FDA Expands Lilly's ERBITUX® (cetuximab) Label with Combination of BRAFTOVI® (encorafenib) for the Treatment of BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC) after Prior Therapy

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ERBITUX® is the first and only anti-EGFR antibody approved, in combination with encorafenib, specifically for adults with previously treated metastatic CRC with a BRAF V600E mutation

INDIANAPOLIS, Sept. 28, 2021 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that the U.S. Food and Drug Administration (FDA) has granted approval of a new indication for ERBITUX® (cetuximab injection) in combination with BRAFTOVI® (encorafenib), marketed by Pfizer, Inc., for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.[1] ERBITUX is the first and only anti-EGFR antibody approved, in combination with encorafenib, for this indication and is based on results from Pfizer's BEACON CRC trial, the only Phase 3 trial to specifically study patients with previously treated metastatic CRC with a BRAF V600E mutation. With this approval, ERBITUX has now received seven FDA approvals to treat certain types of CRC and squamous cell carcinoma of the head and neck.

"The BEACON study showed that the combination of ERBITUX and encorafenib significantly improved overall survival in patients with metastatic colorectal cancer with a BRAF V600E mutation – a subtype that typically has worse outcomes compared to those without the mutation," said David Hyman, M.D., chief medical officer, oncology at Lilly. "We are grateful to Pfizer for their collaboration as we've worked to bring this treatment regimen to patients."

Based on results from the BEACON CRC trial, ERBITUX plus encorafenib showed a median overall survival (OS) of 8.4 months (95% CI: 7.5, 11.0), compared to 5.4 months (95% CI: 4.8, 6.6) for the control arm (irinotecan with ERBITUX or FOLFIRI with ERBITUX) ([HR 0.60, (95% CI: 0.45, 0.79), p=0.0003]). Additionally, ERBITUX plus encorafenib showed an objective response rate (ORR) of 20% (95% CI: 13%, 29%), compared to 2% (95% CI: 0%, 7%) for the control arm (p<0.0001), and a median progression-free survival (mPFS) of 4.2 months (95% CI: 3.7, 5.4), compared to 1.5 months for the control arm (95% CI: 1.4, 1.7) ([HR 0.40, (95% CI: 0.31, 0.52), p<0.0001]).

Efficacy Results

Endpoint	ERBITUX with encorafenib N=220	ERBITUX with irinotecan or ERBITUX with FOLFIRI N=221
OS		
Number of Events (%)	93 (42)	114 (52)
Median OS, months (95% CI)	8.4 (7.5, 11.0)	5.4 (4.8, 6.6)
HR (95% CI)[a,b]	0.60 (0.45, 0.79)	
p-value[a,c]	0.0003	
ORR (per BICR)		
ORR (95% CI)[d]	20% (13%, 29%)	2% (0%, 7%)
CR	5%	0%
PR	15%	2%
p-value[a,e]	<0.0001	
Median DoR, months (95% CI)	6.1 (4.1, 8.3)	NR (2.6, NR)
PFS (per BICR)		
Number of events (%)	133 (60)	128 (58)
Progressive disease	110 (50)	101 (46)
Death	23 (10)	27 (12)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.4, 1.7)
HR (95% CI)[a,b]	0.40 (0.31, 0.52)	
p-value[a,f]	<0.0001	

[a]Stratified by ECOG PS, source of ERBITUX (US-licensed versus EU-approved) and prior irinotecan use at randomization

[b]Stratified Cox proportional hazard model

[c]Stratified log-rank test, tested at alpha level of 0.0084

[d]ERBITUX/encorafenib arm (n=113) and control arm (n=107)

[e]Cochran-Mantel-Haenszel test; tested at alpha level of 0.05

[f] Stratified log-rank test, tested at alpha level of 0.0234

The safety of ERBITUX (400 mg/m2 initial infusion, followed by 250 mg/m2 weekly) in combination with encorafenib (300 mg once daily) was evaluated in 216 patients with BRAF V600E mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BEACON CRC).

The most common (≥25%) adverse reactions in patients receiving ERBITUX in combination with encorafenib were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash.

The labeling for ERBITUX includes warnings and precautions for infusion reactions, cardiopulmonary arrest, pulmonary toxicity, dermatologic toxicity, hypomagnesemia and accompanying electrolyte abnormalities, and embryo-fetal toxicity. Please see below for full Important Safety Information.

On April 8, 2020, Pfizer's encorafenib was approved by the FDA for this indication, based on data from the BEACON CRC study.

About the BEACON CRC Study
Encorafenib in combination with ERBITUX was evaluated in the randomized, active-controlled, open-label, multicenter, Phase 3 BEACON CRC trial. Eligible patients were required to have BRAF V600E mutant metastatic CRC, as detected by an FDA-approved test, with disease progression after one or two prior regimens. Patients were randomized 1:1:1 to one of the following treatment arms:

- Encorafenib 300 mg orally once daily in combination with ERBITUX (encorafenib/ ERBITUX arm)
- Encorafenib 300 mg orally once daily in combination with ERBITUX and binimetinib
- Irinotecan with ERBITUX or FOLFIRI with ERBITUX (control arm)

The major efficacy outcome measure was OS. Additional efficacy outcome measures included PFS, ORR, and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomized patients. ORR and DoR were assessed in the subset of the first 220 patients included in the randomized portion of the encorafenib/ERBITUX and control arm of the study. A total of 220 patients were randomized to the encorafenib/ERBITUX arm and 221 to the control arm. The trial was conducted at over 200 investigational sites in North America, South America, Europe and the Asia Pacific region.

About Colorectal Cancer
Worldwide, colorectal cancer (CRC) is the second leading cause of cancer death. With approximately 1.9 million new diagnoses in 2020, CRC is third most common type of cancer in men and the second most common in women.[1] In the U.S. alone, an estimated 149,500 people will be diagnosed with cancer of the colon or rectum in 2021, and approximately 53,000 are estimated to die of the disease each year.[2] BRAF mutations are estimated to occur in up to 15 percent of people with metastatic CRC and represent a poor prognosis for these patients.[3, 4, 5, 6, 7, 8] The BRAF V600E mutation is the most common BRAF mutation and the risk of mortality in CRC patients with the BRAF V600E mutation is more than two times higher than for those with wild-type BRAF.[5, 6]

Indications and Usage for ERBITUX® (cetuximab) injection

Head and Neck Cancer
ERBITUX (cetuximab) is approved:

- ERBITUX, in combination with radiation therapy (RT), 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 and fluorouracil (CT) for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN
- ERBITUX, as a single agent, is indicated for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed

Metastatic 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 an FDA-approved test for this use:

- In combination with FOLFIRI (irinotecan, 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

Limitations of Use: ERBITUX is not indicated for treatment of RAS-mutant colorectal cancer or when the results of the RAS mutation tests are unknown

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer
ERBITUX is indicated, in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

IMPORTANT SAFETY INFORMATION FOR ERBITUX® (cetuximab)

WARNING: INFUSION REACTIONS AND CARDIOPULMONARY ARREST

Infusion Reactions
- **ERBITUX can cause serious and fatal infusion reactions. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients receiving ERBITUX in clinical trials.**

• The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal). Consider testing patients for alpha-gal IgE antibodies using FDA-cleared methods prior to initiating ERBITUX. Negative results for alpha-gal antibodies do not rule out the risk of severe infusion reactions.

• Approximately 90% of the severe infusion reactions occurred with the first infusion of ERBITUX despite premedication with antihistamines.

- **Serious infusion reactions, requiring immediate medical intervention, included symptoms of 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.**
- **Caution must be exercised with every ERBITUX infusion as infusion reactions may occur during or several hours following completion of the infusion.**
- **Premedicate with a histamine-1 (H_1) receptor antagonist as recommended.**
- **Monitor patients for at least 1 hour following each ERBITUX infusion in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. In patients requiring treatment for infusion reactions, monitor for more than 1 hour to confirm resolution of the reaction. Interrupt the infusion and upon recovery, resume the infusion at a slower rate or permanently discontinue ERBITUX based on severity.**

Cardiopulmonary Arrest

• ERBITUX can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 patients with squamous cell carcinoma of the head and neck receiving radiation therapy and ERBITUX in BONNER. In 3 patients with prior history of coronary artery disease, death occurred 27, 32, and 43 days respectively 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. In EXTREME, fatal cardiac disorders and/or sudden death occurred in 3% of the 219 patients with squamous cell carcinoma of the head and neck treated with a cetuximab product in combination with platinum-based therapy and fluorouracil.

- **Carefully consider the use of ERBITUX with radiation therapy, or with platinum-based therapy with fluorouracil, in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias.**
- **Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX therapy.**

Pulmonary Toxicity

- ERBITUX can cause interstitial lung disease (ILD). ILD, which was fatal in one case, occurred in <0.5% of 1570 patients receiving ERBITUX in clinical trials. Monitor patients for signs and symptoms of pulmonary toxicity. Interrupt or permanently discontinue ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD.

Dermatologic Toxicities

- ERBITUX can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (e.g., *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis
  - Acneiform rash occurred in 82% of the 1373 patients who received ERBITUX across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 10% of patients. Acneiform rash usually developed within the first 2 weeks of therapy; the rash lasted more than 28 days after stopping ERBITUX in most patients.
  - Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has been observed in patients who received ERBITUX. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis).
  - Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae.
  - Sun exposure may exacerbate these effects. Instruct patients to limit sun exposure during ERBITUX therapy.
  - Withhold, reduce dose or permanently discontinue ERBITUX based on severity of acneiform rash or mucocutaneous disease.

Risks Associated with Use in Combination with Radiation and Cisplatin

- ERBITUX is not indicated for the treatment of SCCHN in combination with radiation 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 and 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 4% of patients in the ERBITUX combination arm and 3% in the control arm.
- In the ERBITUX arm, 2% experienced myocardial ischemia compared to 0.9% in the control arm.
- The addition of ERBITUX to radiation and cisplatin did not improve progression-free survival (the primary endpoint).

Hypomagnesemia and Accompanying Electrolyte Abnormalities

- ERBITUX can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in study CA225-025 and two other clinical trials in patients with colorectal cancer (CRC) or head and neck cancer, including Grades 3 and 4 in 6% to 17%. In EXTREME, where a cetuximab product was administered in combination with platinum-based therapy, the addition cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No patient experienced grade 3 or 4 hypomagnesemia. The onset of hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating ERBITUX.
    - Monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of ERBITUX.
    - 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 CRC 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 and hereafter referred to as "Ras" or when the Ras status is unknown.
- Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials, including CRYSTAL, were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. Confirm Ras mutation status in tumor specimens prior to initiating ERBITUX.

Embryo-Fetal Toxicity

- Based on animal data and its mechanism of action, ERBITUX can cause fetal harm when administered to a pregnant woman. There are no available data for ERBITUX exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryolethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ERBITUX and for 2 months after the last dose of ERBITUX. Verify pregnancy status in females of reproductive potential prior to initiating ERBITUX.

Adverse Reactions

- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with carcinomas of the head and neck receiving ERBITUX in combination with radiation therapy (n=208) versus radiation alone (n=212) (BONNER) were acneiform rash (87% vs 10%), radiation dermatitis (86% vs 90%), weight loss (84% vs 72%), asthenia (56% vs 49%), nausea (49% vs 37%), increased alanine transaminase (43% vs 21%), increased aspartate transaminase (38% vs 24%), increased alkaline phosphatase (33% vs 24%), fever (29% vs 13%), emesis (29% vs 23%), pharyngitis (26% vs 19%) and dehydration (25% vs 19%). The most common grade 3 and 4 adverse reactions for ERBITUX in combination with radiation therapy (≥10%) versus radiation alone included: radiation dermatitis (23% vs 18%), acneiform rash (17% vs 1%), and weight loss (11% vs 7%). The overall incidence of late radiation toxicities (any grade) was higher for patients receiving ERBITUX in combination with radiation therapy, versus radiation therapy alone. The following sites were affected: salivary glands (65% vs 56%), larynx (52% vs 36%), subcutaneous tissue (49% vs 45%), mucous membrane (48% vs 39%), esophagus (44% vs 35%), skin (42% vs 33%). The incidence of Grade 3 or 4 late radiation toxicities was similar between radiation therapy alone and the ERBITUX with radiation treatment groups.
- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with carcinomas of the head and neck receiving a cetuximab product in combination with platinum-based therapy and fluorouracil (CT) (n=219) versus CT alone (n=215) (EXTREME) were acneiform rash (70% vs 2%), nausea (54% vs 47%), infection (44% vs 27%), rash (28% vs 2%), diarrhea (26% vs 16%) and anorexia (25% vs 14%). The most common grade 3 and 4 adverse reaction for a cetuximab product in combination with CT (≥10%) versus CT alone was infection (11% vs 8%). Because ERBITUX provides approximately 22% higher exposure relative to the cetuximab product used in EXTREME, 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 common adverse reactions (all grades; incidence ≥25%) seen in patients with K-Ras wild-type, EGFR-expressing mCRC treated with a cetuximab product in combination with FOLFIRI (n=317) versus FOLFIRI alone (n=350) (CRYSTAL) were acne-like rash (86% vs 13%), diarrhea (66% vs 60%), neutropenia (49% vs 42%), rash (44% vs 4%), stomatitis (31% vs 19%), anorexia (30% vs 23%), dermatitis acneiform (26% vs <1%) and pyrexia (26% vs 14%). The most common grade 3 and 4 adverse reactions (≥10%) included: neutropenia (31% vs 24%), acne-like rash (18% vs <1%), and diarrhea (16% vs 10%). ERBITUX provides approximately 22% higher exposure compared to the cetuximab product used in CRYSTAL; however, the safety data from CRYSTAL is consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication.

- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with K-Ras wild-type, EGFR-expressing mCRC treated with ERBITUX + best supportive care (BSC) (n=118) versus BSC alone (n=124) (CA225-025) were rash/desquamation (95% vs 21%), fatigue (91% vs 79%), nausea (64% vs 50%), pain-other (59% vs 37%), dry skin (57% vs 15%), constipation (53% vs 38%), dyspnea (49% vs 44%), pruritus (47% vs 11%), neuropathy-sensory (45% vs 38%), diarrhea (42% vs 23%), vomiting (40% vs 26%), headache (38% vs 11%), infection without neutropenia (38% vs 19%), other-dermatology (35% vs 7%), stomatitis (32% vs 10%), nail changes (31% vs 4%), cough (30% vs 19%), insomnia (27% vs 13%) and fever (25% vs 16%). The most common grade 3 and 4 adverse reactions (≥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 common adverse reactions (all grades) seen in patients with EGFR-expressing recurrent mCRC (n=354) treated with ERBITUX plus irinotecan in clinical trials (CP02-9923 and BOND) were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3-4 adverse reactions included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).
- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with BRAF V600E mutation-positive mCRC treated with ERBITUX in combination with encorafenib (N=216) versus ERBITUX with irinotecan or ERBITUX with FOLFIRI (N=193) (BEACON) were fatigue (51% vs 50%), nausea (34% vs 41%), diarrhea (33% vs 48%), dermatitis acneiform (32% vs 43%), abdominal pain (30% vs 32%), decreased appetite (27% vs 27%), arthralgia (27% vs 3%) and rash (26% vs 26%). Other clinically important adverse reactions occurring in <10% of patients who received ERBITUX in combination with encorafenib were pancreatitis. The most common laboratory abnormalities (all grades; incidence ≥20%) seen in patients receiving ERBITUX in combination with encorafenib versus ERBITUX with irinotecan or ERBITUX with FOLFIRI (BEACON) were anemia (34% vs 48%) and lymphopenia (24% vs 35%).

Use in Specific Populations

- **Lactation:** There is no information regarding the presence of ERBITUX in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG antibodies can be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ERBITUX, advise women not to breastfeed during treatment with ERBITUX and for at least 2 months after the last dose of ERBITUX.
- **Pediatric Use:** The safety and effectiveness of ERBITUX in pediatric patients have not been established. No new safety signals were identified in pediatric patients when ERBITUX in combination with irinotecan was administered in an open-label, single-arm dose-finding study in 27 patients with refractory solid tumors aged 1 to 12 years old and in 19 patients aged 13 to 18 years old.
  Geriatric Use: In SCCHN clinical studies of ERBITUX there were insufficient number of patients >65 years of age to determine whether they respond differently from younger patients.

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Please see full Prescribing Information for ERBITUX, including Boxed Warnings regarding infusion reactions and cardiopulmonary arrest.

About Lilly Oncology
For more than 50 years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly's commitment to people with cancer, please visit www.LillyOncology.com.

About Eli Lilly and Company
Lilly is a global health care leader that unites caring with discovery to create medicines that 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 lilly.com and lilly.com/newsroom. P-LLY

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Lilly Forward-Looking Statement
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about ERBITUX as a treatment for adult patients with metastatic colorectal cancer with a BRAF V600E mutation, and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date or that ERBITUX will receive additional regulatory approvals or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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