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ORIGINAL REPORT

Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To evaluate the efficacy and safety of bevacizumab when added to first-line oxaliplatin-based chemotherapy (either capecitabine plus oxaliplatin [XELOX] or fluorouracil/folinic acid plus oxaliplatin [FOLFOX-4]) in patients with metastatic colorectal cancer (MCRC).

Patients and Methods
Patients with MCRC were randomly assigned, in a 2 × 2 factorial design, to XELOX versus FOLFOX-4, and then to bevacizumab versus placebo. The primary end point was progression-free survival (PFS).

Results
A total of 1,401 patients were randomly assigned in this 2 × 2 analysis. Median progression-free survival (PFS) was 9.4 months in the bevacizumab group and 8.0 months in the placebo group (hazard ratio [HR], 0.83; 97.5% CI, 0.72 to 0.95; $P = .0023$). Median overall survival was 21.3 months in the bevacizumab group and 19.9 months in the placebo group (HR, 0.89; 97.5% CI, 0.76 to 1.03; $P = .077$). Response rates were similar in both arms. Analysis of treatment withdrawals showed that, despite protocol allowance of treatment continuation until disease progression, only 29% and 47% of bevacizumab and placebo recipients, respectively, were treated until progression. The toxicity profile of bevacizumab was consistent with that documented in previous trials.

Conclusion
The addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved PFS in this first-line trial in patients with MCRC. Overall survival differences did not reach statistical significance, and response rate was not improved by the addition of bevacizumab. Treatment continuation until disease progression may be necessary in order to optimize the contribution of bevacizumab to therapy.

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INTRODUCTION

Bevacizumab (Avastin; Genentech Inc, South San Francisco, CA) is a humanized recombinant monoclonal antibody which binds to and blocks the activity of all isoforms of vascular endothelial growth factor-A (VEGF-A). A pivotal phase III study[1] demonstrated that the addition of bevacizumab to irinotecan plus bolus fluorouracil and leucovorin conferred clinically significant improvements in overall survival (OS), progression-free survival (PFS), as well as response rate (RR), in patients with previously untreated metastatic colorectal cancer (MCRC). Bevacizumab was also shown to produce similar benefits in OS, PFS, and RR when combined with fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) in the second-line setting.[2]

We had initially begun a randomized phase III trial, designated NO16966, comparing the standard FOLFOX-4[3] regimen to the combination of capecitabine and oxaliplatin (XELOX).[4] After the pivotal phase III data for bevacizumab became public in June 2003,[1] the NO16966 protocol was amended to a randomized, 2 × 2 factorial design with two coprimary objectives. The first coprimary objective was to show the PFS noninferiority of XELOX with or without bevacizumab versus FOLFOX-4 with or without bevacizumab.[1] The second coprimary objective, which is the focus of this report, was to evaluate the effect on PFS of bevacizumab versus placebo when combined with oxaliplatin-based chemotherapy (XELOX or FOLFOX-4).

PATIENTS AND METHODS

Patient Population

Patients age ≥ 18 years with histologically confirmed MCRC, one or more unidimensionally measurable lesions, who were not felt to be amenable to curative resection, with an Eastern Cooperative Oncology Group

(ECOG) performance status of ≤ 1, and a life expectancy of longer than 3 months, were enrolled. No prior systemic therapy for MCRC or previous treatment with oxaliplatin or bevacizumab were allowed. Radiotherapy or surgery for MCRC was permitted if completed ≥ 4 weeks before random assignment.

Patients were required to have adequate hematologic/clotting, hepatic, and renal function. Pregnant or breast-feeding women were excluded. Other key exclusion criteria were: clinically significant cardiovascular disease; clinically detectable ascites; use of full-dose anticoagulants or thrombolytics; known CNS metastases; serious nonhealing wound, ulcer, or bone fracture; clinically significant bleeding diathesis or coagulopathy; and proteinuria ≥ 500 mg/24 hours.

Treatment Plan

Patients were randomly assigned to treatment using an interactive voice response system. Randomization was stratified by region, ECOG performance status, liver as a metastatic site, alkaline phosphatase level, and number of metastatic sites (organs).

Bevacizumab or placebo (bevacizumab vehicle) was administered as a 30- to 90-minute intravenous infusion before oxaliplatin at a dose of 7.5 mg/kg on day 1 of a 3-week cycle when given with XELOX or 5 mg/kg on day 1 of a 2-week cycle when given with FOLFOX-4. XELOX consisted of a 2-hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 1,000 mg/m^2 twice daily on days 1 through 14 (28 doses) of a 21-day cycle. The FOLFOX-4 regimen was as previously described.[3]

Treatment was supposed to be continued until disease progression (PD) or for 48 weeks (ie, up to 16 cycles of XELOX or 24 cycles of FOLFOX-4), whichever came first. Patients who completed the 48-week study treatment phase without PD were eligible to enter the poststudy treatment phase and continue treatment until PD. Patients whose tumors became operable, and underwent resection, were allowed to enter the poststudy treatment phase. The protocol specified that if one of the regimen components was discontinued due to toxicity, treatment could be continued with the remaining components.

Assessments

Medical history, physical examination, chest x-ray, ECG, and carcinoembryonic antigen measurement were performed within 21 days of starting treatment. Assessments of vital signs, ECOG performance status, height, weight, and routine blood analysis (hematology and chemistry) were performed within 7 days of starting treatment. During treatment, physical examination, hematology, and biochemistry analyses were repeated on day 1 of every treatment cycle.

Tumor assessments (computed tomography scan, magnetic resonance imaging) were made within 28 days of starting study treatment and repeated after every 6 weeks of planned therapy (ie, after every two XELOX cycles or every three FOLFOX-4 cycles) and at the end of treatment. Response Evaluation Criteria in Solid Tumors guidelines[6] were used to define all responses. Confirmation of response was required after ≥ 4 weeks. Tumor responses were assessed both by investigators and an independent response review committee. After completion of study treatment, patients receiving follow-up every 3 months until PD and/or death.

Patients were evaluated for adverse events during therapy and until 28 days after the last study drug dose. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3. Predefined adverse events of special interest for bevacizumab were: proteinuria, hypertension, wound healing complications, thromboembolic events, gastrointestinal perforation, abscess or fistula, and bleedings.

Statistical Analysis

The intent-to-treat (ITT) patient population included all patients who signed the informed consent form and underwent random assignment. The safety population was defined as all patients receiving at least one dose of study drug. Patients in the placebo arm who received at least one dose of bevacizumab by mistake were analyzed for safety in the bevacizumab arm. All efficacy and safety analyses comparing bevacizumab versus placebo were restricted to the 2 × 2 factorial study population.

As a first step, the analysis of pooled XELOX-containing versus pooled FOLFOX-4–containing arms was performed. If positive, an interaction test was performed on PFS to check for any interaction between the different treatment components (FOLFOX-4, XELOX, bevacizumab, nonbevacizumab). Independent of the interaction test, a clinical assessment of treatment effect was also performed. An interaction could be ruled out if the statistical interaction test was not significant and the clinical assessment revealed no clinically relevant difference. If an interaction was ruled out, the pooled analysis remained the primary analysis. If an interaction could not be ruled out, then results in the bevacizumab and nonbevacizumab treatment subgroups would have had to be considered.

PFS was the primary study end point, and was defined as the time from random assignment to the first documentation of PD (per investigator assessment), or death from any cause. Patients undergoing curative metastasectomy were censored at the time for surgery. A general PFS definition was specified for the primary analysis, which included progression or death regardless of whether or not the patient remained on protocol therapy at the time of the event.

Secondary efficacy end points were PFS using an on-treatment definition (same as general PFS; however, for events that occurred more than 28 days after the last intake of study medication, the patient was censored back to the date of last known nonprogression), OS, RR, duration of response, and time to treatment failure.

The analysis of study NO16966 was event-driven. The final analysis was to be done when 1,200 PFS events had occurred in the eligible patient population for the noninferiority comparison ensuring 90% power at an α level of 2.5%. At the same time, 985 events in ITT would have been expected to occur in the 2 × 2 factorial bevacizumab versus placebo comparison. Based on a hazard ratio (HR) of 0.75, this ensured 98% power for the pooled superiority comparison.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Approval of the protocol was obtained at each participating site from an independent ethics committee or institutional review board. Written informed consent was obtained from all patients before study participation.

RESULTS

Patient Population

Between February 2004 and February 2005, a total of 1,401 patients were randomly assigned in the 2 × 2 factorial (bevacizumab *v* placebo) part of the study that is reported here (Fig 1). A total of 1,400 patients made up the ITT population for the test of superiority of bevacizumab versus placebo (one patient was mistakenly randomly assigned twice). Baseline demographic and clinical characteristics were well balanced between treatment arms (Table 1).

Efficacy

The cutoff date for the main analysis was January 31, 2006 (median duration of follow-up of 15.6 months); however, in order to present more mature information for OS, results are presented for a cutoff date of January 31, 2007 (median duration of follow-up of 27.6 months).

Both a clinically relevant and statistically significant ($P = .7025$) treatment interaction was ruled out. Therefore, the planned pooled analysis of the bevacizumab- versus placebo-containing arms (FOLFOX-4 and bevacizumab plus XELOX and bevacizumab *v* FOLFOX-4 and placebo plus XELOX plus placebo) was the main analysis. Overall, 699 patients comprised the bevacizumab-containing arms and 701 comprised the placebo-containing arms. The data relating to the noninferiority of XELOX to FOLFOX-4 will be presented as a separate article.[5]

PFS, the primary study end point, was significantly increased with bevacizumab compared with placebo when combined with

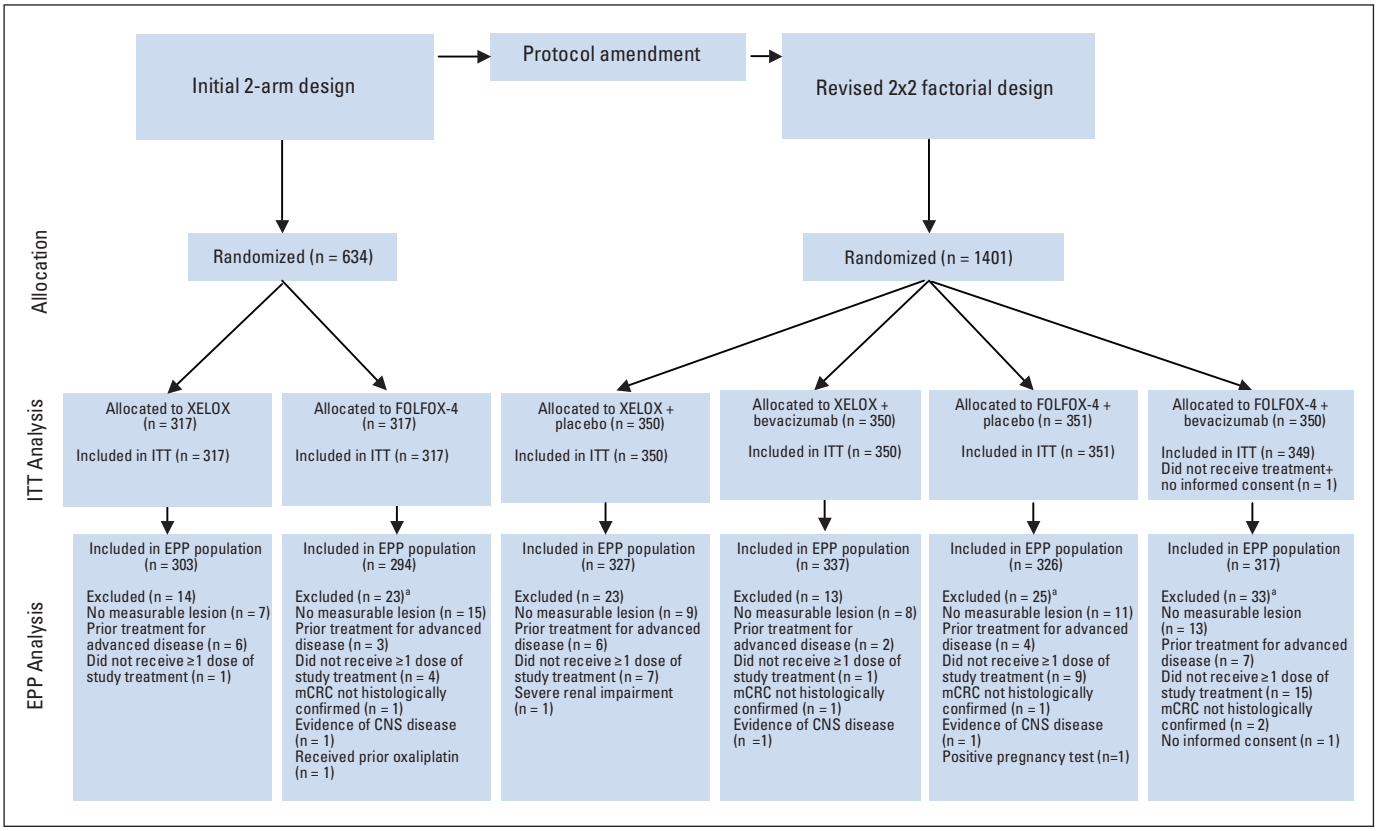

Fig 1. CONSORT diagram. XELOX, capecitabine and oxaliplatin; FOLFOX-4, fluorouracil/folinic acid plus oxaliplatin; ITT, intent-to-treat; EPP, eligible patient population.

oxaliplatin-based chemotherapy (HR, 0.83; 97.5% CI, 0.72 to 0.95; $P = .0023$), the median PFS duration being 9.4 months with bevacizumab plus chemotherapy versus 8.0 months with placebo plus chemotherapy (Figure 2; Table 2). Using the prespecified secondary analysis of on-treatment PFS (ie, taking in account only progression or death events occurring within 28 days from the last dose of any component of study treatment), the median on-treatment PFS was 10.4 months with chemotherapy plus bevacizumab versus 7.9 months with chemotherapy plus placebo (HR, 0.63; 97.5% CI, 0.52 to 0.75; $P < .0001$; Table 2).

In a planned subset analysis, the impact of bevacizumab addition on PFS was assessed for each chemotherapy regimen. Using the general PFS definition, statistical superiority of bevacizumab versus placebo was evident in the XELOX subgroup (HR, 0.77; 97.5% CI, 0.63 to 0.94; $P = .0026$), but did not reach the significance level in the FOLFOX-4 subgroup (HR, 0.89; 97.5% CI, 0.73 to 1.08; $P = .1871$; online-only Table A1). Using the on-treatment PFS definition, significant results were evident in both the XELOX (HR, 0.61; 97.5% CI, 0.48 to 0.78; $P < .0001$) and FOLFOX-4 subgroups (HR, 0.65; 97.5% CI, 0.50 to 0.84; $P = .0002$).

The details of other secondary end points are presented in Table 2. Median OS was 21.3 months with bevacizumab plus chemotherapy and 19.9 months with placebo plus chemotherapy. This difference did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76 to 1.03; $P = .077$; Fig 3). For results by treatment subgroup see online-only TableA1.

RR, as assessed by investigators, was similar in the bevacizumab plus chemotherapy versus placebo plus chemotherapy groups (47% *v* 49%; odds ratio [OR], 0.90; 97.5% CI, 0.71 to 1.14; $P = .31$). According to the independent response review committee assessment, RR were also similar in both bevacizumab- and placebo-containing arms (38% *v* 38%; OR, 1.00; 97.5% CI, 0.78 to 1.28; $P = .99$).

Fifty-nine patients (8.4%) in the bevacizumab-containing arms and 43 patients (6.1%) in the placebo-containing arms underwent an attempt at curative metastasectomy. Data on the number who achieved a complete R0 resection of all disease are not available at this time.

There were no major imbalances between the treatment groups with respect to the use of second-line therapy: bevacizumab-containing arms (46%) and placebo-containing arms (53%). The most common agents used were: irinotecan (34% with bevacizumab *v* 42% with placebo); FU (23% *v* 31%); capecitabine (8% *v* 7%); cetuximab (9% *v* 12%); and bevacizumab (3% *v* 5%).

Treatment Exposure

The median duration of treatment was similar in the bevacizumab- (190 days) and placebo-containing arms (176 days). Few patients (9% in the bevacizumab-containing arms and 6% in the placebo-containing arms) continued into the poststudy treatment phase (beyond 48 weeks). Treatment was discontinued because of PD in 29% of patients (n = 203) in the bevacizumab-containing arms and 47% of patients (n = 329) in the placebo-containing arms (Table 3), indicating that a large proportion of patients stopped treatment earlier than allowed by the study protocol. The median dose intensity (ie, ratio of dose received to dose planned) of each chemotherapy component and

Table 1. Baseline Patient Characteristics (intent-to-treat population)

Characteristic	Placebo + FOLFOX-4 or XELOX		Bevacizumab + FOLFOX-4 or XELOX		FOLFOX-4 + Placebo		FOLFOX-4 + Bevacizumab		XELOX + Placebo		XELOX + Bevacizumab	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	701		699		351		349		350		350	
Sex												
Male	391	56	418	60	186	53	205	59	205	59	213	61
Female	310	44	281	40	165	47	144	41	145	41	137	39
Age, years												
Median	60.0		60.0		60		60		61		61	
Range	18-83		18-86		26-83		19-82		18-83		18-86	
ECOG performance status												
0	418	60	405	58	211	60	198	57	207	59	207	59
1	281	40	289	42	138	40	147	43	143	41	142	41
2	0	0	1	< 1	0	0	0	0	0	0	1	< 1
Primary tumor site												
Colorectal	55	8	60	9	25	7	28	8	30	9	32	9
Colon	465	66	459	66	232	66	223	64	233	67	236	67
Rectal	181	26	180	26	94	27	98	28	87	25	82	23
Stage at first diagnosis												
Local regional	279	40	250	36	141	40	128	37	138	39	122	35
Metastatic	422	60	449	64	210	60	221	63	212	61	228	65
No. of metastatic sites												
0	1	< 1	1	< 1	1	< 1	1	< 1	0	0	0	0
1	297	42	284	41	142	41	150	43	155	44	134	38
2	234	33	253	36	122	35	132	38	112	32	121	35
3	123	18	108	16	65	19	44	13	58	17	64	18
≥ 4	46	7	53	8	21	6	22	6	25	7	31	9
Alkaline phosphatase												
Abnormal	296	42	302	44	147	42	146	42	149	43	156	45
Normal	401	58	390	56	201	58	199	58	200	57	191	55
Prior adjuvant therapy												
No	525	75	535	77	266	76	261	75	259	74	274	78
Yes	176	25	164	24	85	24	88	25	91	26	76	22

Abbreviations: FOLFOX-4, infused fluorouracil, folinic acid and oxaliplatin; XELOX, capecitabine and oxaliplatin; ECOG, Eastern Cooperative Oncology Group.

bevacizumab and placebo was high (≥ 89%), and similar between the bevacizumab- and placebo-containing arms (online-only Table A2).

Safety

Table 4 presents details of adverse events leading to treatment discontinuation and predefined adverse events of special interest to bevacizumab. A higher proportion of patients discontinued study treatment because of adverse events in the bevacizumab-containing arms compared with the placebo-containing arms (30% *v* 21%). However, treatment discontinuations due to grade 3/4 adverse events were recorded in 21% of patients in the bevacizumab-containing arms versus 15% of patients in the placebo-containing arms, indicating that discontinuations due to grade 1/2 adverse events were not uncommon (10% *v* 6%). Further, most of these treatment discontinuations were attributable to chemotherapy-related events rather than events felt to be potentially related to bevacizumab; the most common reasons for treatment discontinuation were neurotoxicity, gastrointestinal events, general disorders, and hematologic events. Events felt to be potentially related to bevacizumab accounted for treatment discontinuation in 5% and 2% of patients in the bevacizumab- and placebo-containing arms, respectively.

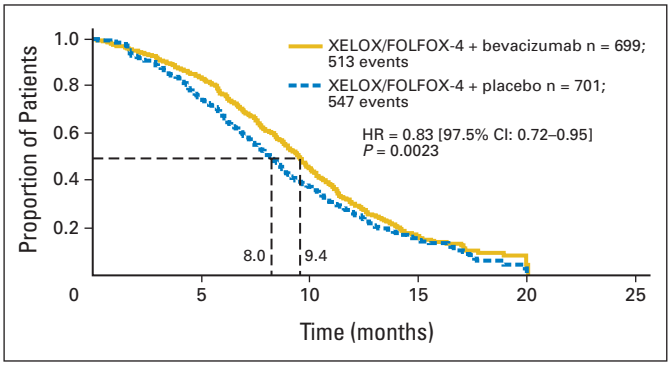

Fig 2. Progression-free survival (intent to treat population). XELOX, capecitabine and oxaliplatin; FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio.

The overall incidence of predefined grade 3/4 events felt to be potentially related to bevacizumab was 16% in the bevacizumab-containing arms and 8% in the placebo-containing arms (Table 4). The most common of these were thromboembolic events. The occurrence of grade 3/4 hypertension and bleeding was 2% to 4% of patients. Grade 3/4 gastrointestinal perforations, proteinuria, fistula/intra-abdominal abscess, and wound healing complications were all

Table 2. Analysis of Efficacy (intent-to-treat population)

End Point	Placebo + FOLFOX-4 or XELOX	Bevacizumab + FOLFOX-4 or XELOX	*P*
No. of patients	701	699	
Primary			
Median progression-free survival, months*	8.0	9.4	.0023
Hazard ratio	0.83		
97.5% CI	0.72 to 0.95		
Secondary			
Median progression-free survival, months†	7.9	10.4	< .0001
Hazard ratio	0.63		
97.5% CI	0.52 to 0.75		
Median time to treatment failure, months‡	6.0	6.9	.0030
Hazard ratio	0.84		
97.5% CI	0.74 to 0.96		
Median overall survival, months§	19.9	21.3	.0769
Hazard ratio	0.89		
97.5% CI	0.76 to 1.03		
Median duration of response, months	7.4	8.45	.0307
Hazard ratio	0.82		
97.5% CI	0.66 to 1.01		

Abbreviations: FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; XELOX, capecitabine and oxaliplatin.
*General definition (see Statistical Analysis).
†On-treatment definition (see Statistical Analysis).
‡Safety population.
§Cut-off date of January 31, 2007.

rare (< 1% of patients). No new bevacizumab-related safety signals were identified. Of the four gastrointestinal perforation events in the bevacizumab-containing arms, three events resolved without sequelae after stopping study treatment and one event was fatal. One of two gastrointestinal perforations that occurred among placebo-treated patients was fatal.

Overall, 144 patients (21%) in the bevacizumab-containing arms and 104 patients (15%) in the placebo-containing arms received concomitant anticoagulant therapy at some time point during the study. The proportion of patients experiencing bleeding events in the bevacizumab-containing arms was similar in those with (24%) or without (28%) concurrent anticoagulation therapy.

The incidence of grade 3/4 adverse events was approximately 5% higher among patients in the bevacizumab-containing arms versus the placebo-containing arms (Table 4). In general, the addition of bevacizumab caused no clinically relevant aggravation of grade 3/4 chemotherapy-related toxicity, although there were differences in gastrointestinal events (mainly diarrhea and vomiting; 32% *v* 27%), cardiac disorders (4% *v* < 1%), and hand-foot syndrome (7% *v* 3%) in the bevacizumab- versus placebo-containing arms. A by-patient review of cardiac events showed no common underlying pattern for the patients with these events. The remainder of the increase in grade 3/4 adverse events was accounted for by small increases in events with known associations with bevacizumab as discussed earlier (Table 4).

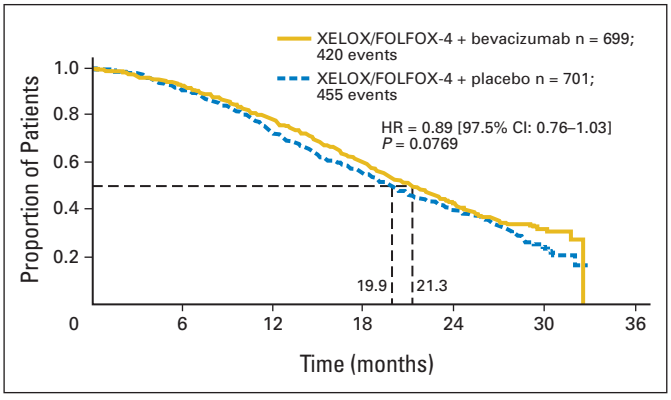

Fig 3. Overall survival (intent to treat population). XELOX, capecitabine and oxaliplatin; FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; HR, hazard ratio.

Table 3. Reasons for Treatment Discontinuation During Primary Treatment Phase (intent-to-treat population)

Reason	Placebo + FOLFOX-4 or XELOX		Bevacizumab + FOLFOX-4 or XELOX	
	No.	%	No.	%
No. of patients	701		699	
Safety	150	21	226	32
Adverse event*	143	20	210	30
Death	7	1	16	2
Non-safety	472	67	366	52
Progressive disease	329	47	203	29
Violation of selection criteria at entry	7	1	6	< 1
Other protocol violation	2	< 1	1	< 1
Refused treatment†	58	8	64	9
Failure to return	0	0	2	< 1
Other	76	11	90	13

Abbreviations: FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; XELOX, capecitabine and oxaliplatin.
*Includes intercurrent illness.
†Includes "did not co-operate" and "withdrew consent".

Table 4. Selected Adverse Events (safety population)

Adverse Event	Placebo + FOLFOX-4 or XELOX		Bevacizumab + FOLFOX-4 or XELOX	
	No.	%	No.	%
No. of patients	675		694	
Events leading to treatment discontinuation				
Any	141	21	207	30
Grade 3/4	101	15	145	21
Adverse events of special interest to bevacizumab	16	2	36	5
Grade 3/4				
Any adverse event	505	75	555	80
Adverse events of special interest to bevacizumab	57	8	111	16
Venous thromboembolic events	33	5	54	8
Hypertension	8	1	26	4
Bleeding	8	1	13	2
Arterial thromboembolic events*	7	1	12	2
Gastrointestinal perforations	2	< 1	4	< 1
Wound healing complications	2	< 1	1	< 1
Fistula/intra-abdominal abscess	—	—	6	1
Proteinuria	—	—	4	< 1

Abbreviations: FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin; XELOX, capecitabine and oxaliplatin.
*Also includes ischemic cardiac events.

The rate of treatment-related mortality within 28 days from last dose was similar in the bevacizumab and placebo groups (n = 14 [2.0%] and n = 10 [1.5%], respectively), as was the 60-day all-cause mortality rate (n = 14 [2.0%] and n = 11 [1.6%], respectively).

DISCUSSION

Taken together with previous randomized phase II and III studies conducted in the first-line setting,[1,7-9] this study confirms that bevacizumab improves PFS when combined with chemotherapy for MCRC. The effect size was smaller than in previous studies,[1,7] and, unlike two prior phase III trials,[1,2] the observed trend in an improvement in OS did not reach statistical significance. Several factors may have contributed to this outcome. First, the overall treatment duration of bevacizumab and placebo (median ≈ 6 months) was similar in both treatment arms, while the duration of PFS was longer in the bevacizumab arm. The study protocol, like the prior protocols, allowed for treatment until PD. This finding of lack of treatment with bevacizumab until PD contrasts markedly with the previous studies, in which the duration of treatment in the bevacizumab arms was considerably longer (1.5 or 3 months) than in the control arms.[1,2] The magnitude of benefit offered by bevacizumab in this study was considerably larger in the predefined on-treatment PFS analysis (HR, 0.63), which adjusts for preprogression alterations to study therapy (such as early study treatment discontinuation), than in the primary analysis, which used a general approach (HR, 0.83). In contrast to the bevacizumab arms, the two PFS definitions did not have any substantial impact on the Kaplan-Meier curves of the placebo arms. These findings suggest that the duration of bevacizumab therapy is likely to be important, and that treatment until PD may be necessary to maximize the clinical benefit derived from bevacizumab therapy.

The reasons for the lack of treatment with bevacizumab or with chemotherapy until progression on this trial are not clear. One possibility is that when a cumulative toxicity, such as neurotoxicity or fatigue, reached a point at which the patient may have requested drug discontinuation, some investigators may not have fully appreciated that the protocol specifically permitted the discontinuation of one or more drugs while allowing for the continuation of others. Thus, for example, while discontinuation of oxaliplatin with continuation of fluoropyrimidine and bevacizumab was permitted, our analysis shows that this course of action was rarely taken.

In previous trials of bevacizumab in the first-line setting, RR increased by ≥ 10% versus the comparator regimen[1,7,8] and, in the second-line setting, bevacizumab in combination with FOLFOX-4 demonstrated a 13% improvement in RR compared with FOLFOX-4 alone.[2] Improved RR was not observed in the bevacizumab-containing arms of this trial. Considering the consistent increase in RR across tumor types, including CRC, previously observed with bevacizumab,[1,2,10-12] this result may represent an outlier. However, given that this is a placebo-controlled trial, larger than any previous trial, and the results were confirmed by third-party review, the finding of a lack of improvement in RR cannot be easily dismissed. In contrast to OS and PFS, the discontinuation of bevacizumab before progression in some patients would not be expected to impact RR.

The OS benefit seen for bevacizumab in this trial did not reach statistical significance. Second- and further-line treatment regimens were comparable between the study arms, and only very few patients (3% in the bevacizumab and 5% in the placebo group) received bevacizumab in further lines. Therefore, it is unlikely that the survival results were confounded by cross-over. The lack of continuation of either bevacizumab or fluoropyrimidine (capecitabine or FU/leucovorin) until progression may have blunted the contribution of bevacizumab, thereby diminishing its impact on OS and PFS in this trial.

The safety profile of bevacizumab documented in this trial was similar to that observed in previous clinical trials[1,2,13] and large multinational observational studies.[14,15] It is also notable that there was no increased bleeding risk in patients receiving bevacizumab and concomitant anticoagulation therapy compared with patients without concomitant anticoagulation.

In conclusion, this trial reached its primary objective by showing a statistically significant increase in PFS through the addition of bevacizumab to oxaliplatin-based chemotherapy in first-line MCRC. No increase in RR was seen. The observed difference in OS did not reach statistical significance. Continuation of bevacizumab, and most likely fluoropyrimidine therapy as well, until PD appears to be critical with regards to the magnitude of clinical benefit derived from bevacizumab.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).