September 28, 2015

Lilly's CYRAMZA® (ramucirumab) Significantly Improves Progression-Free Survival in Phase II Bladder Cancer Trial

-- Ramucirumab Combination Reduced Disease Progression or Death by 61 Percent --
-- New Phase III Trial Currently Enrolling Patients --

INDIANAPOLIS, Sept. 28, 2015 /PRNewswire/ -- A Phase II study of Eli Lilly and Company's (NYSE: LLY) CYRAMZA® (ramucirumab) in combination with docetaxel met its primary endpoint, demonstrating a statistically significant increase in progression-free survival (PFS) for patients with locally advanced or metastatic urothelial carcinoma who failed prior platinum-based therapy. Bladder cancer accounts for the vast majority of all urothelial carcinoma.

Final results of the Phase II trial were presented at the European Cancer Congress (ECC2015) in Vienna, Austria (Abstract #2508) on September 27. Based on these findings, Lilly recently initiated a Phase III trial called RANGE, which has begun to enroll patients.

"We are encouraged with these promising findings that could help lead to much-needed progress in this area - people with advanced urothelial carcinoma have limited treatment options today," said Daniel Petrylak, M.D., professor of medicine (medical oncology) and of urology at Yale University Cancer Center and the study's principal investigator. "This is an aggressive type of cancer and unfortunately, despite available first-line therapies, most patients who have disease progression eventually succumb to their disease. Currently, there are no agents specifically approved in the U.S., nor is there a consistently-employed single standard of care in the U.S. or globally, for the treatment of second-line bladder cancer."

The three-arm trial evaluated 140 patients with advanced carcinoma of the urothelial tract (bladder, urethra, ureter, or renal pelvis) who, after a first-line platinum-based chemotherapy regimen, had relapsed up to one year following the initial treatment. Patients were randomized to receive either a combination of ramucirumab and docetaxel (n=46), docetaxel alone (n=45), or a combination of icrucumab and docetaxel (n=49). Treatment continued until disease progression or toxicity levels resulted in an interruption of treatment with one or more of the study medicines.

Median PFS, the study's primary endpoint, was 5.4 months (HR 0.389; 95% CI: 0.389 0.235-0.643; $p < 0.001$) on the ramucirumab-docetaxel arm as compared to 2.8 months for patients treated with docetaxel alone, and 1.6 months for those treated with icrucumab and docetaxel. Objective response rate (ORR) results - or patients who achieved either a complete response or partial response to treatment - also favored the ramucirumab combination arm with a significantly higher confirmed ORR (24%) compared to those on the docetaxel arm (9%) and the icrucumab combination arm (12%). A statistically significant benefit in disease control rate - or patients who achieved complete response, partial response, or stable disease - was identified on the ramucirumab arm (78%) versus the docetaxel arm (58%) and the icrucumab arm (45%). While the study was not powered for overall survival (OS), results favored the ramucirumab combination arm, but were not statistically significant, with 10.4 months median OS identified on the ramucirumab arm compared to 9.2 months on the docetaxel arm and 6.7 months on the icrucumab arm.

The observed safety findings are consistent with prior Phase III studies of ramucirumab and docetaxel. The most common (> 5% incidence) grade ≥3 adverse events occurring at a higher rate on the ramucirumab-plus-docetaxel arm compared to the docetaxel arm were fatigue (35% vs. 13%), febrile neutropenia (17% vs. 13%), pneumonia (13% vs. 9%), anemia (13% vs. 7%), sepsis (11% vs. 7%), edema (9% vs. 2%), diarrhea (7% vs. 2%), intestinal obstruction (7% vs. 2%), urinary tract infection (7% vs. 2%), hypertension (7% vs. 0%), stomatitis (7% vs. 0%), and thrombocytopenia (7% vs. 0%).

The Phase III RANGE study, which is currently enrolling patients, is a randomized, double-blind, placebo-controlled study of ramucirumab and docetaxel versus placebo and docetaxel in patients with locally advanced or unresectable metastatic urothelial carcinoma whose disease progressed on or after platinum-based chemotherapy (ClinicalTrials.gov Identifier: NCT02426125).

"We are pleased to advance this CYRAMZA regimen into Phase III clinical development and look forward to that trial's results," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "Our excitement with the overall clinical development of CYRAMZA continues to grow, with the RANGE trial in bladder cancer marking another tumor type in late-stage evaluation in this broad development program."

About Urothelial Carcinoma and Bladder Cancer

Urothelial carcinoma are cancers that arise in the urothelial or transitional cells that line the urinary collecting system including the bladder, which is the most common site for this type of tumor. Other potential primary sites of this cancer include the renal pelvis, ureter, and urethra.

Bladder cancer is the sixth most common and deadly cancer in the U.S.,[i] with an estimated 74,000 new cases and 16,000 deaths expected in 2015.[ii] Globally, bladder cancer ranks ninth in the top most common cancers overall, and the ninth leading cause of cancer-related death, affecting approximately 430,000 people per year and resulting in more than 165,000 deaths.[i]

About CYRAMZA® (ramucirumab)
In the U.S., CYRAMZA (ramucirumab) is approved for use as a single agent or in combination with paclitaxel as a treatment for people with advanced or metastatic gastric (stomach) or gastroesophageal junction (GEJ) adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy. It is also approved in combination with docetaxel as a treatment for people with metastatic non-small cell lung cancer (NSCLC) whose cancer has progressed on or after platinum-based chemotherapy. Additionally, it is approved with FOLFIRI as a treatment for people with metastatic colorectal cancer (mCRC) whose cancer has progressed on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

There are several additional 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. This broad global development program has enrolled more than 7,000 patients across more than 50 trials of CYRAMZA worldwide.

CYRAMZA is an antiangiogenic therapy. It is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that specifically binds and blocks activation of VEGF Receptor 2 by blocking the binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. CYRAMZA inhibited angiogenesis in an *in vivo* animal model.

About Angiogenesis and VEGF Protein
Angiogenesis is the process of making new blood vessels. 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.

INDICATIONS
Gastric Cancer
CYRAMZA, as a single agent or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Non-Small Cell Lung Cancer
CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

Colorectal Cancer
CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

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

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal 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. In study 2, which evaluated CYRAMZA plus paclitaxel in advanced gastric cancer, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, 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%), in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (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 (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, 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 advanced gastric cancer clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect

wound healing. Discontinue CYRAMZA therapy in patients with impaired 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.

Proteinuria Including Nephrotic Syndrome

- In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are $\geq$ 2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to < 2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels > 3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA. In study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in $\geq$ 5% of patients receiving CYRAMZA and $\geq$ 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 $\geq$ 1% and < 5% of CYRAMZA-treated patients vs placebo 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%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in $\geq$ 5% of patients receiving CYRAMZA plus paclitaxel and $\geq$ 2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs

0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).

- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥ 1% and < 5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Most Common Adverse Reactions—Combination With Docetaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥ 5% of patients receiving CYRAMZA plus docetaxel and ≥ 2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; < 1% vs < 1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs < 1%), thrombocytopenia (13% vs 5%; 3% vs < 1%), lacrimation increased (13% vs 5%; < 1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥ 65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients < 65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA in study 3 were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥ 3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥ 3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥ 3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- Clinically relevant adverse reactions reported in ≥ 1% and < 5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Most Common Adverse Reactions—Combination With FOLFIRI

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥ 5% of patients receiving CYRAMZA plus FOLFIRI and ≥2% higher than placebo plus FOLFIRI in study 4 were diarrhea (60% vs 51%; 11% vs 10%), neutropenia (59% vs 46%; 38% vs 23%), decreased appetite (37% vs 27%; 2% vs 2%), epistaxis (33% vs 15%; 0% vs 0%), stomatitis (31% vs 21%; 4% vs 2%), thrombocytopenia (28% vs 14%; 3% vs < 1%), hypertension (26% vs 9%; 11% vs 3%), peripheral edema (20% vs 9%; < 1% vs 0%), proteinuria (17% vs 5%; 3% vs < 1%), palmar-plantar erythrodysesthesia syndrome (13% vs 5%; 1% vs < 1%), gastrointestinal hemorrhage events (12% vs 7%; 2% vs 1%), hypoalbuminemia (6% vs 2%; 1% vs 0%). Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reactions reported in ≥ 1% and < 5% of CYRAMZA plus FOLFIRI-treated patients in study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).
- Thyroid-stimulating hormone (TSH) was evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Patients received periodic TSH assessments until 30 days after the last dose of study treatment. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and irinotecan or its active metabolite, SN-38.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and pediatric development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see full Prescribing Information for CYRAMZA, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.

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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 newsroom.lilly.com/social-channels.

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This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about CYRAMZA (ramucirumab) as a potential treatment for patients with locally advanced or metastatic urothelial carcinoma and reflects Lilly's current belief. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of 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 ramucirumab will achieve its primary study endpoints or receive regulatory approvals. 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.

[i] World Health Organization. "GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012" http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. (Accessed September 25, 2015).

[ii] American Cancer Society. "What are the key statistics about bladder cancer?" http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics. (Accessed September 25, 2015).

Refer To: Tracy Henrikson; tracy.henrikson@lilly.com; (609) 240-3902 (Lilly)
Neil Hochman; n.hochman@togorun.com; (212) 453-2067 (TogoRun)

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