VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Safety and Efficacy of Oxaliplatin and Fluoropyrimidine Regimens With or Without Bevacizumab As First-Line Treatment of Metastatic Colorectal Cancer: Results of the TREE Study

Howard S. Hochster, Lowell L. Hart, Ramesh K. Ramanathan, Barrett H. Childs, John D. Hainsworth, Allen L. Cohn, Lucas Wong, Louis Fehrenbacher, Yousif Abubakr, M. Wasif Saif, Lee Schwartzberg, and Eric Hedrick

From the New York University Cancer Institute, New York, NY; Florida Cancer Specialists, Fort Myers, FL; University of Pittsburgh Cancer Institute, Pittsburgh, PA; sanofi-aventis, Bridgewater, NJ; Sarah Cannon Cancer Center, Nashville; West Cancer Clinic, Memphis, TN; Rocky Mountain Cancer Center, Denver, CO; Scott & White Hospital, Center for Cancer Prevention and Care, Temple, TX; Department of Oncology/Hematology, Kaiser Permanente, Vallejo Medical Center, Vallejo, CA; Florida Oncology Association, Jacksonville, FL; Yale University School of Medicine, New Haven, CT; and Genentech BioOncology, South San Francisco, CA.

Submitted December 2, 2007; accepted April 1, 2008.

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

Corresponding author: Howard S. Hochster, MD, New York University Cancer Institute, 160 East 34th St, New York, NY 10016; e-mail: Howard.Hochster@med.nyu.edu.

0732-183X/08/2621-3523/$20.00

DOI: 10.1200/JCO.2007.15.4138

ABSTRACT

Purpose
To evaluate the safety and efficacy of three oxaliplatin and fluoropyrimidine regimens, with or without bevacizumab, as first-line treatment for metastatic colorectal cancer (CRC).

Patients and Methods
Patients with histologically documented metastatic or recurrent CRC and no prior treatment for advanced disease were randomly assigned to mFOLFOX6 (bolus and infusion fluorouracil [FU] and leucovorin [LV] with oxaliplatin), bFOL (bolus FU and low-dose LV with oxaliplatin), or CapeOx (capecitabine with oxaliplatin), respectively (Three Regimens of Eloxatin Evaluation [TREE-1]). The study was later modified such that subsequent patients were randomized to the same regimens plus bevacizumab (TREE-2).

Results
A total of 150 and 223 patients were randomly assigned in the TREE-1 and TREE-2 cohorts, respectively. Incidence of grade 3/4 treatment-related adverse events during the first 12 weeks of treatment were 59%, 36%, and 67% for mFOLFOX6, bFOL, and CapeOx, respectively, (TREE-1) and 59%, 51%, and 56% for the corresponding treatments plus bevacizumab (TREE-2; primary end point). CapeOx toxicity in TREE-1 included grade 3/4 diarrhea (31%) and dehydration (27%); capecitabine dose reduction to 1,700 mg/m^2/d in TREE-2 resulted in improved tolerance. Overall response rates were 41%, 20%, and 27% (TREE-1) and 52%, 39%, and 46% (TREE-2); median overall survival (OS) was 19.2, 17.9, and 17.2 months (TREE-1) and 26.1, 20.4, and 24.6 months (TREE-2). For all treated patients, median OS was 18.2 months (95% CI, 14.5 to 21.6; TREE-1) and 23.7 months (95% CI, 21.3 to 26.8; TREE-2).

Conclusion
The addition of bevacizumab to oxaliplatin and fluoropyrimidine regimens is well tolerated as first-line treatment of mCRC and does not markedly change overall toxicity. CapeOx tolerability and efficacy is improved with reduced-dose capecitabine. First-line oxaliplatin and fluoropyrimidine-based therapy plus bevacizumab resulted in a median OS of approximately 2 years.

J Clin Oncol 26:3523-3529. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Oxaliplatin-based therapy is standard first-line treatment for advanced or metastatic colorectal cancer (mCRC). FOLFOX4, a regimen of oxaliplatin added to LV5FU2—bimonthly leucovorin (LV) plus bolus and infusional fluorouracil (FU)—improves progression-free survival (PFS; 9.0 *v* 6.2 months; $P = .0003$) and overall response rate (ORR; 50.7% *v* 22.3%; $P = .0001$) compared with LV5FU2.[1] FOLFOX also improved response and survival compared with irinotecan plus bolus FU and LV (IFL) in US Intergroup Study N9741.[2] The Three Regimens of Eloxatin Evaluation (TREE) study in advanced CRC was initiated to investigate the tolerability of oxaliplatin when combined with three different fluoropyrimidine regimens: modified FOLFOX6 (mFOLFOX6) utilizing infusional administration of FU, bFOL including bolus intravenous (IV) administration of FU plus low-dose LV, and CapeOx including an oral agent, capecitabine. Bevacizumab combined with either first-line FU-based chemotherapy (weekly FU/LV or bolus IFL) or second-line FOLFOX4 improved

overall survival (OS), PFS, and response rate in patients with mCRC.[3-5] In response to emerging data on the efficacy of bevacizumab in mCRC at the time TREE was completing accrual, the study was amended to subsequently evaluate the safety and efficacy of adding bevacizumab to each of the original oxaliplatin and fluoropyrimidine regimens. The resulting two cohorts of this study are hereafter referred to as TREE-1 and TREE-2.

PATIENTS AND METHODS

Study Design and Treatment

TREE-1 and TREE-2 were two sequentially conducted, randomized, open-label cohorts in this study. TREE-1 was initiated in November 2002 and TREE-2 in October 2003 after a protocol amendment to add bevacizumab to chemotherapy. A central registry was used to randomly assign patients to treatment (1:1:1). In TREE-1, patients received mFOLFOX6 (oxaliplatin 85 mg/m^2 IV with LV 350 mg IV over 2 hours plus FU 400 mg/m^2 IV bolus and 2,400 mg/m^2 continuous infusion over 46 hours every 2 weeks), bFOL (oxaliplatin 85 mg/m^2 IV on days 1 and 15 and LV 20 mg/m^2 IV over 10 to 20 minutes followed by FU 500 mg/m^2 IV push on days 1, 8, and 15 every 4 weeks), or CapeOx (oxaliplatin 130 mg/m^2 IV on day 1 and capecitabine 1,000 mg/m^2 orally twice daily on days 1 to 15 every 3 weeks). In TREE-2, patients received one of the same three chemotherapy regimens as in TREE-1 but with the addition of bevacizumab; the capecitabine starting dose was also modified (see below). Bevacizumab was administered before chemotherapy at a dosage of 5 mg/kg IV every 2 weeks (FOLFOX and bFOL regimens) or 7.5 mg/kg IV every 3 weeks (CapeOx regimen). Treatment continued until disease progression, unacceptable toxicity, extended toxicity-related dose delay, or withdrawal of consent. Based on preliminary safety data from TREE-1 and data safety monitoring committee recommendation, the capecitabine dose was reduced to 850 mg/m^2 twice per day in TREE-2 (650 mg/m^2 twice per day for patients with a creatinine clearance of 30 to 50 mL/min).

Toxicities were graded by the National Cancer Institute Common Toxicity Criteria, version 2.0, or as mild, moderate, severe, or life-threatening. Neurosensory toxicities were graded on interference with function and/or activities of daily living. One dose reduction was permitted for oxaliplatin (85 to 65 mg/m^2 or 130 to 100 mg/m^2), two for FU bolus/infusion (bolus, 400 to 300, then 200 mg/m^2 or bolus, 500 to 400, then 300 mg/m^2; infusion, 2,400 to 1,900, then 1,500 mg/m^2), two for capecitabine (TREE-1: 2,000 to 1,500, then 1,000 mg/m^2/d; TREE-2: 1,700 to 1,300, then 850 mg/m^2/d), and none for LV. Grade 3 paresthesias and dysesthesias lasting longer than 7 days required a 25% oxaliplatin dose reduction. Oxaliplatin was discontinued for grade 4 paresthesia/dysesthesia, or persistent grade 3 paresthesia/dysesthesia. For grade 3 hemorrhage, thrombosis, or requirement for surgery, bevacizumab was withheld until the toxicity resolved, or for 28 days after surgery. Bevacizumab was discontinued for grade 4 or uncontrolled grade 3 hypertension, bleeding, thrombosis, or proteinuria.

Patients

Patients had histologically documented mCRC or recurrent CRC and had not received prior therapy for metastatic or recurrent disease. Adjuvant FU/LV and/or IFL $\geq$ 6 months before study registration was permitted. Main eligibility criteria included: age $\geq$ 18 years; $\geq$ 1 unidimensionally measurable lesion; Eastern Cooperative Oncology Group performance status 0 or 1; adequate hematologic (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L), hepatic (total bilirubin $\leq$ 2.0$\times$ upper limit of normal [ULN], serum transaminases $\leq 3.0 \times$ ULN), and creatinine $\leq 1.5 \times$ ULN; and written informed consent. Additional eligibility criteria for TREE-2 were hemoglobin $\geq$ 8.0 g/dL; coagulation parameters (prothrombin and partial thromboplastin times) within normal limits; and urinary protein less than 1+. Exclusion criteria included: myocardial infarction within 6 months, current congestive heart disease, or nonstable coronary artery disease; peripheral neuropathy; interstitial pneumonia or extensive lung fibrosis; uncontrolled infection; malabsorption syndrome; dihydropyrimidine dehydrogenase deficiency, therapeutic warfarin, or uncontrolled hypertension.

The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by an institutional review board at each participating center.

Evaluations

Baseline radiologic tumor assessments and clinical assessments were performed within 28 days and 7 days before therapy initiation, respectively. Clinical assessments and toxicities were recorded on day 1 of each cycle and at the end of treatment. Tumor assessments were repeated every 12 weeks in TREE-1 and every 6 weeks in TREE-2. Responses were evaluated by the Response Evaluation Criteria in Solid Tumors and confirmed by computed tomography or magnetic resonance imaging after 4 to 6 weeks.[6] After treatment discontinuation, patients in TREE-2 were followed for survival at 3-month intervals for at least 2 years and every 6 months thereafter until lost to follow-up or consent withdrawal; these data were collected for patients in TREE-1 who consented retrospectively.

Statistics

All analyses are for the as-treated population, which includes all randomly assigned patients receiving at least one treatment. The primary end point was the overall incidence of grade 3/4 adverse events (AEs) possibly or probably related to study drug during the first 12 weeks of treatment for each of the TREE-2 treatment groups. Secondary end points included: AEs during the first 12 weeks of treatment in TREE-1; all AEs occurring during or within 30 days of treatment; ORR (complete response + partial response); time to treatment failure (TTF); time to progression (TTP); and OS. TTF was defined as the time from random assignment to first documented tumor progression, discontinuation of all study treatment, or death from any cause, whichever came first. TTP was defined as the time from random assignment to first documented progression or all-cause mortality in the absence of previously documented tumor progression. Patients beginning chemotherapy with new agents were censored at that time. Median TTF, TTP, and survival and corresponding 95% CI were estimated using the Kaplan-Meier method.

Accrual of 70 patients per arm was deemed sufficient to detect a 15% increase in the overall incidence of grade 3/4 AEs for the experimental treatments compared with historical controls based on a one-group χ^2 test with a nominal one-sided .05 significance level and 80% power within the 50% to 70% AE rate of historical controls.

RESULTS

Patient Characteristics

Between December 2002 and November 2003, 150 patients were enrolled in TREE-1 at 33 United States centers and randomly assigned to treatment with mFOLFOX6 (n = 50), bFOL (n = 50), or CapeOx (n = 50). Between November 2003 and April 2004, 223 patients were enrolled in TREE-2 at 57 centers in the United States and randomly assigned to the corresponding treatment arms plus bevacizumab (n = 75, n = 74, n = 74, respectively). Baseline characteristics were similar across all groups, except for prior adjuvant chemotherapy, male:female ratio, and primary site of diagnosis (Table 1).

Treatment

In TREE-1, 147 of 150 patients were treated (one was ineligible for prior chemotherapy and two did not start treatment). Discontinuations from mFOLFOX6, bFOL, and CapeOx were mostly attributable to AEs (29%, 46%, and 52%, respectively) or disease progression (43%, 42%, and 25%, respectively); CapeOx was tolerated least well. Treatment delays were most common with mFOLFOX6 (81% of

Table 1. Demographic and Baseline Characteristics

Characteristic	%					
	TREE-1			TREE-2		
	mFOLFOX6	bFOL	CapeOx	mFOLFOX6 + Bev	bFOL + Bev	CapeOx + Bev
No. of patients	49	50	48	71	70	72
Age, years						
Median	62	62	62.5	64	57	62
Range	35-79	31-84	32-84	31-83	30-85	32-82
Sex						
Female	43	38	35	39	51	42
Male	57	62	65	61	49	58
ECOG PS						
0	61	58	52	61	54	65
1	39	42	48	39	46	35
Prior adjuvant chemotherapy						
Primary site	45	16	27	24	31	31
Colon	55	74	75	65	66	69
Colon/rectum	27	14	19	17	11	24
Rectum	18	12	6	17	21	7
Other	0	0	0	1	1	0
Sites of metastases						
Liver	76	76	65	73	74	83
Lung	47	50	50	42	41	44
Other	55	68	65	42	37	33

Abbreviations: TREE, Three Regimens of Eloxatin Evaluation; mFOLFOX6, bolus and infusion fluorouracil and leucovorin with oxaliplatin; bFOL, bolus fluorouracil and low-dose leucovorin with oxaliplatin; CapeOx, capecitabine with oxaliplatin; bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status.

patients) although the number of cycles administered was highest in this arm (Table 2). Most common causes of delay were neutropenia and thrombocytopenia with mFOLFOX6 and bFOL and diarrhea, nausea, and dehydration with CapeOx. Oxaliplatin dose reductions were most common with mFOLFOX6 (50% of patients), reflecting the longest time on study (Table 2). Median relative dose intensity for oxaliplatin was ≥ 82% for all arms.

In TREE-2, 213 of 223 patients were treated (six withdrew consent, three had serious AEs or complications pretreatment, and one deteriorated clinically pretreatment). Discontinuations from treatment with mFOLFOX6, bFOL, and CapeOx were mostly for AEs (45%, 47%, and 51%, respectively) or disease progression (27%, 33%, and 25%, respectively). Treatment delay was most frequent with mFOLFOX6 plus bevacizumab (73%; Table 2). Treatment delays were most often attributable to neutropenia (all arms) or diarrhea (CapeOx plus bevacizumab). The oxaliplatin relative dose intensity was ≥ 84% for all arms.

Table 2. Treatment Administration

Parameter	TREE-1			TREE-2		
	mFOLFOX6	bFOL	CapeOx	mFOLFOX6 + Bev	bFOL + Bev	CapeOx + Bev
No. of patients	49	50	48	71	70	72
Duration of therapy, weeks						
Median	24	22	18	20	24	19
Range	2-52	4-60	3-83	4-78	4-76	3-85
No. of cycles*	490	275	282	794	389	535
Patients receiving > 1 cycle, %	98	88	83	100	91	92
Patients with ≥ 1 delay†, %	81	64	63	73	59	62
Patients with oxaliplatin dose reduction‡, %	50	32	20	54	45	50
Median RDI, %						
Oxaliplatin	82	88	94	84	87	91
FU/capecitabine	81	86	80	81	85	76
Bev	NA	NA	NA	88	92	96

Abbreviations: TREE, Three Regimens of Eloxatin Evaluation; mFOLFOX6, bolus and infusion fluorouracil and leucovorin with oxaliplatin; bFOL, bolus fluorouracil and low-dose leucovorin with oxaliplatin; CapeOx, capecitabine with oxaliplatin; Bev, bevacizumab; FU, fluorouracil; NA, not applicable; RDI, relative dose intensity.
*Cycle duration was 14 days for mFOLFOX6, 28 days for bFOL, and 21 days for CapeOx ± bevacizumab.
†> 3 days; denominator is the number of patients receiving > 1 cycle.
‡No of patients (%) with ≥ 1 cycle of oxaliplatin ≤ 80% of day 1 receiving of previous cycle; denominator is the number of patients receiving > 1 cycle.

In TREE-1, 69% of patients received subsequent anticancer therapy, including 41% who received a biologic agent (bevacizumab, n = 31; cetuximab, n = 28; other biologic agents, n = 3); 36 patients received oxaliplatin. Of those patients for whom data are available in TREE-2, 74% received subsequent anticancer treatment and this included a biologic agent in 38% of patients (bevacizumab, n = 70; cetuximab, n = 50; other biologic agents, n = 2); 62 patients received subsequent oxaliplatin.

Safety and Tolerability

In TREE-1, 59%, 36% and 67% of patients in the mFOLFOX6, bFOL, and CapeOx arms, respectively, had at least one grade 3/4 during the first 12 weeks of treatment (Table 3). In TREE-2, the corresponding incidences were 59%, 51%, and 56% (Table 3). For CapeOx, grade 3/4 dehydration was lower in TREE-2 (8%) than in TREE-1 (27%) due to the reduced capecitabine dose. Grade 3/4 hand-foot syndrome was most common with CapeOx (19%) and CapeOx plus bevacizumab (10%). Grade 3/4 neutropenia was most frequent with mFOLFOX6 (with or without bevacizumab). Rates of febrile neutropenia were 4%, 0%, and 2% in the mFOLFOX6, bFOL, and CapeOx arms, respectively, in TREE-1, and 3%, 1%, and 0%, respectively, in TREE-2. In TREE-2, 16% of patients received granulocyte colony-stimulating factors (data not available for TREE-1). In both cohorts, neurotoxicity (paresthesia) was predominantly grade 1/2, with no grade 4. The use of prophylactic calcium and magnesium salts was not allowed initially, but was permitted after the third treatment cycle for neuropathic symptoms, and was given to 15 patients (10%) in TREE-1, most of whom were in the mFOLFOX6 arm, and to 44 patients (21%) in TREE-2, equally distributed across the arms.

In TREE-2, bevacizumab-related toxicity (treatment arms combined) included bowel perforation (n = 5), sepsis (n = 3), impaired wound healing (n = 3), grade 3/4 hypertension (n = 13), and grade 3/4 proteinurea (n = 2). The overall incidence of bleeding events was highest in the mFOLFOX6 with or without bevacizumab treatment arms: (TREE-1, 22%; TREE-2, 45%). However, there were no grade 3/4 bleeding events in the mFOLFOX6 arm in TREE-1 while two (3%) grade 3 bleeding events occurred in the mFOLFOX6 plus bevacizumab arm (TREE-2).

Four patients in TREE-1 and six patients in TREE-2 had AEs leading to death within 30 days of the last treatment. In TREE-1, one patient in the CapeOx arm died due to grade 4 dehydration and diarrhea considered treatment related. In TREE-2, deaths arising from treatment-related AEs occurred in three patients in the bFOL plus bevacizumab arm (grade 4 septic shock, perforated ulcer, peritonitis, and intestinal perforation) and in three patients in the CapeOx plus bevacizumab arm (grade 4 cerebrovascular accident and arrhythmia, and grade 3 small intestinal obstruction). No treatment-related deaths

Table 3. Incidence of Grade 3 and Grade 4 Adverse Events

	Patients (%)					
	TREE-1			TREE-2		
Parameter	mFOLFOX6	bFOL	CapeOx	mFOLFOX6 + Bev	bFOL + Bev	CapeOx + Bev
No. of events	49	50	48	71	70	72
Events occurring during the first 12 weeks of treatment						
Related to treatment*	59	36	67	59	51	56
95% CI	44 to 73	23 to 51	52 to 80	47 to 71	39 to 64	43 to 67
Regardless of causality	76	44	73	65	60	58
95% CI	61 to 87	30 to 59	58 to 85	53 to76	48 to 72	46 to 70
Selected events occurring during or within 30 days of treatment†						
Anemia	8	2	6	0	4	0
Leukopenia	4	2	2	7	4	0
Neutropenia	53	18	15	49	19	10
Thrombocytopenia	6	8	10	3	11	7
Abdominal pain	2	4	13	6	4	10
Diarrhea	31	26	31	11	26	19
Nausea or vomiting	31	24	38	7	24	21
Fatigue	8	14	6	13	7	11
PT	NR	NR	NR	6	1	4
Dehydration	8	12	27	6	14	8
Paresthesia‡	18	10	21	11	9	11
Hand-foot syndrome	8	2	19	0	0	10
Deep vein thrombosis	6	2	0	4	1	3
Hypertension	0	0	2	7	13	15

NOTE. Adverse events were coded using MedDRA Version 8.1.

Abbreviations: TREE, Three Regimens of Eloxatin Evaluation; mFOLFOX6, bolus and infusion fluorouracil and leucovorin with oxaliplatin; bFOL, bolus fluorouracil and low-dose leucovorin with oxaliplatin; CapeOx, capecitabine with oxaliplatin; Bev, bevacizumab; NR, not reported; PT, prothrombin time.

*Possible or probable relationship to chemotherapy administration.

†All adverse events, regardless of causality.

‡Grade 1: paresthesias/dysesthesias that do not interfere with function; grade 2: paresthesias/dysesthesias interfering with function, but not activities of daily living (ADL); grade 3: paresthesias/dysesthesias with pain or functional impairment that also interfere with ADL; grade 4: persistent paresthesias/dysesthesias that are disabling or life-threatening.

were reported in the FOLFOX with or without bevacizumab arms. Overall 60-day mortality was 3.4% and 1.9% in the TREE-1 and TREE-2 cohorts, respectively.

Efficacy

In both TREE-1 and TREE-2, the highest confirmed ORRs occurred with mFOLFOX6 (41% and 52%; Table 4) but statistically there were no differences in ORRs within each cohort. In TREE-1, median TTF was longer for mFOLFOX6 (6.5 months; 95% CI, 5.4 to 8.3), although differences were not statistically significant; whereas in TREE-2, median TTF was similar across treatment arms (Table 4). In TREE-2, almost all patients received oxaliplatin until study treatment was discontinued (Fig 1), up to an 84-week maximum. Patients received a median of eight treatment cycles and the median treatment duration was 20 weeks. From week 30 to week 78, a total of five patients remained on study receiving fluoropyrimidine with bevacizumab (two to four patients at any time).

Median TTP and OS results for the individual treatment regimens in TREE-1 and TREE-2 are summarized in Table 4 and Figures 2A and 2B. Median survival was 18.2 months for all TREE-1 patients (95% CI, 14.5 to 21.6) and 23.7 months for the TREE-2 arms combined (95% CI, 21.3 to 26.8; Fig 2C). At the time of follow-up, 70% of patients in TREE-1% and 61% of patients in TREE-2 had died.

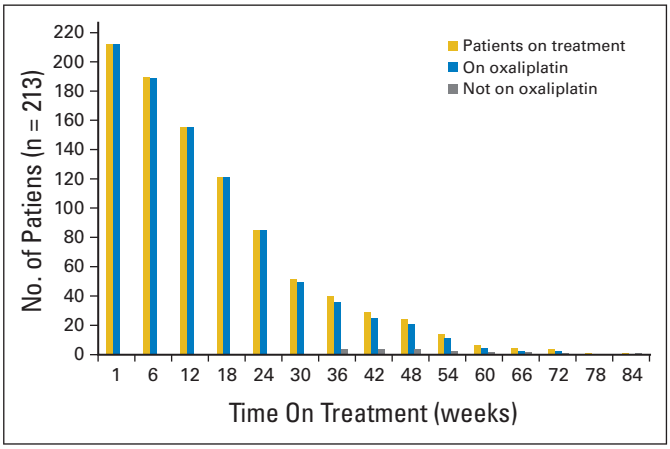

Fig 1. Number of patients on treatment (Three Regimens of Eloxatin Evaluation [TREE]-2 cohort; n = 213) by time and by therapy with or without oxaliplatin.

DISCUSSION

The TREE study evaluated the feasibility of administering oxaliplatin in combination with three different fluoropyrimidine regimens (continuous infusion, bolus, and oral), with or without bevacizumab, as first line-therapy for mCRC. All three oxaliplatin and fluoropyrimidine regimens were well tolerated and the addition of bevacizumab

Table 4. Efficacy Results

	Patients (%)					
	TREE-1			TREE-2		
End Point	mFOLFOX6	bFOL	CapeOx	mFOLFOX6 + Bev	bFOL + Bev	CapeOx + Bev
No. of patients	49	50	48	71	70	72
Response*						
CR	0	0	2	6	6	3
PR	41	20	25	46	33	43
SD	24	42	40	39	37	31
PD	27	26	10	6	13	8
ORR	41	20	27	52	39	46
95% CI	27 to 56	10 to 34	15 to 42	40 to 64	27 to 51	34 to 58
Median TTF†, months	6.5	4.9	4.4	5.8	5.5	5.5
95% CI	5.4 to 8.3	3.5 to 6.1	3.0 to 5.8	4.9 to 6.7	4.0 to 6.6	4.7 to 6.5
Median TTP‡, months	8.7	6.9	5.9	9.9	8.3	10.3
95% CI	6.5 to 9.8	4.2 to 8.0	5.1 to 7.4	7.9 to 11.7	6.6 to 9.9	8.6 to 12.5
Median OS, months	19.2	17.9	17.2	26.1	20.4	24.6
95% CI	14.2 to 24.9	11.5 to 24.6	12.5 to 22.3	18.0 to NE	18.4 to 25.3	21.4 to 31.6
1-yr survival	77.2	60.0	65.0	84.1	75.2	77.8

Abbreviations: TREE, Three Regimens of Eloxatin Evaluation; mFOLFOX6, bolus and infusion fluorouracil and leucovorin with oxaliplatin; bFOL, bolus fluorouracil and low-dose leucovorin with oxaliplatin; CapeOx, capecitabine with oxaliplatin; Bev, bevacizumab; CR, complete response; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; TTF, time to treatment failure; TTP, time to progression.

*Confirmed tumor response data (Response Evaluation Criteria in Solid Tumors) are shown.

†TTF was censored at the last date the patient was known to be on treatment for patients who were still on study treatment at the time of the analysis, who permanently discontinued study treatment before objective tumor progression, or who experienced a medical event requiring treatment discontinuation. TTF was also censored at the time of starting new antitumor treatment for patients who received nonstudy antitumor treatment before evidence of objective tumor progression, discontinuation of all study treatment, or death. In TREE-2, patients who discontinued oxaliplatin due to an oxaliplatin-related adverse event but who continued fluoropyrimidine or bevacizumab were censored at the time of study treatment discontinuation due to oxaliplatin-related adverse event.

‡TTP was censored at the last date the patient was known to be progression free for patients who did not have objective tumor progression and who were either still on study at the time of the analysis or who were removed from follow-up before documentation of objective tumor progression. For patients who received second-line treatment prior to progression or death, TTP was censored at the time of starting the new therapy. Median follow-up durations were 16.9, 15.1, 15.0, 17.9, 17.6, and 18.5 months, respectively.

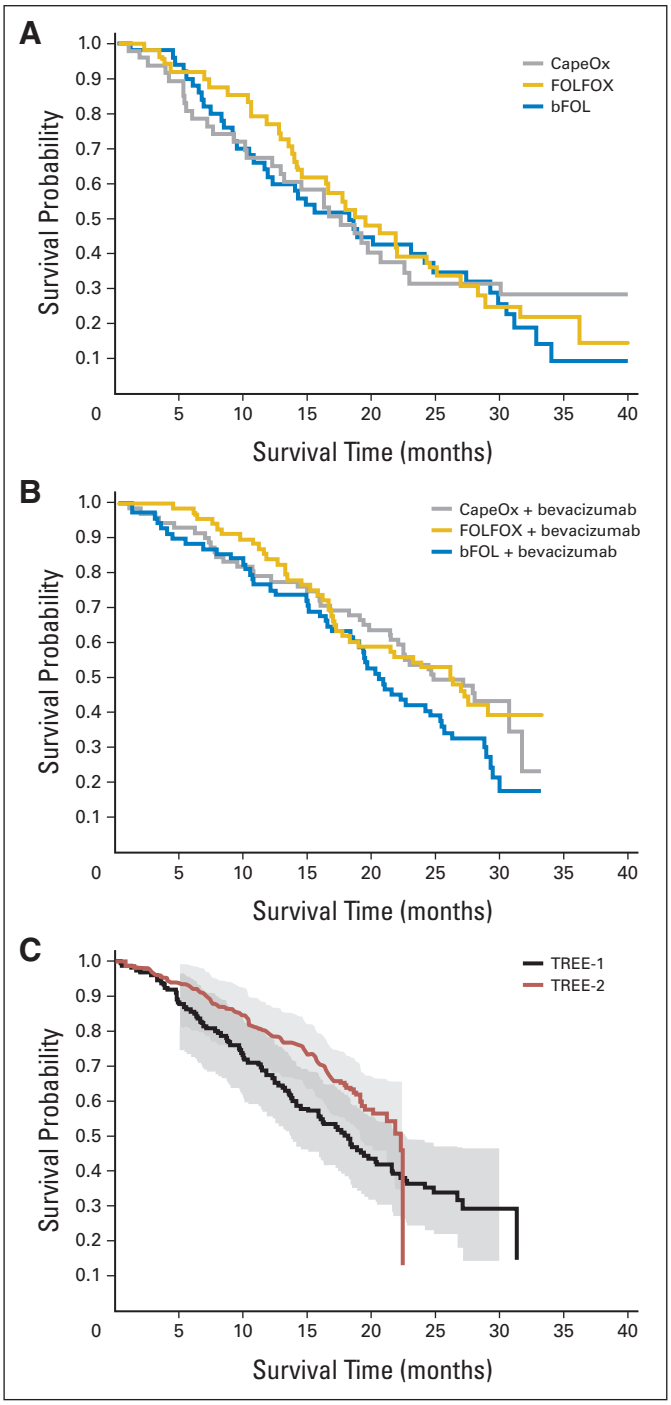

Fig 2. Kaplan-Meier plots of overall survival. (A) Three Regimens of Eloxatin Evaluation (TREE)-1 cohort, individual treatment regimens; (B) TREE-2 cohort, individual treatment regimens; (C) TREE-1 cohort, combined treatment regimens and TREE-2 cohort, combined treatment regimens (shaded areas show 95% Hall-Wellner confidence bands).

did not significantly alter the toxicity profiles. ORR, TTP, and OS were improved in the TREE-2 cohort compared with TREE-1 suggesting that bevacizumab improved the efficacy of oxaliplatin and fluoropyrimidine therapy. Because the study was not designed to compare the TREE-1 and TREE-2 patient cohorts, such a statistical analysis was not conducted.

The addition of bevacizumab to oxaliplatin and fluoropyrimidine regimens had no major impact on toxicity. Importantly, the toxicity profile of bevacizumab in TREE-2 was consistent with other reports.[3-5,7,8] The incidence of grade 3/4 hypertension in TREE-2 (7% to 15% grade 3) was similar to that with bevacizumab 5 mg/kg in combination with FU/LV (9%) or IFL (11% grade 3) as first-line therapy for mCRC.[3,4] The incidences of grade 3/4 proteinuria (TREE-2, 0% to 1% grade 3; IFL plus bevacizumab, 1% grade 3), grade 3/4 bleeding events (TREE-2, 1% to 3% grade 3; IFL plus bevacizumab, 3%), and any grade gastrointestinal perforation (TREE-2, 3% to 4%; IFL plus bevacizumab, 2%) were also comparable with previous data.[3] Our results provide the first evidence that bevacizumab can be added to first-line oxaliplatin-based regimens without altering the toxicity profile of chemotherapy, and with predictable bevacizumab-related toxicity.

Although CapeOx had the highest overall incidence of grade 3/4 toxicities and the shortest TTF in TREE-1, reducing the capecitabine dose from 2,000 to 1,700 mg/m^2/d in TREE-2 improved the toxicity profile. While median dose intensity for capecitabine was 74% in TREE-1% and 79% in TREE-2, the number of cycles requiring more than 25% dose reduction were 55% in TREE-1 and 25% in TREE-2. Notably, the incidence of grade 3/4 dehydration with CapeOx was reduced from 27% in TREE-1 to 8% in TREE-2; and grade 3/4 diarrhea was reduced from 31% in TREE-1 to 19% in TREE-2. Lowering the capecitabine dose also improved efficacy, as patients stayed on treatment longer. In fact, CapeOx had the worst toxicity profile and the shortest TTF in TREE-1, but was comparable with FOLFOX in TREE-2. In this study, CapeOx with a reduced capecitabine dose of 1,700 mg/m^2/d was a much improved regimen.

ORRs were higher in each of the treatment arms in TREE-2 than in the corresponding arms in TREE-1 and were highest for mFOLFOX6 with (52%) or without bevacizumab (41%). The effect appeared independent of the fact that almost twice as many patients in TREE-2 received calcium and magnesium salts for neurotoxicity. TTF was similar in the two cohorts, apparently due to cumulative neurotoxicity, which was unchanged with the addition of bevacizumab. TTP was also longer for each regimen in the TREE-2 cohort than for the corresponding regimen in the TREE-1 cohort. Although patients were not considered to have progressed until evidence of disease progression, they were censored at the time of second-line therapy in our analysis, possibly before objective evidence of progression. Chemotherapy was stopped for observation in fewer than 5% of cases; however, only five patients continued on study with fluoropyrimidine and bevacizumab alone after reaching the maximum cumulative doses of oxaliplatin resulting in neurotoxicity. Our analysis of general TTP (time until actual disease progression) or an on-study TTP (censoring patients at the time of discontinuing all study drugs) showed no overall difference in the median values or Kaplan-Meier curves.

In this study, median OS (20.4 to 26.1 months) was impressive for the TREE-2 cohort and approached 2 years (23.7 months) when data for all three regimens were combined. This is among the longest median OS reported to date in any prospective randomized clinical trial for mCRC. A similar proportion of patients in TREE-1 (69%) and TREE-2 (74%) received poststudy anticancer treatment; however, more patients in TREE-2 received a subsequent biologic agent combined with additional chemotherapy (14% *v* 38%). We cannot estimate the effect of this difference on OS.

The observation that bevacizumab appears to improve the efficacy of oxaliplatin and fluoropyrimidine therapy is consistent with other studies showing high efficacy for first-line chemotherapy regimens plus bevacizumab for mCRC. In these studies, TTP or PFS ranged from 9 to 11 months, representing an increase in disease-free survival of approximately 4 months with the addition of bevacizumab.[3,4,9,10] The TREE-2 results are also consistent with the Eastern Cooperative Oncology Group E3200 study in which the addition of bevacizumab to second-line FOLFOX significantly improved PFS (7.3 *v* 4.7 months; hazard ratio [HR], 0.61; $P < .0001$) and median OS (12.9 *v* 10.8 months; HR, 0.75; $P = .0011$).[5] However, these results were not verified in the randomized NO16966 trial, which compared FOLFOX or CapeOx with or without bevacizumab (n = 1,400).[11] In that trial a significant improvement in median PFS was reported with the addition of bevacizumab (9.4 *v* 8.0 months; HR, 0.83, $P = .002$)[11] but there was no effect on OS (21.3 *v* 19.9 months; HR, 0.89; $P = .077$; unpublished data presented at the 43rd annual meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007).

In conclusion, oxaliplatin and fluoropyrimidine chemotherapy with or without bevacizumab had a predictable safety profile and acceptable tolerability, regardless of the fluoropyrimidine regimen. In this study, based on sequential historical cohorts, bevacizumab appeared to further improve the efficacy of oxaliplatin and fluoropyrimidine chemotherapy in terms of ORR, TTP, and OS, although a preliminary report of a large randomized phase III trial did not show a similar magnitude of effect for PFS or OS.[11] It is likely that these differences are a result of variations in treatment patterns during the period leading up to determination of the treatment failure end point, and in subsequent therapy administered, although this cannot be fully determined until final results are available.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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 or Leadership Position: Barrett H. Childs, Sanofi-aventis (C); Eric Hedrick, Genentech BioOncology (C) **Consultant or Advisory Role:** Howard S. Hochster, Sanofi-aventis (C), Genentech BioOncology (C); Lucas Wong, Genentech (C) **Stock Ownership:** Barrett H. Childs, Sanofi-aventis; Eric Hedrick, Genentech **Honoraria:** Howard S. Hochster, Sanofi-aventis, Genentech; Ramesh K. Ramanathan, Sanofi-aventis, Genentech; Allen L. Cohn, Genentech, Bristol-Myers Squibb Co, Amgen; Lucas Wong, Genentech; M. Wasif Saif, Roche, Amgen, Genentech, Bristol-Myers Squibb Co, Sanofi-aventis **Research Funding:** Howard S. Hochster, Sanofi-aventis, Genentech BioOncology; Lowell L. Hart, Sanofi-aventis; Lucas Wong, Sanofi-aventis, Genentech; Louis Fehrenbacher, Genentech; M. Wasif Saif, Taiho, Samyang, Confirma Biotech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Howard S. Hochster, Barrett H. Childs, Eric Hedrick
Administrative support: Barrett H. Childs
Provision of study materials or patients: Howard S. Hochster, Lowell L. Hart, Ramesh K. Ramanathan, John D. Hainsworth, Allen L. Cohn, Lucas Wong, Louis Fehrenbacher, Yousif Abubakr, M. Wasif Saif, Lee Schwartzberg
Collection and assembly of data: Howard S. Hochster, Barrett H. Childs, Lucas Wong, Louis Fehrenbacher, Yousif Abubakr, M. Wasif Saif
Data analysis and interpretation: Howard S. Hochster, Barrett H. Childs
Manuscript writing: Howard S. Hochster, Barrett H. Childs
Final approval of manuscript: Howard S. Hochster, Lowell L. Hart, Ramesh K. Ramanathan, Barrett H. Childs, John D. Hainsworth, Louis Fehrenbacher, M. Wasif Saif, Lee Schwartzberg, Eric Hedrick

REFERENCES

1. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000
2. Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23-30, 2004
3. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004
4. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al: Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21:60-65, 2003
5. Giantonio BJ, Catalano PJ, Meropol NJ, et al: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539-1544, 2007
6. Gwyther SG, Therasse P, Arbuck SG, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000
7. Yang JC, Haworth L, Sherry RM, et al: A randomized trial of bevacizumab, an antivascular endothelial cell growth factor antibody, for metastatic renal cancer. N Engl J Med 349:427-434, 2003
8. Kozloff M, Cohn A, Christiansen N, et al: Safety of bevacizumab (BV) among patients (pts) receiving first line chemotherapy for metastatic colorectal cancer: Updated results from a large observational study in the U.S. (BRITE). Gastrointestinal Cancers Symposium, 2006 (abstr 247) http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=41&abstractID=405 Last accessed 20 February 2008
9. Bendell JC, Fernando N, Morse M, et al: A phase II study of oxaliplatin, capecitabine, and bevacizumab in the treatment of metastatic colorectal cancer. J Clin Oncol 24:156s, 2006 (suppl; abstr 3541)
10. Emmanouilides C, Sfakiotaki G, Androulakis N, et al: Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: A multicenter phase II study. BMC Cancer 30;7:91, 2007
11. Saltz L, Clarke S, Diaz-Rubio E, et al: Bevacizumab in combination with XELOX or FOLFOX-4: updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. J Clin Oncol 25, 2007 (suppl; abstr 4028)

Acknowledgment

We thank Gilbert Jirau-Lucca (sanofi-aventis) and Beth Berry (Prologue Research International) for their help in conducting this trial.