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Lilly's CYRAMZA™ (ramucirumab) Significantly Improves Overall Survival In Phase III Non Small Cell Lung Cancer Study

-- REVEL Data Published in The Lancet, Presented at Annual ASCO Meeting --

CHICAGO, June 2, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced detailed results from REVEL, a global Phase III study of CYRAMZA™ (ramucirumab) in combination with chemotherapy in patients with second-line non-small cell lung cancer (NSCLC). Data from the trial were published today in *The Lancet* and also presented at the American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract #LBA8006). REVEL is the first positive Phase III study of a biologic in combination with chemotherapy to demonstrate improved overall survival compared to chemotherapy alone in second-line NSCLC.

Lung cancer is the leading cause of cancer death in the U.S. and most other countries, and non-small cell lung cancer accounts for 85 percent of all lung cancer cases. It is estimated that approximately half of NSCLC patients are receiving treatment in the second-line setting. Despite currently available therapies, there continues to be a need for new second-line treatment options for patients with NSCLC.

"While there have been other recent Phase III studies that have evaluated the addition of a cytotoxic or targeted agent in previously-treated NSCLC patient populations, none have demonstrated improved overall survival in the total patient population," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "We are pleased that CYRAMZA demonstrated a significant survival improvement in a difficult-to-treat patient population where there continues to be a major unmet medical need in both nonsquamous and squamous NSCLC patients. These data build on Lilly's continued commitment to discovering potential new treatment options for the large numbers of people fighting lung cancer. They also add to our growing clinical data set for CYRAMZA, which is being studied in multiple tumor types."

The global, randomized, double-blind REVEL trial compared CYRAMZA plus docetaxel to placebo plus docetaxel in NSCLC patients with progression after platinum-based chemotherapy for locally-advanced or metastatic disease. The international study included a total of 1,253 nonsquamous and squamous NSCLC patients from 26 countries on six continents. Overall survival (OS) was the trial's primary endpoint and secondary endpoints included progression-free survival (PFS) and objective response rate (ORR).

Patients treated on the CYRAMZA-plus-docetaxel arm (n=628) achieved a median OS of 10.5 months compared to 9.1 months for patients on the placebo-plus-docetaxel arm (n=625). The OS hazard ratio was 0.86 (95% CI, 0.751-0.979, p=0.023), which corresponds to a 14 percent reduction in risk of death.

Median PFS was 4.5 months on the CYRAMZA-plus-docetaxel arm compared to 3.0 months on the placebo-plus-docetaxel arm, with a PFS hazard ratio of 0.76 ($p < 0.001$), which corresponds to a 24 percent reduction in risk of progression or death. ORR was 23 percent on the CYRAMZA-plus-docetaxel arm and 14 percent on the placebo-plus-docetaxel arm ($p < 0.0001$).

"In the REVEL study, CYRAMZA demonstrated statistically significant improvement across multiple efficacy endpoints including overall survival, progression-free survival and overall response rate. The improvement of overall survival and progression-free survival on the CYRAMZA-plus-docetaxel arm was also consistent across the majority of subgroups including histology," said Maurice Perol, M.D., of the Leon-Berard Cancer Centre in France and co-lead investigator of the REVEL study. "Overall, these results are very encouraging for those of us who treat lung cancer patients."

The most common (> 5% incidence) Grade > /=3 adverse events occurring more frequently in patients on the CYRAMZA arm were neutropenia (48.8% vs. 39.8%), febrile neutropenia (15.9% vs. 10.0%), fatigue (14.0% vs 10.5%), leukopenia (13.7% vs. 12.5%), and hypertension (5.6% vs. 2.1%). Grade 5 adverse events were comparable between arms (5.4% vs. 5.8%). Patients on the CYRAMZA arm experienced more bleeding/hemorrhage events (all grade) (28.9 % vs 15.2%) but the rate of Grade > /=3 bleeding / hemorrhage events were similar between arms (2.4% vs 2.3%).

Dr. Perol presented the REVEL data at ASCO and Edward Garon, M.D., director of the Thoracic Oncology Program at the David Geffen School of Medicine at UCLA / Translational Oncology Research Laboratory and co-lead investigator of the REVEL study, is the lead author in *The Lancet* publication of the data.

Lilly intends to submit the first application of these data to regulatory authorities in the second half of 2014.

About the REVEL Trial
REVEL was a global, randomized, double-blind Phase III study of ramucirumab plus docetaxel compared to placebo plus docetaxel in NSCLC patients with progression after prior platinum-based chemotherapy for locally-advanced or metastatic disease. Initiated in 2010, the global study enrolled 1,253 patients across 26 countries on six continents. The primary endpoint (also referred to as the major efficacy outcome measure) of the REVEL trial was overall survival and secondary endpoints (also referred to as the supportive efficacy outcome measures) included: progression-free survival; objective response rate; quality of life; and safety. The study included nonsquamous and squamous NSCLC patients.

About Lung Cancer
Lung cancer is the leading cause of cancer death in the U.S. and most other countries, killing nearly 1.6 million people worldwide each year.[1] In the U.S., lung cancer is responsible for nearly 30 percent of all cancer deaths, more than those from breast, colon and prostate cancers combined.[2] Stage IV NSCLC is a very difficult-to-treat cancer and the prognosis for patients with NSCLC is poor when locally advanced or metastatic.[3] NSCLC is much more common than other types of lung cancer, and accounts for 85 percent of all lung cancer cases. Patients with squamous cell carcinoma represent about 30 percent of all patients affected by NSCLC, while non-squamous patients represent about 70 percent.[4] It is estimated that approximately half of NSCLC patients are receiving treatment in the second-line setting.[5]

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.[6]

About CYRAMZA™ (ramucirumab)
CYRAMZA as a single agent is approved 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.

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] International Agency for Research on Cancer. GLOBOCAN 2012. Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr. Accessed June 1, 2014.

[2] American Cancer Society, *Cancer Facts & Figures 2012*. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Accessed June 1, 2014.

[3] National Cancer Institute, *General information about non-small cell lung cancer.* http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page1. Accessed June 1, 2014.

[4] American Cancer Society, *What is non-small cell lung cancer?* http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-

cancer-what-is-non-small-cell-lung-cancer. Accessed June 1, 2014.
[5] Diagnosed Combo Lot Yearly, April 2014. IntrinsiQ LLC an AmerisourceBergen Specialty Group Company. Accessed May 2014.
[6] 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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