Randomized Phase III Trial Showed ERBITUX® (Cetuximab) Significantly Improved Secondary Endpoints of Progression-Free Survival and Disease Control in Metastatic Colorectal Cancer Patients

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- As previously announced, primary endpoint not met; plausibly confounded by survival benefit of post-study treatment with ERBITUX

- Data was presented during the Annual Meeting of the American Association for Cancer Research

NEW YORK--(BUSINESS WIRE)--ImClone Systems Incorporated (NASDAQ: IMCL) and Bristol-Myers Squibb Company (NYSE: BMY) today announced detailed results from the EPIC study—a randomized, open-label, multi-center Phase III trial—comparing ERBITUX® (Cetuximab) plus irinotecan to irinotecan alone in patients with metastatic colorectal cancer (mCRC) who failed first-line therapy. Results showed that the secondary endpoints of progression-free survival and response rate were significantly higher in the ERBITUX-irinotecan arm. The median time of survival without disease progression was improved by 54% in the patients who received ERBITUX plus irinotecan. This benefit produced a significant 31% reduction in the risk of disease progression (Hazard ratio, 0.692; 95% CI = 0.617–0.776; p<0.0001). Additionally, patients in the ERBITUX-irinotecan arm were four times more likely to experience a 50% reduction in tumor size over patients treated with irinotecan alone (p<0.0001).

“The improvement in progression-free survival and response rate expands our understanding of the significant activity of ERBITUX,” said Eric Rowinsky, M.D., Chief Medical Officer and Senior Vice President of ImClone Systems. “We believe these outcomes add to the existing clinical evidence demonstrating the safety and effectiveness of ERBITUX in combination with chemotherapy.”

As previously reported, the study’s primary endpoint of overall survival was not different between the two groups (Hazard ratio, 0.975; 95.03% CI = 0.854 – 1.114; p=0.7115). Analysis of the data show that a considerable number of patients randomized to the irinotecan arm went on to receive ERBITUX with or without irinotecan after failing irinotecan alone. Extensive post-trial use of ERBITUX may explain the lack of difference in overall survival between the two arms despite substantial improvement in secondary endpoints.

“We intend to use the results of this study to further understand the potential of ERBITUX in the treatment of colorectal cancer patients.” said Martin Birkhofer, M.D., Vice President, Oncology Global Medical Affairs, Bristol-Myers Squibb.

The EPIC trial (ERBITUX Plus Irinotecan in Colorectal Cancer) enrolled 1,298 irinotecan-naïve mCRC patients whose disease was not responding to first-line oxaliplatin-based chemotherapy. After randomization, patients were treated until their disease progressed. Upon disease progression, study treatment was stopped and further treatment was at the discretion of the physician. Patients who received combination ERBITUX plus irinotecan experienced median overall survival of 10.71 months and median progression-free survival of 4 months; in this treatment group, overall response rate was achieved in 16.4% of patients and 61.4% of patients experienced disease control. Patients who received irinotecan alone experienced median overall survival of 9.99 months and median progression-free survival of 2.6 months; in this treatment group, overall response rate was achieved in 4.2% of patients and 45.8% of patients experienced disease control.

Grade 3/4 adverse events included rash (ERBITUX-irinotecan arm: 8.2% vs. irinotecan arm: 0.5%), infusion reaction (1.4% vs. 0.8%) and hypomagnesemia (3.3% vs. 0.4%). Other common non-hematologic adverse events included: diarrhea (28.8% vs. 16.2%) and fatigue (9.2% vs. 4.9%).

About Colorectal Cancer

In the U.S., approximately 154,000 people will be diagnosed with cancer of the colon or rectum this year. Half of these patients have metastatic disease, or cancer that has spread to other organs, at the time of diagnosis. EGFR is expressed in up to 77.7% of colorectal cancer tumors. Colorectal cancer is the third most common cancer in both men and women.
About ERBITUX® (Cetuximab)

ERBITUX is a monoclonal antibody (lgG1 Mab) designed to inhibit the function of a molecular structure expressed on the surface of normal and tumor cells called the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1). In vitro assays and in vivo animal studies have shown that binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. In vitro, ERBITUX can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. While the mechanism of ERBITUX' anti-tumor effect(s) in vivo is unknown, all of these processes may contribute to the overall therapeutic effect of ERBITUX. EGFR is part of a signaling pathway that is linked to the growth and development of many human cancers, including those of the head and neck, colon and rectum.

ERBITUX (Cetuximab), in combination with radiation therapy, is indicated for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck. ERBITUX as a single agent is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed.

ERBITUX is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma (mCRC) in combination with irinotecan for patients who are refractory to irinotecan-based chemotherapy, and as a single agent for patients who are intolerant to irinotecan-based therapy. The effectiveness of ERBITUX for the treatment of EGFR-expressing mCRC cancer is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX for the treatment of EGFR-expressing mCRC.

For full prescribing information, including boxed WARNINGS regarding infusion reactions and cardiopulmonary arrest, visit http://www.ERBITUX.com.

Important Safety Information

Grade 3/4 infusion reactions, rarely with fatal outcome (<1 in 1000), occurred in approximately 3% (46/1485) of patients receiving ERBITUX (Cetuximab) therapy. These reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension, and/or cardiac arrest. Severe infusion reactions require immediate and permanent discontinuation of ERBITUX therapy.

Most reactions (90%) were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. Caution must be exercised with every ERBITUX infusion as there were patients who experienced their first severe infusion reaction during later infusions. A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

Cardiopulmonary arrest and/or sudden death occurred in 2% (4/208) of patients with squamous cell carcinoma of the head and neck treated with radiation therapy and ERBITUX as compared to none of 212 patients treated with radiation therapy alone. Fatal events occurred within 1 to 43 days after the last ERBITUX treatment. ERBITUX in combination with radiation therapy should be used with caution in patients with known coronary artery disease, congestive heart failure and arrhythmias. Close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium during and after ERBITUX therapy is recommended.

Severe cases of interstitial lung disease (ILD), which was fatal in one case, occurred in less than 0.5% of 774 patients with advanced colorectal cancer (mCRC) receiving ERBITUX. There was one case of ILD reported in 796 patients with head and neck cancer receiving ERBITUX in clinical studies.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In 208 patients receiving ERBITUX alone, 76% (N=103) experienced acneform rash (1% severe). In patients with mCRC, acneform rash was reported in 89% (686/774) of all treated patients, and was severe in 11% (84/774). Subsequent to the development of severe dermatologic toxicities, complications including S. aureus sepsis and abscesses requiring incision and drainage were reported. Sun exposure may exacerbate these effects. A related nail disorder, occurring in 12% (0.4% Grade 3) of patients, was characterized as a paronychal inflammation.

The safety of ERBITUX in combination with radiation therapy and cisplatin has not been established. Death and serious cardiotoxicity were observed in a single-arm trial with ERBITUX, delayed, accelerated (concomitant boost) fractionation radiation therapy, and cisplatin (100 mg/m2) conducted in patients with locally advanced squamous cell carcinoma of the head and neck. Two of 21 patients died, one as a result of pneumonia and one of an unknown cause. Four patients discontinued treatment due to adverse events. Three of these discontinuations were due to cardiac events (myocardial infarction in one patient and arrhythmia, diminished cardiac output, and hypotension in the other patient).

The incidence of hypomagnesemia (both overall and severe [NCI CTC Grades 3 & 4]) was increased in patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone based on ongoing, controlled clinical trials in 244 patients. Approximately one-half of these patients receiving ERBITUX experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. Patients receiving ERBITUX therapy should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia during, and up to 8 weeks following the completion of, ERBITUX therapy.

The most serious adverse reactions associated with ERBITUX in combination with radiotherapy in 208 patients with head and neck cancer were infusion reaction (3%), cardiopulmonary arrest (2%), dermatologic toxicity (2.5%), mucositis (6%), radiation dermatitis (3%), confusion (2%), and diarrhea (2%).

The most serious adverse reactions associated with ERBITUX in mCRC clinical trials (N=774) were infusion reaction (3%), dermatologic toxicity (1%), interstitial lung disease (0.4%), fever (5%), sepsis (3%), kidney failure (2%), pulmonary embolus (1%), dehydration (5% in patients receiving ERBITUX with irinotecan, 2% in patients receiving ERBITUX as a single agent) and diarrhea (6% in patients receiving ERBITUX with irinotecan, 0.2% in patients receiving ERBITUX as a single agent).
The overall incidence of late radiation toxicities (any grade) was higher with ERBITUX in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65%/56%), larynx (52%/36%), subcutaneous tissue (49%/45%), mucous membranes (48%/39%), esophagus (44%/35%), skin (42%/33%), brain (11%/9%), lung (11%/8%), spinal cord (4%/3%), and bone (4%/5%) in the ERBITUX and radiation versus radiation alone arms, respectively.

The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms.

The most common adverse events seen in patients with carcinomas of the head and neck receiving ERBITUX in combination with radiation therapy (n=208) versus radiation alone (n=212) were mucositis-stomatitis (93%/94%), acneform rash (87%/10%), radiation dermatitis (86%/90%), weight loss (84%/72%), xerostomia (72%/71%), dysphagia (65%/63%), asthenia (56%/49%), nausea (49%/37%), constipation (35%/30%) and vomiting (29%/23%). The most common adverse events seen in patients with carcinomas of the head and neck receiving ERBITUX as a single agent (N=103) were acneform rash (76%), asthenia (45%), pain (28%), fever (27%) and weight loss (27%).

The most common adverse events seen in patients with mCRC receiving ERBITUX with irinotecan (n=354) or ERBITUX as a single agent (n=420) were acneform rash (88%/90%), asthenia/malaise (73%/48%), diarrhea (72%/25%), nausea (55%/29%), abdominal pain (45%/26%), vomiting (41%/25%), fever (34%/27%), constipation (30%/26%), and headache (14%/26%).

About ImClone Systems

ImClone Systems Incorporated is committed to advancing oncology care by developing a portfolio of targeted biologic treatments designed to address the medical needs of patients with a variety of cancers. The Company's research and development programs include growth factor blockers and angiogenesis inhibitors. ImClone Systems' strategy is to become a fully integrated biopharmaceutical company, taking its development programs from the research stage to the market.

ImClone Systems' headquarters and research operations are located in New York City, with additional administration and manufacturing facilities in Branchburg, New Jersey.

Certain matters discussed in this news release may constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and the Federal securities laws. Although the company believes that the expectations reflected in such forward-looking statements are based upon reasonable assumptions it can give no assurance that its expectations will be achieved. Forward-looking information is subject to certain risks, trends and uncertainties that could cause actual results to differ materially from those projected. Many of these factors are beyond the company's ability to control or predict. Important factors that may cause actual results to differ materially and could impact the company and the statements contained in this news release can be found in the company's filings with the Securities and Exchange Commission, including quarterly reports on Form 10-Q, current reports on Form 8-K and annual reports on Form 10-K. For forward-looking statements in this news release, the company claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995. The company assumes no obligation to update or supplement any forward-looking statements whether as a result of new information, future events or otherwise.

About Bristol-Myers Squibb

Bristol-Myers Squibb is dedicated to the discovery, development and exhaustive exploration of innovative cancer fighting therapies designed to extend and enhance the lives of patients living with cancer. More than 40 years ago, Bristol-Myers Squibb built a unified vision for the future of cancer treatment. With expertise, dedication and resolve, that vision led to the development of a diverse global portfolio of anti-cancer therapies that are an important cornerstone of care today. Hundreds of scientists at Bristol-Myers Squibb's Pharmaceutical Research Institute are studying ways to improve current cancer treatments and identify better, more effective medicines for the future.

Bristol-Myers Squibb is a global pharmaceutical and related health care products company whose mission is to extend and enhance human life.

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995, regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. There can be no guarantee that a registrational submission will be made to the FDA based on the data described in this press release or if such registrational submission is made, that it would receive FDA approval. Forward-looking statements in this press release should be evaluated with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2006 and in our Quarterly Reports on Form 10-Q. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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