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Lilly Announces Top-Line Results Of Phase III Hepatocellular Carcinoma Trial

INDIANAPOLIS, June 11, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that the Phase III REACH trial of CYRAMZA™ (ramucirumab) in patients with hepatocellular carcinoma, also known as liver cancer, did not meet its primary endpoint; overall survival favored the CYRAMZA arm but was not statistically significant. Encouraging single-agent CYRAMZA activity was observed, with meaningful improvements in key secondary endpoints of progression-free survival, overall response rate and time to progression.

The global, randomized, double-blind REACH trial compared CYRAMZA plus best supportive care to placebo plus best supportive care as a second-line treatment in patients with hepatocellular carcinoma (HCC) after being treated with sorafenib in the first-line setting. The top-line safety data were consistent with what was seen in previous single-agent CYRAMZA studies. The most common (> 5% incidence) grade > /=3 adverse events occurring at a higher rate on the CYRAMZA arm compared to the control arm were hypertension and asthenia (fatigue).

"Although the REACH study did not achieve statistical significance for survival, we are encouraged by the efficacy seen overall, especially in specific subpopulations. We plan to discuss these results with regulatory authorities," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology.

Liver cancer is a very difficult-to-treat tumor type and no Phase III study has been able to demonstrate improved survival in the second-line setting. This is an area of very high unmet need for which there are no approved therapies.

Lilly plans to present data from the REACH trial at a scientific meeting later this year.

CYRAMZA has been granted Orphan Drug Designation for treatment of hepatocellular carcinoma in the U.S. and EU. Orphan drug status is given - in the U.S. by the FDA's Office of Orphan Products Development (OOPD) and in the EU by the European Commission - to medicines that have demonstrated promise for the treatment of rare diseases.

Notes to Editor

About the REACH trial

REACH is a global, randomized, double-blind Phase III study of CYRAMZA plus best supportive care compared to placebo and best supportive care as a second-line treatment in patients with hepatocellular carcinoma who have been previously treated with sorafenib in the first-line setting. Initiated in 2010, the study enrolled 565 patients across 27 countries; as defined in the trial protocol, the primary analyses are focused on patients with a Child-Pugh score of < 7 (Child-Pugh Class A only). The primary endpoint (also referred to as the major efficacy outcome measure) of the REACH trial was overall survival and key secondary endpoints (also referred to as the supportive efficacy outcome measures) include: progression-free survival; overall response rate; time to progression; and safety.

About Hepatocellular Carcinoma

Liver cancer is the sixth most common cancer worldwide and the second-leading cause of cancer-related death. Each year approximately 780,000 new cases of liver cancer are diagnosed worldwide and over 740,000 will die of the disease.[1] According to the World Health Organization, approximately 30,000 people are diagnosed with liver cancer and 24,000 will die from the disease each year in the United States. In Europe and Japan, an estimated 63,000 and 36,000 people are diagnosed with liver cancer and 62,000 and 33,000 will die, respectively.[1] More than 80% of primary carcinomas of the liver are hepatocellular carcinomas (HCC) or hepatomas.[2]

In general, most patients with advanced HCC have liver damage and have limited treatment options. Once they have developed advanced disease, surgery is not an option for the majority of advanced HCC patients, as the tumor has often grown or metastasized to the extent that resection is not feasible. Specifically, once patients enter the second-line setting, there are no approved therapies and supportive care is the standard in this patient population. Overall, the prognosis for advanced HCC patients is typically very poor.

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.[3]

About CYRAMZA™ (ramucirumab)
CYRAMZA as a single agent is approved in the U.S. for patients with advanced gastric cancer 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.

CYRAMZA, which Lilly gained through its 2008 acquisition of ImClone Systems, is being investigated in clinical trials as a single agent and in combination with other anti-cancer therapies for the treatment of multiple tumor types. Overall, three Phase III trials of CYRAMZA have demonstrated improved overall survival and progression free survival. In addition to the first two in gastric cancer, there is a third, in non-small cell lung cancer. Another Phase III study, in breast cancer, did not meet its endpoint of improved progression-free survival. Top-line results for RAISE, a Phase III trial of CYRAMZA as a potential treatment for metastatic colorectal cancer, are expected later this year.

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) occurring in > /=5% of patients receiving CYRAMZA and > /=2% higher than placebo in Study 1 were hypertension (16% vs 8%), diarrhea (14% vs 9%), headache (9% vs 3%), and hyponatremia (6% vs 2%).
- 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 at http://pi.lilly.com/us/cyramza-pi.pdf.

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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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[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM.
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[2] CancerMPact®. Kantar Health. Available from: www.cancermpact.com. Accessed on June 10, 2014.

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

Contact:

Tracy Henrikson (Lilly Oncology)	Neil Hochman (TogoRun)
908-243-9945 (office)	212-453-2067 (office)
609-240-3902 (mobile)	516-784-9089 (mobile)
Email: tracy.henrikson@imclone.com	Email: n.hochman@togorun.com

Logo - http://photos.prnewswire.com/prnh/20031219/LLYLOGO

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