Lilly Phase 3 REACH-2 Trial Data Published in The Lancet Oncology Shows Improvement in Overall Survival with CYRAMZA® (ramucirumab) in Second-Line AFP-High Hepatocellular Carcinoma Patients

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REACH-2 is the first positive Phase 3 hepatocellular carcinoma trial in a biomarker-selected population known for poor prognosis

Pooled data analyses of AFP-High patients in the REACH-2 and REACH trials showed an improvement of 3.1 months in median overall survival

INDIANAPOLIS, Jan. 18, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced that results from the global Phase 3 REACH-2 study of CYRAMZA® (ramucirumab) as a single agent in the second-line treatment of people with AFP-High (alpha-fetoprotein ≥400 ng/mL) hepatocellular carcinoma (HCC) were published online today in *The Lancet Oncology*. Data from REACH-2 are also being presented today at the 2019 Gastrointestinal Cancers Symposium in San Francisco. HCC is also known as liver cancer, which is a leading cause of cancer-related death worldwide.[1] In the U.S., liver cancer is one of the few major cancers with incidence rates that continue to rise every year[2] and is the fastest rising cause of cancer death.[3]

REACH-2 showed a statistically significant improvement in the primary endpoint of overall survival (OS) as well as in the secondary endpoint of progression-free survival (PFS). The safety profile observed in the REACH-2 study was consistent with what has been previously observed for single-agent CYRAMZA in patients with HCC. Additionally, in a pooled analysis comprised of all AFP-High HCC patients across both the REACH-2 and REACH studies, CYRAMZA treatment also resulted in an improvement in median OS.

"AFP has been used as a prognostic factor for hepatocellular carcinoma for decades. Some studies have suggested that AFP-producing tumors have an aggressive phenotype and increased angiogenesis," 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 and REACH trials. "These results not only further add to the body of evidence that poor prognosis tumors with elevated AFP may have a distinct biology, but also show a tailored treatment approach is feasible."

REACH-2, the first positive Phase 3 HCC trial in a biomarker-selected patient population, evaluated the benefit of CYRAMZA treatment in AFP-High HCC patients who were intolerant to, or had disease progression while on or following treatment with, sorafenib. Approximately half of all advanced HCC patients are AFP-High, and these patients are among those with the poorest prognosis relative to the general HCC patient population.

On the primary endpoint of OS, treatment with CYRAMZA significantly improved the OS of patients compared to placebo (HR 0.71; 95% CI, 0.53-0.95; P=0.02). The median OS was 8.5 months with CYRAMZA (95% CI, 7.0-10.6), compared to 7.3 months with placebo (95% CI, 5.4-9.1). On the secondary endpoint of PFS, median PFS was significantly improved with CYRAMZA (2.8 months [95% CI, 2.8-4.1] vs. 1.6 months for placebo [95% CI, 1.5-2.7]) (HR 0.45; 95% CI, 0.34-0.60; P<0.0001). Objective response rate (ORR) was numerically higher with CYRAMZA compared to placebo (4.6% vs. 1.1%; P=0.1697). Disease control rate (ORR + stable disease) was higher with CYRAMZA than with placebo (59.9% vs. 38.9%).

In a pooled analysis of AFP-High patients (n=542) from REACH-2 and REACH, which provided a larger data set to assess outcomes in this particular patient population, CYRAMZA improved OS compared to placebo (HR 0.69; 95% CI, 0.57-0.84; P=0.0002), and an improvement of 3.1 months in median OS was observed (8.1 and 5.0 months with CYRAMZA and placebo, respectively). The HR for OS across all pre-specified pooled subgroup analyses favored the CYRAMZA treatment arm. PFS, ORR and disease control rate were consistent with those in REACH and REACH-2, and supported the pooled OS result.

"Demonstrating a significant improvement in survival for this group of patients with advanced liver cancer and elevated AFP is particularly exciting as these patients have the poorest prognosis – with an expected survival of only a few months following first-line treatment if they don't go onto a second-line therapy. Treatment options are still limited in second-line liver cancer, and CYRAMZA is the first treatment specifically evaluated in this biomarker-selected population of liver cancer patients," said Maura Dickler, M.D., vice president, late phase development, Lilly Oncology. "The published results of REACH-2 demonstrate the potential for CYRAMZA to make an impact on the treatment of people with this aggressive cancer, which is encouraging for healthcare providers and the patient community."

The safety profile observed in the REACH-2 study was consistent with what has been previously observed for single-agent CYRAMZA in patients with HCC. The Grade ≥3 adverse events occurring at a rate of five percent or greater in the CYRAMZA arm were hypertension and hyponatremia (low sodium).

These data were first presented at the 2018 Annual Meeting of the American Society of Clinical Oncology (ASCO) and 2018 World Congress on Gastrointestinal Cancer.

Lilly has made regulatory submissions in the U.S., European Union and Japan based on the REACH-2 results. CYRAMZA is not yet approved for the HCC indication.

Notes to Editors

About REACH-2

REACH-2 is a global, randomized, double-blind, placebo-controlled Phase 3 study of CYRAMZA and best supportive care (BSC) compared to placebo and BSC in hepatocellular carcinoma (HCC) patients who were intolerant to, or who had disease progression while on or following treatment with, sorafenib and had a high alpha-fetoprotein (AFP-High), defined as an AFP of ≥400 ng/mL.

Initiated in 2015, the study has enrolled 292 patients across 20 countries in North America, Asia, Europe and Latin America. Patients were assigned to 8 mg/kg of intravenous CYRAMZA (n=197) or placebo (n=95) at every two weeks until disease progression, unacceptable toxicity, or withdrawal of consent, with all patients receiving BSC. The primary endpoint of the REACH-2 trial is overall survival (OS) and key secondary endpoints include progression-free survival, objective response rate, quality of life and safety.

The design of the REACH-2 trial was based on the findings of the Phase 3 REACH study,[4] which also evaluated single-agent CYRAMZA in the second-line treatment of HCC following first-line treatment with sorafenib. The REACH trial's primary endpoint of OS favored the CYRAMZA arm but was not statistically significant. However, in the prespecified subgroup of patients with baseline AFP-High treatment with CYRAMZA led to an improvement in OS (7.8 months versus 4.2 months in placebo; HR=0.674 (95% CI: 0.508, 0.895)). No OS benefit was observed in patients with baseline AFP <400 ng/mL (OS HR=1.093; 95% CI: 0.836, 1.428). The OS result in the subgroup with AFP-High was supported by improvements in key secondary endpoints and a safety profile consistent with what has been previously observed for single-agent CYRAMZA.

About REACH

REACH is a global, randomized, double-blind Phase 3 study of CYRAMZA plus best supportive care compared to placebo plus best supportive care as a second-line treatment in patients with hepatocellular carcinoma who have been previously treated with sorafenib in the first-line setting. Initiated in 2010, the study enrolled 565 patients across 27 countries; as defined in the trial protocol, the primary analyses are focused on patients with a Child-Pugh score of <7 (Child-Pugh Class A only). The primary endpoint of the REACH trial was overall survival and key secondary endpoints include: progression-free survival; objective response rate; time to progression; and safety.

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.[5,6] It is estimated that approximately half of all people with advanced HCC are AFP-High (≥400 ng/mL) and these patients are known to have a poorer prognosis relative to the general HCC patient population.[4]

About Liver Cancer

Liver cancer is the sixth most common cancer worldwide and the fourth-leading cause of cancer-related death. Each year an estimated 841,080 new cases of liver cancer are diagnosed worldwide, and an estimated 781,631 will die due to the disease. According to the World Health Organization, approximately 38,000 people are diagnosed with liver cancer, and 30,000 will die from the disease each year in the United States.[1] Liver cancer is one of the only major cancers with incidence rates that continue to rise every year in the United States[2] and is the fastest rising cause of cancer death.[3] In Europe and Japan, an estimated 82,000 and 36,000 people are diagnosed with liver cancer, and 77,000 and 29,000 will die, respectively.[1]

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.[4]

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; and, lack of access to viral hepatitis disease therapy and the persistent risk of cancer even after viral hepatitis cure.[7]

About Angiogenesis and VEGF Protein

Angiogenesis is the process of making new blood vessels. In a person with cancer, angiogenesis creates new blood vessels that give a tumor its own blood supply, allowing it to grow and spread.

Some tumors create proteins called VEGF. These proteins attach to the VEGF receptors of blood vessel cells causing new blood vessels to form around the tumors, enabling growth. Blocking the VEGF protein from linking to the blood vessels helps to inhibit tumor growth by slowing angiogenesis and the blood supply that feeds tumors. Of the three known VEGF receptors, VEGF Receptor 2 is linked most closely to VEGF-induced tumor angiogenesis.

About CYRAMZA® (ramucirumab)

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

CYRAMZA is being investigated in a broad global development program that has enrolled more than 14,000 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 specifically binds and blocks activation of VEGF Receptor 2 by blocking the binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. CYRAMZA inhibited angiogenesis in an *in vivo* animal model.

INDICATIONS

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

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

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

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

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

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

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

Warnings and Precautions

Hemorrhage

- In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel in advanced gastric cancer, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%), in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- Four of 570 patients (0.7%) who received CYRAMZA as a single agent in advanced gastric cancer clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

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

Thyroid Dysfunction

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

Embryofetal Toxicity

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

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients vs placebo in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1

was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Most Common Adverse Reactions—Combination With Docetaxel

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

Most Common Adverse Reactions—Combination With FOLFIRI

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

- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus FOLFIRI-treated patients in study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).
- Thyroid-stimulating hormone (TSH) was evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

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

Use in Specific Populations

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

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

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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 http://newsroom.lilly.com/social-channels. 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 the REACH-2 trial and CYRAMZA as a potential 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 regulatory approval for hepatocellular carcinoma 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.

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