ImClone Systems and Bristol-Myers Squibb Announce Revisions to ERBITUX® (cetuximab) U.S. Product Labeling for Metastatic Colorectal Cancer

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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 U.S. Food and Drug Administration (FDA) has approved revisions to the U.S. prescribing information for ERBITUX® (cetuximab) concerning the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC). The labeling revisions include a modification to the indication, which now includes a statement that retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for ERBITUX in patients whose tumors had K-ras mutations in codon 12 or 13 and that the use of ERBITUX is not recommended for the treatment of colorectal cancer with these mutations. Revisions concerning the use of ERBITUX in colorectal cancer tumors with K-ras mutations were also made to the clinical studies and clinical pharmacology sections of the product’s prescribing information.

Recently, both the American Society of Clinical Oncology and the National Comprehensive Cancer Network issued guidelines recommending that all mCRC patients be tested for K-ras gene mutations prior to treatment with an anti-EGFR monoclonal antibody therapy (mAb). Based upon these expert guidelines and the recent labeling update, ImClone Systems, Bristol-Myers Squibb and Lilly recommend that all patients should be tested for K-ras mutational status when considering treatment options for colorectal cancer patients.

In mCRC, ERBITUX is approved by the FDA as: a single agent for the treatment of EGFR-expressing mCRC after failure of both irinotecan- and oxaliplatin-based regimens; a single agent for the treatment of EGFR-expressing mCRC in patients who are intolerant to irinotecan-based regimens; and in combination with irinotecan for the treatment of EGFR-expressing mCRC 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. Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for ERBITUX in patients whose tumors had K-ras mutations in codon 12 or 13. Use of ERBITUX is not recommended for the treatment of colorectal cancer with these mutations.

An estimated 40 percent of patients with mCRC have K-ras mutations while the majority, approximately 60 percent, has a wild-type K-ras gene. Signal transduction through the EGFR results in activation of wild-type K-ras protein. However, in cells with activating K-ras somatic mutations, the mutant K-ras protein is continuously active and appears independent of EGFR regulation.

“This revision is being included in the labeling of EGFR monoclonal antibody inhibitors with metastatic colorectal cancer indications in the U.S. and is the result of a collaborative dialogue between the FDA, the industry and the public about the role of the K-ras biomarker in metastatic colorectal cancer patients being considered for therapy,” said Eric K. Rowinsky, M.D., Executive Vice President and Chief Medical Officer of ImClone Systems.

This revision is based on retrospective analyses across seven randomized clinical trials that suggest anti-EGFR mAbs are not effective for the treatment of patients with mCRC containing K-ras mutations. In these trials, patients received standard of care (i.e., BSC or chemotherapy) and were randomized to receive an anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies, investigational tests were used to detect K-ras mutations in codon 12 or 13. The percentage of study populations for which K-ras status was assessed ranged from 23% to 92%.

“The inclusion of K-ras as a biomarker in the ERBITUX labeling helps physicians to better understand the most appropriate use of the drug in the management of patients with metastatic colorectal cancer,” said Fouad Namouni, M.D., Executive Director, ERBITUX, Oncology Medical Strategy for Bristol-Myers Squibb.

For Full Prescribing Information, including BOXED WARNINGS, visit http://www.ERBITUX.com.

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. Signal transduction through the EGFR results in activation of wild-type K-ras protein. However, in cells with activating K-ras somatic mutations, the mutant K-ras protein is
continuously active and appears independent of EGFR regulation. 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.

Important Safety Information Including BOXED WARNINGS

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
  - Immediately interrupt and permanently discontinue ERBITUX infusions for serious infusion reactions
  - 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

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, paronychial inflammation, infectious sequelae (eg, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, chelitis), 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

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

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 may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. 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 metastatic colorectal cancer studies were infusion reactions, dermatologic toxicity, 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 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 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 ≥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
Additional information about ImClone, a wholly-owned subsidiary of Eli Lilly and Company, is available at [www.imclone.com](http://www.imclone.com).

About Eli Lilly and Company
Additional information about Lilly is available at [www.lilly.com](http://www.lilly.com).

About Bristol-Myers Squibb
Additional information about Bristol-Myers Squibb is available at [www.bms.com](http://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. 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 statement and risk factors discussion in Bristol-Myers Squibb’s and Lilly’s Annual Reports on Form 10-K, 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.

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English

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