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Early-Phase Immuno-Oncology Studies of Lilly's ALIMTA® (pemetrexed) and CYRAMZA® (ramucirumab) with Merck's KEYTRUDA® (pembrolizumab) Show Encouraging Results in Non-Small Cell Lung Cancer

Patients Receiving ALIMTA-KEYTRUDA-Carboplatin Combination Demonstrate Response Rate of 71 Percent
Majority of NSCLC Patients Receiving CYRAMZA-KEYTRUDA Combination Experience Decrease in Target Lesions
Responses Observed Regardless of PD-L1 Expression

CHICAGO, June 5, 2016 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that clinical study data from two of its ongoing immuno-oncology clinical collaborations with Merck (known as MSD outside the U.S. and Canada) were presented this weekend at the 52nd Annual Meeting of the American Society of Clinical Oncology (ASCO). Specifically, data were presented from two early-phase trials evaluating ALIMTA® (pemetrexed)-plus-carboplatin and CYRAMZA® (ramucirumab), respectively, in combination with Merck's KEYTRUDA® (pembrolizumab), in patients with non-small cell lung cancer (NSCLC).

"These early data from the combinations of ALIMTA and KEYTRUDA in front-line nonsquamous NSCLC and CYRAMZA and KEYTRUDA in later lines of NSCLC are encouraging," said Richard Gaynor, M.D., senior vice president, product development and medical affairs for Lilly Oncology. "We eagerly await Phase 2 and Phase 3 data with the ALIMTA and KEYTRUDA combinations and more mature data with the CYRAMZA and KEYTRUDA combination, in NSCLC, gastric and bladder cancers, to better understand the role of immuno-oncology combinations in improving patient outcomes in these settings."

Dr. Gaynor added, "These data also reflect the progress that Lilly is making in its oncology R&D strategy to develop cancer treatments across three key areas of disease modification: tumor cell signaling, tumor microenvironment and immuno-oncology. This approach allows for testing of combinations of internally derived agents to address tumor heterogeneity and drug resistance."

"We are pleased that these combination regimens are showing response rates in hard-to-treat tumor types across a range of treatment settings," said Eric Rubin, M.D., vice president and therapeutic area head, oncology early-stage development, Merck Research Laboratories. "We believe combination regimens will play a key role in expanding the benefit of immuno-oncology to more patients and look forward to working with Lilly to further explore these important combinations."

KEYNOTE-021

KEYNOTE-021 is a multi-cohort Phase 1/2 study evaluating the safety and preliminary efficacy of pembrolizumab plus platinum-doublet chemotherapy (including pemetrexed), immunotherapy or EGFR-targeted therapy for advanced NSCLC. Preliminary results for cohorts A and C were previously presented,[1] and data presented at ASCO this year reflect a longer follow-up period. This ASCO presentation focused on Phase 1 evaluations of cohorts A-C, of which patients in cohort C (n=24) receive pemetrexed (500 mg/m^2), carboplatin AUC 5 and pembrolizumab (2 or 10 mg/kg) (randomized 1:1) as a front-line treatment every three weeks for four cycles, followed by pemetrexed and pembrolizumab for up to two years.

In KEYNOTE-021, patients in cohort C achieved an objective response rate (ORR) of 71 percent, with one complete response and 16 partial responses to treatment. Notably, ORRs across all PD-L1 expression groups in cohort C were 69 percent or greater. Cohort C patients harboring tumors with PD-L1 expression of at least 50 percent (tumor proportion score (TPS) of ≥50%) attained an ORR of 75 percent; those with a PD-L1 TPS ≥1 percent and < 1 percent achieved ORRs of 69 percent and 75 percent, respectively. Patients in cohort C attained a median progression-free survival (PFS) of 10.2 months (95% CI, 6.3-15.2). Overall survival data are not yet mature (95% CI, 13.9-NR). As was previously reported,[1] one dose-limiting toxicity of grade 3 toxic epidermal necrolysis was reported in cohort C (pembrolizumab 10mg/kg); this patient subsequently discontinued because of this adverse event (AE). The only other grade ≥3 immune-related AE occurring on

cohort C was colitis (n=1).

KEYNOTE-189, a randomized Phase 3 study evaluating pemetrexed-plus-platinum with and without pembrolizumab as initial therapy in NSCLC patients (similar to cohort C in KEYNOTE-021), is currently enrolling. This study was also featured in a Trials-in-Progress poster at ASCO this year.

KEYNOTE-098

KEYNOTE-098, aka I4T-MC-JVDF, is a Lilly-sponsored Phase 1 study evaluating the safety and preliminary efficacy of the combination of ramucirumab with pembrolizumab in NSCLC, gastric/gastroesophageal junction (GEJ) adenocarcinoma, and transitional cell carcinoma of the urothelium (the most common type of bladder cancer). The primary safety and preliminary efficacy data being presented at ASCO this year are from cohort C (n=27), consisting of patients with NSCLC receiving treatment after prior therapy (ramucirumab 10 mg/kg plus pembrolizumab 200 mg every three weeks). This cohort included patients with nonsquamous and squamous forms of NSCLC.

In these preliminary results from KEYNOTE-098, there were no unexpected safety events reported and grade 3/4 toxicities were low (9%) in patients with NSCLC, gastric/GEJ adenocarcinoma or urothelial carcinoma. A majority of cohort C (NSCLC) patients (20/25) experienced a decrease in target lesions; this group spanned the spectrum of PD-L1 status, from negative (40%) and not reported (25%) to weak-positive (5%) and strong-positive (30%). Patients in cohort C achieved an ORR of 26 percent, with one complete response (a patient who is PD-L1 negative and had three prior treatments) and six partial responses (one of which is a patient who is PD-L1 negative and five of which had two prior treatments that included neoadjuvant/adjuvant [before/after surgical treatment] and advanced disease) to ramucirumab-pembrolizumab therapy. Responses were seen in both nonsquamous and squamous NSCLC patients. In addition, cohort C patients achieved a disease control rate (DCR) of 85 percent, and 59 percent of patients reported stable disease. These data support continued investigation of the combination of ramucirumab and pembrolizumab.

Pemetrexed (marketed under the brand name ALIMTA®) is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. *In vitro* studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides.

Ramucirumab (marketed under the brand name 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. Ramucirumab inhibited angiogenesis in an *in vivo* animal model.

There are several additional studies underway or planned to investigate ramucirumab as a single agent and in combination with other anti-cancer therapies for the treatment of multiple tumor types. This broad global development program has enrolled more than 8,500 patients across more than 60 trials of ramucirumab worldwide.

Pembrolizumab (marketed under the brand name KEYTRUDA®) is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to help detect and fight tumor cells. Pembrolizumab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes, which may affect both tumor cells and healthy cells.

NOTES TO EDITORS

About ALIMTA® (pemetrexed)
In 2004, ALIMTA received consecutive approvals: it was the first agent to be approved in combination with cisplatin as a treatment for patients with malignant pleural mesothelioma, whose disease is unresectable or who are otherwise not candidates for curative surgery, and then as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after prior treatment.

In 2008, ALIMTA, in combination with cisplatin, was approved as an initial chemotherapy treatment for locally advanced or metastatic NSCLC for patients with nonsquamous histology. At the time of this initial treatment approval, the FDA also approved a change to the indication for subsequent treatment. ALIMTA is now indicated as a single agent for the treatment of patients with locally advanced or metastatic, nonsquamous NSCLC after prior therapy.

In 2009, ALIMTA was approved as a maintenance therapy for locally advanced or metastatic NSCLC, specifically for patients with a nonsquamous histology whose disease has not progressed after four cycles of platinum-based initial chemotherapy.

In 2012, ALIMTA was approved by the FDA as maintenance therapy for locally advanced or metastatic NSCLC, following initial ALIMTA-plus-cisplatin treatment for locally advanced or metastatic nonsquamous NSCLC.

ALIMTA is not indicated for treatment of patients with squamous cell NSCLC. Myelosuppression is usually the dose-limiting toxicity with ALIMTA therapy.

Indications and Important Safety Information for ALIMTA® (pemetrexed for injection)

Indications
ALIMTA is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer.

ALIMTA is indicated for the maintenance treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

ALIMTA is indicated as a single agent for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy.

Limitations of Use: ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer.

ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.

Important Safety Information

Myelosuppression is usually the dose-limiting toxicity with ALIMTA therapy.

Contraindication
ALIMTA is contraindicated in patients who have a history of severe hypersensitivity reaction to pemetrexed.

Warnings and Precautions
Prior to treatment with ALIMTA, patients must be instructed to initiate supplementation with oral folic acid. Additionally, intramuscular injections of vitamin B_{12} are also required prior to ALIMTA treatment. Folic acid and vitamin B_{12} supplementation should be continued throughout treatment as they may reduce the severity of treatment-related hematologic and GI toxicities.

Dexamethasone or its equivalent should be administered the day before, the day of, and the day after ALIMTA treatment.

ALIMTA can suppress bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia). Reduce doses for subsequent cycles based on hematologic and nonhematologic toxicities.

ALIMTA should not be administered to patients with a creatinine clearance < 45 mL/min. One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B_{12} died of drug-related toxicity following administration of ALIMTA alone.

Caution should be used when administering NSAIDs concurrently with ALIMTA to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of ALIMTA. In the absence of data regarding potential interaction between ALIMTA and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following ALIMTA administration. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity. No dose adjustment of ALIMTA is needed with concomitant NSAIDs in patients with normal renal function.

Do not initiate a cycle of treatment in patients unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3, and creatinine clearance is ≥45 mL/min.

Pregnancy Category D—ALIMTA may cause fetal harm when administered to a pregnant woman. Women should be apprised of the potential hazard to the fetus and should be advised to use effective contraceptive measures to prevent pregnancy during treatment with ALIMTA.

Drug Interactions
See Warnings and Precautions for specific information regarding NSAID administration in patients with renal insufficiency.

Concomitant administration of nephrotoxic drugs or substances that are tubularly secreted could result in delayed clearance of ALIMTA.

Use in Specific Patient Populations
It is recommended that nursing be discontinued if the mother is being treated with ALIMTA or discontinue the drug, taking into account the importance of the drug for the mother.

Efficacy of ALIMTA in pediatric patients has not been demonstrated. The most common toxicities reported in the studied pediatric patients were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

Dosage and Administration Guidelines
Complete blood cell counts, including platelet counts and periodic chemistry tests, which include renal and hepatic function tests, should be performed on all patients receiving ALIMTA.

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Modify or suspend therapy according to the Dosage Reduction Guidelines in the full Prescribing Information.

Abbreviated Adverse Reactions (% incidence) - 1st-line advanced nonsquamous non-small cell lung cancer (NS NSCLC)
The most severe adverse reactions (grades 3-4) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, for the 1st-line treatment of patients with advanced nonsquamous non-small cell lung cancer (NSCLC) were neutropenia (15% vs 27%); leukopenia (5% vs 8%); thrombocytopenia (4% vs 13%); anemia (6% vs 10%); fatigue (7% vs 5%); nausea (7% vs 4%); vomiting (6% vs 6%); anorexia (2% vs 1%); creatinine elevation (1% vs 1%); and diarrhea (1% vs 2%).

Common adverse reactions (all grades) with ALIMTA in combination with cisplatin versus gemcitabine in combination with cisplatin, respectively, were nausea (56% vs 53%); fatigue (43% vs 45%); vomiting (40% vs 36%); anemia (33% vs 46%); neutropenia (29% vs 38%); anorexia (27% vs 24%); constipation (21% vs 20%); leukopenia (18% vs 21%); stomatitis/pharyngitis (14% vs 12%); alopecia (12% vs 21%); diarrhea (12% vs 13%); thrombocytopenia (10% vs 27%); neuropathy/sensory (9% vs 12%); taste disturbance (8% vs 9%); rash/desquamation (7% vs 8%); dyspepsia/heartburn (5% vs 6%); and creatinine elevation (10% vs 7%).

Abbreviated Adverse Reactions (% incidence) - Maintenance in advanced NS NSCLC following non-ALIMTA containing, platinum-based induction therapy
The most severe adverse reactions (grades 3-4) with ALIMTA as a single agent versus placebo, respectively, for the maintenance treatment of patients with locally advanced nonsquamous non-small cell lung cancer (NS NSCLC) following non-ALIMTA containing platinum-based induction therapy were anemia (3% vs 1%); neutropenia (3% vs 0%); leukopenia (2% vs 1%); fatigue (5% vs 1%); nausea (1% vs 1%); anorexia (2% vs 0%); mucositis/stomatitis (1% vs 0%); diarrhea (1% vs 0%); infection (2% vs 0%); and neuropathy-sensory (1% vs 0%).

Common adverse reactions (all grades) with ALIMTA as a single agent versus placebo, respectively, after non-ALIMTA containing platinum-based induction therapy were anemia (15% vs 6%); neutropenia (6% vs 0%); leukopenia (6% vs 1%); increased ALT (10% vs 4%); increased AST (8% vs 4%); fatigue (25% vs 11%); nausea (19% vs 6%); anorexia (19% vs 5%); vomiting (9% vs 1%); mucositis/stomatitis (7% vs 2%); diarrhea (5% vs 3%); infection (5% vs 2%); neuropathy-sensory (9% vs 4%); and rash/desquamation (10% vs 3%).

Abbreviated Adverse Reactions (% incidence) - Maintenance in advanced NS NSCLC following ALIMTA plus cisplatin induction therapy
The most severe adverse reactions (grades 3-4) with ALIMTA as a single agent versus placebo, respectively, for the maintenance treatment of patients with locally advanced nonsquamous non-small cell lung cancer (NS NSCLC) following ALIMTA plus cisplatin induction therapy were anemia (4.8% vs 0.6%); neutropenia (3.9% vs 0%); and fatigue (4.5% vs 0.6%).

Common adverse reactions (all grades) with ALIMTA as a single agent versus placebo, respectively, following ALIMTA plus cisplatin induction therapy were anemia (15% vs 4.8%); neutropenia (9% vs 0.6%); fatigue (18% vs 11%); nausea (12% vs 2.4%); vomiting (6% vs 1.8%); mucositis/stomatitis (5% vs 2.4%); and edema (5% vs 3.6%).

Abbreviated Adverse Reactions (% incidence) - 2nd-line advanced NS NSCLC
The most severe adverse reactions (grades 3-4) with ALIMTA as a single agent versus docetaxel, respectively, for the 2nd-line treatment of patients with advanced non-small cell lung cancer (NSCLC) were neutropenia (5% vs 40%); leukopenia (4% vs 27%); thrombocytopenia (2% vs 0%); anemia (4% vs 4%); fatigue (5% vs 5%); nausea (3% vs 2%); anorexia (2% vs 3%); vomiting (2% vs 1%); increased ALT (2% vs 0%); increased AST (1% vs 0%); and stomatitis/pharyngitis (1% vs 1%).

Common adverse reactions (all grades) with ALIMTA as a single agent versus docetaxel, respectively, were fatigue (34% vs 36%); nausea (31% vs 17%); anorexia (22% vs 24%); anemia (19% vs 22%); vomiting (16% vs 12%); stomatitis/pharyngitis (15% vs 17%); rash (14% vs 6%); diarrhea (13% vs 24%); leukopenia (12% vs 34%); thrombocytopenia (8% vs 1%); increased ALT (8% vs 1%); increased AST (7% vs 1%); constipation (6% vs 4%); fever (8% vs 8%); pruritus (7% vs 2%); alopecia (6% vs 38%); and neutropenia (11% vs 45%).

Abbreviated Adverse Reactions (% incidence) - MPM
The most severe adverse reactions (grades 3-4) with ALIMTA in combination with cisplatin versus cisplatin alone, respectively, for the treatment of patients with malignant pleural mesothelioma (MPM) were neutropenia (23% vs 3%); leukopenia (15% vs 1%); thrombocytopenia (5% vs 0%); anemia (4% vs 0%); nausea (12% vs 6%); vomiting (11% vs 4%); fatigue (10% vs 9%); creatinine elevation (1% vs 1%); stomatitis/pharyngitis (3% vs 0%); anorexia (1% vs 1%); diarrhea (4% vs 0%); constipation (1% vs 1%); dyspepsia (1% vs 0%); dehydration (4% vs 1%); neuropathy-sensory (0% vs 1%); rash (1% vs 0%); and creatinine clearance decrease (1% vs 2%).

Common adverse reactions (all grades) with ALIMTA in combination with cisplatin versus cisplatin alone, respectively, were neutropenia (56% vs 13%); leukopenia (53% vs 17%); anemia (26% vs 10%); thrombocytopenia (23% vs 9%); nausea (82% vs 77%); vomiting (57% vs 50%); fatigue (48% vs 42%); creatinine elevation (11% vs 10%); creatinine clearance decreased (16% vs 18%); conjunctivitis (5% vs 1%); anorexia (20% vs 14%); diarrhea (17% vs 8%); constipation (12% vs 7%); dyspepsia (5% vs 1%); dehydration (7% vs 1%); neuropathy-sensory (10% vs 10%); taste disturbance (8% vs 6%); rash (16% vs 5%); alopecia (11% vs 6%); and stomatitis/pharyngitis (23% vs 6%).

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For more complete information for Alimta, please see full Prescribing Information **and** Patient Information.

About CYRAMZA® (ramucirumab)
INDICATIONS

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

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

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

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

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

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

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

Warnings and Precautions

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

Arterial Thromboembolic Events (ATEs)
Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

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

Infusion-Related Reactions (IRRs)
Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations
CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in advanced gastric cancer clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

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

Clinical Deterioration in Child-Pugh B or C Cirrhosis
Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS has been reported at a rate of < 0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome
In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥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. Patients received periodic TSH assessments until 30 days after the last dose of study treatment. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

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

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and pediatric development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise

women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

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

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About Lilly Oncology
For more than 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
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Lilly Forward-Looking Statement
This press release contains "forward-looking statements" (as that term is defined in the United States Private Securities Litigation Reform Act of 1995) regarding the research collaborations between Lilly and Merck evaluating ALIMTA (plus carboplatin) with KEYTRUDA and CYRAMZA with KEYTRUDA for the treatment of non-small cell lung cancer, and reflects Lilly's current beliefs. However, there are substantial risks and uncertainties in the process of drug research, development and commercialization. Among other risks, there can be no guarantee that these investigational combination regimens will receive regulatory approval, or, if approved, will achieve intended benefits or become commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ materially from Lilly's expectations, please see the company's latest Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements for events occurring after the date of this release.

[1] Papadimitrakopoulou V et al. J Clin Oncol. 2015;33 (15_suppl):8031.

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