Blockbuster biotech deal pays off

Now with FDA approval, Erbitux and other MAb drugs are chasing huge potential profits.

BY KIMBERLY S. CLEAVES

Alliances between biotechnology companies and pharmaceutical producers are steadily increasing, and there are always a few of the new collaborations each year that stand out from the rest. With more competition for compounds and the complexities involved in bringing new drugs to market, the drug industry is finding that what makes an attractive drug candidate is not necessarily the "commercial appeal of the product or scope," as reported at Allicense, a conference hosted by Recombinant Capital, Inc., that brings together executives from leading pharmaceutical firms, biotech companies, and medical institutions. "More often, it is hard not to focus on the immense sums of money involved that automatically thrust the companies and their products in the spotlight," Allicense says.

PHOTO: MERCK

Erbitux is one of a new generation of monoclonal antibody anticancer drugs.

A deal around ImClone Systems' anticancer drug Erbitux (cetuximab) started making headlines in September 2001, when Bristol-Myers Squibb (BMS) agreed to pay $2 billion for marketing rights and a 20% stake in ImClone while the drug was still in clinical trials and on the FDA's fast track for review. The enormous value of the deal thrust ImClone and BMS into immediate prominence and broke new ground for the licensing of a late-stage compound. ImClone became the darling of Wall Street and the biotechnology industry, which called the drug a major advance. Until that time, the largest pharmaceutical–biotech alliance—between Bayer and CuraGen for $1.3 billion in January 2001 to discover and develop drugs to treat obesity and diabetes—was considered the industry's pathbreaking deal.

The ImClone–BMS collaboration was heralded as one of the five best biotech–pharmaceutical alliances of 2001 and was nominated for the Allicense 2002 Breakthrough Alliance award.

A checkered past

But all this acclaim quickly came to an end when, in December 2001, the FDA took the unusual step of refusing to accept the Biologics License Application (BLA) for Erbitux. On January 4, 2002, a story based on a leaked copy of the FDA's "refusal to file" letter was published in *The Cancer Letter*, a weekly newsletter covering oncology. *The Cancer Letter* reported that "the clinical trial was not adequate and well-controlled," even though Samuel Waksal, ImClone founder, president, and CEO, had told analysts and reporters that the FDA had signed off on the trial. The FDA rejection letter sent ImClone's stock plummeting, which sparked numerous unfavorable events for the company. These included a management shakeup, investor lawsuits, and eventual convictions for insider trading. BMS demanded a new deal, and it subsequently renegotiated with ImClone to have greater input in the product's development based on its drug and oncology development experience.

The ImClone episode was a "seminal event for the industry," says G. Steven Burrill, CEO of the merchant bank Burrill & Co., causing Wall Street and investors to rewrite their views of the biotech industry. "ImClone's lasting contribution isn't the Erbitux story," he explains; "it's that it has changed forever the value proposition on Wall Street. Investors paid a big price and have concluded that they do not want to own uncertainty."

Meanwhile, development and approval of

FDA-approved monoclonal antibodies

Product	Trade name	Manufacturer	Used to treat	Approved in
Rituximab	Rituxan	Genentech	Non-Hodgkin's lymphoma	1997
Trastuzumab	Herceptin	Genentech	Metastatic breast cancer	1998
Gemtuzumab ozogamicin	Mylotarg	Wyeth	Acute myelogenous leukemia (AML)	2000
Alemtuzumab	Campath	Millennium Pharmaceuticals	Chronic lymphocytic leukemia (CLL)	2001
Ibritumomab tiuxetan	Zevalin	IDEC Pharmaceuticals and Schering AG	Non-Hodgkin's lymphoma	2002
Tositumomab	Bexxar	Corixa and GlaxoSmithKline	Non-Hodgkin's lymphoma	2003
Cetuximab	Erbitux	ImClone and Bristol-Myers Squibb	Colorectal cancer	2004
Bevacizumab	Avastin	Genentech	Colorectal cancer	2004

Source: American Cancer Society.

Erbitux in Europe, where Merck KGaA has product rights, progressed more smoothly. Unlike BMS, Merck was more closely involved with the development process; in 1998 it purchased Erbitux product rights outside the United States for $60 million.

Erbitux is one of a promising new generation of monoclonal antibodies (MAbs), targeted against cancer, that block certain proteins that spur tumor growth. It is a first-of-its-kind antibody approved for use in combination with irinotecan for treating patients with epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer who are intolerant to irinotecan-based chemotherapy and for use as a single agent in treating colorectal cancer. Erbitux blocks the EGFR, which is expressed in more than 80% of advanced metastatic colorectal cancers, and reduces both the invasion of normal tissues by tumor cells and the spread of tumors to new sites.

On the basis of convincing efficacy and safety data, the Swiss Agency for Therapeutic Products (Swissmedic) approved Erbitux in December 2003 under an accelerated registration procedure for use in colorectal cancer patients who no longer respond to irinotecan treatment. This was the first approval of the drug anywhere in the world. Approval for Erbitux in the European Union is expected this year.

The Swiss approval was largely based on Merck's Bowel Oncology with Cetuximab Antibody (BOND, as designated by Merck) study, which showed that the Erbitux and irinotecan combination benefited more than half of the patients. Using the BOND data, BMS and ImClone were able to bolster and resubmit their Erbitux BLA, which the FDA accepted for review in October 2003. Also included in the U.S. submission was randomized two-arm Phase II clinical trial data of patients given either Erbitux alone or in combination with irinotecan.

Although Erbitux is not a cure, and it does have some serious side effects, it has been found to slow disease progression by up to several months. "Survival was not a major component of the randomized trial comparing Erbitux alone or in combination with irinotecan. The major end points focused on were rates and time-to-progression, both of which were better in the combination therapy," says Patricia Keegan, director of the FDA's Division of Therapeutic Biological Oncology Products. And Karen Wiess, director of the Office of Drug Evaluation VI of CDER (Center for Drug Evaluation and Research), points out that "ImClone has commitments to conduct or complete ongoing trials, two of which were initiated in 2003 and are ongoing, to verify the overall clinical benefit."

At the recent Lehman Brothers Annual Global Healthcare Conference, newly appointed ImClone CEO Daniel Lynch said, "By midyear, data from the IMCL-9815 clinical trial involving 424 patients could form the basis for an application to the FDA." Still, notes the FDA's Keegan, "the fact that it's an effective therapy for tumor reduction is in itself likely to be a benefit to patients."

Since 2001, when Erbitux's roller-coaster ride to approval began, patients have clamored for the drug.

With no other treatment available for patients who have failed other options, the FDA approved Erbitux on February 12 under its accelerated approval process, which allows for the approval of products for cancer and other life-threatening diseases based on early evidence of effectiveness.

Commercial appeal

A potentially life-threatening disease, colon cancer is the second-leading cause of cancer-related deaths in the United States, according to the Centers for Disease Control and Prevention, and the third-most-common cancer affecting Americans. However, there is hope, as new drugs for colorectal cancer are emerging after several years of limited treatment options, the American Society of Clinical Oncology reports.

Global sales of irinotecan (Pharmacia's Camptosar, Aventis and Yakult's Campto), approved by the FDA in 1996 for treating recurrent colon cancer, exceeded $700 million in 2003. And, as reported in their January 22 earnings statement, Sanofi-Synthélabo's sales of Eloxatin (oxaliplatin), used to treat advanced colon or rectal cancer, rose 125.8% to $1.03 billion in 2003—primarily in the colorectal cancer market. Sanofi-Synthélabo expects sales of about $1.9 billion by 2006 as it extends its use.

Decision Resources, Inc., a market research and advisory firm, forecasts that "Sanofi-Synthélabo's Eloxatin and Pharmacia/Aventis's Campto/Camptosar will significantly contribute to the short-term growth of the colorectal cancer drug market." According to a recent Pharmacor study entitled *Colorectal Cancer*, "Combined sales of these agents will climb to more than $2.1 billion in 2012."

"However, from 2007 to 2011, the market's growth will significantly drop to 4.4%," says Mohamed Muhsin, an analyst at Decision Resources, "because irinotecan goes off-patent in seven major pharmaceutical markets: the United States, France, Germany, Italy, Spain, the United Kingdom, and Japan."

However, for Erbitux sales to reach $1 billion, it would likely have to be approved as a treatment for other EGFR-expressing cancers or for first-line use in colorectal cancer. Erbitux is currently being studied in other EGFR-expressing tumors, such as non-small-cell lung cancer, where it faces competition from AstraZeneca's small-molecule EGFR kinase inhibitor Iressa (gefitinib), approved last year, and Genentech's recently approved Avastin (bevacizumab). Erbitux, Iressa, and Avastin all show promise in shrinking tumors, slowing the progression of disease, and potentially extending life, according to clinical trial results. For example, AstraZeneca's Iressa Phase II clinical data shows the drug shrank tumors in 75% of patients when taken in combination with chemotherapy, where chemotherapy alone shrank tumors in 38%. Ironically, the FDA accepted an application for Iressa on the same day it rejected the one for Erbitux.

Meanwhile, Genentech's Avastin Phase III clinical data shows an improvement in

progression-free survival and a prolongation in the median survival of patients treated with the drug plus chemotherapy. While Avastin could be used as a standard treatment for people newly diagnosed with the disease, and thus have a broader market potential, Erbitux is indicated only for patients who have failed other options.

Also in the MAb pipeline is another direct Erbitux competitor, Abgenix and Amgen's ABX-EGF, the next most advanced EGFR inhibitor for second-line treatment of colorectal cancer. It is a fully human MAb that has exhibited high binding affinity and the ability to eliminate tumors. ABX-EGF is in Phase II trials for kidney, lung, prostate, and colorectal cancers and has "demonstrated single-agent activity and a good pharmacokinetic and tolerability profile," Abgenix says.

Yet another unresolved issue for ImClone and BMS is the manufacture and supply of Erbitux. The FDA has given Lonza Biologics plc (U.K.) approval to contract-manufacture Erbitux. "Inventory previously produced at Lonza Biologics' facility will serve as supply for the initial demand for Erbitux," according to ImClone and BMS.

However, ImClone has been investing heavily in its own production capacity. But the FDA had requested more information on a larger group of patients treated with Erbitux produced at ImClone's facility. As a result, ImClone withdrew its manufacturing facility from its BLA and submitted a supplemental application for the facility in February. The FDA's response is expected by September. If the production facility is approved, ImClone believes it can "meet full commercial demand for Erbitux on an ongoing basis."

Since 2001, when Erbitux's roller-coaster ride to approval began, patients have clamored for the drug. Erbitux's full potential either with a variety of chemotherapy agents or as a single agent is still unknown, however, and the FDA cautions that Erbitux has not been shown to prolong lives.

ImClone CEO Lynch intends to "continue to direct the company's talent and resources toward the advancement of our clinical programs, most notably Erbitux." The recent Erbitux "achievements will pave the way for the company to become a profitable, fully integrated biopharmaceutical company. We look forward to leveraging these successes to further expand our resources, grow the company, and build shareholder value over the long term," Lynch adds. On March 12, ImClone received a $250 million milestone payment from BMS.

And on March 25, ImClone partner Merck KGaA received a favorable decision from the Committee for Proprietary Medicinal Products (CPMP) to recommend Erbitux for approval. "The recommendation of the CPMP will be forwarded to the European Commission and marks a positive step toward approval of Erbitux, which is anticipated in mid-2004," Merck says. The drug—possibly one of the most costly biotechnology cancer drugs developed—just may help ImClone record its first-ever profit in 2005. ■