

An illustration of two men in suits pulling a heavy blue curtain. The curtain is decorated with a pattern of small yellow stars and a crescent moon. Behind the curtain, a bright green field stretches to a horizon under a blue sky with white clouds. The man on the left is wearing a yellow suit and hat, and the man on the right is wearing a red suit and hat. They are both leaning forward, pulling the curtain with ropes.

# The Vectibix™ Launch:

*A Look at the Commercialization  
of this New Fully-Humanized  
Antibody for Colorectal Cancer*

By Erinn H. Goldman, PhD

Amgen's Vectibix™ was approved in September 2006 as a third-line agent for the treatment of metastatic colorectal cancer. Although oncologists are excited by its favorable safety profile, the licensing of this drug as a single third-line agent may hamper its use.

In 2004, the FDA approved two novel monoclonal antibodies for the treatment of metastatic colorectal cancer: Avastin® [bevacizumab, Genentech], which is directed against the vascular endothelial growth factor receptor (VEGFR), and Erbitux® [cetuximab developed by ImClone, marketed by Bristol-Myers Squibb], which is directed against the epidermal growth factor receptor (EGFR). These targeted agents have generated a great deal of interest in the oncology community due to their efficacy in combination with other chemotherapy regimens and their relatively low toxicity.

Interestingly, though Avastin is thought to inhibit angiogenesis, and Erbitux is proposed to inhibit EGFR signaling and consequent cell proliferation and survival, the exact mechanism of action of these drugs is unknown. In fact, David Cunningham's 2004 study published in the *New England Journal of Medicine* revealed that response to Erbitux was completely independent of EGFR expression, suggesting that the drug may work through another pathway.

Regardless of their proposed mechanism of actions, the new biological agents for metastatic colorectal cancer are associated with

dramatic improvements in patient outcomes, as evidenced by an increase in median overall survival from roughly 14 months to beyond 20 months.

### Launching Vectibix

Amgen has recently entered the oncology therapeutics market with its anti-EGFR drug Vectibix (panitumumab). Unlike its predecessors Avastin and Erbitux, Vectibix is an entirely human antibody. Since chimeric antibodies have been shown to induce an anti-mouse immune response, a fully human antibody may minimize the likelihood of a humoral response against the therapeutic antibody, thereby maximizing treatment efficacy over a long period. Such human monoclonal antibodies may be more suitable for the chronic treatment and management of patients with cancer and may reduce the risk of the infusion reactions commonly experienced during administration of antibodies. Another potential advantage to Vectibix is that this agent is dosed every other week, unlike Erbitux which is dosed weekly, and patients do not need to be premedicated.

Vectibix received Fast Track designation from the FDA in July 2005 and was approved in September 2006 for patients who had failed prior standard chemotherapy. Importantly, the current label for Vectibix does not indicate its use in combination therapy. Since previous studies have shown that [cont. on pg 12 >>](#)



Amgen's Vectibix Packaging

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single-agent monoclonal antibodies are not as effective as combination therapy, it is unlikely that Vectibix will be widely prescribed as a single-agent for metastatic patients. Though promising in early studies and unique in its design, Vectibix may have difficulty establishing a foothold in the colorectal cancer market until it gets approved in combination with other standard agents.

“Vectibix has enough positive features to be prescribed. The lack of infusion reaction seen with this agent, and the fact that it is administered every other week, give it major advantages over Erbitux,” said Alan Venook, MD, Director of University of California San Francisco/Mt. Zion Cancer Center Clinical Research Office and lead author of several major clinical trials investigating monoclonal antibodies in metastatic colorectal cancer.

“The real issue here could be reimbursement,” said Venook. The label for Vectibix does not include combination therapies so insurance plans may not cover it. According to Dr. Venook, the use of this drug will likely be determined more by insurers than by doctors.

This sentiment is echoed among community oncologists. According to Al Brady, MD, of Washington Hematology/Oncology Specialists in Yakima, Washington, “Vectibix has a favorable toxicity profile and will likely replace Erbitux completely. If I knew that the drug would be paid for then I would definitely use it, but until it is approved for something other than as a third-line single-agent I won’t prescribe it, because I know it won’t be reimbursed by insurers.”

### Making Vectibix Affordable to Patients

Perhaps in part to address this concern, Amgen recently launched a comprehensive financial assistance program that will include a “cap” on out-of-pocket co-payments for patients with cancer receiving Vectibix. Through Amgen Oncology Assistance (AOA), US patients who are not insured, underinsured, or unable to afford their insurance

co-payments will receive financial support for Amgen’s cancer medicines. Regardless of their income or insurance, once a patient spends five percent of their adjusted gross income on Vectibix, he or she will become eligible for the Amgen SAFETY NET Foundation. This program provides Amgen oncology medicines free to qualifying uninsured patients. The Amgen Safety Net Foundation was the first of its kind in the oncology field and was soon copied by Genentech in a similar program for Avastin patients.

When asked if the AOA would cover the cost of Vectibix in cases where insurance companies do not, Amgen spokesperson Christine Regan said, “Amgen is bound by the indication listed in the label for promotional purposes and does not market any of its products for off-label uses. However, we do not deny enrollment into any of our assistance programs for patients who receive our medicines for a use their physician believes is medically appropriate.”

In another move to make Vectibix more accessible to patients, Amgen set the price of the antibody 20 percent below Erbitux. But Vectibix will still carry a hefty pricetag, a testament to the astronomical cost of these biological agents. An infusion every two weeks will cost \$4000, or more than \$100,000 for a year’s treatment.

A Phase III randomized, open-label study of Vectibix as a first-line agent has recently completed enrollment. The results of this trial are eagerly awaited by the Amgen Corporation because it may lead to the licensing of Vectibix in combination therapy for first-line treatment of metastatic colorectal cancer.

Regan told Oncology Business Review that these data are imminent. “We expect to have the response rate data available for local reads (not the centrally adjudicated response rate data) in the fourth quarter of this year, and expect to make this information available on our fourth quarter earnings call,” she stated.



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Amgen also has eight ongoing trials investigating the safety and efficacy of Vectibix for earlier lines of colorectal, adjuvant colorectal, and head and neck cancer.

### The View from Genentech

Genentech's VEGF inhibitor Avastin is the furthest along in the treatment algorithm for colorectal cancer. It—in combination with intravenous 5-fluorouracil-based chemotherapy—is the only monoclonal antibody approved as a first-line treatment option for metastatic colorectal cancer. Avastin generated \$555 million in annual sales for the Genentech Corporation in 2004 and growth in sales is expected if this drug shows survival benefits in two ongoing Phase III trials with various combinations of standard chemotherapy, Erbitux, and Vectibix.

Avastin has demonstrated efficacy in three large randomized Phase III trials. In the first licensing trial, treatment-naive patients with

colorectal cancer treated with Avastin in combination with IFL as a first-line regimen survived approximately five months longer and disease-free survival was four months longer than patients receiving IFL alone.

Avastin has also been shown to improve outcomes in combination with a variety of oxaliplatin regimens, including FOLFOX4 (infusional 5-FU, and leucovorin), modified FOLFOX, bFOL (oxaliplatin, bolus LV, bolus FU), and CapeOX (oxaliplatin plus capecitabine). One study, ECOG E3200, revealed that Avastin is active in combination with oxaliplatin-containing regimens, but not as a single agent.

Though occurrences are rare, Avastin is associated with potentially fatal toxicities, which have limited its use in certain patient populations. The drug is associated with increased incidence of hypertension and, infrequently, arterial thromboembolic events (e.g. stroke, myocardial infarction, angina—particularly in elderly patients), [cont. on pg 14 >>](#)

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hemorrhage, impaired wound healing, and has a 2.1 percent increase in risk of gastrointestinal perforation. These potential adverse events make Avastin inappropriate for use in patients with pre-existing heart conditions and other comorbidities.

### What ImClone is Doing

ImClone/BMS's Erbitux was approved by the FDA based on the results of BOND I, an open-label study showing that it is effective as a second-line regimen in combination with irinotecan. It is currently approved for second-line use in patients who have failed an irinotecan-based regimen or who cannot tolerate irinotecan.

The follow-up study, BOND II, was a Phase II randomized study comparing Avastin plus Erbitux with or without irinotecan as second-line therapy for irinotecan-refractory patients. The data showed that the Avastin/Erbitux combination is tolerable and can enhance the efficacy of other chemotherapeutic agents.

Erbitux generated over \$360 million dollars in worldwide sales for ImClone/BMS in 2004.

### Issues with Patenting Monoclonal Antibodies

On September 18, 2006, a Manhattan judge named three Israeli scientists with the Yeda Research and Development Company as sole inventors of the patent covering the use of certain monoclonal antibodies in combination with anti-neoplastic agents for the treatment of cancer. The impact of this decision on ImClone/BMS operations is unknown. ImClone/BMS is appealing the decision and claims that transfer of inventorship would make the patent invalid under current law. The company plans to file a declaratory judgment action against Yeda seeking a declaration of patent invalidity and non-infringement in the instance where Yeda maintains sole inventorship.

### Head-to-Head Comparison Trial of Monoclonal Antibodies

The demonstrated ability of Avastin and Erbitux to enhance chemotherapeutic

response in patients with metastatic colorectal cancer has led to a randomized, open-label Phase III trial to evaluate the agents in combination with FOLFOX or FOLFIRI as first-line therapy.

Physicians can select whether patients receive FOLFOX or FOLFIRI and patients are randomized to one of three arms: FOLFOX or FOLFIRI + Avastin, FOLFOX or FOLFIRI + Erbitux, or FOLFOX or FOLFIRI + Avastin and Erbitux. The study plans to accrue over 2000 patients and its primary objective will be to evaluate overall survival.

This head-to-head comparison of Avastin or Erbitux may lead to one of these monoclonal antibodies gaining prominence over the other in the treatment of metastatic colorectal cancer. Alternatively, the study may reveal that combining these agents enhances therapeutic effect. In any case, this will be an important study and its results may change the standard of care for treating metastatic colon cancer. Data showing Erbitux-associated survival advantages could move this agent up the treatment algorithm to become a first-line regimen in metastatic colorectal cancer.

The next year will likely be a momentous time for colorectal cancer treatment and we could see a change in the standard of care for this disease in the immediate future. Results from the Phase III trial evaluating Avastin and/or Erbitux in combination with FOLFOX or FOLFIRI as first-line therapy and the Phase III study of Avastin and/or Vectibix with an oxaliplatin- or irinotecan-based chemotherapy regimen could establish an optimal therapeutic regimen for patients with metastatic colorectal cancer, a particularly difficult-to-treat population. Given the global burden of colorectal cancer, such a change in the recommended treatment algorithm will have substantial financial implications for Amgen, BMS/ImClone, and Genentech, the three companies marketing targeted biological agents for this indication. **EHG**