Title

MAVERICC, a Randomized, Biomarker-stratified, Phase II Study of mFOLFOX6-Bevacizumab versus FOLFIRI-Bevacizumab as First-line Chemotherapy in Metastatic Colorectal CancerPhase II study of mFOLFOX6-BV vs. FOLFIRI-BV in mCRC

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MAVERICC, a Randomized, Biomarker-stratified, Phase II Study of mFOLFOX6-Bevacizumab versus FOLFIRI-Bevacizumab as First-line Chemotherapy in Metastatic Colorectal Cancer

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Abstract

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Disclosure of Potential Conflicts of Interest

L. Yau holds ownership interest (including patents) in Genentech. I. Bosanac holds ownership interest (including patents) in F. Hoffmann-La Roche Ltd. N. Choong is an employee of Genentech and holds ownership interest (including patents) in Roche. C. Mancao holds ownership interest (including patents) in Roche GNE. H.-J. Lenz is a consultant/advisory board member for Genentech. No potential conflicts of interest were disclosed by the other authors.

Purpose: MAVERICC compared the efficacy and safety of modified leucovorin/5-fluorouracil/oxaliplatin plus bevacizumab (mFOLFOX6-BV) with leucovorin/5-fluorouracil/irinotecan plus bevacizumab (FOLFIRI-BV) in patients with previously untreated metastatic colorectal cancer (mCRC).

Patients and Methods: MAVERICC was a global, randomized, open-label, phase II study. Primary objectives were to assess associations between (i) excision repair cross-complementing 1 (ERCC1) expression with progression-free survival (PFS), and (ii) plasma VEGF A (VEGF-A) with PFS in patients with previously untreated mCRC receiving mFOLFOX6-BV or FOLFIRI-BV. Before randomization, patients were stratified by tumoral ERCC1/β-actin mRNA expression level and region.

Results: Of 376 enrolled patients, 188 each received mFOLFOX6-BV and FOLFIRI-BV. PFS and overall survival (OS) were comparable between FOLFIRI-BV and mFOL-FOX6-BV, with numerically higher PFS [HR = 0.79; 95% CI (confidence interval): 0.61–1.01; $P = 0.06$] and OS (HR = 0.76; 95% CI: 0.56–1.04; $P = 0.09$) observed for FOLFIRI-BV. In the high ERCC1 subgroup, PFS and OS were comparable between treatment groups (PFS, HR = 0.84; 95% CI: 0.56–1.26; $P = 0.40$; OS, HR = 0.80; 95% CI: 0.51–1.26; $P = 0.33$). Across treatment groups, high plasma VEGF-A levels (>5.1 pg/mL) were observed with shorter PFS (HR = 1.19; 95% CI: 0.93–1.53; $P = 0.17$) and significantly shorter OS (HR = 1.64; 95% CI: 1.20–2.24; $P < 0.01$) versus low levels (≤5.1 pg/mL). Safety findings for FOLFIRI-BV or mFOLFOX6-BV were comparable with those reported previously.

Conclusions: First-line FOLFIRI-BV and mFOLFOX6-BV had comparable PFS and OS, similar to results in patients with high baseline tumor ERCC1 levels. There were no new safety signals with these bevacizumab-containing regimens.

Translational Relevance

In the phase II MAVERICC study, first-line treatment of metastatic colorectal cancer (mCRC) with leucovorin/5-fluorouracil/oxaliplatin plus bevacizumab (mFOLFOX6-BV) or leucovorin/5-fluorouracil/irinotecan plus bevacizumab (FOLFIRI-BV) resulted in comparable progression-free survival (PFS) and overall survival (OS), although there was a numerical trend toward longer PFS and OS with FOLFIRI-BV versus mFOLFOX6-BV. These results suggest that FOLFIRI in combination with bevacizumab is promising when compared with mFOLFOX6. MAVERICC was the first prospective mCRC study using gene expression data from both tissue (excision repair cross-complementing 1 gene expression levels) and blood (plasma VEGF A protein levels) to evaluate the efficacy of mCRC chemotherapy regimens. Ongoing biomarker work is expected to further delineate biomarker-driven subsets that may benefit from a particular chemotherapy backbone.

Introduction

Standard-of-care for patients with previously untreated metastatic colorectal cancer (mCRC) includes modified leucovorin/5-fluorouracil/oxaliplatin (mFOLFOX6) or leucovorin/5-fluorouracil/irinotecan (FOLFIRI) with or without addition of a targeted biologic agent (1, 2). Together with fluorouracil-based chemotherapy, bevacizumab, a recombinant monoclonal VEGF inhibitor, improves mCRC survival (3, 4). Although there appears to be no survival

difference between mFOLFOX6 or FOLFIRI chemotherapy backbones (5), it remains unknown whether there is a preferred backbone for bevacizumab therapy. In addition, there are currently no validated predictive biomarkers for oxaliplatin-, irinotecan-, or bevacizumab-based therapies.

Identifying predictive biomarkers may lead to more personalized, optimized mCRC treatments. High tumor excision repair cross-complementing group 1 (ERCC1) expression is associated with poor clinical outcomes following oxaliplatin-based combination therapy (6–8). Intratumoral ERCC1 expression may be a marker for chemoresistance to platinum compounds in patients with mCRC (6). A meta-analysis of 1,787 patients with gastric cancer and colorectal cancer demonstrated that *ERCC1* and *ERCC2* polymorphisms are useful prognostic factors in oxaliplatin-based chemotherapies (9). In addition, a 3-gene signature that included ERCC1 was reported as a potential predictive biomarker for irinotecan sensitivity in gastric cancer (10). Plasma VEGF-A has also been explored as a potential biomarker for clinical outcomes with oxaliplatin-and irinotecan-based chemotherapy regimens (11–14). In a study investigating irinotecan-based regimens combined with bevacizumab as first-line mCRC treatment, *VEGF* genotypes were found to be potentially predictive for clinical outcomes (14). However, the predictive role of plasma VEGF-A across tumor types is unclear (11–13).

To define the optimal mCRC treatment regimen, the Marker Evaluation for Avastin Research in Colorectal Cancer (MAVERICC) study compared the efficacy and safety of mFOLFOX6-BV with FOLFIRI-BV in patients with previously untreated mCRC, stratified by ERCC1 expression levels. MAVERICC was the first prospective study evaluating tumoral ERCC1 and plasma VEGF-A as potential biomarkers for outcomes following first-line (1L) treatment with oxaliplatin and bevacizumab.

Patients and Methods

Study design

MAVERICC was a global, randomized, open-label, phase II, multicenter study. Eligible patients with mCRC were randomized 1:1 to (i) intravenous bevacizumab (5 mg/kg) with 2-hour intravenous infusion of modified folinic acid (leucovorin, 400 mg/m^2) and oxaliplatin (85 mg/m^2), followed by 400 mg/m^2 i.v. bolus and 2,400 mg/m^2 46-hour continuous intravenous infusion of 5-fluorouracil (mFOLFOX6-BV), or (ii) intravenous bevacizumab (5 mg/kg) with a 2-hour intravenous infusion of modified folinic acid (leucovorin, 400 mg/m^2) and irinotecan (180 mg/m^2), followed by 400 mg/m^2 i.v. bolus and 2,400 mg/m^2 46-hour continuous intravenous infusion of 5 fluorouracil (FOLFIRI-BV). Patients were stratified by ERCC1/β-actin mRNA expression [high ($>1.7 \times 10^{-3}$) or low ($\leq 1.7 \times 10^{-3}$)] and by geographic regions: United States (US), Canada/Estonia/Ireland (ex-US1), and Switzerland/Norway/Portugal (ex-US2).

The trial comprised a 21-day screening period, treatment phase, 2 follow-up safety visits occurring 28 (±3) days and 3 months (±7 days) after last treatment dose, and a survival follow-up period. Patients received treatment every 2 weeks and remained on treatment

until disease progression (PD) or unacceptable toxicity. If oxaliplatin or irinotecan were discontinued, bevacizumab and 5-fluorouracil or capecitabine were continued until PD.

Tumor ERCC1 levels were determined centrally at Response Genetics Inc. (now Cancer Genetics), using a proprietary RT-PCR technology (US patent 6,248,535). Screening blood samples for plasma VEGF-A levels were collected and measured with immunologic multiparametric chip technology at MicroCoat Biotechnologie GmbH. KRAS exon 2 status was assessed.

Study population

Adults (≥18 years) with histologically or cytologically confirmed mCRC and ≥1 measurable and unresectable lesion were recruited. Inclusion criteria included Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, liver, and renal function. Exclusion criteria included prior systemic mCRC treatment (except palliative radiosensitizers) or adjuvant chemotherapy completed <12 months before randomization.

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent, and the study was approved by relevant Institutional Review Board or independent ethics committee at each participating site.

Objectives and outcome measures

Primary objectives were to evaluate associations between (i) ERCC1 expression with progression-free survival (PFS), and (ii) plasma VEGF-A with PFS in patients with previously untreated mCRC receiving mFOLFOX6-BV or FOLFIRI-BV. The primary efficacy outcome measure was PFS, defined as time from randomization to documented PD, as determined by RECIST v1.1, or death on study, whichever occurred first.

Secondary objectives were to assess associations between (i) ERCC1 expression (high vs. low) with efficacy outcomes [OS, objective response (OR), or hepatic metastases resection rates] and risk of developing specific toxicities, (ii) pVEGF-A [high (>5.1 pg/mL) vs. low (≤5.1 pg/mL), cut at median levels] and OS or risk of specific toxicities, and (iii) chemotherapy arm with PFS by ERCC1 (high/low) and VEGF-A (high/low) biomarker subgroups. OS was defined as time from randomization to death from any cause. OR was assessed using RECIST v1.1 (every 6 weeks). PFS and OS in tumor location subgroups were explored.

Statistical analyses

Assuming a median PFS of 10 months for 1L patients with mCRC and 1:1 randomization of 360 patients, the study was expected to provide 80% and 89% power to detect HRs of 0.70 and 0.67, respectively, on PFS, between treatment groups. Within high ERCC1 levels, the study would provide 71% power to detect a HR of 0.64 between treatments, assuming a 50% prevalence of high ERCC-1 levels (i.e., 180 patients per ERRC1 subgroup). These estimates were based on two-sided log-rank tests at 0.05 significance.

Efficacy analyses were performed on the intent-to-treat (ITT) population. Cox proportional hazard models with stratification were utilized for PFS comparisons between treatment groups and biomarker subgroups. For PFS comparison between treatment groups, the Cox model was stratified by geographic region and ERCC1 expression levels (high/low). The Cox model was stratified by geographic region for comparison between tumor levels of ERCC1, and was unstratified for comparison between mFOLFOX6-BV and FOLFIRI-BV within each ERCC1 subgroup. For comparison between VEGF-A levels, the Cox model was stratified by ERCC1 levels.

OS analyses were performed similarly. OR rates (ORR) for mFOLFOX6-BV and FOLFIRI-BV groups were compared using the two-sided Cochran–Mantel–Haenszel test stratified by ERCC1 levels and geographic region.

Safety data were summarized by treatment groups for the safety-evaluable population, defined as all ITT patients who received ≥1 partial or complete dose of study treatment. Adverse events (AE) were coded by the Medical Dictionary for Regulatory Activities (MedDRA 18.1), and graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0).

Results

Patient demographics

In total, 376 patients (ITT population) were enrolled across 52 study sites in the United States, exUS1, and exUS2 ($n = 318$ patients, US; $n = 58$ patients, all other countries); 188 each were randomized to mFOLFOX6-BV or FOLFIRI-BV. Median follow-up was 18.4 months (interquartile range: 12.0–25.4 months) in mFOLFOX6-BV and 18.6 months (interquartile range: 11.8–24.9 months) in FOLFIRI-BV. In mFOLFOX6-BV, the median number of oxaliplatin and fluoropyrimidine cycles was 11 (range: 1–43) and 13 (range: 1–70), respectively. In mFOLFIRI-BV, the median number of irinotecan and fluoropyrimidine cycles was 14 (range: 1–59) and 15 (range: 1–59), respectively. The median number of bevacizumab cycles was 12 (range: 1–70) and 14 (range: 1–59) in the mFOLFOX6-BV and FOLFIRI-BV groups, respectively. Demographic and baseline characteristics of the ITT population were generally well balanced between treatment groups (Table 1). One and 6 patients were not evaluable for ERCC1 and VEGF-A levels, respectively.

Clinical efficacy

In the ITT population, a numerically greater median PFS [HR = 0.79; 95% CI (confidence interval): 0.61–1.01; $P = 0.06$] and OS (HR = 0.76; 95% CI: 0.56–1.04; $P = 0.09$) were observed in the FOLFIRI-BV group (Fig. 1). PFS (HR 0.99; 95% CI: 0.77–1.28; $P = 0.96$) and OS (HR = 1.19; 95% CI: 0.87–1.62; $P = 0.28$) were comparable in the ERCC1 subgroups. In the ERCC1-high subgroup, PFS (HR = 0.84; 95% CI: 0.56–1.26; $P = 0.39$) and OS (HR = 0.80; 95% CI: 0.51–1.26; $P = 0.33$) were comparable between FOLFIRI-BV and mFOLFOX6-BV groups (Fig. 2A–C). Similar results were observed for PFS (HR 0.76; 95% CI: 0.55–1.03; $P = 0.08$) and OS (HR = 0.74; 95% CI: 0.49–1.12; $P = 0.15$) in the ERCC1-low subgroup (Fig. 2C–E).

Across treatment groups, patients with high VEGF-A levels had shorter median PFS (HR = 1.19; 95% CI: 0.93–1.53; $P = 0.17$) and significantly shorter median OS (HR = 1.64; 95% CI: 1.20–2.24; $P = < 0.01$) than patients with low VEGF-A levels. Median OS was 22.8 months (95% CI: 18.76–27.27) in the VEGF-A–high group and 27.9 months (95% CI: 24.97–36.01) in the VEGF-A–low group. Results for PFS and OS by site of origin in both mFOLFOX6-BV and FOLFIRI-BV groups are shown in Table 2. Generally, FOLFIRI-BV treatment resulted in numerically longer median PFS and OS versus mFOLFOX6-BV; these differences were also observed across the ERCC1 and VEGF-A combination categories, and within right- or left-sided tumor categories (Table 2).

A similar proportion of patients treated with FOLFIRI-BV and mFOLFOX6-BV achieved OR (ORR, 65.4% vs. 61.2%; Supplementary Table S1). Response rates to FOLFIRI-BV in ERCC1-high and -low tumors were generally similar. However, for mFOLFOX6-BV, ERCC1-low tumors had numerically higher ORR (63.7%) than ERCC1-high tumors (56.3%). In the subgroup analysis of ERCC1 by VEGF-A, ORRs were similar between treatment groups within each subgroup except the ERCC1 high/VEGF-A high subgroup, where a greater proportion of patients treated with FOLFIRI-BV achieved OR than mFOLFOX6-BV (ORR, 64.5% vs. 39.3%); however, as the number of patients in these subgroups were limited, results should be interpreted with caution (Supplementary Table S2).

Liver resection rates were generally comparable between treatment groups, both in the ITT population and within the subgroup of patients with high ERCC1 levels at baseline (Supplementary Table S3).

Safety

The safety-evaluable population included 368 patients ($n = 185$, mFOLFOX6-BV; $n = 183$, FOLFIRI-BV). All patients in the mFOLFOX6-BV group and 99% of patients in the FOLFIRI-BV group had ≥1 treatment-emergent AE (TEAE; Table 3). Overall, grade ≥3 AE rates were similar between mFOLFOX6-BV and FOLFIRI-BV [148/185 (80.0%) vs. 149/183 (81.4%), respectively]. Grade 5 AEs were reported in 10 patients ($n = 6$, mFOLFOX6-BV; $n = 4$, FOLFIRI-BV).

The proportion of patients with ≥1 TEAE leading to study treatment withdrawal was greater in the mFOLFOX6-BV group than the FOLFIRI-BV group (47.0% vs. 23.5%), primarily due to a high percentage (42.2%) in the mFOLFOX6-BV group who experienced ≥1 TEAE requiring oxaliplatin withdrawal. ERCC1 levels were not correlated with oxaliplatin tolerability in the mFOLFOX6-BV group, as similar rates of AEs leading to oxaliplatin withdrawal were observed [ERCC1 high: 30/64 (46.9%) vs. ERCC1 low: 48/121 (39.7%)].

Similar rates for AE of special interest (AESI) were observed in both treatment groups (30.3%, mFOLFOX6-BV; 31.1%, FOLFIRI-BV). The most frequently reported AESIs in both groups were grade ≥3 uncontrolled hypertension and ≥3 venous thromboembolic events.

Discussion

MAVERICC was the first prospective mCRC study using biomarker data in both tissue (ERCC1 gene expression levels) and blood (plasma VEGF-A protein levels) to explore treatment efficacy of mFOLFOX6-BV and FOLFIRI-BV. To define the optimal mCRC treatment regimen, tumor ERCC1 and pVEGF-A were studied as potential biomarkers for oxaliplatin- and bevacizumab-containing regimens. Consistent with prior findings (5), FOLFIRI-BV and mFOLFOX6-BV showed comparable PFS in the 1L treatment of mCRC, although a numerically greater median PFS was observed with FOLFIRI-BV treatment. Among patients with high tumor ERCC1 levels, there was no statistically significant difference between treatment arms for PFS or OS, but a numerical trend toward PFS improvement was again seen in the FOLFIRI-BV group. Baseline VEGF-A subgroups also showed comparable PFS, though a longer median OS was observed in patients with low versus high pVEGF-A levels at baseline.

Overall, compared with mFOLFOX6-BV, a numerical trend for longer median PFS and OS was observed following FOLFIRI-BV within each combination of the ERCC1 and VEGF-A subgroups. A previous study reported a similar trend toward improved median PFS (12.1 months vs. 10.7 months; HR, 0.905; 95% CI: 0.723–1.133) and OS (31.4 months vs. 30.1 months; HR, 0.990; 95% CI: 0.785–1.249) with FOLFIRI-BV versus mFOLFOX6-BV in patients with mCRC (15). These results suggest that FOLFIRI may be a better partner for bevacizumab compared with mFOLFOX6 in terms of efficacy outcomes, and further improvements in efficacy may be optimized with an appropriate molecularly defined subgroup. Furthermore, in our study, the ITT population showed PFS and OS benefits with FOLFIRI-BV among right- and left-sided tumors. The role of sidedness in response is being explored with next-generation sequencing. One hypothesis, focusing on oxaliplatin, is related to the association between KRAS mutations and inability to induce ERCC1. KRAS-mutated cell lines are more sensitive to oxaliplatin than KRAS–wild-type cell lines (16), and some studies have found that KRAS mutations are prognostic in colorectal cancer (17, 18). ERCC1 evaluation without considering KRAS status may be one reason no difference was observed, and extended RAS analyses are underway. Though no statistically significant difference in PFS between the treatment groups was observed, exploratory biomarker work is underway to further delineate biomarker-driven subsets that may benefit from a particular chemotherapy backbone. Safety findings in this trial were comparable with previous reports (3, 4).

A lower-than-expected prevalence of tumor ERCC1 in the study population suggests biomarker results observed in MAVERICC should be interpreted with caution. Studies with larger ERCC1 and VEGF-A subgroups may better discern differences between the treatment regimens. ERCC1 and VEGF-A levels were measured at baseline only, so potential longitudinal study–treatment effects on these biomarkers remain unknown. In addition, patients were not stratified by KRAS status.

In summary, mFOLFOX6-BV and FOLFIRI-BV appeared to be comparable when used as 1L mCRC treatment, although there was a numerical trend toward longer PFS and OS with FOLFIRI-BV versus mFOLFOX6-BV. Neither ERCC1 nor VEGF-A levels were associated

with efficacy, and OR and liver resection rates were comparable between the chemotherapy groups. No new safety signals were identified with these bevacizumab-containing regimens. Additional biomarker evaluations from MAVERICC, including next-generation sequencing and NanoString data, are underway. Results from completed genome-wide association studies will be reported separately. This was the first prospective study using gene expression data in both blood and tissue, and may be hypothesis-generating regarding the observed improvement with FOLFIRI-BV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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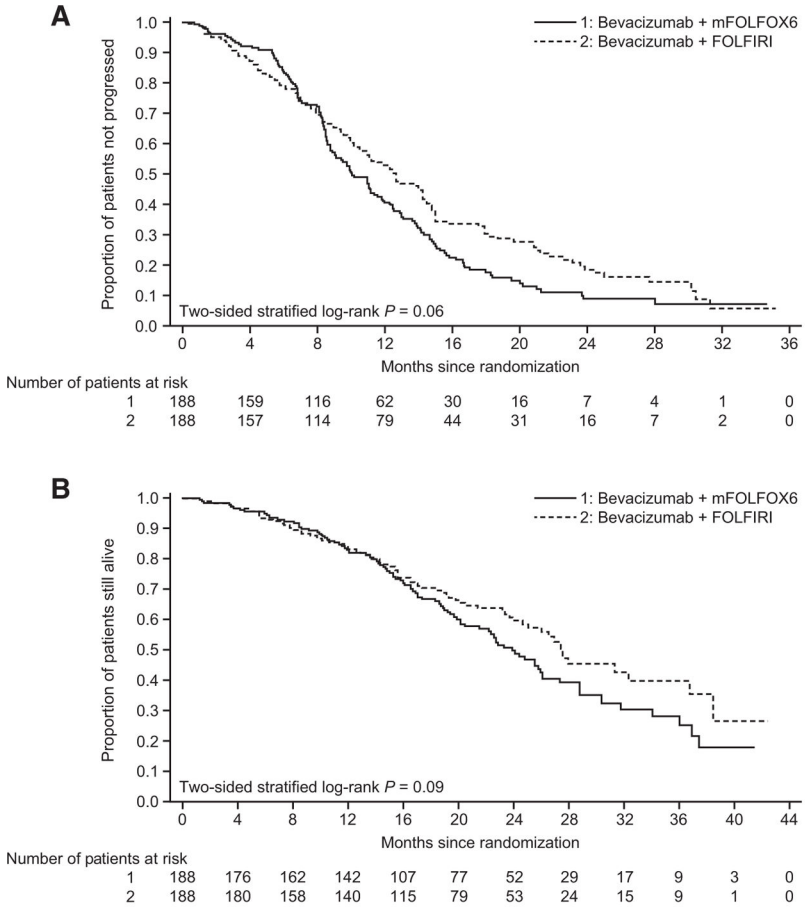

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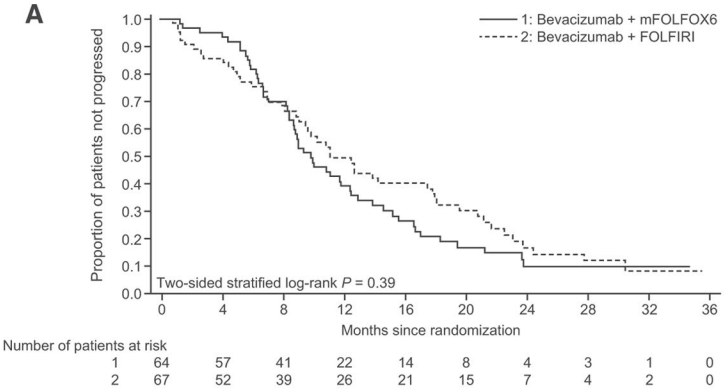
	mFOLFOX6-BV (*n* = 188)	FOLFIRI-BV (*n* = 188)	HR (relative to mFOLFOX6-BV)
Median PFS, mo (95% CI)	10.1 (8.8–11.6)	12.6 (10.5–14.3)	0.79 (95% CI 0.61–1.01), *P* = 0.06
Median OS, mo (95% CI)	23.9 (20.4–26.1)	27.5 (24.6–36.7)	0.76 (95% CI 0.56–1.04) *P* = 0.09

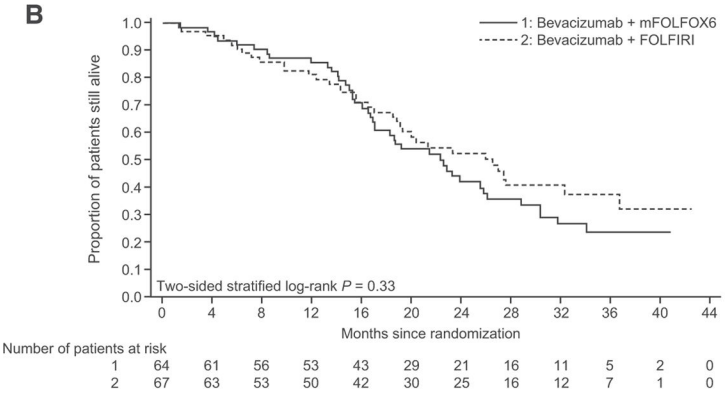
Figure 1.

PFS (**A**), OS (**B**), and median PFS and OS values (**C**) by treatment group. mo, month.

A



B



C

		mFOLFOX6-BV (*n* = 64)	FOLFIRI-BV (*n* = 67)	HR
ERCC-1 expression high (>1.7) (*n* = 131)	Median PFS, mo (95% CI)	9.9 (8.5–12.5)	11.2 (9.1–17.8)	0.84 (95% CI 0.56–1.26), *P* = 0.39
	Median OS, mo (95% CI)	22.5 (17.0–26.1)	26.5 (19.1–36.7)	0.80 (95% CI 0.51–1.26), *P* = 0.33
ERCC-1 expression low (≤1.7) (*n* = 244)	Median PFS, mo (95% CI)	11.0 (8.5–12.3)	12.7 (10.5–14.5)	0.76 (95% CI 0.55–1.03), *P* = 0.08
	Median OS, mo (95% CI)	25.5 (20.4–28.8)	27.9 (25.0–38.4)	0.74 (95% CI 0.49–1.12), *P* = 0.15

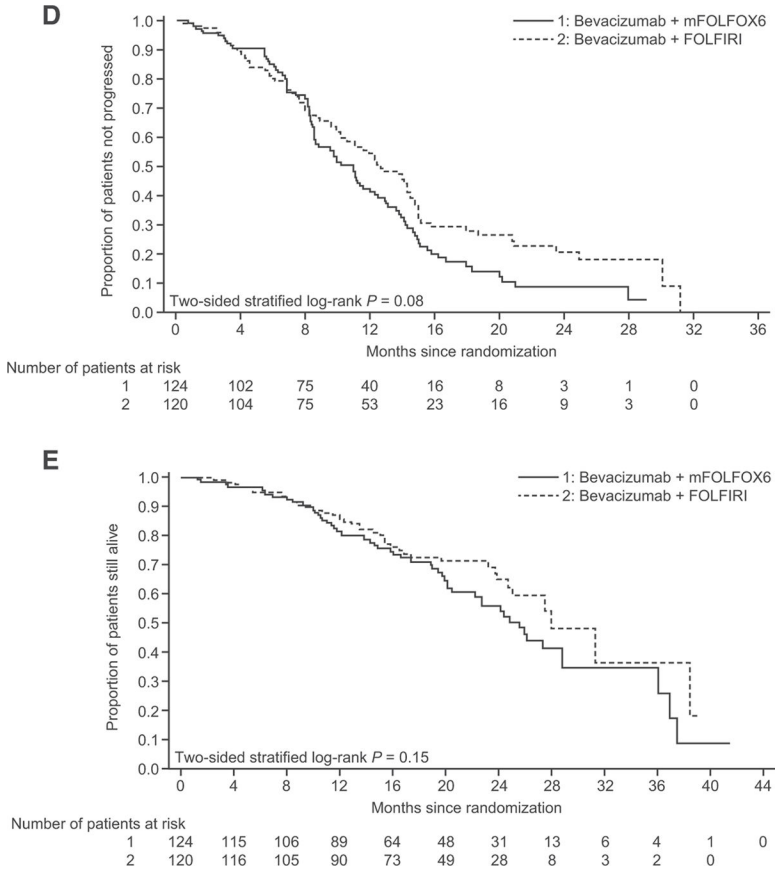


Figure 2.

PFS (**A**) and OS (**B**) in the ERCC1-high subgroup; median PFS and OS values by ERCC1 subgroup and treatment group (**C**); PFS (**D**) and OS (**E**) in the ERCC1-low subgroup. mo, month.

Table 1.

Baseline characteristics

	mFOLFOX6-BV (*n* = 188)	**FOLFIRI-BV (*n* = 188)**
Median age, years (range)	61.0 (31–87)	61.0 (34–81)
Sex, *n* (%)		
Male	122 (64.9)	117 (62.2)
Female	66 (35.1)	71 (37.8)
ECOG performance status, *n* (%)		
0	93 (49.5)	110 (58.5)
1	94 (50.0)	77 (41.0)
Cancer type, *n* (%)		
Colon	131 (69.7)	135 (71.8)
Rectal	50 (26.6)	48 (25.5)
Colon and rectal	7 (3.7)	5 (2.7)
Prior cancer surgery, *n* (%)	118 (62.8)	112 (59.6)
Prior adjuvant therapy, *n* (%)	22 (11.7)	20 (10.6)
Liver-limited disease, *n* (%)	44 (23.4)	36 (19.1)
Tumor location, *n* (%)		
Right	75 (39.9)	79 (42.0)
Left	113 (60.1)	109 (58.0)
Tumor ERCC1 (x10^{-3} ERCC1/β-actin mRNA), mean (SD)	1.6 (1.34)	1.8 (1.32)
High (>1.7), *n* (%)	64 (34.0)	67 (35.6)
Low (≤1.7), *n* (%)	124 (66.0)	120 (63.8)
pVEGF-A, (pg/mL), mean (SD)	9.4 (12.79)	9.1 (12.31)
High (>5.1), *n* (%)	94 (50.0)	91 (48.4)
Low (≤5.1), *n* (%)	90 (47.9)	95 (50.5)
KRAS exon 2 status, *n* (%)		
Wild-type	107 (56.9)	101 (53.7)
Mutation	65 (34.6)	63 (33.5)
Unknown	16 (8.5)	24 (12.8)

ECOG, Eastern Cooperative Oncology Group; ERCC1, excision repair cross-complementing 1; FOLFIRI-BV, leucovorin/5-fluorouracil/irinotecan plus bevacizumab; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; mFOLOX6-BV, modified leucovorin/5-fluorouracil/oxaliplatin plus bevacizumab; mRNA, messenger ribonucleic acid; pVEGF-A, plasma VEGF A.

Table 2.

PFS and OS by treatment, location of primary tumor, and ERCC1- and VEGF-A–level subgroups

		mFOLFOX6-BV Median PFS, mo (95% CI)	FOLFIRI-BV Median PFS, mo (95% CI)	mFOLFOX6-BV Median OS, mo (95% CI)	FOLFIRI-BV Median OS, mo (95% CI)
Right-sided tumor		10 (8.4–12.5; *n* = 75)	11.2 (7.6–14.5; *n* = 79)	22.7 (18.7–27.3; *n* = 75)	27.4 (19.6–NE; *n* = 79)
Left-sided tumor		10.2 (8.6–12.5; *n* = 113)	13.8 (11.1–15.0; *n* = 109)	24.1 (21.5–28.8; *n* = 113)	27.5 (24.6–38.4; *n* = 109)
ERCC1 high	VEGF-A high	8.8 (5.9–10.0; *n* = 28)	11.2 (8.1–18.1; *n* = 31)	17.1 (14.1–23.2; *n* = 28)	20.3 (15.5–27.5; *n* = 31)
	VEGF-A low	12.5 (9.4–15.6; *n* = 35)	12.7 (8.2–20.8; *n* = 35)	25.5 (18.3–34.0; *n* = 35)	32.3 (19.2–NE; *n* = 35)
ERCC1 low	VEGF-A low	9.8 (8.2–12.5; *n* = 66)	11.1 (8.2–14.3; *n* = 59)	24.8 (16.5–28.8; *n* = 66)	27.5 (17.3–31.3; *n* = 59)
	VEGF-A low	11.1 (8.5–13.1; *n* = 55)	14.3 (11.6–15.0; *n* = 60)	25.9 (20.4–NE; *n* = 55)	27.9 (24.6–NE; *n* = 60)

NOTE: Observed *n* = 369/376 for ERCC1 and VEGF-A subgroups. One patient was not evaluable for ERCC1 level and 6 patients were not evaluable for VEGF-A levels. Abbreviations: ERCC1, excision repair cross-complementing 1; mo, month; NE, not estimable.

Table 3.

TEAEs and AESIs with incidence ≥1%

	mFOLFOX6-BV (*n* = 185)	FOLFIRI-BV (*n* = 183)
Total number of deaths, *n* (%)	96 (52)	73 (40)
Deaths related to AE, *n* (%)	8 (4)	6 (3)
Death related to study drug	3 (2)	2 (1)
Number of patients with at least 1 TEAE, *n* (%)	185 (100)	181 (99)
Grade ≥3 TEAE, *n* (%)	148 (80)	149 (81)
TEAE leading to withdrawal from any study treatment, *n* (%)	87 (47)	43 (23)
TEAE leading to study discontinuation, *n* (%)	27 (15)	17 (9)
Number of patients with at least 1 AESI[a] (%)	56 (30)	57 (31)
Uncontrolled hypertension (grade ≥3)	27 (15)	23 (13)
Venous thromboembolic events (grade ≥3)	14 (8)	18 (10)
Gastrointestinal perforation (any grade)	8 (4)	4 (2)
Bleeding other than pulmonary or central nervous system bleeding (grade ≥3)	6 (3)	4 (2)
Bowel obstruction (grade ≥2)	5 (3)	3 (2)
Arterial thromboembolic events (any grade)	4 (2)	9 (5)
Proteinuria (grade ≥3)	4 (2)	2 (1)
Central nervous system bleeding (grade ≥2)	1 (0.5)	2 (1)
Wound dehiscence (grade ≥3)	1 (0.5)	2 (1)
Left ventricular systolic dysfunction (grade ≥4)	1 (0.5)	0 (0)

Abbreviations: AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.

[a]The following adverse events of special interest (AESIs) were predefined for this study: uncontrolled hypertension (grade ≥3), proteinuria (grade 3), arterial thromboembolic event (any grade), venous thromboembolic event (symptomatic grade 3 or 4), left ventricular systolic dysfunction (grade 4), nephrotic syndrome, gastrointestinal perforation (any grade), tracheoesophageal fistula (any grade), fistula (grade 4), bowel obstruction not fully recovered (grade ≥2), wound dehiscence (grade ≥3), pulmonary hemorrhage (grade 2, 3, or 4), central nervous system (CNS) hemorrhage (grade 2, 3, or 4), bleeding other than pulmonary or CNS bleeding (grade ≥3), reversible posterior leukoencephalopathy syndrome (any grade), and AEs leading to bevacizumab or chemotherapy discontinuation. AESIs were defined by their possible association with bevacizumab treatment and occurrence on or after the first treatment until 3 months after the last administration of study drug or study discontinuation/termination, whichever is earlier. The following AESIs did not occur in any patients in this study: nephrotic syndrome, tracheoesophageal fistula, fistula (grade ≥4), pulmonary hemorrhage (grade ≥2), reversible posterior leukoencephalopathy syndrome.