



ImClone Systems and Bristol-Myers Squibb Update the Status of Non-Small Cell Lung Cancer Supplemental Biologics Application Submission for ERBITUX[®]

NEW YORK--([BUSINESS WIRE](#))--[ImClone Systems](#), a wholly-owned subsidiary of [Eli Lilly and Company](#) (NYSE: LLY), and [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced that the companies have decided, after discussion with the U.S. Food and Drug Administration (FDA), to withdraw, and eventually resubmit, the advanced non-small cell lung cancer (NSCLC) supplemental Biologics License Application (sBLA) for ERBITUX[®] (cetuximab). This decision was based upon a Chemistry Manufacturing and Controls (CMC) matter with regard to the pre-clinical pharmacokinetic comparability of the U.S. marketed version of ERBITUX with the clinical supplies used by Merck KGaA (ImClone's partner for ERBITUX outside of North America).

It is important to note that the discussions with FDA do not have any impact on currently-marketed ERBITUX, including the safety and efficacy of the product for approved indications.

About Lung Cancer

The American Cancer Society estimates that in the United States, more than 215,000 people were diagnosed with lung cancer in 2008, which accounts for about 15 percent of all cancer diagnoses. Approximately 87 percent of these patients were diagnosed with NSCLC, with many being diagnosed with locally advanced or metastatic disease. More than 161,000 deaths from lung cancer were expected to occur in 2008 – accounting for about 29 percent of all cancer deaths.

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 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. *In vitro* 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 egarding infusion reactions and cardiopulmonary arrest, visit <http://www.ERBITUX.com>.

IMPORTANT SAFETY INFORMATION

Infusion Reactions

- 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, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest
- Most (90%) of the severe infusion reactions 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

- 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

Pulmonary Toxicity

- 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

Dermatologic Toxicities

- In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (eg, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, 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

ERBITUX Plus Radiation Therapy and Cisplatin

- 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

Electrolyte Depletion

- 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

Late Radiation Toxicities

- 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

Pregnancy

- 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

Adverse Events

- 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 $\geq 25\%$) 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 $\geq 50\%$) 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 for ERBITUX in combination with radiation therapy ($\geq 10\%$) 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 $\geq 50\%$) were fatigue (89%), rash/desquamation (89%), abdominal pain (59%), and pain-other (51%). The most common grade 3/4 adverse events ($\geq 10\%$) included: fatigue (33%), pain-other (16%), dyspnea (16%), abdominal pain (14%), infection without neutropenia (13%), rash/desquamation (12%), and other-gastrointestinal (10%)
- The most frequent adverse events seen in patients with metastatic colorectal cancer (n=354) treated with ERBITUX plus irinotecan in clinical trials (incidence $\geq 50\%$) were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3/4 adverse events ($\geq 10\%$) included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%)

About ImClone Systems

ImClone Systems, a wholly-owned subsidiary of Eli Lilly and Company, is 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. ImClone's research and development programs include growth factor blockers and angiogenesis inhibitors. ImClone's research operations are located in New York City, with additional administration and manufacturing facilities in Branchburg, New Jersey. Additional information about ImClone is available at www.imclone.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers – through medicines and information – for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to extend and enhance human life. For more information, visit www.bms.com.

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. Among other risks, there can be no guarantee that the supplemental application will be approved. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's and Lilly's businesses, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's and Lilly's Annual Reports on Form 10-K for the year ended December 31, 2007, in their Quarterly Reports on Form 10-Q and their Current Reports on Form 8-K. Neither Bristol-Myers Squibb nor Lilly undertakes any obligation to publicly update any forward-looking statement, whether as a result of new information, future

events or otherwise.