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ORIGINAL REPORT

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EPIC: Phase III Trial of Cetuximab Plus Irinotecan After Fluoropyrimidine and Oxaliplatin Failure in Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose
To determine whether adding cetuximab to irinotecan prolongs survival in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine and oxaliplatin.

Patients and Methods
This multicenter, open-label, phase III study randomly assigned 1,298 patients with epidermal growth factor receptor–expressing mCRC who had experienced first-line fluoropyrimidine and oxaliplatin treatment failure to cetuximab (400 mg/m^2 day 1 followed by 250 mg/m^2 weekly) plus irinotecan (350 mg/m^2 every 3 weeks) or irinotecan alone. Primary end point was overall survival (OS); secondary end points included progression-free survival (PFS), response rate (RR), and quality of life (QOL).

Results
Median OS was comparable between treatments: 10.7 months (95% CI, 9.6 to 11.3) with cetuximab/irinotecan and 10.0 months (95% CI, 9.1 to 11.3) with irinotecan alone (hazard ratio [HR], 0.975; 95% CI, 0.854 to 1.114; $P = .71$). This lack of difference may have been due to post-trial therapy: 46.9% of patients assigned to irinotecan eventually received cetuximab (87.2% of those who did, received it with irinotecan). Cetuximab added to irinotecan significantly improved PFS (median, 4.0 v 2.6 months; HR, 0.692; 95% CI, 0.617 to 0.776; $P \leq .0001$) and RR (16.4% v 4.2%; $P < .0001$), and resulted in significantly better scores in the QOL analysis of global health status ($P = .047$). Cetuximab did not exacerbate toxicity, except for acneform rash, diarrhea, hypomagnesemia, and associated electrolyte imbalances. Neutropenia was the most common severe toxicity across treatment arms.

Conclusion
Cetuximab and irinotecan improved PFS and RR, and resulted in better QOL versus irinotecan alone. OS was similar between study groups, possibly influenced by the large number of patients in the irinotecan arm who received cetuximab and irinotecan poststudy.

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INTRODUCTION

Management of metastatic colorectal cancer (mCRC) has evolved over the past decade. Patients receiving irinotecan (Camptosar; Pfizer Inc, New York, NY),[1-4] oxaliplatin (Eloxatin; Sanofi-aventis U.S. LLC, Bridgewater, NJ)[5-7] and fluorouracil (FU) achieve the best outcomes (median survival (MS), approximately 21 months), regardless of treatment sequence.[7,8] Biologic therapies provide further improvements. The antiangiogenic monoclonal antibody bevacizumab (Avastin; Genentech Inc, South San Francisco, CA) improves survival in bevacizumab-naïve patients

when added to first-line[9] or second-line chemotherapy,[10] but seems inactive in refractory disease.[10,11] Biologics targeting the epidermal growth factor receptor (EGFR) are effective in disease refractory to FU, irinotecan, and oxaliplatin.[12,13]

Cetuximab (ERBITUX; ImClone Systems Inc, New York, NY, and Bristol-Myers Squibb Co, Princeton, NJ), a chimeric monoclonal immunoglobulin 1 that binds to the EGFR, blocks signal transduction, modulates tumor growth,[14,15] and may mediate antibody-dependent cell-mediated cytotoxicity.[16] Cetuximab and irinotecan have produced among the highest response rates (RR;

approximately 23%) observed in refractory patients, and the pattern of activity in irinotecan-refractory patients suggests cetuximab restores chemosensitivity.[14] Cetuximab is also active as a single agent, producing objective RR between 9% and 12%,[12,14,17] and improving survival when compared with best supportive care in refractory patients.[18] The role of cetuximab-based combinations in first-line therapy is under investigation.[19,20]

The ERBITUX Plus Irinotecan for Metastatic Colorectal Cancer (EPIC) study was designed to determine whether adding cetuximab to irinotecan as second-line therapy would prolong survival in irinotecan-naïve patients with EGFR-expressing mCRC. Second-line was defined as failure of prior fluoropyrimidine and oxaliplatin therapy.

PATIENTS AND METHODS

Study Design and Eligibility Criteria

In this open-label, randomized, phase III study, patients from 221 sites worldwide were randomly assigned 1:1 to receive cetuximab/irinotecan or irinotecan alone. The randomization was stratified by study site and Eastern Cooperative Oncology Group (ECOG) performance status (PS, 0 to 1 v 2).

Eligibility required bidimensionally measurable (≥ 1 tumor with 1 diameter ≥ 20 mm and the other ≥ 10 mm), histologically documented mCRC with immunohistochemical evidence of EGFR expression. Failure (disease progression/discontinuation due to toxicity) within 6 months of the last-dose of first-line fluoropyrimidine and oxaliplatin treatment for metastatic disease was required. Previous irinotecan or anti-EGFR therapies were excluded; prior bevacizumab was allowed.

This study was performed after approval by a local human investigations committee and in accord with an assurance filed with and approved by the department of health and human services where appropriate. Informed consent was obtained from each participant.

Treatment

The only irinotecan regimen approved by the US Food and Drug Administration and the European Medicines Agency for pretreated patients at the time of design was irinotecan monotherapy (every 3 weeks), therefore it was chosen as comparator. Patients assigned to the irinotecan and cetuximab arm received an initial 400-mg/m^2 cetuximab dose (2-hour intravenously [IV]), and then 250 mg/m^2 (1-hour IV) weekly, preceded by premedication with antihistamine. Irinotecan 350 mg/m^2 (90-minute IV; 300 mg/m^2 for patients ≥ 70 years, those with ECOG PS of 2, or with prior pelvic/abdominal irradiation) was administered every 3 weeks in both treatment arms, starting 1 hour after cetuximab-infusion completion for patients in the cetuximab arm. Treatment continued until disease progression or unacceptable toxicity. There were no poststudy treatment limitations.

Dose Modifications

Grade 3/4 hypersensitivity required cetuximab discontinuation; infusion was slowed to one half of the initial rate in case of grade 1/2 allergic/hypersensitivity reactions. Cetuximab was withheld for grade 3 acneform rash, until resolution to grade 2 or lower. Severe toxicities warranting irinotecan and/or cetuximab dose reductions included grade 3/4 neutropenia, thrombocytopenia, neutropenic fever, diarrhea, or grade 3 nausea/vomiting. Both agents were discontinued for grade 4 nonhematologic toxicities, and patients were observed until resolution.

Assessments

Tumor response was evaluated every 6 weeks (computed tomography/magnetic resonance imaging scans of abdomen, pelvis, and chest; x-rays acceptable to confirm bone-scan findings) using modified WHO criteria.
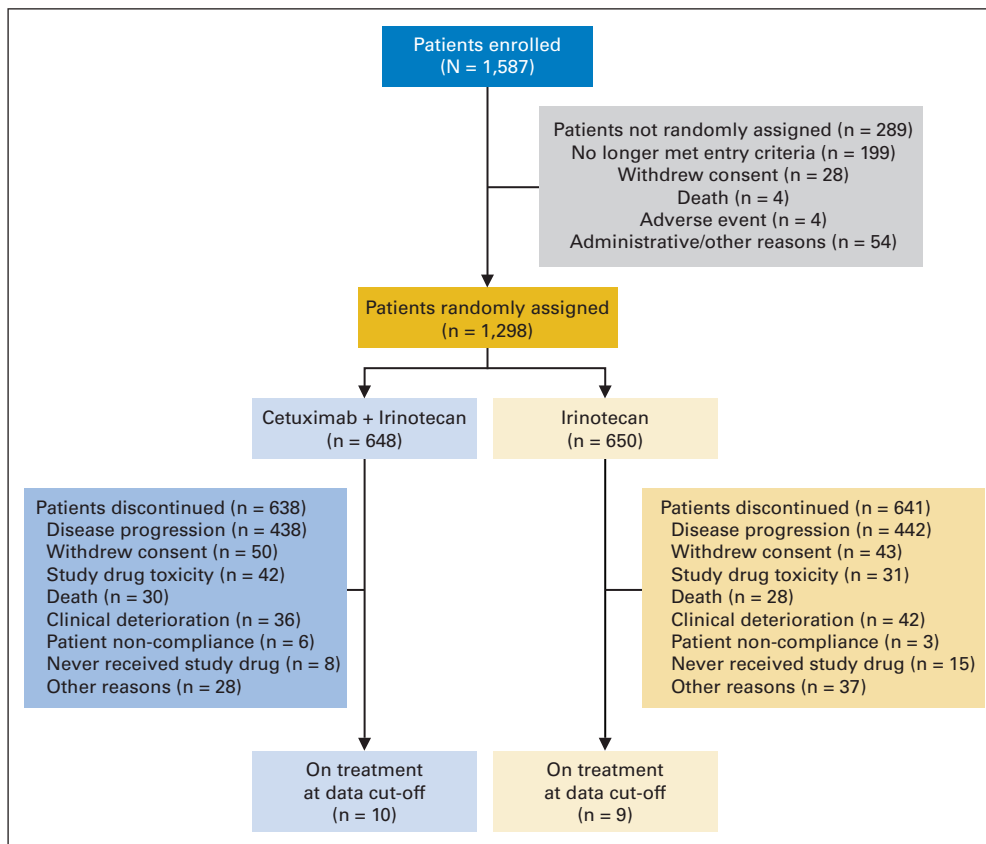

Fig 1. Patient disposition.

Objective responses required a $\geq$ 50% reduction (relative to baseline) in the area of all index lesions (investigator selected), confirmed $\geq$ 4 weeks later. Disease progression was defined by a 25% increase in the index-lesion area relative to the smallest area recorded, by progression of nonmeasurable lesions, or by appearance of new lesions. Quality of life (QOL) was assessed at baseline, after 3 weeks, and then every 6 weeks until the first post-therapy follow-up visit using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30,[21] administered before study-related procedures or clinician assessments. Physical examinations and toxicity assessments were performed before each cycle and after therapy completion. Blood counts were evaluated weekly during the first two cycles and then before each cycle. A protocol amendment in February 2005 initiated routine monitoring of blood magnesium levels, as part of laboratory testing. Adverse events and laboratory examinations were graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Follow-up assessment was conducted 6 weeks after treatment completion. Subsequent therapy and survival were monitored every 3 months.

Interim Analyses

Two independent interim analyses (after 400 and 800 randomly assigned patients) were conducted by the data safety monitoring board: a safety review, and a survival comparison/safety review, respectively. Both result sets were unknown by the sponsors until after database lock.

Statistical Analyses

The primary study end point was survival. This study required 850 events to complete and had 90% power for demonstrating a statistically significant

	Cetuximab + Irinotecan		Irinotecan		Total	
Characteristic	No.	%	No.	%	No.	%
No. of patients	648		650		1,298	
Median age, years	61		62		62	
Range	23-85		21-90		21-90	
Sex						
Male	405	62.5	411	63.2	816	62.9
Female	243	37.5	239	36.8	482	37.1
Race						
White	589	90.9	600	92.3	1,189	91.6
Black	29	4.5	24	3.7	53	4.1
Asian	19	2.9	16	2.5	35	2.7
Other	11	1.7	10	1.5	21	1.6
ECOG performance status						
0-1	608	93.8	611	94.0	1,219	93.9
2	35	5.4	35	5.4	70	5.4
Not reported	5	0.8	4	0.6	9	0.7
Prior therapy						
Chemotherapy	648	100	650	100	1,298	100
Adjuvant	167	25.8	179	27.5	346	26.7
Metastatic	645	99.5	644	99.1	1,289	99.3
Radiation therapy	114	17.6	135	20.8	249	19.2
Bevacizumab	84	13.0	82	12.6	166	12.8
First-line therapy						
Median duration, days	162.0		162.5		162.0	
Range	1-1,147		2-1,276		1-1,276	
Reason off therapy						
Disease progression	426	65.7	417	64.2	843	64.9
Toxicity	100	15.4	107	16.5	207	15.9
Other	112	17.3	113	17.4	225	17.3
Disease sites						
Liver	500	77.2	489	75.2	989	76.2
Lung	327	50.5	333	51.2	660	50.8
Lymph node	163	25.2	184	28.3	347	26.7
Other visceral site	70	10.8	62	9.5	132	10.2
Peritoneum	59	9.1	70	10.8	129	9.9
No. of disease sites						
1	214	33.0	201	30.9	415	32.0
$\geq$ 2	431	66.5	440	67.7	871	67.1
Missing	3	0.5	9	1.4	12	0.9
EGFR staining intensity						
None	2	0.3	0	0	2	0.2
Weak (1+)	202	31.2	224	34.5	426	32.8
Moderate (2+)	280	43.2	255	39.2	535	41.2
Strong (3+)	132	20.4	133	20.5	265	20.4
Missing	32	4.9	38	5.8	70	5.4

Table 1. Patient Demographics and Clinical Characteristics

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
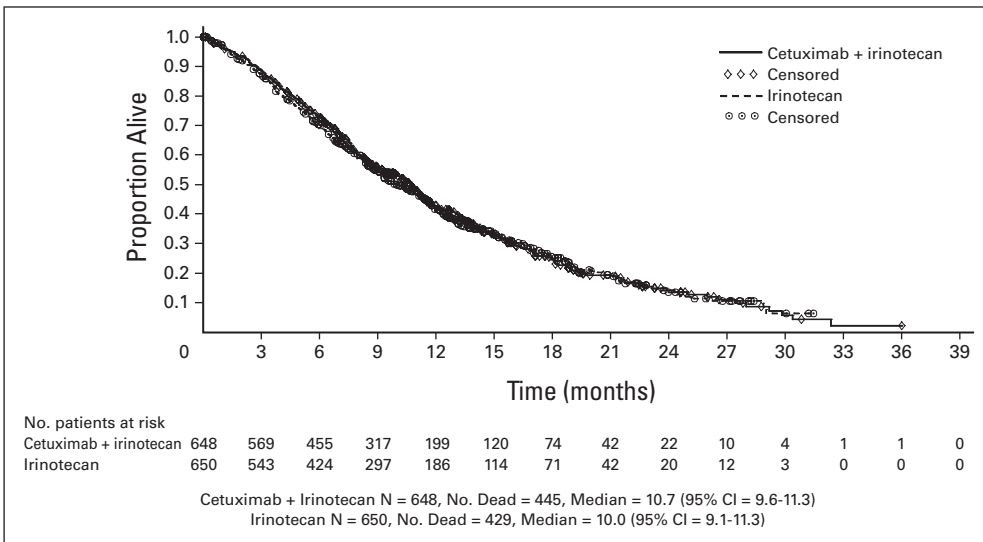
Fig 2. Kaplan-Meier analysis of overall survival.

survival difference, assuming a true HR (cetuximab and irinotecan to irinotecan) of 0.80. An O'Brien and Fleming type α spending function was used to ensure an overall, two-sided, type I error rate of 5%. Survival was compared between treatment arms using a two-sided log-rank test stratified by ECOG PS (0 to 1 v 2). This analysis was supplemented by Kaplan-Meier curves, and estimates of OS, HR, and associated confidence intervals (HR CI level was adjusted for the interim analysis).

Progression-free survival (PFS; defined as time to progression or death, and evaluated similar to survival) and rates of tumor response were determined from study-investigator assessments, without independent review for these secondary end points. Tumor response was compared between treatment arms using a Cochran-Mantel-Haenszel test stratified by ECOG PS (0 to 1 v 2). The duration of treatment was the period from the first dose until the last plus 21 days for irinotecan and plus 7 days for cetuximab. Time to response was computed for those patients with a response (complete or partial).

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30 score changes from baseline were compared between treatment arms by a Wei-Lachin test. Adverse events were categorized using the MedDRA dictionary, version 9.1. Analyses of survival, PFS, tumor response, and QOL were done on an intent-to-treat basis. Safety analyses were restricted to treated subjects.

RESULTS

Patient Characteristics and Disposition

From May 2003 to February 2006, 1,587 patients were enrolled; 1,410 with EGFR-positive tumors by immunohistochemistry. After meeting all eligibility criteria, 1,298 patients were randomly assigned, 648 to cetuximab and irinotecan and 650 to irinotecan alone (Fig 1). Demographic and clinical characteristics of study patients were well balanced between treatment arms (Table 1).

Treatment Exposure

Median treatment duration was longer for the cetuximab and irinotecan combination: cetuximab for 14.0 weeks (range, 0.7 to 97.9), irinotecan for 13.1 weeks (range, 0.7 to 89.1), versus 9.9 weeks for irinotecan alone (range, 0.4 to 71.0). Irinotecan delivery (treatment delay rates and median dose intensity) was comparable in the two
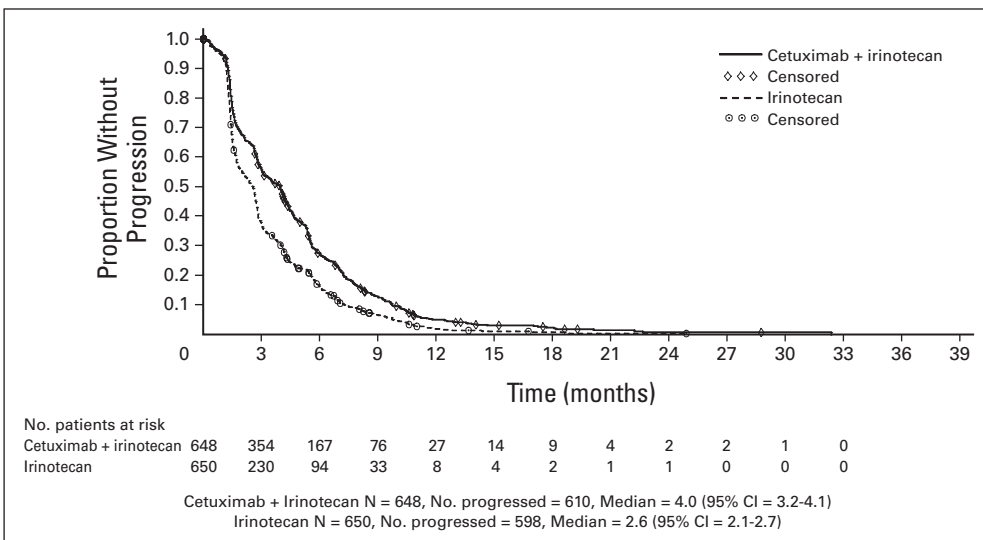

Fig 3. Kaplan-Meier analysis of progression-free survival.

groups, but the irinotecan cumulative dose was higher with cetuximab and irinotecan (median, 1,395 v 1,048 mg/m^2).

Reductions in irinotecan dose were more frequent in the cetuximab and irinotecan arm (43.7% v 36.2%), mostly due to toxicity such as gastrointestinal events (13.2% v 9.5%) and delayed hematologic recovery (12.5% v 9.7%). The cetuximab dose was reduced in 129 patients (20.2%), including 28 patients (4.4%) due to skin toxicity.

Efficacy

At the time of the data cutoff, 203 patients in the cetuximab and irinotecan arm (31.3%) and 221 patients in the irinotecan arm (34.0%) were alive. OS was comparable between treatments (log-rank $P = .71$): the HR was 0.975 (95% CI, 0.854 to 1.114, adjusted for an interim analysis). MS was 10.7 months (95% CI, 9.6 to 11.3) with cetuximab/irinotecan and 10.0 months (95% CI, 9.1 to 11.3) with irinotecan alone (Fig 2). The survival results may have been confounded by poststudy therapy: 46.9% of patients assigned to the irinotecan arm went on to receive cetuximab poststudy (87.2% of those, in combination with irinotecan).

PFS was significantly longer in the cetuximab and irinotecan arm (log-rank $P \leq .0001$): the HR of cetuximab/irinotecan to irinotecan was 0.692 (95% CI, 0.617 to 0.776), indicating a 31% reduction in risk of progression. Median PFS was 4.0 months (95% CI, 3.2 to 4.1) with cetuximab and irinotecan and 2.6 months (95% CI, 2.1 to 2.7) with irinotecan alone; 6-month PFS rates were 27.4% (95% CI, 23.9 to 30.9) and 16.3% (95% CI, 13.3 to 19.2), respectively, and 9-month PFS rates were 12.6% (95% CI, 10.0 to 15.3) versus 6.5% (95% CI, 4.5 to 8.5; Fig 3).

The overall RR with cetuximab and irinotecan was 16.4% (95% CI, 13.6 to 19.4), compared with 4.2% (95% CI, 2.8 to 6.0) with irinotecan alone ($P < .0001$; Table 2). Nine patients receiving the combination had complete responses versus 1 patient receiving irinotecan alone. The median time to response (2.5 v 2.7 months) and the median duration of response (5.7 v 5.5 months) did not differ between treatment groups.

Consistent with the overall results, predetermined subgroup analyses showed superior PFS and RR with cetuximab and irinotecan regardless of age (< 65 v ≥ 65 years), sex, race, and PS strata (not shown).

QOL

Cetuximab and irinotecan were significantly more effective in maintaining overall QOL. Advantages were seen with cetuximab and irinotecan in 10 of 15 scales, including fatigue ($P = .005$), nausea/vomiting ($P < .001$), insomnia ($P = .04$), pain ($P < .001$), and diarrhea ($P = .02$), as well as domains such as global health status ($P = .047$), physical functioning ($P = .002$), role functioning ($P = .003$), emotional functioning ($P = .002$), and cognitive functioning ($P < .001$) (Fig 4); no differences were seen in the social-functioning domain ($P = .774$). Compliance with the questionnaire was not significantly different between treatment arms (56.3% v 56.1% at 15 weeks); the differences in QOL, apparent by the end of the first treatment cycle, remained throughout the study.

Safety

Overall, the safety profile of the cetuximab and irinotecan combination was consistent with prior studies,[14] without meaningful increases in toxicity over irinotecan alone except for acneform rash and diarrhea. Ninety-seven patients died within 30 days of the last treatment: 57 patients in the cetuximab and irinotecan arm (8.9%) and 40 patients in the irinotecan arm (6.4%). Seven deaths (five and two patients, respectively) were attributed to study drug toxicity.

Neutropenia and diarrhea were the most common grade 3/4 adverse events, consistent with the profile of irinotecan; both occurred more frequently with cetuximab and irinotecan (Table 3). Severe febrile neutropenia was reported in 8.3% and 6.4% of patients in the cetuximab and irinotecan and irinotecan groups, respectively. Grade 3/4 infusion reactions occurred in 1.4% of cetuximab and irinotecan patients and 0.8% of those on irinotecan alone. Drug-related acneform rash occurred in most patients (76.3%) receiving cetuximab, becoming severe in 51 cases (8.0%). Hypomagnesemia (and other electrolyte imbalances) was more frequent with cetuximab and irinotecan (33.8% v 8.4% with irinotecan), but with few severe cases (3.3% v 0.4%) and no clinically relevant adervse effects.

Rates of toxicity-related therapy discontinuation were similar across treatment arms (6.5% for irinotecan and cetuximab v 4.8% for irinotecan). Hospitalizations for gastrointestinal (15.4% v 12.6%) and hematologic toxicities (9.7% v 7.9%) were slightly higher in the cetuximab and irinotecan arm.

Drug-related serious adverse events were reported in 186 patients (29.2%) and 142 patients (22.6%) in the cetuximab and irinotecan and irinotecan groups, respectively, most commonly diarrhea (11.9% v 9.4%), febrile neutropenia (7.7% v 6.2%), and vomiting (4.4% v 3.3%).

Post-Hoc Analyses

Two analyses were done in order to elucidate the potential effect of poststudy therapy. An exploratory analysis evaluated survival in patients randomly assigned before cetuximab received regulatory approval in each study country (n = 459), censoring alive subjects once cetuximab was approved in their markets. MS was 10.5 months in the cetuximab and irinotecan arm and 8.6 months in the irinotecan alone
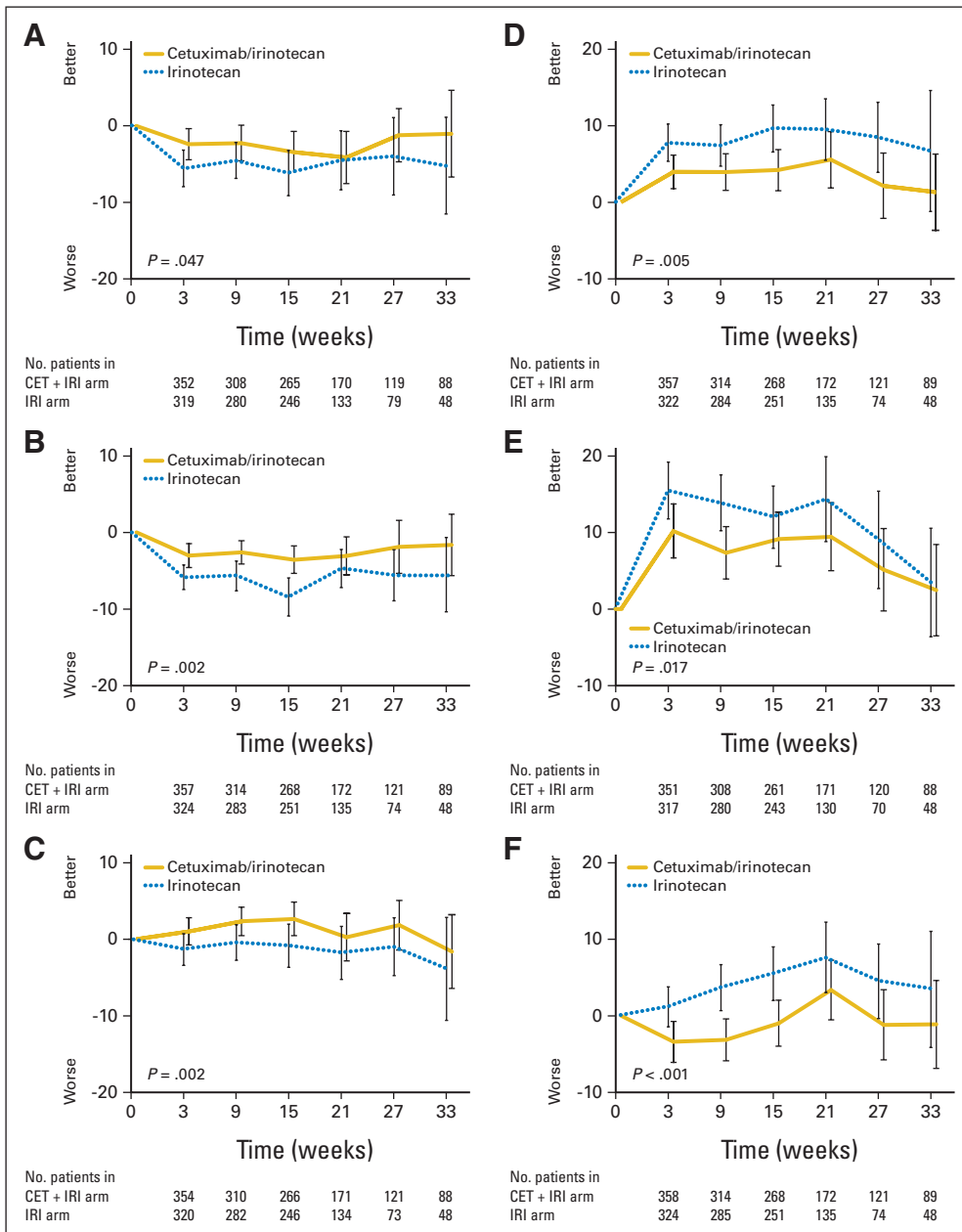
Table 2. Treatment Responses					
	Cetuximab + Irinotecan		Irinotecan		
Best Response	No.	%	No.	%	P^*
No. of patients	648		650		
CR	9	1.4	1	0.2	
PR	97	15.0	26	4.0	
SD	292	45.1	271	41.7	
PD	174	26.9	243	37.4	
Not determinable	56	8.6	72	11.1	
Never treated	8	1.2	17	2.6	
Unknown†	12	1.9	20	3.1	
Objective response‡	106	16.4	27	4.2	< .0001
Disease control§	398	61.4	298	45.8	< .0001

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Cochran-Mantel-Haenszel test stratified by Eastern Cooperative Oncology Group performance status at random assignment 0-1 v 2.
†Patients for whom no best response was provided by the investigator. Includes some subjects who were still on study at the time the database was closed.
‡Best response either CR or PR.
§Best response CR, PR, or SD.

Fig 4. Quality-of-life analysis across treatment arms. Change from baseline in (A) global health status, (B) physical functioning, (C) emotional functioning, (D) fatigue, (E) diarrhea, and (F) pain on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30. CET, cetuximab; IRI, irinotecan.

arm (Fig A1A, online only). This difference was not statistically significant (*P* = .60). This exploratory analysis, however, was highly underpowered (number of events, 123).

A second post hoc exploratory analysis was a nonrandomized examination of survival outcomes in patients from the irinotecan-only arm. Those without any poststudy therapy (n = 229) had a MS of 3.9 months (95% CI, 3.5 to 4.9), those treated poststudy, but without cetuximab (n = 116) had a MS of 10.1 months (95% CI, 9.0 to 13.2), and MS for those who received subsequent cetuximab (n = 305) was 13.0 months (95% CI, 12.2 to 15.0; Fig A1B, online only). There is an inherent potential for bias in a nonrandomized comparison such as this, however, the two patient subgroups of interest (those receiving subsequent therapy with or without cetuximab) seemed to be reasonably balanced. Baseline features (such as age, sex, or race) were similar in both groups, as were prognostic characteristics, such as time until

discontinuation of study therapy (median, 2.8 months for both groups) and the distribution of performance status at time of last study dose (PS 0 for 46% and 47% of patients, PS 1 for 50% in both groups, and PS 2 for 4% and 3%, respectively). In the interest of completeness, a similar analysis was carried out in the experimental arm. For patients treated with cetuximab and irinotecan on study who did not receive any poststudy therapy (n = 279), MS was 6.31 months (95% CI, 5.3 to 7.1); for those that received therapy poststudy but without cetuximab (n = 296), MS was 13.0 months (95% CI, 11.6 to 13.9); finally, for patients in the experimental arm receiving poststudy therapy with cetuximab (n = 73), MS was 16.2 months (95% CI, 12.8 to 27.4; Fig A1C, online only). For this posthoc analysis of survival in patients in the experimental arm that went to receive poststudy therapy, the median time to study-therapy discontinuation for patients with or without poststudy cetuximab was 4.8 and 4.1 months, respectively; the

Table 3. Most Common Drug-Related Nonhematologic AEs and On-Study Laboratory Abnormalities

| | Cetuximab + Irinotecan | | | | Irinotecan | | | |
| | Any Grade | | Grade 3/4 | | Any Grade | | Grade 3/4 | |
Parameter	No.	%	No.	%	No.	%	No.	%
No. of patients		638				629		
Any drug-related AE	635	99.5	396	62.1	607	96.5	274	43.6
Nonhematologic								
Diarrhea*†	518	81.2	181	28.4	452	71.9	99	15.7
Acneform rash*†‡	487	76.3	52	8.2	31	4.9	1	0.2
Nausea	345	54.1	28	4.4	334	53.1	27	4.3
Fatigue†	257	40.3	49	7.7	221	35.1	21	3.3
Vomiting	245	38.4	33	5.2	217	34.5	34	5.4
Anorexia*	160	25.1	17	2.7	117	18.6	15	2.4
Abdominal pain	147	23.0	24	3.8	121	19.2	16	2.5
Asthenia*	142	22.3	29	4.5	112	17.8	28	4.5
Select nonhematologic laboratory abnormalities								
Hypomagnesemia*†§	91	33.8	9	3.3	19	8.4	1	0.4
No. of patients		269				225		
Hypokalemia*†	153	25.8	27	4.5	71	12.4	12	2.1
No. of patients		594				572		
Hypocalcemia*	107	18	19	3.2	62	10.8	9	1.6
No. of patients		593				572		
Hematologic laboratory abnormalities								
Anemia	527	85.3	16	2.6	520	87.2	19	3.2
No. of patients		618				596		
Neutropenia*†	385	62.4	196	31.8	331	55.6	151	25.4
No. of patients		617				595		
Thrombocytopenia	165	26.8	11	1.8	167	28.1	4	0.7
No. of patients		615				594		

Abbreviation: AE, adverse event.
*Comparison of the toxicity for any grade significant at the 5% level.
†Comparison of the toxicity for grades 3/4 significant at the 5% level.
‡Acneform rash is a composite category that includes the following events: rash, rash pustular, rash erythematous, dermatitis acneiform, dermatitis exfoliative, rash papular, rash pruritic, rash generalised, rash macular, rash maculo-papular, acne, acne pustular, skin desquamation, and dry skin.
§The monitoring of serum magnesium was implemented after the trial had been initiated.

distribution of performance status at time of last study dose was PS 0 for 43.8% and 55.7% of patients, PS 1 for 48.0% and 43.6%, and PS 2 for 8.2% and 1.7%, respectively.

DISCUSSION

EPIC demonstrated significant improvements in PFS and RR with the addition of cetuximab to irinotecan. This study, however, failed to meet its primary end point, showing no statistically significant differences in survival between cetuximab and irinotecan and irinotecan alone.

Postprotocol treatment may have affected survival, given the substantial proportion (46.9%) of initial irinotecan patients who subsequently received a cetuximab-based regimen, an effective standard treatment after irinotecan failure.[14] Posthoc exploratory analyses suggest that poststudy cetuximab may have reduced any potential difference across treatment arms, prolonging survival in the patients who received it. These findings are inconclusive, but consistent with those from the recent phase III NCIC-017 study, in which cetuximab significantly improved survival compared to best supportive care (HR, 0.766; 95% CI, 0.637 to 0.921; $P = .0046$) in patients previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin.[18] The lack of

survival difference, however, may not be entirely due to a cross-over effect, since, in other settings, trials have documented survival differences even after cross-over.[22,23]

The effect of poststudy therapies on early-line clinical trials in mCRC is not unprecedented,[24] with some authors questioning the reliability of OS versus PFS as end point in early therapy settings.[8,25] Survival was the appropriate choice as primary end point for a trial designed to affect clinical practice. However, this study illustrates the challenges of studying commercially available agents early in the course of disease, and the complicating effects of postprotocol factors.

The improved efficacy in secondary end points that are well-documented and valid in mCRC,[25,26] and the QOL results obtained with cetuximab must not be overlooked. In this trial, adding cetuximab to irinotecan reduced the risk of progression by 31%, and improved median PFS by 55%, and RR by nearly four-fold, including a higher number of complete responses (nine v first). The QOL assessments also support this benefit. Global health status as well as physical, emotional, and cognitive functioning were significantly better with cetuximab and irinotecan. These results are the best reported to date after oxaliplatin plus FU and leucovorin (FOLFOX) failure.[7]

The safety profile of cetuximab plus irinotecan in this study was manageable, predictable, and consistent with prior studies.[14] The addition of cetuximab to irinotecan did not result in meaningful increases in toxicity, except for acneform rash, diarrhea, and electrolyte imbalances. Whether these increases are due to cetuximab itself, or a byproduct of the higher cumulative irinotecan dose with the combination, is unclear, and these findings warrant careful evaluation of the patients appropriate for this regimen. Nonetheless the nearly 50% rate of patients still receiving combination treatment at 15 weeks further reassures of its tolerability.

Several caveats surround these results, apart from the potential effect of poststudy cross-over. The absence of independent radiology-review system is a weakness of particular concern given the weight of the PFS and RR end points in the final results of the study. Nevertheless, the differences observed make a compelling argument for the therapeutic effect of cetuximab. The application of a self-reported questionnaire to assess QOL in a nonblinded study can also be considered problematic. It could be argued, however, that this is a method to assess patients' individual experiences; in this case, the consistency of the results across most scales probably points to a bona-fide effect. Also, this standard tool lacks specific acneform-rash scores, a limiting aspect for studies of EGFR inhibitors. Until this deficiency is addressed, scores such as social functioning may provide a partial indication of the potential effect of acneform rash in the QOL of patients.

It is almost certain that outcomes with cetuximab will be enhanced by patient selection. Remarkably, randomized trastuzumab trials conducted in preselected patients with breast cancer could demonstrate survival benefits, even after a cross-over.[23] Recent reports indicate that the presence of mutations on the *KRAS* gene is a strong predictor of nonresponsiveness to cetuximab,[27-29] and that overexpression of the EGFR ligands amphiregulin and epiregulin may be a robust marker of response.[28] While trials are ongoing to validate these biomarkers, whether a pronounced benefit could be documented in any of these subpopulations in EPIC is under study.

As the evaluation of cetuximab continues, with ongoing or recently-completed randomized trials in first-line (Cancer and Leukemia Group B 80203, Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer, and Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer),[19,20,30] with bevacizumab (Cancer and Leukemia Group B 80405), and in the adjuvant setting (North Central Cancer Treatment Group N0147), the data from this EPIC study join the recent NCIC-017 results, showing that cetuximab provides OS and PFS, as well as RR and QOL, benefits in multirefractory patients.[18] EPIC is the largest comparative trial investigating the efficacy and tolerability of cetuximab added to irinotecan after FOLFOX failure, demonstrating PFS and RR improvements in irinotecan-naïve patients consistent with prior studies in refractory disease. With these results, the inclusion of cetuximab among the core agents in the optimal management of mCRC[8,31] is well supported. Ongoing studies will further define the optimal use of cetuximab throughout CRC treatment settings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Saltz LB, Cox JV, Blanke C, et al: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905-914, 2000

2. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 355:1041-1047, 2000

3. Cunningham D, Pyrhönen S, James RD, et al: Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413-1418, 1998

4. Rougier P, Van Cutsem E, Bajetta E, et al: Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407-1412, 1998

5. 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

6. Colucci G, Gebbia V, Paoletti G, et al: Phase III randomized trial of FOLFIRI versus FOLFOX4 in

the treatment of advanced colorectal cancer: A multicenter study of the Gruppo Oncologico dell'Italia Meridionale. J Clin Oncol 23:4866-4875, 2005

7. Tournigand C, André T, Achille E, et al: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 22:229-237, 2004

8. Grothey A, Sargent D, Goldberg RM, et al: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 22:1209-1214, 2004

9. 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

10. Giantonio BJ, Catalano PJ, Meropol NJ, et al: High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. J Clin Oncol 23:1s, 2005 (suppl; abstr 2)

11. Chen HX, Mooney M, Boron M, et al: Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: An NCI treatment referral center trial TRC-0301. J Clin Oncol 24:3354-3360, 2006

12. Lenz H-J, Van Cutsem E, Khambata-Ford S, et al: Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. J Clin Oncol 24:4914-4921, 2006

13. Van Cutsem E, Peeters M, Siena S, et al: Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25:1658-1664, 2007

14. Cunningham D, Humblet Y, Siena S, et al: Cetuximab monotherapy and cetuximab plus irino-tecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337-345, 2004

15. ImClone Systems Incorporated and Bristol-Myers Squibb Company: ERBITUX (Cetuximab) Package Insert. New York, NY, ImClone Systems Incorporated, and Princeton, NJ, Bristol-Myers Squibb Company

16. Kawaguchi Y, Kono K, Mimura K, et al: Cetuximab induce antibody-dependent cellular cytotoxicity against EGFR-expressing esophageal squamous cell carcinoma. Int J Cancer 120:781-787, 2006

17. Saltz LB, Meropol NJ, Loehrer PJ Sr, et al: Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 22:1201-1208, 2004

18. Jonker DJ, O'Callaghan, Karapetis CS, et al: Cetuximab for the treatment of colorectal cancer. N Engl J Med 357:2040-2048, 2007

19. Venook A, Niedzwiecki D, Hollis D, et al: Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. J Clin Oncol 24:148s, 2006 (abstr 3509)

20. Van Cutsem E, Nowacki M, Lang I, et al: Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. J Clin Oncol 24:164s, 2007 (abstr 4000)

21. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

22. Richardson PG, Sonneveld P, Schuster M, et al: Bortezomib or high-dose dexaxmethasone for relapsed multiple myeloma. N Engl J Med 352:2487-2498, 2005

23. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001

24. 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

25. Saltz LB: Metastatic colorectal cancer: Is there one standard approach? Oncology 19:1147-1160, 2005

26. Johnson JR, Williams G, Pazdur R: End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 21:1404-1411, 2003

27. Lievre A, Bachet JB, Le Corre D, et al: KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 66:3992-3995, 2006

28. Khambata-Ford S, Garret CR, Meropol NJ, et al: Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 25:3230-3237, 2007

29. Finocchiaro C, Capuzzo F, Janne PA, et al: EGFR, HER2 and K-Ras as predictive factors for cetuximab sensitivity in colorectal cancer. J Clin Oncol 25:168s, 2007 (abstr 4021)

30. Bokemeyer C, Bondarenko I, Makhson A, et al: Cetuximab plus 5-FU/FA/oxalipaltin (FOLFOX-4) versus FOLFOX-4 in the first-line treatment of metastatic colorectal cancer (mCRC): OPUS, a randomized phase II study. J Clin Oncol 25:172s, 2007 (abstr 4035)

31. Grothey A, Sargent D: Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. J Clin Oncol 23:9441-9442, 2005

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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®).