original reports

ANCHOR CRC: Results From a Single-Arm, Phase II Study of Encorafenib Plus Binimetinib and Cetuximab in Previously Untreated *BRAF*^{V600E}-Mutant Metastatic Colorectal Cancer

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abstract

PURPOSE The positive BEACON colorectal cancer (CRC) safety lead-in, evaluating encorafenib + cetuximab + binimetinib in previously treated patients with *BRAF*^{V600E}-mutated metastatic CRC (mCRC), prompted the design of the phase II ANCHOR CRC study (ClinicalTrails.gov identifier: NCT03693170). ANCHOR CRC aimed to evaluate efficacy, safety, and quality of life with first-line encorafenib + binimetinib + cetuximab in *BRAF*^{V600E}-mutated mCRC.

METHODS In this multicenter, open-label, single-arm study, patients with *BRAF*^{V600E}-mutated mCRC received oral encorafenib 300 mg once daily and binimetinib 45 mg twice daily in 28-day cycles, plus intravenous cetuximab 400 mg/m^2 once on Day 1 of Cycle 1, then 250 mg/m^2 once weekly for the first seven cycles, and 500 mg/m^2 once on Days 1 and 15 from Cycle 8 onward. The primary end point was locally assessed confirmed objective response rate (cORR), and secondary end points included centrally assessed cORR, progression-free survival, overall survival (OS), quality of life, and safety and tolerability.

RESULTS Among 95 patients, the locally assessed cORR was 47.4% (95% CI, 37.0 to 57.9) with all partial responses. Since the lower limit of the 95% CI exceeded 30%, the primary end point was met. With a median follow-up duration of 20.1 months, the median progression-free survival on the basis of local assessments was 5.8 months and the median OS was 18.3 months. Treatment was well tolerated, with no unexpected toxicities. Using Patient Global Impression of Changes, substantial improvement in symptoms was consistently reported in ≥ 30% of patients from Cycle 3 to Cycle 10.

CONCLUSION The ANCHOR CRC study showed that the scientifically driven combination of encorafenib + binimetinib + cetuximab was active in the first-line setting of *BRAF*^{V600E}-mutated mCRC with a manageable safety profile. Further first-line evaluation is ongoing (ClinicalTrails.gov identifier: NCT04607421).

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The *BRAF*^{V600E} mutation is estimated to occur in 10%-15% of patients with metastatic colorectal cancer (mCRC) and confers a poor prognosis.[1-3] Previous studies with chemotherapy-based regimens have shown poor outcomes in these patients.[2,4-12] International guidelines recommend doublet or triplet chemotherapy with or without vascular endothelial growth factor inhibitors for patients with *RAS* wild-type/*BRAF*-mutated mCRC.[13-15] In patients with *BRAF*^{V600E}-mutated mCRC, the median overall survival (OS) reported with first-line fluorouracil, leucovorin, and irinotecan (FOLFIRI) or doublet chemotherapy with or without the epidermal growth factor receptor (EGFR) antibody cetuximab was 10-14 months, the median progression-free survival (PFS) was 6-8 months, and the objective response rate (ORR) was 15%-19%.[16]

A study comparing first-line treatment of *BRAF*^{V600E}-mutant mCRC with fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus the vascular endothelial growth factor inhibitor bevacizumab versus FOLFOXIRI + cetuximab showed no advantage of using cetuximab combined with triplet chemotherapy, reporting an ORR of 51.4% and a median PFS and OS of 8.3 and 16.8 months, respectively, in patients treated with FOLFOXIRI + bevacizumab.[17]

Clinical data indicate limited activity of single-agent BRAF inhibitors in *BRAF*^{V600E}-mutated CRC.[18] Preclinical studies suggest that BRAF inhibitor activity in

CONTEXT

Key Objective

This phase II, multicenter, open-label, single-arm study evaluated the feasibility of combination of the BRAF inhibitor encorafenib, the antiepidermal growth factor receptor monoclonal antibody cetuximab, and the mitogen-activated protein kinase inhibitor binimetinib as first-line treatment of patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer (mCRC).

Knowledge Generated

Triplet therapy with encorafenib + binimetinib + cetuximab was associated with disease control in the majority of patients and a manageable safety profile in patients with *BRAF*^{V600E}-mutant mCRC, suggesting that it may be an option for patients not eligible to receive standard first-line therapy.

Relevance *(A.H. Ko)*

BRAF inhibitor-based targeted combination therapy represents a viable alternative to consider as first-line therapy for those patients with *BRAF*^{V600E}-mutant mCRC who are ineligible to receive, or who decline, a standard chemotherapy-based regimen.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

CRC is attenuated because of feedback activation of EGFR, leading to continuous cell proliferation.[19,20] EGFR activation leads to reactivation of RAS and the generation of BRAF inhibitor–resistant dimers. EGFR-mediated extracellular-regulated kinase reactivation can be targeted by concurrently inhibiting EGFR and/or downstream extracellular regulated kinase signaling potentially through combination therapy with BRAF, mitogen-activated protein kinase (MEK), and EGFR inhibitors.[21-23]

The combination of the BRAF inhibitor encorafenib plus cetuximab (with or without the MEK inhibitor binimetinib) was investigated in the randomized phase III BEACON CRC study in previously treated patients with *BRAF*^{V600E}-mutated CRC.[24,25] Results of the safety lead-in showed an ORR of 48% among 29 patients with *BRAF*^{V600E}-mutated mCRC after treatment with the triplet regimen (encorafenib + binimetinib + cetuximab).[25] Moreover, the triplet regimen appeared to be well tolerated and the response rate appeared to be higher in patients who received fewer prior lines of therapy,[25] prompting the design of the phase II ANCHOR CRC study (encorAfenib, biNimetinib, and Cetuximab in patients witH previOusly untreated BRAF-mutant ColoRectal Cancer).

The ANCHOR CRC study was conducted to investigate the efficacy, safety, quality of life (QoL), and pharmacokinetics of encorafenib + binimetinib + cetuximab as first-line treatment of patients with *BRAF*^{V600E}-mutant mCRC. Here, we present the efficacy, tolerability, and QoL results of the study.

METHODS

Study Design

This multicenter, open-label, single-arm, phase II study (ClinicalTrials.gov identifier: NCT03693170) had a two-stage design, with inclusion of 40 patients in Stage 1[26] and 50 patients in Stage 2. Stage 2 enrollment was only initiated after ≥ 12 responses had been observed in 40 treated patients. The cutoff date of the primary analysis was June 29, 2020.[27] The cutoff date of the current efficacy analysis was April 12, 2021, and subsequently updated on August 10, 2022, for the OS analysis. The study Protocol (online only) was approved by local ethics committees and complied with all international regulations, including the Declaration of Helsinki. Safety information was regularly reviewed by an independent Data Safety Monitoring Committee. All patients provided written informed consent for participation in the study.

Patients

Eligible patients were adults (≥ 18 years) with histologically or cytologically confirmed CRC, evidence of metastatic disease, and presence of the *BRAF*^{V600E} mutation in tumor tissue, determined by local assay at any time before screening and confirmed by central laboratory. Patients also had measurable disease per Response Evaluation Criteria in Solid Tumors v1.1 and were eligible to receive cetuximab, according to the approved label, on the basis of *RAS* mutation status. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and adequate renal, hepatic, cardiac, bone marrow functions, and electrolyte levels.

Patients were excluded from the study if they had received prior systemic therapy for metastatic disease; prior treatment with any RAF or MEK inhibitor, cetuximab, or any other EGFR inhibitor; or had symptomatic brain metastases. Other eligibility criteria are listed in the Data Supplement (online only).

Study Treatment

All patients received 28-day cycles of oral encorafenib 300 mg once daily, oral binimetinib 45 mg twice daily, and intravenous cetuximab 400 mg/m^2 once on Day 1 of Cycle 1, then 250 mg/m^2 once every week for the first seven cycles,

and 500 mg/m^2 once on Days 1 and 15 from Cycle 8 onward. After the outbreak of the COVID-19 pandemic, an Urgent Safety Measure was implemented, whereby cetuximab infusions could be administered every 2 weeks at a dose of 500 mg/m^2 once regardless of the cycle number (ie, on Days 1 and 15 of each cycle). Treatment was continued until disease progression (PD), unacceptable toxicity, patient's decision, withdrawal of consent, initiation of subsequent anticancer therapy, or death.

Study End Points

The primary efficacy end point of the study was confirmed ORR (cORR) on the basis of local tumor assessments. Secondary efficacy end points included cORR on the basis of central tumor assessments; locally and centrally assessed duration of response (DOR) and time to response (TTR); and the locally assessed PFS, OS, QoL, and safety and tolerability. Secondary end point definitions are provided in the Data Supplement.

Outcome Measures

Patients were assessed every 6 weeks for the first 12 weeks, then every 8 weeks thereafter. cORR, DOR, TTR, and PFS were assessed using Response Evaluation Criteria in Solid Tumors v1.1. QoL was assessed from baseline to the end of the study using the 5-Level EuroQol 5-Dimension visual analog scale, the European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 global health status, and Patient Global Impression of Changes.

Adverse events (AEs) and serious AEs (SAEs) were evaluated throughout the study up to a 30-day safety follow-up visit and were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. The cutoff date for the safety analysis was June 29, 2020.

Statistical Analyses

The estimated sample size was based on a two-stage study design with nominal alpha and beta values of 2.5% and 20%, respectively. The null hypothesis of the true response rate being 30% (ie, the maximum unacceptable probability of response) was tested against a one-sided alternative. The null hypothesis was rejected if the lower limit of the 95% CI was $>$ 30% (ie, $\geq$ 37 confirmed responses in 90-92 treated patients). On the basis of 90 patients, this design yielded a one-sided type I error rate of 1.6% and a power of 80% when the true response rate was 45%.

The primary end point was analyzed using 95% CI for the full analysis set (FAS; ie, all patients who received $\geq$ 1 dose of study treatment) and for the efficacy analysis set (ES; ie, all included patients who received $\geq$ 1 dose of study treatment and who had a centrally confirmed *BRAF*^{V600E} mutation). Furthermore, a subgroup analysis of locally assessed cORR in the ES was undertaken in patient subgroups stratified by age ($<$ 65 or $\geq$ 65 years), sex (male or female), baseline C-reactive protein, carcinoembryonic antigen and cancer antigen 19-9 levels ($\leq$ upper limit of normal or $>$ upper limit of normal), primary tumor location (right or left colon), number of metastases (1, 2, or $>$ 2), and ECOG PS (0 or 1). A forest plot was used to display the cORR and Clopper-Pearson (exact) binomial 95% CI for each subgroup. Centrally assessed cORR was also analyzed in the FAS.

PFS (in both FAS and ES), OS (in FAS), and DOR and TTR (in FAS confirmed responders) were analyzed using the Kaplan-Meier method, with estimated medians and 95% CIs presented. Results of QoL questionnaires in the FAS were summarized descriptively. For the safety analyses, the maximum grade or severity of AEs was evaluated for each Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term in the FAS.

RESULTS

Study Population

Of 125 patients assessed for eligibility, 95 were treated at 68 sites in Austria, Belgium, France, Italy, Japan, the Netherlands, Spain, United Kingdom, and the United States. The reasons for study exclusion were eligibility criteria not met (n = 29) and experiencing an AE (small intestine obstruction) during the screening period (n = 1; Fig 1). Baseline patient demographics and clinical characteristics are shown in Table 1. The majority of patients were female (54%), were age $\geq$ 65 years (55%), and had transverse and right colon primary tumors (60%) and $\geq$ 2 metastatic sites (76%).

Efficacy

The study met its primary end point, with 44 confirmed responses in the ES (n = 92), corresponding to a locally

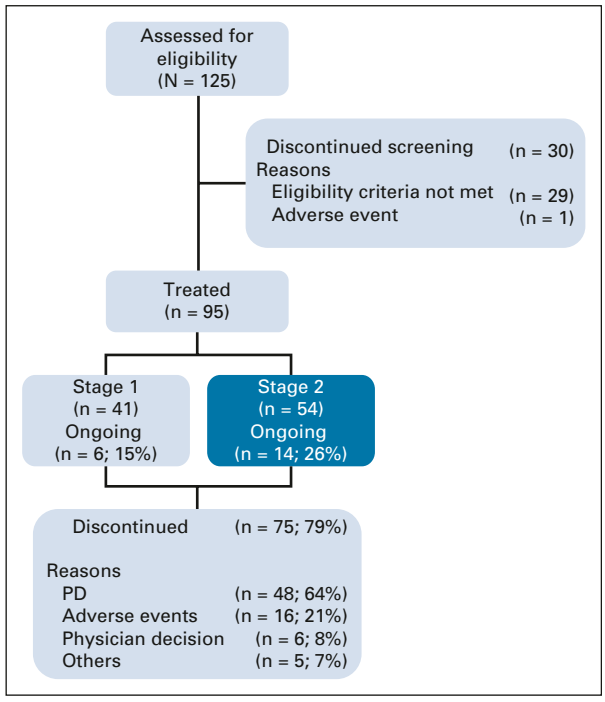

FIG 1. Flow diagram (data cutoff date: June 29, 2020). PD, progressive disease.

TABLE 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Encorafenib + Binimetinib + Cetuximab (n = 95)
Age, years, median (range)	65 (30-84)
Age group, years, No. (%)	
< 65	43 (45.3)
65-74	40 (42.1)
75	12 (12.6)
Sex, No. (%)	
Female	51 (53.7)
ECOG PS, No. (%)	
0	43 (45.3)
1	52 (54.7)
Time since initial diagnosis, days, median (range)	66 (19-3,235)
Location of primary tumor, No. (%)	
Right side (right colon/transverse)	57 (60.0)
Left side (including rectum)	37 (38.9)
BRAF^{V600E} mutation centrally confirmed, No. (%)	92 (96.8)
No. of organs affected by metastasis, No. (%)	
1	23 (24.2)
≥ 2	72 (75.8)
Metastatic site locations, No. (%)	
Liver	52 (54.7)
Liver only	7 (7.4)
Lymph node	49 (51.6)
Peritoneum/omentum	46 (48.4)
Lung	35 (36.8)
Prior systemic therapy setting, No. (%)	
Neoadjuvant	3 (3.2)
Adjuvant	17 (17.9)
Locally advanced	2 (2.1)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

assessed cORR of 47.8% (95% CI, 37.3 to 58.5), with the lower limit of the 95% CI for cORR exceeding the prespecified rate of > 30%. The locally assessed cORR in the FAS was 47.4% (45 of 95 patients; 95% CI, 37.0 to 57.9); all patients achieved partial response. In the ES and FAS, stable disease was achieved by 37 of 92 patients (40.2%) and 39 of 95 patients (41.1%), giving a disease control rate of 88.0% (81 of 92 patients) and 88.4% (84 of 95 patients), respectively. The centrally assessed cORR in the FAS was 46.3% (95% CI, 36.0 to 56.8), with complete response observed in three patients (3.2%) and partial response in 41 patients (43.2%). Discrepancies in complete response rates between the local investigator and central assessment appeared to be related to differences in classification of tertiary lymphoid structures. The cORR analysis, subgroup analysis, and a waterfall plot of the best percentage change from baseline in tumor measurements are summarized in the Data Supplement.

The median DOR was 5.1 months both by local (n = 45; 95% CI, 3.8 to 8.5) and central review (n = 44; 95% CI, 3.4 to 6.8). Also, the median TTR was 1.4 months both by local (95% CI, 1.4 to 1.5) and central review (95% CI, 1.3 to 1.4).

The median duration between first study treatment administration and the cutoff date was 20.1 months.

In the PFS analysis on the basis of local assessments in the FAS, there were 75 events in 95 evaluable patients (78.9%) and the estimated median PFS was 5.8 (95% CI, 4.6 to 6.6) months (Fig 2A). The PFS analysis in the ES is presented in the Data Supplement.

In the OS analysis from August 10, 2022, there were 73 events in 95 patients (77%) and the estimated median OS was 18.3 (95% CI, 14.1 to 21.1) months (Fig 2B). Estimated 12-, 18-, and 24-month OS rates were 65%, 50%, and 35%, respectively. The median time to subsequent therapy or death was 6.9 (95% CI, 5.5 to 8.3) months. Fifty-seven (60%) patients received ≥ 1 other antineoplastic therapy after progression. The most common subsequent therapies included FOLFOX with or without bevacizumab or cetuximab (n = 29), FOLFOXIRI with or without bevacizumab (n = 16), FOLFIRI with or without bevacizumab or aflibercept (n = 15), and immunotherapy (n = 5; Data Supplement). Four patients stopped the study because of PD but continued to receive encorafenib + cetuximab with or without binimetinib off-study at the investigator's suggestion. Of note, one patient discontinued for curative surgery (transverse complete resection) completed with 6-month FOLFOX; at the cutoff date (10 months later), the patient was alive.

QoL

Study treatment was not associated with any significant changes in 5-Level EuroQol 5-Dimension or European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 scores (Fig 3). Using Patient Global Impression of Changes, substantial improvements in symptoms (ie, much improved or very much improved) were consistently reported by ≥ 30.4% of patients in the FAS between Cycle 3 Day 1 and Cycle 10 Day 1 (range, 30.4%-52.0%). No patients reported a clear worsening in symptoms (ie, much worse or very much worse) up to Cycle 22 Day 1. At later time points (from Cycle 17 Day 1 onward), the low number of patients who completed the questionnaire (≤ 10) hindered meaningful data interpretation.

Safety and Tolerability

The median (range) duration of exposure was 4.96 (0.09-15.40) months for encorafenib, 4.67 (0.07-14.95) months for binimetinib, and 4.96 (0.23-15.15) months for cetuximab. Median (range) relative dose intensities were 95.4%

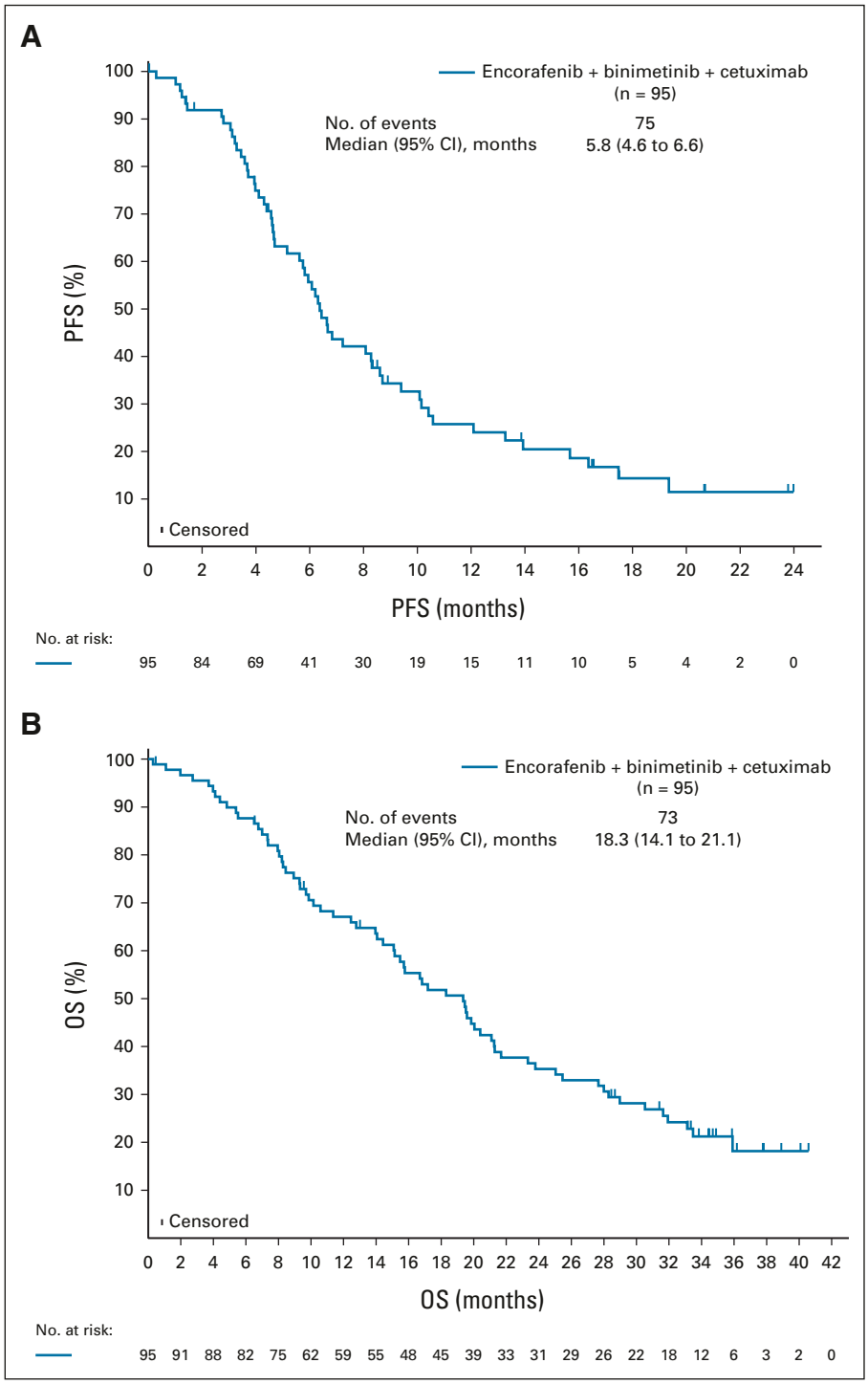

FIG 2. Kaplan-Meier plots of (A) PFS and (B) OS in the full analysis set (n = 95). FAS, full analysis set; OS, overall survival; PFS, progression-free survival.

(31%-100%) for encorafenib, 93.3% (3%-100%) for binimetinib, and 93.8% (5%-109%) for cetuximab.

AEs were reported in 99% of patients, with 52% experiencing SAEs (Table 2). Three patients experienced AEs leading to death, including intestinal obstruction not related to treatment, and acute renal failure and pneumonitis suspected to be treatment-related. The acute renal failure was of functional origin in the context of diarrhea for the previous 2 weeks. The most commonly reported all-grade AEs (Table 3) were diarrhea (67%), nausea (45%), dermatitis acneiform (40%), and rash (40%); Grade ≥ 3 AEs were anemia (11%), asymptomatic lipase increase (11%), diarrhea (10%), and nausea (8%).

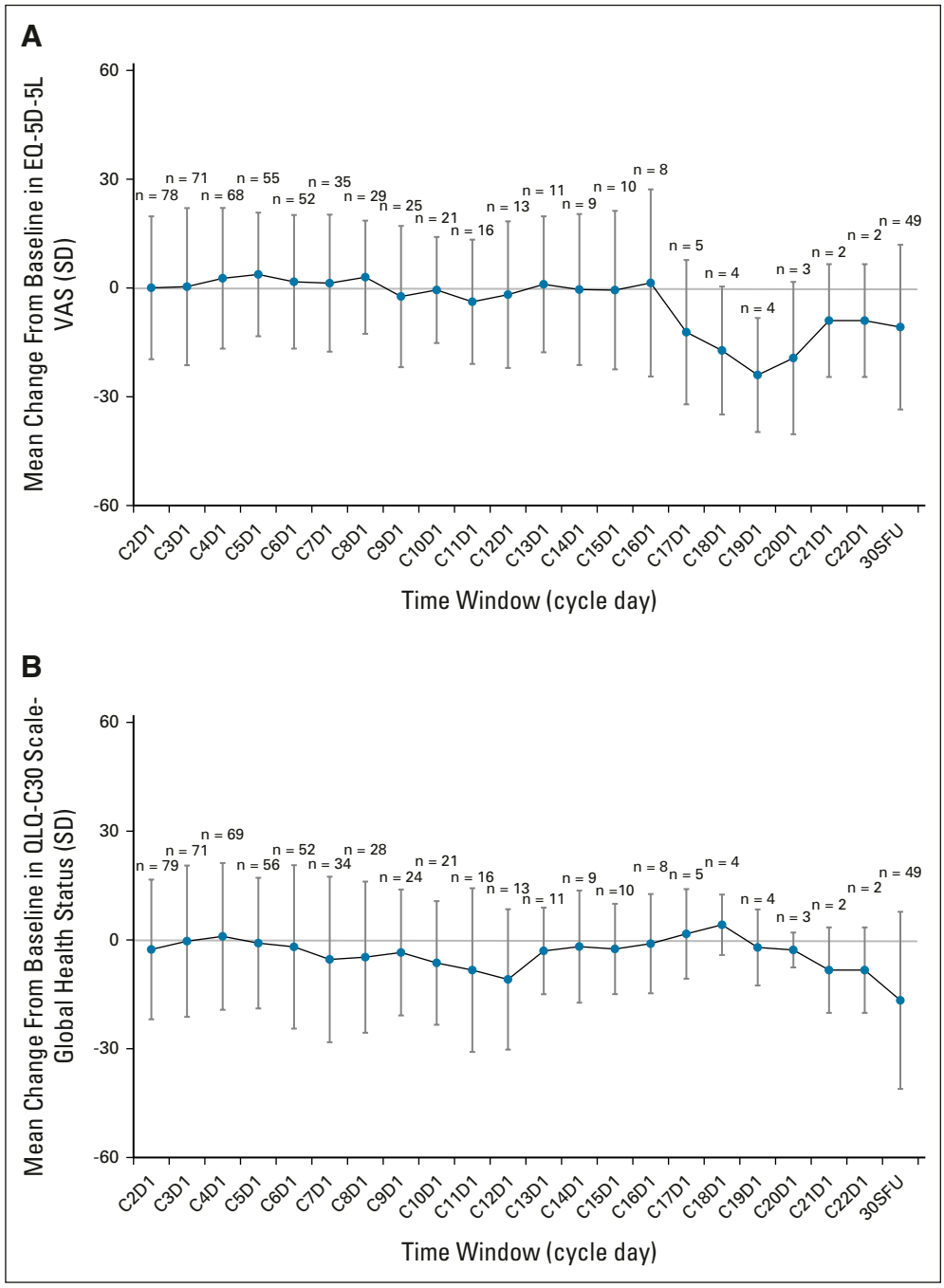

FIG 3. Mean ± SD change from baseline in (A) EQ-5D-5L VAS scores and (B) European Organization for Research and Treatment of Cancer QLQ-C30 global health status scores in the full analysis set (n = 95). C, cycle; D, day; EQ-5D-5L, 5-Level EuroQol 5-Dimension; FAS, full analysis set; QLQ-C30, Quality of Life Questionnaire Core 30; SD, standard deviation; SFU, standard follow-up; VAS, visual analog scale.

The most frequent all-grade SAEs were intestinal obstruction (17%), renal failure (8%), nausea (5%), and abdominal pain, diarrhea, and vomiting (each 4%). The most frequent Grade ≥ 3 SAEs were intestinal obstruction (15%), renal failure (7%), nausea (5%), and abdominal pain (4%; Table 3). Among 16 patients with intestinal obstruction, the obstruction site was the large intestine in six, small intestine in four, and not otherwise specified in six. Of eight patients with renal failure, six had acute renal failure and two had renal failure (not otherwise specified).

DISCUSSION

To our knowledge, ANCHOR CRC is the largest prospective study using BRAF inhibitor–based therapy, without chemotherapy, in the first-line treatment of patients with *BRAF*^{V600E}-mutant mCRC. The study met its primary end

TABLE 2. Safety Summary (Any-Grade AEs)

AE	Encorafenib + Binimetinib + Cetuximab (n = 95), No. (%)
Any AE	94 (98.9)
Any SAE	49 (51.6)
Any AE leading to dose interruption/reduction of ≥ 1 study drug	71 (74.7)
Any AE leading to discontinuation of ≥ 1 study drug	23 (24.2)
Any AE leading to death	3 (3.2)[a]

NOTE. The cutoff date for the safety analysis was June 29, 2020.
Abbreviations: AE, adverse event; SAE, serious adverse event.
[a]AEs leading to death were intestinal obstruction (not related to treatment), acute renal failure (suspected to be treatment-related), and pneumonitis (suspected to be treatment-related).

TABLE 3. Most Frequent AEs (> 10%) and SAEs (> 2%), Regardless of Study Treatment

By MedDRA Preferred Term	Encorafenib + Binimetinib + Cetuximab (n = 95)	
	All Grades	Grade ≥ 3
AEs, No. (%)		
Diarrhea	64 (67.4)	9 (9.5)
Nausea	43 (45.3)	8 (8.4)
Dermatitis acneiform	38 (40.0)	3 (3.2)
Rash	38 (40.0)	1 (1.1)
Vomiting	36 (37.9)	3 (3.2)
Abdominal pain	31 (32.6)	4 (4.2)
Dry skin	30 (31.6)	1 (1.1)
Asthenia	30 (31.6)	2 (2.1)
Constipation	25 (26.3)	0
Anemia	25 (26.3)	10 (10.5)
Decreased appetite	22 (23.2)	3 (3.2)
Fatigue	18 (18.9)	0
Dyspnea	15 (15.8)	0
Pyrexia	14 (14.7)	1 (1.1)
Vision blurred	13 (13.7)	0
Pruritus	12 (12.6)	0
Lipase elevated[a]	12 (12.6)	10 (10.5)
Dysgeusia	12 (12.6)	0
Skin fissures	11 (11.6)	0
Paronychia	11 (11.6)	0
Amylase elevated[b]	10 (10.5)	4 (4.2)
Headache	10 (10.5)	0
Back pain	10 (10.5)	1 (1.1)
SAEs, No. (%)		
Intestinal obstruction[b]	16 (16.8)	14 (14.7)
Renal failure	8 (8.4)	7 (7.4)
Nausea	5 (5.3)	5 (5.3)
Abdominal pain	4 (4.2)	4 (4.2)
Diarrhea	4 (4.2)	3 (3.2)
Vomiting	4 (4.2)	2 (2.1)
Pyrexia	2 (2.1)	1 (1.1)
Anemia	2 (2.1)	1 (1.1)

NOTE. The cutoff date for the safety analysis was June 29, 2020.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.
[a]Asymptomatic.
[b]Reported as large intestinal obstruction (n = 6; 6.3%), small intestinal obstruction (n = 4; 4.2%), subileus obstruction (n = 1; 1.1%), and intestinal obstruction not otherwise specified (n = 5; 5.3%).

point, with a cORR of 47.4%. The triplet combination of encorafenib + binimetinib + cetuximab was associated with a median PFS of 5.8 months and a median OS of 18.3 months and was well tolerated with a manageable tolerability profile and no unexpected toxicities. The most frequent AEs were comparable with those observed with the same triplet combination in the BEACON CRC study,[24] with the exception of intestinal obstruction and renal failure being more frequently reported as SAEs in our study (17% and 8%, respectively). Intestinal obstruction appeared to be related to underlying disease and/or disease progression, rather than study treatment, and higher frequency may reflect more aggressive disease in a first-line study population. Renal failure events were primarily prerenal acute kidney injury; acute tubular necrosis and nephrolithiasis were noted in two patients.

Although cross-study comparisons have limited validity, overall, these results compare well with those of standard first-line chemotherapy-based regimens in *BRAF*^{V600E}-mutated mCRC.[4,8,17,28] In a pooled analysis of the CRYSTAL (FOLFIRI with or without cetuximab) and OPUS (FOLFOX-4 with or without cetuximab) studies, patients with *BRAF*^{V600E}-mutated mCRC (n = 70) had an ORR of 21.9% with first-line chemotherapy + cetuximab versus 13.2% with chemotherapy alone and a median OS of 14.1 versus 9.9 months, respectively.[4] A meta-analysis of 10 RCTs with *BRAF* and *KRAS* status data in the ARCAD database suggests that chemotherapy + anti-EGFR therapy is ineffective as first-line treatment for patients with *BRAF*-mutated mCRC.[29] In the TRIBE study of first-line FOLFIRI or FOLFOXIRI + bevacizumab, patients with *BRAF*-mutated mCRC had a median OS of 10.7 and 19.0 months, respectively, and a median PFS of 5.5 and 7.5 months, respectively.[8] In the FIRE-4.5 study, patients with *BRAF*^{V600E}-mutated mCRC had an ORR of 51.4% with first-line FOLFOXIRI + bevacizumab and 40.3% with FOLFOXIRI + cetuximab, with a median PFS of 8.3 and 5.9 months, respectively (log-rank $P = .03$).[17] However, of note, the patient population in the current study was older (median age of 65 years and 13% were age ≥ 75 years) and had advanced disease at diagnosis (55% of patients had an ECOG PS of 1, 76% had ≥ 2 metastatic sites, 48% had

peritoneal metastasis, and 54.7% had synchronous metastatic disease). By contrast, in the pooled analysis of CRYSTAL and OPUS, only 34%-44% of patients were age ≥ 65 years and only 19%-32% of patients had > 2 metastatic sites.[4] In the TRIBE, the median age was 60 years and 12%-13% of patients had an ECOG PS of 1-2.[8]

A possible reason for the prolonged OS relative to PFS observed in the current study is the preserved effectiveness of poststudy treatments. Targeted therapy provides an important treatment option that was not accessible for patients in older studies. In line with this, two thirds of patients in our study (67%) went on to receive second-line therapy, a larger proportion than that suggested by patient-level data from three large randomized studies (FOCUS, COIN, and PICCOLO), where 33% of patients with *BRAF*-mutated CRC received second-line therapy.[30]

These results of ANCHOR CRC are also consistent with those of the triplet regimen (encorafenib + binimetinib + cetuximab) as second- and third-line treatment in the BEACON CRC study.[24] In the overall population, the ORR was 26.8% (95% CI, 21 to 33.1), the median PFS was 4.5 months (95% CI, 4.2 to 5.4), and the median OS was 9.3 months (95% CI, 8.2 to 10.8). Of note, in patients with only one prior line of treatment who received triple therapy (n = 146), the ORR was 28% (95% CI, 21 to 36). In ANCHOR CRC, a higher ORR and a prolonged OS were observed. The PFS may be explained by several differences in the baseline characteristics between these two studies, with more patients having an ECOG PS of 1 and peritoneal metastases being enrolled in the ANCHOR CRC. Further research to explore the role of the triplet regimen is warranted.

A limitation of the current study is that it was a nonrandomized study with ORR as the primary objective, thus lacking comparator arms including standard-of-care therapy (chemotherapy + bevacizumab). Other limitations are the unknown number of patients with tumor microsatellite instability-high/deficient mismatch repair cancers and the possible impact on OS of immuno-oncology treatment received.

In conclusion, the ANCHOR CRC study met its primary end point, with a response rate of 47.4% and a median PFS of 5.8 months. A median OS of 18.3 months in patients receiving first-line encorafenib + binimetinib + cetuximab is among the longest survival observed in a population of *BRAF*-mutant patients. These results highlight the benefit of the triplet regimen in previously untreated patients with $BRAF^{V600E}$-mutated mCRC, suggesting that it may be an option for patients not eligible to receive standard first-line therapy. Additional development in first line, assessing the combination of multiple types of molecules, is ongoing.

BREAKWATER (ClinicalTrails.gov identifier: NCT04607421), an open-label, multicenter, randomized phase III study, will further evaluate the efficacy and tolerability of first-line encorafenib + cetuximab with or without chemotherapy (FOLFOX) versus standard-of-care therapy in 705 patients with $BRAF^{V600E}$-mutant mCRC, nonmicrosatellite instability-high, or deficient mismatch repair. The study is currently recruiting, and primary results are expected by the end of 2024.

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DISCLAIMER

The authors hereby confirm that all work presented in this manuscript is original research.

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