ERBITUX(R) (Cetuximab) Data Demonstrate Improved Overall Survival in First-Line Treatment of Advanced Non-Small Cell Lung Cancer

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Landmark Phase 3 Study Results Presented at American Society of Clinical Oncology Annual Meeting

NEW YORK--(BUSINESS WIRE)--ImClone Systems Incorporated (NASDAQ: IMCL) and Bristol-Myers Squibb Company (NYSE: BMY) today announced results that show the addition of ERBITUX® (cetuximab) to platinum-based chemotherapy significantly increased overall survival in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC), when compared with platinum-based chemotherapy alone. This improvement in survival was observed across all histological subtypes, patient performance status (a measure of well-being), age groups, previous smoking history, and gender. Results from the landmark Phase 3 clinical trial were presented today during a plenary session at the 44th Annual Meeting of the American Society of Clinical Oncology in Chicago.

The pivotal, multinational study (Abstract #3), known as FLEX (First-line in Lung cancer with ErbituX) was planned and conducted by Merck KGaA, Darmstadt, Germany, and enrolled more than 1,100 patients with Stage IIIb or Stage IV NSCLC who had not previously received chemotherapy. Unlike previous pivotal studies of monoclonal antibodies in NSCLC, the FLEX study enrolled patients with a broad range of performance capabilities and histological subtypes – reflective of physicians’ everyday practice. For patients receiving ERBITUX in combination with chemotherapy, median overall survival was prolonged by 1.2 months when compared to chemotherapy alone (11.3 months vs 10.1 months) for an hazard ratio of 0.871 [95% CI = 0.762-0.996], p=0.044.

“Lung cancer is notoriously difficult to treat and these results are particularly exciting as they represent a significant advancement in the study of non-small cell lung cancer,” commented Professor Robert Pirker, lead investigator and Professor of Internal Medicine at the University of Vienna, Austria. “If approved, this will open new first-line treatment options for patients with non-small cell lung cancer regardless of histological subtypes, and may set a new standard in the first-line treatment of this disease.”

“Based on these results, ERBITUX is now the first anti-EGFR (epidermal growth factor receptor)-targeted therapy to improve overall survival for the initial treatment of non-small cell lung cancer as well as the first monoclonal antibody to improve survival across all histological subtypes, when added to platinum-based chemotherapy,” said Martin Birkhofer, M.D., Vice President, Oncology Global Medical Affairs, Bristol-Myers Squibb. “This is also now the third tumor type where ERBITUX has demonstrated an improvement in survival.”

“We look forward to submitting a supplemental biologics license application, or sBLA, later this year for ERBITUX to be used in the first-line treatment of patients with non-small cell lung cancer on the basis of the FLEX study results,” said Eric K. Rowinsky, M.D., Executive Vice President and Chief Medical Officer of ImClone. “Obtaining this sBLA is an important step in the companies’ efforts to maximize the potential of ERBITUX through additional approvals for new indications and earlier-stage settings.”

“The lung cancer community is extremely encouraged by the FLEX data which indicate that ERBITUX improved overall survival in a ‘real world’ non-small cell lung cancer patient population – as this is a disease that kills more people in the United States each year than all the other major cancers combined,” said Laurie Fenton Ambrose, President of Lung Cancer Alliance (www.lungcanceralliance.org).

Details of the Study Results

In the FLEX trial, patients with Stage IIIb or Stage IV NSCLC were randomized to receive either ERBITUX in combination with platinum-based chemotherapy, cisplatin/vinorelbine (n=557), or platinum-based chemotherapy alone (n=568). Ninety-four percent of patients in the ERBITUX plus chemotherapy arm had Stage IV (metastatic) NSCLC and 17 percent had an Eastern Cooperative Oncology Group (ECOG) performance status of 2, which is indicative of extensive tumor burden and an overall poor prognosis. The primary endpoint was overall survival.

With regard to safety, grade 3/4 adverse events were reported in 91 percent of patients in the ERBITUX plus chemotherapy arm compared with 86 percent of patients in the chemotherapy alone arm. Grade 3/4 adverse events reported in patients in the ERBITUX plus chemotherapy versus chemotherapy alone arms included: neutropenia (53 percent vs 51 percent.), febrile neutropenia (22 percent vs 15 percent), anemia (14 percent vs 17 percent), acne-like rash (10 percent vs 0.2 percent).
diarrhea (5 percent vs 2 percent), and infusion-related reactions (4 percent vs <1 percent).

**About Lung Cancer**

The American Cancer Society estimates that in the United States, more than 215,000 people will be diagnosed with lung cancer in 2008, which accounts for about 15 percent of all cancer diagnoses. Approximately 87 percent of these patients will be diagnosed with NSCLC, with many being diagnosed with locally advanced or metastatic disease. Lung cancer is the leading cause of cancer-related death in men and women, with more than 161,000 deaths expected to occur in 2008 – accounting for about 29 percent of all cancer deaths. In 2008, it is estimated that more Americans will die from lung cancer than breast, prostate, and colorectal cancers combined.

**About ERBITUX® (Cetuximab)**

ERBITUX (cetuximab) is a monoclonal antibody (IgG1 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 *vivo* 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 *vivo*, ERBITUX can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. In *vivo* assays and *in vivo* animal studies have shown that ERBITUX inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of ERBITUX were observed in human tumor xenografts lacking EGFR expression.

**Squamous Cell Carcinoma of the Head and Neck (SCCHN)**

ERBITUX, in combination with radiation therapy, is indicated for the initial 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.

**Colorectal Cancer**

ERBITUX, as a single agent, is indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. ERBITUX, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens.

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

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

**IMPORTANT SAFETY INFORMATION**

Grade 3/4 infusion reactions occurred in approximately 3% of patients receiving ERBITUX (Cetuximab) in clinical trials, with fatal outcome reported in less than 1 in 1000. Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of ERBITUX, included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, loss of consciousness, and/or cardiac arrest. Most reactions (90%) were associated with the first infusion of ERBITUX despite premedication with antihistamines. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions. Monitor patients for 1 hour following ERBITUX infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Longer observation periods may be required in patients who require treatment for infusion reactions.

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 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. Carefully consider the use of ERBITUX in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease, congestive heart failure or arrhythmias in light of these risks. Closely monitor serum electrolytes including serum magnesium, potassium, and calcium during and after ERBITUX therapy.

Interstitial lung disease (ILD), which was fatal in one case, occurred in 4 of 1570 (<0.5%) patients receiving ERBITUX in clinical trials. Interrupt ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX where ILD is confirmed.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (eg, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, cheilitis), and hypertrichosis, occurred in patients receiving ERBITUX therapy. Acneform rash occurred in 76-88% of 1373 patients receiving ERBITUX in clinical trials. Severe acneform rash occurred in 1-17% of patients. Acneform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae. Sun exposure may exacerbate these effects.

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, radiation therapy, and cisplatin (100 mg/m²) 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. Two of these discontinuations were due to cardiac events.

Hypomagnesemia occurred in 55% (199/365) of patients receiving ERBITUX and was severe (NCI CTC grades 3 & 4) in 6-17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of ERBITUX therapy. Monitor patients periodically for hypomagnesemia, hypocalcemia and hypokalemia, during, and for at least 8 weeks following the completion of, ERBITUX therapy. Replete electrolytes as necessary.

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%), and skin (42%/33%) in the ERBITUX and radiation versus radiation alone arms, respectively. The incidence of grade 3 or 4 late radiation toxicities were similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms.

In women of childbearing potential, appropriate contraceptive measures must be used during treatment with ERBITUX and for 6 months following the last dose of ERBITUX. ERBITUX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

The most serious adverse reactions associated with ERBITUX across all studies were infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

The most common adverse reactions associated with ERBITUX (incidence ≥25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The most frequent 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) (incidence ≥50%) were acneform rash (87%/10%), radiation dermatitis (86%/90%), weight loss (84%/72%), and asthenia (56%/49%). The most common grade 3/4 adverse events (≥10%) included: radiation dermatitis (23%), acneform rash (17%), and weight loss (11%).

The most frequent adverse events seen in patients with metastatic colorectal cancer (n=288) in the ERBITUX + best supportive care arm (incidence ≥ 50%) were fatigue (89%), rash/desquamation (89%), abdominal pain (59%), and pain-other (51%). The most common grade 3/4 adverse events ≥10% included: fatigue (33%), pain-other (16%), dyspnea (16%), abdominal pain (14%), infection without neutropenia (13%), rash/desquamation (12%), and gastrointestinal-other (10%).

The most frequent adverse events seen in patients with metastatic colorectal cancer (n=354) treated with ERBITUX plus irinotecan in clinical trials (incidence ≥ 50%) were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3/4 adverse events ≥10% included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

**About ImClone Systems**

ImClone Systems Incorporated is a fully integrated biopharmaceutical company committed to advancing oncology care by developing and commercializing 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' headquarters and research operations are located in New York City, with additional administration and manufacturing facilities in Branchburg, New Jersey. For more information about ImClone Systems, please visit the Company's web site at [http://www.imclone.com](http://www.imclone.com).

ERBITUX® is a registered trademark of ImClone Systems Incorporated.

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 a global biopharmaceutical and related health care products company whose mission is to extend and enhance human life. Visit Bristol-Myers Squibb at [www.bms.com](http://www.bms.com).

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