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ORIGINAL REPORT

Randomized, Controlled Trial of Irinotecan Plus Infusional, Bolus, or Oral Fluoropyrimidines in First-Line Treatment of Metastatic Colorectal Cancer: Results From the BICC-C Study

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ABSTRACT

Purpose
This phase III study compared the safety and efficacy of the following three different irinotecan-containing regimens in the first-line treatment of metastatic colorectal cancer: irinotecan plus infusional fluorouracil (FU)/leucovorin (LV) (FOLFIRI), irinotecan plus bolus FU/LV (mIFL), and irinotecan plus oral capecitabine (CapeIRI).

Patients and Methods
A total of 430 previously untreated metastatic colorectal cancer patients were randomly assigned to receive FOLFIRI (n = 144), mIFL (n = 141), or CapeIRI (n = 145). Patients were concurrently randomly assigned to a double-blind treatment with celecoxib or placebo. After a protocol amendment, an additional 117 patients were randomly assigned to either FOLFIRI plus bevacizumab (FOLFIRI+Bev; n = 57) or mILF plus bevacizumab (mIFL+Bev; n = 60), whereas the CapeIRI arm was discontinued. The primary study end point was progression-free survival (PFS), with secondary end points of overall survival (OS), response rate, and toxicity.

Results
Median PFS was 7.6 months for FOLFIRI, 5.9 months for mIFL ($P = .004$ for the comparison with FOLFIRI), and 5.8 months for CapeIRI ($P = .015$). Median OS was 23.1 months for FOLFIRI, 17.6 months for mIFL ($P = .09$), and 18.9 months for CapeIRI ($P = .27$). CapeIRI was associated with higher rates of severe vomiting, diarrhea, and dehydration. After the amendment to add bevacizumab, the median survival time has not yet been reached for FOLFIRI+Bev and was 19.2 months for mIFL+Bev ($P = .007$). FOLFIRI+Bev was associated with a higher rate of ≥ grade 3 hypertension than mIFL+Bev.

Conclusion
FOLFIRI and FOLFIRI+Bev offered superior activity to their comparators and were comparably safe. An infusional schedule of FU should be the preferred irinotecan-based regimen in first-line metastatic colorectal cancer.

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INTRODUCTION

Among patients with previously untreated metastatic colorectal cancer, the addition of irinotecan to either bolus[1] or infusional fluorouracil (FU)/leucovorin (LV)[2] significantly improved progression-free survival (PFS), overall survival (OS), and response rate compared with a comparable FU/LV regimen alone. Despite these findings, the optimum means of delivering FU has remained controversial. Although cross-study comparisons suggest that combinations using an infusional schedule of FU with irinotecan may be more effective and better tolerated than a comparable regimen using a bolus schedule of FU, no study has directly compared an infusional to a bolus schedule of FU in combination with irinotecan. Moreover, although phase II studies of capecitabine in combination with irinotecan reported comparable response rates to those previously reported with FU/LV and irinotecan,[3-6] few randomized trials have directly compared irinotecan-based regimens using oral capecitabine or intravenous (IV) FU/LV.

In 2003, we initiated a multicenter, randomized, phase III trial in patients with previously untreated metastatic colorectal cancer to compare the safety and efficacy of an infusional schedule of FU/LV with irinotecan (FOLFIRI) with the safety

and efficacy of combinations using either bolus FU/LV with irinotecan (mIFL) or oral capecitabine with irinotecan (CapeIRI). In April 2004, after US Food and Drug Administration approval of bevacizumab, the trial was amended to compare FOLFIRI plus bevacizumab (FOLFIRI+Bev) with mIFL plus bevacizumab (mIFL+Bev), whereas, because of toxicity concerns, further enrollment onto CapeIRI was discontinued. Herein, we report the comparative chemotherapy efficacy and toxicity results for all patients enrolled onto this trial.

PATIENTS AND METHODS

All patients were required to have histologically confirmed, metastatic adenocarcinoma of the colon or rectum with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST)[7]; age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; adequate bone marrow (absolute neutrophil or granulocyte counts ≥ 1,500/μL and platelets ≥ 100,000/μL), hepatic (total serum bilirubin ≤ the institutional upper limit of normal and AST ≤ 5× institutional upper limit of normal), and renal function (serum creatinine ≤ 1.6 mg/dL or creatinine clearance ≥ 40 mL/min); and no previous chemotherapy for metastatic disease. Previous adjuvant chemotherapy must have been completed at least 12 months before inclusion, and any major surgery must have been completed ≥ 4 weeks before the first bevacizumab dose. Patients were excluded if they had received prior therapy with irinotecan, topotecan, or bevacizumab; had known CNS metastases; had inadequately controlled hypertension, unstable angina, myocardial infarction, stroke or transient ischemic attack, uncontrolled ventricular cardiac arrhythmia, pulmonary embolism, or deep vein thrombosis within the past 6 months; had Gilbert's disease; were pregnant or lactating; were actively using cyclooxygenase-2 inhibitors or nonsteroidal anti-inflammatory drugs; or chronically used more than 325 mg/d of aspirin.

Random Assignment and Stratification

Beyond the comparison of three irinotecan/fluoropyrimidine chemotherapy combinations, this trial also examined the safety and efficacy of adding celecoxib or placebo to systemic chemotherapy as a secondary objective. Therefore, the study initially used a 3 × 2 factorial design, randomly assigning patients to one of three open-label chemotherapy arms as well as to double-blind treatment with celecoxib or placebo control (designated as period 1). Eligible patients were stratified by age (≤ 70 or > 70 years old), ECOG PS (0 or 1), and low-dose aspirin use (≤ 325 mg/d; yes or no). As part of a study amendment in April 2004 that added bevacizumab to chemotherapy, one of the chemotherapy arms was discontinued (CapeIRI) because of the greater toxicity of the CapeIRI arm and the paucity of safety data for the combination of CapeIRI with bevacizumab. The study was modified thereafter to a 2 × 2 factorial design (designated as period 2).

The protocol was reviewed and approved by the institutional review board of each participating institution. Each patient provided written informed consent. An independent data monitoring committee was responsible for safeguarding the interests of study participants, assessing the safety and efficacy of the study treatment, and monitoring the overall conduct of the clinical study.

Between February 2003 and December 2004, patients were enrolled at 99 sites and four countries (United States, Canada, Australia, and New Zealand). The study was sponsored by Pfizer Global Pharmaceuticals. The comparison for celecoxib and placebo will be reported in detail elsewhere.

Chemotherapy

During period 1, FOLFIRI (Table 1) consisted of irinotecan 180 mg/m^2 IV over 90 minutes, LV 400 IV mg/m^2 over 2 hours, and FU 400 mg/m^2 IV bolus, followed by FU 2,400 mg/m^2 IV over a 46-hour infusion, repeated every 2 weeks. mIFL represented a modification of the schedule of FU/LV plus irinotecan (IFL) described by Saltz et al,[1] consisting of irinotecan 125 mg/m^2 IV over 90 minutes, LV 20 mg/m^2 IV bolus, and FU 500 mg/m^2 IV bolus administered on days 1 and 8, repeated every 3 weeks. CapeIRI consisted of irinotecan 250 mg/m^2 IV over 90 minutes on day 1 and oral capecitabine 1,000 mg/m^2 twice per day on days 1 through 14, repeated every 3 weeks.

Table 1. Study Treatment Regimens for Periods 1 and 2

Period and Regimen	Description
Period 1	
FOLFIRI, day 1 every 2 weeks	Irinotecan, 180 mg/m^2 IV over 90 min; LV, 400 mg/m^2 IV over 2 h; FU, 400 mg/m^2 IV bolus; FU, 2,400 mg/m^2 IV continuous infusion over 46 h
mIFL, every 3 weeks	Irinotecan, 125 mg/m^2 IV over 90 min on days 1 and 8; LV, 20 mg/m^2 IV bolus on days 1 and 8; FU, 500 mg/m^2 IV bolus on days 1 and 8
CapeIRI, every 3 weeks	Irinotecan, 250 mg/m^2 IV over 90 min on day 1; capecitabine, 1,000 mg/m^2 by mouth twice per day on days 1-14
Period 2	
FOLFIRI+Bev, day 1 every 2 weeks	Irinotecan, 180 mg/m^2 IV over 90 min; LV, 400 mg/m^2 IV over 2 h; FU, 400 mg/m^2 IV bolus; FU, 2,400 mg/m^2 IV continuous infusion over 46 h; Bev, 5 mg/kg IV
mIFL+Bev, every 3 weeks	Irinotecan, 125 mg/m^2 IV over 90 min on days 1 and 8; LV, 20 mg/m^2 IV bolus on days 1 and 8; FU, 500 mg/m^2 IV bolus on days 1 and 8; Bev, 7.5 mg/kg IV on day 1 only

Abbreviations: FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; IV, intravenous; FU, fluorouracil; LV, leucovorin; min, minute; h, hour; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; CapeIRI, capecitabine/irinotecan; Bev, bevacizumab.

During Period 2, after the addition of bevacizumab to FOLFIRI and mIFL, FOLFIRI+Bev consisted of the aforementioned FOLFIRI regimen with bevacizumab 5 mg/kg IV on day 1, repeated every 2 weeks. mIFL+Bev consisted of the aforementioned mIFL regimen with bevacizumab 7.5 mg/kg IV on day 1, repeated every 3 weeks. After activation of this study amendment, patients randomly assigned to FOLFIRI or mIFL during period 1 had the option of adding bevacizumab to their current regimen. Among patients enrolled during period 1, 16 patients on the FOLFIRI arm added bevacizumab to their regimen, and seven patients on the mIFL arm added bevacizumab to their regimen. During both period 1 and period 2, patients were concurrently treated with either oral celecoxib 400 mg twice per day without interruption or placebo tablets. (Pfizer Inc, New York, NY, provided celecoxib for this study and approved the study protocol.)

Patients were treated with chemotherapy (in conjunction with twice-daily celecoxib or placebo) until progressive disease (PD), unacceptable toxicities caused by chemotherapy, or withdrawal of patient consent. Celecoxib/placebo administration for all patients remaining on study was permanently discontinued on January 19, 2005, after an announcement concerning the potential association of celecoxib with increased risk of major cardiovascular events in a long-term, colorectal adenoma prevention study (the Adenoma Prevention With Celecoxib trial).[8]

Standard intra- and intercycle dose modifications for FU, capecitabine, and irinotecan (based on the package insert for irinotecan[9]) were prescribed if grade 2 to 4 toxicities occurred (based on National Cancer Institute Common Toxicity Criteria, version 2.0). LV, bevacizumab, and celecoxib doses were not altered.

Study Assessments

Baseline evaluations consisted of physical examination, ECG, medical and oncologic history, ECOG PS, CBC with differential, hepatic and renal function tests, urinary protein, carcinoembryonic antigen, prothrombin time/international normalized ratio (for patients on anticoagulation), and serum pregnancy test for women of reproductive potential. Baseline evaluations occurred within 14 days of the first study medication dose, except for hematology (within 7 days of first dose) and ECG (within 3 months of first dose).

Baseline tumor assessments were performed within 21 days before the first study medication dose; all patients were to have a computed tomography (CT)/magnetic resonance imaging (MRI) of the abdomen/pelvis and chest x-ray or CT/MRI of the chest. During chemotherapy, a follow-up CT/MRI of the abdomen/pelvis and chest x-ray or chest CT/MRI were to be performed every 6 weeks. Assessments were performed every 6 weeks until PD or on chemotherapy discontinuation. If a patient's disease was in response or stable at the time of treatment withdrawal, the patient was observed every 6 weeks until PD. After PD, the patient was observed every 3 months for survival. All follow-up tumor assessments were to be performed using the same radiographic methods as those used at baseline. Tumor response classification was based on RECIST guidelines.[7] To evaluate safety of the study treatments, adverse events, laboratory test results, and changes in vital signed were recorded at every study visit using the National Cancer Institute Common Toxicity Criteria, version 2.0.

Statistical Considerations

Detailed methodology for summarization and statistical analyses of the data collected in this study was documented in a statistical analysis plan, which was developed and finalized with oversight by the independent data monitoring committee before breaking the treatment blind. The primary efficacy end point was PFS, which was defined as the time from random assignment to the first documentation of PD. The primary efficacy analysis compared PFS between FOLFIRI and mIFL patients. First documentation of PD was based on the definition of PD based on the RECIST guidelines, the investigator's clinical judgment of PD, or death as a result of any cause in the absence of previously documented PD. For patients without documented PD, data were censored on the date of the last tumor assessment with nonprogression status or, for patients who started a second-line therapy, at the date of the start of new therapy.

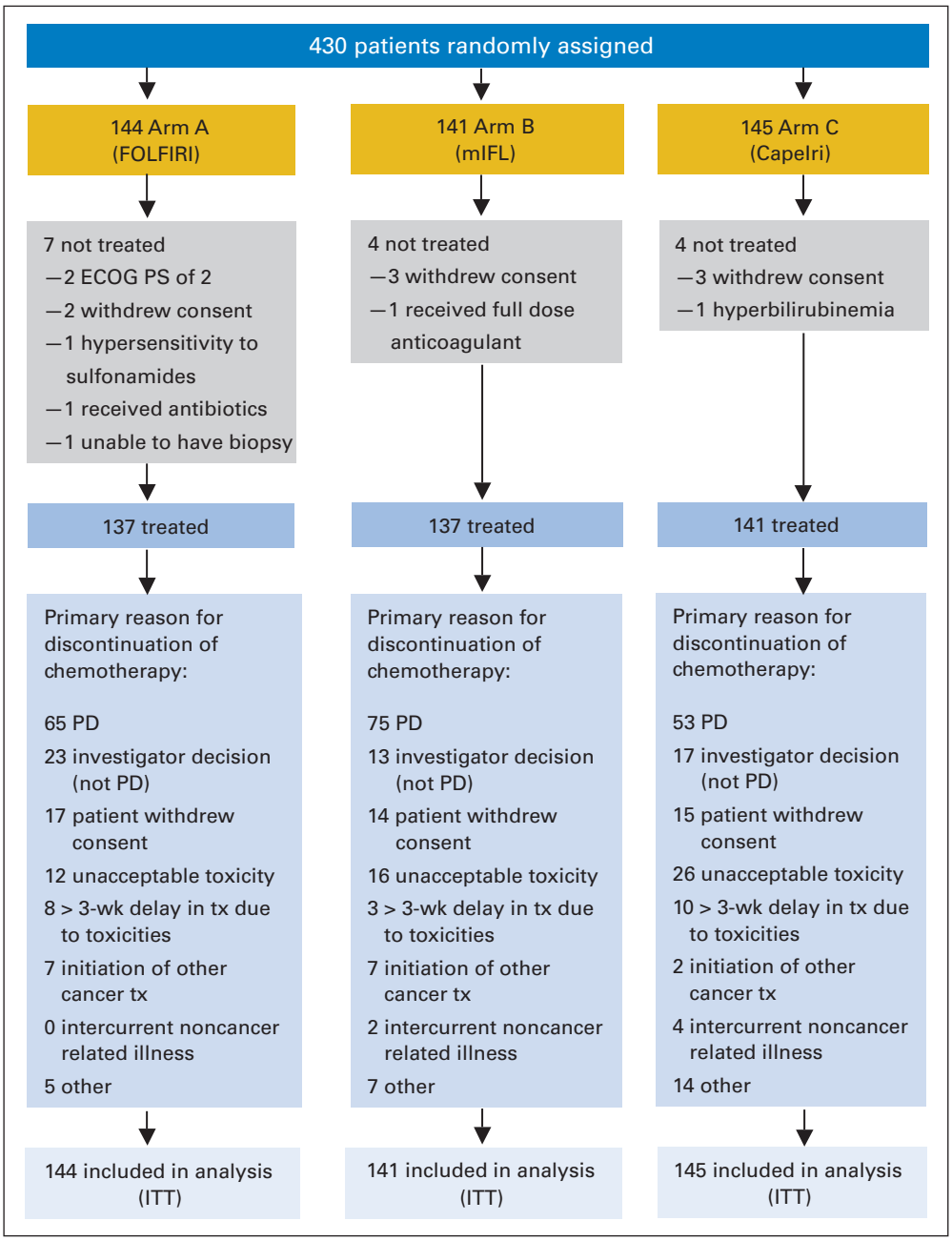

Fig 1. CONSORT diagram for period 1. FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; Capelri, irinotecan plus oral capecitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; wk, week; tx, treatment; ITT, intention-to-treat.

Secondary efficacy end points included PFS compared between all other chemotherapy arms, OS, 1-year survival, and overall response (complete response + partial response). OS time was defined as the time from the date of random assignment to the date of death; in the absence of confirmation of death, data were censored at the last date the patient was known to be alive.

Analyses for PFS and OS were conducted using a log-rank test with stratification for age (≤ 70 or > 70 years), ECOG PS (0 or 1), low-dose aspirin use at random assignment (yes or no), and celecoxib/placebo treatment (celecoxib or placebo). Overall response was analyzed using a Cochran-Mantel-Haenszel test with stratification as described earlier.[10] The Kaplan-Meier method was used to calculate PFS, OS, and 1-year survival rates.[11] The hazard ratio (HR) and 95% CI for the treatment comparisons were obtained from a Cox proportional hazards model using the same variables as described earlier as covariates.[12] All statistical tests were two-sided, using a significance level of 5%. No adjustments for multiple comparisons were made.

Efficacy analyses included all patients randomly assigned on an intent-to-treat basis. Safety analyses included all treated patients and were summarized descriptively. As predefined in the amended protocol, results for period 1 (before the addition of bevacizumab) and period 2 (after the addition of bevacizumab) were analyzed separately. All efficacy and safety analyses reported were performed using a data cutoff of November 17, 2006.

Initially, the sample size for the study was projected to be 900 patients; however, after the report of cardiovascular safety concern with celecoxib, accrual to the trial diminished markedly, despite discontinuation of the celecoxib/placebo assignment. Ultimately, after consultation with a physician advisory board and study investigators, enrollment was terminated in March 2005 with 547 total patients enrolled.

RESULTS

Patient Enrollment and Characteristics

Between February 2003 and March 2004, 430 patients were randomly assigned to FOLFIRI, mIFL, or CapeIRI (period 1; Fig 1). Between April 2004 and December 2004, 117 patients were randomly

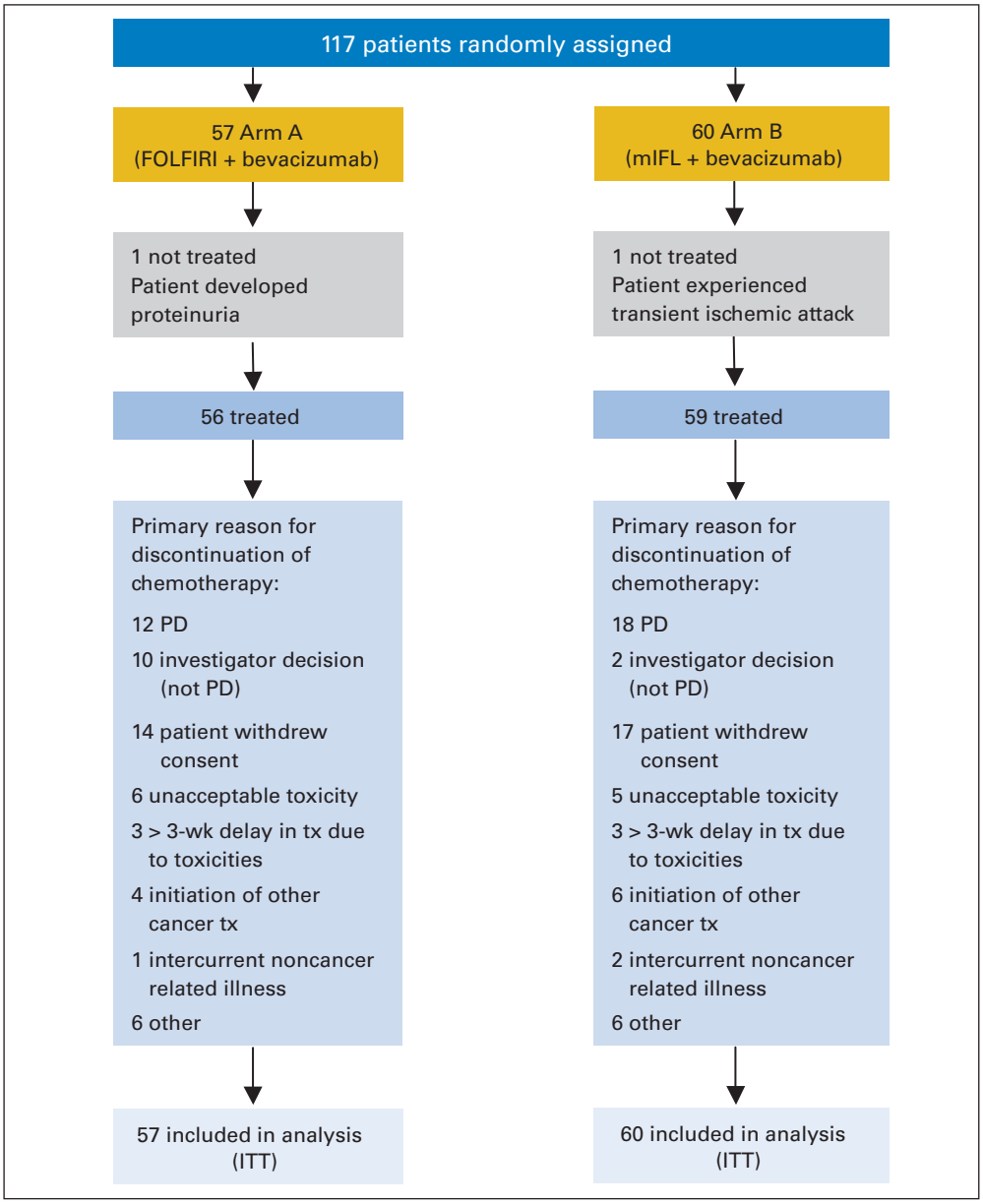

Fig 2. CONSORT diagram for period 2. FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; PD, progressive disease; wk, week; tx, treatment; ITT, intention-to-treat.

assigned to either FOLFIRI+Bev or mIFL+Bev (period 2; Fig 2). In both enrollment periods, treatments arms seemed well balanced (Table 2). Among all patients, 17 patients (3%) did not receive study treatment and, therefore, were excluded from toxicity analyses.

Efficacy

Period 1. With a median follow-up time of 34 months, PFS was significantly improved for patients who received FOLFIRI (median PFS, 7.6 months) when compared with mIFL (median PFS, 5.9 months; $P = .004$; HR for disease progression or death = 1.51; 95% CI, 1.16 to 1.97; Fig 3A). Similar differences in PFS were observed for the comparison between FOLFIRI and CapeIRI (median PFS, 5.8 months; $P = .015$; HR = 1.36; 95% CI, 1.04 to 1.80). In contrast, PFS did not differ significantly between mIFL and CapeIRI ($P = .46$; HR = 1.05; 95% CI, 0.81 to 1.38).

Median OS time was 23.1 months for patients treated with FOLFIRI, 17.6 months for patients treated with mIFL, and 18.9 months for patients treated with CapeIRI (Fig 3B). These differences in OS between chemotherapy arms did not achieve statistical significance ($P = .09$ for the comparison between FOLFIRI and mIFL). The proportion of patients alive at 1 year was 75% for the FOLFIRI-treated group, 65% for the mIFL-treated group, and 66% for CapeIRI-treated group.

The overall objective response rates did not differ significantly between chemotherapy arms in period 1 (47.2% for FOLFIRI, 43.3% for mIFL, and 38.6% for CapeIRI). Complete responses were seen in 5.6%, 4.3%, and 2.8% of patients in the FOLFIRI, mIFL, and CapeIRI arms, respectively. The rates of utilization of poststudy salvage chemotherapy did not differ significantly between the three first-line chemotherapy arms in period 1 (77% for FOLFIRI, 75% for mIFL, and 77% for CapeIRI).

Period 2. With a median follow-up time of 22.6 months, median PFS time was 11.2 months for patients treated with FOLFIRI+Bev and 8.3 months for patients treated with mIFL+Bev (Fig 4A). The difference in PFS between chemotherapy arms was not statistically significant.

OS was significantly greater for patients who received FOLFIRI+Bev (median OS, not yet reached) when compared with patients treated with mIFL+Bev (median OS, 19.2 months; $P = .007$; HR for death = 2.34; 95% CI, 1.34 to 4.12; Fig 4B). The proportion of patients alive at 1 year was 87% for FOLFIRI+Bev and 61% for mIFL+Bev.

The overall objective response rates did not differ significantly between chemotherapy arms in period 2 (57.9% for FOLFIRI+Bev and 53.3% for mIFL+Bev). Complete responses were seen in 5.3% and 5.0% of patients in the FOLFIRI+Bev and mIFL+Bev arms, respectively. The rates of utilization of poststudy salvage chemotherapy did not differ significantly between the two first-line chemotherapy arms in period 2 (68% for FOLFIRI+Bev and 68% for mIFL+Bev).

Tolerability

Period 1. CapeIRI was associated with the highest rates of grade 3 or higher nausea, vomiting, diarrhea, dehydration, and hand-foot syndrome (Table 3). In contrast, FOLFIRI was associated with the lowest rates of diarrhea and febrile neutropenia. Discontinuation of study treatment for unacceptable toxicity was more common among patients treated with CapeIRI (25.5%) when compared with either FOLFIRI (14.6%) or mIFL (13.9%). Death rates within the first 60 days of treatment were 3.6% for patients receiving FOLFIRI, 5.1% for patients receiving mIFL, and 3.5% for patients receiving CapeIRI.

We considered the possibility that the inferior PFS for CapeIRI compared with FOLFIRI in period 1 might reflect the higher rate of treatment discontinuation as a result of unacceptable toxicity associated with CapeIRI. Therefore, we repeated the analysis of PFS for all patients enrolled onto period 1 after excluding patients who discontinued treatment as a result of toxicity within the first 30 days. Nonetheless, PFS remained significantly better for patients who received FOLFIRI (median, 8.0 months) when compared with either mIFL (median, 5.9 months; $P = .006$) or CapeIRI (median, 6.2 months; $P = .01$).

Table 2. Baseline Patient Characteristics

	Period 1						Period 2			
	FOLFIRI (n = 144)		mIFL (n = 141)		CapeIRI (n = 145)		FOLFIRI+Bev (n = 57)		mIFL+Bev (n = 60)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years										
Median	61		62		62		59		60	
Range	31-87		29-80		20-85		32-81		35-84	
Male sex	92	63.9	83	58.9	79	54.5	30	52.6	38	63.3
Race										
White	129	89.6	126	89.4	122	84.1	38	66.7	51	85.0
Black	6	4.2	7	5.0	16	11.0	9	15.8	8	13.3
Other	9	6.3	8	5.7	7	4.8	10	17.5	1	1.7
ECOG PS										
0	75	52.1	70	49.6	70	48.3	31	54.4	31	51.7
1	69	47.9	71	50.4	75	51.7	25	43.9	29	48.3
2							1	1.8		
Primary tumor site										
Colon	100	69.4	91	64.5	103	71.0	35	61.4	42	70.0
Rectum/rectosigmoid	44	30.6	50	35.5	42	29.0	22	38.6	18	30.0

Abbreviations: FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; CapeIRI, capecitabine/irinotecan; Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status.

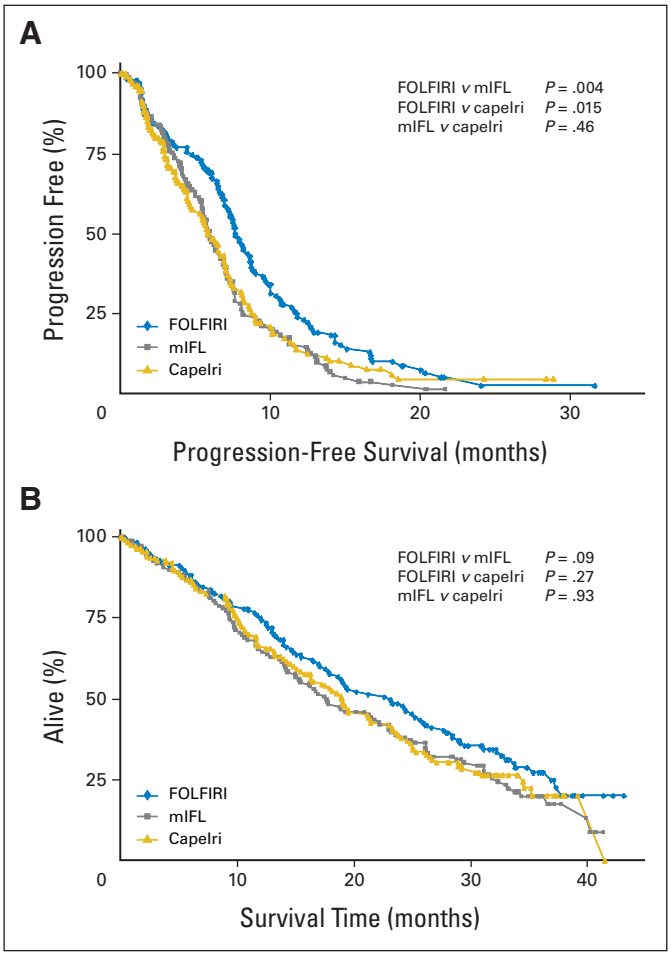

Fig 3. Arm A: Progression-free survival for period 1. Arm B: Overall survival for period 1. FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; CapeIRI, capecitabine/irinotecan.

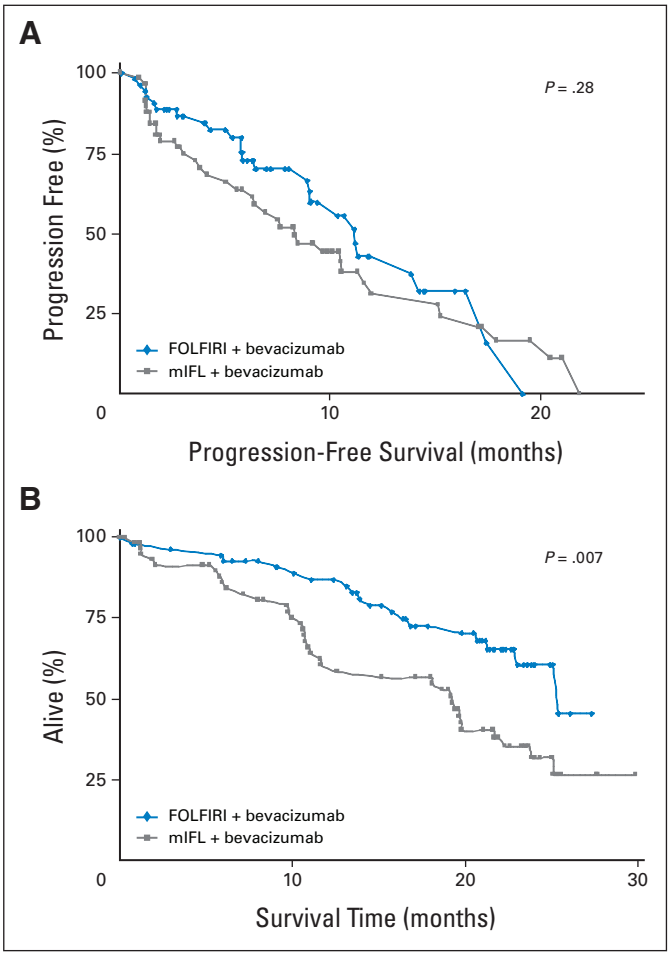

Fig 4. (A) Progression-free survival for period 2. (B) Overall survival for period 2. FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin.

Period 2. Compared with mIFL+Bev, rates of grade 3 or higher nausea, vomiting, dehydration, and febrile neutropenia were modestly higher among patients receiving FOLFIRI+Bev, whereas hypertension was substantially higher for FOLFIRI+Bev (Table 4). The rate of discontinuation of study treatment as a result of unacceptable toxicity was 16.1% for FOLFIRI+Bev and 13.6% for mIFL+Bev. Death rates within the first 60 days of treatment were 1.8% for patients receiving FOLFIRI+Bev and 6.8% for patients receiving mIFL+Bev.

DISCUSSION

This study in the first-line treatment of metastatic colorectal cancer demonstrates that a combination of irinotecan with an infusional schedule of FU/LV (FOLFIRI) offers superior efficacy when compared with irinotecan with either a bolus schedule of FU/LV (mIFL) or oral capecitabine (CapeIRI). Consistent with these findings, after the addition of bevacizumab, FOLFIRI+Bev conferred a significant survival benefit when compared with mIFL+Bev.

Earlier randomized trials comparing infusional to bolus FU/LV suggested that infusional schedules offered both superior efficacy and tolerability.[1,2] In a previous Intergroup study of first-line therapy for metastatic colorectal cancer (N9741), an infusional schedule of FU/LV with oxaliplatin (FOLFOX) provided superior efficacy to a bolus schedule of IFL[13]; in contrast, studies comparing FOLFOX with FOLFIRI demonstrated similar efficacy.[14,15] Given the results from the current study, the superiority of FOLFOX over bolus IFL reported in N9741 may reflect differences in the FU schedule, rather than intrinsic differences between oxaliplatin- and irinotecan-based regimens. Notably, the recent Three Regimens of Eloxatin Evaluation-1 (TREE-1) trial in first-line metastatic colorectal cancer similarly suggests that infusional FOLFOX is superior to a bolus regimen of FU/LV with oxaliplatin.[16]

Phase II studies of the current schedule of oral capecitabine with irinotecan suggested acceptable response rates and tolerability.[3-6] However, in the current study, CapeIRI was less effective and more toxic than FOLFIRI. Although we considered the possibility that the inferior efficacy results for CapeIRI might reflect early treatment discontinuation as a result of toxicity, the superior PFS for FOLFIRI (*v* CapeIRI) remained unchanged after excluding those patients who discontinued therapy early as a result of unacceptable toxicity. The greater toxicity for CapeIRI in the current trial may reflect the greater propensity for capecitabine-related toxicity among US and other non-European patients relative to European populations.[17] Conceivably,

Table 3. Common Grade 3 or Greater Adverse Events in Period 1

Adverse Event ≥ Grade 3	FOLFIRI (n = 137)		mIFL (n = 137)		CapeIRI (n = 141)	
	No.	%	No.	%	No.	%
Nausea	12	8.8	10	7.3	26	18.4
Vomiting	12	8.8	10	7.3	22	15.6
Diarrhea	19	13.9	26	19.0	67	47.5
Dehydration	8	5.8	10	7.3	27	19.1
Neutropenia	59	43.1	56	40.9	45	31.9
Febrile neutropenia	5	3.6	17	12.4	10	7.1
Hand-foot syndrome	0	0	0	0	14	9.9

Abbreviations: FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; CapeIRI, capecitabine/irinotecan.

alternative doses and schedules of the combination of capecitabine and irinotecan could provide a superior efficacy and tolerability profile than the regimen used in the current trial.

In previously untreated metastatic colorectal cancer, Hurwitz et al[18] demonstrated the superiority of bolus IFL plus bevacizumab when compared with IFL with placebo. In the current trial, median PFS times for both mIFL and FOLFIRI improved with the addition of bevacizumab (5.9 *v* 8.3 months for mIFL and mIFL+Bev, respectively; and 7.6 *v* 11.2 months for FOLFIRI and FOLFIRI+Bev, respectively), although one must view such cross-period comparisons cautiously. The median OS time for mIFL+Bev in the current trial (19.2 months) seemed similar to the IFL/bevacizumab combination in the trial by Hurwitz et al[18] (20.3 months). However, in the current study, we found that the FOLFIRI+Bev combination offered a superior survival rate when compared with mIFL+Bev. Finally, the median PFS time for FOLFIRI+Bev (11.2 months) in the current study seems comparable to the median PFS times found in recent randomized trials that examined FOLFOX with bevacizumab (9.4 to 9.9 months).[16,19]

As described, our trial did close before its targeted accrual goal; consequently, statistical power, particularly for the comparison in period 2, was diminished. Furthermore, although the rates of utilization of poststudy salvage chemotherapy did not differ significantly according to the treatment arms, details regarding the specific agents used were not uniformly recorded. Nonetheless, our study is among the few randomized studies that compared various irinotecan/fluoropyrimidine combinations. Ultimately, both FOLFIRI and FOLFIRI+Bev offered superior activity to their comparators and were comparably safe. Consequently, when using an irinotecan-based regimen in the treatment of first-line metastatic colorectal cancer, an infusional schedule of FU should be the preferred approach.

Table 4. Common Grade 3 or Greater Adverse Events in Period 2

Adverse Event ≥ Grade 3	FOLFIRI+Bev (n = 56)		mIFL+Bev (n = 59)	
	No.	%	No.	%
Nausea	6	10.7	3	5.1
Vomiting	6	10.7	3	5.1
Diarrhea	6	10.7	7	11.9
Dehydration	3	5.4	1	1.7
Neutropenia	30	53.6	17	28.8
Febrile neutropenia	3	5.4	1	1.7
Hypertension	7	12.5	1	1.7

Abbreviations: FOLFIRI, infusional fluorouracil/leucovorin/irinotecan; mIFL, modified bolus irinotecan/fluorouracil/leucovorin; Bev, bevacizumab.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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