



## Lilly's CYRAMZA® (ramucirumab) Becomes First FDA-Approved Biomarker-Driven Therapy in Patients with Hepatocellular Carcinoma

May 13, 2019

**This new indication - the fifth FDA approval for CYRAMZA in an advanced or metastatic cancer - is for the second-line treatment of patients with hepatocellular carcinoma (HCC) who are AFP-High (AFP ≥400 ng/mL)**  
**Approximately forty percent of all patients with advanced HCC are AFP-High and are a patient population that can have more aggressive disease and a poorer prognosis**  
**Concurrent with this approval, the FDA has also removed the boxed warning from the CYRAMZA labeling**

INDIANAPOLIS, May 13, 2019 /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), as a single agent, 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. Concurrent with this FDA approval – the fifth for CYRAMZA – the FDA has also removed the boxed warning from the CYRAMZA labeling.

HCC is the most common form of liver cancer, which is the fourth-leading cause of cancer-related death worldwide.<sup>1,2</sup> In the U.S., liver cancer is one of the few major cancers with incidence rates that continue to rise every year<sup>3</sup> and is the fastest rising cause of cancer death.<sup>4</sup>

AFP is a prognostic biomarker that can be assessed through a simple blood test, now allowing physicians to select patients who may benefit from treatment and to monitor disease progression in advanced HCC.<sup>5-8</sup>

"This approval of CYRAMZA is an important step forward in the treatment of advanced hepatocellular carcinoma," said Andrew X. Zhu, M.D., director of Liver Cancer Research at Massachusetts General Hospital Cancer Center, professor of medicine at Harvard Medical School and principal investigator of the REACH-2 trial. "While there have been some recent advances, there are still limited treatment options for people with this type of cancer and – until now – there was no treatment option specifically indicated for patients with increased alpha-fetoprotein concentrations. These patients can have more aggressive disease and a poorer prognosis with increased angiogenesis."

This approval is based on the results from the REACH-2 study, the first positive Phase 3 HCC trial in a biomarker-selected patient population. [REACH-2](#) is a global, randomized, double-blind, placebo-controlled Phase 3 study of CYRAMZA compared to placebo in patients with HCC who have been treated with sorafenib and are AFP-High (AFP ≥400 ng/mL).

"This new indication for CYRAMZA further reinforces Lilly's ongoing commitment to delivering meaningful medicines that are tailored for people with advanced cancers and the physicians that work in partnership with them," said Anne White, president of Lilly Oncology. "Our work is focused on helping people who are living with cancer and Lilly is making strides in its efforts to develop precision medicine-based therapies for patients, to give them a fighting chance against their disease."

"There is an urgent need for new liver cancer treatments that take into account the things that make each patient unique, particularly for those with advanced stages of the disease," said Donna Cryer, president and CEO of the [Global Liver Institute](#). "We welcome this approval and the hope it may bring to people living with this devastating disease."

This approval adds to the body of evidence demonstrating the safety of CYRAMZA. The FDA has removed the boxed warning from the CYRAMZA labeling which highlighted warnings pertaining to hemorrhage, gastrointestinal perforation and impaired wound healing. The updated CYRAMZA labeling continues to provide important information on these specific risks, as well as other adverse events, to physicians and the patients that work in partnership with them so that they can make informed decisions regarding cancer care.

The labeling for CYRAMZA contains warnings and precautions for hemorrhage and GI hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforations, a potentially fatal event; impaired wound healing; arterial thromboembolic events (ATEs), including serious and sometimes fatal events; hypertension; infusion-related reactions; worsening of pre-existing hepatic impairment, reversible posterior leukoencephalopathy syndrome (RPLS); 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, RPLS, or nephrotic syndrome. CYRAMZA should be withheld prior to surgery and discontinued if a patient develops wound healing complications.

The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated HCC patients at a rate of ≥15 percent and ≥2 percent 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%). **Please see Important Safety Information below.**

### **REACH-2 Trial Results Supporting the Approval**

In the REACH-2 trial, CYRAMZA showed a statistically significant benefit in the primary endpoint of overall survival (OS) and in the secondary endpoint of progression-free survival (PFS).

#### **REACH-2 Trial**

<b>Endpoint</b>	<b>CYRAMZA + BSC</b>	<b>Placebo + BSC</b>
	<b>N=197</b>	<b>N=95</b>

<b>OS</b>		
Number of deaths (%)	147 (75%)	74 (78%)
	8.5	7.3
Median in months (95% CI)	(7.0–10.6)	(5.4–9.1)
Hazard ratio (95% CI)	0.71 (0.53–0.95)	
p-Value	0.020	
<b>PFS</b>		
Number of deaths (%)*	172 (87%)	86 (91%)
Median in months (95% CI)	2.8 (2.8–4.1)	1.6 (1.5–2.7)
Hazard ratio (95% CI)	0.45 (0.34–0.60)	
p-Value	<0.0001	
<b>ORR†‡</b>		
Overall response rate (95% CI)	4.6% (1.7–7.5)	1.1% (0.0–3.1)

Abbreviations: BSC = best supportive care; CI = confidence interval

\* 26 of 172 events in CYRAMZA-treated patients and 9 of 86 events in placebo-treated patients were deaths.

† Does not include stable disease; all responses were partial.

‡ Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

The REACH-2 study design was informed by findings from the [REACH](#) study, which uncovered AFP as a potential predictive biomarker in HCC.

CYRAMZA was discontinued due to adverse reactions in 18 percent of CYRAMZA-treated patients, with proteinuria being the most frequent (2%). The most common adverse reactions of any grade observed in single agent CYRAMZA-treated HCC patients at a rate of  $\geq 15$  percent and  $\geq 2$  percent higher than placebo were fatigue (36%), peripheral edema (25%), hypertension (25%), abdominal pain (25%), decreased appetite (23%), proteinuria (20%), nausea (19%), and ascites (18%). The most common serious adverse reactions with CYRAMZA were ascites (3%) and pneumonia (3%). The most common laboratory abnormalities occurring in  $>30$  percent of patients and  $\geq 2$  percent higher than placebo were thrombocytopenia (46%), hypoalbuminemia (33%), and hyponatremia (32%).

Lilly has also submitted applications for marketing authorization in the European Union and Japan based on the REACH-2 results and regulatory action in these geographies is expected in mid-2019.

The National Comprehensive Cancer Network<sup>®</sup> (NCCN<sup>®</sup>) Guidelines recognize ramucirumab (CYRAMZA<sup>®</sup>) as a Category 1 recommendation treatment option for second-line HCC patients who have AFP  $\geq 400$  ng/mL and have been treated with sorafenib.<sup>9</sup>

With this approval, Lilly has now received five FDA approvals for CYRAMZA to treat four of the world's most deadly cancers. These approvals are based on a demonstrated survival benefit in Phase 3 studies of advanced forms of gastric and gastroesophageal junction adenocarcinoma, metastatic non-small cell lung cancer, metastatic colorectal cancer, and AFP-High HCC. Two of these studies have shown the proven benefit of CYRAMZA as a single agent in treating advanced gastric cancer and AFP-High HCC.

Additionally, Lilly recently announced top-line results from its Phase 3 study of CYRAMZA in EGFR-mutated metastatic non-small cell lung cancer. These results will be presented at the American Society of Clinical Oncology 2019 Annual Meeting and are the basis for global regulatory submissions planned in mid-2019.

## **Notes to Editors**

### **About Alpha-Fetoprotein**

Alpha-fetoprotein (AFP) is a glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including HCC, hepatoblastoma, and nonseminomatous germ cell tumors of the ovary and testis. A person's AFP, measured in nanograms per milliliter (ng/mL), is assessed through a blood test. An AFP level of less than 10 ng/mL is generally considered normal for adults.<sup>10</sup> It is estimated that approximately forty percent of all people with advanced HCC are AFP-High (AFP  $\geq 400$  ng/mL) and these patients are known to have a poorer prognosis relative to the general HCC patient population.<sup>11</sup> Specifically, these patients can have more aggressive disease and a poorer prognosis with increased angiogenesis, tumor activity, and tumor burden. Tumor burden is the amount of cancer in a person's body.

### **About Hepatocellular Carcinoma**

Hepatocellular carcinoma (HCC) is the most common form of liver cancer – accounting for up to ninety percent of all cases.<sup>12</sup> Liver cancer is the sixth most common cancer worldwide and the fourth-leading cause of cancer-related death. Each year approximately 841,000 new cases of liver cancer are diagnosed worldwide, and more than 781,000 will die of the disease. In Europe and Japan, an estimated 82,000 and 36,000 people are diagnosed with liver cancer, and 62,000 and 33,000 will die, respectively. In the U.S., approximately 38,000 people are diagnosed with liver cancer, and 30,000 will die from the disease each year.<sup>1</sup> Liver cancer is one of the few major cancers with incidence rates that continue to rise every year in the U.S.<sup>3</sup> and is the fastest rising cause of cancer death.<sup>4</sup>

The prognosis for advanced HCC patients is typically very poor. Surgery is not an option for the majority of advanced HCC patients, as the tumor has often grown or metastasized to the extent that resection is not feasible. Advanced HCC is a disease with few approved systemic treatments, and most patients have significant liver damage which can further limit therapy options. Once patients who are AFP-High enter the second-line treatment setting, the expected survival is three to five months if untreated.<sup>11</sup>

Despite recent advances in the treatment of chronic liver disease, the incidence of HCC is still expected to rise in the coming decades due to several factors: under-diagnosis of chronic liver disease; increasing prevalence of diabetes, obesity and fatty liver disease; lack of access to viral hepatitis disease therapy; and the persistent risk of cancer even after viral hepatitis cure.<sup>13</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 110 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.

### **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.

#### **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.

### **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**

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including two 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.
- 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 IRRs occurred between <1-9%. Grade 3-5 IRRs incidence was <1%.
- Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Premedicate prior to each CYRAMZA infusion. Reduce the infusion rate by 50% for Grade 1-2 IRRs. Permanently discontinue CYRAMZA for Grade 3-4 IRRs.

#### **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%).

#### **Reversible Posterior Leukoencephalopathy Syndrome**

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with CYRAMZA.
- Confirm the diagnosis of RPLS with magnetic resonance imaging and permanently 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**

- 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 events with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- 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 IRRs. 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 IRRs 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 events 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 IRRs (9%), hepatic encephalopathy (5%) including 1 fatal event, and hepatorenal syndrome (2%) including 1 fatal event.

Please see full [Prescribing Information](#) for CYRAMZA.

RB-P HCP ISI 10MAY2019

#### **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 <http://newsroom.lilly.com/social-channels>. P-LLY

PP-RB-US-1734 05/2019 ©Lilly USA, LLC 2019. ALL RIGHTS RESERVED.

CYRAMZA<sup>®</sup> is a trademark owned by or licensed to Eli Lilly and Company, its subsidiaries, or affiliates.

National Comprehensive Cancer Network<sup>®</sup> and NCCN<sup>®</sup> are trademarks owned by the National Comprehensive Cancer Network, Inc.

#### **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 CYRAMZA as a treatment for patients with hepatocellular carcinoma, 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 additional regulatory approvals or 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> Ferlay J, Shin HR, Bray F et al. GLOBOCAN 2018 Fact Sheet, Estimated Cancer Incidence, Mortality and Prevalence Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2018. Available at [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). Accessed on May 10, 2019.

<sup>2</sup> Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: Epidemiology, etiology, and carcinogenesis. *J Carcinog*. 2017;16:1.

<sup>3</sup> Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7-30.

<sup>4</sup> Islami F, Miller KD, Siegel RL, et al. Disparities in liver cancer occurrence in the United States by race/ethnicity and state. *CA Cancer J Clin*. 2017;67:273-289.

<sup>5</sup> Mitsuhashi N, Kobayashi S, Doki T, et al. Clinical significance of  $\alpha$ -fetoprotein: involvement in proliferation, angiogenesis, and apoptosis of hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2008;23(7, pt 2):e189-e197.

<sup>6</sup> Gopal P, Yopp AC, Waljee AK, et al. Factors that affect accuracy of  $\alpha$ -fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2014;12(5):870-877.

<sup>7</sup> Chan SL, Chan ATC, Yeo W. Role of alpha-fetoprotein in hepatocellular carcinoma: prognostication, treatment monitoring or both? *Future Oncol*. 2009;5(6):889-899.

<sup>8</sup> Mizejewski GJ. Does alpha-fetoprotein contribute to the mortality and morbidity of human hepatocellular carcinoma? A commentary. *J Hepatocell Carcinoma*. 2016;3:37-40

<sup>9</sup> Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Hepatobiliary Cancers V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed May 10, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content use or application and disclaims any responsibility for their application or use in any way. Category 1 recommendations are made based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

<sup>10</sup> University of Rochester Medical Center. Health Encyclopedia: Alpha-Fetoprotein Tumor Marker (Blood). Available at [https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=alpha\\_fetoprotein\\_tumor\\_marker](https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=alpha_fetoprotein_tumor_marker). Accessed May 10, 2018.

<sup>11</sup> Zhu AX, Park JO, Ryoo BY et al. Ramucirumab Versus Placebo as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma Following First-Line Therapy with Sorafenib (REACH): A Randomised, Double-Blind, Multicentre, Phase 3 Trial. *Lancet Oncol*. 2015;16(7): 859-870

<sup>12</sup> National Organization for Rare Disorders. Hepatocellular Carcinoma. Available at: <https://rarediseases.org/rare-diseases/hepatocellular-carcinoma>. Accessed May 10, 2019.

<sup>13</sup> Venook AP, Papandreou C, Furuse J et al. The Incidence and Epidemiology of Hepatocellular Carcinoma: A Global and Regional Perspective. *The Oncologist*. 2010;15(suppl 4): 5-13.

Refer to:

Tracy Henrikson; [tracy.henrikson@lilly.com](mailto:tracy.henrikson@lilly.com); 609-454-7116 (media)

Kevin Hern; [hern\\_kevin\\_r@lilly.com](mailto:hern_kevin_r@lilly.com); 317-277-1838 (investors)



 View original content to download multimedia: <http://www.prnewswire.com/news-releases/lillys-cyramza-ramucirumab-becomes-first-fda-approved-biomarker-driven-therapy-in-patients-with-hepatocellular-carcinoma-300848620.html>

SOURCE Eli Lilly and Company