



April 16, 2015

## Lilly, Bristol-Myers Squibb Restructure Erbitux® (cetuximab) Collaboration in North America

### *Full Commercialization Rights Transferred to Lilly*

INDIANAPOLIS & NEW YORK--(BUSINESS WIRE)-- [Eli Lilly and Company](#) (NYSE:LLY) and [Bristol-Myers Squibb Company](#) (NYSE:BMJ) today announced that the companies have agreed to transfer rights to *Erbitux*® (cetuximab) in North America, including the U.S., Canada, and Puerto Rico, from Bristol-Myers Squibb to Lilly. Rights include, but are not limited to, full commercialization and manufacturing operational responsibilities. The companies' decision comes after a 14-year successful collaboration, which includes Lilly's wholly-owned subsidiary ImClone LLC. Bristol-Myers Squibb and Lilly will work closely to ensure a smooth transition on this important product for patients with certain advanced colorectal and head and neck cancers.

"Fully bringing *Erbitux* into the Lilly Oncology portfolio accelerates Lilly's commitment and leadership in gastrointestinal cancers to include an effective treatment for advanced colorectal cancer as well as head and neck cancer," said Sue Mahony, Ph.D., senior vice president and president of Lilly Oncology. "Our good work on *Erbitux* began with its development at ImClone and has continued with Bristol-Myers Squibb. We look forward to carrying on these efforts for people battling select advanced colorectal and head and neck cancers."

"Bristol-Myers Squibb is incredibly proud to have built *Erbitux* into a major brand and an important therapy for so many patients with certain colorectal and head and neck cancers," said Murdo Gordon, head of worldwide markets, Bristol-Myers Squibb. "This agreement further aligns our Oncology organization with our prioritized opportunities in immuno-oncology, across both solid tumors and hematologic malignancies."

The transition is expected to be completed in the fourth quarter of 2015. Bristol-Myers Squibb will receive tiered royalties based on net product sales in North America after the completion of the transition through September 2018.

### **About *Erbitux***

*Erbitux* is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

#### **Head and Neck Cancer**

- *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 (SCCHN)
- *Erbitux* is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic 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* is indicated for the treatment of *KRAS* (wild-type), epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use:

- in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan

Limitation of Use: *Erbitux* is not indicated for treatment of *Ras-mutant* colorectal cancer or when the results of the *Ras* mutation tests are unknown.

### **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 infusion for serious infusion reactions**
- **Approximately 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. In 3 patients with prior history of coronary artery disease, death occurred 27, 32, and 43 days after the last dose of ERBITUX. One patient with no prior history of coronary artery disease died one day after the last dose of ERBITUX. Fatal cardiac disorders and/or sudden death occurred in 7 (3%) of the 219 patients with squamous cell carcinoma of the head and neck treated with platinum-based therapy with 5-fluorouracil (5-FU) and European Union (EU)-approved cetuximab as compared to 4 (2%) of the 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin**
  - **Carefully consider the use of ERBITUX in combination with radiation therapy or platinum-based therapy with 5-FU 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 Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD**

## Dermatologic Toxicities

- **In clinical studies of ERBITUX, dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (eg, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis, occurred in patients receiving ERBITUX therapy.**
- **Acneiform rash occurred in 76-88% of 1373 patients receiving ERBITUX in Studies 1, 3, 5, and 6. Severe acneiform rash occurred in 1-17% of patients. Acneiform rash usually developed within the first 2 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**
- **Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Erbitux. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens Johnson syndrome or toxic epidermal necrolysis)**
- **Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae**
- **Sun exposure may exacerbate these effects**

## ERBITUX Plus Radiation Therapy and Cisplatin

- In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3-4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone
- Adverse reactions with fatal outcome were reported in 20 patients (4.4%) in the ERBITUX combination arm and 14 patients (3.0%) in the control arm
- Nine patients in the ERBITUX arm (2.0%) experienced myocardial ischemia compared to 4 patients (0.9%) in the control arm
- The addition of ERBITUX to radiation and cisplatin did not improve progression-free survival (the primary endpoint)

### **Electrolyte Depletion**

- Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in Study 5 and two other clinical trials in colorectal cancer and head and neck cancer, respectively, and was severe (NCI CTC grades 3 & 4) in 6-17%. In Study 2 the addition of EU-approved cetuximab to cisplatin and 5-FU resulted in an increased incidence of hypomagnesemia (14% vs 6%) and of grade 3-4 hypomagnesemia (7% vs 2%) compared to cisplatin and 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs 4%). No patient experienced grade 3-4 hypomagnesemia in either arm in the carboplatin subgroup. 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

### **Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC**

- Erbitux is not indicated for the treatment of patients with colorectal cancer that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras
- Based on retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials of anti-EGFR-directed monoclonal antibodies, including Study 4, use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity

### **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% vs 56%), larynx (52% vs 36%), subcutaneous tissue (49% vs 45%), mucous membranes (48% vs 39%), esophagus (44% vs 35%), and skin (42% vs 33%) in the ERBITUX and radiation versus radiation-alone arms, respectively
  - The incidence of grade 3 or 4 late radiation toxicities was similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms

### **Pregnancy and Nursing**

- In women of childbearing potential and men, 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
- It is not known whether ERBITUX is secreted in human milk. IgG antibodies, such as ERBITUX, can be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ERBITUX, a decision should be made whether to discontinue nursing or to discontinue ERBITUX, taking into account the importance of ERBITUX to the mother. If nursing is interrupted, based on the mean half-life of cetuximab, nursing should not be resumed earlier than 60 days following the last dose of ERBITUX

### **Adverse Reactions**

- The most **serious adverse reactions** associated with ERBITUX are 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  $\geq 25\%$ ) across all studies were cutaneous

adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection

- The most frequent adverse reactions 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 acneiform rash (87% vs 10%), radiation dermatitis (86% vs 90%), weight loss (84% vs 72%), and asthenia (56% vs 49%). The most common grade 3/4 adverse reactions for ERBITUX in combination with radiation therapy ( $\geq 10\%$ ) versus radiation alone included: radiation dermatitis (23% vs 18%), acneiform rash (17% vs 1%), and weight loss (11% vs 7%)
- The most frequent adverse reactions seen in patients with carcinomas of the head and neck receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU (CT) (n=219) versus CT alone (n=215) (incidence  $\geq 40\%$ ) were acneiform rash (70% vs 2%), nausea (54% vs 47%), and infection (44% vs 27%). The most common grade 3/4 adverse reactions for cetuximab in combination with CT ( $\geq 10\%$ ) versus CT alone included: infection (11% vs 8%). Since U.S.-licensed ERBITUX provides approximately 22% higher exposure relative to the EU-approved cetuximab, the data provided above may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX
- The most frequent adverse reactions seen in patients with *KRAS* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer treated with EU-approved cetuximab + FOLFIRI (n=317) versus FOLFIRI alone (n=350) (incidence  $\geq 50\%$ ) were acne-like rash (86% vs 13%) and diarrhea (66% vs 60%). The most common grade 3/4 adverse reactions ( $\geq 10\%$ ) included: neutropenia (31% vs 24%), acne-like rash (18% vs < 1%), and diarrhea (16% vs 10%). U.S.-licensed ERBITUX provides approximately 22% higher exposure to cetuximab relative to the EU-approved cetuximab. The data provided above are consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication. The tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX
- The most frequent adverse reactions seen in patients with *KRAS* mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer treated with ERBITUX + best supportive care (BSC) (n=118) versus BSC alone (n=124) (incidence  $\geq 50\%$ ) were rash/desquamation (95% vs 21%), fatigue (91% vs 79%), nausea (64% vs 50%), dry skin (57% vs 15%), pain-other (59% vs 37%), and constipation (53% vs 38%). The most common grade 3/4 adverse reactions ( $\geq 10\%$ ) included: fatigue (31% vs 29%), pain-other (18% vs 10%), rash/desquamation (16% vs 1%), dyspnea (16% vs 13%), other-gastrointestinal (12% vs 5%), and infection without neutropenia (11% vs 5%)
- The most frequent adverse reactions seen in patients with EGFR-expressing metastatic colorectal cancer (n=354) treated with ERBITUX plus irinotecan in clinical trials (incidence  $\geq 50\%$ ) were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3/4 adverse reactions ( $\geq 10\%$ ) included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%)

Please read the [U.S. Full Prescribing Information](#) including **Boxed WARNINGS**.

## About Eli Lilly and Company

Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at [www.lilly.com](http://www.lilly.com) and <http://newsroom.lilly.com/social-channels>.

## About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [www.bms.com](http://www.bms.com) or follow us on Twitter at <http://twitter.com/bmsnews>.

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## Bristol-Myers Squibb and Eli Lilly and Company Forward-Looking Statement

*This press release contains "forward-looking statements" (as that term is defined in the Private Securities Litigation Reform Act of 1995) regarding the parties' North American collaboration for ERBITUX. 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 transition will be completed in the timeframe described in this release. In addition, the amount of royalties paid to Bristol-Myers Squibb through September 2018 may differ 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 for the year ended December 31, 2014, 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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