Five-Year Data and Prognostic Factor Analysis of Oxaliplatin and Irinotecan Combinations for Advanced Colorectal Cancer: N9741

Hanna K. Sanoff, Daniel J. Sargent, Megan E. Campbell, Roscoe F. Morton, Charles S. Fuchs, Ramesh K. Ramanathan, Stephen K. Williamson, Brian P. Findlay, Henry C. Pitot, and Richard M. Goldberg

From the Department of Medicine, Division of Hematology/Oncology; and the Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; Division of Biostatistics, Mayo Clinic, Rochester, MN; Community Clinical Oncology Program, IA Oncology Research Association, Des Moines, IA; Dana-Farber Cancer Institute, Boston, MA; University of Pittsburgh, Pittsburgh, PA; University of Kansas Medical Center, Kansas City, KS; National Cancer Institute of Canada, Saint Catharines, Ontario, Canada.

Submitted May 8, 2008; accepted July 23, 2008; published online ahead of print at www.jco.org on November 10, 2008.

Supported by National Institutes of Health Grants No. CA25224, CA32102, CA38926, CA21115, and CA77202; and by Pfizer Oncology and Sanofi-Aventis.

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

Corresponding author: Richard Goldberg, MD, University of North Carolina at Chapel Hill, Hematology-Oncology, 3009 Old Clinic Building, CB 7305, Chapel Hill, NC 27599-7305; e-mail: goldberg@med.unc.edu.

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®).

© 2008 by American Society of Clinical Oncology

0732-183X/08/2635-5721/\$20.00

DOI: 10.1200/JCO.2008.17.7147

A B S T R A C T

Purpose

In this report, we update survival (OS) and time-to-progression (TTP) data for the Intergroup trial N9741 after a median 5 years of follow-up by using risk-stratified and prognostic factor analyses to determine if treatment outcomes differ in specific patient subgroups.

Patients and Methods

A total of 1,691 patients were randomly assigned to one of seven fluorouracil-, oxaliplatin-, and irinotecan-containing regimens. OS and TTP were calculated by treatment arm and baseline risk group (on the basis of WBC, performance status, number of sites of disease, and alkaline phosphatase). Multivariate prognostic factor analysis was used to assess clinical factors for their relationships to OS, TTP, response, and toxicity by using Cox and logistic regression models.

Results

The observed 5-year survival with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) of 9.8% was better than with irinotecan plus bolus fluorouracil and leucovorin (IFL; 3.7%; $P = .04$) or with bolus irinotecan/oxaliplatin (IROX; 5.1%; $P = .128$). OS and TTP were significantly longer for FOLFOX (20.2 months and 8.9 months, respectively) than for IFL (14.6 months and 6.1 months, respectively; $P < .001$ for both) or for IROX (17.3 months and 6.7 months, respectively; $P < .001$ for both). OS differed by risk group: 20.7 months for low risk, 17.4 months for intermediate risk, and 9.4 months for high risk ($P < .001$). FOLFOX treatment was superior in all risk groups and was the most powerful prognostic factor for OS, TTP, response rate, and toxicity.

Conclusion

The 9.8% 5-year OS in patients with metastatic colorectal cancer who were treated with first-line FOLFOX sets a new benchmark. Neither baseline risk group nor any prognostic factor examined was predictive of treatment-specific outcome. However, treatment efficacy and patient longevity varied as a function of risk group.

J Clin Oncol 26:5721-5727. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Novel agents have considerably improved the prognosis of patients who have metastatic colorectal cancer (MCRC). Combination chemotherapy with oxaliplatin, fluorouracil (FU), and leucovorin (LV), known together as FOLFOX, is now a routine part of MCRC treatment, in part because of the results of North Central Cancer Treatment Group (NCCTG) trial N9741—the first trial that demonstrated improved survival for patients who received FOLFOX compared with the standard of care, in this case irinotecan plus bolus FU and leucovorin (IFL).¹

Despite progress in the treatment of MCRC, tumors are heterogeneous; a substantial minority of

patients still fare poorly and have minimal response to treatment and rapid disease progression that culminates in death within a year of diagnosis. To understand this heterogeneity, studies have evaluated molecular markers of tumor resistance and clinical characteristics to predict treatment response. In a pooled analysis of source data from patients treated with FU for MCRC on 22 clinical trials, Köhne et al² divided patients into three prognostic groups by using baseline factors of Eastern Cooperative Oncology Group performance status (ECOG PS), WBC, alkaline phosphatase (ALK), and number of sites of metastatic disease.² These low-risk patients had a median survival of 15 months, intermediate-risk patients had 11 months, and the high-risk patients had 6 months.

The prognostic classification of Köhne et al² is a useful research tool, which permits stratification to ensure balanced random assignment, or permits the design of trials that specifically address treatment in patients who have poor prognoses. In clinical practice, the enhanced prognostic resolution provided by such models is of modest relevance—such metrics identify patients who are likely to fare poorly, but treatment strategies for high- and low-risk patients are similar.

Risk-stratified analysis (RSA) is a tool that makes use of models of baseline patient risk to explore if treatment benefit (or harm) differs by risk. RSA is advocated as a potentially powerful tool for the presentation of clinical trial results, because, if treatment benefit varies substantially by risk, this would inform treatment decision making. RSA is considered more powerful than traditional subgroup analyses, which cannot account for the multiple prognostic factors that may coexist in a given patient.³

In this report, we update overall survival (OS) and time to progression (TTP) from N9741 after a median of 5 years of follow-up, and we present risk-stratified results by using the Köhne et al² model. We also present a post hoc prognostic factor analysis aimed at investigating baseline clinical factors prognostic of cancer and toxicity outcomes, and we explore whether any clinical factors predict a differential likelihood of benefit from a treatment regimen and, therefore, would be useful for treatment decision making.

PATIENTS AND METHODS

Study Overview

A total of 1,691 patients were enrolled onto one of seven treatment arms of trial N9741 between October 1998 and July 2002 (Table 1). One thousand eight patients were randomly assigned to receive either weekly bolus IFL, FOLFOX, or bolus irinotecan/oxaliplatin (IROX). One hundred eighty-three patients were treated on four other arms (Other) between October 1998 and April of 2000 (Appendix Table A1, online only).¹ These arms were discontinued, because IFL became the new standard therapy for MCRC, and because the daily bolus oxaliplatin and irinotecan regimens were associated with an increased risk of toxicity.⁴

Patients were enrolled through five cooperative oncology groups: NCCTG (lead); Cancer and Leukemia Group B; ECOG; Southwestern Oncology Group; and National Cancer Institute of Canada. Eligibility criteria of note, described in detail elsewhere,¹ included unresectable colorectal cancer, no prior treatment for advanced disease (adjuvant FU was allowed if > 12 months had elapsed), ECOG PS of 0 to 2, and normal organ function.

Patients were randomly assigned via a dynamic allocation to ensure a balanced treatment assignment for PS, prior adjuvant chemotherapy, prior immunotherapy, age, and random assignment location. Treatment was given until time of disease progression, unmanageable toxic effects, or withdrawal of consent. The protocol was approved by the appropriate human investigations committee at participating sites.

Study Measures

The primary objective was to compare TTP in the IFL arm to the experimental arms (FOLFOX and IROX). Secondary end points included OS, response rate (RR), and toxicity.

TTP was calculated from study entry to disease progression. Deaths within 30 days of treatment discontinuation were considered progression. OS was calculated from enrollment to death or last contact. Patients who died or who were lost to follow-up were assumed to have progressed at the time they were last documented as free from progression, unless contradictory data were available. Response was classified as follows: complete response, disappearance of all disease and no new lesions; partial response, at least a 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions; progression, at least a 25% increase in the size of measurable tumor or any new disease.

Toxicity was graded by using the National Cancer Institute Common Toxicity Criteria, version 2.0. Paresthesia that interfered with activities of daily living or that caused disability were graded as 3 or 4, respectively.

Prognostic Factors

We assessed the relationship between baseline clinic factors of patients treated on all study arms and outcomes of OS, TTP, RR, any toxicity of grade 3 or greater, hematologic toxicity of grade 3 or greater, and nonhematologic toxicity of grade 3 or greater. The following baseline factors were included on the basis of literature review and clinical experience of the investigators: treatment arm, age, sex, prior adjuvant therapy, body mass index (BMI), PS, number of metastatic sites, location of metastatic disease, absolute neutrophil count (ANC), hemoglobin (Hgb), platelet count (Plt), total bilirubin (Bili), ALK, and AST.

The multiple imputation technique, whereby values for variables missing at random are predicted from a multivariable model on the basis of the values of other variables for that patient, was used to complete missing data. Patients enrolled through Southwest Oncology Group (n = 269) were missing all baseline data except age, sex, prior adjuvant therapy, and BMI. These Southwest Oncology Group patients did not differ from the rest of the patient population when the factors that were available for all were compared. Nine patients were omitted from the analysis because of missing values for disease site (n = 3), outliers (n = 5), and an administrative random assignment error (n = 1). For statistical modeling, the following variables were modeled by using a logarithmic transformation: Plt, ALK, ANC, AST, Bili, and BMI.

Risk-Stratified Analysis

Patients were placed into risk groups on the basis of the Köhne et al model² by using baseline WBC, number of metastatic sites, ALK, and PS. The low-risk group included patients with a PS of 0 or 1 and one site of metastatic disease. The intermediate-risk group included patients with a PS of 0 or 1, greater than one site of metastatic disease, and ALK less than 300 U/L; or a PS greater than 1, WBC less than $10 \times 10^9/L$, and one site of metastatic disease. The high-risk group included patients with a PS of 0 or 1, greater than one site of metastatic disease, and $ALK \geq 300 U/L$; or a PS greater than 1 and WBC greater than $10 \times 10^9/L$; or a PS greater than 1, WBC less than $10 \times 10^9/L$, and greater than one site of metastatic disease. WBC was not collected at enrollment; therefore, we estimated WBC from ANC on the basis of the following equation: $ANC = -0.7 + 0.8 \times WBC$.⁵

Statistical Considerations

Survival and TTP were updated to include events that occurred until December 19, 2007. OS and TTP were calculated by the Kaplan-Meier method. Cox proportional hazards modeling was used to calculate hazard ratios (HR) and confidence intervals. For the RSA, OS and TTP were compared by risk group within each treatment arm.

The association between prognostic factors and outcomes of interest were explored for all factors; multivariate associations were modeled by the Cox proportional hazards method for TTP and OS and by multiple logistic regression for RR and toxicity. Factors were considered for inclusion in the models as potentially associated with the outcome of interest if univariate *P* value were less than or equal to .25, and they were retained in the multivariate models if their associated multivariate *P* values were less than .05. Results are presented as adjusted HRs and odds ratios (ORs). Relationships were modeled in all patients and separately by treatment arm. As adjustment for treatment arm did not change the magnitude of any association, and no treatment arms by prognostic factor interactions were identified, results from the models that included all patients are reported.

RESULTS

Updated Survival

After a median follow-up of 5 years, the Kaplan-Meier–estimated 5-year OS for all patients was 6.4% (Fig 1). The 5-year survival of FOLFOX-treated patients of 9.8% (95% CI, 7.7% to 12.3%) was significantly better than that of IFL (3.7%; 95% CI, 2.3% to 6.1%;

Table 1. Patient Characteristics

Characteristic	All (N = 1,682)	FOLFOX (n = 691)	IFL (n = 428)	IROX (n = 380)	Other (n = 183)
Age, years					
Median	61	61	61	61	62
SD	11.5	11.6	11.4	11.5	11.4
Sex, %					
Male	61	59	65	60	58
Female	39	41	35	40	42
Prior adjuvant tx, %	15	16	14	14	14
ECOG PS, %					
0	52	50	54	52	54
1	42	44	41	42	40
2	6	6	5	6	6
No. of disease sites, %					
1	36	37	35	36	36
2	35	34	37	35	36
≥ 3	29	29	28	29	28
Disease site, %					
Liver	27	27	29	28	26
Liver + other	55	53	57	53	55
Other	18	20	14	19	19
Hemoglobin, %					
< 11	23	23	24	21	25
11 to 12	20	21	20	18	23
12 to 13.5	30	29	30	32	32
≥ 13.5	26	28	25	29	20
Platelets					
Median	318,000	320,000	322,477	315,500	312,000
SD	133,512	139,287	133,821	129,996	115,305
Total bilirubin					
Median	0.5	0.5	0.5	0.5	0.5
SD	0.27	0.28	0.26	0.25	0.27
ALK					
Median	125.0	121.0	133.0	122.0	117.0
SD	125.6	119.0	126.9	133.2	133.3
AST					
Median	27	26	29	28	27
SD	25.7	25.4	27.2	24.6	25.7
ANC					
Median	5,300	5,229	5,317	5,488	5,170
SD	2,500	2,379	2,585	2,729	2,241
BMI					
Median	26.4	26.5	26.3	26	27.2
SD	5.4	5.1	5.5	5.7	5.4

NOTE. Values are based on a single imputation for missing data, but all imputations did not meaningfully differ.

Abbreviations: FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IFL, irinotecan plus bolus fluorouracil and leucovorin; IROX, irinotecan and oxaliplatin; SD, standard deviation; tx, therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ALK, alkaline phosphatase; AST, aspartate aminotransferase; ANC, absolute neutrophil count; BMI, body mass index.

$P = .04$) and was higher than that of IROX (5.1%; 95% CI, 3.3% to 8.0%; $P = .128$). Corresponding median survivals were 20.2 months for FOLFOX, 14.6 months for IFL (log-rank $P < .001$), and 17.3 months for IROX (log-rank $P < .001$). TTP also was significantly longer for patients who received FOLFOX (8.9 months) than for those who received IFL (6.1 months; log-rank $P < .001$) or IROX (6.7 months; log-rank $P < .001$).

After cessation of protocol-directed therapy, 76% of patients received additional chemotherapy, which ranged from 66% of patients treated with the chemotherapy regimens in the Other treatment arm to 82% of patients treated with FOLFOX (Appendix Table A2, online only). Sixty-four percent of patients received irinotecan after

FOLFOX failure compared with 40% of patients who received oxaliplatin after IFL failure.

In the RSA that was based on the Köhne et al model,² all outcomes varied by risk group. Median OS for the low-risk group (20.8 months) was greater than for the intermediate- (17.4 months) and high-risk (9.4 months) groups ($P < .001$; Table 2; Fig 2A). Median TTP for the low-risk group (8.3 months) was also greater than for the intermediate- (7.1 months) and high-risk (5.4 months) groups ($P < .001$). FOLFOX resulted in longer OS and TTP than IFL and IROX in all risk groups. There was a trend toward greater survival benefit from FOLFOX in low-risk versus high-risk patients, though the treatment arm by risk group interaction failed to meet statistical

Fig 1. (A) Overall survival and (B) time to progression. IFL, irinotecan plus bolus fluorouracil and leucovorin; FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IROX, irinotecan and oxaliplatin.

significance ($P = .79$). No such trend was found for TTP by risk group (HR of FOLFOX v IFL: low-risk, 1.64; intermediate-risk, 1.38; high-risk, 1.59; interaction $P = .80$).

Stratification by PS yielded similar outcomes as RSA: OS for PS of 0 was 20.4 months; for PS of 1, 14.8 months; and for PS of 2,

Fig 2. Overall survival (OS) by baseline risk: (A) OS by risk group; (B) OS by performance status (PS).

9.1 months ($P < .001$; Fig 2B). Stratification by risk group, however, better discriminated between high- and intermediate-risk groups, and the high-risk group was twice the size of the patient population that had a PS of 2.

Of the patients who survived 5 years ($n = 85$), 26% had a CR to chemotherapy, and 7% underwent resection. Among 5-year survivors

Table 2. Overall Survival by Treatment Arm: Risk-Stratified Analysis

Treatment Arm by Risk Group	No. of Patients	Overall Survival		Analysis		P
		Median (Months)	95% CI	HR	95% CI	
Low						
FOLFOX	247	27.5	22.6 to 29.9	1		
IFL	146	18.2	15.8 to 20.7	1.68	1.35 to 2.08	< .0001
IROX	135	19.7	17.2 to 23.3	1.47	1.18 to 1.84	.0006
Intermediate						
FOLFOX	384	19.2	17.9 to 20.8	1		
IFL	227	13.8	12.2 to 16.4	1.48	1.25 to 1.75	< .0001
IROX	196	17.8	16.1 to 19.8	1.29	1.08 to 1.55	.0047
High						
FOLFOX	60	10.7	8.2 to 12.4	1		
IFL	55	9.4	6.3 to 12.4	1.27	0.87 to 1.85	.2086
IROX	49	9.1	6.0 to 12.3	1.27	0.87 to 1.87	.2186

Abbreviations: HR, hazard ratio; FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IFL, irinotecan plus bolus fluorouracil and leucovorin; IROX, irinotecan and oxaliplatin.

in the FOLFOX arm ($n = 49$), 15 had CR, and five underwent resection (Table 3). The majority of 5-year survivors on all arms remain alive with disease (53 [62%] of 85).

Factors Prognostic of Benefit

Treatment with FOLFOX was the factor most strongly associated with improved cancer outcomes (Fig 3). Compared with IFL, FOLFOX treatment conferred a 37% reduction in death (HR, 0.63; 95% CI, 0.55 to 0.72), a 33% reduction in progression (HR, 0.67; 95% CI, 0.59 to 0.76), and a doubling in the odds of response (OR, 2.00; 95% CI, 1.52 to 2.54). There was no significant difference in OS, TTP, or RR between IFL, IROX or Other treatment arms. No interactions of prognostic factor by treatment arm were significant for OS, TTP, or RR, which suggests that no factor predicts differential benefit for a treatment regimen.

After FOLFOX, PS and the number of metastatic sites were most strongly associated with OS. Compared with patients who had only one site of metastatic disease (20.7 months), those with two sites (17.5 months; HR, 1.30; 95% CI, 1.14 to 1.48) and three sites (14.8 months; HR, 1.51; 95% CI, 1.33 to 1.73) had shorter survival. A higher ANC, ALK, and AST, and a low Hgb were also associated with shorter survival. The risk of death was greater in patients aged 70 years and older compared with those aged younger than 40 years (HR, 1.34; 95% CI, 1.04 to 1.72), but there was no association between advanced age and TTP or RR, which suggests that the OS association may not be from age-related differences in treatment efficacy.

As with OS, poorer PS and more sites of metastatic disease were strongly associated with shorter TTP, as were higher ANC and AST. Obese patients had a longer TTP than normal-weight patients and had a median TTP of 8.0 months (HR, 0.80; 95% CI, 0.70 to 0.92) for patients with a BMI of 30 to 40, 9.8 months (HR, 0.81; 95% CI, 0.60 to 1.11) for patients with a BMI ≥ 40 , and 6.7 months for those with a BMI of 18.5 to 25. TTP was similar for underweight, overweight, and normal-weight patients. Obesity, however, was not associated with either OS or RR.

Other than FOLFOX, RR was associated only with PS and prior adjuvant therapy. Patients who had a PS of 1 (RR, 37%; OR, 0.84; 95% CI, 0.66 to 1.07) and a PS of 2 (RR, 27%; OR, 0.59; 95% CI, 0.36 to 0.98) were less likely to respond than those who had a PS of 0 (RR, 40%). Those who received adjuvant therapy were less likely to respond (RR, 30% v 39%; OR, 0.64; 95% CI, 0.47 to 0.87), though prior adjuvant therapy was not associated with TTP or OS.

Factors Prognostic of Toxicity

Treatment arm was the factor most prognostic of severe toxicity. The likelihood of experiencing any grade 3 or greater toxicity was

greatest with FOLFOX (81%, FOLFOX; 73%, IFL; 78%, IROX; OR v IFL, 1.68; 95% CI, 1.25 to 2.25). Six percent of patients in the FOLFOX arm had grade 3 or greater neurotoxicity as their only severe nonhematologic toxicity. We found no interaction of prognostic factor by treatment arm for toxicity outcomes, which suggests that none of the factors that we evaluated can predict greater toxicity from one treatment than another.

The odds of experiencing any grade 3 or greater toxicity and grade 3 or greater hematologic toxicity were increased by higher Bili and ALK. Men were less likely than women to experience any severe toxicity (74%, men; 81%, women; OR, 0.62; 95% CI, 0.49 to 0.80) and severe hematologic toxicity (44%, men; 56%, women; OR, 0.57; 95% CI, 0.46 to 0.70). Severe hematologic toxicity was also associated with overweight (though not obese or underweight) patients, with high ANC, and with low Hgb. A poorer PS and prior adjuvant therapy were associated with an increased odds of severe nonhematologic toxicity.

DISCUSSION

The 9.8% 5-year survival observed for FOLFOX-treated patients in this trial sets a new benchmark in clinical trials for patients who have MCRC. This compares with a 1% 5-year survival in a prior pooled analysis of 32 NCCTG trials of MCRC.⁶ In this update of a phase III study that compares first-line chemotherapy with FOLFOX and IROX to IFL, the initially reported results have been maintained: FOLFOX is superior to IFL, has a 2.8-month improvement in TTP, and has a 5.6-month improvement in OS. Among the 5-year survivors ($n = 85$), six underwent resection, and 22 had a clinical CR, which suggests that most survived with drug therapy alone. With the longer median survivals recently reported,⁷⁻⁹ we expect 5-year survival will exceed 10% in newer studies that include biologic agents.

By using RSA, we found that FOLFOX is superior to IFL regardless of baseline risk. Similarly, in our prognostic factor analysis, treatment with FOLFOX was the most important prognostic factor for good cancer outcomes. Thus, although potentially useful for clinical trial design, the prognostic factors explored seem to add little to clinical treatment decision making. We did confirm the prognostic utility in combination chemotherapy of many factors that were previously identified in trials of FU-only therapy.

Poor PS was associated with a shorter OS and TTP and with the lowest RR. This is consistent with a recent pooled analysis of patients treated on phase III trials of MCRC that showed that patients who had a PS of 2 had a lower RR, a shorter TTP, and a shorter OS.¹⁰ Despite their poorer prognosis, however, patients who had a PS of 2 in the pooled analysis derived the same relative benefit from superior regimens as

Table 3. Characteristics of 5-Year Survivors by Arm

Characteristic	All (N = 85)		FOLFOX (n = 49)		IFL (n = 13)		IROX (n = 18)		Other (n = 5)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Progression free	30	35	17	35	6	46	6	33	1	20
Resected	6	7	5	10	0	0	1	6	0	0
CR	22	26	15	31	4	31	3	17	0	0

Abbreviations: FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IFL, irinotecan plus bolus fluorouracil and leucovorin; IROX, irinotecan and oxaliplatin; CR, complete response.

Fig 3. Multivariate prognostic factor analysis: (A) Overall survival; (B) time to progression; (C) response rate; (D) any grade ≥ 3 toxicity. Trt, treatment; IFL, irinotecan plus bolus fluorouracil and leucovorin; FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IROX, irinotecan and oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; Hgb, hemoglobin; ANC, absolute neutrophil count; BMI, body mass index; Adj., adjuvant; ALK, alkaline phosphatase; Tot Bili, total bilirubin.

did patients who had a PS of 0 to 1, which suggests that aggressive regimens should not be withheld from patients who have a PS of 2.

In contrast, we found a nonsignificant trend for a reduced survival benefit from FOLFOX compared with IFL in the high-risk (HR, 1.27) than in the low-risk (HR, 1.68) patients. The same trend was found in PS subgroup analysis, as there was a lessened risk reduction in OS from FOLFOX in patients who had a PS of 2 than in those who had a PS of 0 or 1 (data not shown). TTP, however, was consistently better in FOLFOX-treated patients regardless of baseline PS or risk group. The numbers of patients in both poor-prognosis groups was small in this trial, which highlights the need for pooled analyses to provide more conclusive data on the treatment benefit in poor-prognosis patients.

We found no association between age and TTP, response, or toxicity. Those patients older than 70 years had shorter median survival than patients who were younger than 40 years; given the similar RR and TTP, this is likely because of causes other than the efficacy of first-line therapy, such as competing causes of mortality or less frequent use of second-line therapy, and it is consistent with prior reports of cancer outcomes in the elderly.¹¹⁻¹³ We also confirmed that women who have MCRC are more likely to suffer severe chemotherapy toxicity than men,¹⁴ though other cancer outcomes did not differ by sex. Interestingly, obesity was associated with longer TTP; yet, as high BMI was not associated with improved RR or OS, and as obese patients with

colorectal cancer have been reported to have poorer cancer outcomes,¹⁵ our finding may have been the result of chance.

Prior adjuvant therapy did not affect TTP or OS, though RR was lower in previously treated patients. We did not collect data on which adjuvant therapy was given. As enrollment occurred between 1998 and 2002, most patients who received adjuvant therapy likely were treated with FU/LV. Our findings suggest at least some patients who were previously treated with FU/LV continue to benefit from FU-based combination therapy.

A 9.8% 5-year survival is a marked improvement in long-term outcomes in a disease for which, until recently, the median survival was 6 to 9 months, and only a rare patient survived to 5 years. Despite these advances, there remains marked heterogeneity in survival. We were able to identify factors associated with worse survival and to confirm the prognostic utility of the Köhne et al² model, which was developed in the era of FU monotherapy and in the setting of combination chemotherapy. Although we found a trend suggestive of a reduced OS benefit from FOLFOX in poor-risk patients, FOLFOX was the best treatment choice for all groups studied. RSA may be a more powerful tool to compare the likelihood of benefit by risk group for more similarly effective regimens (eg, FOLFOX v irinotecan with infusional FU/LV). We believe RSA is a potentially powerful tool for

presenting clinical trial results, and we recommend that it be incorporated into future reports of phase III trials in adjuvant and advanced disease settings.

Though tools such as RSA might help us better design and interpret clinical trial data, continued search for markers of differential benefit is critical to improve outcome, cost-effectiveness, and tolerability of cancer treatment. Advances such as identification of pharmacogenetic differences in drug handling and intrinsic tumor resistance mechanisms (eg, mutated K-Ras) will be essential as we learn to tailor therapy to each individual patient.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Daniel J. Sargent, Sanofi-aventis (C), Pfizer Inc (C); Ramesh K. Ramanathan, Sanofi-aventis (C); Richard M. Goldberg, Sanofi-aventis

(C), Pfizer Inc (C) **Stock Ownership:** None **Honoraria:** Charles S. Fuchs, Sanofi-aventis, Pfizer Inc; Ramesh K. Ramanathan, Sanofi-aventis; Richard M. Goldberg, Sanofi-aventis, Pfizer Inc **Research Funding:** Stephen K. Williamson, Sanofi-aventis, Pfizer Inc; Richard M. Goldberg, Sanofi-aventis, Pfizer Inc **Expert Testimony:** Richard M. Goldberg, Sanofi-aventis (C), Pfizer Inc (C) **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Hanna K. Sanoff, Daniel J. Sargent, Megan E. Campbell, Roscoe F. Morton, Charles S. Fuchs, Ramesh K. Ramanathan, Stephen K. Williamson, Brian P. Findlay, Henry C. Pitot, Richard M. Goldberg

Provision of study materials or patients: Roscoe F. Morton, Charles S. Fuchs, Ramesh K. Ramanathan, Stephen K. Williamson, Brian P. Findlay, Henry C. Pitot, Richard M. Goldberg

Collection and assembly of data: Daniel J. Sargent, Roscoe F. Morton, Charles S. Fuchs, Ramesh K. Ramanathan, Stephen K. Williamson, Brian P. Findlay, Henry C. Pitot, Richard M. Goldberg

Data analysis and interpretation: Hanna K. Sanoff, Daniel J. Sargent, Megan E. Campbell, Richard M. Goldberg

Manuscript writing: Hanna K. Sanoff, Daniel J. Sargent, Megan E. Campbell, Charles S. Fuchs, Richard M. Goldberg

Final approval of manuscript: Hanna K. Sanoff, Daniel J. Sargent, Megan E. Campbell, Roscoe F. Morton, Charles S. Fuchs, Ramesh K. Ramanathan, Stephen K. Williamson, Brian P. Findlay, Henry C. Pitot, Richard M. Goldberg

REFERENCES

- 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
- Köhne CH, Cunningham D, Di CF, et al: Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: Results of a multivariate analysis of 3825 patients. *Ann Oncol* 13:308-317, 2002
- Kent DM, Hayward RA: Limitations of applying summary results of clinical trials to individual patients: The need for risk stratification. *JAMA* 298:1209-1212, 2007
- Delaunoi T, Goldberg RM, Sargent DJ, et al: Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: Results from Intergroup Trial N9741. *Cancer* 101:2170-2176, 2004
- Benson AB 3rd, Read TR, Goebel SL, Koeller JM, Tormey DC: Correlations between leukocyte count and absolute granulocyte count in patients receiving cancer chemotherapy. *Cancer* 56:1350-1355, 1985
- Hobday T, Cha S, Sargent D, et al: Long term survivors (LTS) of metastatic colorectal cancer (MCRC) treated with chemotherapy only: A North Central Cancer Group (NCCTG) Review. *J Clin Oncol* 21:174a, 2002 (suppl; abstr 693)
- Tournigand C, Cervantes A, Figuer A, et al: OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—A GERCOR study. *J Clin Oncol* 24:394-400, 2006
- Saltz L, Clarke S, Diaz-Rubio E, et al: Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. *J Clin Oncol* 25:170s, 2007 (suppl; abstr 4028)
- Fuchs CS, Marshall J, Mitchell E, et al: 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. *J Clin Oncol* 25:4779-4786, 2007
- Goldberg RM, Köhne CH, Seymour MT, et al: A pooled safety analysis examining the effect of performance status on outcomes in nine first-line treatment trials of 6,286 patients with metastatic colorectal cancer. *J Clin Oncol* 25:166s, 2007 (suppl; abstr 4011)
- Sargent DJ, Goldberg RM, Jacobson SD, et al: A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 345:1091-1097, 2001
- Goldberg RM, Tabah-Fisch I, Bleiberg H, et al: Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 24:4085-4091, 2006
- Folprecht G, Seymour MT, Saltz L, et al: Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: Combined analysis of 2,691 patients in randomized controlled trials. *J Clin Oncol* 26:1443-1451, 2008
- Sloan JA, Goldberg RM, Sargent DJ, et al: Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. *J Clin Oncol* 20:1491-1498, 2002
- Dignam JJ, Polite BN, Yothers G, et al: Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *J Natl Cancer Inst* 98:1647-1654, 2006