



## **FDA Advisory Committee Votes in Favor of Lilly's CYRAMZA® (ramucirumab) as First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer**

February 27, 2020

### **Regulatory submission based on the positive Phase 3 RELAY study of CYRAMZA in combination with erlotinib for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating EGFR mutations**

INDIANAPOLIS, Feb. 26, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that a U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) voted 6-5 that CYRAMZA® (ramucirumab) plus erlotinib demonstrated a favorable benefit/risk profile for patients with untreated metastatic EGFR-positive non-small cell lung cancer (NSCLC), based on the results of the positive Phase 3 RELAY study.

"Given the unmet need that remains in treating metastatic EGFR-mutated non-small cell lung cancer, we are encouraged that the majority of these experts agree CYRAMZA plus erlotinib has a favorable benefit/risk profile for the first-line treatment of these patients," said Maura Dickler, M.D., vice president of late phase development, Lilly Oncology. "We believe in the clinical meaningfulness of the data from the RELAY trial, which targeted the VEGFR and EGFR pathways together. We look forward to continuing to work with the FDA on this application to offer a new front-line treatment option for people with metastatic EGFR-mutated non-small cell lung cancer."

The ODAC considered the safety and efficacy data from the Phase 3 RELAY trial, which is the basis for the CYRAMZA supplemental Biologics License Application (sBLA) currently under review by the FDA. 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 – the time patients live without their disease getting worse – compared to erlotinib alone. Median PFS on the CYRAMZA-plus-erlotinib arm was 19.4 months compared to 12.4 months on the placebo-plus-erlotinib arm, an improvement of seven months (HR 0.59; 95% CI, 0.46-0.79;  $P < 0.0001$ ). The safety profile observed in the RELAY study was consistent with what has been previously observed for CYRAMZA in Phase 3 clinical trials and the established safety profile of erlotinib. The most common (>5% incidence) Grade  $\geq 3$  adverse events occurring at a higher rate ( $\geq 5\%$  difference) on the CYRAMZA-plus-erlotinib arm compared to the placebo-plus-erlotinib arm were hypertension, dermatitis acneiform (an acne-like rash), and diarrhea.

There is no cure for people with metastatic EGFR-mutated lung cancer and disease progression following acquired resistance remains a challenge. Most patients receive several lines of treatment and the therapeutic regimen prescribed for first-line treatment can impact a person's options for later lines of therapy. Globally, tyrosine kinase inhibitors (TKIs) – including erlotinib, which was used in the trial – are the current standard treatment option for EGFR-mutated NSCLC. There remains an ongoing need for additional first-line therapeutic options that provide clinically meaningful benefits – including delaying disease progression and use of chemotherapy as long as possible. Moreover, new treatment options could allow oncologists greater choice on how to use the available agents, in shared decision-making with their patients.

Advisory committees provide the FDA with independent opinions and recommendations from outside medical experts during the drug review process. The FDA is not obligated to follow their recommendation, but it often does.

Lilly has also made regulatory submissions outside the U.S. based on the RELAY data. In January 2020, the European Commission granted European Union approval for CYRAMZA in combination with erlotinib for the first-line treatment of adult patients with metastatic NSCLC with activating EGFR mutations. Lilly has submitted in Japan and expects regulatory action in the second half of 2020.

#### **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 (epidermal growth factor receptor) exon 19 deletions or exon 21 (L858R) substitution mutations. EGFR-targeting tyrosine kinase inhibitors (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 progression-free survival (PFS); key secondary endpoints include safety, response rate, overall survival (OS), and patient-reported outcomes. 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 live without their cancer growing or spreading after starting treatment – by seven months compared to placebo plus erlotinib (N=225) [19.4 months with the CYRAMZA-containing arm compared to 12.4 months with the placebo-containing arm (HR 0.59; 95% CI, 0.46-0.79;  $P < 0.0001$ )]. Improvements with CYRAMZA plus erlotinib were also consistently observed across secondary and exploratory endpoints including duration of response, PFS2 and time on targeted therapy. Improvements were also consistently seen across all specified subgroups, including patients with tumors that had exon 19 and 21 mutations. OS was immature at the time of analysis. The trial will continue until it reaches its final number of OS events.

The most common mechanism of acquired resistance to first-line treatment with first-and second-generation EGFR-TKI is the T790M mutation, with

approximately 30 to 60 percent of patients whose disease progresses acquiring the mutation. In RELAY, the rate of T790M mutations following disease progression was similar between treatment groups.

The most common Grade  $\geq 3$  adverse events occurring at a rate of five percent or greater in the CYRAMZA-containing arm were hypertension (N=52 [24%, Grade 3 only]), dermatitis acneiform (an acne-like rash) (N=33 [15%, Grade 3 only]), and diarrhea (N=16 [7%, Grade 3 only]).

Detailed RELAY efficacy and safety results were published in [The Lancet Oncology](#).

### **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.<sup>1</sup> In the U.S., lung cancer is the second most common cancer and the leading cause of cancer death, responsible for approximately 22 percent of all cancer deaths – more than those from colorectal, breast and prostate cancers combined.<sup>2</sup> 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.<sup>3</sup> Non-small cell lung cancer (NSCLC) is much more common than other types of lung cancer and accounts for about 80 to 85 percent of all lung cancer cases.<sup>4</sup> Stage IV NSCLC is a very difficult-to-treat cancer and the prognosis is poor for metastatic NSCLC.<sup>5</sup> Fifty percent of NSCLC patients present with advanced or metastatic disease at diagnosis.<sup>6</sup> The five-year survival rate for metastatic NSCLC is six percent.<sup>7</sup>

EGFR is a protein that helps cells grow and divide. When the EGFR gene is mutated it can cause the protein to be overactive, resulting in the formation of cancer cells. EGFR mutations may occur in 10 to 35 percent of NSCLC tumors globally.<sup>8</sup> In the U.S., it is estimated that approximately 15 percent of people diagnosed with NSCLC have an EGFR mutation.<sup>9</sup> 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.<sup>10,11,12</sup> Regardless of ethnicity, these mutations are commonly found in females, non-smokers and those with adenocarcinoma histology.<sup>13,14</sup> The most common activating mutations in EGFR are deletions within exon 19 and a substitution in exon 21 (L858R), which are present in over 90 percent of EGFR-mutated tumors. The presence of these activating EGFR mutations in advanced NSCLC is associated with sensitivity to small-molecule EGFR TKIs.<sup>11,12</sup>

### **About CYRAMZA® (ramucirumab)**

In the U.S., CYRAMZA (ramucirumab) has five 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.

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.

## **U.S. 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 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.

### **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  $\geq 400$  ng/mL and have been treated with sorafenib.

## **U.S. IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)**

### **Warnings and Precautions**

#### **Hemorrhage**

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade  $\geq 3$  hemorrhagic events. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage occurred between 13-44%. 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 chronic therapy with NSAIDs or other anti-platelet therapy

other than once daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from REVEL; 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. Across five clinical studies in 1916 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**

- Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR2 antagonist, 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 28 days following a major surgical procedure and until the wound is fully healed. Discontinue CYRAMZA in patients who develop wound healing complications that require medical intervention.

#### **Arterial Thromboembolic Events**

- Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 2-3%. 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 in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension occurred between 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%.
- 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**

- Infusion-related reactions (IRR), including severe and life threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. 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. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR occurred between <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**

- Posterior Reversible Encephalopathy Syndrome (PRES) (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with CYRAMZA. Symptoms

of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.

- Confirm the diagnosis of PRES with magnetic resonance imaging and 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**

- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-20%. Grade  $\geq 3$  proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is 2+ or greater, perform a 24-hour urine collection for protein measurement. 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**

- Across five clinical studies in 1916 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**

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal 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 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.

#### **Most Common Adverse Reactions—CYRAMZA Administered as a Single Agent (REGARD)**

- 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 REGARD 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 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  $\geq 1\%$  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  $\geq 3$ ) 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%.

#### **Most Common Adverse Reactions—CYRAMZA Administered in Combination with Paclitaxel (RAINBOW)**

- The most commonly reported adverse reactions (all Grades; Grade  $\geq 3$ ) occurring in  $\geq 5\%$  of patients receiving CYRAMZA with paclitaxel and  $\geq 2\%$  higher than placebo with paclitaxel in RAINBOW 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 reactions in patients who received 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  $\geq 2\%$  of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in  $\geq 1\%$  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.

#### **Most Common Adverse Reactions— CYRAMZA Administered in Combination with Docetaxel (REVEL)**

- The most commonly reported adverse reactions (all Grades; Grade 3-4) occurring in  $\geq 5\%$  of patients receiving CYRAMZA with docetaxel and  $\geq 2\%$  higher than placebo with docetaxel in REVEL 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 reactions in patients who received 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  $\geq 3$  pulmonary hemorrhage was 1% for CYRAMZA with docetaxel compared to 6% overall incidence and 1% for Grade  $\geq 3$  pulmonary hemorrhage for placebo with docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of Grade  $\geq 3$  pulmonary hemorrhage was 2% for CYRAMZA with docetaxel compared to 12% overall incidence and 2% for Grade  $\geq 3$  pulmonary hemorrhage for placebo with docetaxel.
- Clinically relevant adverse reactions reported in  $\geq 1\%$  and  $<5\%$  of CYRAMZA with docetaxel-treated patients in REVEL were hyponatremia (4.8%) and proteinuria (3.3%).

#### **Most Common Adverse Reactions— CYRAMZA Administered in Combination with FOLFIRI (RAISE)**

- The most commonly reported adverse reactions (all Grades; Grade  $\geq 3$ ) occurring in  $\geq 5\%$  of patients receiving CYRAMZA with FOLFIRI and  $\geq 2\%$  higher than placebo with FOLFIRI in RAISE 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%), and hypoalbuminemia (6% vs 2%; 1% vs 0%). 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  $\geq 1\%$  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.

#### **Most Common Adverse Reactions— CYRAMZA Administered as a Single Agent (REACH-2)**

- The most commonly reported adverse reactions (all Grades; Grade  $\geq 3$ ) occurring in  $\geq 10\%$  of patients receiving CYRAMZA and  $\geq 2\%$  higher than placebo in REACH-2 were fatigue (36% vs 20%; 5% vs 3%), peripheral edema (25% vs 14%; 2% vs 0%), hypertension (25% vs 13%; 13% vs 5%), abdominal pain (25% vs 16%; 2% vs 2%), decreased appetite (23% vs 20%; 2% vs 1%), proteinuria (20% vs 4%; 2% vs 0%), nausea (19% vs 12%; 0% vs 0%), ascites (18% vs 7%; 4% vs 1%), headache (14% vs 5%; 0% vs 1%), epistaxis (14% vs 3%;  $<1\%$  vs 0%), insomnia (11% vs 6%; 0% vs 1%), pyrexia (10% vs 3%; 0% vs 0%), vomiting (10% vs 7%; 0% vs 0%), and back pain (10% vs 7%;  $<1\%$  vs 1%). The most common laboratory abnormalities (all Grades; Grade  $\geq 3$ ) occurring in  $\geq 15\%$  of patients receiving CYRAMZA and  $\geq 2\%$  higher than placebo were thrombocytopenia (46% vs 15%; 8% vs 1%), hypoalbuminemia (33% vs 16%;  $<1\%$  vs 0%), hyponatremia (32% vs 25%; 16% vs 5%), neutropenia (24% vs 12%; 8% vs 3%), and hypocalcemia (16% vs 5%; 2% vs 0%).
- 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  $\geq 1\%$  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](http://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](http://www.lilly.com) and [lilly.com/newsroom](http://lilly.com/newsroom). P-LLY

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#### 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 the RELAY trial and CYRAMZA as a potential treatment for patients with metastatic EGFR mutation-positive non-small cell lung cancer 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 receive regulatory approval for EGFR mutation-positive metastatic non-small cell lung cancer or 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.

<sup>1</sup> International Agency for Research on Cancer. 2018 Lung Cancer Fact Sheet. Available at: <http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf>. Accessed February 24, 2020.

<sup>2</sup> American Cancer Society. Cancer Facts and Figures 2020. Available at: <https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590> Accessed February 24, 2020.

<sup>3</sup> American Cancer Society. Key Statistics for Lung Cancer. Available at <https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html>. Accessed February 24, 2020.

<sup>4</sup> American Cancer Society. What is non-small cell lung cancer? Available at: <http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer>. Accessed February 24, 2020.

<sup>5</sup> American Cancer Society. Non-Small Cell Lung Cancer Survival Rates, by Stage. Available at: <http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates>. Accessed February 24, 2020.

<sup>6</sup> Riess, J. Shifting Paradigms in Non-Small Cell Lung Cancer: An Evolving Therapeutic Landscape Supplement. *Am J Manag Care*. 2013;19:S390-S397.

<sup>7</sup> [Cancer.Net](#). Lung Cancer – Non Small Cell: Statistics. Available at: <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>. Accessed February 24, 2020.

<sup>8</sup> Dong L, Lei D, Zhang H. Clinical strategies for acquired epidermal growth factor receptor tyrosine kinase inhibitor resistance in non-small-cell lung cancer patients. *Oncotarget*. 2017 Sep 8; 8(38): 64600–64606.

<sup>9</sup> Li Y, Appius A, Pattipaka T, Feyereislova A, Cassidy A, Ganti AK. Real-world management of patients with epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer in the USA [published correction appears in *PLoS One*. 2019 Feb 20;14(2):e0212831]. *PLoS One*. 2019;14(1):e0209709. Published 2019 Jan 4. doi:10.1371/journal.pone.0209709.

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