ORIGINAL ARTICLE

Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer

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ABSTRACT

BACKGROUND

A fluoropyrimidine plus irinotecan or oxaliplatin, combined with bevacizumab (a monoclonal antibody against vascular endothelial growth factor), is standard first-line treatment for metastatic colorectal cancer. Before the introduction of bevacizumab, chemotherapy with fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) showed superior efficacy as compared with fluorouracil, leucovorin, and irinotecan (FOLFIRI). In a phase 2 study, FOLFOXIRI plus bevacizumab showed promising activity and an acceptable rate of adverse effects.

METHODS

We randomly assigned 508 patients with untreated metastatic colorectal cancer to receive either FOLFIRI plus bevacizumab (control group) or FOLFOXIRI plus bevacizumab (experimental group). Up to 12 cycles of treatment were administered, followed by fluorouracil plus bevacizumab until disease progression. The primary end point was progression-free survival.

RESULTS

The median progression-free survival was 12.1 months in the experimental group, as compared with 9.7 months in the control group (hazard ratio for progression, 0.75; 95% confidence interval [CI], 0.62 to 0.90; P=0.003). The objective response rate was 65% in the experimental group and 53% in the control group (P=0.006). Overall survival was longer, but not significantly so, in the experimental group (31.0 vs. 25.8 months; hazard ratio for death, 0.79; 95% CI, 0.63 to 1.00; P=0.054). The incidences of grade 3 or 4 neurotoxicity, stomatitis, diarrhea, and neutropenia were significantly higher in the experimental group.

CONCLUSIONS

FOLFOXIRI plus bevacizumab, as compared with FOLFIRI plus bevacizumab, improved the outcome in patients with metastatic colorectal cancer and increased the incidence of some adverse events. (Funded by the Gruppo Oncologico Nord Ovest and others; ClinicalTrials.gov number, NCT00719797.)

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Primary treatment with two-drug combinations of fluorouracil (plus leucovorin) and either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) plus bevacizumab are widely adopted treatments for metastatic colorectal cancer.[1,2] Initial treatment strategies led to similar results regardless of which drug — irinotecan or oxaliplatin — was used[3]; therefore, the choice of the primary treatment regimen is commonly based on the physician's or patient's preferences, regional differences, and whether the patient has or has not already received an adjuvant oxaliplatin-containing treatment.[4]

In the pivotal phase 3, randomized study AVF2107g,[1] the addition of bevacizumab to irinotecan and bolus fluorouracil (plus leucovorin) led to an improvement in objective response rate, progression-free survival, and overall survival. Bevacizumab was added to irinotecan and infusional fluorouracil in a phase 4 trial, producing similar results.[5]

A triple-drug combination of fluorouracil (plus leucovorin), oxaliplatin, and irinotecan (FOLFOXIRI) proved to be feasible and highly active in phase 2 studies.[6,7] In a phase 3 study conducted by the Gruppo Oncologico Nord Ovest (GONO), 12 cycles of treatment with FOLFOXIRI showed a superior response rate, progression-free survival, and overall survival as compared with 12 cycles of FOLFIRI.[8]

The efficacy and safety of FOLFOXIRI plus bevacizumab were previously tested in a phase 2 study,[9] and a response rate of 77% was reported; median progression-free survival was 13.1 months, and median overall survival was 30.9 months. The rate of adverse events was consistent with the rate shown in the phase 3 study conducted by GONO[8] and was higher than the rate associated with FOLFOX or FOLFIRI. On the basis of such promising results, we conducted the present randomized study of FOLFOXIRI plus bevacizumab as compared with FOLFIRI plus bevacizumab in patients with previously untreated metastatic colorectal cancer.

Methods

Study Design and Oversight

The Triplet plus Bevacizumab (TRIBE) study was a phase 3, randomized, open-label, multicenter trial conducted in 34 Italian centers and involving patients with unresectable metastatic colorectal cancer who had not received chemotherapy or biologic therapy for their metastatic disease but may have received adjuvant chemotherapy earlier in the disease course. The study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Approval for the protocol was obtained from the local ethics committee for each participating site. All patients provided written informed consent, including a separate, specific signature consenting to blood sampling and specimen donation for translational analyses.

Patients were assigned in a 1:1 ratio to receive up to 12 cycles of FOLFOXIRI plus bevacizumab (experimental group) or FOLFIRI plus bevacizumab (control group). Maintenance treatment with fluorouracil plus bevacizumab until tumor progression was then administered in both groups. Stratification criteria were Eastern Cooperative Oncology Group (ECOG) performance status (a score of 0 vs. 1 or 2 on a scale of 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing symptoms), center, and previous adjuvant treatment (yes vs. no).

The primary end point was progression-free survival, defined as the time from randomization to disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0,[10] or death from any cause. Tumor assessment was centrally reviewed. Secondary end points included response rate, overall survival rate, resection rate of metastases, and rate of adverse events. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[11]

The study was designed by the three senior academic investigators and sponsored by GONO. Bevacizumab for the treatment of patients enrolled in the experimental group was supplied by F. Hoffmann–La Roche, which had no other role in the study. Data were collected by the sponsor and were analyzed by the statistician. The three senior academic investigators had access to all the data and vouch for the completeness and accuracy of the reported data and adherence to the protocol, which is available with the full text of this article at NEJM.org. The preliminary draft of the manuscript was written by the first and second authors with the assistance of the corresponding author. All the authors revised subsequent drafts and made the decision to submit

the manuscript for publication. No one who is not an author contributed to the manuscript.

PATIENTS

Main inclusion criteria were an age between 18 and 75 years, ECOG performance status score of 2 or less (patients above 70 years of age were eligible if their ECOG performance status score was 0), histologically confirmed adenocarcinoma of the colon or rectum, a first occurrence of metastatic disease that was deemed unresectable with curative intent, measurable disease according to RECIST version 1.0, and adequate functioning of the bone marrow, liver, and kidneys. Main exclusion criteria were adjuvant treatment with oxaliplatin completed less than 12 months before relapse, peripheral neuropathy of grade 1 or higher according to CTCAE version 3.0, evidence of bleeding diathesis or coagulopathy, uncontrolled hypertension, clinically significant cardiovascular events within 6 months before study entry, serious cardiac events requiring medication, New York Heart Association class II or higher heart failure, and the need for full-dose anticoagulation.

TREATMENT

Patients in the control group received up to 12 cycles of FOLFIRI plus bevacizumab, consisting of a 30-minute infusion of bevacizumab at a dose of 5 mg per kilogram of body weight, a 60-minute infusion of irinotecan at a dose of 180 mg per square meter of body-surface area, a 120-minute infusion of leucovorin at a dose of 200 mg per square meter, and a bolus of fluorouracil at a dose of 400 mg per square meter followed by a 46-hour continuous infusion of fluorouracil to a total dose of 2400 mg per square meter. Cycles were repeated every 14 days. Patients in the experimental group received up to 12 cycles of FOLFOXIRI plus bevacizumab, consisting of a 30-minute infusion of bevacizumab at a dose of 5 mg per kilogram, a 60-minute infusion of irinotecan at a dose of 165 mg per square meter, and a 120-minute infusion of oxaliplatin at a dose of 85 mg per square meter and a concomitant 120-minute infusion of leucovorin at a dose of 200 mg per square meter, followed by a 48-hour continuous infusion of fluorouracil to a total dose of 3200 mg per square meter. Cycles were repeated every 14 days.

Thereafter, in both groups, maintenance treatment with bevacizumab, fluorouracil, and leucovorin was continued until disease progression, the occurrence of an unacceptable adverse event, or withdrawal of consent. In cases of prespecified adverse events, treatment modifications were permitted according to study protocol.

ASSESSMENTS

Tumor assessment by means of computed tomography was performed every 8 weeks until the evidence of disease progression. At the start of every cycle, the patients' medical history, ECOG performance status, results of physical examination, and adverse events were recorded.

To assess *KRAS* and *BRAF* mutational status, DNA was extracted from archival tissue specimens from the primary tumor or metastasis. *KRAS* codons 12, 13, and 61 and *BRAF* codon 600 were centrally analyzed by means of pyrosequencing, as previously reported.[11]

STATISTICAL ANALYSIS

The trial was planned as a phase 3, randomized study. We planned to enroll 450 patients in order to observe 379 events of disease progression or death from any cause; with that number of events, it was estimated that the study would have 80% power to detect a hazard ratio for progression of 0.75 at a two-sided significance level of 5%. All efficacy analyses were performed on an intention-to-treat basis. The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method. Distributions of time-to-event variables were estimated with the use of the Kaplan–Meier product-limit method. The stratified log-rank test was used as the primary analysis for comparison of treatment groups. Cox proportional-hazards modeling was also performed as supportive analyses. Subgroup analyses of progression-free survival were performed by means of an interaction test to determine the consistency of the treatment effect according to key baseline characteristics. Overall survival was analyzed with the same methods as those used for the analysis of progression-free survival. The objective response rate, the resection rate for metastases, and the incidence of adverse events in the two groups were compared with the use of the chi-square test for heterogeneity or with Fisher's exact test when appropriate. All statistical tests were two-sided, and P values of 0.05 or less were considered to indicate statistical significance. Odds ratios and 95% confidence

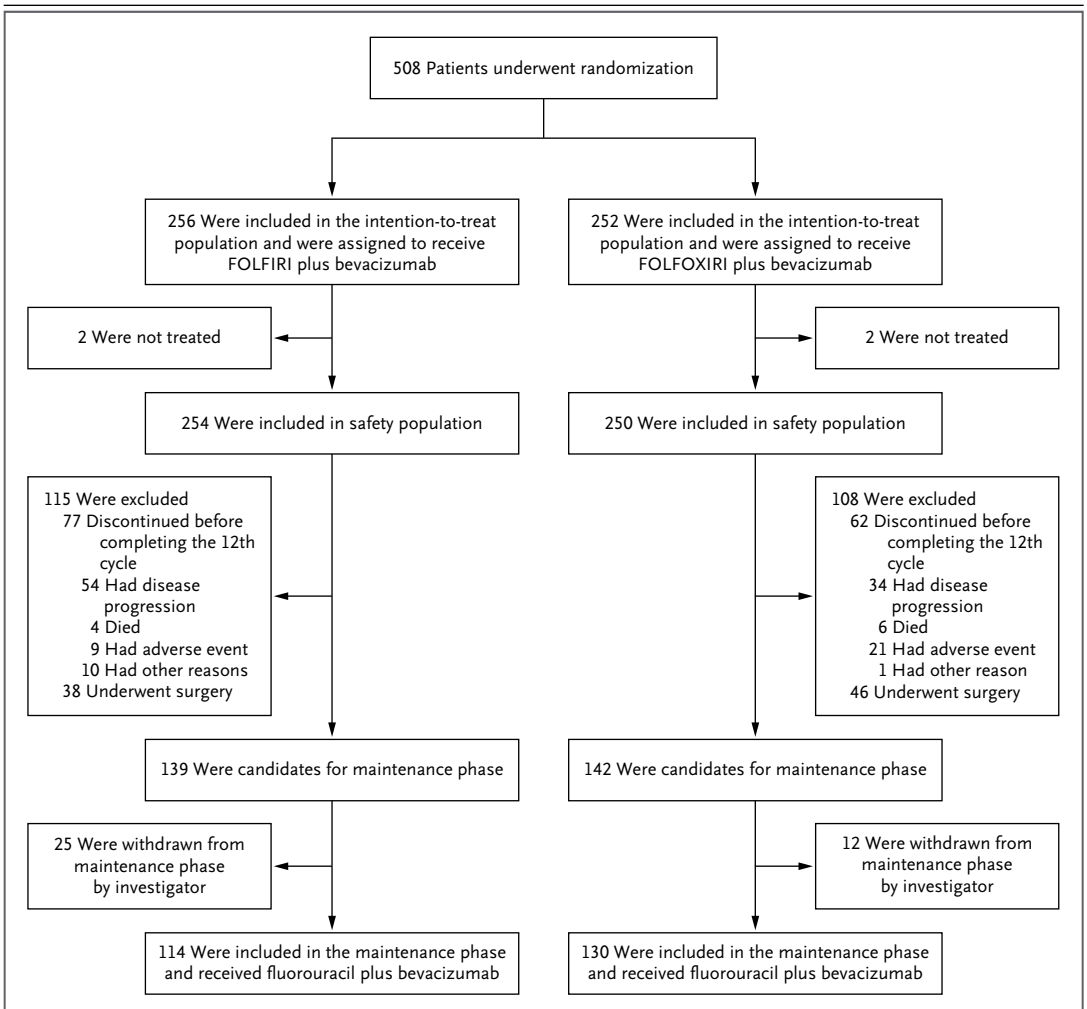

Figure 1. Randomization and Treatment.

FOLFIRI denotes fluorouracil, leucovorin, and irinotecan; and FOLFOXIRI fluorouracil, leucovorin, oxaliplatin, and irinotecan.

intervals were estimated with a logistic-regression model, and hazard ratios and 95% confidence intervals were estimated with a Cox proportional-hazards model. No adjustment for multiple comparisons was made.

RESULTS

STUDY POPULATION

From July 2008 through May 2011, a total of 508 patients from 34 Italian centers were enrolled in the study; 256 patients were randomly assigned to FOLFIRI plus bevacizumab (control group) and 252 to FOLFOXIRI plus bevacizumab (experimental group) and were included in the intention-to-treat population. Two patients in each group did not receive any cycle of treatment according to their random assignment and therefore were not included in the safety population, which comprised patients who had received at least one cycle of the assigned treatment (Fig. 1). The cutoff date for the collection of follow-up data was April 26, 2013.

Demographic and baseline characteristics of the patients were similar in the two groups (Table 1), but a higher percentage of patients in the experimental group than in the control group had a primary tumor in the right colon

(34.9% vs. 23.8%, P=0.02). Altogether, 89.8% of the study population had a score of 0 on the ECOG performance status scale, 79.5% presented with synchronous metastases, 32.7% had an unresected primary tumor, and 12.6% had previously received an adjuvant treatment. Of all the enrolled patients, 79.3% had multiple sites of metastases, and 20.7% had disease limited to the liver. *KRAS* was analyzed in 407 patients (80.1%), and *BRAF* in 406 patients (79.9%); 39.4% had *KRAS* mutations, and 5.5% had *BRAF* mutations.

The median number of cycles administered per patient as induction treatment was 12 (range, 1 to 25) in the control group and 11 (range, 1 to 21) in the experimental group. According to the investigator's choice, 23 patients in the control group and 12 patients in the experimental group received more than the 12 planned cycles, resulting in a protocol violation. More cycles were delayed in the experimental group than in the control group (16.4% vs. 6.1%, P<0.001), and more cycles were administered with a reduced dose (21.4% vs. 8.2%, P<0.001). Dose reductions were not permitted for bevacizumab. In the control group, the average relative dose intensities of fluorouracil and irinotecan were 83% and 84%, respectively. In the experimental group, the average relative dose intensities of fluorouracil, irinotecan, and oxaliplatin were 73%, 74%, and 75%, respectively. More patients in the control group than in the experimental group discontinued treatment because of disease progression (20.1% vs. 12.8%, P=0.03).

A total of 139 patients in the control group and 142 patients in the experimental group were candidates for maintenance therapy after the induction phase (Fig. 1); 114 patients in the control group (82.0%) and 130 patients in the experimental group (91.5%) actually received maintenance therapy.

Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	FOLFIRI plus Bevacizumab (N=256)	FOLFOXIRI plus Bevacizumab (N=252)
Age — yr		
Median	60.0	60.5
Range	29–75	29–75
Sex — no. (%)		
Male	156 (60.9)	150 (59.5)
Female	100 (39.1)	102 (40.5)
ECOG performance status — no. (%)		
0	229 (89.5)	227 (90.1)
1–2	27 (10.5)	25 (9.9)
Site of primary tumor — no. (%)		
Right colon	61 (23.8)	88 (34.9)†
Left colon or rectum	179 (70.0)	152 (60.3)
Missing data	16 (6.2)	12 (4.8)
Previous adjuvant therapy — no. (%)	32 (12.5)	32 (12.7)
Time to metastases — no. (%)		
Synchronous	207 (80.9)	197 (78.2)
Metachronous	49 (19.1)	55 (21.8)
Metastases — no. (%)		
Confined to liver	46 (18.0)	59 (23.4)
At multiple sites	210 (82.0)	193 (76.6)
Unresected primary tumor — no. (%)	89 (34.8)	77 (30.6)
Köhne prognostic score — no. (%)		
High-risk	29 (11.3)	18 (7.1)
Intermediate-risk	113 (44.2)	111 (44.0)
Low-risk	105 (41.0)	108 (42.9)
Missing data	9 (3.5)	15 (6.0)
KRAS — no. (%)		
Nonmutated	99 (38.7)	94 (37.3)
Mutated	96 (37.5)	104 (41.3)
Not definable	6 (2.3)	8 (3.2)
Missing data	55 (21.5)	46 (18.2)
BRAF — no. (%)		
Nonmutated	183 (71.5)	182 (72.2)
Mutated	12 (4.7)	16 (6.3)
Not definable	6 (2.3)	7 (2.8)
Missing data	55 (21.5)	47 (18.7)

* ECOG denotes Eastern Cooperative Oncology Group; FOLFIRI fluorouracil, leucovorin, and irinotecan; and FOLFOXIRI fluorouracil, leucovorin, oxaliplatin, and irinotecan.

† A significantly higher percentage of patients in the group assigned to FOLFOXIRI plus bevacizumab than in the group assigned to FOLFIRI plus bevacizumab had a primary tumor in the right colon (P=0.02).

EFFICACY

The median duration of follow-up was 32.2 months (range, 24.7 to 40.6). The progression-free survival analysis was based on 439 events among the 508 patients (86.4%). More events occurred in the 256 patients in the control group than in the 252 patients in the experimental group (226 [88.3%] vs. 213 [84.5%]). The median progression-free survival times were 12.1

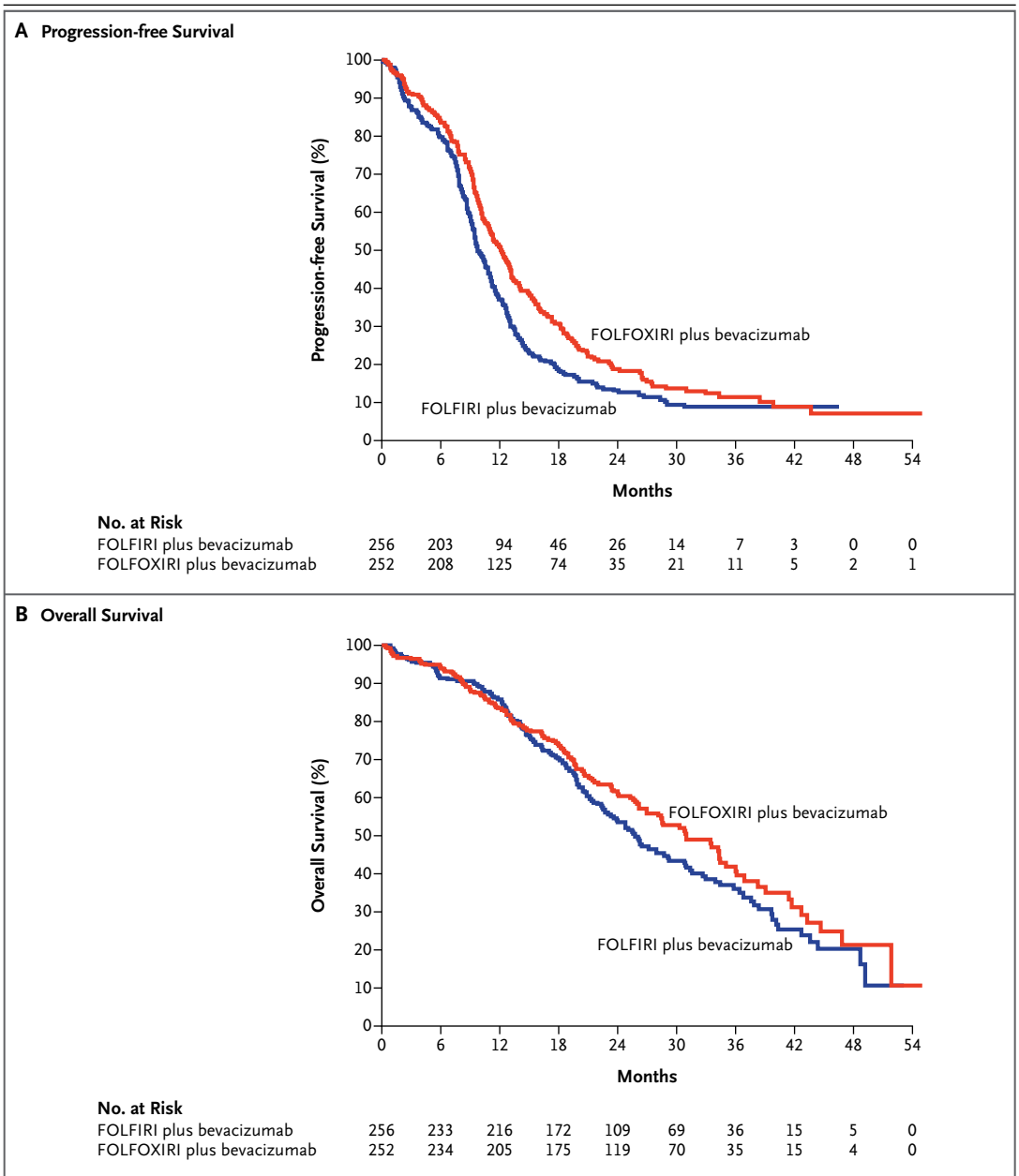

Figure 2. Kaplan–Meier Estimates of Progression-free and Overall Survival, According to Treatment Group.

Median progression-free survival was 9.7 months in the group receiving FOLFIRI plus bevacizumab (control group) and 12.1 months in the group receiving FOLFOXIRI plus bevacizumab (experimental group). Median overall survival was 25.8 months in the control group and 31.0 months in the experimental group.

months for FOLFOXIRI plus bevacizumab and 9.7 months for FOLFIRI plus bevacizumab. FOLFOXIRI plus bevacizumab was associated with a 25% reduced risk of progression as compared with FOLFIRI plus bevacizumab (hazard ratio for progression, 0.75; 95% confidence interval [CI], 0.62 to 0.90; P=0.003) (Fig. 2A). An ECOG performance status score of 1 or 2, a primary tumor in the right colon, synchronous metastases, disease not confined to the liver, an unresected primary tumor, a high score on the Köhne index[12] (a model in which the prognosis of patients with metastatic colorectal cancer is classified as low-risk, intermediate-risk, or high-

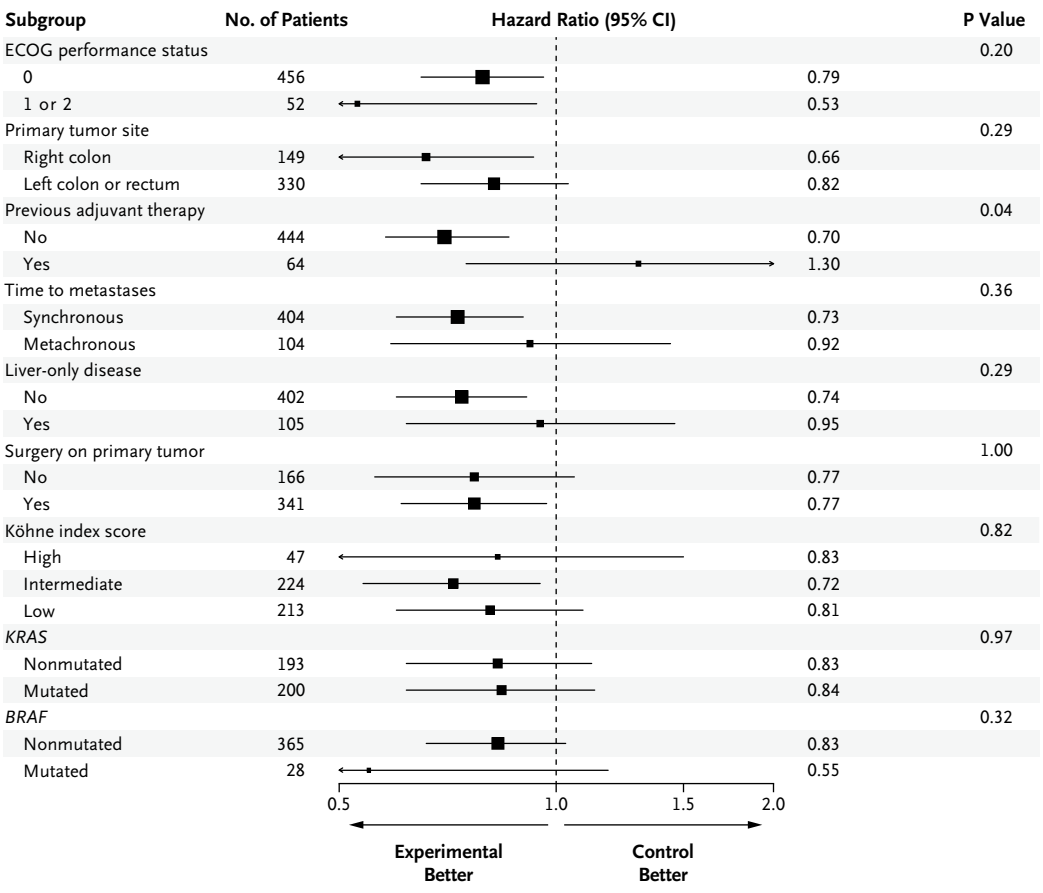

Figure 3. Forest Plot of the Treatment Effect on Progression-free Survival in Subgroup Analyses.

The size of the squares is proportional to the size of the corresponding subgroup. Control denotes FOLFIRI plus bevacizumab, ECOG Eastern Cooperative Oncology Group, and experimental FOLFOXIRI plus bevacizumab.

risk according to ECOG performance status, number of metastatic sites, white-cell count, and alkaline phosphatase level; see the Supplementary Appendix, available at NEJM.org), and a *BRAF* mutation were identified as adverse prognostic factors for progression-free and overall survival in the univariate model (see the Supplementary Appendix). At an exploratory analysis adjusting for these variables, the hazard ratio for progression associated with FOLFOXIRI plus bevacizumab was 0.75 (95% CI, 0.62 to 0.92; P=0.006). *BRAF* mutational status was not included in the adjusted model because data were missing for 20.1% of the patients. The benefit of FOLFOXIRI plus bevacizumab with respect to progression-free survival was homogeneous in clinical and molecular subgroups, except for patients who had previously received adjuvant treatment. A significant interaction between exposure to a previous adjuvant treatment and progression-free survival was observed (P=0.04) (Fig. 3).

The response rate was 53.1% in the control group, as compared with 65.1% in the experimental group (odds ratio, 1.64; 95% CI, 1.15 to 2.35; P=0.006) (Table 2). The rate of R0 resection of metastases (i.e., no macroscopic or microscopic residual tumor) was not significantly different in treatment groups (12% in the control group vs. 15% in the experimental group, P=0.33).

The overall survival analysis was based on 286 deaths among the 508 patients (56.3%). More deaths occurred in the control group than in the experimental group (155 [60.5%] vs. 131 [52.0%]). The median overall survival times were

Table 2. Efficacy in the Intention-to-Treat Population, According to Treatment Group.*

Variable	FOLFIRI plus Bevacizumab (N=256)	FOLFOXIRI plus Bevacizumab (N=252)	Hazard Ratio or Odds Ratio (95% CI)†	P Value
Progression-free survival				
Progression event — no. of patients (%)	226 (88.3)	213 (84.5)	0.75 (0.62–0.90)	0.003
Months of progression-free survival — median (95% CI)	9.7 (9.3–10.9)	12.1 (10.9–13.2)		
Response — no. (%)				
Complete response	8 (3.1)	12 (4.8)		
Partial response	128 (50.0)	152 (60.3)		
Stable disease	82 (32.0)	62 (24.6)		
Progressive disease	27 (10.6)	16 (6.3)		
Not evaluated	11 (4.3)	10 (4.0)		
Overall response rate				
No. (%)	136 (53.1)	164 (65.1)	1.64 (1.15–2.35)	0.006
95% CI	46.8–59.3	58.8–70.9		
Overall survival				
Deaths — no. (%)	155 (60.5)	131 (52.0)	0.79 (0.63–1.00)	0.054
Months of overall survival — median (95% CI)	25.8 (22.7–30.8)	31.0 (26.9–35.1)		

* CI denotes confidence interval.
† The ratios listed are hazard ratios, except for the overall response rate, for which the odds ratio is shown.

31.0 months in the experimental group and 25.8 months in the control group, which corresponds to a hazard ratio for death of 0.79 (95% CI, 0.63 to 1.00; P=0.054); this decrease did not meet the criterion for statistical significance. At the exploratory analysis adjusting for prognostic variables, the hazard ratio for death with FOLFOXIRI plus bevacizumab was 0.72 (95% CI, 0.56 to 0.94; P=0.01) (Fig. 2B).

SAFETY

Treatment-related grade 3 or 4 adverse events occurring in at least 3% of patients are summarized in Table 3. The incidence of grade 3 or 4 neutropenia, diarrhea, stomatitis, and neurotoxicity (i.e., peripheral neuropathy) was significantly higher in the experimental group than in the control group. No significant differences in bevacizumab-related adverse events were observed between groups. The incidence of serious adverse events was similar in the two groups (19.7% in the control group and 20.4% in the experimental group, P=0.91).

A total of 142 (91.6%) of the deaths in the control group and 121 (92.4%) of the deaths in the experimental group were attributed to disease progression. In each group, a similar number of patients died as a result of adverse events (4 [1.6%] in the control group and 6 [2.4%] in the experimental group).

SUBSEQUENT TREATMENTS

Second-line treatment was administered in 173 patients in the control group and in 166 patients in the experimental group (see Table S5 in the Supplementary Appendix). Among patients receiving a second-line treatment, a higher percentage of patients in the control group than in the experimental group received an oxaliplatin-containing regimen (64% vs. 23%). In the control group, another 14% of patients received oxaliplatin as part of the third-line or fourth-line treatment. In the control group, 31% of patients continued bevacizumab beyond disease progression, as did 30% in the experimental group, and 29% of patients in the control group and 33% in the experimental group received an anti–epidermal growth factor receptor monoclonal antibody as second- or third-line treatment.

DISCUSSION

This phase 3, randomized study showed improved progression-free survival among patients

with metastatic colorectal cancer after treatment with the combination of FOLFOXIRI plus bevacizumab as compared with FOLFIRI plus bevacizumab (hazard ratio for progression, 0.75; 95% CI, 0.62 to 0.90; P=0.003). The median progression-free survival was prolonged by 2.4 months, reaching 12.1 months in the experimental group. Moreover, an absolute increase of 12.0% in response rate was reported, and median overall survival was extended, but not significantly so, by 5.2 months, from 25.8 to 31.0.

In line with the findings in previous trials,[8,9] treatment with FOLFOXIRI or FOLFOXIRI plus bevacizumab was feasible in a multicenter collaboration. The intensification of the treatment was associated with a significant increase in the rates of grade 3 or 4 neurotoxicity, stomatitis, diarrhea, and neutropenia. However, no significant differences between treatment groups in the rates of febrile neutropenia, serious adverse events, or deaths due to treatment-related toxic effects were observed. In our opinion, early recognition and active management of adverse events is crucial. The percentage of bevacizumab-related adverse events was consistent with the percentages in previous trials, and no significant differences between groups were reported, thus showing that chemotherapy intensification does not influence the safety profile of the antiangiogenic agent. A limitation is that we did not assess patients' health-related quality of life.

To exploit the potential benefit of a more intensive treatment without compromising its feasibility, specific selection criteria were adopted. Patients older than 75 years of age were excluded, and for those between 70 and 75 years of age, an ECOG performance status of 0 was required. Subgroup analyses did not reveal any interaction between baseline characteristics and treatment effect, with the exception of previous exposure to adjuvant chemotherapy. Indeed, patients who previously received adjuvant treatment, which contained oxaliplatin in 64% of cases, derived no benefit from treatment intensification. Therefore, patients who have received adjuvant chemotherapy are not ideal candidates for an intensified up-front chemotherapy.

No significant interaction between the extent of the metastatic disease (confined to the liver vs. not confined to the liver) and treatment effect was apparent. In the present trial, most patients had diffuse, extrahepatic disease. We did not focus on the challenge of converting patients with liver metastases into candidates for surgical resection and cannot assess the role of intensified therapy toward that goal.

Table 3. Most Common Grade 3 or 4 Adverse Events.*

Event	FOLFIRI plus Bevacizumab (N=254)	FOLFOXIRI plus Bevacizumab (N=250)	P Value
	no. (%)		
Neutropenia	52 (20.5)	125 (50.0)	<0.001
Febrile neutropenia	16 (6.3)	22 (8.8)	0.32
Diarrhea	27 (10.6)	47 (18.8)	0.01
Stomatitis	11 (4.3)	22 (8.8)	0.048
Nausea	8 (3.2)	7 (2.8)	1.00
Vomiting	8 (3.2)	11 (4.4)	0.49
Asthenia	23 (9.1)	30 (12.0)	0.31
Peripheral neuropathy	0	13 (5.2)	<0.001
Hypertension	6 (2.4)	13 (5.2)	0.11
Venous thromboembolism	15 (5.9)	18 (7.2)	0.59
Serious adverse events	50 (19.7)	51 (20.4)	0.91

* Events listed are those that occurred in at least the 3% of patients in either treatment group.

From a clinical perspective, the up-front concomitant use of the three cytotoxic agents raises questions about possible options for subsequent salvage therapy. Unfortunately, data on the outcome of second and subsequent therapies were not collected systematically in this study. However, 78% of patients who were randomly assigned to receive the experimental treatment received components of the primary regimen as part of their second-line treatment after they had disease progression. The overall survival benefit with the four-drug regimen might not have been observed if the efficacy of these salvage treatments had been compromised. A maintenance phase and a continuum of care for patients with metastatic colorectal cancer are supported by recent results and recommended by major guidelines.[4,13-15]

Another question is whether chemotherapy plus bevacizumab should be the preferred option for patients with nonmutated *RAS* tumors. Preliminary data on triplet chemotherapy plus cetuximab or panitumumab were promising, and randomized studies are ongoing. A recent phase 3, randomized trial[16] comparing FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab showed

no significant difference between treatment groups in the response rate, the primary end point, or progression-free survival in the nonmutated *RAS* subgroup. However, treatment with FOLFIRI plus cetuximab was associated with an improvement in overall survival as compared with FOLFIRI plus bevacizumab. In our trial, the treatment effect was independent of *KRAS* status.

In conclusion, our findings show that 6 months of induction treatment with FOLFOXIRI plus bevacizumab (as compared with FOLFIRI plus bevacizumab), followed by maintenance therapy, significantly improved the efficacy of first-line therapy. The cost was an increase in the incidence of adverse events.

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