The addition of oxaliplatin and irinotecan to the armamentarium for the treatment of colorectal cancer (CRC) has resulted in significant improvements in response rates and survival. Targeted therapies directed at the epidermal growth factor pathway and the vascular endothelial growth factor pathway are beginning to play a role in the treatment of CRC. Bevacizumab is a monoclonal antibody that has been evaluated in randomized studies. In a randomized phase II study, the combination of 5-fluorouracil/leucovorin (5-FU/LV) was compared with 5-FU/LV plus bevacizumab, and a randomized phase III trial evaluated the addition of bevacizumab to the irinotecan/5-FU/LV (IFL) regimen compared with IFL plus placebo. The results of these studies will be reviewed in detail. The role of bevacizumab with other first-line combinations in the treatment of patients with advanced CRC is being evaluated in ongoing clinical trials. Additionally, the activity of bevacizumab is being evaluated for use in the second-line treatment setting for patients with CRC.

Globally, colorectal cancer (CRC) is the third most frequent cancer, with an estimated 945,000 new cases diagnosed and an estimated 492,000 deaths from the disease in 2000.1 There were approximately 2.4 million patients worldwide in 2000 that had been diagnosed with CRC in the previous 5 years. The cornerstone of chemotherapy in CRC has been fluoropyrimidine-based for over 50 years; however, standard care for CRC has shifted in recent years to combination regimens that include oxaliplatin or irinotecan, such as FOLFOX (5-fluorouracil [5-FU]/leucovorin [LV]/oxaliplatin) and FOLFIRI (infusional 5-FU/LV/irinotecan), because these regimens have showed improved survival in patients with metastatic CRC. The development of target therapies offers the potential for improving survival, with a decreased incidence of severe toxicities.

Alterations in cell physiology that dictate malignant growth include unlimited cell growth, insensitivity to anti-growth signals, reduced sensitivity to apoptosis, functional immortality, development and maintenance of vasculature (angiogenesis), and invasion and metastasis.2 For several decades, researchers proposed that new blood vessel formation, or angiogenesis, was important for cancer growth. It is now known that angiogenesis is one characteristic that is shared by most, if not all types, of human cancers. It has been linked to increased growth and metastatic potential and therefore has become an attractive therapeutic target. Angiogenesis is carefully regulated and occurs as an orderly series of events via an angiogenic switch. Tumors appear to activate this angiogenic switch by affecting the balance of angiogenic inhibitors and inducers that allow tumor cell proliferation to exceed apoptosis.2 New blood vessels formed by angiogenesis in tumors are structurally and functionally different than their normal counterparts and are characterized as being leaky and tortuous, containing fewer pericytes than normal vessels, exhibiting the presence of growth and survival factors, and having a preferential expression of key endothelial cell factors such as integrins. They also differ in their gene composition. Figure 1 shows the differences between normal and tumor vasculature.

One of the primary activators of angiogenesis is vascular endothelial growth factor (VEGF). VEGF increases vascular permeability and stimulates endothelial cell proliferation. Many tumors, including CRC, show an increased expression of VEGF compared with corresponding normal tissue. In CRC, VEGF also plays a role in prognosis. Preclinical data show that microvessel density and VEGF levels correlate with recurrence probability, showing that there is a link between VEGF expression and angiogenesis, and clinical outcome.3 Anti-angiogenic agents that are being developed for use in
various types of cancers fall into three primary classes of agents that: (1) specifically inhibit new vessels, (2) target and destroy existing tumor blood vessels, and (3) are cytotoxic to tumor and endothelial cells. Integration of these agents into first-line therapy in the treatment of patients with recurrent or metastatic CRC may provide additional benefit over that seen with traditional cytotoxic agents. Because these antiangiogenic agents can target the vasculature of the tumor directly and normalize the vasculature before cytotoxic destruction, efficacy may be increased by increasing access of chemotherapy to the tumor. In addition, these antiangiogenic agents may possess the ability to overcome acquired drug resistance because they target the tumor vasculature, which is genetically stable. Finally, traditional cytotoxic agents and anti-angiogenic agents may potentially demonstrate synergy by targeting both the tumor and tumor-stromal compartments.

Bevacizumab is a recombinant humanized monoclonal antibody that binds to and inhibits the VEGF that plays a critical role in the formation of new blood vessels to the tumor. In the United States, bevacizumab is approved, in combination with an intravenous (IV) 5-FU–based chemotherapy, for the first-line treatment of patients with metastatic carcinoma of the colon or rectum.

The integration of bevacizumab into fluoropyrimidine-based regimens began in a randomized phase II trial comparing bevacizumab (at two dose levels) plus 5-FU and LV with 5-FU/LV alone as first-line therapy in patients with metastatic CRC, to determine time to disease progression (TTP) and response rate (RR). Secondary endpoints included overall survival (OS), and duration of response. A total of 104 patients were enrolled in the trial. All patients received 5-FU 500 mg/m² plus LV 200 mg/m² weekly for 6 weeks followed by 2 weeks’ rest; 36 patients received 5-FU/LV alone, 35 patients received 5-FU/LV and bevacizumab 5 mg/kg every 2 weeks, and 33 patients received 5-FU/LV and bevacizumab 10 mg/kg, every 2 weeks. Median TTP was 5.2 months in patients who received 5-FU/LV alone compared with 9 months in patients who received 5-FU/LV plus bevacizumab 5 mg/kg and 7.2 months in patients who received 5-FU/LV plus bevacizumab 10 mg/kg. The differences in TTP were statistically significant between patients who received 5-FU/LV alone and those who received 5-FU/LV plus bevacizumab 5 mg/kg ($P = .005$, log-rank). The overall RR was 32%; patients who received 5-FU/LV alone had an overall RR of 17%, compared with 40% in patients who received 5-FU/LV plus bevacizumab 5 mg/kg, and 24% in patients who received 5-FU/LV plus bevacizumab 10 mg/kg. In addition, median survival was longer in patients who received 5-FU/LV plus bevacizumab: 13.8 months in patients who received 5-FU/LV alone, 21.5 months in patients who received 5-FU/LV plus bevacizumab 5 mg/kg, and 16.1 months in patients who received 5-FU/LV plus bevacizumab 10 mg/kg. The efficacy data for this study are summarized in Table 1. Thrombosis was the most significant adverse event and was fatal in one patient who died as a result of a pulmonary embolus and received 5-FU/LV plus bevacizumab 10 mg/kg. Three additional patients discontinued bevacizumab therapy because of thrombosis.

Hurwitz et al conducted a randomized phase III study of bevacizumab in combination irinotecan/bolus 5-FU/LV (IFL) as first-line therapy in patients with metastatic CRC. The
primary endpoint of the study was OS and secondary endpoints included progression-free survival, RR, duration of response, safety, and quality of life. Initially, accrued patients were randomly assigned to one of three study arms: (1) IFL plus placebo, (2) IFL plus bevacizumab, or (3) 5-FU/LV plus bevacizumab. An interim analysis was conducted after accrual of approximately 100 patients in each of the three study arms, and at this time, the third arm, 5-FU/LV plus bevacizumab, was discontinued because no unexpected toxicities were seen with the combination of IFL and bevacizumab. All patients then received IFL (irinotecan 125 mg/m², 5-FU 500 mg/m² and leucovorin 20 mg/m² weekly for 4 weeks of a 6-week cycle) with either bevacizumab or placebo. Patients receiving bevacizumab could continue therapy past disease progression in combination with second-line therapy. A total of 923 patients were enrolled in the study; 402 patients received IFL plus bevacizumab, 411 patients received IFL plus placebo; and 110 patients received 5-FU/LV plus bevacizumab. Primary inclusion criteria included patients with previously untreated, measurable metastatic CRC who had an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, renal, and hepatic function. Key exclusion criteria included central nervous system metastasis, clinically significant atherosclerotic vascular disease, adjuvant therapy within the previous 12 months, proteinuria >500 mg/24 hours, and full-dose anti-coagulation therapy or history of coagulopathy.

The primary OS endpoint was significantly longer in the IFL plus bevacizumab group (20.3 months) than in the IFL plus placebo group (15.6 months; P < .001), representing a reduction in the risk of death of 34% in patients receiving bevacizumab with IFL. Median duration of progression-free survival was 10.6 months in patients who received bevacizumab in combination with 6.2 months in patients who received IFL plus placebo, corresponding with a hazard ratio for progression of 0.54 (P < .001). The RRs in the two groups were 44.8% versus 34.8% (P = .004) and the median duration of response was 10.4 months versus 7.1 months for the IFL plus bevacizumab and IFL plus placebo groups, respectively. These efficacy data are summarized in Table 2.8

The incidence of grade 3 or 4 adverse events was approximately 10% higher in patients who received IFL plus bevacizumab compared with those with IFL plus placebo, due in part to a higher incidence of grade 3 hypertension requiring treatment and an increased incidence of grade 4 diarrhea and leukopenia. There were no significant differences in the incidence of adverse events leading to hospitalization, discontinuation from study treatment, or in the 60-day death rate between the two groups. Although phase I and II studies had identified increased hemorrhage, thromboembolism, proteinuria, and hypertension as possible bevacizumab-related adverse events, in this study, only the incidence of hypertension was increased in patients who received bevacizumab plus IFL compared with those who received IFL plus placebo. The incidence of grade 3 hypertension in patients receiving IFL plus bevacizumab was 11% versus 2.3% in patients who received IFL with placebo.

At the 2004 annual meeting of the American Society of Clinical Oncology (New Orleans), a retrospective subset analysis was presented on the impact of post-progression therapy on survival of patients in this randomized phase III trial.9 Post-progression therapy was left to the discretion of the investigator, including continuation of bevacizumab in patients who had received it as first-line therapy. In patients who received IFL plus placebo, 122 patients received a non-oxaliplatin-based post-progression therapy, and 109 received oxaliplatin-based therapy. Of the patients who received IFL plus bevacizumab, 125 patients received a non-oxaliplatin-based post-progression therapy and 97 patients received an oxaliplatin-based therapy. Median survival was 15.8 months in patients who received IFL and placebo as first-line therapy and a non-oxaliplatin-based regimen as second-line therapy, and 22.2 months in patients who re-

### Table 1 Efficacy in Randomized Phase II Trial With Bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>MS (mos)</th>
<th>Median TTP (mos)</th>
<th>RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU/LV</td>
<td>13.8</td>
<td>5.2</td>
<td>17</td>
</tr>
<tr>
<td>5-FU/LV plus bevacizumab 5 mg/kg</td>
<td>21.5</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>5-FU/LV plus bevacizumab 10 mg/kg</td>
<td>16.1</td>
<td>7.2</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU/LV, 5-fluorouracil/leucovorin; MS, median survival; RR, response rate; TTP, time to disease progression.

Data from Kabbinavar et al.7

### Table 2 Efficacy in Randomized Phase III Trial With Bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>MS (mos)</th>
<th>Median PFS (months)</th>
<th>RR (%)</th>
<th>Median Duration of Response (mos)</th>
<th>1-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFL plus placebo</td>
<td>15.6</td>
<td>6.2</td>
<td>34.8 (2.2% CR, 32.6% PR)</td>
<td>7.1</td>
<td>63.4</td>
</tr>
<tr>
<td>IFL plus bevacizumab</td>
<td>20.3</td>
<td>10.6</td>
<td>44.8 (3.7% CR, 41% PR)</td>
<td>10.4</td>
<td>74.3</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; IFL, irinotecan/5-fluorouracil/leucovorin; MS, median survival; PFS, progression-free survival; PR, partial response; RR, response rate.

Data from Hurwitz et al.8
received an oxaliplatin-based post-progression therapy. Of the patients who had received IFL and bevacizumab as first-line therapy and a non-oxaliplatin–based second-line therapy, median survival was 19.6 months, and 25.1 months in patients who received an oxaliplatin-based second-line therapy. These results suggest that a treatment strategy incorporating all active agents with demonstrated activity in metastatic CRC (5-FU, LV, irinotecan, oxaliplatin, and bevacizumab), optimizes OS when administered over the course of disease.9

**Ongoing Clinical Trials of Bevacizumab With Combination Regimens**

Based on the recent data from Goldberg et al10 that showed an improved median survival with FOLFOX compared with IFL, 19.5 months and 15 months (P = .001), respectively, Giantonio et al11 of the Eastern Cooperative Oncology Group recently completed accrual to a randomized phase III (E3200) trial evaluating the use of bevacizumab in combination with FOLFOX4 to ascertain if an additional survival benefit can be obtained with the addition of bevacizumab to FOLFOX4. Patients received bevacizumab 10 mg/kg in combination with FOLFOX4 (oxaliplatin 85 mg/m² on day 1 with LV 200 mg/m² over 2 hours and 5-FU 400 mg/m² IV bolus followed by 5-FU 600 mg/m² continuous infusion for 22 hours, days 1 and 2), or FOLFOX4 or bevacizumab alone. (The bevacizumab single-agent arm was closed to accrual early because an interim analysis showed that the efficacy of single-agent bevacizumab was inferior to that of the other two arms.) The primary endpoint of the study was duration of survival and the secondary endpoint was overall RR. Patients must have been previously treated with a fluoropyrimidine and single-agent irinotecan or an irinotecan-based regimen. At the time of the preliminary safety analyses, 757 patients were evaluable for toxicity. Six deaths have been reported as possibly related to treatment: two patients experienced sudden death (n = 2), pneumonitis (1), aspiration (1), central nervous system hemorrhage (1), and bowel perforation (1). Based on these preliminary data, the investigators concluded that the addition of bevacizumab to FOLFOX4 does not significantly alter the toxicity profile of FOLFOX4. Also, the preliminary safety data support the previously described association of bleeding and hypertension with bevacizumab; however, an increased risk of thromboembolism is not yet evident.11

Another randomized phase III trial, Southwest Oncology Group S0303, evaluated a modified FOLFOX6 regimen of oxaliplatin 85 mg/m², LV 400 mg/m², and 5-FU 400 mg/m² IV bolus on day 1, followed by 5-FU 2.4 mg/m² continuous infusion over 46 to 48 hours on days 1 through 3 with bevacizumab versus oxaliplatin 130 mg/m² on day 1 with capecitabine 1,000 mg/m² on days 1 through 15 every 3 weeks (CAPOX), with bevacizumab as first-line therapy in patients with previously untreated recurrent or metastatic CRC. This study was closed to accrual in September 2004 because it was difficult to accrue patients who did not have a guarantee of receiving bevacizumab.12

Other ongoing clinical trials are evaluating the use of bevacizumab with other combinations. A randomized phase III study is comparing capecitabine plus oxaliplatin (XELOX) with or without bevacizumab with FOLFOX4 with or without bevacizumab. Study objectives are to show that: (1) the combination of XELOX with or without bevacizumab is at least as effective as the combination of FOLFOX4 with or without bevacizumab in terms of TTP or death in previously untreated patients with metastatic CRC, and (2) bevacizumab in combination with either XELOX or FOLFOX4 is better than chemotherapy alone.13

A second ongoing randomized phase III clinical trial compares the efficacy and safety of bevacizumab and oxaliplatin combined with a fluoropyrimidine in patients with metastatic or recurrent CRC. Patients will be randomly assigned to receive bevacizumab and oxaliplatin with one of two dose levels of 5-FU and LV, or a combination of bevacizumab, oxaliplatin, and capcitabine. Accrual for this study is under way.14

Finally, bevacizumab is also being investigated in combination with other novel agents. A randomized phase II trial is evaluating the combination of bevacizumab and cetuximab, with or without irinotecan, to evaluate the TTP, objective RR, OS, safety, tolerability, and adverse event profiles in patients with irinotecan-refractory metastatic CRC. An additional objective is to correlate a panel of molecular markers with clinical outcome in patients treated with the two regimens.15

**Discussion**

It is clear that the addition of bevacizumab to the combination of 5-FU/LV or IFL significantly improves survival when administered as first-line therapy to patients with recurrent or metastatic CRC. Questions remain as to the utility of bevacizumab when administered in combination with other 5-FU-containing regimens, and when administered as second-line therapy. Recently completed or ongoing studies are evaluating the efficacy and safety of bevacizumab in combination with other 5-FU–containing regimens (eg, FOLFOX, XELOX) and will determine whether the survival benefit seen with bevacizumab in combination with 5-FU/LV or IFL will also be observed with other 5-FU–based regimens. Clinical trials are also investigating the utility of bevacizumab as a component of a 5-FU–based regimen to determine if the survival benefit seen in patients with advanced CRC as first-line therapy will occur in CRC patients who receive it as second-line therapy as well. Finally, clinical trials are needed to investigate the effectiveness of bevacizumab in other tumor types.

**References**

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