

Adjuvant Therapy With the Monoclonal Antibody Edrecolomab Plus Fluorouracil-Based Therapy Does Not Improve Overall Survival of Patients With Stage III Colon Cancer

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ABSTRACT

Purpose

Edrecolomab (ED) is a murine monoclonal antibody targeting the EpCam antigen. This phase III randomized multicenter trial investigated the benefit of adding ED to fluorouracil (FU) based therapy in patients with stage III colorectal cancer.

Patients and Methods

Patients with stage III colon cancer were randomly assigned to one of two treatments after curative surgery. Patients in arm 1 received five infusions of ED together with FU-based chemotherapy; patients in arm 2 received FU-based chemotherapy alone. The primary end point was overall survival (OS).

Results

One thousand eight hundred thirty-nine patients were randomly assigned; results were analyzed on an intent-to-treat basis. Patient characteristics were well-balanced across treatment arms. Five-year follow-up has been completed. Patients randomly assigned to ED plus FU-based therapy showed a 5-year survival rate of 69.6% while for patients receiving FU-based therapy, the rate was 68.2%. The hazard ratio for death with ED plus FU-based therapy compared to FU-based therapy was 0.896 (95% CI, 0.752 to 1.068), which was not statistically significant ($P = .220$). The adverse effect profiles of the two treatment arms were similar, with the main adverse effects being diarrhea, abdominal pain, and nausea. Anaphylaxis occurred in fewer than 1% of patients receiving ED.

Conclusion

For patients with stage III colon cancer, the addition of ED to FU-based therapy had no statistically significant effect on OS.

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INTRODUCTION

In the absence of adjuvant therapy, patients with surgically resected stage III colon cancer have an unacceptably high rate of recurrence: 5-year survival rates for patients receiving no adjuvant therapy were 50% to 56% for stage III disease.¹ Moertel and colleagues² showed that 12 months of fluorouracil (FU) and levamisole (LEV) reduced the recurrence rate by 40%. Subsequent clinical trials confirmed that 6 months of FU and leucovorin (LEU) was similarly effective.³ Despite effective adjuvant treatment, many patients experience disease recurrence and death from disseminated disease. Thus, there is a need for more effective adjuvant treatments for colon cancer.

Edrecolomab is a murine IgG2a monoclonal antibody that recognizes a cell surface glycoprotein that is preferentially expressed on adenocarcinomas. This 17-1A antigen is also known as EGP-2, EpCAM, CO17-1A, or GA733-2. It has been shown to mediate antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity in vitro experiments⁴ and to evoke a humoral immune cascade with the production of anti-idiotypic response in vivo.^{5,6,7}

Edrecolomab (ED) was first investigated in advanced disease but did not show consistent clinical benefit.⁷ It was thought that ED would be more effective against micrometastatic disease, a concept supported by evidence that the monoclonal antibody had cytoreduction effects on tumor cells

within the bone marrow of patients with cancer.⁸ This concept was subsequently studied in the adjuvant setting by Riethmüller and colleagues⁹ who conducted a multicenter, randomized trial of ED versus no further treatment after surgical resection in patients with Dukes' C cancer of the colon or rectum. In this study, 189 patients with stage III colon or rectal cancer were randomly assigned in the postoperative setting to ED alone or observation. This trial showed a relative decrease of 32% in mortality ($P < .01$), and of 23% in disease recurrence, with ED monotherapy, at a median follow-up of 7 years.¹⁰ These encouraging results supported the initiation of two phase III studies in patients with stage III colon cancer, the study reported here (157-001) and a companion study conducted in Europe, Australia, New Zealand, and South Africa (157-002). Study 157-001 involved a two-armed comparison of ED plus chemotherapy versus chemotherapy alone. Study 157-002, an independently conducted three-armed study, added an ED monotherapy arm. This study has been reported: it failed to show benefit from the addition of ED to FU plus leucovorin and showed inferior outcome in the ED monotherapy arm compared with the chemotherapy arm.¹¹

PATIENTS AND METHODS

Study Population

Between March 1995 and May 1999, 1,839 patients with resected stage III colon cancer were randomly assigned into this multinational, open-label study, at 129 participating institutions in three countries (United States, Canada, and Argentina). Eligibility criteria included complete resection with negative resection margins, age ≥ 18 years, and normal chest x-ray and computed tomography or magnetic resonance imaging of the abdomen within 6 weeks before random assignment. Patients were excluded if they had carcinoma of the rectum (defined by surgical observation), prior radiotherapy, chemotherapy, or immunotherapy. Eligibility of patients with T4 lesions required sponsor review of the pathology and operative reports. Random assignment of patients was stratified by regional node involvement and study site.

Study Treatment

While adjuvant therapy used at the time of the study initiation was 12 months of FU and LEV,² during the early course of the study, 90% of participating centers adopted 6 months of FU and LEU as their standard of care. The trial design was therefore modified to allow each site to select either LEV or LEU as the only modulator in both arms. Thus, the two treatment arms of the study were: arm 1: combination therapy (ED plus FU/LEV or ED plus FU/LEU); and arm 2: chemotherapy alone (FU/LEV or FU/LEU).

ED was administered by 2-hour intravenous infusion five times: a 500-mg initial infusion, then four 100-mg infusions at 4-week intervals, the first of these given on the first day of chemotherapy. Premedication for ED could include antihistamines and antiemetics but not corticosteroids. The FU/LEU protocol involved LEU 20 mg/m² followed immediately by FU 425 mg/m² as bolus intravenous injections, daily for 5 days, repeated every 28 days for the first three courses, then every 35 days for the succeeding three of a total of six courses. The first cycle of FU/LEU was given at least 14 days after the first dose of ED and up to 56 days after surgery.

Patients were assessed for survival and disease recurrence every 3 months for 24 months and every 6 months thereafter until completion of study (5 years postsurgery), withdrawal from study, or death. Disease recurrence was assessed by measurement of CEA and radiological examination.

Adverse events and standard hematology and clinical chemistry results were monitored throughout the study and graded using the Southwest Oncology Group criteria.¹² If an adverse event occurred during or after an ED infusion, the investigator could change the infusion rate or discontinue infusion temporarily or permanently. Dose modification or discontinuation based on adverse events from a previous cycle was permitted. Quality of life was

addressed in patients using Functional Assessment of Cancer Therapy–Colorectal (FACT-C), version 3. Patients were asked to complete the questionnaire between 7 and 24 days after surgery and at 3, 6, 9, 12, 15, 18, 21, and 24 months after surgery.

Statistical Analysis

The study was designed to test the primary objective of a 23% reduction in mortality at 3 years, in the combination arm compared with the chemotherapy arm, with 80% power and an overall two-sided 5% significance level. This required a total of 353 deaths for the final analysis, with a recruitment of 1,800 patients, 900 in each arm, and median follow-up of 2.1 years. These values were estimated according to the methods discussed by Machin and Campbell¹³ based on the assumption that 3-year overall survival (OS) in the chemotherapy arm would be 70% and in the combination arm 77%. A planned interim analysis was conducted when the total number of deaths across both arms reached 176. This analysis used O'Brien and Fleming stopping boundaries implementing the Lan and DeMets α -spending function approach.¹⁴ The results of the interim analysis were blinded to the sponsor and reviewed by the data safety monitoring board.

The key secondary end points were: disease-free survival (DFS; time to disease recurrence or death), disease-free interval (DFI; time to disease recurrence), time to colon cancer-related death (CCRD), quality of life, and safety.

The time-to-event end points were compared across the study arms using Kaplan-Meier curves, hazard ratios (HRs), 3- and 5-year percentage survival estimates, and associated 95% CIs. The primary assessment of efficacy was based on log-rank tests stratified by nodal status (N1 v N2 and N3), type of chemotherapy (FU/LEU or FU/LEV) and geographical region.

All efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomly assigned patients. In addition, a confirmatory analysis of the primary end point was performed using the evaluable population, which consisted of patients in the ITT population excluding major protocol violators. All analyses of safety data were performed on the safety population, defined as all randomly assigned patients who received at least one dose of study treatment. Final clinical efficacy results were unblinded when the protocol-specified number of events had occurred on June 11, 2001.¹⁵ Updated 5-year follow-up results for all patients for OS and CCRD reflected the data on March 6, 2005.

RESULTS

Patient Characteristics

One thousand eight hundred thirty-nine patients were included in the ITT population (924 in the combination therapy arm, 915 in the chemotherapy arm); 1,796 patients were included in the safety population (901 in the combination therapy arm, 895 in the chemotherapy arm; Fig 1); and 1,739 patients were included in the assessable population (866 in the combination therapy arm, 873 in the chemotherapy arm).

Patient characteristics, which are summarized in Table 1, were well-balanced across the treatment arms and were similar to those reported in other studies.¹⁶ In both arms, 53% of patients were male and the median age was 61 years. Prestudy staging was similar across treatment arms. Patients with T4 tumors (6%) were screened for eligibility by both study site and sponsor.

Study Treatment

Adjuvant treatment was to be started within 42 days of surgery. The overall median time to the start of treatment was 35 days.

ED treatment was completed according to protocol by the majority of patients, with 90% of patients receiving at least 80% of the intended cumulative dose of 900 mg. Adverse events and consent

Table 1. Summary of Patient Demographics and Clinical Characteristics

Patient Characteristic	Regimen											
	ED + FU/LEV		ED + FU/LEU		ED + Chemotherapy		FU/LEV		FU/LEU		Chemotherapy	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Randomly assigned	210		714		924		211		704		915	
Male	122	58	371	52	493	53	107	51	374	53	481	53
Female	88	42	343	48	431	47	104	49	330	47	434	47
Median age, years	61		61		61		62		61		61	
White	188	90	623	87	811	88	179	85	621	88	800	87
Black	16	8	53	7	69	7	23	11	48	7	71	8
Stage												
Primary tumor												
T1	9	4	22	3	31	3	2	< 1	27	4	29	3
T2	28	13	85	12	113	12	25	12	73	10	98	11
T3	160	76	565	79	725	78	170	81	557	79	727	79
T4	13	6	42	6	55	6	14	7	47	7	61	7
Lymph node												
N1	135	64	460	64	595	64	136	64	477	68	613	67
N2	72	34	243	34	315	34	68	32	220	31	288	31
N3	3	1	11	2	14	2	7	3	7	< 1	14	2

Abbreviations: ED, edrecolomab; LEV, levamisole; LEU, leucovorin; FU, fluorouracil.

withdrawals were the primary reasons for not completing the course of ED therapy. In patients receiving FU/LEU, the median cumulative FU dose was 11,050 mg/m² in both arms.

Two hundred sixty-eight patients (29%) in the ED plus FU-based chemotherapy arm and 272 patients (30%) in the FU-based chemotherapy alone arm received one or more subsequent cancer therapies for treatment of disease recurrence at any time through to the end of the 5-year follow-up period of the study.

Efficacy

The follow-up analysis of OS, the primary end point, at 5 years in the ITT population showed no statistical difference between those patients receiving ED plus FU-based chemotherapy and those patients receiving FU-based chemotherapy alone (HR, 0.896; 95% CI, 0.752 to

1.068; $P = .220$; Table 2; Fig 2). The 3-year survival rates with were 82.2% on combination therapy (95% CI, 79.6% to 84.7%) and 80.3% on chemotherapy (95% CI, 77.6% to 83.0%), a difference of 1.9%. Survival rates at 5 years with were 69.6% in the combination therapy arm (95% CI, 66.4% to 72.7%), and 68.2% in the chemotherapy arm (95% CI, 65.0% to 71.5%). Table 2 also includes the results from 2001, and shows a statistically significant difference in OS that was not confirmed in the updated analysis.

Table 3 presents the OS results for each chemotherapy regimen based on the results from the final results of 2001. Although the chemotherapy regimens were not significantly different in their effect on OS, the trend was for a greater treatment difference between combination therapy and chemotherapy alone for FU/LEU than for FU/LEV.

Table 2. Primary Efficacy Parameter by Treatment: Overall Survival (ITT and assessable population)

Arm	No.	Deaths				3-Year OS		5-Year OS	
		No.	HR	95% CI	P	%	95% CI	%	95% CI
ITT, update 2005									
Combination	924	253	0.896	0.752 to 1.068	.220	82.2	79.6 to 84.7	69.6	66.4 to 72.7
Chemotherapy	915	264				80.3	77.6 to 83.0	68.2	65.0 to 71.5
ITT, final 2001 ¹⁵									
Combination	924	169	0.785	0.638 to 0.967	.023	81.6	78.7 to 84.4	—	—
Chemotherapy	915	203				78.9	75.9 to 81.9	—	—
Assessable									
Combination	866	154	0.754	0.607 to 0.935	.010	82.2	79.3 to 85.1	—	—
Chemotherapy	873	192				79.4	76.4 to 82.4	—	—

NOTE. HR < 1 indicates a lower risk of event on ED + FU-based chemotherapy than on FU-based chemotherapy alone. P value computed using a log-rank test, stratified by grouped site, nodal status, and type of chemotherapy.

Abbreviations: ITT, intent to treat; HR, hazard ratio; OS, overall survival; ED, edrecolomab; FU, fluorouracil.

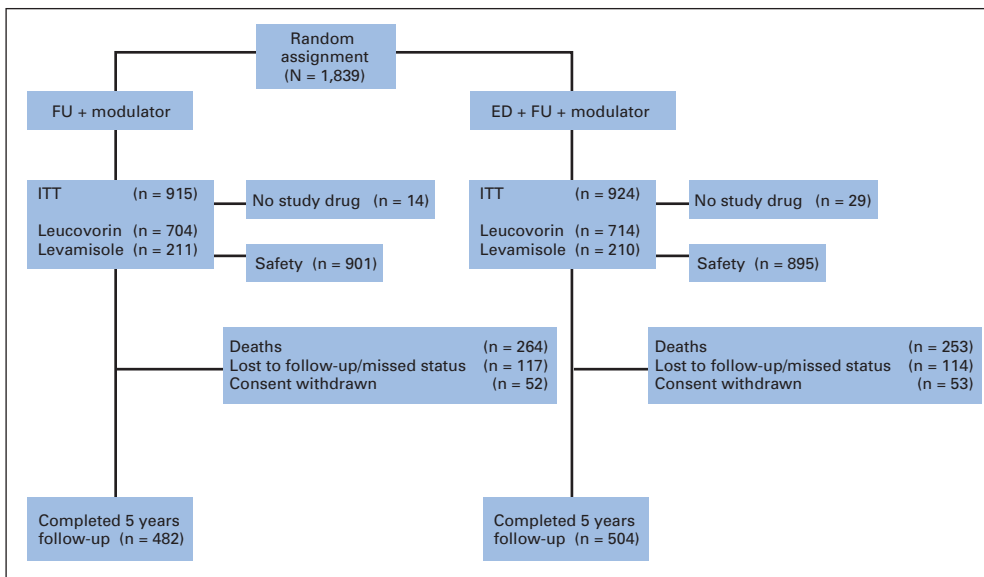


Fig 1. CONSORT diagram. FU, fluorouracil; ED, edrecolomab; ITT, intent to treat.

DFS, DFI, Time to CCRD

At the time of final analysis in 2001, there was a trend toward slightly increased DFS (HR for recurrence or death, 0.895) and DFI (HR for recurrence, 0.868) in patients treated with combination therapy compared to FU-based therapy, but

these were not statistically significant (Table 4). Time to CCRD was significantly prolonged in patients receiving combination therapy (HR for colon cancer–related death, 0.729; $P = .007$), but this benefit was not maintained at the time of the updated analysis (HR, 0.848; $P = .092$).

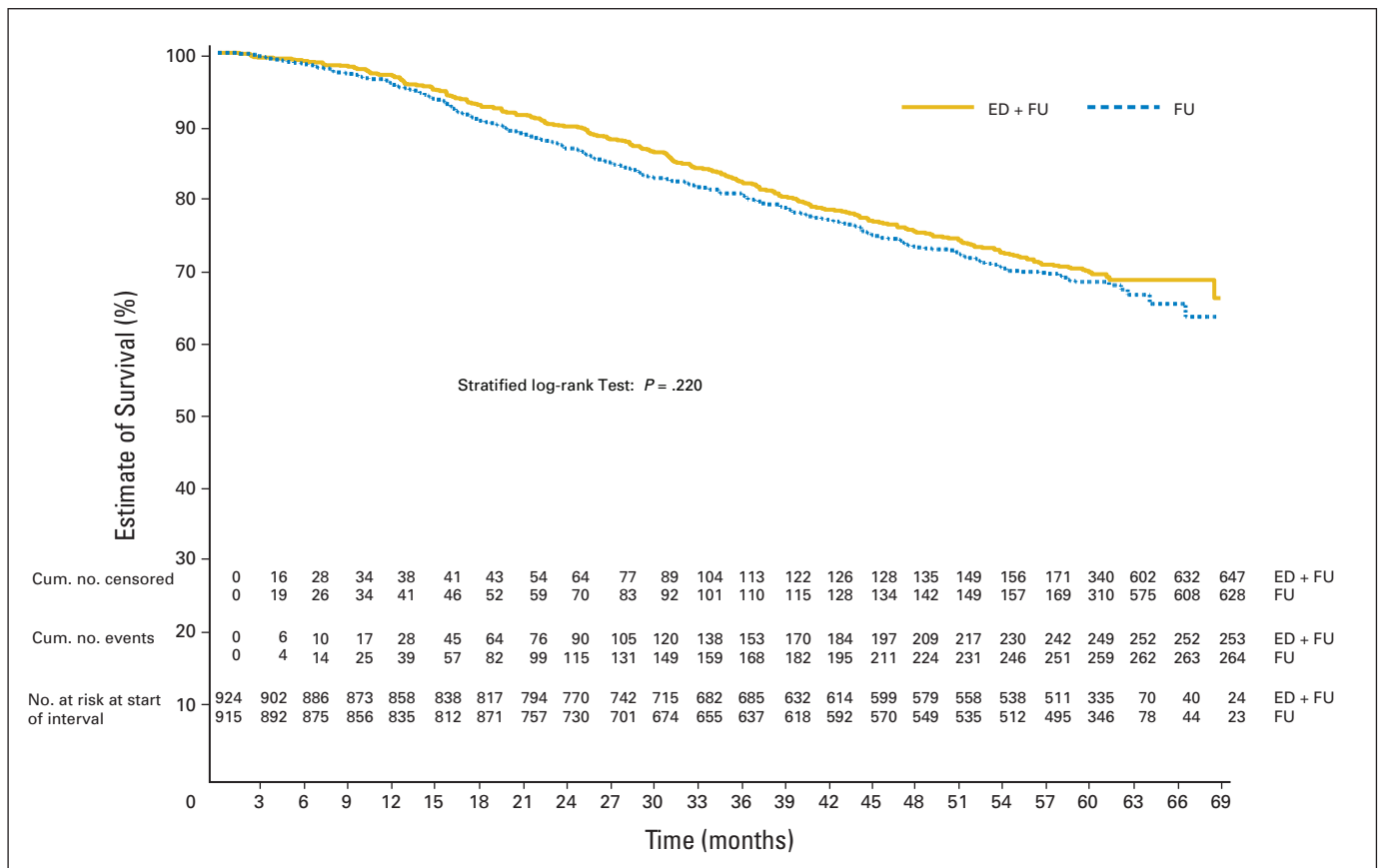


Fig. 2. Kaplan-Meier overall survival curves by treatment. ED, edrecolomab; FU, fluorouracil; cum., cumulative.

Table 3. Comparison of Primary Efficacy (overall survival) Parameter: Subgroup Analysis by Modulator (final 2001¹⁵)

Arm	No.	Deaths	Hazard Ratio for Death	95% CI	P
FU/LEV					
Combination	210	58	0.865	0.602 to 1.243	.433
Chemotherapy	211	65			
FU/LEU					
Combination	714	111	0.749	0.581 to 0.966	.025
Chemotherapy	704	138			

NOTE. Hazard ratio < 1 indicates a lower risk of event in experimental arm (ED + FU/LEV or ED + FU/LEU) than in control. Abbreviations: FU, fluorouracil; LEV, levamisole; LEU, leucovorin; ED, edrecolomab.

Toxicity

More than 99% of patients in both arms experienced adverse events, 26% of patients on both arms experienced a serious adverse event (SAE), and 12% to 16% of patients had adverse events that led to permanent discontinuation of study drug. Serious adverse events included any experience which was fatal, life-threatening, incapacitating, requiring hospitalization, involving overdose, or was otherwise judged by the investigator to be serious. The addition of ED to FU-based therapy did not significantly change the incidence of total adverse events or serious adverse events.

Key adverse events are summarized in Table 5. The most commonly observed nonhematologic toxicity was diarrhea (80%), followed by nausea (72%), and malaise or fatigue (66%). The most common hematologic toxicity was neutropenia. The pattern of grade 3 and 4 toxicities was similar across treatment arms, with the most common nonhematologic toxicities being diarrhea and nausea and the most common hematologic toxicity was neutropenia.

There was an increase in the incidence of abdominal pain/discomfort (37% v 32%) and musculoskeletal pain (23% v 16%) with the addition of ED to FU-based therapy in the combination therapy arm.

Hypersensitivity reactions, defined as any adverse events possibly involving an immune response and occurring within one day of the ED infusion, were observed in 31% of patients. These included fever (8% overall), flushing (6%), hypotension (< 1%), skin rash (3%), and breathing disorders (< 1%). The frequency of grade 3 or 4 severity of each was less than 1%. Anaphylaxis was observed in four patients (< 1%) receiving ED plus FU-based therapy and none of the patients receiving FU-based therapy alone. There were 10 deaths within 28 days of last study treatment on the combination treatment arm compared with eight deaths on the chemotherapy arm.

Quality of Life

Among all patients, 902 in the combined therapy arm (98%) and 891 in the FU-based chemotherapy alone arm (97%) completed the FACT-C questionnaire at baseline. Of those remaining in the trial at 12 and 24 months, 678 patients (87%) and 487 patients (75%) in the combined therapy arm and 620 patients (81%) and 438 patients (73%) of patients in the FU-based chemotherapy alone arm completed FACT-C. There was no significant difference between the medians of health status or FACT-C total scores between the two treatment arms at any of the scheduled assessment times.

DISCUSSION

This multicenter, randomized, phase III study was conducted to determine if the addition of ED to FU-based therapy would improve 3-year OS of patients with stage III colon cancer. The difference in OS between the two treatment arms was not statistically significant at the time of the 5-year follow-up analysis (2005). There was no significant difference in DFS or DFI at the time of final analysis or 5-year follow-up analysis. The lack of ED-related improvement in OS in either the 157-001 or 157-002 trials indicates that this monoclonal therapy is not useful for the treatment of patients with stage III colon cancer. In addition, two randomized phase III trials of ED monotherapy versus no treatment in patients with stage II colon cancer showed no benefit from this treatment.^{17,18}

In considering the initial statistical result (2001)¹⁵ and the follow-up statistical result (2005), the 3-year DFS estimate is in concordance with the 5-year survival rate and not the 3-year survival rate. This finding is consistent with the conclusions of Sargent et al.¹⁹ When

Table 4. Secondary Efficacy Parameters by Treatment (final 2001¹⁵)

Arm	No.	Events	HR	95% CI	P	3-Year Survival (%)	95% CI
DFS							
Combination	924	271	0.895	0.756 to 1.060	0.198	67.5	64.1 to 70.9
Chemotherapy	915	282				66.6	63.1 to 70.0
DFI							
Combination	924	245	0.868	0.728 to 1.036	0.116	69.9	66.6 to 73.2
Chemotherapy	915	262				68.1	64.6 to 71.5
Time to CCRD							
Combination	924	135	0.729	0.579 to 0.917	0.007	84.5	81.8 to 87.3
Chemotherapy	915	173				81.3	78.4 to 84.2

Abbreviations: HR, hazard ratio; DFS, disease-free survival; DFI, disease-free interval; CCRD, colon cancer-related death.

Table 5. Key Adverse Events by Treatment

Toxicity/Adverse Event	Combination		Chemotherapy	
	%	Grade (%)	%	Grade (%)
Diarrhea	81	18	80	16
Nausea	71	5	72	6
Abdominal pain/discomfort	37	6	32	4
Malaise/fatigue	66	4	66	3
Vomiting	28	3	29	3
Mucositis	27	5	29	4
Alopecia	31	< 1	28	< 1
Eye disorders	22	< 1	19	< 1
Granulocytopenia	8	6	9	7
Rash	28	< 1	21	< 1
Fever	24	< 1	17	< 1
Musculoskeletal pain	23	3	16	< 1
Headache	21	< 1	14	< 1
Flushing	11	< 1	4	0
Hypotension	3	< 1	3	< 1
Granulocytopenic fever	3	3	3	3

the 5-year OS and 3-year DFS from this study are compared with their pooled results of 18 phase III studies with 20,898 patients with stage III colon cancer, the resulting data point lies close to the authors' regression curve. This is further confirmation that a 3-year DFS estimate is a useful surrogate for 5-year OS.

Three-year survival rates for FU-based therapy, with either LEU or LEV, have steadily increased since its introduction in the adjuvant setting. The survival rate in study 157-001 was 79% and in study 157-002 was 76%. The treatment arms containing the FU plus LEU therapy administered identical dosing schedules in the 157-001 and 157-002 studies. The median cumulative FU dose of 11,900 mg/m² in the 157-002 control arm was somewhat higher than the median dose of 11,050 mg/m² for 157-001. In addition, both studies had identical entry criteria and follow-up assessments, recruitment was conducted during the same time period, and clinical results were site-monitored in a similar manner. Under these similar clinical study conditions, the OS for 157-001 appeared better than that for 157-002. The differences in patients recruited with T4 lesions between the two studies would not entirely explain this finding, and other prognostic factors within the trial populations seem similar. Is there a difference between regions in the application of subsequent therapy, palliative therapy, or a difference in the pharmacogenetics of the populations in their re-

sponse to fluoropyrimidines? Careful epidemiologic study using these studies findings as an index case would be required to answer these questions. While the drug-related toxicity produced by both regimens was qualitatively similar, by events, there were generally more grade 3/4 adverse events in the 157-001 trial compared with the 157-002 trial. This would suggest that the slightly higher doses in the 157-002 study produced less toxicity but less clinical benefit.

In conclusion, the combination of FU-based therapy and ED was well tolerated in this population and did not extend OS compared with those patients receiving chemotherapy alone. E does not provide clinical benefit in patients with stage III colon cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

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Table A1. Investigators and Sites

Investigator Name	Institution
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Irving Berkowitz, MD	Christiana Care Health Services, Newark, DE
Stephen A. Bernard, MD	University of North Carolina, Chapel Hill, NC
Bernard Bernhardt, MD	Advanced Oncology Associates, Armonk, NY
Luigi Bertoli, MD	CRC Inc, Hoover, AL
Leela Bhupalam, MD	University of Louisville, Louisville, KY
Laszlo Boros, MD	Interlakes Hematology/Oncology, Rochester, NY
Linda Bosserman, MD	Wilshire Oncology Medical Group Inc, Pomona, CA
Patrick Byrne, MD	Northern Virginia Oncology Group PC, Fairfax, VA
Michael A. Carducci, MD	Bunting Blaustein Oncology Research, Johns Hopkins University, Baltimore, MD
Thomas Cartwright, MD	Ocala Oncology Center, Ocala, FL
Eric M. Cheflen, MD	St. Elizabeth Health Center, Youngstown, OH
Edward Chu, MD	VA Connecticut Health Care System, West Haven, CT
Gerald Clamon, MD	University of Iowa Hospitals and Clinics, Iowa City, IA
Torey Clark, MD	American Medical Research Institute, Cumming, GA
Everardo Cobos, MD	Texas Tech University Health Science Center, Lubbock, TX
Alan Cohen, MD	Dial Research Associates Inc, Nashville, TN
Gary Cohen, MD	Greater Baltimore Medical Center, Baltimore, MD
Jeffrey Crawford, MD	Duke University Medical Center, Durham, NC
Christopher Desch, MD	VA Cancer Institute, Richmond, VA
Philip DeSimone, MD	Veterans Administration Medical Center, Lexington, KY
Nikolay Dimitrov, MD	Great Lakes Cancer Institute, Lansing, MI
Tracy Dobbs, MD	East Tennessee Oncology/Hematology, Knoxville, TN
Laura Donahue, MD	North Shore University Hospital, Manhasset, NY
Peter Eisenberg, MD	California Cancer Care, Greenbrae, CA
John E. Feldman, MD	Mobile Infirmary Medical Center, Mobile, AL
Jose A. Figueroa, MD	Joe Arrington Cancer Research and Treatment Center, Lubbock, TX
George Geils, MD	Charleston Hematology/Oncology, PA, Charleston, SC
Sabastian George, MD	Cancer and Blood Institute, Rancho Mirage, CA
Indrani Gill, MD	Riverside, CA
Jack Goldberg, MD	Cooper Cancer Institute, Voorhees, NJ
Alan Grosbach, MD	Christus Schumpert Medical Center, Shreveport, LA
Ronald Hart, MD	Oncology Alliance, Glendale, WI
Jimmie Harvey, MD	Clinical Research Consults Inc, Hoover, AL
Charles A. Henderson, MD	Peachtree Hematology/Oncology, Atlanta, GA
Robert Hirsch, MD	South Florida Hematology/Oncology, Boca Raton, FL
Howard Hochster, MD	NYU Medical Center, New York, NY
Jeremy K. Hon, MD	Comprehensive Cancer Institute, Huntsville, AL
Robert J. Jacobson, MD	Good Samaritan Cancer Institute, West Palm Beach, FL
Richard G. Just, MD	Scripps Memorial Hospital, La Jolla, CA
Glen Justice, MD	Pacific Coast Hematology/Oncology, Fountain Valley, CA
Leonard Kalman, MD	Oncology/Hematology Group of South Florida, Miami, FL
Carl Kardinal, MD	Ochsner Cancer Institute, New Orleans, LA
Frederic C. Kass, MD	Cancer Center of Santa Barbara, Santa Barbara, CA
Alan Keller, MD	US Oncology, Houston, TX
Alan Keller, MD	Cancer Care Associates, Tulsa, OK
Robert Kerr, MD	Southwest Regional Cancer Center, Austin, TX
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Table A1. Investigators and Sites (continued)

Investigator Name	Institution
Ali Khojasteh, MD	Capitol Comprehensive Cancer Care Clinic, Jefferson City, MO
Alan Koletsy, MD	Comprehensive Cancer Care Specialists, Boca Raton, FL
Donald Lawrence, MD	New England Medical Center, Boston, MA
Wilfried Leder, MD	The Christ Hospital Cancer Center, Cincinnati, OH
Gershon Locker, MD	Kellogg Cancer Care Center, Evanston, Evanston, IL
Patrick Loehrer, MD	Indiana Cancer Pavillion, Indianapolis, IL
Michael M. Long, MD	Cancer Resource Network, Mesa, AZ
F. Roy MacKintosh, MD, PhD	Sierra Biomedical Research Corporation, Reno, NV
Stefan Madajewicz, MD	SUNY at Stony Brook, Stony Brook, NY
Robert Lee Marsh, MD	M. D. Anderson Cancer Center Orlando, Orlando, FL
Rodolfo Martinez, MD	Southwest Hematology and Oncology, Lubbock, TX
Spence McCachren, MD	Thompson Cancer Survival Center, Knoxville, TN
G. Duncan McCarroll, MD	Bexar Diagnostic Medicine Associates, PA, San Antonio, TX
Richard Mercier, MD	Marshfield Clinic, Marshfield, WI
Jeffrey Miller, MD	Central Maine Medical Center, Lewiston, ME
Robert S. Miller, MD	Sacramento Center for Hematology and Oncology, Sacramento, CA
William Miller, MD	Scripps Clinical and Research Foundation, La Jolla, CA
Curtis Miyamoto, MD	Hahnemann University Hospital, Philadelphia, PA
Robert Nagourney, MD	Oncology Hematology Consultants, Long Beach, CA
John Nemunaitis, MD	US Oncology, Dallas, TX
OCOG	1775 Moriah Woods Blvd, Memphis, TN
Ira Oliff, MD	Midwest Cancer Research Group Inc, Northfield, IL
Mark O'Rourke, MD	Hematology and Oncology Associates Inc, Greenville, SC
Robert Pelley, MD	The Cleveland Clinic Foundation, Cleveland, OH
Jonathan Polikoff, MD	Kaiser Permanente, San Diego, CA
William Popovic, MD	Illinois Oncology, LTD, Belleville, IL
Kenneth Przywara, MD	Resurrection Professional Building, Chicago, IL
Mark Redrow, MD	MD Anderson Oncology Alliance, Fort Worth, TX
James A. Reeves Jr, MD	SFBC Ft Myers, Ft Myers, FL
Robert Reynolds, MD	Walt Disney Memorial Cancer Institute, Orlando, FL
Shelby Rifkin, MD	Northwest Medical Specialist Inc, Arlington Heights, IL
Paul Ritch, MD	Froedtert Memorial Lutheran Hospital-East, Milwaukee, WI
Richard Rosenbluth, MD	Northern NJ Cancer Center, Hackensack, NJ
Kala Seetharaman, MD	St Vincent Hospital at Worcester Medical Center, Worcester, MA
Brian Samuels, MD	Oncology Specialists, SC, Parkridge, IL
Jeffrey G. Schneider, MD	200 Old Country Road, Suite 250, Mineola, NY
Joseph Schulz, MD	Virginia Oncology Associates, Newport News, VA
Arun Sheth, MD	Hospice of Lourdes Hospital, Binghamton, NY
Robert Siegel, MD	Hartford Hospital, Hartford, CT
Joseph Sinkovics, MD	St Joseph's Cancer Institute, Tampa, FL
Lynn Steinbrenner, MD	VA Western New York Healthcare System, Buffalo, NY
Patrick Travis, MD	Highlands Medical Group Inc, Springdale, AR
Robert Wadleigh, MD	Department of Veteran Affairs Medical Center, Washington, DC
Tracey F. Weisberg, MD	Maine Center for CA Medicine and Blood Disorders, Scarborough, ME
Ilene Weitz, MD	UCLA-North, Los Angeles, CA
Robert Whitehead, MD	University of Texas Medial Branch, Galveston, TX
Canada	
Margot Burnell, MD	St John Regional Hospital, Saint John, New Brunswick
Felix Couture, MD	Hotel Dieu de Quebec, Quebec City, Quebec
Felix Couture, MD	Hotel Dieu de Levis, Levis, Quebec
Christine Cripps, MD	Ottawa Regional Cancer Center, Ottawa, Ontario
Murray Davidson, MD	St Joseph's Health Care, Toronto, Ontario
Dagny Dryer, MD	Queen Elizabeth Hospital, Charlottetown, Prince Edward Island
Anthony Fields, MD	Cross Cancer Institute, Edmonton, Alberta
Brian Findlay, MD	Hotel Dieu Hospital, St Catharines, Ontario
Colin Germond, MD	NE Ontario Regional Cancer Center, Sudbury, Ontario
Charles Olweney, MD	St Boniface General Hospital, Winnipeg, Manitoba
Walter Kocha, MD	London Regional Cancer Center, London, Ontario
Bernard Lesperance, MD	Hospital du Sacre-Coeur de Montreal, Montreal, Quebec
Wycliffe Lofters, MD	Kingston Regional Treatment Center, Kingston, Ontario

(continued on following page)

Table A1. Investigators and Sites (continued)

Investigator Name	Institution
Bryn Pressnail, MD	Royal Victoria Hospital, Barrie, Ontario
Jean Maroun, MD	Ottawa General Hospital, Ottawa, Ontario
Amit Oza, MD	Princes Margaret Hospital, Toronto, Ontario
Martin Potvin, MD	Hospital Laval, Ste-Foy, Quebec
Stephen Reingold, MD	Peel Memorial Hospital, Brampton, Ontario
Michael Thrilwell, MD	Montreal General Hospital, Montreal, Quebec
David Walde, MD	Algoma Dist Group Health Center, Sault Ste Marie, Ontario
Rafal Wierzbicki, MD	St Joseph's Health Center, Peterborough, Ontario
Ralph Wong, MD	Bliss Murphy Cancer Center, St John's, Ontario
Alfred Wong, MD	Tom Baker Cancer Center, Calgary, Alberta
South America	
Reinaldo Chacon, MD	Instituto Alexander Fleming, Capitol Federal, Argentina
Marcelo Muino, MD	Hospital Juan A. Fernandez, Buenos Aires, Argentina