

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 3, 2004

VOL. 350 NO. 23

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairouz Kabbinavar, M.D.

ABSTRACT

BACKGROUND

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has shown promising preclinical and clinical activity against metastatic colorectal cancer, particularly in combination with chemotherapy.

METHODS

Of 813 patients with previously untreated metastatic colorectal cancer, we randomly assigned 402 to receive irinotecan, bolus fluorouracil, and leucovorin (IFL) plus bevacizumab (5 mg per kilogram of body weight every two weeks) and 411 to receive IFL plus placebo. The primary end point was overall survival. Secondary end points were progression-free survival, the response rate, the duration of the response, safety, and the quality of life.

RESULTS

The median duration of survival was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 ($P < 0.001$). The median duration of progression-free survival was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo (hazard ratio for disease progression, 0.54; $P < 0.001$); the corresponding rates of response were 44.8 percent and 34.8 percent ($P = 0.004$). The median duration of the response was 10.4 months in the group given IFL plus bevacizumab, as compared with 7.1 months in the group given IFL plus placebo (hazard ratio for progression, 0.62; $P = 0.001$). Grade 3 hypertension was more common during treatment with IFL plus bevacizumab than with IFL plus placebo (11.0 percent vs. 2.3 percent) but was easily managed.

CONCLUSIONS

The addition of bevacizumab to fluorouracil-based combination chemotherapy results in statistically significant and clinically meaningful improvement in survival among patients with metastatic colorectal cancer.

From Duke University, Durham, N.C. (H.H.); Kaiser Permanente, Vallejo, Calif. (L.F.); Genentech, South San Francisco, Calif. (W.N., S.G., E.H., N.F., G.F., B.R., R.R.); Ocala Oncology, Ocala, Fla. (T.C.); Sarah Cannon Cancer Center, Nashville (J.H.); Hematology and Oncology Associates of Northeastern Pennsylvania, Scranton, Pa. (W.H.); Vanderbilt University, Nashville (J.B.); California Pacific Medical Center, San Francisco (A.B.); and the University of California at Los Angeles, Los Angeles (F.K.). Address reprint requests to Dr. Hurwitz at the Department of Medical Oncology and Transplantation, Rm. 3802 Red Zone, Duke South Clinics, Box 3052, Duke University Medical Center, Durham, NC 27710, or at hurwi004@mc.duke.edu.

N Engl J Med 2004;350:2335-42.

Copyright © 2004 Massachusetts Medical Society.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF), a diffusible glycoprotein produced by normal and neoplastic cells, is an important regulator of physiologic and pathologic angiogenesis.¹ Preclinical studies have shown that a murine antihuman monoclonal antibody against VEGF can inhibit the growth of human tumor xenografts,² and a humanized variant of this antibody (bevacizumab [Avastin])³ is being evaluated in clinical trials as a treatment for various cancers.

In addition to its direct antiangiogenic effects, bevacizumab may also improve the delivery of chemotherapy by altering tumor vasculature and decreasing the elevated interstitial pressure in tumors.^{4,5} In a phase 2 trial of the treatment of colorectal cancer, the addition of bevacizumab to fluorouracil plus leucovorin⁶ increased the response rate, the median time to disease progression, and the median duration of survival. The current phase 3 trial was designed to determine whether the addition of bevacizumab to a combination of irinotecan, fluorouracil, and leucovorin (IFL)⁷ improves survival among patients with metastatic colorectal cancer more than does a regimen of IFL plus placebo.

METHODS

PATIENTS

Eligible patients had histologically confirmed metastatic colorectal carcinoma, with bidimensionally measurable disease. Other inclusion criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status⁸ of 0 or 1, a life expectancy of more than three months, and written informed consent. Adequate hematologic, hepatic, and renal function (including urinary excretion of no more than 500 mg of protein per day) was also required.

Exclusion criteria included prior chemotherapy or biologic therapy for metastatic disease (adjuvant or radiosensitizing use of fluoropyrimidines with or without leucovorin or levamisole more than 12 months before study entry was permitted), receipt of radiotherapy within 14 days before the initiation of study treatment, major surgery within 28 days before the initiation of study treatment, clinically significant cardiovascular disease, clinically detectable ascites, pregnancy or lactation, regular use of aspirin (more than 325 mg per day) or other nonsteroidal antiinflammatory agents, preexisting bleeding diatheses or coagulopathy or the need for

full-dose anticoagulation, and known central nervous system metastases.

The protocol was approved by the institutional review boards of all participating institutions and carried out in accordance with the Declaration of Helsinki, current Food and Drug Administration Good Clinical Practices, and local ethical and legal requirements.

STUDY DESIGN

Eligible patients were assigned to treatment with the use of a dynamic randomization algorithm that was designed to achieve overall balance between groups; randomization was stratified according to study center, baseline ECOG performance status (0 vs. 1), site of primary disease (colon vs. rectum), and number of metastatic sites (one vs. more than one). Initially, patients were randomly assigned in a 1:1:1 ratio to receive IFL plus placebo, IFL plus bevacizumab, or fluorouracil and leucovorin plus bevacizumab (Table 1), each of which was to continue until disease progression or unacceptable adverse effects occurred or for a maximum of 96 weeks.

An interim analysis was scheduled to be performed after 300 patients underwent randomization, at which time an unblinded, independent data-monitoring committee was to assess the safety of IFL plus bevacizumab, on the basis of all the available safety information, including the number of deaths in each group, but in the absence of information related to tumor response. If the data-monitoring committee found no untoward adverse events attributable to the addition of bevacizumab to IFL, the enrollment of patients in the group assigned to receive fluorouracil and leucovorin plus bevacizumab was to be discontinued, and additional patients would be randomly assigned in a 1:1 ratio to receive either IFL plus placebo or IFL plus bevacizumab. However, if the data-monitoring committee concluded that the safety profile of IFL plus bevacizumab was unacceptable, assignment to that treatment was to be discontinued, and patients would instead be randomly assigned in a 1:1 ratio to receive either the combination of fluorouracil and leucovorin plus bevacizumab or IFL plus placebo.

Tumor responses and progression were determined with the use of the Response Evaluation Criteria in Solid Tumors.⁹ At the time of disease progression, the treatment assignment was revealed

and patients could be offered second-line treatment. Such patients in the group assigned to bevacizumab-containing treatment had the option to continue bevacizumab during this second-line treatment. No crossovers were allowed in the group given IFL plus placebo. Patients assigned to a treatment containing bevacizumab who had no signs of progressive disease at the end of the 96-week study period could continue to receive bevacizumab in a separate extension study. Patients in a group receiving bevacizumab who had a confirmed complete response or unacceptable adverse effects from chemotherapy could discontinue chemotherapy and receive bevacizumab alone.

Bevacizumab (or placebo) was administered concomitantly with chemotherapy. Doses of bevacizumab and chemotherapy were recalculated if a patient's weight changed by at least 10 percent during the study. Standard intracycle and intercycle dose modifications of irinotecan and fluorouracil (according to the package insert)¹⁰ were permitted in patients with treatment-related adverse events. The doses of leucovorin and bevacizumab were not altered.

In the analysis of survival and subsequent treatment, all patients were followed until death, loss to follow-up, or termination of the study.

ASSESSMENTS

After the baseline evaluation, tumor status was assessed every 6 weeks for the first 24 weeks of the study and then every 12 weeks for the remainder of therapy. All complete and partial responses⁹ required confirmation at least four weeks after they were first noted.

Safety was assessed on the basis of reports of adverse events, laboratory-test results, and vital-sign measurements. Adverse events were categorized according to the Common Toxicity Criteria of the National Cancer Institute, version 2, in which a grade of 1 indicates mild adverse events, a grade of 2 moderate adverse events, a grade of 3 serious adverse events, and a grade of 4 life-threatening adverse events. Prespecified safety measures included the incidence of all adverse events, all serious adverse events, and adverse events that have been associated with bevacizumab — hypertension, thrombosis, bleeding of grade 3 or 4, and proteinuria — as well as diarrhea of grade 3 or 4, and changes from baseline in various laboratory values and vital signs.

Table 1. First-Line Treatment Regimens.*

Treatment	Starting Dose	Schedule
Irinotecan	125 mg/m ² of body-surface area	Once weekly for
Fluorouracil	500 mg/m ²	4 wk; cycle re-
Leucovorin	20 mg/m ²	peated every 6 wk
Placebo		Every 2 wk
Irinotecan	125 mg/m ²	Once weekly for
Fluorouracil	500 mg/m ²	4 wk; cycle re-
Leucovorin	20 mg/m ²	peated every 6 wk
Bevacizumab	5 mg/kg of body weight	Every 2 wk
Fluorouracil	500 mg/m ²	Once weekly for
Leucovorin	500 mg/m ²	6 wk; cycle re-
		peated every 8 wk
Bevacizumab	5 mg/kg	Every 2 wk

* Treatment with fluorouracil, leucovorin, and bevacizumab was discontinued after the safety of adding bevacizumab to the regimen of irinotecan, fluorouracil, and leucovorin was confirmed. Confirmation occurred after the randomization of 313 patients. All drugs were given intravenously.

To monitor the safety of the regimen of IFL plus placebo and of IFL plus bevacizumab, the incidence of death, serious adverse events, diarrhea of grade 3 or 4, bleeding of grade 3 or 4 from any source, and thrombosis was monitored during the study in an unblinded fashion by the data-safety monitoring committee until the completion of recruitment or the time of the interim analysis of efficacy, whichever came first.

STATISTICAL ANALYSIS

The primary outcome measure was the duration of overall survival; survival was measured without regard to subsequent treatments. There was no crossover between groups, however. Secondary outcome measures were progression-free survival, objective response rates (complete and partial responses), the duration of responses, and the quality of life.

For patients who were alive at the time of analysis, data on survival were censored at the time of the last contact. Progression-free survival was defined as the time from randomization to progression or death during the study, with death during the study defined as any death that occurred within 30 days after the last dose of bevacizumab or chemotherapy. For patients without disease progression at the time of the final analysis, data on progression-free survival were censored at the last assessment of tumor status or on day 0 if no further assessment was performed after baseline. Patients without adequate follow-up data were categorized as having no response.

Table 2. Selected Demographic and Baseline Characteristics.*

Characteristic	IFL plus Placebo (N=411)	IFL plus Bevacizumab (N=402)
Sex (%)		
Male	60	59
Female	40	41
Mean age (yr)	59.2	59.5
Race (%)†		
White	80	79
Black	11	12
Other	9	9
Location of center (%)		
United States	99	99
Australia or New Zealand	<1	<1
ECOG performance status (%)		
0	55	58
1	44	41
2	<1	<1
Type of cancer (%)		
Colon	81	77
Rectal	19	23
Number of metastatic sites (%)		
1	39	37
>1	61	63
Prior cancer therapy (%)		
Adjuvant chemotherapy	28	24
Radiation therapy	14	15
Median duration of metastatic disease (mo)	4	4

* There were no significant differences between groups. IFL denotes irinotecan, fluorouracil, and leucovorin, and ECOG Eastern Cooperative Oncology Group.

† Race was attributed by the investigators.

Table 3. Analysis of Efficacy.*

End Point	IFL plus Placebo	IFL plus Bevacizumab	P Value
Median survival (mo)	15.6	20.3	<0.001
Hazard ratio for death		0.66	
One-year survival rate (%)	63.4	74.3	<0.001
Progression-free survival (mo)	6.2	10.6	<0.001
Hazard ratio for progression		0.54	
Overall response rate (%)	34.8	44.8	0.004
Complete response	2.2	3.7	
Partial response	32.6	41.0	
Median duration of response (mo)	7.1	10.4	0.001
Hazard ratio for relapse		0.62	

* IFL denotes irinotecan, fluorouracil, and leucovorin.

To detect a hazard ratio of 0.75 for death in the group given IFL plus bevacizumab as compared with the control group, approximately 385 deaths were required. All calculations were performed with

the log-rank test and involved two-sided P values, with an alpha value of 0.05, a statistical power of 80 percent, and one interim analysis of efficacy.

Interim analyses were conducted in an unblinded fashion by an independent data-monitoring committee. An interim analysis of safety was conducted after the random assignment of approximately 100 patients to each group. A second interim analysis of safety and efficacy was performed after 193 deaths had occurred (half the number of required events). According to the protocol, these interim efficacy analyses were governed by a formal group sequential stopping rule based on an O'Brien–Fleming spending function.

Efficacy analyses were performed according to the intention-to-treat principle. Safety analyses included all patients who received at least one dose of study medication.

The study was designed by Genentech in collaboration with the investigators. Genentech collected and analyzed the data; all authors had access to the primary data. The decision to publish the paper was made by all the investigators. The article was written by Dr. Hurwitz.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between September 2000 and May 2002, 923 patients underwent randomization at 164 sites in the United States, Australia, and New Zealand. After 313 patients had been randomly assigned to one of the three groups — 100 to IFL plus placebo, 103 to IFL plus bevacizumab, and 110 to fluorouracil, leucovorin, and bevacizumab — assignment to the group given fluorouracil, leucovorin, and bevacizumab was halted (the results in this group are not reported). This step was required by the protocol after the first formal interim analysis of safety concluded that the regimen of IFL plus bevacizumab had an acceptable safety profile and that assignment to this group could continue.

The intention-to-treat analysis of the primary end point of overall survival included 411 patients in the group given IFL plus placebo and 402 patients in the group given IFL plus bevacizumab. Table 2 shows selected demographic and baseline characteristics, which were well balanced between the groups. Similar numbers of patients in each group had previously undergone surgery or received radiation therapy or adjuvant chemotherapy for colorectal cancer.

TREATMENT

The median duration of therapy was 27.6 weeks in the group given IFL plus placebo and 40.4 weeks in the group given IFL plus bevacizumab. The percentage of the planned dose of irinotecan that was given was similar in the two groups (78 percent in the group given IFL plus placebo and 73 percent in the group given IFL plus bevacizumab).

As of April 2003, 33 patients in the group given IFL plus placebo and 71 in the group given IFL plus bevacizumab were still taking their assigned initial therapy. The rates of use of second-line therapies that may have affected survival, such as oxaliplatin or metastasectomy, were well balanced between the two groups. In both groups, approximately 50 percent of patients received some form of second-line therapy; 25 percent of all patients received oxaliplatin, and less than 2 percent of patients underwent metastasectomy.

EFFICACY

The median duration of overall survival, the primary end point, was significantly longer in the group given IFL plus bevacizumab than in the group given IFL plus placebo (20.3 months vs. 15.6 months), which corresponds to a hazard ratio for death of 0.66 ($P<0.001$) (Table 3 and Fig. 1), or a reduction of 34 percent in the risk of death in the bevacizumab group. The one-year survival rate was 74.3 percent in the group given IFL plus bevacizumab and 63.4 percent in the group given IFL plus placebo ($P<0.001$). In the subgroup of patients who received second-line treatment with oxaliplatin, the median duration of overall survival was 25.1 months in the group given IFL plus bevacizumab and 22.2 months in the group given IFL plus placebo.

The addition of bevacizumab to IFL was associated with increases in the median duration of progression-free survival (10.6 months vs. 6.2 months; hazard ratio for progression, 0.54, for the comparison with the group given IFL plus placebo; $P<0.001$); response rate (44.8 percent vs. 34.8 percent; $P=0.004$); and the median duration of response (10.4 months vs. 7.1 months; hazard ratio for progression, 0.62; $P=0.001$) (Table 3). Figure 2 shows the Kaplan–Meier estimates of progression-free survival. Treatment effects were consistent across prespecified subgroups, including those defined according to age, sex, race, ECOG performance status, location of the primary tumor, presence or absence of prior adjuvant therapy, duration

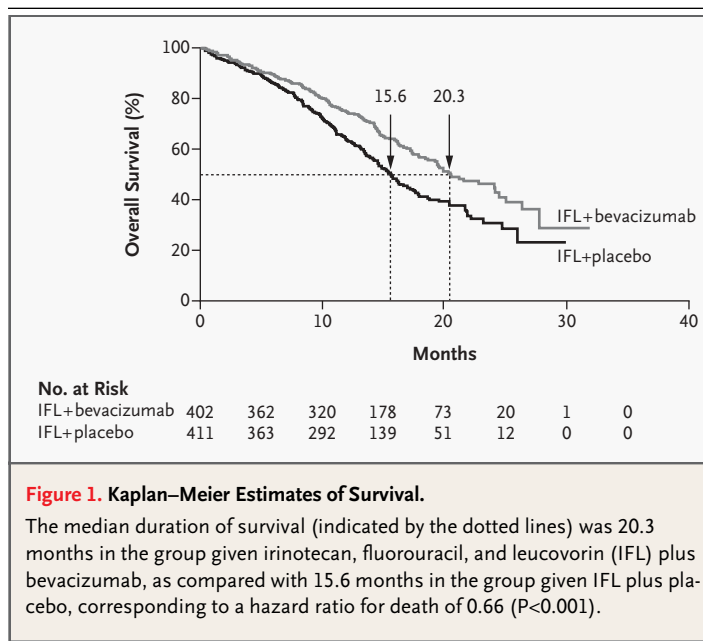


Figure 1. Kaplan–Meier Estimates of Survival.

The median duration of survival (indicated by the dotted lines) was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 ($P<0.001$).

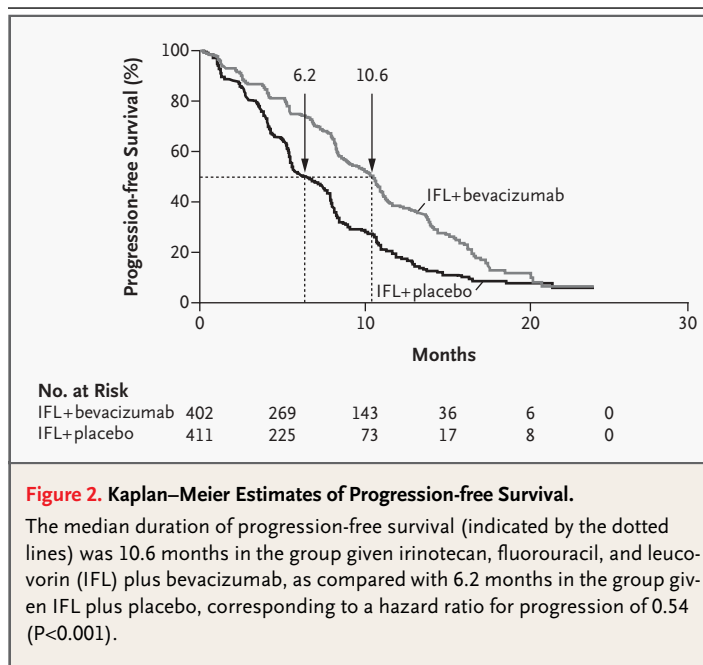


Figure 2. Kaplan–Meier Estimates of Progression-free Survival.

The median duration of progression-free survival (indicated by the dotted lines) was 10.6 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo, corresponding to a hazard ratio for progression of 0.54 ($P<0.001$).

of metastatic disease, number of metastatic sites, years since the diagnosis of colorectal cancer, presence or absence of prior radiotherapy, baseline tumor burden, and serum concentrations of albumin, alkaline phosphatase, and lactate dehydrogenase (data not shown).

SAFETY

Table 4 presents the incidence of selected grade 3 or 4 adverse events during the assigned treatment, without adjustment for the median duration of therapy (27.6 weeks in the group given IFL plus placebo and 40.4 weeks in the group given IFL plus bevacizumab). The incidence of any grade 3 or 4 adverse events was approximately 10 percentage points higher among patients receiving IFL plus bevacizumab than among patients receiving IFL plus placebo, largely because of an increase in the incidence of grade 3 hypertension (requiring treatment) and small increases in the incidence of grade 4 diarrhea and leukopenia. However, there was no significant difference in the incidence of adverse events leading to hospitalization or to the discontinuation of study treatment or in the 60-day rate of death from any cause.

Phase 1 and 2 trials had identified hemorrhage, thromboembolism, proteinuria, and hypertension as possible bevacizumab-associated adverse effects. However, in our study, only the incidence of hypertension was clearly increased in the group given IFL plus bevacizumab, as compared with the group given IFL plus placebo. All episodes of hypertension were manageable with standard oral antihypertensive agents (e.g., calcium-channel blockers, angiotensin-converting-enzyme inhibitors, and diuretics). There were no discontinuations of bevacizumab therapy, hypertensive crises, or deaths related to hypertension in the bevacizumab group.

Rates of grade 2 or 3 proteinuria (there were no episodes of grade 4 proteinuria or nephrotic syndrome) and grade 3 or 4 bleeding from any cause were similar in the two groups, although all three cases of grade 4 bleeding were in the group given IFL plus bevacizumab. The incidence of all venous and arterial thrombotic events was 19.4 percent in the group given IFL plus bevacizumab and 16.2 percent in the group given IFL plus placebo ($P=0.26$).

Gastrointestinal perforation occurred in six patients (1.5 percent) receiving IFL plus bevacizumab. One patient died as a direct result of this event, whereas the other five recovered (three of them were able to restart treatment without subsequent complications). Of the six patients with a perforation, three had a confirmed complete or partial response to IFL plus bevacizumab. Factors other than the study treatment that may have been associated with gastrointestinal perforation were colon surgery within the previous two months in two patients and peptic-ulcer disease in one patient.

Table 4. Selected Adverse Events.*		
Adverse Event	IFL plus Placebo (N=397)	IFL plus Bevacizumab (N=393)
	<i>percent</i>	
Any grade 3 or 4 adverse event	74.0	84.9†
Adverse event leading to hospitalization	39.6	44.9
Adverse event leading to discontinuation of treatment	7.1	8.4
Adverse event leading to death	2.8	2.6
Death within 60 days	4.9	3.0
Grade 3 or 4 leukopenia	31.1	37.0
Grade 3 or 4 diarrhea	24.7	32.4
Hypertension		
Any	8.3	22.4†
Grade 3	2.3	11.0†
Any thrombotic event	16.2	19.4
Deep thrombophlebitis	6.3	8.9
Pulmonary embolus	5.1	3.6
Grade 3 or 4 bleeding	2.5	3.1
Proteinuria		
Any	21.7	26.5
Grade 2	5.8	3.1
Grade 3	0.8	0.8
Gastrointestinal perforation	0.0	1.5

* Data were not adjusted for differences in the median duration of therapy between the group given irinotecan, fluorouracil, and leucovorin (IFL) plus placebo and the group given IFL plus bevacizumab (27.6 weeks vs. 40.4 weeks).

† $P<0.01$. Only patients who received at least one study-drug treatment are included.

DISCUSSION

The results of this phase 3 study provide support for the use of antiangiogenic agents in the treatment of cancer. When this trial was designed and initiated, the addition of irinotecan to fluorouracil and leucovorin had just been shown to prolong survival in patients with metastatic colorectal cancer and was considered the new standard first-line therapy for this disease. Our randomized trial was designed to compare the relative safety and efficacy of two regimens for metastatic colorectal cancer: IFL alone and with bevacizumab, a humanized monoclonal antibody against VEGF.

We found that the addition of bevacizumab to IFL improved overall survival. Furthermore, the in-

crease of 4.7 months in the median duration of survival attributable to bevacizumab is as large as or larger than that observed in any other phase 3 trial for the treatment of colorectal cancer.¹¹ The median survival of 20.3 months in the bevacizumab-treated population occurred in spite of the limited availability of oxaliplatin for second-line therapy during this trial.

As compared with IFL alone, the regimen of IFL plus bevacizumab increased progression-free survival from a median of 6.2 months to 10.6 months, the overall response rate from 34.8 percent to 44.8 percent, and the median duration of response from 7.1 months to 10.4 months. These improvements are clinically meaningful. We would not have predicted that the absolute improvement in the response rate of 10 percent with IFL plus bevacizumab would have been associated with an increase in survival of this magnitude. This observation suggests that the primary mechanism of bevacizumab is the inhibition of tumor growth, rather than cytoreduction.

This clinical benefit was accompanied by a relatively modest increase in side effects of treatment, which were easily managed. There was an absolute increase of approximately 10 percent in the overall incidence of grade 3 and 4 adverse effects, attributable largely to hypertension requiring treatment, diarrhea, and leukopenia. The 60-day rates of death from any cause, hospitalization, and discontinuation of treatment were not significantly increased by the addition of bevacizumab to IFL.

Previous phase 1 and 2 clinical trials suggested that treatment with bevacizumab alone or with chemotherapy resulted in an increased incidence of thrombosis, bleeding, proteinuria, and hypertension.^{6,12} With the exception of hypertension, we did not find an excess of these side effects as compared with their incidence in the group given IFL plus placebo — thus highlighting the importance of randomized, placebo-controlled studies for the evaluation of safety as well as efficacy. One new potential adverse effect that we did find was gastrointestinal perforation. This complication was uncommon and had variable clinical presentations. Severe bowel complications, particularly in patients with neutropenia, have been reported with IFL and other chemotherapy regimens for colorectal cancer,^{7,13} and in one series, fistulas were reported in over 2 percent of patients treated with fluorouracil-based regimens.¹⁴ No such events oc-

curred in the group given IFL plus placebo, whereas six cases were observed in the group given IFL plus bevacizumab (1.5 percent), sometimes in the setting of overall tumor responses. Although three of these six patients were able to restart treatment without subsequent complications, one patient died and two discontinued therapy permanently as a result of this complication. VEGF is associated with wound healing,^{15,16} and VEGF inhibitors can inhibit dermal-wound angiogenesis in patients with cancer. Although infrequent and associated with colorectal cancer and its complications, the risk of this adverse event may be increased by bevacizumab therapy.

Recently, oxaliplatin has been approved in the United States for both second-line and first-line treatment of colorectal cancer.¹⁷ Although there are not yet sufficient long-term data on the efficacy of bevacizumab in combination with oxaliplatin-based regimens, studies addressing the role of these combinations are ongoing.¹⁸ The improvement in the clinical outcome afforded by the addition of bevacizumab to IFL or to fluorouracil alone^{6,19} suggests that blocking VEGF may be a broadly applicable approach to the treatment of colorectal cancer.

In summary, the addition of bevacizumab to bolus IFL conferred a clinically meaningful and statistically significant improvement in overall survival, progression-free survival, and response rate. These results suggest that bevacizumab plus fluorouracil-based chemotherapy should be considered a new option for the treatment of metastatic colorectal cancer.

Funded by Genentech. Dr. Hurwitz was supported in part by a Career Development Grant (K23 CA085582-04).

Dr. Hurwitz reports having received consulting fees from Genentech, Pfizer, and Imclone; lecture fees from Genentech and Pfizer; and research support from AstraZeneca, Cephalon, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, and Sanofi-Synthelabo; Dr. Cartwright consulting fees from Genentech; Dr. Hainsworth lecture fees from Genentech and research support from Genentech, Sanofi-Synthelabo, and Novartis; Dr. Heim consulting fees from Genentech and having equity in Genentech; Dr. Berlin consulting fees from Genentech and Pfizer and lecture fees from Sanofi-Synthelabo; and Dr. Kabbavar lecture fees from Genentech. Ms. Griffing and Ms. Rogers and Drs. Ferrara, Novotny, Holmgren, and Fyfe are employees of Genentech and report having equity in Genentech. Dr. Ross was an employee of Genentech during the trial.

We are indebted to the patients who participated in this study, their families, and their support teams; to the health care teams at each center; to the members of the Data and Safety Monitoring Board — Richard Schilsky (chair), Robert Mayer, Alan Venook, and Lee-Jen Wei — and to the members of the Data Coordinating Center (Statistics Collaborative) for their invaluable assistance in the conduct of this study.

REFERENCES

1. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003;9:669-76.
2. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* 1993;362:841-4.
3. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res* 1997;57:4593-9.
4. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med* 2001;7:987-9.
5. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med* 2004;10:145-7.
6. Kabbinnar F, Hurwitz H, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;21:60-5.
7. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000;343:905-14.
8. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205-16.
10. CPT-11 (Camptosar). Kalamazoo, Mich.: Pharmacia & Upjohn, 2002 (package insert).
11. 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* 2004;22:23-30.
12. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial cell growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427-34.
13. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001;19:3801-7.
14. Tebbutt NC, Norman AR, Cunningham D, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. *Gut* 2003;52:568-73.
15. Nissen NN, Polverini PJ, Koch AE, Volin MV, Gamelli RL, DiPietro LA. Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. *Am J Pathol* 1998;152:1445-52.
16. Hurwitz H, Holden SN, Eckhardt SG, et al. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF signaling, in patients with solid tumors. *Prog Proc Am Soc Clin Oncol* 2002;21:82. abstract.
17. Oxaliplatin. (Eloxatin). New York: Sanofi-Synthelabo, 2004 (package insert).
18. Benson AB, Catalano PJ, Meropol NJ, O'Dwyer PJ, Giantonio BJ. Bevacizumab (anti-VEGF) plus FOLFOX4 in previously treated advanced colorectal cancer (advCRC): an interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200. *Prog Proc Am Soc Clin Oncol* 2003;22:243. abstract.
19. Hurwitz H, Fehrenbacher L, Cartwright T, et al. A phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC: efficacy results in arm 3 (5-FU/LV/BV) and other exploratory analyses. Presented at the 94th AACR Annual Meeting, Washington, D.C., July 11-14, 2003. abstract. (Accessed on May 10, 2004, at <http://www.aacr.org/1132ag.asp>.)

Copyright © 2004 Massachusetts Medical Society.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal's* Editorial Offices.