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Original Article

Cetuximab and Irinotecan With or Without Bevacizumab in Refractory Metastatic Colorectal Cancer: BOND-3, an ACCRU Network Randomized Clinical Trial

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Abstract

Background: Combination irinotecan and cetuximab is approved for irinotecan-refractory metastatic colorectal cancer (mCRC). It is unknown if adding bevacizumab improves outcomes.

Patients and Methods: In this multicenter, randomized, double-blind, placebo-controlled phase II trial, patients with irinotecan-refractory *RAS*-wildtype mCRC and no prior anti-EGFR therapy were randomized to cetuximab 500 mg/m^2, bevacizumab 5 mg/kg, and irinotecan 180 mg/m^2 (or previously tolerated dose) (CBI) versus cetuximab, irinotecan, and placebo (CI) every 2 weeks until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), and adverse events (AEs).

Results: The study closed early after the accrual of 36 out of a planned 120 patients due to changes in funding. Nineteen patients were randomized to CBI and 17 to CI. Baseline characteristics were similar between arms. Median PFS was 9.7 versus 5.5 months for CBI and CI, respectively (1-sided log-rank $P = .38$; adjusted hazard ratio [HR] = 0.64; 95% confidence interval [CI], 0.25-1.66). Median OS was 19.7 versus 10.2 months for CBI and CI (1-sided log-rank $P = .02$; adjusted HR = 0.41; 95% CI, 0.15-1.09). ORR was 36.8% for CBI versus 11.8% for CI ($P = .13$). Grade 3 or higher AEs occurred in 47% of patients receiving CBI versus 35% for CI ($P = .46$).

Conclusion: In this prematurely discontinued trial, there was no significant difference in the primary endpoint of PFS between CBI and CI. There was a statistically significant improvement in OS in favor of CBI compared with CI. Further investigation of CBI for the treatment of irinotecan-refractory mCRC is warranted.

Clinical Trial Registration: NCT02292758

Key words: colorectal neoplasm; cetuximab; bevacizumab; irinotecan.

Implications for Practice

The BOND-3 trial studies dual-antibody therapy with anti-VEGF and anti-EGFR agents in irinotecan-refractory metastatic colorectal cancer (mCRC). Data from the BOND-1 and BOND-2 trials suggest efficacy and safety of dual-antibody therapy in refractory mCRC. Although these therapies together have been ineffective in first-line treatment of mCRC, BOND-3 showed that this combination may have efficacy without significant additional toxicity, perhaps because irinotecan-refractory mCRC may represent a distinct therapeutic setting. Dual-antibody therapy in irinotecan-refractory CRC merits additional study given the need for effective treatment strategies in this population.

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Introduction

Colorectal cancer (CRC) remains the second most common cause of cancer death in the US, and the 5-year relative survival rate of metastatic CRC (mCRC) is low at about 14%.[1] The mainstay of first-line treatment of mCRC is fluoropyrimidine-based chemotherapy with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), plus the addition of either bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), or an anti-epidermal growth factor receptor (EGFR) antibody if the tumor is located in the left colon or rectum and *RAS* wild type.[2-4] However, after progression on these therapies, treatment options for mCRC are limited. The combination of irinotecan, a topoisomerase I inhibitor, and cetuximab, a monoclonal antibody against EGFR, has shown benefit in irinotecan-refractory mCRC compared to cetuximab alone as reported in the BOND-1 study.[5] Combination irinotecan, cetuximab, and bevacizumab were also studied in this population in the BOND-2 trial and demonstrated efficacy compared to cetuximab and bevacizumab.[6] Previous data show that dual-antibody therapy in combination with chemotherapy is ineffective in the first-line treatment of mCRC.[7,8] However, data from BOND-1 and BOND-2 suggest possible efficacy and tolerability of this combination in refractory disease.[5-8] We investigated the efficacy and safety of irinotecan and cetuximab with or without bevacizumab in irinotecan-refractory mCRC in the BOND-3 trial.

Patients and Methods

The BOND-3 trial was a multi-center, double-blind, placebo-controlled randomized phase II clinical trial. This study was approved by local institutional review boards at each registering institution. Participants were enrolled at 7 centers in the US from July 2015 until the trial closed early in January 2018 due to slow accrual and withdrawal of industry funding.

The primary endpoint was progression-free survival (PFS), defined as the time from randomization to first disease progression (per RECIST 1.1) or death from any cause. Secondary endpoints included: overall survival (OS), defined as the time from randomization to death from any cause; objective response rate (ORR), defined as achieving a complete or partial response (per RECIST 1.1); and adverse events, reported using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[9,10] Patients were evaluated before treatment initiation and every 8 weeks.

Eligibility criteria included were the following: metastatic or locally advanced (unresectable) *RAS*-wildtype CRC (patients were excluded for mutations in exons 2,3, or 4 of KRAS and/or NRAS), failure of at least one fluoropyrimidine- and irinotecan-containing chemotherapy regimen, and receipt of bevacizumab in at least one prior line of therapy for mCRC. Patients were excluded if they received prior anti-EGFR therapy.

Patients were randomized 1:1, stratified by a number of prior lines of therapy for metastatic disease (1 vs ≥2) and bevacizumab receipt in immediate prior line of therapy (yes vs no), to receive cetuximab (500 mg/m^2), bevacizumab (5 mg/kg), and irinotecan (180 mg/m^2 or previously tolerated dose) (CBI) versus cetuximab, irinotecan, and placebo (CI) every 2 weeks until disease progression, intolerable toxicity, or withdrawal of consent. Randomization was performed using the Pocock and Simon dynamic allocation procedure.[11]

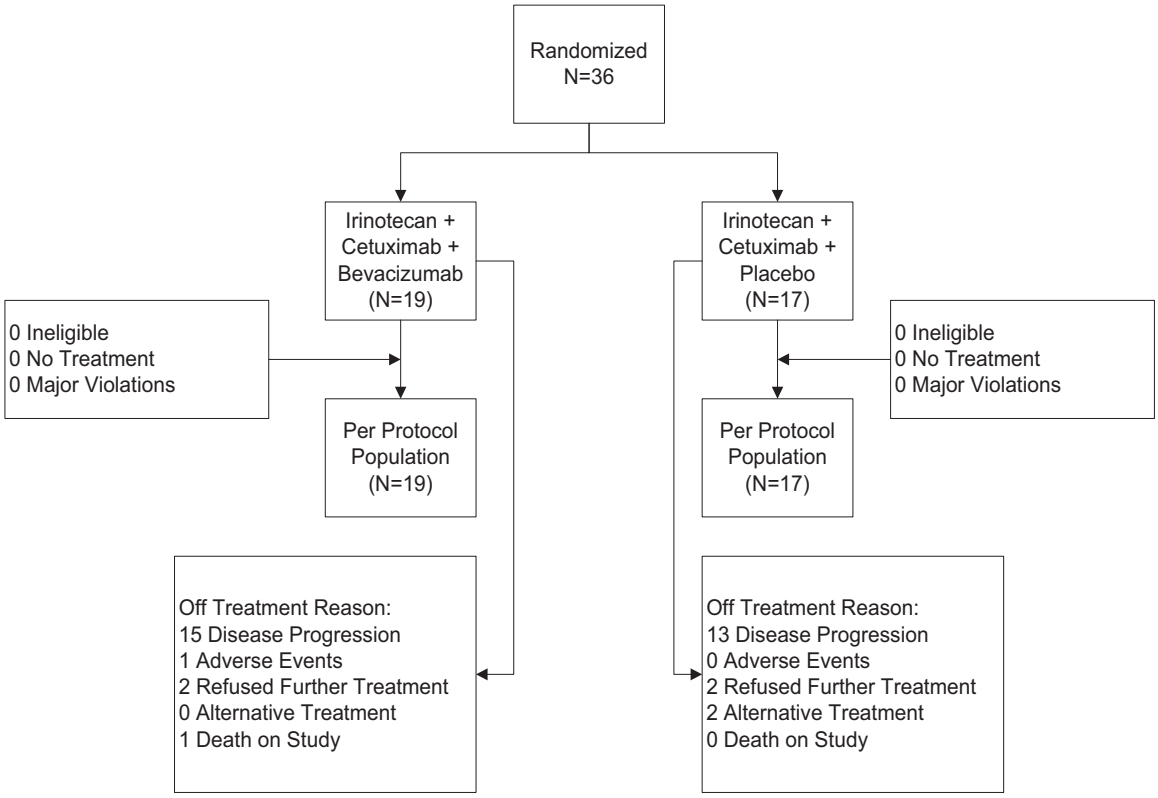
The original protocol, effective December 2014, required 92 PFS events from a planned sample size of 120 patients, which provided 80% power to detect a hazard ratio (HR) of 0.64 for PFS with a 1-sided log-rank test at a significance level of 0.1. In May 2017, due to slow accrual, the trial was amended to reduce sample size to 60 patients (55 PFS events), which provided 80% power to detect an HR of 0.562 with a 1-sided log-rank test[12] at a significance level of 0.1 (Trial protocol is available in the Supplementary Material). All log-rank tests performed and corresponding *P*-values reported were 1-sided at a significance level of .1.

The primary analysis was performed in the intent-to-treat population. Median PFS and OS were estimated using the Kaplan-Meier method.[13] Hazard ratios for PFS and OS were estimated using multivariable Cox proportional hazard models stratified by the stratification factors used for randomization.[14] Models were adjusted a priori for age, gender, race (white vs others), number of metastatic sites (1 vs 2 vs 3+), performance status (0 vs 1), and primary tumor site (colon vs rectum/rectosigmoid vs multiple). Baseline characteristics were compared using Wilcoxon rank-sum and chi-square tests.[15,16] Relative dose intensity, defined as the total dose of protocol therapy received (sum of total dose received at each cycle) divided by the total planned dose (the sum of planned doses at each cycle) was compared using the Wilcoxon rank-sum test. ORR was compared between treatment arms using Fisher's exact test.[17] Rates of adverse events (AEs) were compared using the chi-square test.

Results

Between July 2015 and December 2017, 36 patients were enrolled and randomized to receive CBI (n = 19) or CI (n = 17) (Fig. 1). Median follow-up at the time of data freeze (March 20, 2019) for those still alive (N = 9) was 2.96 years (95% confidence interval [CI]: 1.43, 2.96). Baseline characteristics were similar between arms (Table 1). Twenty-eight patients (78%) had 2 or more metastatic sites. Thirty-four patients (94%) were treated with 2 or more prior chemotherapy regimens. All patients had received prior bevacizumab with 34 (94%) patients receiving bevacizumab in the immediate prior treatment regimen. There were no significant differences in relative dose intensity (RDI) received between arms. For cetuximab, the median RDI was 98.5% in the CBI arm versus 95.5% in the CI arm (P = .43). The median RDI for bevacizumab/placebo was 96% versus 94% in the CBI versus CI arm, respectively (P = .43), and the median RDI for irinotecan was 89% in the CBI arm versus 90% in the CI arm (P = .53). Eleven patients (57.9%) in the CBI arm received full-dose irinotecan (180 mg/m^2) throughout the treatment course, similar to the CI arm, in which 10 patients (58.8%) received full dose irinotecan throughout (P = .95). There was no significant difference in primary tumor location (eg, colon vs rectum/rectosigmoid vs multiple) in patients on the CBI arm versus the CI arm (P = .62).

The median PFS was 9.7 months for the CBI arm versus 5.5 months for the CI arm (1-sided log-rank P = .38; Fig. 2). After multivariable adjustment, HR for PFS was 0.64 (95% CI, 0.25-1.66; P = .36). The median OS was 19.7 months versus 10.2 months for CBI and CI, respectively (1-sided log-rank P = .02) with multivariable HR for OS of 0.41 (95% CI,



Patient flow through BOND-3 trial of cetuximab and irinotecan with or without bevacizumab.

Figure 1. CONSORT Diagram: Patient flow through BOND-3 trial of cetuximab and irinotecan with or without bevacizumab.

0.15-1.09; P = .07). The ORR was 36.8% in the CBI group compared with 11.8% in the CI group (P = .13).

There were no significant differences in the frequency of grade 1 and 2 AEs between arms. The most common grade 1 and 2 AEs in patients treated with CBI versus CI were the following: acneiform rash (84.2% vs 88.2%), hypertension (78.9% vs 70.6%), maculopapular rash (73.7% vs 88.2%), diarrhea (68.4% vs 58.8%), hypomagnesemia (68.4% vs 70.6%), decreased neutrophil count (36.8% vs 41.2%), and decreased platelet count (26.3% vs 23.5%). Grade 3 or higher AEs occurred in 47% of patients receiving CBI versus 35% for CI (P = .46; Table 2). This includes 1 grade 5 AE, on-study death, in the CBI arm, due to disease progression unrelated to protocol treatment. The most common grade 3 and 4 AEs in patients on CBI versus CI were the following: diarrhea (10.5% vs 11.8%), hypertension (10.5% vs 5.9%), decreased neutrophil count (10.5% vs 0%), hypomagnesemia (10.5% vs 0%), dehydration (10.5% vs 0%), and acute kidney injury (10.5% vs 0%). There were no reported thrombotic or bleeding events in either arm. One patient receiving CBI came off treatment due to an AE (grade 3 acneiform rash).

Discussion

This prematurely discontinued trial showed no significant difference in the primary endpoint of PFS for treatment with CBI compared to CI in irinotecan-refractory mCRC. However, despite not meeting accrual goals, this trial demonstrated significant improvement in OS, one of the secondary endpoints, for patients treated with CBI. The promising results seen even within a small sample size suggest a potential benefit of treatment with CBI in patients with irinotecan- and bevacizumab-refractory mCRC.

While the BOND-2 trial studied CBI in irinotecan-refractory CRC, the comparison arm was treatment with cetuximab and bevacizumab without irinotecan. The response rate (RR) and time to progression (TTP) seen with CBI in BOND-2 (37% and 7.9 months, respectively) were higher than with CI in the BOND-1 trial (RR 23% and TTP 4 months), in which CI was compared to cetuximab alone. While these data, albeit obtained before RAS selection, suggested the possible benefit of CBI over CI, the 2 regimens had not been directly compared, and therefore BOND-3 was designed. Our data support the potential efficacy of CBI compared with CI in irinotecan-refractory mCRC. Moreover, our findings are consistent with results from the TML trial, which showed a survival benefit with the continuation of bevacizumab into second-line treatment following progression on first-line treatment.[18] Our findings add to those from the E7208 trial which studied irinotecan and cetuximab (IC) versus irinotecan, cetuximab, and the anti-VEGFR antibody ramucirumab (ICR) in patients with advanced CRC that progressed on oxaliplatin-containing chemotherapy. The E7208 trial similarly found that the dual-antibody therapy regimen was effective and tolerable.[19] Unlike in this prematurely discontinued trial, the dual-antibody regimen in the fully enrolled E7028 trial was used in irinotecan-naive patients and showed an improvement in the primary endpoint of PFS and not in the secondary endpoint of OS.

Table 1. Baseline characteristics of study population.

	CBI (*N* = 19)	CI (*N* = 17)	Total (*N* = 36)	*P*-value
Age, median (Q1, Q3 in years)	58.0 (47.0, 64.0)	54.0 (50.0, 68.0)	55.0 (48.0, 65.5)	.59[a]
Sex, *n* (%)				.75[b]
Female	9 (47.4)	7 (41.2)	16 (44.4)	
Male	10 (52.6)	10 (58.8)	20 (55.6)	
Race, *n* (%)				.86[b]
White	15 (78.9)	15 (88.2)	30 (83.3)	
Black or African American	2 (10.5)	0 (0.0)	2 (5.6)	
Asian	1 (5.3)	1 (5.9)	2 (5.6)	
Not reported	1 (5.3)	1 (5.9)	2 (5.6)	
Ethnicity, *n* (%)				1.00[b]
Hispanic	2 (10.5)	1 (5.9)	3 (8.3)	
Other	17 (89.5)	16 (94.1)	33 (91.7)	
Number of prior chemotherapy regimens for metastatic disease, *n* (%)				1.00[b]
1	1 (5.3)	1 (5.9)	2 (5.6)	
2+	18 (94.7)	16 (94.1)	34 (94.4)	
Bevacizumab received in the immediate prior treatment regimen, *n* (%)				.49[b]
Yes	17 (89.5)	17 (100.0)	34 (94.4)	
No	2 (10.5)	0 (0.0)	2 (5.6)	
Primary tumor site, *n* (%)				.62[b]
Colon	13 (68.4)	10 (58.8)	23 (63.9)	
Rectum/Rectosigmoid	3 (15.8)	5 (29.4)	8 (22.2)	
Multiple	3 (15.8)	2 (11.8)	5 (13.9)	
Number of metastatic sites, *n* (%)				.29[b]
1	3 (15.8)	5 (29.4)	8 (22.2)	
2	8 (42.1)	3 (17.6)	11 (30.6)	
3+	8 (42.1)	9 (52.9)	17 (47.2)	
ECOG PS[c], *n* (%)				1.00[b]
0	14 (73.7)	12 (70.6)	26 (72.2)	
1	5 (26.3)	5 (29.4)	10 (27.8)	

[a]The *P*-value for comparison in age was calculated using the Wilcoxon rank-sum test.
[b]The *P*-value for comparison of age, sex, race, number of patients receiving bevacizumab in immediate prior regimen, number of prior chemotherapy regimens, number of metastatic sites, ECOG, was calculated using the chi-Square *P*-value.
[c]ECOG PS 0 indicates full activity without restriction. ECOG PS 1 indicates restriction in physically strenuous activity, but able to ambulate and perform light or sedentary work.
Abbreviations: CBI, irinotecan, cetuximab, and bevacizumab; CI, irinotecan and cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status.

The suggested efficacy of dual-antibody therapy in irinotecan-refractory mCRC but not in first-line treatment of mCRC reinforces the need for an improved understanding of the mechanism of these therapies in different treatment settings. While single-antibody therapy with anti-EGFR or anti-VEGF agents improves outcomes in the treatment of metastatic disease, these agents have not shown efficacy in the treatment of locoregional disease.[20, 21] This may be due to factors related to tumor dormancy or due to molecular differences in the tumor and/or its microenvironment in early-stage disease for which research is ongoing.[22, 23] Similarly, the changes in the tumor biology and microenvironment associated with irinotecan-refractory disease may impact the mechanism and efficacy of anti-EGFR or anti-VEGF treatment. For example, there are preclinical data that anti-EGFR therapy combined with irinotecan may reverse the irinotecan-refractory nature of some tumors.[24] While there is some promising preclinical studies of combined blockade of VEGFR and EGFR pathways, both additional preclinical and clinical study of dual-antibody therapy in refractory disease will be important in optimizing the role of these agents in the treatment of mCRC.[25-27]

Despite the small sample size, it is encouraging that there were no significant differences in the frequency of grade 3 and 4 AEs between arms. While there was a small increase in the frequency of hypertension in the CBI arm compared with the CI arm, there was an absence of other side effects typically associated with bevacizumab, such as bleeding or thrombotic events. It is possible this is because all of the patients in this trial had received and tolerated prior bevacizumab, or this could be due to the small sample size. Nevertheless, a larger sample size will be necessary for further study of adverse events.

The strengths of BOND-3 include its study design as a multi-center, randomized, double-blind, placebo-controlled trial. In addition, the trial had strict eligibility criteria requiring demonstration of extended *RAS*-wildtype status and documented radiographic progression on at least one

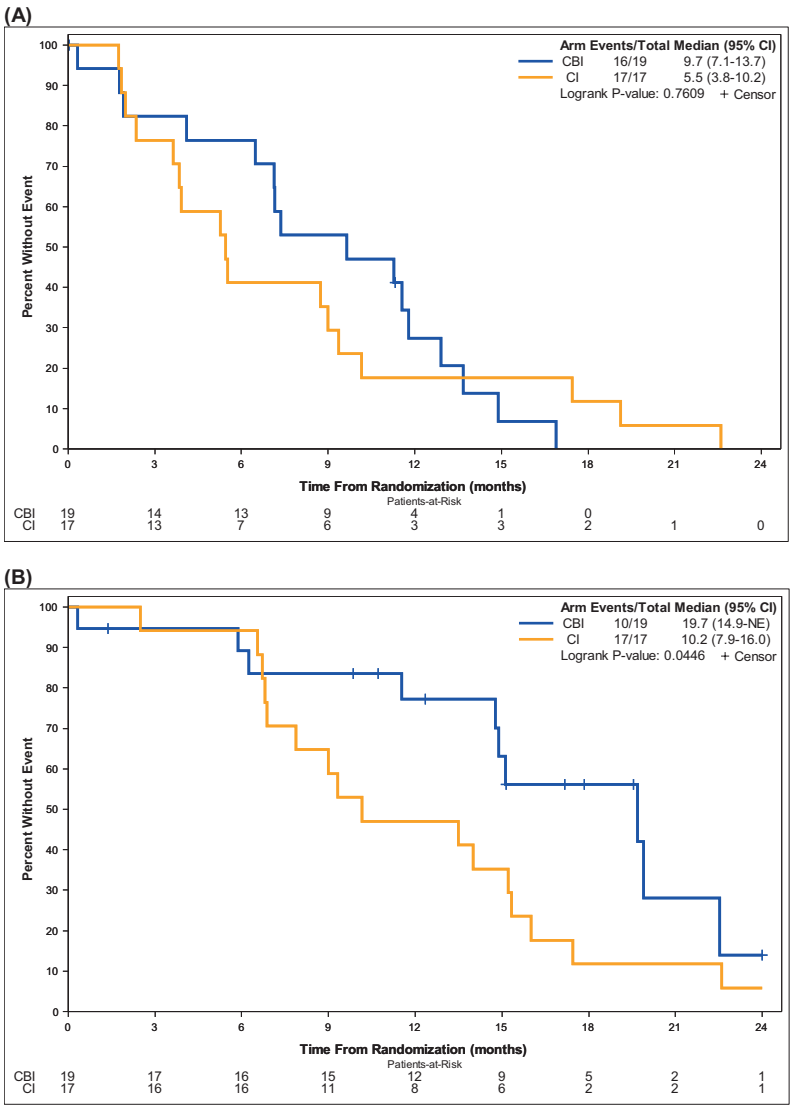


Figure 2. Kaplan-Meier estimates of (**A**) progression-free survival and (**B**) overall survival by treatment group. Abbreviations: CBI, cetuximab, bevacizumab, and irinotecan; CI, cetuximab and irinotecan.

fluoropyrimidine- and irinotecan-containing chemotherapy. Several limitations deserve comment. The study was prematurely discontinued due to changes in funding during the enrollment period resulting in a small sample size, therefore results should be interpreted with caution and require confirmation in future trials. The changes in funding were related to unanticipated challenges with accrual; one such challenge was that some centers routinely treat mCRC patients with anti-EGFR therapy early on in their course, after which patients were ineligible for this trial. Although BOND-3 was a multi-center trial with both academic and community sites, patients were largely enrolled from a single tertiary academic center. Another limitation is that the small sample size precludes correlative biomarker studies and subgroup analyses. Importantly, while general primary tumor location (eg, colon vs rectum/rectosigmoid vs multiple) was obtained, data on primary tumor sidedness (eg, right colon vs left colon) was not collected, as the study was initiated before the discovery of sidedness as a prognostic and predictive marker of patient outcome among RAS wild-type tumors.[3,28] These data are of particular interest given the findings that recently emerged suggesting that tumor sidedness predicts efficacy of anti-EGFR therapy in the treatment of *RAS* wild-type mCRC.[2-4,29] Future investigation of dual-antibody therapy should include a collection of specific data on primary tumor site such that differences in survival and response rate for left- versus right-sided mCRCs could be studied.

Conclusion

Acknowledging the small sample size, BOND-3 showed no significant difference in the primary endpoint of PFS and a statistically significant improvement in the secondary endpoint of OS for treatment with cetuximab, irinotecan, and bevacizumab compared with cetuximab, irinotecan, and placebo in refractory mCRC. Further trials are warranted to assess the benefit of dual-antibody treatment with bevacizumab and cetuximab in this population.

Table 2. Frequency of adverse events.

	CBI, *n* (%)	CI, *n* (%)
Acneiform rash		
Grade 1-2	16 (84.2)	15 (88.2)
Grade 3-4	1 (5.3)	0 (0)
Hypertension		
Grade 1-2	15 (78.9)	12 (70.6)
Grade 3-4	2 (10.5)	1 (5.9)
Maculopapular rash		
Grade 1-2	14 (73.7)	15 (88.2)
Grade 3-4	0 (0)	0 (0)
Diarrhea		
Grade 1-2	13 (68.4)	10 (58.8)
Grade 3-4	2 (10.5)	2 (11.8)
Hypomagnesemia		
Grade 1-2	13 (68.4)	12 (70.6)
Grade 3-4	2 (10.5)	0 (0)
Decreased neutrophil count		
Grade 1-2	7 (36.8)	7 (41.2)
Grade 3-4	2 (10.5)	0 (0)
Decreased platelet count		
Grade 1-2	5 (26.3)	4 (23.5)
Grade 3-4	0 (0)	1 (5.9)
Nausea		
Grade 1-2	1 (5.3)	2 (11.8)
Grade 3-4	0 (0)	0 (0)
Vomiting		
Grade 1-2	1 (5.3)	2 (11.8)
Grade 3-4	1 (5.3)	1 (5.9)
Dehydration		
Grade 1-2	0 (0)	1 (5.9)
Grade 3-4	2 (10.5)	0 (0)
Acute kidney injury		
Grade 1- 2	0 (0)	0 (0)
Grade 3-4	2 (10.5)	0 (0)
Sepsis		
Grade 1-2	0 (0)	0 (0)
Grade 3-4	1 (5.3)	0 (0)
Hypotension		
Grade 1-2	0 (0)	0 (0)
Grade 3-4	1 (5.3)	0 (0)
Alopecia		
Grade 1-2	0 (0)	1 (5.9)
Grade 3-4	0 (0)	0 (0)
Constipation		
Grade 1-2	1 (5.3)	0 (0)
Grade 3-4	0 (0)	0 (0)
Back pain		
Grade 1-2	0 (0)	0 (0)
Grade 3-4	1 (5.3)	1 (5.9)
Oral mucositis		
Grade 1-2	0 (0)	1 (5.9)
Grade 3-4	1 (5.3)	0 (0)
Proteinuria		
Grade 1-2	1 (5.3)	0 (0)
Grade 3-4	1 (5.3)	0 (0)
Fever		
Grade 1-2	0 (0)	0 (0)
Grade 3-4	0 (0)	1 (5.9)
Fatigue		
Grade 1-2	0 (0)	1 (5.9)
Grade 3-4	0 (0)	0 (0)
Hypoglycemia		
Grade 1-2	0 (0)	0 (0)
Grade 3-4	0 (0)	1 (5.9)
Hepatobiliary disorder, unspecified		
Grade 1-2	0 (0)	0 (0)
Grade 3-4	0 (0)	1 (5.9)

Abbreviations: CBI, cetuximab, bevacizumab, and irinotecan; CI, cetuximab and irinotecan.

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Conflict of Interest

Matthew B. Yurgelun: Janssen Pharmaceuticals (C/A, RF, SAB), UpToDate (peer review services); **Jeffrey A. Meyerhardt**: Array Biopharma (C/A), Ignyta (H), COTA Healthcare (C/A), Boston Biomedical (RF), Taiho Pharmaceutical (National Comprehensive Cancer Network grant review panel); **Douglas A. Rubinson**: Augmenix (C/A); **Deborah Schrag**: Journal of the American Medical Association (C/A), AACR (RF), GRAIL (RF); **Tanios Bekaii-Saab**: Array Biopharma (C/A), Pfizer (C/A, RF), Seattle Genetics (C/A, RF), Bayer (C/A), Genentech (C/A, RF), Incyte (C/A), Merck (C/A, RF), AbbVie (C/A), Boehringer Ingelheim (C/A), Janssen (C/A), Eisai (C/A), Daichii Sankyo (C/A), Natera (C/A), TreosBio (C/A), Celularity (C/A), Exact Science (C/A), Sobi (C/A), Beigene (C/A), Kanaph (C/A), Xilis (C/A), AstraZeneca (C/A, DSMB), Foundation Medicine (C/A), Agios (RF), Arys (RF), Arcus (RF), Atreca (RF), Boston Biomedical (RF), Bayer (RF), Amgen (RF), Celgene (RF), Lilly (RF, DSMB), Ipsen (RF), Clovis (RF), Novartis (RF), Mirati (RF), Merus (RF), Abgenomics (RF), Incyte (RF), BMS (RF), Exelixis (DMSB), PanCan (DSMB, 1Globe (DSMB), Imugene (SAB), Imuneering (SAB), Sun Biopharma (SAB). **Charles S. Fuchs**: CytomX Therapeutics (Leadership, OI, C/A), Entrinsic Health (C/A, OI), Agios (C/A); Bain Capital (C/A); Bayer (C/A); Celgene (C/A), Dicerna (C/A), Five Prime Therapeutics (C/A); Genentech/Roche (C/A),Gilead Sciences (C/A); KEW (C/A), Lilly (C/A), Merck (C/A), Merrimack (C/A), Pfizer (C/A), Sanofi (C/A), Taiho Pharmaceutical (C/A), Unum Therapeutics (C/A). During the development, enrollment, data analysis, and manuscript drafting of this trial, he did not work for Genentech. He now leads the oncology and hematology global product development at Genentech. **Kimmie Ng**: Seattle Genetics (C/A), Array Biopharma (C/A), BiomX (C/A), X-Biotix Therapeutics (C/A), Bicara (C/A), Pharmavite (RF), Evergrande Group (RF), Revolution Medicines (RF), Janssen (RF), Genentech/Roche (RF, C/A), Gilead Sciences (RF), Celgene (RF), Trovagene (RF),

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Author Contributions

Conception/design: M.L.-S., F.-S.O., J.A.M., T.B.-S., C.S.F., K.N. Provision of study material or patients: M.B.Y., D.A.R., D.S., S.R.D., P.J.S., D.J.W., D.B.W., M.F., J.A.M., T.B.-S., C.S.F., K.N. Collection and/or assembly of data: F.-S.O., T.J.Z., E.N.H., S.R.S., S.N. Data analysis and interpretation: M.L.-S., F.-S.O., J.A. M., T.B.-S., C.S. F., K.N. Manuscript writing: M.L.-S., K.N. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared at reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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