Lilly's CYRAMZA® (ramucirumab) Receives FDA Approval as First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer

May 30, 2020

CYRAMZA, in combination with erlotinib, now approved for the treatment of people with untreated metastatic non-small cell lung cancer (NSCLC) with certain activating EGFR mutations, based on the positive global Phase 3 RELAY study

CYRAMZA regimen reduced the risk of disease progression or death by 41 percent compared to erlotinib in this patient population

INDIANAPOLIS, May 29, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that the U.S. Food and Drug Administration (FDA) has approved CYRAMZA® (ramucirumab injection, 10 mg/mL solution), in combination with erlotinib, for the first-line treatment of people with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations. With this approval, CYRAMZA has now received six FDA approvals to treat certain types of lung, liver, stomach and colorectal cancers.

CYRAMZA plus erlotinib is the first and only FDA-approved anti-VEGFR/EGFR TKI combination therapy for metastatic EGFR-mutated NSCLC. This approval is based on the efficacy and safety from the global, randomized, placebo-controlled Phase 3 RELAY trial. In the RELAY study, CYRAMZA, a VEGF receptor 2 antagonist, in combination with erlotinib, a globally approved EGFR-targeting tyrosine kinase inhibitor (TKI), demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) – the time patients lived without their cancer growing or spreading after starting treatment – compared to placebo in combination with erlotinib [19.4 months in the CYRAMZA-containing arm compared to 12.4 months in the placebo-containing arm (HR=0.59; 95% CI, 0.46, 0.76; p<0.0001)]. The PFS treatment effect was consistent across exon 19 and exon 21 subgroups. The overall safety profile observed in the RELAY study was consistent with that of its individual components. RELAY is the second positive Phase 3 trial of CYRAMZA in metastatic NSCLC. The first was REVEL, which supported the approval of CYRAMZA plus docetaxel as a treatment for people with metastatic NSCLC whose cancer has progressed after prior platinum-based chemotherapy.

"The approval of this new first-line metastatic EGFR-mutated non-small cell lung cancer regimen, which inhibits the VEGFR and EGFR pathways together, is an important milestone in the treatment of this disease. It is wonderful that patients now have multiple options for initial therapy capable of delaying disease progression for considerably longer than erlotinib, which has been our traditional standard approach," said Edward Garon, M.D., David Geffen School of Medicine, University of California, and North America lead investigator of the RELAY trial. "Ramucirumab, in combination with erlotinib, is a welcomed first-line option to offer our patients with metastatic EGFR-mutated non-small cell lung cancer."

"This CYRAMZA combination regimen represents a new and meaningful treatment option for people with metastatic EGFR-mutated non-small cell lung cancer, and we are proud that it has been approved by the FDA for patients with this disease and the doctors who treat them," said Anne White, president of Lilly Oncology. "Today's approval underscores Lilly's continued commitment to people living with lung cancer and to delivering meaningful medicines that are tailored for those with advanced or metastatic cancers. It also further reinforces the value that CYRAMZA can provide in treating certain advanced or metastatic cancers."

Fifty percent of people with NSCLC present with advanced or metastatic disease at diagnosis.[1] The five-year survival rate for metastatic NSCLC patients is six percent.[2] In the U.S., it is estimated that approximately 15 percent of people diagnosed with NSCLC have an EGFR mutation.[3]

"We're encouraged by CYRAMZA's latest approval, which represents one step towards our goal of making EGFR-mutated non-small cell lung cancer into a manageable chronic disease," said Ivy Elkins, cofounder of EGFR Resisters. "Each new treatment option gives hope to those living with this disease and provides oncologists with more options that may help slow the spread of this deadly cancer, which is an important goal for many patients."

The labeling for CYRAMZA contains warnings and precautions for hemorrhage and gastrointestinal (GI) hemorrhage, including severe and sometimes fatal events; GI perforations, a potentially fatal event; impaired wound healing; arterial thromboembolic events (ATEs), including serious and sometimes fatal events; hypertension; infusion-related reactions (IRR) including severe and life-threatening reactions; worsening of pre-existing hepatic impairment; Posterior Reversible Encephalopathy Syndrome (PRES); proteinuria including nephrotic syndrome; thyroid dysfunction; and embryo-fetal toxicity. CYRAMZA should be permanently discontinued in patients who experience severe bleeding, a GI perforation, an ATE, uncontrolled hypertension, Grade 3 or 4 IRR, PRES, or nephrotic syndrome. Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least two weeks following a major surgical procedure and until adequate wound healing.

The most common adverse reactions (all grades) observed in CYRAMZA with erlotinib-treated patients at a rate of ≥30% of patients and ≥2% higher than placebo with erlotinib-treated patients were infections, hypertension, stomatitis, proteinuria, alopecia, and epistaxis. The most common laboratory abnormalities ≥30% and ≥2% higher than the placebo were increased alanine aminotransferase, increased aspartate aminotransferase, anemia, thrombocytopenia, and neutropenia. **Please see Important Safety Information below**.

In addition to a recent approval for CYRAMZA in the European Union based on the RELAY results, Lilly has made a submission in Japan with regulatory action expected by the end of 2020.

Click here to view the EGFR-mutated NSCLC fact sheet.
Click here to view the CYRAMZA product photo.
Click here to view the CYRAMZA logo.

About the RELAY Trial
RELAY is a global randomized, double-blind, placebo-controlled Phase 3 study of CYRAMZA in combination with erlotinib, compared to placebo in combination with erlotinib, as a first-line treatment in previously untreated patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. EGFR-targeting TKIs are the current standard treatment options for EGFR-mutated NSCLC. Erlotinib, the TKI included in the RELAY trial regimen, is a globally approved treatment option for this type of lung cancer.

Initiated in 2015, the study randomized 449 patients across North America, Europe and Asia. The primary endpoint of the RELAY trial is PFS; key secondary endpoints include safety, overall response rate (ORR), duration of response (DoR), and overall survival (OS). On the primary endpoint of investigator-assessed PFS, CYRAMZA plus erlotinib (N=224) demonstrated statistically significant and clinically meaningful improvement in median PFS – the time patients lived without their cancer growing or spreading after starting treatment – by seven months compared to placebo plus erlotinib (N=225) [19.4 months in the CYRAMZA-containing arm compared to 12.4 months in the placebo-containing arm (HR=0.59; 95% CI, 0.46, 0.76; p<0.0001)]. The PFS treatment effect was consistent across exon 19 and exon 21 subgroups. At the time of the final analysis of PFS, OS data were not mature as only 26 percent of planned events for the final analysis had occurred (HR=0.83, 95% CI: 0.53, 1.30). A final OS analysis is planned when at least 300 events have occurred.

RELAY Trial Efficacy Results Supporting Approval

Endpoint	**CYRAMZA + erlotinib N=224**	**Placebo + erlotinib N=225**
Progression-Free Survival (primary outcome measure)		
Number of events (%)[a]	122 (55%)	158 (70%)
Median – months (95% CI)	19.4 (15.4, 21.6)	12.4 (11.0, 13.5)
Hazard Ratio (95% CI)	0.59 (0.46, 0.76)	
Stratified Log-rank p-value	<0.0001	
Overall Response Rate (Complete Response + Partial Response) (secondary outcome measure)		
Rate – percent (95% CI)	76% (71, 82)	75% (69, 80)
Duration of Response (DoR) (secondary outcome measure)		
	N=171	**N=168**
Median – months (95% CI)	18.0 (13.9, 19.8)	11.1 (9.7, 12.3)

Abbreviations: CI = confidence interval
[a] 4 of 122 events in CYRAMZA-treated patients and 1 of 158 events in placebo-treated patients were deaths.

Treatment discontinuation of all study drugs due to adverse reactions occurred in 13 percent of CYRAMZA with erlotinib-treated patients, with increased alanine aminotransferase (1.4%) and paronychia (1.4%) being the most common. The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (8.6%) and hyperbilirubinemia (6%).

Detailed RELAY efficacy and safety results were published in *The Lancet Oncology*.

Notes to Editors

About Lung Cancer and EGFR Mutations
Globally, lung cancer is the leading cause of cancer death, killing nearly 1.8 million people worldwide each year.[4] In the U.S., lung cancer is the second most common cancer (not counting skin cancer) and the leading cause of cancer death, responsible for almost 25 percent of all cancer deaths – more than those from colorectal, breast and prostate cancers combined.[5] It is estimated that there will be 228,820 new cases of lung cancer and 135,720 deaths from lung cancer in the U.S. in 2020.[4] Non-small cell lung cancer (NSCLC) is much more common than other types of lung cancer and accounts for about 85 percent of all lung cancers.[6] Stage IV NSCLC is a very difficult-to-treat cancer and the prognosis is poor for metastatic NSCLC.[7] Fifty percent of NSCLC patients present with advanced or metastatic disease at diagnosis.[1] The five-year survival rate for metastatic NSCLC is six percent.[2]

EGFR is a protein that helps cells grow and divide. When the EGFR gene is mutated it can cause the protein to be overactive, causing cells to grow and divide more quickly. EGFR mutations may occur in 10 to 35 percent of NSCLC tumors globally.[8] In the U.S., it is estimated that approximately 15 percent of people diagnosed with NSCLC have an EGFR mutation.[3] Activating EGFR mutations are found in about 10 to 20 percent of Caucasian patients with lung adenocarcinomas and in up to 40 to 60 percent of Asian patients.[9,10,11] Regardless of ethnicity, these mutations are commonly found in females, non-smokers and those with adenocarcinoma histology.[12,13] The most common activating mutations in EGFR are deletions within exon 19 and a substitution in exon 21 (L858R). These mutations are present in 90 percent of EGFR-mutated NSCLC tumors. The presence of these activating EGFR mutations in advanced NSCLC is associated with sensitivity to small-molecule EGFR TKIs.[10,11]

About CYRAMZA® (ramucirumab)
In the U.S., CYRAMZA (ramucirumab) has six FDA approvals to treat four different types of cancers. CYRAMZA is being investigated in a broad global development program that has enrolled more than 15,000 patients across more than 100 trials worldwide. These include several studies investigating CYRAMZA in combination with other anti-cancer therapies for the treatment of multiple tumor types. To date, more than 150,000 patients have been treated with CYRAMZA.

CYRAMZA is an antiangiogenic therapy. It is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that binds specifically to VEGFR-2, thereby blocking the binding of the receptor ligands (VEGF-A, VEGF-C, and VEGF-D) – which may slow tumor growth. 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 binding to the receptors located on the surface of 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 FOR CYRAMZA

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 erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.

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 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.

Hepatocellular Carcinoma

CYRAMZA, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha-fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Patients with NSCLC receiving therapeutic anticoagulation or with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving chronic therapy with NSAIDs or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major blood vessel invasion or intratumor cavitation were excluded from REVEL and RELAY; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Gastrointestinal Perforations

- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies, excluding RELAY, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension

ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. In 221 patients with NSCLC receiving CYRAMZA in combination with erlotinib in the RELAY study, the incidence of new or worsening hypertension was higher (45%), as was the incidence of Grade 3-5 hypertension (24%). Of the patients experiencing new or worsening hypertension in RELAY (N=100 CYRAMZA and erlotinib; N=27 placebo and erlotinib), 13% of those treated with CYRAMZA and erlotinib required initiation of 3 or more antihypertensive medications compared to 4% of patients treated with placebo and erlotinib.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRR)

- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1- 9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3- 4 IRR.

Worsening of Pre-existing Hepatic Impairment

- 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.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome (PRES)

- PRES (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

Embryo-Fetal Toxicity

- CYRAMZA can cause fetal harm when administered to pregnant women. 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 3 months after the last dose.

Lactation

- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Adverse Reactions

REGARD:

- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated gastric cancer patients at a rate of ≥5% and ≥2% higher than placebo were hypertension (16% vs 8%), diarrhea (14% vs 9%), headache (9% vs 3%), and hyponatremia (6% vs 2%).
- The most common serious adverse reactions 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.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in REGARD were neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- 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 IRR. In REGARD, 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 REGARD was 0.8% and the rate of IRR was 0.4%.

RAINBOW:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia (57% vs 44%), neutropenia (54% vs 31%), diarrhea (32% vs 23%), epistaxis (31% vs 7%), hypertension (25% vs 6%), peripheral edema (25% vs 14%), stomatitis (20% vs 7%), proteinuria (17% vs 6%), thrombocytopenia (13% vs 6%), hypoalbuminemia (11% vs 5%), and gastrointestinal hemorrhage events (10% vs 6%).
- The most common serious adverse reactions with CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

REVEL:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with docetaxel at a rate of ≥5% and ≥2% higher than placebo with docetaxel were neutropenia (55% vs 46%), fatigue/asthenia (55% vs 50%), stomatitis/mucosal inflammation (37% vs 19%), epistaxis (19% vs 7%), febrile neutropenia (16% vs 10%), peripheral edema (16% vs 9%), thrombocytopenia (13% vs 5%), lacrimation increased (13% vs 5%), and hypertension (11% vs 5%).
- The most common serious adverse reactions with CYRAMZA with docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA with docetaxel-treated patients versus 37% in patients who received placebo with docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA with docetaxel-treated patients (9%) than in placebo with docetaxel-treated patients (5%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were IRR (0.5%) and epistaxis (0.3%).
- For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of Grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA with docetaxel compared to 6% overall incidence and 1% for Grade ≥3 pulmonary hemorrhage for placebo with 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 with docetaxel compared to 12% overall incidence and 2% for Grade ≥3 pulmonary hemorrhage for placebo with docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA with docetaxel-treated patients in REVEL were hyponatremia (4.8%) and proteinuria (3.3%).

RELAY:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with erlotinib at a rate of ≥ 5% and ≥2% higher than placebo with erlotinib were infections (81% vs 76%), diarrhea (70% vs 71%), hypertension (45% vs 12%), stomatitis (42% vs 36%), alopecia (34% vs 20%), epistaxis (34% vs 12%), proteinuria (34% vs 8%), peripheral edema (23% vs 4%), headache (15% vs 7%), gastrointestinal hemorrhage (10% vs 3%), gingival bleeding (9% vs 1%), and pulmonary hemorrhage (7% vs 2%).
- The most common serious adverse reactions with CYRAMZA with erlotinib were pneumonia (3.2%), cellulitis (1.8%), and pneumothorax (1.8%). Red blood cell transfusions were given to 3.2% of CYRAMZA-treated patients versus 0 patients who received placebo.
- Treatment discontinuation of all study drugs due to adverse reactions occurred in 13% of CYRAMZA with erlotinib-treated patients, with increased alanine aminotransferase (1.4%) and paronychia (1.4%) being the most common. The most

common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (8.6%) and hyperbilirubinemia (6%).
- Of the 221 patients who received CYRAMZA with erlotinib, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 6%).

RAISE:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with FOLFIRI at a rate of ≥5% and ≥2% higher than placebo with FOLFIRI were diarrhea (60% vs 51%), neutropenia (59% vs 46%), decreased appetite (37% vs 27%), epistaxis (33% vs 15%), stomatitis (31% vs 21%), thrombocytopenia (28% vs 14%), hypertension (26% vs 9%), peripheral edema (20% vs 9%), proteinuria (17% vs 5%), palmar-plantar erythrodysesthesia syndrome (13% vs 5%), gastrointestinal hemorrhage events (12% vs 7%), and hypoalbuminemia (6% vs 2%). Twenty percent of patients treated with CYRAMZA with FOLFIRI received granulocyte colony- stimulating factors.
- The most common serious adverse reactions with CYRAMZA with 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 with FOLFIRI-treated patients (29%) than in placebo with FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA with FOLFIRI as compared to placebo with FOLFIRI were neutropenia (12.5% vs 5.3%) and thrombocytopenia (4.2% vs 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 reaction reported in ≥1% and <5% of patients receiving CYRAMZA with FOLFIRI was gastrointestinal perforation (1.7%), including 4 fatal events.
- Thyroid-stimulating hormone (TSH) levels were evaluated in 224 patients (115 CYRAMZA with FOLFIRI-treated patients and 109 placebo with FOLFIRI-treated patients) with normal baseline TSH levels. Increased TSH levels were observed in 53 (46%) patients treated with CYRAMZA with FOLFIRI compared with 4 (4%) patients treated with placebo with FOLFIRI.

REACH-2:

- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated HCC patients at a rate of ≥10% and ≥2% higher than placebo were fatigue (36% vs 20%), peripheral edema (25% vs 14%), hypertension (25% vs 13%), abdominal pain (25% vs 16%), decreased appetite (23% vs 20%), proteinuria (20% vs 4%), nausea (19% vs 12%), ascites (18% vs 7%), headache (14% vs 5%), epistaxis (14% vs 3%), insomnia (11% vs 6%), pyrexia (10% vs 3%), vomiting (10% vs 7%), and back pain (10% vs 7%).
- The most common serious adverse reactions with CYRAMZA were ascites (3%) and pneumonia (3%).
- Treatment discontinuations due to adverse reactions occurred in 18% of CYRAMZA-treated patients, with proteinuria being the most frequent (2%).
- Clinically relevant adverse reactions reported in ≥1% and <10% of CYRAMZA-treated patients in REACH-2 were IRR (9%), hepatic encephalopathy (5%) including 1 fatal event, and hepatorenal syndrome (2%) including 1 fatal event.

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Please see full U.S. Prescribing Information for CYRAMZA.

About Lilly Oncology
For more than 50 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 create medicines that 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 lilly.com/newsroom. P-LLY

Lilly Forward-Looking Statement
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Lilly's CYRAMZA (ramucirumab), in combination with erlotinib, for the first-line treatment of people with metastatic non-small cell lung cancer with EGFR

exon 19 deletions or exon 21 (L858R) mutations 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. Among other things, there can be no guarantee that CYRAMZA will continue to be commercially successful. 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.

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