: 1386–1422, 2016 [PubMed: 27380959]
7. Falcone A, Ricci S, Brunetti I, et al.: Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and
irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. J Clin Oncol 25: 1670–1676, 2007 [PubMed: 17470860]

8. Souglakos J, Androulakis N, Syrigos K, et al.: FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): A multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer 94:798–805, 2006 [PubMed: 16508637]

9. Cremolini C, Loupakis F, Masi G, et al.: FOLFOXIRI or FOLFOXIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: A propensity score-adjusted analysis from two randomized clinical trials. Ann Oncol 27:843–849, 2016 [PubMed: 26861604]

10. Loupakis F, Cremolini C, Masi G, et al.: Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 371:1609–1618, 2014 [PubMed: 25337750]

11. Cremolini C, Loupakis F, Antoniotti C, et al.: FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: Updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 16:1306–1315, 2015 [PubMed: 26338525]

12. Ursem C, Atreya CE, Van Loon K: Emerging treatment options for BRAF-mutant colorectal cancer. Gastrointest Cancer 8:13–23, 2018 [PubMed: 29628780]

13. Ulivi P, Capelli L, Valgiusti M, et al.: Predictive role of multiple gene alterations in response to cetuximab in metastatic colorectal cancer: A single center study. J Transl Med 10:87, 2012 [PubMed: 22569004]

14. Saridaki Z, Tzardi M, Sfakianaki M, et al.: BRAFV600E mutation analysis in patients with metastatic colorectal cancer (mCRC) in daily clinical practice: Correlations with clinical characteristics, and its impact on patients’ outcome. PLoS One 8:e84604, 2013 [PubMed: 24367680]

15. Seymour MT, Brown SR, Middleton G, et al.: Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): A prospectively stratified randomised trial. Lancet Oncol 14:749–759, 2013 [PubMed: 23725851]

16. Morris V, Overman MJ, Jiang Z-Q, et al.: Progression-free survival remains poor over sequential lines of systemic therapy in patients with BRAF-mutated colorectal cancer. Clin Colorectal Cancer 13:164–171, 2014 [PubMed: 25069797]

17. Peeters M, Oliner KS, Price T, et al.: Updated analysis of KRAS/NRAS and BRAF mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC). J Clin Oncol 32, 2014 (suppl 5s; abstr 3568)

18. Mitani S, Taniguchi H, Honda K, et al.: Analysis of efficacy and prognostic factors in second-line chemotherapy for BRAF V600E mutant metastatic colorectal cancer. Ann Oncol 28, 2017 (abstr 532)

19. Kopetz S, McDonough SL, Lenz H-J, et al.: Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). J Clin Oncol 35, 2017 (suppl; abstr 3505)

20. Bristol-Myers Squibb: Opdivo USPI. https://packageinserts.bms.com/pi/pi_opdivo.pdf

21. Merck: Keytruda USPI. https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

22. Venderbosch S, Nagtegaal ID, Maughan TS, et al.:Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: A pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 20:5322–5330, 2014 [PubMed: 25139339]

23. Lochhead P, Kuchiba A, Imamura Y, et al.: Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. J Natl Cancer Inst 105: 1151–1156, 2013 [PubMed: 23878352]

24. Roma C, Rachighio AM, Pasquale R, et al.: BRAF V600E mutation in metastatic colorectal cancer: Methods of detection and correlation with clinical and pathologic features. Cancer Biol Ther 17:840–848, 2016 [PubMed: 27261210]

25. Flaherty KT, Puzanov I, Kim KB, et al.: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809–819, 2010 [PubMed: 20818844]

26. Flaherty KT, Infante JR, Daud A, et al.: Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 367:1694–1703, 2012 [PubMed: 23020132]
27. Boni A, Cogdill AP, Dang P, et al.: Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. Cancer Res 70:5213–5219, 2010 [PubMed: 20551059]

28. Wilmott JS, Long GV, Howle JR, et al.: Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res 18: 1386–1394, 2012 [PubMed: 22156613]

29. Dummer R, Ascierto PA, Gogas HJ, et al.: Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 19:1315–1327, 2018 [PubMed: 30219628]

30. Long GV, Stroyakovskiy D, Gogas H, et al.: Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. Lancet 386:444–451, 2015 [PubMed: 26037941]

31. Long GV, Hauschild A, Santinami M, et al.: Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 377:1813–1823, 2017 [PubMed: 28891408]

32. Chapman PB, Hauschild A, Robert C, et al.: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364:2507–2516, 2011 [PubMed: 21639808]

33. Chapman PB, Solit DB, Rosen N: Combination of RAF and MEK inhibition for the treatment of BRAF-mutated melanoma: Feedback is not encouraged. Cancer Cell 26:603–604, 2014 [PubMed: 25517746]

34. Planchard D, Besse B, Groen HJM, et al.: Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant non-small cell lung cancer: An open-label, multicentre phase 2 trial. Lancet Oncol 17:984–993, 2016 [PubMed: 27283860]

35. Hyman DM, Puzanov I, Subbiah V, et al.: Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 373:726–736, 2015 [PubMed: 26287849]

36. Loupakis F, Cremoni C, Salvatore L, et al.: FOLFOXIRI plus bevacizumab as first-line treatment in BRAF mutant metastatic colorectal cancer. Eur J Cancer 50: 57–63, 2014 [PubMed: 24138831]

37. Kopetz S, Desai J, Chan E, et al.: Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. J Clin Oncol 33:4032–4038, 2015 [PubMed: 26460303]

38. Seligmann JF, Fisher D, Smith CG, et al.: Investigating the poor outcomes of BRAF-mutant advanced colorectal cancer: Analysis from 2530 patients in randomised clinical trials. Ann Oncol 28:562–568, 2017 [PubMed: 27793800]

39. Prahallad A, Sun C, Huang S, et al.: Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature 483:100–103, 2012 [PubMed: 22281684]

40. Corcoran RB, Ebi H, Turke AB, et al.: EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. Cancer Discov 2:227–235, 2012 [PubMed: 22448344]

41. Hong DS, Morris VK, El Osta B, et al.: Phase IB study of vemurafenib in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with BRAFV600E mutation. Cancer Discov 6:1352–1365, 2016 [PubMed: 27729313]

42. Connolly K, Brungs D, Szeto E, et al.: Anticancer activity of combination targeted therapy using cetuximab plus vemurafenib for refractory BRAF (V600E)-mutant metastatic colorectal carcinoma. Curr Oncol 21:e151–e154, 2014 [PubMed: 24523613]

43. Corcoran RB, André T, Attrey CE, et al.: Combined BRAF, EGFR, and MEK inhibition in patients with BRAF(V600E)-mutant colorectal cancer. Cancer Discov 8: 428–443, 2018 [PubMed: 29431699]

44. Corcoran RB, Dias-Santagata D, Bergethon K, et al.: BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation. Sci Signal 3:ra84, 2010 [PubMed: 21098728]

45. Corcoran RB, Attrey CE, Falchook GS, et al.: Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAFV600-mutant colorectal cancer. J Clin Oncol 33:4023–4031, 2015 [PubMed: 26392102]

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)

47. Dummer R, Ascierto PA, Gogas H, et al.: Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. J Clin Oncol 36, 2018 (suppl 15; abstr 9504)

48. Array BioPharma: Braftovi USPI. http://www.arraybiopharma.com/documents/Braftovi_Prescribing_information.pdf

49. Array BioPharma: Mektovi USPI. http://www.arraybiopharma.com/documents/Mektovi_Prescribing_information.pdf

50. Van Cutsem E, Cuyle P, Huijberts S, et al.: BEACON CRC study safety lead-in: Assessment of the BRAF inhibitor encorafenib + MEK inhibitor binimetinib + anti-epidermal growth factor receptor antibody cetuximab for BRAF V600E metastatic colorectal cancer. Ann Oncol 29, 2018 (suppl 5; abstr mdy149.026)

51. Eli Lilly: Erbitux USPI. http://pi.lilly.com/us/erbitux-uspi.pdf

52. Umer-Bloch U, Umer M, Jaberg-Bentele N, et al.: MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: Long-term ophthalmic effects. Eur J Cancer 65:130–138, 2016 [PubMed: 27497344]

53. Delord JP, Robert C, Nyakas M, et al.: Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF-mutant melanoma. Clin Cancer Res 23:5339–5348, 2017 [PubMed: 28611198]
FIG 1.
Patient disposition. (*) One treated patient had a non-V600 BRAF mutation (BRAF G466V). (†) Includes two patients with changes in condition or development of an intercurrent illness. (‡) Dose interruption for more than 28 consecutive days. (§) As of the data cutoff date of September 2, 2018. AE, adverse event.
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.
FIG 3.
Kaplan-Meier plots of (A) progression-free survival (PFS; local assessment) and (B) overall survival (OS). NR, not reached.
### TABLE 1.
Baseline Patient and Tumor Characteristics (safety population)

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

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.
| Event                                      | No. of Patients (%) With Adverse Event of Any Grade (N = 30) |
|--------------------------------------------|------------------------------------------------------------|
| Total patients with any adverse event‡     | 30 (100.0)                                                 |
| Diarrhea                                   | 23 (76.7)                                                  |
| Dermatitis acneiform                       | 20 (66.7)                                                  |
| Fatigue                                    | 19 (63.3)                                                  |
| Nausea                                     | 19 (63.3)                                                  |
| Dry skin                                   | 15 (50.0)                                                  |
| Vomiting                                   | 15 (50.0)                                                  |
| Anemia                                     | 12 (40.0)                                                  |
| Decreased appetite                         | 12 (40.0)                                                  |
| Abdominal pain                             | 11 (36.7)                                                  |
| Blood creatine phosphokinase increased     | 11 (36.7)                                                  |
| Pyrexia                                    | 11 (36.7)                                                  |
| Dyspnea                                    | 10 (33.3)                                                  |
| Constipation                               | 9 (30.0)                                                   |
| Arthralgia                                 | 8 (26.7)                                                   |
| Blood creatinine increased                 | 8 (26.7)                                                   |
| Skin fissures                              | 8 (26.7)                                                   |
| Vision blurred                             | 8 (26.7)                                                   |
| AST increased                              | 6 (20.0)                                                   |
| Asthenia                                   | 6 (20.0)                                                   |
| Malaise                                    | 6 (20.0)                                                   |
| Myalgia                                    | 6 (20.0)                                                   |
| Palmar-plantar erythrodysesthesis syndrome  | 6 (20.0)                                                   |
| Rash maculopapular                         | 6 (20.0)                                                   |
| Back pain                                  | 5 (16.7)                                                   |
| Dizziness                                  | 5 (16.7)                                                   |
| Ejection fraction decreased                 | 5 (16.7)                                                   |
| Edema peripheral                           | 5 (16.7)                                                   |
| Peripheral sensory neuropathy              | 5 (16.7)                                                   |
| Rash                                       | 5 (16.7)                                                   |
| Rash pustular                              | 5 (16.7)                                                   |
| Urinary tract infection                    | 5 (16.7)                                                   |

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.
### TABLE 3.
Grade 3 or 4 Adverse Events, Regardless of Causality, Reported in Two or More Patients (safety population)

| Preferred Term | No. of patients (%) with grade 3 or 4 Event (N = 30) |
|----------------|-----------------------------------------------------|
| Total patients with any grade 3 or 4 adverse event† | 21 (70.0) |
| Fatigue        | 4 (13.3) |
| AST increased  | 3 (10.0) |
| Urinary tract infection | 3 (10.0) |
| Anemia         | 3 (10.0) |
| Blood creatine phosphokinase increased | 3 (10.0) |
| Decreased appetite | 2 (6.7) |
| Dyspnea        | 2 (6.7) |
| Nausea         | 2 (6.7) |
| Vomiting       | 2 (6.7) |
| ALT increased  | 2 (6.7) |
| Hypokalemia    | 2 (6.7) |
| Hypophosphatemia | 2 (6.7) |

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.
| Confirmed Best Overall Response | Local assessment \(^*\) | Central assessment |
|--------------------------------|--------------------------|-------------------|
|                                | ORR (CR + PR)            | ORR (CR + PR)     |
|                                | 14 (48)                  | 12 (41)           |
|                                | 95% CI (%)               | 95% CI (%)        |
|                                | 29 to 68                 | 24 to 61          |
| CR                             | 3 (10)                   | 2 (7)             |
| PR                             | 11 (38)                  | 10 (34)           |
| SD                             | 13 (45)                  | 13 (45)           |
| PD                             | 0                        | 0                 |
| Not evaluable for response     | 2 (7)                    | 4 (14)            |

NOTE. Data in tables represent No. (%) unless otherwise indicated.

Abbreviations: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

* Patients with BRAF V600E mutations.

\(^{†}\) Confirmed responses per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
Author/s:
Van Cutsem, E; Huijberts, S; Grothey, A; Yaeger, R; Cuyle, P-J; Elez, E; Fakih, M; Montagut, C; Peeters, M; Yoshino, T; Wasan, H; Desai, CJ; Ciardiello, F; Gollerkeri, A; Christy-Bittel, J; Maharry, K; Sandor, V; Schellens, JH; Kopetz, S; Taberner, J

Title:
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

Date:
2019-06-10

Citation:
Van Cutsem, E., Huijberts, S., Grothey, A., Yaeger, R., Cuyle, P. -J., Elez, E., Fakih, M., Montagut, C., Peeters, M., Yoshino, T., Wasan, H., Desai, C. J., Ciardiello, F., Gollerkeri, A., Christy-Bittel, J., Maharry, K., Sandor, V., Schellens, J. H., Kopetz, S. & Taberner, J. (2019). 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. JOURNAL OF CLINICAL ONCOLOGY, 37 (17), pp.1460--+. https://doi.org/10.1200/JCO.18.02459.

Persistent Link:
http://hdl.handle.net/11343/248281

File Description:
published version

License:
CC BY-NC-ND