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## Lilly's CYRAMZA™ (ramucirumab) Becomes First FDA-approved Treatment for Advanced Gastric Cancer After Prior Chemotherapy

INDIANAPOLIS, April 21, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the U.S. Food and Drug Administration (FDA) has approved CYRAMZA™ (ramucirumab) as a single agent treatment for patients with advanced or metastatic gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. With this approval, CYRAMZA becomes the first FDA-approved treatment for patients in this setting.

To view the multimedia assets associated with this release, please click: <http://www.multivu.com/mnr/7139451-lilly-cyramza-fda-approval>

"Lilly Oncology is committed to delivering innovative medicines that extend the lives of people with cancer," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "Until now, there were no FDA-approved options for patients in this indication. We are pleased that the FDA has approved CYRAMZA for these patients. This is an aggressive disease that is difficult to treat, and the prognosis has typically been very poor."

The CYRAMZA (ramucirumab injection 10 mg/mL solution) approval is based on results of REGARD, a multicenter, randomized, placebo-controlled, double-blind trial of patients with locally advanced or metastatic gastric cancer including GEJ adenocarcinoma previously treated with fluoropyrimidine- or platinum-containing chemotherapy. It is the first Phase III trial to show improved overall survival and progression-free survival with a biologic agent in advanced gastric cancer after prior chemotherapy. Results demonstrated that CYRAMZA (8 mg/kg by infusion every two weeks) plus best supportive care (BSC), as compared to placebo plus BSC, increased the median overall survival of patients with advanced gastric cancer by 37 percent (median overall survival of 5.2 months [95% confidence interval (CI) 4.4, 5.7] vs. 3.8 months [95% CI 2.8, 4.7] for placebo,  $P=0.047$ , hazard ratio 0.78 [95% CI 0.60, 0.998]). Additionally, CYRAMZA significantly improved progression-free survival, demonstrating a 62 percent increase in median progression-free survival (2.1 months [95% CI 1.5, 2.7] vs. 1.3 months [95% CI 1.3, 1.4] for placebo,  $P < 0.001$ , hazard ratio 0.48 [95% CI 0.38, 0.62]).

The labeling for CYRAMZA contains a Boxed Warning regarding increased risk of hemorrhage, including severe and sometimes fatal events. CYRAMZA should be discontinued in patients who experience severe bleeding. The most commonly reported adverse reactions (all grades) in REGARD, occurring in at least 5 percent of patients receiving CYRAMZA and at a rate at least 2 percent higher than those receiving placebo, 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 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. Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade greater than or equal to 3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in the REGARD trial was 0.8% and the rate of infusion-related reactions was 0.4%. This is not a complete list of adverse reactions. For full safety information, see the Important Safety Information at the end of this press release and the full Prescribing Information.

"There is a high unmet medical need in patients with this disease," said Charles Fuchs, M.D., M.P.H., principal investigator of the REGARD trial and director, Gastrointestinal Malignancy Program, Dana-Farber Cancer Institute. "This approval represents a meaningful advance for patients and gives those of us who treat them an important new second-line treatment option."

"As someone who has experienced firsthand the limited options available to treat this devastating disease, I consider this approval to be much needed. This is a significant moment for many patients and their families," said Debbie Zelman, president and founder of a leading international patient advocacy organization, [Debbie's Dream Foundation](#), which is dedicated to raising awareness about gastric cancer, advancing funding for research, and providing education and support to those affected by the disease. Zelman founded the organization following her own gastric cancer diagnosis. Lilly Oncology and Debbie's Dream Foundation have established a partnership to improve patient and caregiver awareness of and access to gastric cancer resources.

CYRAMZA 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<sup>i,ii</sup>. 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.

FDA approval of CYRAMZA marks a pivotal regulatory milestone in Lilly's research and development program for the molecule, which it acquired when it purchased ImClone Systems in 2008. CYRAMZA has been granted Orphan Drug Designation by the FDA for this indication. Orphan drug status is given in the U.S. by the FDA's Office of Orphan Products Development (OOPD) to medicines that show promise for the treatment of rare diseases. Lilly expects to make CYRAMZA available in the coming weeks and is committed to offering patient assistance programs for eligible patients receiving CYRAMZA treatment.

Patients, physicians, pharmacists or other healthcare professionals with additional questions about CYRAMZA should contact The Lilly Answer Center at 1-800-LillyRx or visit [www.Lilly.com](http://www.Lilly.com).

### **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.<sup>iii</sup>

### **About CYRAMZA™ (ramucirumab)**

CYRAMZA (pronounced "si - ram - ze") as a single agent is the first and only treatment 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.

### **About REGARD**

REGARD is a global, randomized, double-blinded, placebo-controlled Phase III study of CYRAMZA and BSC compared to placebo and BSC as treatment in patients with locally advanced or metastatic gastric cancer including gastroesophageal junction adenocarcinoma following progression after initial fluoropyrimidine- or platinum-containing chemotherapy. In total, 355 patients were randomized in 29 countries. The major efficacy outcome measure (i.e., primary endpoint) of the REGARD trial was overall survival and the supportive efficacy outcome measure (i.e., secondary endpoint) was progression-free survival.

### **About Gastric Cancer**

Gastric (stomach) cancer is a major health problem. It is the fifth most common cancer in the world and is the third-leading cause of cancer death. There were nearly one million new cases worldwide in 2012 (631,000 men, 320,000 women) with approximately 723,000 deaths (469,000 men, 254,000 women).<sup>iv</sup> Stomach cancer is more prevalent in countries outside the U.S. and EU.<sup>v</sup> In the U.S., it is estimated that approximately 22,000 people will be diagnosed with gastric cancer in 2014.<sup>vi</sup>

Gastric cancer is a disease in which cancer cells form in the stomach. It develops slowly, usually over many years, and often goes undetected.<sup>vii</sup> As stomach cancer advances, it can travel through the bloodstream and spread to organs such as the liver, lungs, and bones.<sup>viii</sup>

The most common type of stomach cancer is called adenocarcinoma, which starts from one of the common cell types found in the lining of the stomach.<sup>ix</sup>

### **Lilly PatientOne**

The Lilly PatientOne program addresses financial and coverage issues for qualified uninsured, underinsured and insured patients who are prescribed a Lilly Oncology product. Lilly PatientOne provides reimbursement assistance for eligible patients who are prescribed a Lilly Oncology product, such as information about coding and billing, prior authorization, benefits investigation, and denied claim appeals, as well as operating a patient assistance program. To learn more, visit [www.LillyPatientOne.com](http://www.LillyPatientOne.com) or call 1-866-4PatOne (1-866-472-8663).

### **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  $\geq 5\%$  of patients receiving CYRAMZA and  $\geq 2\%$  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  $\geq 1\%$  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  $\geq 3$ ) 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](http://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](http://www.lilly.com) and <http://newsroom.lilly.com/social->

[channels.](#)

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## P-LLY

*This press release contains forward-looking statements about the potential of CYRAMZA (ramucirumab) as a treatment of advanced stomach cancer or gastroesophageal junction (GEJ) adenocarcinoma 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 can be no guarantee that future study results and patient experience will be consistent with the study findings to date. There can also be no guarantee that CYRAMZA will receive regulatory approval for any future indications or that it will prove to be commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see the company's latest Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements.*

<sup>i</sup> Shibuya M. Vascular endothelial growth factor-dependent and -independent regulation of angiogenesis. *BMB Rep.* 2008;41(4):278-286.

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

<sup>iii</sup> Spratlin J. Ramucirumab (IMC-1121B): monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. *Curr Oncol Rep.* 2011;13(2):97-102.

<sup>iv</sup> Globocan 2012 Cancer Fact Sheet. Stomach cancer estimated incidence, mortality and prevalence worldwide in 2012. [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). Accessed January 21, 2014.

<sup>v</sup> Globocan 2012 Cancer Fact Sheet. Stomach cancer estimated incidence, mortality and prevalence worldwide in 2012. [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). Accessed January 21, 2014

<sup>vi</sup> American Cancer Society. What are the key statistics about stomach cancer? <http://www.cancer.org/Cancer/StomachCancer/DetailedGuide/stomach-cancer-key-statistics>. Updated February 22, 2013. Accessed September 25, 2013.

<sup>vii</sup> American Cancer Society. What is stomach cancer? <http://www.cancer.org/Cancer/StomachCancer/index>. Updated February 22, 2013. Accessed January 21, 2014.

<sup>viii</sup> American Cancer Society. What is stomach cancer? <http://www.cancer.org/Cancer/StomachCancer/index>. Updated February 22, 2013. Accessed January 21, 2014.

<sup>ix</sup> National Center for Biotechnology Information. Gastric cancer. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001270/>. Updated November 17, 2012. Accessed January 21, 2014.

**Contact:** Tracy Henrikson (Lilly Oncology)  
609-240-3902 (mobile)  
Email: [tracy.henrikson@imclone.com](mailto:tracy.henrikson@imclone.com)

Mary Coyle (TogoRun)  
212-453-2089 (office)  
917-975-6615 (mobile)  
Email: [m.coyle@togorun.com](mailto:m.coyle@togorun.com)

Keri McGrath (Lilly Oncology)  
317-370-8394 (mobile)  
Email: [mcgrath\\_happe\\_keri\\_s@lilly.com](mailto:mcgrath_happe_keri_s@lilly.com)

