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Lilly Announces CYRAMZA™ Phase III Second-line Colorectal Cancer Trial Meets Primary Endpoint of Overall Survival

-- Ramucirumab Plus FOLFIRI Improved Survival in Metastatic Colorectal Cancer following Progression on a Bevacizumab-Based Regimen --

INDIANAPOLIS, Sept. 12, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that the RAISE trial, a Phase III study of ramucirumab (CYRAMZA™) in combination with chemotherapy in patients with metastatic colorectal cancer (mCRC), met its primary endpoint of overall survival. The global, randomized, double-blind study compared ramucirumab plus FOLFIRI to placebo plus FOLFIRI as a second-line treatment in patients with mCRC after treatment with bevacizumab, oxaliplatin and a fluoropyrimidine in the first-line setting.

RAISE showed a statistically significant improvement in overall survival in patients treated with ramucirumab plus FOLFIRI compared to placebo plus FOLFIRI. The study also showed a statistically significant improvement in progression-free survival in the ramucirumab-plus-FOLFIRI arm compared to the placebo-plus-FOLFIRI arm. The most common (> 5% incidence) grade > /=3 adverse events occurring at a higher rate on the ramucirumab-plus-FOLFIRI arm compared to the control arm were neutropenia, fatigue, hypertension, and diarrhea.

Despite advances in treating colorectal cancer in recent years, the mortality rate remains significant. It is the fourth leading cause of cancer death worldwide and the second leading cause of cancer death in the U.S.

"Patients with metastatic colorectal cancer - particularly those in the second-line setting - continue to need new treatment options that improve survival," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "We are pleased that the RAISE study demonstrated a survival benefit and are hopeful that ramucirumab will become a new anti-angiogenic treatment option after first-line bevacizumab-containing therapy for metastatic colorectal cancer patients."

Lilly plans to present data from the RAISE trial at a scientific meeting in 2015 and expects to initiate regulatory submissions in the first half of 2015.

Dr. Gaynor added, "We now have four Phase III ramucirumab trials that improved survival in three of the world's most common and deadly cancers--gastric, lung, and colorectal--supporting global regulatory submissions in multiple indications. The RAISE data also build on Lilly's growing presence in gastrointestinal cancer therapy."

Ramucirumab is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that specifically binds VEGF Receptor 2 and blocks binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. VEGF Receptor 2 is an important mediator in the VEGF pathway.[i,ii] In an *in vivo* animal model, ramucirumab inhibited angiogenesis. Angiogenesis is a process by which new blood vessels form to supply blood to normal healthy tissues as well as tumors, enabling the cancer to grow.

Notes to Editor

About the RAISE trial

RAISE is a global, randomized, double-blind Phase III study of ramucirumab plus FOLFIRI (irinotecan, folinic acid and 5-fluorouracil) compared to placebo and FOLFIRI as a second-line treatment in patients with mCRC who have progressed on or after first-line treatment with bevacizumab, oxaliplatin and a fluoropyrimidine. Of the approximate 33,000 patients currently being treated in the second-line mCRC setting in the U.S., roughly one-third would have been eligible for the RAISE trial based on this first-line treatment.[iii]

Initiated in 2010, the study enrolled more than 1,000 patients across 26 countries. The primary endpoint (also referred to as the major efficacy outcome measure) of the RAISE trial was overall survival and key secondary endpoints (also referred to as the supportive efficacy outcome measures) included: progression-free survival; overall response rate; and safety.

About Colorectal Cancer

Colorectal cancer (CRC) is the fourth leading cause of cancer death worldwide, killing nearly 700,000 people in 2012.[iv] Only

lung, liver, and stomach cancers caused more cancer-related deaths.[iv] In 2012, the global incidence of CRC is estimated to be over 1.3 million.[iv] CRC is the second leading cause of cancer death in the U.S.[v]

CRC is a cancer that develops in the colon or the rectum, which are both parts of the gastrointestinal system. Metastatic CRC (mCRC) occurs when the disease has spread to at least one distant organ, such as the liver, lungs, or lining of the abdomen. One out of five CRC patients is diagnosed with metastatic disease.[vi] The five-year survival rate for patients with mCRC is 11.7 percent.[vii]

About Angiogenesis
Angiogenesis is the process of making new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. Chemical signals in the body stimulate the repair of damaged blood vessels and formation of new blood vessels during this process.

In a person with cancer, angiogenesis creates new blood vessels that give a tumor its own blood supply, allowing it to grow and spread.

Some tumors create proteins called VEGF. These proteins attach to the VEGF receptors of blood vessel cells causing new blood vessels to form around the tumors, enabling growth. Blocking the VEGF protein from linking to the blood vessels helps to inhibit tumor growth by slowing angiogenesis and the blood supply that feeds tumors.

Of the three known VEGF receptors, VEGF Receptor 2 is linked most closely to VEGF-induced tumor angiogenesis.[viii]

About ramucirumab (CYRAMZA™)
Ramucirumab, marketed as CYRAMZA, is approved for use as a single agent in the U.S. for patients with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have progressed after prior fluoropyrimidine- or platinum-containing chemotherapy. CYRAMZA inhibited angiogenesis in an in vivo animal model. CYRAMZA is a VEGF Receptor 2 antagonist that specifically binds and blocks activation of VEGF Receptor 2 and blocks binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D.

There are several studies underway or planned to investigate CYRAMZA as a single agent and in combination with other anti-cancer therapies for the treatment of multiple tumor types.

Indication for CYRAMZA
CYRAMZA as a single agent is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE
CYRAMZA increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Study 1; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events

- Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA is an antiangiogenic therapy with the potential to adversely affect wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of < 0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Most Common Adverse Reactions

- The most commonly reported adverse reactions (all grades; grade 3-4) occurring in ≥5% of patients receiving CYRAMZA and > /=2% higher than placebo in Study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in Study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in > /=1% and < 5% of CYRAMZA-treated patients in Study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade > /=3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In Study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in Study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.
- As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, 33/443 (7.4%) CYRAMZA-treated patients with post-baseline serum samples tested positive for anti-ramucirumab antibodies using an enzyme-linked immunosorbent assay (ELISA). However, this assay has limitations in detecting anti-ramucirumab antibodies in the presence of ramucirumab; therefore, the incidence of antibody development may not have been reliably determined. Neutralizing antibodies were detected in 1 of the 33 patients who tested positive for anti-ramucirumab antibodies.

Drug Interactions

- No formal drug interaction studies have been conducted.

Use in Specific Populations

- Pregnancy Category C: Based on its mechanism of action, CYRAMZA may cause fetal harm. Advise females of reproductive potential to avoid getting pregnant, including use of adequate contraception, while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA. Animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no adequate or well-controlled studies of ramucirumab in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.
- Nursing Mothers: It is recommended to discontinue nursing or discontinue CYRAMZA due to the potential risks to the nursing infant.
- Females of Reproductive Potential: Advise females of reproductive potential that CYRAMZA may impair fertility.

Please see full Prescribing Information for CYRAMZA, including Boxed Warning for hemorrhage.

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About Lilly Oncology
For more than fifty 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 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 and http://newsroom.lilly.com/social-channels.

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This press release contains forward-looking statements about the potential of CYRAMZA™ (ramucirumab) as a treatment of various cancers and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that future studies will be positive or that ramucirumab will receive additional regulatory approvals or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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[i] Shibuya M. Vascular endothelial growth factor-dependent and -independent regulation of angiogenesis. BMB Rep. 2008;41 (4):278-286.

[ii] Spratlin J. Ramucirumab (IMC-1121B): monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. Curr Oncol Rep. 2011;13(2):97-102.

[iii] IntrinsiQ, June 2014 for 2nd Line Drug Treated patient population as well as Bev + oxal-based CT Prior Treatment.

[iv] Globocan: Estimated Cancer Incidence, Mortality and Prevalence Worldwide, 2012.

[v] American Cancer Society, *Cancer Facts & Figures 2012*. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf (Accessed: September 11, 2014).

[vi] Decision Resources Patient Base, 2014.

[vii] National Cancer Institute SEER 18 2004-2010, All Races, Both Sexes by SEER Summary Stage 2000.

[viii] Spratlin J. Ramucirumab (IMC-1121B): monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. Curr Oncol Rep. 2011;13(2):97-102.

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