VOLUME 25 · NUMBER 12 · APRIL 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab in Combination With Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for Previously Treated Metastatic Colorectal Cancer: Results From the Eastern Cooperative Oncology Group Study E3200

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Submitted October 23, 2006; accepted January 23, 2007.

Supported in part by Public Health Service Grants No. CA23318, CA66636, CA21115, CA15488, CA27525, CA17145; the National Cancer Institute, National Institutes of Health; and the Department of Health and Human Services.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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

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0732-183X/07/2512-1539/$20.00

DOI: 10.1200/JCO.2006.09.6305

ABSTRACT

Purpose
Colorectal cancer is the second leading cause of cancer mortality in the United States. Antiangiogenic therapy with bevacizumab combined with chemotherapy improves survival in previously untreated metastatic colorectal cancer. This study was conducted to determine the effect of bevacizumab (at 10 mg/kg) on survival duration for oxaliplatin-based chemotherapy in patients with previously treated metastatic colorectal cancer.

Patients and Methods
Eight hundred twenty-nine metastatic colorectal cancer patients previously treated with a fluoropyrimidine and irinotecan were randomly assigned to one of three treatment groups: oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) with bevacizumab; FOLFOX4 without bevacizumab; or bevacizumab alone. The primary end point was overall survival, with additional determinations of progression-free survival, response, and toxicity.

Results
The median duration of survival for the group treated with FOLFOX4 and bevacizumab was 12.9 months compared with 10.8 months for the group treated with FOLFOX4 alone (corresponding hazard ratio for death = 0.75; $P = .0011$), and 10.2 months for those treated with bevacizumab alone. The median progression-free survival for the group treated with FOLFOX4 in combination with bevacizumab was 7.3 months, compared with 4.7 months for the group treated with FOLFOX4 alone (corresponding hazard ratio for progression = 0.61; $P < .0001$), and 2.7 months for those treated with bevacizumab alone. The corresponding overall response rates were 22.7%, 8.6%, and 3.3%, respectively ($P < .0001$ for FOLFOX4 with bevacizumab *v* FOLFOX4 comparison). Bevacizumab was associated with hypertension, bleeding, and vomiting.

Conclusion
The addition of bevacizumab to oxaliplatin, fluorouracil, and leucovorin improves survival duration for patients with previously treated metastatic colorectal cancer.

J Clin Oncol 25:1539-1544. © 2007 by American Society of Clinical Oncology

INTRODUCTION

In the United States colorectal cancer is the country's second leading cause of cancer death[1]; a majority of the 150,000 annual new diagnoses will have metastatic disease during the course of illness.[2] Recent improvements in chemotherapy have extended survival duration for these patients. For example, initial treatment with fluorouracil and irinotecan results in a median survival approaching 15 months,[3,4] and second-line therapy with oxaliplatin further improves disease control.[5,6] Yet, despite these advances, nearly all patients with metastatic colorectal cancer will succumb to their disease.

Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis, the altered regulation of which is associated with several diseases including malignancy. Bevacizumab, a recombinant humanized monoclonal antibody with a high binding specificity for VEGF, prevents its interaction with receptors on vascular endothelial cells and thereby abrogates VEGF-receptor–mediated intracellular signaling and resultant biologic effects.[7] In phase I studies, bevacizumab was well tolerated as a single agent and in combination with

chemotherapy.[8,9] Improvements in clinical efficacy have been described when bevacizumab is added to fluorouracil-based chemotherapy for metastatic colorectal cancer.[10-12]

We report the results of a randomized phase III study designed to determine the effect on survival duration for chemotherapy with the oxaliplatin-containing regimen FOLFOX4 with or without bevacizumab, and for bevacizumab as a single agent, in patients with previously treated metastatic colorectal cancer.

PATIENTS AND METHODS

Eligibility Criteria and Patient Evaluation

This multi-institutional, cooperative group, open-label, randomized phase III study was for patients with histologically confirmed colorectal cancer that was advanced or metastatic and measurable as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).[13] Prior chemotherapy with irinotecan and a fluoropyrimidine for advanced disease was required, and the previous use of oxaliplatin or bevacizumab was not permitted. A history of hypertension was allowed provided that blood pressure readings were maintained below 150/100 mmHg on a stable antihypertensive regimen. Patients with a baseline urinalysis demonstrating protein were required to have less than 500 mg of protein excreted over a 24-hour period.

Those patients with a history of major surgery within 28 days, radiotherapy within 14 days, a hypersensitivity to recombinant murine monoclonal antibodies, or a thrombotic or hemorrhagic event within 6 months of study entry, and those requiring therapeutic anticoagulation were excluded from the study. Low-dose warfarin used for the maintenance of venous access devices was permitted, as was daily aspirin use of 325 mg or less. The institutional review boards of all participating institutions approved the protocol, and all patients provided written consent to participate.

Pretreatment evaluations included a complete medical history and physical examination, a CBC, a limited chemistry profile, prothrombin time, international normalized ratio, and partial thromboplastin time. A baseline radiographic tumor evaluation was required within 4 weeks before study registration. An interim medical history, physical examination, and the laboratory studies listed herein were repeated before the start of each cycle of therapy, and a CBC was obtained weekly. Tumor assessment was performed after every fourth cycle of therapy. Patients without progressive disease were allowed to continue on study. All patients were followed for disease progression and death.

Toxicity was assessed according to the Common Toxicity Criteria version 2 (http://ctep.cancer.gov). The occurrence of any grade 3 or 4 toxicity (with the exception of alopecia, fatigue, anorexia, and nausea and vomiting that could be controlled with antiemetics) required that treatment be withheld until resolution, and dose modifications of specific drugs were made on the basis of the particular adverse event.

Treatment

Eligible patients were randomly assigned in a 1:1:1 ratio to receive FOLFOX4 in combination with bevacizumab; FOLFOX4 without bevacizumab; or bevacizumab alone (Table 1). Random assignment was stratified on the basis of prior radiation therapy and Eastern Cooperative Group (ECOG) performance status. Treatment in all three arms of the study was administered every 14 days, and this period constituted one cycle of therapy.

Statistical Design and Analysis

The primary end point of this study was overall survival. The original design had a greater than 90% power to detect a 50% improvement in median overall survival (from 7 to 10.5 months); however, with a faster than anticipated accrual, the study was modified to maintain its power by setting the accrual to 880 patients, providing a greater than 95% power to detect a 50% difference in overall survival with 13 months of follow-up before the final analysis.

Interim efficacy analyses were to be performed at the first scheduled meeting of the ECOG Data Monitoring Committee after the study reached at least 50% and 75% information, and the final analysis (100% information) was to be conducted 31 months after the start of accrual. The O'Brien-Fleming group sequential boundary function[14] was used to adjust for the sequential testing, and the use function methodology of Lan and DeMets[15] was employed to adjust the boundaries when the actual interim analyses did not correspond to the projected information times of 50% and 75%. This study was also monitored for early stopping in favor of the null hypothesis using repeated CI methodology similar to that described by Jennison and Turnbull.[16]

The distribution of patient characteristics was evaluated using χ^2 tests for association. The midrank Wilcoxon test for ordered categoric outcomes and the Jonckheere-Terpstra test[17] for testing two ordinal categories were used, as appropriate, to compare distributions of toxicity with ordinal levels. Survival curves were estimated by the Kaplan-Meier method,[18] with differences assessed by the log-rank test.[19] Proportional hazards regression models[20] of disease-free and overall survival to identify simultaneously significant prognostic covariates were based on the likelihood ratio test.

Overall survival was defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive. Progression-free survival was defined as the time from random assignment to progression, censoring patients without progression at the date of last disease assessment. Cases without evidence of progression dying within 4 months of the last disease assessment were counted as events of progression at the time of death. Second primary colon or rectal cancers were considered events as of the date of diagnosis.

Table 1. Treatment Regimens

Arm	Dosage	Administration	Schedule
Arm A: FOLFOX4 + bevacizumab			
Oxaliplatin	85 mg/m^2	IV 120 minutes	Day 1
Leucovorin	200 mg/m^2	IV 120 minutes	Days 1 and 2
Fluorouracil	400 mg/m^2	IV bolus, followed by	
Fluorouracil	600 mg/m^2	IV over 22 hours	Days 1 and 2
Bevacizumab	10 mg/kg	30-90 minutes	Day 1
Arm B: FOLFOX4			
Oxaliplatin	85 mg/m^2	IV 120 minutes	Day 1
Leucovorin	200 mg/m^2	IV 120 minutes	Days 1 and 2
Fluorouracil	400 mg/m^2	IV bolus, followed by	
Fluorouracil	600 mg/m^2	IV over 22 hours	Days 1 and 2
Arm C: bevacizumab			
Bevacizumab	10 mg/kg	30-90 minutes	Day 1

Abbreviations: FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IV, intravenous.

The study was designed by the principal investigator (B.J.G.) in collaboration with members of the ECOG Gastrointestinal Cancer Committee and representatives from the Cancer Treatment Evaluation Program of the National Cancer Institute.

RESULTS

Patient Characteristics

A total of 829 patients were enrolled onto the study between November 2001 and April 2003 from 221 sites in the United States and South Africa. Nine patients who received treatment were determined to be ineligible, and 21 randomly assigned patients did not receive their assigned therapy.

In February 2003, the bevacizumab-alone arm of the study was closed to accrual after an interim analysis that suggested inferior survival when compared with the chemotherapy-containing arms of the study.

The intent-to-treat analysis of the primary end point of overall survival included 286 patients in the FOLFOX4-plus-bevacizumab arm, 291 patients in the FOLFOX4-alone arm, and 243 patients in the bevacizumab-alone arm. Treatment assignment was balanced by sex, age, ECOG performance status, and prior radiation therapy exposure (Table 2).

Treatment Duration and Toxicity

Patients randomly assigned to be treated with FOLFOX4 and bevacizumab had a median duration of therapy of 10 cycles, compared with seven cycles for those assigned to the FOLFOX4-alone arm and four cycles for those assigned to the bevacizumab-alone arm.

Selected grade 3 or 4 adverse events are presented in Table 3. The occurrence of any grade 3 or 4 adverse event was greater for those individuals treated with the combination of FOLFOX4 plus bevacizumab compared with patients treated with chemotherapy alone (75% *v* 61%). For the individuals treated with FOLFOX4 plus bevacizumab, there were higher rates of grades 3 or 4 neuropathy, hypertension, bleeding, and vomiting when compared with those who received FOLFOX4 without bevacizumab. The majority of the bleeding events in the patients treated with FOLFOX4 in combination with bevacizumab were from the GI tract. The grade 4 bleeding event required an intervention to achieve hemostasis. There were no significant differences in the incidence of adverse events leading to treatment discontinuation or in 60-day all-cause mortality rates.

Adverse events that may be related to arterial thromboembolism (cardiac ischemia—representing the sum of the number of nonoverlapping cases of myocardial infarction and troponin elevation—and cerebrovascular accidents) were infrequent and did not occur to a statistically significant greater degree in the patients who received the combination therapy. In addition, grade 3 or 4 proteinuria was rare.

Bevacizumab as a single agent was associated with a 36% overall incidence of grade 3 or 4 toxicity.

Grade 3 hypertension (requiring therapy) occurred in 7% of patients and grade 3 vomiting in 5% of patients. Of the five bleeding events associated with bevacizumab as a single agent, three occurred in the GI tract, and two were caused by hematuria (one patient had grade 1 hematuria at baseline).

Two deaths attributed to bleeding occurred; both resulted from CNS hemorrhage, with one occurring in each of the bevacizumab-containing arms of the study.

There were six reports of bowel perforation, three in each of the bevacizumab-containing arms of the study. Four of the perforations occurred after the first cycle of therapy, one after the third cycle of therapy, and one 3 months after the last administration of bevacizumab. There have been no reports of bowel perforation in the FOLFOX4 arm of the study. Two individuals who experienced bowel perforation died as a result of the event; death occurred 3 months after the last dose of bevacizumab in an individual being treated with irinotecan who was found to have small-bowel necrosis and a small-bowel perforation at surgery; death occurred in an individual who developed a perforation (confirmed by computed tomography scan) 4 days after first administration of therapy that was not considered operable.

Table 2. Baseline Patient Characteristics

Characteristic	FOLFOX4 + Bevacizumab (n = 286)	FOLFOX4 (n = 291)	Bevacizumab (n = 243)
Age, years			
Median	62.0	60.8	59.6
Range	21-85	25-84	23-82
Female sex, %	39.5	39.2	40.7
Performance status, %			
0	48.9	51.2	48.6
1	46.9	43.0	43.6
2	4.2	5.8	7.8
Prior radiation therapy, %	25.9	24.7	25.9
Disease site			
Liver	73.4	75.9	70.8
Lung	55.5	51.2	59.7

Abbreviation: FOLFOX4, oxaliplatin, fluorouracil, and leucovorin.

Efficacy

The addition of bevacizumab to FOLFOX4 resulted in a statistically significant improvement in overall survival (Table 4; Fig 1). At a median follow-up of 28 months, patients treated with bevacizumab in combination with FOLFOX4 had a median survival of 12.9 months compared with 10.8 months for those treated with FOLFOX4 alone (hazard ratio = 0.75; $P = .0011$). The median survival for those treated with bevacizumab alone was 10.2 months.

In addition, the combination of bevacizumab and FOLFOX4 resulted in a statistically significant improvement in progression-free survival compared with those treated with chemotherapy alone (7.3 *v* 4.7 months; hazard ratio for progression = 0.61; $P < .0001$; Table 4; Fig 2). The median progression-free survival for patients treated with bevacizumab alone was 2.7 months.

Using the RECIST criteria[13] for response, 22.7% of patients treated with FOLFOX and bevacizumab achieved a confirmed response to therapy compared with 8.6% of patients treated with FOLFOX alone ($P < .0001$) and 3.3% of patients treated with bevacizumab alone (Table 4). The response assessments were reported by the investigators and not independently reviewed.

DISCUSSION

Refinements to first-line combination chemotherapy,[3,4,10,21,22] including the addition of bevacizumab to irinotecan, fluorouracil and

Table 3. Percentage of Adverse Events

Adverse Event	% FOLFOX4 + Bevacizumab (n = 287) Grade 3	FOLFOX4 + Bevacizumab (n = 287) Grade 4	% FOLFOX4 (n = 285) Grade 3	FOLFOX4 (n = 285) Grade 4	% Bevacizumab (n = 234) Grade 3	Bevacizumab (n = 234) Grade 4	*P* (A *v* B)
Hypertension	5.2	1.0	1.4	0.4	7.3	0	.008
Bleeding	3.1	0.3	0.4	0	2.1	0	.011
Vomiting	8.7	1.4	2.8	0.4	4.7	0	.001
Proteinuria	0.7	0	0	0	0	0	.50
Neuropathy	16	0.3	8.8	0.4	0.4	0.4	.011
Thromboembolism	3.1	0.3	1.1	1.4	0	0.4	.62
Cardiac ischemia	0.3	0.3	0	0.4	0	0	.62*
Cerebrovascular ischemia	0.3	0	0	0	0	0.4	
Any adverse event	49.5	25.8	36.1	24.9	27.8	8.1	.004
Adverse event leading to treatment discontinuation	23.4		23.9		12.0		
Death from any cause within 60 days from start of therapy	5		4		6		

Abbreviation: FOLFOX4, oxaliplatin, fluorouracil, and leucovorin.
*Cardiac ischemia and cerebrovascular ischemia combined.

leucovorin,[11] have improved survival duration for patients with advanced colorectal cancer. The data reported herein show that bevacizumab improves progression-free survival and overall survival when added to FOLFOX4 for patients with metastatic colorectal cancer previously treated with a fluoropyrimidine and irinotecan. To our knowledge, this is the first study to demonstrate a survival benefit in this patient population for both bevacizumab and for an oxaliplatin-containing regimen. FOLFOX4 in combination with bevacizumab achieves a median duration of survival of 12.9 months compared with 10.8 months for FOLFOX4 alone and 10.2 months for bevacizumab alone.

The significance of our findings extends beyond the demonstration of effective second-line therapy for this disease. A recently published phase III study of first-line therapy for metastatic colorectal cancer reported a median survival of 19.5 months for FOLFOX4,[4] establishing that regimen as the standard of care for initial treatment in the United States. The improvement in median overall survival by 2 months in the current study is of particular importance, because an equal if not greater gain may be expected by adding bevacizumab to first-line treatment with FOLFOX4.

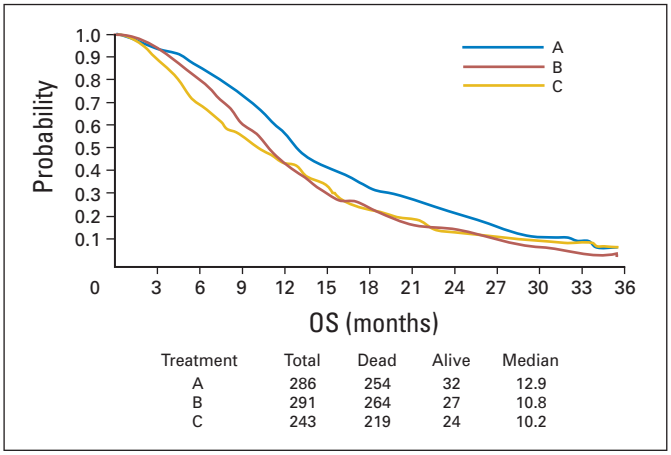
The dose of bevacizumab used in this study was selected on the basis of preclinical and clinical data that support a dose-response effect for the agent.[23-27] However, a small phase II study of bevacizumab combined with fluorouracil and leucovorin for initial treatment of metastatic colorectal cancer suggested that a dose of 5 mg/kg was more effective when compared with a dose of 10 mg/kg.[11] Because that study was neither designed nor powered to provide a definitive dose comparison, we concluded from a review of its findings that a dose of 10 mg/kg is active when combined with chemotherapy.[11] Although the present study's results prove that assumption to be correct, they do not provide insight into the relative efficacy between the two doses used in treating colorectal cancer.

Combining bevacizumab with FOLFOX4 resulted in a 14% overall increase in grade 3 and 4 toxicity. Grade 3 or 4 hypertension, bleeding, and vomiting were infrequent, but found to be associated with the combination of bevacizumab and FOLFOX4. Hypertension has been reported by others for bevacizumab therapy.[10] This is the first phase III study in colorectal cancer, however, to associate grade 3 and 4 bleeding with the drug's use. The increased incidence of sensory neuropathy is expected, given the longer duration of therapy (and thus, greater oxaliplatin exposure) for those treated within the combination arm. The finding of bowel perforation is consistent with the existing clinical experience for

Table 4. Efficacy Results

Measure	FOLFOX4 + Bevacizumab	FOLFOX4	Bevacizumab	*P* (A *v* B)
Median survival, months	12.9	10.8	10.2	.0011
Hazard ratio for death	0.75			
Progression-free survival, months	7.3	4.7	2.7	< .0001
Hazard ratio for progression	0.61			
1-year survival, %	56	43	44	
Response, %				< .0001
Overall	22.7	8.6	3.3	
Complete	1.7	0.7	0	
Partial	21.0	7.9	3.3	

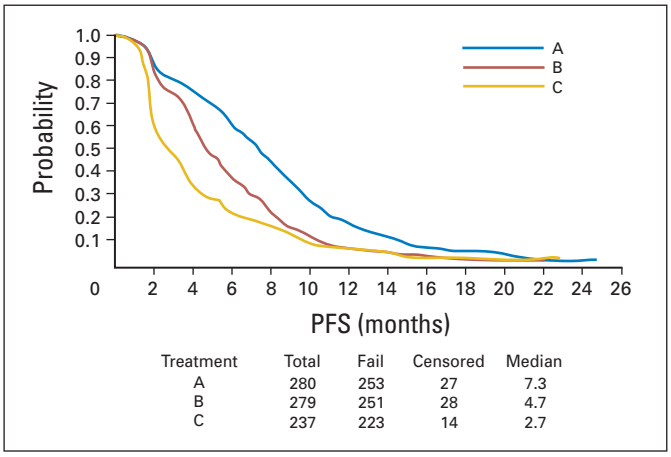
Abbreviation: FOLFOX4, oxaliplatin, fluorouracil, and leucovorin.



Treatment	Total	Dead	Alive	Median
A	286	254	32	12.9
B	291	264	27	10.8
C	243	219	24	10.2

Fig 1. Kaplan-Meier estimates of survival by treatment. The median duration of survival for the group treated with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) in combination with bevacizumab was 12.9 months, as compared with 10.8 months for the group treated with FOLFOX4 alone, corresponding to a hazard ratio for death of 0.75 ($P = .0011$). The median survival for those treated with bevacizumab alone was 10.2 months. OS, overall survival.

bevacizumab in metastatic colorectal cancer.[10] In addition, the rates of adverse events attributable to bevacizumab in the present study are similar to other reports in advanced colorectal cancer using a lower dose of the agent, which suggests that the higher dose of bevacizumab does not incur greater toxicity.[10-12]



Treatment	Total	Fail	Censored	Median
A	280	253	27	7.3
B	279	251	28	4.7
C	237	223	14	2.7

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS). The median PFS for the group treated with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) in combination with bevacizumab was 7.3 months, as compared with 4.7 months for the group treated with FOLFOX4 alone, corresponding to a hazard ratio for progression of 0.61 ($P < .0001$). The median PFS for those treated with bevacizumab alone was 2.7 months.

As a single agent, bevacizumab provided little clinical benefit in this population of patients. Although the median survival for patients treated with bevacizumab is similar to that for patients treated with FOLFOX4, this may have been influenced by postprogression therapy.

In conclusion, antiangiogenic therapy with bevacizumab in combination with the oxaliplatin-based regimen FOLFOX4 prolongs survival for patients with previously treated metastatic colorectal cancer. These findings add to the existing experience for bevacizumab in colorectal cancer, suggesting that improvements in clinical outcome do not appear to be limited to a single chemotherapy regimen. Moreover, the gain in survival duration demonstrated by the addition of bevacizumab to second-line therapy with FOLFOX4 supports the use of this combination as initial treatment of metastatic colorectal cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** Bruce J. Giantonio, Genentech Sanofi-Aventis; Neal J. Meropol, Pfizer Genentech Bristol Myers Squibb Amgen; Peter J. O'Dwyer, Genentech; Edith P. Mitchell, Genentech Sanofi-Aventis Pfizer; Steven R. Alberts, Sanofi-Aventis; Al B. Benson III, Genentech Pfizer **Stock:** N/A **Honoraria:** Bruce J. Giantonio, Genentech Sanofi-Aventis; Peter J. O'Dwyer, Genentech; Edith P. Mitchell, Genentech Sanofi-Aventis Pfizer; Al B. Benson III, Genentech Pfizer **Research Funds:** Peter J. O'Dwyer, Genentech; Edith P. Mitchell, Sanofi-Aventis Pfizer; Al B. Benson III, Genentech Pfizer **Testimony:** N/A **Other:** N/A

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Acknowledgment

We thank Helen X. Chen, MD, and Richard Kaplan, MD, of the National Cancer Institute; the staff at the ECOG Operations Office; and Maryann Redlinger, Kristi Kafel, and Cecile Miller for their valuable assistance as liaisons to the study chair.