

# Integrating targeted agents into planning strategies for the treatment of metastatic colorectal cancer

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The introduction of the targeted agents bevacizumab and cetuximab in 2004 has had a significant impact on the management of metastatic colorectal cancer (mCRC). These targeted agents allow clinicians to offer more treatment options and lines of therapy, as well as to extend the duration of therapy. Moreover, the toxicities of the targeted agents generally do not overlap with those of the cytotoxic agents. Bevacizumab is recommended for use in all five first-line regimens for patients with mCRC who can tolerate intensive therapy; cetuximab is recommended for use in later-line therapies. Evidence from key clinical trials shows bevacizumab can achieve a significant survival benefit, and cetuximab has clear single-agent activity and induces responses in a subset of patients; it appears to have a special utility in resensitizing patients to irinotecan. The integration of bevacizumab and cetuximab into first-, second-, and later-line therapies continues to be explored in ongoing trials. Other novel agents that target the epidermal growth factor receptor, the vascular endothelial growth factor receptor, and other growth factor receptor pathways are also well along in clinical development.

**T**he introduction of the targeted agents bevacizumab (Avastin) and cetuximab (Erbix) in 2004 had a significant impact on the management of metastatic colorectal cancer (mCRC). These targeted agents, so-called because they are directed at components of pathways critical to neoplastic transformation, allow clinicians to offer more treatment options and more lines of therapy, as well as to extend the duration of therapy. In the case of cetuximab, it allows re-exposure to the cytotoxic agent irinotecan (Camptosar). Although the toxicities of targeted agents generally do not overlap with those of the cytotoxic agents, they present a new set of management challenges for oncologists.

This article summarizes the current use of the targeted agents bevacizumab and cetuximab in mCRC, with emphasis on their use with cytotoxic agents.

## **Bevacizumab: interrupting the neoplastic process**

Bevacizumab, a humanized monoclonal antibody, targets vascular endothelial growth fac-

tor (VEGF), which is markedly upregulated in mCRC and other malignant tumors. Its mechanism of action is not completely understood. Bevacizumab may exert its antitumor activity primarily via a direct antiangiogenic mechanism or by altering tumor vasculature and vascular permeability. The latter effect could reduce tumor interstitial pressure and thereby may enhance delivery of chemotherapy to the tumor. In mCRC, bevacizumab does not appear to be active as a single agent, although single-agent activity has been observed in some solid tumors, including renal cell and ovarian carcinomas. Its most effective use is in combination with chemotherapy.<sup>1-4</sup> In addition to its activity with both irinotecan- and oxaliplatin (Eloxatin)-based combination chemotherapy in CRC, it also shows promising activity in combination with the targeted agent cetuximab.<sup>5</sup>

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**TABLE 1**  
Efficacy of first-line IFL plus bevacizumab therapy

Outcome	IFL + placebo	IFL + bevacizumab	P value
Median overall survival, mo	15.6	20.3	< 0.001
One-year survival rate, %	63.4	74.3	< 0.001
Progression-free survival, mo	6.2	10.6	< 0.001
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

IFL = irinotecan and bolus 5-fluorouracil/leucovorin  
From Hurwitz et al<sup>7</sup>

The 2006 National Comprehensive Cancer Network (NCCN) guidelines incorporate the use of bevacizumab in all five recommended first-line regimens in patients with advanced or metastatic disease who can tolerate intensive therapy. Bevacizumab is recommended for use with 5-fluorouracil/leucovorin (5-FU/LV), irinotecan or oxaliplatin and infusional 5-FU/LV (FOLFIRI or FOLFOX), irinotecan and bolus 5-FU/LV (IFL), and capecitabine plus oxaliplatin (CAPOX).<sup>6</sup>

### Bevacizumab: benefits appear to be greater in first-line regimens

The pivotal phase III trial by Hurwitz and colleagues, which involved 813 patients with previously untreated mCRC, was designed to show whether the addition of bevacizumab to the IFL regimen improved survival.<sup>7</sup> The results showed statistically significant improvement in all clinical endpoints, including increases in overall survival (OS), response rate (RR), median duration of response, and progression-free survival (PFS) in patients who received first-line bevacizumab and IFL (Table 1). Treatment effects did not differ in any of the predefined subgroups, including age, race, sex, number of metastatic sites, and presence or absence of prior adjuvant therapy or radiotherapy. The reported median OS of 20.3 months for the IFL plus bevacizumab group

was the longest reported at that time for a first-line trial of chemotherapy in mCRC.<sup>7</sup>

This trial's design included initiation of second-line therapy at disease progression. Patients who experienced disease progression following first-line treatment with IFL and bevacizumab and then received an oxaliplatin-containing regimen had an even longer median OS—25.1 months—the longest median OS achieved at that time with first- and second-line therapy in a trial in mCRC.<sup>7</sup> Hedrick and colleagues noted that a treatment strategy incorporating all three active agents (irinotecan, oxaliplatin, and bevacizumab) over the course of mCRC improves OS.<sup>8</sup> These results further suggest that second-line therapy also benefits OS in mCRC.<sup>9</sup>

It is important to note that Hurwitz and colleagues administered irinotecan with bolus 5-FU/LV (the IFL regimen). Today, however, the standard of care is to administer FOLFIRI. It is plausible that the outcomes might have been further improved had the FOLFIRI regimen been used instead of IFL.

In the Eastern Cooperative Oncol-

ogy Group (ECOG) 3200 study, the use of bevacizumab with an oxaliplatin-containing regimen was explored in the second-line setting. The study population included 822 patients who had undergone a 5-FU-based therapy, mostly bolus, and irinotecan, either separately or together, but who had not received bevacizumab. Second-line therapy was bevacizumab alone, FOLFOX alone, or FOLFOX plus bevacizumab. The FOLFOX plus bevacizumab group had a small but statistically significant improvement in median OS compared with the FOLFOX-alone group (12.5 vs 10.7 months;  $P = 0.002$ ; Table 2). The bevacizumab-alone arm in this trial was terminated prematurely due to concerns of inferior efficacy.<sup>10</sup>

The Three Regimens of Eloxatin Evaluation (TREE)-2 trial is assessing bevacizumab in first-line combination chemotherapy with oxaliplatin. It is a small extension of TREE-1, which compared oxaliplatin and bolus, infusional, or oral fluoropyrimidine regimens in first-line use and reported a similar median OS in all treatment groups. Interim TREE-2 results show that adding bevacizumab increased the RR in all groups, but OS data have not yet been reported. A cross-study comparison showed that overall RR improved from 39% among those who received modified FOLFOX in TREE-1 to 49% in those who received this regimen plus bevacizumab in TREE-2.<sup>11</sup>

### Bevacizumab in later-line therapies

Bevacizumab shows greater efficacy when used as earlier-line therapy rather than in later-line settings.

**TABLE 2**  
Efficacy of bevacizumab added to FOLFOX4 in ECOG study 3200

	FOLFOX4 + bevacizumab (n = 290)	FOLFOX4 + placebo (n = 289)	P value
Median overall survival, mo	12.5	10.7	0.002
Progression-free survival, mo	7.4	5.5	0.0003

From Giantonio et al<sup>10</sup>

A recent compassionate-use study reported only a small RR when bevacizumab plus 5-FU/LV was given as third-line therapy to 350 patients who did not respond to previous irinotecan- and oxaliplatin-containing regimens.<sup>12</sup> The benefit of the continued use of bevacizumab after first-line therapy is uncertain. In a phase II trial, a cooperative group led by the Southwest Oncology Group (SWOG) proposes to evaluate continuing versus stopping bevacizumab as part of second-line chemotherapy after patients progress on first-line FOLFOX plus bevacizumab. Because bevacizumab has minimal efficacy as a single agent in mCRC, it is recommended that it be discontinued as a single agent if chemotherapy is discontinued due to toxicity.

### Bevacizumab: toxicity profile

The toxicities of the targeted agents generally do not overlap with those of the cytotoxic agents; they do, however, present unique clinical challenges for clinicians and oncology nurses (Table 3). Bevacizumab's toxicity profile includes hypertension. In a key trial by Hurwitz and colleagues, 22% of patients who were administered bevacizumab had hypertension (50% of these patients had grade 3 hypertension) and were managed with oral antihypertensive medications.<sup>7</sup> This study also revealed a risk of gastrointestinal perforation in patients receiving bevacizumab. VEGF is associated with wound healing, as it promotes blood vessel growth; as such, VEGF inhibitors can inhibit dermal-wound angiogenesis and potentially wound healing in patients with CRC. There is an increased risk of wound-healing complications in patients treated with bevacizumab. Bevacizumab therapy should not be initiated until 1 month after surgery or until wounds fully heal. It should also be discontinued before surgery. Although the optimal time to stop bevacizumab before

**TABLE 3**

### Common toxicities associated with targeted agents

<b>Bevacizumab</b>
Cardiovascular
• Hypertension
• Bleeding
• Thrombosis
• Delayed wound healing
Gastrointestinal perforation
Proteinuria/nephrotic syndrome
<b>Cetuximab</b>
Dermatologic
• Acneform rash
Infusion reactions
Interstitial lung disease
Hypomagnesemia

surgery is not yet known,<sup>7,13</sup> because of its long half-life, 6–8 weeks is the usual practice.

Patients with mCRC receiving chemotherapy and bevacizumab are also at increased risk of arterial thromboembolic events. Older patients and those with a history of significant cardiovascular or cerebrovascular disease are at even higher risk for this complication. In an analysis of data from five randomized controlled trials, which included 1,745 patients with various types of metastatic disease receiving chemotherapy, Skillings and colleagues found that bevacizumab was associated with an approximately twofold increased risk of arterial thromboembolic events. When evaluating patients for therapy, these factors, as well as use of agents that affect clotting or coagulation, should be considered in the decision of whether or not to use bevacizumab in the treatment of an individual patient.<sup>14</sup>

In summary, bevacizumab can effectively augment antitumor activity when combined with chemotherapy in patients with untreated mCRC in both the first- and second-line settings. It is now recommended for use with all five first-line therapies (ie, FOLFOX, FOLFIRI, IFL, 5-FU/LV, and CAPOX) in patients with

mCRC who can tolerate intensive therapy.<sup>4,6</sup> Results from ongoing clinical trials will continue to refine the optimal use of bevacizumab and of combination chemotherapy.

### Cetuximab: another approach to interfering with the neoplastic process

Overexpression of the epidermal growth factor receptor (EGFR) is detected in many cancers, including those of the colon and rectum. Cetuximab is a recombinant monoclonal antibody that binds with high specificity to the extracellular domain of EGFR. Binding of cetuximab to EGFR blocks ligand-induced receptor autophosphorylation and activation of receptor-associated kinases, which, in turn, inhibits cell growth, induces apoptosis, and decreases VEGF production.

### Cetuximab: extending and expanding treatment options

In the current NCCN guidelines, cetuximab is a recommended second-line therapy in patients who have not responded to irinotecan, whose disease has progressed on a prior irinotecan-containing protocol, or who cannot tolerate irinotecan. In third-line therapy, cetuximab is recommended for patients who have failed prior therapies with irinotecan- or oxaliplatin-containing regimens. Cetuximab is also recommended for use as fourth-line therapy with irinotecan in patients who are cetuximab-naïve but who have received irinotecan. This is the first fourth-line therapy for mCRC recommended by the NCCN.<sup>6</sup>

In the pivotal Bowel Oncology with Cetuximab Antibody 007 (commonly called BOND-1) trial, patients whose disease progressed on an irinotecan-containing regimen were randomized to either cetuximab alone (n = 111) or cetuximab plus their previous irinotecan regimen (n = 218).<sup>15</sup> Patients who received cetuximab in combination

TABLE 4

Efficacy of cetuximab alone and combined with irinotecan in BOND-1

Outcome	Cetuximab + irinotecan	Cetuximab	P value
Partial response rate, %	22.9	10.8	0.007
Disease control, %	55.5	32.4	< 0.001
Median overall survival, mo	8.6	6.9	0.48
Median duration of response, mo	5.7	4.2	
Median time to disease progression, mo	4.1	1.5	< 0.001*

\* By log-rank test

From Cunningham et al<sup>5</sup>

with an irinotecan-containing regimen had a significantly higher RR than patients who received cetuximab alone (22.9% vs 10.8%;  $P = 0.007$ ). There were also significant differences in time to progression (TTP) and disease control for the combination therapy (Table 4). Although median OS was not statistically different (8.6 months for the cetuximab and irinotecan group vs 6.9 months for the cetuximab-alone group;  $P = 0.48$ ), patients on the monotherapy arm were allowed to cross over and have irinotecan added at disease progression. In the cetuximab monotherapy arm, 56 patients received additional irinotecan at disease progression. Of these patients, 3.6% had a partial response and another 37.5% had stable disease after crossing over. The investigators concluded from the effectiveness of combining irinotecan with cetuximab in patients with irinotecan-refractory tumors that cetuximab may overcome irinotecan resistance.<sup>15</sup>

### Cetuximab: in first-line regimens

Cetuximab is not recommended for first-line treatment of mCRC; however, its possible use in this setting continues to be explored. To date, three small phase II trials have reported some encouraging results. In combination with FOLFIRI first line, cetuximab produced a partial RR of 46% and a median TTP of 10.9 months.<sup>16</sup> In combination with FOLFOX first line, a 9% complete and 63% partial RR were reported, as well as a TTP

of 10.2 months.<sup>17</sup> In patients who received cetuximab in combination with irinotecan, 5-FU, and folinic acid, Folprecht and colleagues reported a median OS of 33 months, the longest survival seen at that point, and a median TTP of 9.9 months.<sup>18</sup>

### Are two targeted agents better than one?

In BOND-2, a National Cancer Institute-sponsored, multicenter, randomized phase II trial, Saltz and colleagues assessed whether combining two targeted therapies (bevacizumab and cetuximab) alone or with irinotecan would improve outcomes in patients with irinotecan-resistant mCRC.<sup>5</sup> Although this trial was discontinued earlier than planned because of the difficulty in finding bevacizumab-naïve patients, it reported a higher partial RR (37% vs 20%, respectively) and longer TTP (7.9 months vs 5.6 months, respectively) with bevacizumab, cetuximab, and irinotecan compared with cetuximab and bevacizumab.<sup>5</sup> Although BOND-1 and BOND-2 are not directly comparable, the results of these trials suggest that adding bevacizumab to a cetuximab-containing regimen may improve the latter's efficacy in patients who have failed prior chemotherapy.

Phase III randomized trials of bevacizumab and cetuximab are ongoing in Europe and the United States. The results should provide additional direction regarding the role of cetuximab in first-line regimens, as well

as the role of combination targeted therapies. Building on the results of the BOND-2 trial, the Cancer and Leukemia Group B and the SWOG (CALGB/SWOG) 80405 study will evaluate cetuximab, bevacizumab, or the combination of both targeted agents with either FOLFOX or FOLFIRI (a so-called dealer's choice for chemotherapy) in the first-line treatment of mCRC. The primary endpoint of this study is OS.

### Is EGFR testing necessary when using cetuximab?

Clinical development of cetuximab, which has high specificity for EGFR, was based on the assumption that EGFR expression, as assayed by immunohistochemistry (IHC), would be useful in identifying patients with EGFR-positive tumors for treatment. Clinical evidence, however, shows that many patients who have EGFR-negative tumors also respond to cetuximab. In BOND-1, the degree of intensity of EGFR expression did not correlate with clinical response.<sup>15</sup> A recent retrospective study from the Memorial Sloan-Kettering Cancer Center identified 16 patients whose tumors were EGFR negative by IHC testing and who received cetuximab. This analysis showed that four patients (25%) achieved major objective responses and two exhibited minor responses (12.5%).<sup>19</sup> Of note, no clear correlation between response and the development of rash was observed in these patients with EGFR-negative tumors. At this time, selecting or excluding patients for cetuximab therapy based on IHC-determined EGFR status may not be reasonable.

### Cetuximab: toxicity profile

As with bevacizumab, the toxicities associated with cetuximab generally do not overlap with those of the cytotoxic agents. In clinical studies of cetuximab in advanced CRC, acneform rash was reported in 88% of all patients and was severe (grade 3 or

4) in 12%. In some cases, skin drying and fissuring also occurred. Severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. The US Food and Drug Administration recommends that all patients be monitored for 1 hour after cetuximab infusion for the development of infusion reactions, which can be life threatening. Periodic monitoring is also recommended for hypomagnesemia, hypocalcemia, and hypokalemia during therapy and for 8 weeks after a course of cetuximab therapy.<sup>20</sup>

### Other targeted agents under investigation

Several new targeted agents are under development. They include sunitinib (Sutent), vatalanib (PTK787/ZK 222584), and panitumumab. The integration of these new agents into current treatment regimens for mCRC poses challenges, including optimizing use of these agents in combination with other therapies and minimizing toxicities. In addition, there are limited data regarding the use of these agents with the currently available active cytotoxic agents irinotecan or oxaliplatin.

Sunitinib is an orally active inhibitor of multiple tyrosine kinases that has demonstrated direct antitumor and antiangiogenic activity. It targets the vascular endothelial growth factor receptor (VEGFR) and several other receptors, as well as platelet-derived growth factors. In addition, in clinical studies sunitinib has demonstrated activity in several tumor types, including gastrointestinal stromal tumors and renal cell carcinoma.

Vatalanib is an orally active small molecule inhibitor that targets the receptor tyrosine kinase domains of all three members of the VEGFR family. Based on the analysis of the CONFIRM-1 study by Hecht and colleagues, results suggest that adding vatalanib to FOLFOX in the first-

line setting improves PFS.<sup>21</sup>

Panitumumab is a fully human antibody that targets the EGFR. Recently, Hecht and colleagues reported the results of a phase II study showing FOLFIRI plus panitumumab was well tolerated and can be safely administered in the first-line treatment of mCRC.<sup>22</sup> Although data on median OS are not available, median PFS was 10.9 months and 5.6 months when panitumumab was added to FOLFIRI and IFL, respectively.

Early studies have shown that EMD 72000, another humanized monoclonal antibody targeting the EGFR, has antitumor activity in advanced CRC.<sup>23</sup> In addition to these agents, investigations are under way into other potential targets, including mitogen-activated protein kinase and Raf kinases.

### Summary

The targeted agents bevacizumab and cetuximab became available for use in treating mCRC in 2004 and have been rapidly incorporated into therapeutic regimens. Bevacizumab shows a survival benefit when combined with chemotherapy and is recommended for use in all first-line therapies for patients with mCRC, including some patients who are unable to tolerate intensive therapy. Cetuximab is recommended for use in second-, third-, and fourth-line protocols. Cetuximab may be especially useful in overcoming cellular resistance, resensitizing tumors to irinotecan.

The toxicities associated with these agents generally do not overlap with those of the cytotoxic agents. Ongoing clinical trials will help to further define the optimal use of these and future targeted agents in combination with chemotherapy in a strategic treatment plan for mCRC. However, it is increasingly evident that an individualized treatment strategy that delivers all active agents over the course of the disease can optimize OS in mCRC.

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