

Phase II Randomized Trial of Sequential or Concurrent FOLFOXIRI-Bevacizumab Versus FOLFOX-Bevacizumab for Metastatic Colorectal Cancer (STEAM)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic colorectal cancer • Concurrent FOLFOXIRI • Sequential FOLFOXIRI • FOLFOX • Bevacizumab

ABSTRACT

Background. First-line treatment for metastatic colorectal cancer (mCRC) typically entails a biologic such as bevacizumab (BEV) with 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) or 5-fluorouracil/leucovorin/irinotecan (FOLFIRI). STEAM (NCT01765582) assessed the efficacy of BEV plus FOLFOX/FOLFIRI (FOLFOXIRI), administered concurrently (cFOLFOXIRI-BEV) or sequentially (sFOLFOXIRI-BEV, FOLFOX-BEV alternating with FOLFIRI-BEV), versus FOLFOX-BEV for mCRC.

Patients and Methods. Patients with previously untreated mCRC ($n = 280$) were randomized 1:1:1 to cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, or FOLFOX-BEV and treated with 4–6-month induction followed by maintenance. Coprimary objectives were overall response rate (ORR; first-line cFOLFOXIRI-BEV vs. FOLFOX-BEV) and progression-free survival (PFS; pooled first-line cFOLFOXIRI-BEV and sFOLFOXIRI-BEV vs. FOLFOX-BEV). Secondary/exploratory objectives included overall survival (OS), liver resection rates, biomarker analyses, and safety.

Results. ORR was 72.0%, 72.8%, and 62.1% and median PFS was 11.9, 11.4, and 9.5 months with cFOLFOXIRI-BEV,

sFOLFOXIRI-BEV, and FOLFOX-BEV, respectively. OS was similar between arms. ORR between cFOLFOXIRI-BEV and FOLFOX-BEV did not significantly differ ($p = .132$); thus, the primary ORR endpoint was not met. cFOLFOXIRI-BEV and sFOLFOXIRI-BEV numerically improved ORR and PFS, regardless of RAS status. Median PFS was higher with pooled concurrent and sequential FOLFOXIRI-BEV versus FOLFOX-BEV (11.7 vs. 9.5 months; hazard ratio, 0.7; 90% confidence interval, 0.5–0.9; $p < .01$). Liver resection rates were 17.2% (cFOLFOXIRI-BEV), 9.8% (sFOLFOXIRI-BEV), and 8.4% (FOLFOX-BEV). Grade ≥ 3 treatment-emergent adverse events (TEAEs) were observed in 91.2% (cFOLFOXIRI-BEV), 86.7% (sFOLFOXIRI-BEV), and 85.6% (FOLFOX-BEV) of patients, with no increase in serious chemotherapy-associated TEAEs.

Conclusion. cFOLFOXIRI-BEV and sFOLFOXIRI-BEV were well tolerated with numerically improved ORR, PFS, and liver resection rates versus FOLFOX-BEV, supporting triplet chemotherapy plus BEV as a first-line treatment option for mCRC. *The Oncologist* 2019;24:921–932

Implications for Practice: The combination of first-line FOLFIRI with FOLFOX and bevacizumab (concurrent FOLFOXIRI-BEV) improves clinical outcomes in patients with metastatic colorectal cancer (mCRC) relative to FOLFIRI-BEV or FOLFOX-BEV, but it is thought to be associated with increased toxicity. Alternating treatment of FOLFOX and FOLFIRI (sequential FOLFOXIRI-BEV) could improve tolerability. In the phase II STEAM trial, which is the largest study of FOLFOXIRI-BEV in patients in the U.S., it was found that both concurrent and sequential FOLFOXIRI-BEV are active and well tolerated in patients with previously untreated mCRC, supporting the use of these regimens as potential first-line treatment options for this population.

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INTRODUCTION

Colorectal cancer is the fourth most common cancer in the U.S., with more than 135,000 new cases and 50,000 deaths estimated for 2017 [1]. Patients with metastatic colorectal cancer (mCRC) have a 5-year survival rate of less than 14% [1]. Prior to the widespread availability of targeted therapies, management of mCRC commonly employed an infusion of 5-fluorouracil/leucovorin/irinotecan (FOLFIRI) [2, 3] or 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) chemotherapeutic regimens [4]. A triplet approach combining FOLFOX and FOLFIRI, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan (FOLFOXIRI), demonstrated improved response rates and surgical resection rates compared with FOLFIRI alone, with increased but manageable toxicity [5, 6].

Bevacizumab, a humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A, has been shown to improve progression-free survival (PFS) and overall survival (OS) in patients with mCRC when used in combination with chemotherapy [7–9]. As such, the current standard of care for patients with previously untreated mCRC entails the addition of a biologic agent such as bevacizumab to either FOLFOX or FOLFIRI [10], with FOLFOX being more commonly used in the U.S. However, further improvement in the efficacy of frontline regimens is an ongoing objective. One possibility for improving outcomes is intensification of the chemotherapy backbone by replacing FOLFIRI or FOLFOX with FOLFOXIRI, which demonstrated acceptable safety in combination with bevacizumab in patients with mCRC [11].

The phase III TRIBE study comparing FOLFOXIRI plus bevacizumab (FOLFOXIRI-BEV) versus FOLFIRI plus bevacizumab (FOLFIRI-BEV) in patients in Italy demonstrated that FOLFOXIRI-BEV was associated with significant improvements in the overall response rate (ORR; 65% vs. 53%; $p = .006$), PFS (hazard ratio [HR], 0.77; 95% confidence interval [CI] 0.65–0.93; $p = .006$), and OS (HR, 0.80; 95% CI 0.65–0.98; $p = .03$) [12, 13]. The European phase II OLIVIA study of FOLFOXIRI-BEV compared with a modified FOLFOX regimen plus bevacizumab demonstrated a higher tumor response rate (81%; 95% CI 65–91 vs. 62%; 95% CI 45–77), as well as a higher liver resection rate (61% vs. 49%) and improved median PFS (18.6 months; 95% CI 12.9–22.3 vs. 11.5 months; 95% CI 9.6–13.6) for the triplet regimen [14].

Despite the results from TRIBE and OLIVIA, a number of questions remain, including the efficacy and safety of FOLFOXIRI-BEV in patients in the U.S. Additionally, although the overall safety profile of FOLFOXIRI-BEV is generally acceptable, the triplet regimen is associated with increased toxicity compared with the respective control groups [12, 14]. Alternating treatment with FOLFOX and FOLFIRI (i.e., sequential FOLFOXIRI) has been hypothesized to improve the tolerability of the regimen without negatively affecting efficacy [15]. We undertook this study to define the activity and tolerability of concurrent and sequential FOLFOXIRI-BEV in patients with mCRC.

The *Sequencing Triplet with Avastin and Maintenance* (STEAM; NCT01765582) trial is a randomized, multicenter, open-label, U.S.-based, phase II trial investigating FOLFOXIRI-BEV administered concurrently (cFOLFOXIRI-BEV)

or sequentially (sFOLFOXIRI-BEV, i.e., FOLFOX-BEV alternating with FOLFIRI-BEV) versus FOLFOX-BEV in patients with previously untreated mCRC. The primary efficacy endpoints were (a) the overall response rate of cFOLFOXIRI-BEV versus FOLFOX-BEV and (b) PFS of pooled cFOLFOXIRI-BEV and sFOLFOXIRI-BEV versus FOLFOX-BEV. Here, we describe the final efficacy and safety results, as well as selected exploratory biomarker analyses, from the STEAM study.

MATERIALS AND METHODS

Study Design

STEAM is a randomized, open-label, multicenter, phase II study of patients in the U.S. with previously untreated mCRC. After a screening period of up to 21 days, patients were randomized 1:1:1 using a dynamic hierarchical randomization algorithm to a treatment induction phase consisting of cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, or FOLFOX-BEV, followed by a maintenance phase and a planned second-line phase (supplemental online Fig. 1). Patients were stratified by extent of metastatic disease (liver-limited disease vs. non-liver-limited disease), primary tumor location (right vs. left) [16], and study center.

The study protocol was approved by the institutional review boards at each participating study site, and the trial conformed to the principles outlined in the Declaration of Helsinki, the International Conference on Harmonisation E6 guideline for Good Clinical Practice, and applicable local laws. Patients provided written informed consent per institutional guidelines.

The preplanned coprimary efficacy endpoints were investigator-assessed ORR for first-line treatment with cFOLFOXIRI-BEV versus FOLFOX-BEV, and PFS from first-line treatment with pooled FOLFOXIRI-BEV (i.e., concurrent plus sequential FOLFOXIRI-BEV) versus FOLFOX-BEV. Secondary endpoints included safety, OS, and liver resection rate. Assessment of biomarkers associated with treatment outcomes was an exploratory objective.

Patients

Key patient inclusion criteria were histologically confirmed mCRC with at least one measurable lesion considered unresectable at baseline; age of 18–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 if aged <71 years or ECOG performance status of 0 if aged 71–75 years; adequate hematologic, liver, and renal function; and a willingness to comply with the study protocol, including tissue and blood sampling.

Key exclusion criteria included prior systemic treatment for mCRC, except for use of palliative radiosensitizers; adjuvant chemotherapy completed <12 months prior to study enrollment; sensory peripheral neuropathy of grade ≥ 2 ; surgery within 28 days prior to randomization; minor surgery <7 days before or after bevacizumab infusion; current or recent (≤ 10 days prior to the first dose of bevacizumab) use of aspirin >325 mg/day (full-dose anticoagulants were permitted if dose was stable and clinical coagulation

Table 1. Baseline characteristics (intent-to-treat population)

Characteristics	cFOLFOXIRI-BEV (n = 93), n (%)	sFOLFOXIRI-BEV (n = 92), n (%)	FOLFOX-BEV (n = 95), n (%)
Age, median (range), yr	58 (23–75)	56 (25–74)	58 (34–73)
Sex			
Male	51 (55)	52 (57)	59 (62)
Female	42 (45)	40 (43)	36 (38)
ECOG performance status			
0	62 (67)	52 (57)	51 (54)
1	31 (33)	40 (43)	44 (46)
Cancer type at initial diagnosis			
Colon	68 (73)	67 (73)	77 (81)
Rectal	24 (26)	25 (27)	17 (18)
Missing	1 (1)	0 (0)	1 (1)
Location of primary tumor ^a			
Left	50 (54)	53 (58)	55 (58)
Right	43 (46)	39 (42)	40 (42)
Prior cancer surgery	48 (52)	55 (60)	61 (64)
Prior systemic therapy			
Yes	11 (12)	7 (8)	8 (8)
Adjuvant therapy	10 (11)	7 (8)	7 (7)
Nonadjuvant therapy	1 (1)	0 (0)	1 (1)
No	82 (88)	85 (92)	87 (92)
Extent of metastatic disease			
Liver-limited disease	28 (30)	28 (30)	27 (28)
Non-liver-limited disease	65 (70)	64 (70)	68 (72)

^aData are based on tumor locations reported in patient medical histories.

Abbreviations: cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; ECOG, Eastern Cooperative Oncology Group; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab.

parameters were within therapeutic range); and inadequately controlled hypertension, clinically significant cardiovascular disease, serious nonhealing wound, active peptic ulcer, or untreated bone fracture.

Procedures

The induction phase consisted of FOLFOX-BEV, cFOLFOXIRI-BEV (concurrent FOLFOX-BEV and FOLFIRI-BEV), or sFOLFOXIRI-BEV (alternating 4-week administrations of FOLFOX-BEV and FOLFIRI-BEV) by intravenous infusion every 2 weeks for 4 months (supplemental online Fig. 1, supplemental online Table 1). Patients could continue the assigned treatment for up to 2 additional months, at the investigator's discretion, if the patient exhibited a good response and the treatment was well tolerated. Induction treatment was followed by a maintenance phase with intravenous 5-fluorouracil, leucovorin, and bevacizumab every 2 weeks or oral capecitabine plus intravenous bevacizumab every 3 weeks until disease progression. Upon progression, patients were to enter a planned second-line phase consisting of treatment with bevacizumab and a fluoropyrimidine-based chemotherapy of the investigator's choice.

Treatment continued until progression, death, withdrawal of consent, or unacceptable toxicity. If any of the

individual components of the originally assigned regimen were discontinued early, the remaining drugs in the regimen were continued. Two safety follow-up visits occurred 28 (± 3) days and 3 months (± 7 days) after the last dose of study drugs. Patients then entered a survival follow-up period with survival status assessed every 3 months.

Biomarker Assessments

Biomarker-evaluable patients were defined as those who provided informed consent to participate in the tissue biomarker program and had at least one viable sample for analysis. Single-nucleotide variants for *RAS* (*KRAS* and *NRAS*) and *BRAF* were identified by next-generation sequencing using the AVENIO Expanded Kit (Roche, Basel, Switzerland). Secondary sequence analysis was performed through an established Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) bioinformatics pipeline, which included molecular barcoding and integrated digital error suppression methods [17, 18].

Liver Resection and Assessments

Patients with planned resections stopped bevacizumab treatment at least 4–6 weeks prior to surgery and were permitted to restart treatment when ≥ 4 weeks had elapsed

since the surgery. The choice of therapy after resection was at the investigator's discretion from the following options: bevacizumab, 5-fluorouracil, capecitabine, oxaliplatin, irinotecan, or any combination thereof.

After surgery, liver metastasis resections were classified as R0 (complete resection with clear margins ≥ 1 mm), R1 (presence of exposed tumor along the line of transection, presence of tumor cells at the line of transection detected by histologic examination, or < 1 mm microscopic margin), or R2 (macroscopic positive margins or incomplete resection at time of surgery). Liver resection rates were calculated by classification and overall.

To distinguish the effect of treatment from the effect of surgery in the calculation of ORR, Response Evaluation Criteria in Solid Tumors (RECIST) assessments were censored after curative liver resection.

Statistical Analysis

Efficacy analyses were conducted in the intent-to-treat (ITT) population, including all randomized patients regardless of whether treatment was received. Safety analyses were conducted on all patients who received at least one dose of study medication; safety data were summarized by treatment arm based on actual treatment received (i.e., the safety population).

The sample size of 280 patients was based on assumed ORRs of 70%, 65%, and 50% in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms, respectively, and a 43% improvement in median PFS (from 10 months in FOLFOX-BEV to 14.3 months in pooled FOLFOXIRI-BEV). In this scenario and under constant hazard assumptions, the study would have 89% power to detect a difference in ORR between the cFOLFOXIRI-BEV and FOLFOX-BEV arms, with 5% type 1 error (one-sided) and 82% power to detect a difference between the pooled cFOLFOXIRI-BEV and sFOLFOXIRI-BEV and FOLFOX-BEV arms in PFS, with 5% type 1 error (one-sided).

ORR was defined as the percentage of patients assessed by site investigators as having a complete or partial response per RECIST version 1.1 (unconfirmed) in first-line treatment. Logistic regression was used to calculate 90% CI for the odds ratio of the cFOLFOXIRI-BEV or sFOLFOXIRI-BEV arm versus the FOLFOX-BEV arm, stratified by extent of metastatic disease and primary tumor location. *P*-values were determined by a one-sided Cochran-Mantel-Haenszel test, stratified by extent of metastatic disease and primary tumor location.

PFS was defined as the time from randomization to first occurrence of disease progression or death from any cause during first-line treatment, whichever occurred earlier. Patients without an event were censored at their last tumor assessment. The Kaplan-Meier approach was used to estimate median PFS and corresponding CIs for each treatment arm and for combined arms. Cox regression (with proportional hazards), stratified by extent of metastatic disease and primary tumor location, was used to estimate the HR and to calculate its 90% CIs. A one-sided log-rank test between FOLFOXIRI/bevacizumab regimen arms (concurrent and sequential) and the FOLFOX/

bevacizumab arm, stratified by extent of metastatic disease and primary tumor location, provided *p* values.

To adjust for multiplicity due to having two primary endpoints, a fixed-sequence hypothesis testing procedure was to be implemented; however, the study was terminated early. The hypothesis test for ORR was conducted at a one-sided α of 5%. If ORR was significantly higher in the cFOLFOXIRI-BEV arm than in the FOLFOX-BEV arm, PFS was to be tested at a one-sided α of 5% for the pooled cFOLFOXIRI-BEV and sFOLFOXIRI-BEV arms versus the FOLFOX-BEV arm. Except for the primary analysis of ORR and PFS, all *p* values were considered nominal and were not adjusted for multiple comparisons.

On November 10, 2015, Genentech conducted the final analysis of ORR and a planned interim analysis of PFS. Based on the results of these efficacy analyses, Genentech elected to terminate the trial early. This report describes the final efficacy and safety analyses, as well as selected exploratory biomarker analyses, with data based on follow-up until March 14, 2016.

RESULTS

Patients

Between January 23, 2013, and December 26, 2014, 280 patients were randomized in STEAM to the cFOLFOXIRI-BEV ($n = 93$), sFOLFOXIRI-BEV ($n = 92$), or FOLFOX-BEV ($n = 95$) treatment arms (Fig. 1). Within each respective arm, 72 (77.4%), 74 (80.4%) and 72 (75.8%) patients completed cycle 8 (4 months of treatment). Median duration of follow-up was 85.1 weeks (range, 19–148), 84.7 weeks (range, 33–151), and 83.4 weeks (range, 9–132), respectively. Cumulative dose for each drug within each treatment arm are shown in supplemental online Table 2.

Patient demographics and characteristics were generally balanced between treatment arms, although the cFOLFOXIRI-BEV and sFOLFOXIRI-BEV arms had lower proportions of patients with prior surgery for colorectal cancer compared with FOLFOX-BEV (51.6% and 59.8% vs. 64.2%; Table 1). Additionally, more patients in the cFOLFOXIRI-BEV arm had an ECOG status of 0 than those in the sFOLFOXIRI-BEV or FOLFOX-BEV arms (66.7% vs. 56.5% and 53.7%).

Efficacy Outcomes

ORR was 72.0% (67/93, four complete responses [CRs]) in the cFOLFOXIRI-BEV treatment arm, 72.8% (67/92, no CR) in the sFOLFOXIRI-BEV arm, and 62.1% (59/95, 1 CR) in the FOLFOX-BEV arm (Table 2). The stratified odds ratios numerically favored the cFOLFOXIRI-BEV (1.6; 90% CI, 1.0–2.7) and sFOLFOXIRI-BEV (1.7; 90% CI, 1.0–2.8) treatment arms compared with FOLFOX-BEV, and significantly favored pooled concurrent and sequential FOLFOXIRI-BEV versus FOLFOX-BEV (1.6; 90% CI, 1.1–2.6). However, as the coprimary endpoint of ORR for cFOLFOXIRI-BEV versus FOLFOX-BEV treatment did not show a statistically significant difference ($p = .132$), the sponsor elected for early termination of the STEAM study.

Median PFS was 11.9 months in the cFOLFOXIRI-BEV arm, 11.4 months in the sFOLFOXIRI-BEV arm, and

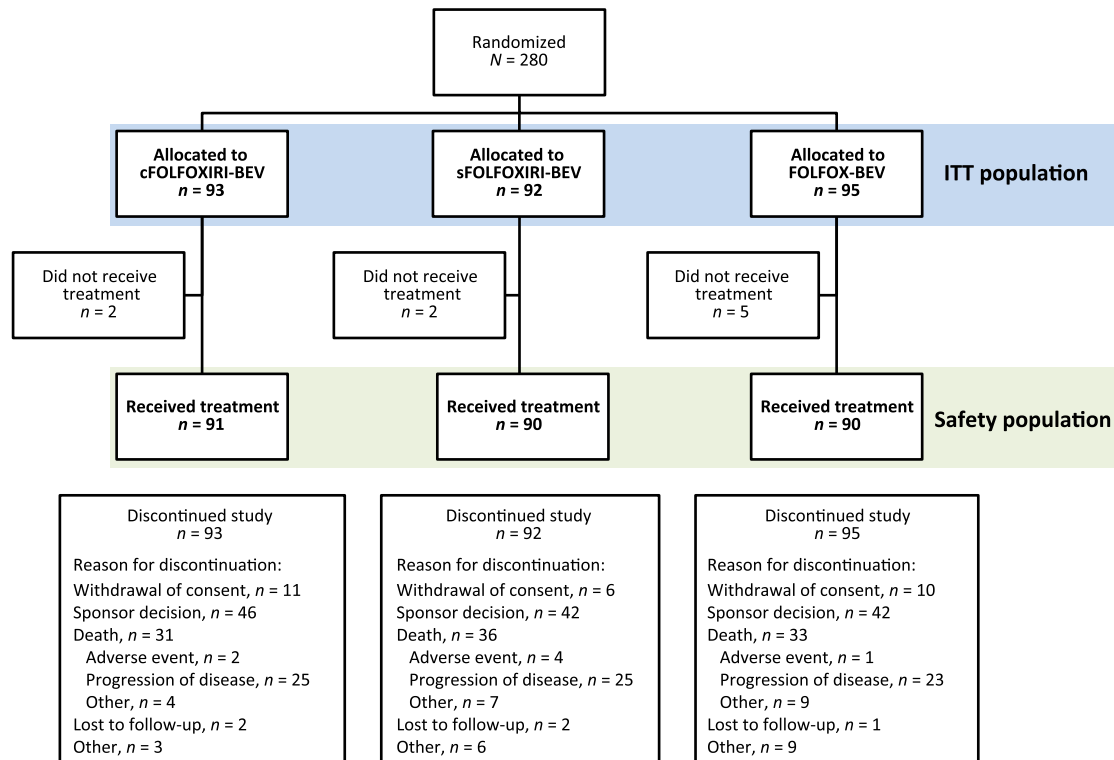


Figure 1. Patient disposition.

Abbreviations: cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; ITT, intent-to-treat; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab.

9.5 months in the FOLFOX-BEV arm. Compared with FOLFOX-BEV, median PFS was higher with pooled concurrent and sequential FOLFOXIRI-BEV (HR, 0.7; 90% CI, 0.5–0.9; Fig. 2A). Estimates for median OS were 34.0, 28.3, and 30.7 months in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV treatment arms, respectively. The differences in OS between FOLFOX-BEV versus cFOLFOXIRI-BEV (HR, 0.8; 90% CI, 0.5–1.2) or sFOLFOXIRI-BEV (HR, 1.0; 90% CI, 0.7–1.5) were not statistically significant (Fig. 2B).

Liver Resection Rates

Liver resection rates during first-line treatment in the ITT population in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms were 17.2% (16/93), 9.8% (9/92), and 8.4% (8/95), respectively; R0 resection rates were 16.1% (15/93), 8.7% (8/92), and 6.3% (6/95). Median first-line treatment cycles prior to liver resection were eight (range, 1–25), eight (range, 4–17), and nine (range, 6–13) cycles in each arm, respectively. In ITT population patients with liver-limited disease, resection rates were 28.6% (8/28), 21.4% (6/28), and 18.5% (5/27) in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms, respectively, and R0 resection rates were 25.0% (7/28), 17.9% (5/28), and 11.1% (3/27). The differences in overall resection rates between the FOLFOXIRI-BEV arms and FOLFOX-BEV did not reach statistical significance.

In addition to the higher first-line resection rate reported with cFOLFOXIRI-BEV, numerically higher rates of overall conversion from unresectable to resectable disease (i.e., the

proportion of patients considered by the investigator to be unresectable at study enrollment who subsequently underwent attempted curative resections of metastases) were also observed with cFOLFOXIRI-BEV (24% [22/93]) and sFOLFOXIRI-BEV (17% [16/92]) versus FOLFOX-BEV (14% [13/95]), with 20% (19/93), 13% (12/92), and 11% (10/95) of patients receiving R0 resections, respectively.

To assess the impact of liver resection on outcomes, sensitivity analyses were conducted for ORR (in which all liver resections were considered to be CRs) and PFS (in which patients with liver metastasectomy were excluded). The results for both measures remained consistent with the primary analyses of ORR and PFS in the first line.

Subgroup Analyses by Molecular Biomarkers and Tumor Location

The biomarker-evaluable populations from the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV treatment arms included 57/93 (61.3%), 67/92 (72.8%), and 58/95 (61.1%) patients, respectively. Baseline characteristics in the biomarker-evaluable population were generally similar between treatment arms with the exception of cancer type, for which patients in the FOLFOX-BEV arm had a higher incidence of colon (vs. rectal) cancer than those in the FOLFOXIRI-BEV arms (supplemental online Table 3). Clinical outcomes in this population were comparable to those in the ITT population (supplemental online Table 4).

ORR, PFS, and OS were evaluated by *RAS* (*KRAS* or *NRAS*) and *BRAF* tumor status (Table 3) in each treatment arm.

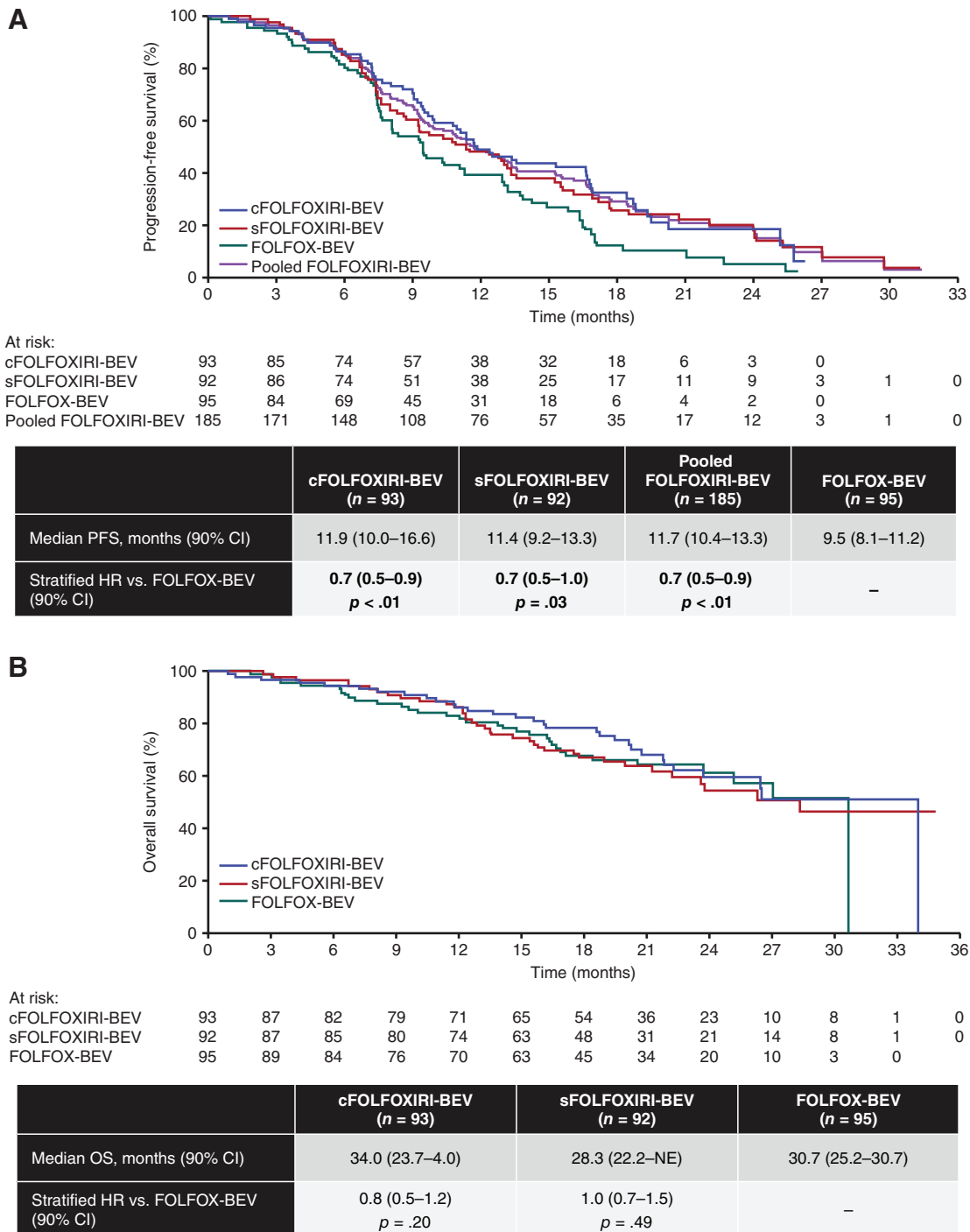


Figure 2. Outcomes by treatment arm (intent-to-treat population). **(A):** PFS. **(B):** OS. A total of 61, 69, and 72 PFS events and 31, 36, and 33 OS events occurred in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms, respectively. The data were calculated by Cox proportional hazards model that also included the extent of metastatic disease (liver-limited vs. not) and tumor location (left vs. right) after correction postrandomization.

Abbreviations: cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; CI, confidence interval; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; FOLFOXIRI-BEV, 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab.

Although numbers were limited, patients with *RAS* wild-type or *BRAF* wild-type tumor status generally had higher ORR and PFS relative to those with *RAS*-mutated or *BRAF*-mutated tumors, respectively. In patients with *RAS* wild-type tumors, those treated with cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV had ORRs of 78.6%, 93.1 %, and 63.0%,

respectively, with the difference between sFOLFOXIRI-BEV and FOLFOX-BEV reaching statistical significance (odds ratio, 7.5; 90% CI, 1.9–29.3; Table 3). Median PFS in the three treatment arms was 16.6, 16.1, and 9.6 months, respectively (Table 3, supplemental online Fig. 2A). cFOLFOXIRI-BEV and sFOLFOXIRI-BEV also produced numerically higher ORR and

Table 2. Overall response rate during first-line treatment (intent-to-treat population)

ORR	cFOLFOXIRI-BEV (n = 93)	sFOLFOXIRI-BEV (n = 92)	FOLFOX-BEV (n = 95)
ORR (CR or PR), n (%)	67 (72.0)	67 (72.8)	59 (62.1)
CR	4 (4.3)	0	1 (1.1)
PR	63 (67.7)	67 (72.8)	58 (61.1)
SD	18 (19.4)	20 (21.7)	24 (25.3)
PD	2 (2.2)	1 (1.1)	6 (6.3)
Unable to evaluate	6 (6.5)	4 (4.3)	6 (6.3)
Unstratified analysis			—
Odds ratio (90% CI)	1.6 (0.9–2.6)	1.6 (1.0–2.8)	
p value (one-sided Pearson χ^2)	.147	.118	
Stratified analysis ^a			—
Odds ratio (90% CI)	1.6 (1.0–2.7)	1.7 (1.0–2.8)	
p value (one-sided Cochran-Mantel-Haenszel) ^a	.132	.119	

^aStratified by extent of metastatic disease (liver-limited disease vs. non-liver-limited disease) and tumor location (right vs. left) after correction postrandomization.

Abbreviations: —, not applicable; cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; CI, confidence interval; CR, complete response; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; ORR, overall response rate during first-line therapy; PD, progressive disease; PR, partial response; SD, stable diseases; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab.

median PFS compared with FOLFOX-BEV in patients with RAS-mutated tumors (ORR, 72.4%, 71.1%, and 64.5%, respectively; median PFS, 12.5, 9.3, and 8.1 months), with statistical significance observed for PFS in the cFOLFOXIRI-BEV versus FOLFOX-BEV arms (HR, 0.5; 90% CI, 0.3–0.9; Table 3, supplemental online Fig. 2B).

In patients with *BRAF* wild-type tumors, treatment with sFOLFOXIRI-BEV versus FOLFOX-BEV improved ORR (80.7% vs. 63.0%; odds ratio, 2.5; 90% CI, 1.2–5.1) and median PFS (12.8 vs. 9.5 months; HR, 0.6; 90% CI, 0.4–0.9; Table 3). PFS was also higher in the cFOLFOXIRI-BEV arm (15.3 vs. 9.5 months; HR, 0.6; 90% CI, 0.4–0.8) compared with FOLFOX-BEV. The number of patients in the *BRAF*-mutated subgroup was small, but in this subset, ORRs were 50.0%, 80.0%, and 75.0% in the cFOLFOXIRI-BEV ($n = 4$), sFOLFOXIRI-BEV ($n = 5$), and FOLFOX-BEV ($n = 4$) treatment arms, and median PFS durations were 7.1, 7.4, and 12.4 months, respectively.

cFOLFOXIRI-BEV and sFOLFOXIRI-BEV conferred numerically higher ORR and median PFS in left-sided tumors compared with FOLFOX-BEV (ORR, 82.4% and 79.2% vs. 57.9%; PFS, 11.1 and 11.5 vs. 9.5 months; Table 3, supplemental online Fig. 2C). In right-sided tumors, numerical improvements for median PFS, but not ORR, were observed for cFOLFOXIRI-BEV and sFOLFOXIRI-BEV versus FOLFOX-BEV (ORR, 61.0% and 66.7% vs. 70.3%; PFS, 16.7 and 10.9 vs. 10.2 months; Table 3, supplemental online Fig. 2D). A multivariate analysis by molecular biomarkers and tumor location found no significant differences in PFS, with the exception of significant improvements with sFOLFOXIRI-BEV versus FOLFOX-BEV treatment in patients with left-sided tumors (supplemental online Table 5). Adjusted HRs for PFS in right- versus left-sided tumors in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms were 0.7 (90% CI, 0.4–1.2), 1.3 (90% CI, 0.8–2.0), and 0.6 (90% CI, 0.3–1.0), respectively.

Safety

All patients except for one in the sFOLFOXIRI-BEV arm experienced at least one treatment-emergent adverse event (TEAE). In the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms, 91.2%, 86.7%, and 85.6% of patients, respectively, had at least one grade ≥ 3 TEAE. Fatal TEAEs were experienced by three, five, and three patients in the three arms, respectively. Small intestine obstruction, sepsis, and death (attributed to disease while on study) each resulted in a fatal adverse event in more than one patient. Serious TEAEs were experienced by 42.9%, 46.7%, and 47.8% of patients in each treatment arm, respectively (Table 4). No new safety signals were observed in patients treated with cFOLFOXIRI-BEV or sFOLFOXIRI-BEV, and incidences of grade 4 and 5 TEAEs were similar between the two arms. There was no increase in serious chemotherapy-associated TEAEs.

The most common grade ≥ 3 TEAEs (occurring in $\geq 10\%$ of patients in any treatment arm) were neutropenia (57.1%, 41.1%, and 35.6% with cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV, respectively), hypertension (22.0%, 22.2%, 15.6%), diarrhea (22.0%, 10.0%, 12.2%), fatigue (12.1%, 5.6%, 5.6%), hypokalemia (11.0%, 6.7%, 6.7%), and anemia (6.6%, 3.3%, 10.0%) (Table 5). Grade ≥ 3 chemotherapy toxicities were more common in the cFOLFOXIRI-BEV arm than in the other two arms, with the exception of febrile neutropenia, constipation, and stomatitis, which were similar across all three treatment arms (Table 5). Granulocyte colony stimulating factor was administered to 45/91 (49.5%), 31/90 (34.4%), and 23/90 (25.6%) patients in the cFOLFOXIRI-BEV, sFOLFOXIRI-BEV, and FOLFOX-BEV arms, respectively.

The incidence of patients with TEAEs of special interest for bevacizumab was somewhat higher in the cFOLFOXIRI-BEV and sFOLFOXIRI-BEV arms compared with FOLFOX-BEV (36.3% and 31.1% vs. 26.7%). Those occurring with $\geq 1\%$ greater frequency in the pooled FOLFOXIRI-BEV group versus FOLFOX-BEV included hypertension (19.9% vs. 13.3%),

Table 3. ORR, PFS, and OS for cFOLFOXIRI-BEV and sFOLFOXIRI-BEV versus FOLFOX-BEV by tumor molecular biomarker status and tumor location

Tumor molecular biomarker status (biomarker-evaluable population)	cFOLFOXIRI-BEV (n = 57)	sFOLFOXIRI-BEV (n = 67)	FOLFOX-BEV (n = 58)
RAS wild-type^a	n = 28	n = 29	n = 27
ORR			
Odds ratio vs. FOLFOX-BEV (90% CI)	2.0 (0.7–5.3)	7.5 (1.9–29.3)	—
ORR %	78.6	93.1	63.0
p value (one-sided Cochran-Mantel-Haenszel) ^b	.256	.016	—
PFS			
Stratified HR vs. FOLFOX-BEV (90% CI) ^c	0.7 (0.4–1.2)	0.6 (0.3–1.0)	—
Median PFS (90% CI), mo	16.6 (8.6–19.4)	16.1 (12.2–17.7)	9.6 (7.5–16.4)
p value (one-sided log-rank) ^b	.210	.022	—
OS			
Stratified HR vs. FOLFOX-BEV (90% CI) ^c	1.1 (0.5–2.5)	1.2 (0.5–2.7)	—
Median OS (90% CI), mo	26.5 (21.8–34.0)	26.3 (19.0–NE)	27.0 (25.2–NE)
p value (one-sided log-rank) ^b	.647	.441	—
RAS mutant	n = 29	n = 38	n = 31
ORR			
Odds ratio vs. FOLFOX-BEV (90% CI)	1.5 (0.6–3.6)	1.4 (0.6–3.2)	—
ORR %	72.4	71.1	64.5
p value (one-sided Cochran-Mantel-Haenszel) ^b	.496	.547	—
PFS			
Stratified HR vs. FOLFOX-BEV (90% CI) ^c	0.5 (0.3–0.9)	0.7 (0.5–1.2)	—
Median PFS (90% CI), mo	12.5 (9.5–16.9)	9.3 (7.5–11.5)	8.1 (7.4–13.0)
p value (one-sided log-rank) ^b	.037	.171	—
OS			
Stratified HR vs. FOLFOX-BEV (90% CI) ^c	1.0 (0.5–2.1)	0.9 (0.5–1.8)	—
Median OS (90% CI), mo	NE (18.7–NE)	NE (21.2–NE)	NE (20.5–NE)
p value (one-sided log-rank) ^b	.593	.356	—
BRAF^d wild-type	n = 53	n = 62	n = 54
ORR			
Odds ratio vs. FOLFOX-BEV (90% CI)	2.0 (1.0–4.1)	2.5 (1.2–5.1)	—
ORR %	77.4	80.7	63.0
p value (one-sided Cochran-Mantel-Haenszel) ^b	.108	.031	—
PFS			
Stratified HR vs. FOLFOX-BEV (90% CI) ^c	0.6 (0.4–0.8)	0.6 (0.4–0.9)	—
Median PFS (90% CI), mo	15.3 (11.4–16.9)	12.8 (10.4–15.3)	9.5 (7.5–11.3)
p value (one-sided log-rank) ^b	.018	.018	—
OS			
Stratified HR vs. FOLFOX-BEV (90% CI) ^c	1.0 (0.6–1.7)	0.9 (0.5–1.5)	—
Median OS (90% CI), mo	26.5 (23.7–34.0)	NE (26.3–NE)	NE (23.7–NE)
p value (one-sided log-rank) ^b	.458	.237	—
Tumor location (ITT population^e)	cFOLFOXIRI-BEV (n = 92)	sFOLFOXIRI-BEV (n = 92)	FOLFOX-BEV (n = 94)
Left	n = 51	n = 53	n = 57
ORR, %	82.4	79.2	57.9
p value (one-sided Cochran-Mantel-Haenszel) ^f	.005	.011	—

(continued)

Table 3. (continued)

Tumor location (ITT population ^e)	cFOLFOXIRI-BEV (n = 92)	sFOLFOXIRI-BEV (n = 92)	FOLFOX-BEV (n = 94)
Median PFS (90% CI), mo	11.1 (9.7–13.4)	11.5 (9.3–13.3)	9.5 (7.6–11.2)
<i>p</i> value (one-sided log-rank) ^f	.138	.056	—
Right	n = 41	n = 39	n = 37
ORR, %	61.0	66.7	70.3
<i>p</i> value (one-sided Cochran-Mantel-Haenszel) ^f	.388	.651	—
Median PFS (90% CI), mo	16.7 (9.5–19.5)	10.9 (7.5–15.6)	10.2 (7.5–14.3)
<i>p</i> value (one-sided log-rank) ^f	.006	.152	—

^a*RAS* wild-type was defined as metastatic colorectal cancer that was wild-type for both *KRAS* and *NRAS*. Ninety-one patients had *KRAS* wild-type metastatic colorectal cancer (regardless of *NRAS* status) in the overall population. In both the *RAS* and *KRAS* wild-type groups, 21 patients had received prior cetuximab or panitumumab treatment.

^bBased on analysis stratified by extent of metastatic disease (liver-limited disease vs. non-liver-limited disease) and tumor location (left vs. right) after correction postrandomization.

^cCox proportional hazards model that also included the extent of metastatic disease (liver-limited vs. non-liver-limited disease) and tumor location (left vs. right) after correction postrandomization.

^dAll *BRAF* mutations were V600 with the exception of four mutations, of which three (L597R, D594G, and K552I) are likely similar to V600 in functionality, and one (S147G) has unknown functional significance.

^eTumor locations are reported with postrandomization corrections from medical history data. Two patients were excluded from the analysis due to unknown tumor location status.

^fBased on analysis stratified by extent of metastatic disease (liver-limited disease vs. nonliver-limited disease) after correction postrandomization.

Abbreviations: —, not applicable; cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; CI, confidence interval; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab.

Table 4. Overview of treatment-emergent adverse events (safety population)

	cFOLFOXIRI-BEV (n = 91), n (%)	sFOLFOXIRI-BEV (n = 90), n (%)	FOLFOX-BEV (n = 90), n (%)
Any TEAE	91 (100)	89 (99)	90 (100)
Grade ≥ 3 TEAE	83 (91)	78 (87)	77 (86)
Any serious TEAE	39 (43)	42 (47)	43 (48)
TEAE of special interest for chemotherapy	57 (63)	45 (50)	39 (43)
TEAE of special interest for bevacizumab	33 (36)	28 (31)	24 (27)
TEAE leading to withdrawal from study treatment	42 (46)	36 (40)	40 (44)
TEAE leading to study discontinuation	2 (2)	2 (2)	1 (1)
Fatal TEAE	3 (3)	5 (6)	3 (3)

Abbreviations: cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; TEAE, treatment-emergent adverse event.

arterial thromboembolic events (3.3% vs. 0%), and proteinuria (1.1% vs. 0%). Bleeding/hemorrhage (1.7% vs. 5.6%) and fistula/abscess (0.6% vs. 2.2%) occurred with lower frequency in the pooled FOLFOXIRI-BEV group versus FOLFOX-BEV.

DISCUSSION

STEAM was the largest study of FOLFOXIRI-BEV in patients in the U.S. and the first to compare a sequential FOLFOXIRI-BEV regimen with FOLFOX-BEV. In this analysis, we observed both numerically higher ORR for cFOLFOXIRI-BEV versus FOLFOX-BEV and an increase in median PFS

for pooled concurrent and sequential FOLFOXIRI-BEV versus FOLFOX-BEV. Biomarker analyses indicated that cFOLFOXIRI-BEV and sFOLFOXIRI-BEV produced numerically higher ORR and median PFS compared with FOLFOX-BEV in patients with wild-type *RAS* or *BRAF* tumors. Consistent with these differences in efficacy, cFOLFOXIRI-BEV treatment also resulted in numerically higher complete liver resection rates compared with FOLFOX-BEV. Because the primary ORR endpoint for STEAM was not met, the study was closed early, and the efficacy data presented in this analysis are final.

These data support the results of the phase III TRIBE study conducted by the Gruppo Oncologico del Nord Ovest, which demonstrated an ORR of 65% for cFOLFOXIRI-BEV

Table 5. Grade ≥ 3 TEAEs occurring in at least five patients (safety population)

Grade ≥ 3 TEAEs	cFOLFOXIRI-BEV (n = 91), n (%)	sFOLFOXIRI-BEV (n = 90), n (%)	FOLFOX-BEV (n = 90), n (%)
Neutropenia^a	52 (57)	37 (41)	32 (36)
Diarrhea	20 (22)	9 (10)	11 (12)
Hypertension	20 (22)	20 (22)	14 (16)
Fatigue	11 (12)	5 (6)	5 (6)
Hypokalemia	10 (11)	6 (7)	6 (7)
Dehydration	8 (9)	3 (3)	5 (6)
Nausea	8 (9)	5 (6)	5 (6)
Pulmonary embolism	7 (8)	6 (7)	5 (6)
Anemia ^b	6 (7)	3 (3)	9 (10)
Neuropathy peripheral	6 (7)	0	6 (7)
Vomiting	6 (7)	2 (2)	4 (4)
Abdominal pain	5 (6)	1 (1)	8 (9)
Ascites	4 (4)	0	2 (2)
Palmar-plantar erythrodysesthesia syndrome	4 (4)	4 (4)	2 (2)
Syncope	4 (4)	2 (2)	4 (4)
Constipation	3 (3)	1 (1)	2 (2)
Decreased appetite	3 (3)	2 (2)	1 (1)
Febrile neutropenia	3 (3)	3 (3)	3 (3)
Thrombocytopenia ^c	3 (3)	3 (3)	0
Large intestine perforation	2 (2)	2 (2)	1 (1)
Leukopenia ^d	2 (2)	5 (6)	2 (2)
Peripheral sensory neuropathy	2 (2)	0	4 (4)
Small intestinal obstruction	2 (2)	3 (3)	5 (6)
Stomatitis	2 (2)	3 (3)	1 (1)
Back pain	1 (1)	2 (2)	3 (3)
Blood bilirubin increased	1 (1)	1 (1)	4 (4)
Hyponatremia	1 (1)	2 (2)	4 (4)
Pneumonia	1 (1)	5 (6)	1 (1)
Sepsis	1 (1)	2 (2)	4 (4)
Urinary tract infection	1 (1)	2 (2)	3 (3)
Hyperglycemia	0	2 (2)	4 (4)

Bolded text indicates TEAEs of interest for chemotherapy.

^aCombines the preferred terms neutropenia and neutrophil count decreased.

^bCombines the preferred terms anemia and hemoglobin decreased.

^cCombines the preferred terms thrombocytopenia and platelet count decreased.

^dCombines the preferred terms leukopenia and white blood cell count decreased.

Abbreviations: cFOLFOXIRI-BEV, concurrent 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; FOLFOX-BEV, 5-fluorouracil/leucovorin/oxaliplatin plus bevacizumab; sFOLFOXIRI-BEV, sequential 5-fluorouracil/leucovorin/oxaliplatin/irinotecan plus bevacizumab; TEAE, treatment-emergent adverse event.

compared with 53% for FOLFIRI-BEV [12, 13], and the phase II OLIVIA trial, a multinational European study, which found a tumor response rate of 81% for FOLFOXIRI-BEV compared with 62% for a modified FOLFOX-BEV regimen [14]. All three studies yielded prolonged PFS for FOLFOXIRI-BEV versus the control arms [12–14]. Intriguingly, results from both STEAM and OLIVIA also suggest that FOLFOXIRI-BEV may have the potential to increase curative liver resection rates compared with FOLFOX-BEV [14]. The overall results from STEAM, TRIBE, and OLIVIA support the application of the triplet regimen in combination with bevacizumab in improving clinical

outcomes compared with either the FOLFOX or FOLFIRI doublet regimens with bevacizumab. Additionally, this study demonstrates that sequential FOLFOXIRI-BEV has activity in colorectal tumors, supporting it as a potential treatment option in patients with mCRC.

Compared with FOLFOX-BEV and FOLFIRI-BEV, FOLFOXIRI-BEV was associated with a manageable increase in toxicity in TRIBE and OLIVIA [12, 14]. No new safety signals were observed with cFOLFOXIRI-BEV or sFOLFOXIRI-BEV in the STEAM analysis, confirming the safety and feasibility of FOLFOXIRI-BEV treatment in patients in the U.S. Although the

incidence of some TEAEs (e.g., grade ≥ 3 neutropenia and diarrhea) were numerically lower in the sFOLFOXIRI-BEV arm compared with cFOLFOXIRI-BEV, the incidence of grade 4 and 5 TEAEs was similar, and we observed no overall differences in safety between the concurrent and sequential regimens.

Tumor location and molecular biomarkers, such as *RAS* and *BRAF*, have been shown to influence clinical outcomes and/or treatment efficacy in colorectal tumors [16, 19]. Although therapies targeting epidermal growth factor receptor are commonly used in the treatment of mCRC, tumors with activating *KRAS* and *NRAS* mutations are typically refractory to these agents. The TRIBE study found that *RAS* and *BRAF* status did not affect the treatment effect of FOLFOXIRI-BEV compared with FOLFIRI-BEV [13]. In the current analysis, cFOLFOXIRI-BEV and sFOLFOXIRI-BEV conferred numerically higher ORR and PFS compared with FOLFOX-BEV independent of *RAS* mutational status. Too few patients in STEAM had *BRAF*-mutated disease to allow correlation with outcomes.

Right-sided tumors are associated with a markedly poorer prognosis compared with left-sided tumors [16]. Interestingly, in this analysis, cFOLFOXIRI-BEV imparted a higher PFS in patients with right-sided tumors than in those with left-sided tumors. cFOLFOXIRI-BEV and sFOLFOXIRI-BEV were associated with high median PFS regardless of tumor sidedness, and improved PFS compared with FOLFOX-BEV in both right- and left-sided tumors. ORR was notably higher with cFOLFOXIRI-BEV and sFOLFOXIRI-BEV treatment in left-sided (but not right-sided) tumors compared with FOLFOX-BEV.

The small numbers of patients in some biomarker subgroups, such as the *BRAF*-mutated group, and the use of 90% CI for ORR, PFS, and OS limited the interpretation of these analyses. Furthermore, because of early closure of the trial, results for OS are immature, and data collected for the second-line treatment phase of the study were insufficient for analyses of efficacy, toxicity, or treatments after protocol. Additional biomarker analyses are ongoing to identify subgroups of patients who might derive the greatest benefits from treatment with FOLFOXIRI-BEV.

The concept of aggressive induction for the treatment of mCRC is supported by the TRIBE study [12, 13]. The use of multiple anticancer agents with distinct mechanisms of action may help prevent the development of resistant clones and provide longer disease control [20]. Our findings suggest that cFOLFOXIRI-BEV and sFOLFOXIRI-BEV are active and well tolerated in patients with mCRC, consistent with prior data from TRIBE and OLIVIA, as well as several recent meta-analyses [21, 22]. cFOLFOXIRI-BEV conferred either statistically significant or strong trends for improvements in both ORR and PFS compared with FOLFOX-BEV, benefits that appeared largely independent of the molecular characteristics or sidedness of the tumor. To further optimize the first-line FOLFOXIRI-BEV treatment strategy, the randomized, phase III TRIBE-2 trial will directly assess whether the use of concurrent FOLFOXIRI-BEV improves survival relative to sequential FOLFOXIRI-BEV [23]. Taken together, these data support the use of concurrent or sequential FOLFOXIRI-BEV as potential first-line treatment options for patients with mCRC who can tolerate these treatment regimens.

CONCLUSION

The phase II randomized STEAM trial was the largest study of FOLFOXIRI-BEV in patients in the U.S. In this study, data showed that both concurrent and sequential FOLFOXIRI-BEV numerically improved clinical outcomes compared with FOLFOX-BEV in patients with mCRC in the first line, with acceptable tolerability. These data confirm the feasibility of these regimens as potential first-line treatments for mCRC; however, the patient population most likely to benefit from triplet chemotherapy with BEV remains to be addressed.

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DISCLOSURES

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