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# Lilly, Merck Enter Collaboration Agreement to Research Immuno-Oncology Combination Regimens in Multiple Types of Cancer

Combinations of KEYTRUDA® (pembrolizumab) with Alimta® (pemetrexed), Cyramza® (ramucirumab), or necitumumab to be explored

KENILWORTH, N.J. & INDIANAPOLIS--(BUSINESS WIRE)-- Merck (NYSE:MRK), known as MSD outside the US and Canada, and Eli Lilly and Company (NYSE:LLY) announced today an oncology clinical trial collaboration to evaluate the safety, tolerability and efficacy of KEYTRUDA® (pembrolizumab), Merck's anti-PD-1 therapy, in combination with Lilly compounds in multiple clinical trials:

- Merck will conduct a Phase 2 study examining the combination of pembrolizumab with pemetrexed in first-line non-squamous, non-small cell lung cancer (NSCLC). This study is currently enrolling.
- Lilly will conduct a multiple-arm Phase 1/2 study examining the combination of ramucirumab with pembrolizumab in multiple tumors. This study is anticipated to begin in 2015.
- Lilly will conduct a Phase 1/2 study examining the combination of necitumumab with pembrolizumab in NSCLC. This study is anticipated to begin in 2015.

The agreement is between Lilly and Merck, through a subsidiary. Additional details of the collaboration were not disclosed.

"Cancer is not one disease but rather more than 200 diseases, all of which have different causes and treatments," said Richard Gaynor, M.D., senior vice president, product development and medical affairs, Lilly Oncology. "Therefore research into combinations of immune-based therapies with other agents that could address these different tumor types is important. This collaboration between Lilly and Merck represents each company's strong commitment to patients fighting these devastating diseases."

"Our understanding of the immune system's role and its impact in the treatment of cancer continues to grow," said Eric Rubin, M.D., vice president, global clinical development, oncology, Merck Research Laboratories. "Collaborations such as this one are important in advancing the investigation of novel immuno-oncology combinations in different cancers, and to achieving our shared goal of bringing meaningful benefits to patients facing cancer."

**About KEYTRUDA® (pembrolizumab)**

KEYTRUDA (pembrolizumab) is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, KEYTRUDA releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

KEYTRUDA is indicated in the United States at a dose of 2 mg/kg every three weeks for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**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 second-line treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy treatment.

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

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 first-line chemotherapy.

In 2012, ALIMTA was approved by the FDA as a continuation maintenance therapy for locally-advanced or metastatic NSCLC, following first-line therapy with ALIMTA plus cisplatin in patients with a nonsquamous histology.

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

**About CYRAMZA® (ramucirumab)**

CYRAMZA as a single agent, or in combination with paclitaxel (a type of chemotherapy), is approved for the treatment of people with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

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.

**About Necitumumab**

Necitumumab is an investigational recombinant human IgG1 monoclonal antibody that is designed to block the ligand binding site of the human epidermal growth factor receptor 1 (EGFR). Activation of EGFR has been correlated with malignant progression, induction of angiogenesis and inhibition of apoptosis or cell death.

**Selected Important Safety Information for KEYTRUDA**

Pneumonitis occurred in 12 (2.9%) of 411 patients with advanced melanoma receiving KEYTRUDA (the approved indication in the United States), including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively. Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 pneumonitis.

Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients respectively, receiving KEYTRUDA. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving KEYTRUDA. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

Hypophysitis occurred in 2 (0.5%) of 411 patients, including a Grade 2 case in 1 and a Grade 4 case in 1 (0.2% each) patient, receiving KEYTRUDA. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold KEYTRUDA for Grade 2; withhold or discontinue for Grade 3; and permanently discontinue KEYTRUDA for Grade 4 hypophysitis.

Nephritis occurred in 3 (0.7%) patients receiving KEYTRUDA, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 nephritis.

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients respectively, receiving KEYTRUDA. Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving KEYTRUDA. Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer corticosteroids for Grade 3 or greater hyperthyroidism. Withhold KEYTRUDA for Grade 3; permanently discontinue KEYTRUDA for Grade 4 hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

Other clinically important immune-mediated adverse reactions can occur. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with KEYTRUDA: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal

insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement of the adverse reaction to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less. Permanently discontinue KEYTRUDA for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

Based on its mechanism of action, KEYTRUDA may cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of KEYTRUDA.

For the treatment of advanced melanoma, KEYTRUDA was discontinued for adverse reactions in 6% of 89 patients who received the recommended dose of 2 mg/kg and 9% of 411 patients across all doses studied. Serious adverse reactions occurred in 36% of patients receiving KEYTRUDA. The most frequent serious adverse drug reactions reported in 2% or more of patients were renal failure, dyspnea, pneumonia, and cellulitis.

The most common adverse reactions (reported in ≥20% of patients) were fatigue (47%), cough (30%), nausea (30%), pruritus (30%), rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%), and diarrhea (20%).

The recommended dose of KEYTRUDA is 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity. No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA. It is not known whether KEYTRUDA is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA. Safety and effectiveness of KEYTRUDA have not been established in pediatric patients.

**Important Safety Information for ALIMTA® (pemetrexed for injection)**

**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%).

**For safety and dosing guidelines, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the accompanying full Prescribing Information.**

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**IMPORTANT SAFETY INFORMATION FOR CYRAMZA**

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

**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. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

**Arterial Thromboembolic Events**

- Serious, sometimes fatal, arterial thromboembolic events (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%). 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**

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (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. 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 is an antiangiogenic therapy with the potential to adversely affect 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.

**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.
- 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%).
- 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).

**Drug Interactions**

- No pharmacokinetic (PK) interactions were observed between ramucirumab (CYRAMZA) and paclitaxel or between ramucirumab (CYRAMZA) and docetaxel.

**Use in Specific Populations**

- Pregnancy Category C: Based on its mechanism of action, CYRAMZA may cause fetal harm. Advise females of reproductive potential to avoid getting pregnant, including use of adequate contraception, while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA. Animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no adequate or well-controlled studies of ramucirumab in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.
- Nursing Mothers: It is recommended to discontinue nursing or discontinue CYRAMZA due to the potential risks to the nursing infant.
- Females of Reproductive Potential: Advise females of reproductive potential that CYRAMZA may impair fertility.

**Please see full Prescribing Information for CYRAMZA, including Boxed Warning for hemorrhage.**

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**Merck's Focus on Cancer**

Our goal is to translate breakthrough science into biomedical innovations to help people with cancer worldwide. For Merck Oncology, helping people fight cancer is our passion, supporting accessibility to our cancer medicines is our commitment, and pursuing research in immuno-oncology and other areas of breakthrough science is our focus to potentially bring new hope to

people with cancer. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

**About Merck**

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.

**About Lilly Oncology**

For more than fifty 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 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 newsroom.lilly.com/social-channels.

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**Merck Forward-Looking Statement**

This news release includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include, but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and healthcare legislation in the United States and internationally; global trends toward healthcare cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in Merck's 2013 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

**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 collaboration between Merck and Lilly. This press release 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 this investigational combination regimen will receive regulatory approval, or, if approved, that it will achieve intended benefits or become a commercially successful product. 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.*

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