



## Lilly Oncology to Present Robust Data across Its Growing Portfolio at ESMO 2019

September 23, 2019

**Verzenio® (abemaciclib) Phase 3 data included in ESMO Presidential Symposium and Official Press Program: Positive overall survival results to be presented from MONARCH 2, evaluating Verzenio with fulvestrant for the treatment of women with HR+, HER2- advanced breast cancer whose cancer grew or spread following endocrine therapy**

**RET-altered thyroid cancer data for selpercatinib[1] (LOXO-292) from the Phase 1/2 LIBRETTO-001 study to be featured in late-breaking oral presentation**

**Lung cancer highlights to include presentation of data from the Phase 3 CYRAMZA® (ramucirumab) RELAY trial and studies of the ALIMTA® (pemetrexed)-KEYTRUDA® (pembrolizumab)-platinum chemotherapy combination**

INDIANAPOLIS, Sept. 23, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced data from a number of studies across the company's oncology product portfolio will be presented at the European Society for Medical Oncology (ESMO) 2019 Congress in Barcelona, Spain, September 27 - October 1, 2019. Data from 14 oral presentations and posters – including five late-breaking abstracts – underscore Lilly Oncology's dedication to developing and delivering innovative new medicines that will make a meaningful difference to people living with cancer.

"Lilly's data to be presented at this year's ESMO truly embody the congress theme of 'translating science into better cancer patient care' in many ways, including the results demonstrating extension of life in women with advanced breast cancer and exciting data from our precision medicine portfolio," said Maura Dickler, M.D., vice president, late phase development, Lilly Oncology. "We are excited to present the statistically significant and clinically meaningful overall survival results for MONARCH 2, a study of Verzenio® plus fulvestrant for women living with HR+, HER2- advanced breast cancer whose cancer grew or spread following endocrine therapy, and registrational data from the LIBRETTO-001 study of our promising, highly selective and potent investigational agent selpercatinib (LOXO-292) in *RET*-altered thyroid cancers."

### Lilly's Commitment to Advanced Breast Cancer Patients

Lilly continues to investigate Verzenio (abemaciclib) across the breast cancer continuum to provide physicians with the information they need as they seek to optimize treatment options for those living with this devastating, complex disease. At ESMO, Lilly will share detailed overall survival (OS) results from the Phase 3 MONARCH 2 trial, which demonstrated Verzenio plus fulvestrant significantly extended life in women with HR+, HER2- advanced breast cancer whose cancer grew or spread following endocrine therapy. Importantly, Verzenio had already shown a significant benefit for progression-free survival (PFS), the study's primary endpoint and basis for regulatory approvals globally. These OS results are to be presented in the ESMO Presidential Symposium and featured in the official ESMO Press Program.

Additional data to be presented include final results from the Phase 2 monarchHER trial evaluating Verzenio in combination with trastuzumab (with or without fulvestrant) in women with previously treated HR+, HER2+ advanced breast cancer. MonarchHER is the first randomized clinical trial of a CDK4 & 6 inhibitor for people with HER2+ advanced breast cancer, who represent approximately 15-20 percent of people living with advanced breast cancer. Findings from MONARCHplus, a Phase 3 trial with two cohorts evaluating the use of Verzenio plus an aromatase inhibitor and Verzenio plus fulvestrant (both versus placebo)—the first randomized clinical trial of a CDK4 & 6 inhibitor in a predominantly Chinese population of women with HR+, HER2- advanced breast cancer—to support registration in China, will also be presented.

### Latest Results of Selpercatinib (LOXO-292)

In a late-breaking oral presentation, Lilly will share the registrational results of selpercatinib (LOXO-292) in *RET*-altered thyroid cancers, from the Phase 1/2 LIBRETTO-001 study. Selpercatinib is a highly selective and potent, oral investigational new medicine being studied for the treatment of advanced cancers that develop due to alterations of the *RET* kinase.

Selpercatinib is being investigated in *RET* fusion-positive cancers across tumor types and *RET*-mutant medullary thyroid cancer (MTC). *RET* fusions have been identified in approximately two percent of non-small cell lung cancer (NSCLC) patients, 10-20 percent of papillary thyroid cancer patients and a subset of other cancers. Activating *RET* point mutations account for approximately 60 percent of MTC. Results presented at ESMO, as well as the [selpercatinib lung cancer data](#) presented at the IASLC World Congress on Lung Cancer (WCLC) earlier this month, will be included as part of a new drug application submission to the U.S. Food and Drug Administration later this year.

### Lung Cancer Data

Lilly has a strong heritage in developing practice-changing medicines for the treatment of lung cancer. Lilly has developed multiple thoracic oncology treatments and continues to study marketed products and investigational molecules in new combinations and settings where they could help specific patient populations. At ESMO, presentations include the first report of a biomarker study in Japanese patients from the Phase 3 RELAY trial and a pooled analysis of data from studies including KEYNOTE-021 and KEYNOTE-189 in patients with brain metastases, as well as tissue tumor mutation burden (tTMB) and outcomes from those same KEYNOTE studies.

RELAY is a global, randomized, double-blind Phase 3 trial evaluating CYRAMZA® (ramucirumab) in combination with erlotinib, compared to placebo in combination with erlotinib, as a first-line treatment in patients with metastatic NSCLC whose tumors have activating EGFR mutations. The RELAY study met its primary endpoint of PFS.

The global, randomized, double-blind Phase 3 KEYNOTE-189 study evaluated ALIMTA® (pemetrexed) in combination with KEYTRUDA® (pembrolizumab) and cisplatin or carboplatin compared with ALIMTA in combination with placebo and cisplatin or carboplatin, in untreated patients with metastatic nonsquamous NSCLC. KEYNOTE-189 enrolled patients regardless of PD-L1 expression and had dual primary endpoints of OS and PFS. The KEYNOTE-189 trial was based on results seen in the Phase 2 KEYNOTE-021 (Cohort G1) study. The KEYNOTE-189 and -021 trials were conducted by Merck (known as MSD outside the U.S. and Canada) in collaboration with Lilly.

Select studies, along with the dates, times and locations of their data sessions, are highlighted below.

#### **Verzenio (abemaciclib)**

**Abstract # 1605: MONARCH 2: Overall survival of abemaciclib plus fulvestrant in patients with HR+, HER2- advanced breast cancer (George W. Sledge)**

Proffered Paper Session: Presentation Number LBA6  
Sunday, September 29, 2019; 16:30 - 18:00; Barcelona Auditorium (Hall 2)

**Abstract # 1470: monarchHER: A randomized Phase 2 study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+, HER2+ advanced breast cancer (ABC) (Sara M. Tolaney)**

Proffered Paper Session: Presentation Number LBA23  
Saturday, September 28, 2019; 10:15 - 11:45; Barcelona Auditorium (Hall 2)

**Abstract # 1076: MONARCHplus: A Phase 3 Trial of Abemaciclib plus Nonsteroidal Aromatase Inhibitor (NSAI) or Fulvestrant (F) for Women with HR+/HER2- Advanced Breast Cancer (ABC) (Zefei Jiang)**

Poster Discussion Session: Presentation Number LBA25  
Sunday, September 29, 2019; 08:30 - 09:50; Cordoba Auditorium (Hall 7)

**Abstract # 1378: MONARCH 3: Updated time to chemotherapy and disease progression following abemaciclib plus aromatase inhibitor (AI) in HR+, HER2- advanced breast cancer (ABC) (Miguel Martin)**

Poster Display Session: Presentation Number 326P  
Sunday, September 29, 2019; 12:00 - 13:00; Poster Area (Hall 4)

**Abstract # 2777: A Phase 2 study of abemaciclib in patients (pts) with brain metastases (BM) secondary to non-small cell lung cancer (NSCLC) or melanoma (MEL). (Solmaz Sahebjam)**

Poster Display Session: Presentation Number 331P  
Sunday, September 29, 2019; 12:00 - 13:00; Poster Area (Hall 4)

#### **Selpercatinib (LOXO-292)**

**Abstract # 2402: Registrational Results of LOXO-292 in Patients with RET-Altered Thyroid Cancers (Lori J. Wirth)**

Proffered Paper Session: Presentation Number LBA93  
Sunday, September 29, 2019; 16:30 - 18:00; Tarragona Auditorium (Hall 7)

#### **CYRAMZA (ramucirumab)**

**Abstract # 2855: Impact of ramucirumab (RAM) + erlotinib (ERL) on EGFR mutations in circulating tumor DNA – The 1st report of a biomarker study in Japanese patients from RELAY: Global Ph3 study of ERL + RAM or placebo (PL) in 1L metastatic NSCLC with EGFR activating mutations (Kazuto Nishio)**

Poster Display Session: Presentation Number 1523P  
Saturday, September 28, 2019; 12:00 - 13:00; Poster Area (Hall 4)

**Abstract # 1192: Ramucirumab in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha fetoprotein (AFP): An exposure–response analysis (Josep Llovet)**

Poster Display Session: Presentation Number 758P  
Sunday, September 29, 2019; 12:00 - 13:00; Poster Area (Hall 4)

**Abstract # 1529: Prognostic and predictive value of baseline alpha-fetoprotein (AFP) in patients with advanced hepatocellular carcinoma (HCC) treated with ramucirumab from two phase 3 studies (REACH, REACH-2) (Andrew X. Zhu)**

Poster Display Session: Presentation Number 753P  
Sunday, September 29, 2019; 12:00 - 13:00; Poster Area (Hall 4)

**Abstract # 1758: Efficacy and safety of ramucirumab (RAM) for advanced hepatocellular carcinoma (HCC) with elevated alpha-fetoprotein (AFP) following first-line sorafenib across age subgroups in two global phase 3 trials (REACH and REACH-2) (Masatoshi Kudo)**

Poster Display Session: Presentation Number 757P  
Sunday, September 29, 2019; 12:00 - 13:00; Poster Area (Hall 4)

**Abstract # 2717: Ramucirumab use in patients with Advanced Gastric Cancer (AGC) or gastro-oesophageal junction (GEJ) adenocarcinoma in Spain: RAMIS observational study (Federico Longo Munoz)**

Poster Display Session: Presentation Number 793P  
Sunday, September 29, 2019; 12:00 - 13:00; Poster Area (Hall 4)

**Abstract # 2108: Biomarker analyses of ramucirumab in patients with platinum refractory urothelial cancer from RANGE, a global, randomized, double-blind, phase 3 study. (Michiel S. Van der Heijden)**

Poster Display Session: Presentation Number 929P  
Monday, September 30, 2019; 12:00 - 13:00; Poster Area (Hall 4)

#### **ALIMTA (pemetrexed)**

**Abstract # 4597: Pembrolizumab (pembro) plus platinum-based chemotherapy (chemo) in NSCLC with brain metastases: Pooled analysis of KEYNOTE-021, 189, and 407 (Steven F. Powell)**

Poster Discussion Session: Presentation Number 1483PD  
Sunday, September 29, 2019; 16:30 - 17:45; Cordoba Auditorium (Hall 7)

**Abstract # 4311: Pembrolizumab (pembro) plus platinum-based chemotherapy (chemo) for metastatic NSCLC: tissue TMB (tTMB) and outcomes in KEYNOTE-021, 189, and 407 (Luis Paz-Ares)**

Proffered Paper Session: Presentation Number LBA80  
Friday, September 27, 2019; 16:00 - 17:30; Barcelona Auditorium (Hall 2)

**Notes to Editors**

**About Verzenio® (abemaciclib)**

Verzenio (abemaciclib) is an inhibitor of cyclin-dependent kinases (CDK)4 & 6, which are activated by binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4 & 6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation.

In vitro, continuous exposure to Verzenio inhibited Rb phosphorylation and blocked progression from G1 to S phase of the cell cycle, resulting in senescence and apoptosis (cell death). Preclinically, Verzenio dosed daily without interruption resulted in reduction of tumor size. Inhibiting CDK4 & 6 in healthy cells can result in side effects, some of which may be serious. Clinical evidence also suggests that Verzenio crosses the blood-brain barrier. In patients with advanced cancer, including breast cancer, concentrations of Verzenio and its active metabolites (M2 and M20) in cerebrospinal fluid are comparable to unbound plasma concentrations.

Verzenio is Lilly's first solid oral dosage form to be made using a faster, more efficient process known as continuous manufacturing. Continuous manufacturing is a new and advanced type of manufacturing within the pharmaceutical industry, and Lilly is one of the first companies to use this technology.

**About Selpercatinib (LOXO-292)**

Selpercatinib, also known as LOXO-292, is a highly selective and potent, oral investigational new medicine in clinical development for the treatment of patients with cancers that harbor abnormalities in the rearranged during transfection (RET) kinase. *RET* fusions and mutations occur across multiple tumor types with varying frequency. Selpercatinib was designed to inhibit native RET signaling as well as anticipated acquired resistance mechanisms.

Selpercatinib has received breakthrough designation for the treatment of patients with:

- Metastatic *RET* fusion-positive non-small cell lung cancer who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy;
- *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options; and for
- Advanced *RET*-fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

**About CYRAMZA® (ramucirumab)**

In the U.S., CYRAMZA (ramucirumab) has five FDA approvals to treat four different types of cancers. CYRAMZA is being investigated in a broad global development program that has enrolled more than 15,000 patients across more than 100 trials worldwide. These include several studies investigating CYRAMZA in combination with other anti-cancer therapies for the treatment of multiple tumor types.

CYRAMZA is an antiangiogenic therapy. It is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that binds specifically to VEGFR-2, thereby blocking the binding of the receptor ligands (VEGF-A, VEGF-C, and VEGF-D) – which may slow tumor growth. CYRAMZA inhibited angiogenesis in an *in vivo* animal model.

**About ALIMTA® (pemetrexed for injection)**

ALIMTA is indicated in combination with pembrolizumab and platinum chemotherapy for the initial treatment of patients with metastatic nonsquamous non-small cell lung cancer, with no EGFR or ALK genomic tumor aberrations. For all FDA-approved indications for ALIMTA, please see full [Prescribing Information](#).

**INDICATION FOR VERZENIO**

Verzenio is indicated for the treatment of HR+, HER2- advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor for postmenopausal women as initial endocrine-based therapy

- in combination with fulvestrant for women with disease progression following endocrine therapy
- as a single agent for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

### IMPORTANT SAFETY INFORMATION FOR VERZENIO® (abemaciclib)

**Diarrhea** occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

**Neutropenia** occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Severe, life-threatening, or fatal **interstitial lung disease (ILD) and/or pneumonitis** can occur in patients treated with Verzenio and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.

Grade ≥3 increases in **alanine aminotransferase (ALT)** (6% versus 2%) and **aspartate aminotransferase (AST)** (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms respectively, in MONARCH 2.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential **hepatotoxicity**, monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

**Venous thromboembolic events** were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause **fetal harm** when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum

recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The most common adverse reactions (all grades,  $\geq 10\%$ ) observed in **MONARCH 3 for Verzenio plus anastrozole or letrozole and  $\geq 2\%$  higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole** were diarrhea (81% vs 30%), neutropenia (41% vs 2%), fatigue (40% vs 32%), infections (39% vs 29%), nausea (39% vs 20%), abdominal pain (29% vs 12%), vomiting (28% vs 12%), anemia (28% vs 5%), alopecia (27% vs 11%), decreased appetite (24% vs 9%), leukopenia (21% vs 2%), creatinine increased (19% vs 4%), constipation (16% vs 12%), ALT increased (16% vs 7%), AST increased (15% vs 7%), rash (14% vs 5%), pruritus (13% vs 9%), cough (13% vs 9%), dyspnea (12% vs 6%), dizziness (11% vs 9%), weight decreased (10% vs 3%), influenza-like illness (10% vs 8%), and thrombocytopenia (10% vs 2%).

The most common adverse reactions (all grades,  $\geq 10\%$ ) observed in **MONARCH 2 for Verzenio plus fulvestrant and  $\geq 2\%$  higher than placebo plus fulvestrant vs placebo plus fulvestrant** were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs  $<1\%$ ), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The most common adverse reactions (all grades,  $\geq 10\%$ ) observed in **MONARCH 1 with Verzenio** were diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), neutropenia (37%), vomiting (35%), infections (31%), anemia (25%), thrombocytopenia (20%), headache (20%), cough (19%), leukopenia (17%), constipation (17%), arthralgia (15%), dry mouth (14%), weight decreased (14%), stomatitis (14%), creatinine increased (13%), alopecia (12%), dysgeusia (12%), pyrexia (11%), dizziness (11%), and dehydration (10%).

The most frequently reported  $\geq 5\%$  Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of **MONARCH 3** were neutropenia (22% vs 2%), diarrhea (9% vs 1%), leukopenia (8% vs  $<1\%$ ), ALT increased (7% vs 2%), and anemia (6% vs 1%).

The most frequently reported  $\geq 5\%$  Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of **MONARCH 2** were neutropenia (27% vs 2%), diarrhea (13% vs  $<1\%$ ), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

The most frequently reported  $\geq 5\%$  Grade 3 or 4 adverse reactions from **MONARCH 1** with Verzenio were neutropenia (24%), diarrhea (20%), fatigue (13%), infections (7%), leukopenia (6%), anemia (5%), and nausea (5%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 3 in  $\geq 10\%$  for Verzenio plus anastrozole or letrozole and  $\geq 2\%$  higher than placebo plus anastrozole or letrozole vs placebo plus anastrozole or letrozole** were increased serum creatinine (98% vs 84%; 2% vs 0%), decreased white blood cells (82% vs 27%; 13% vs  $<1\%$ ), anemia (82% vs 28%; 2% vs 0%), decreased neutrophil count (80% vs 21%; 22% vs 3%), decreased lymphocyte count (53% vs 26%; 8% vs 2%), decreased platelet count (36% vs 12%; 2% vs  $<1\%$ ), increased ALT (48% vs 25%; 7% vs 2%), and increased AST (37% vs 23%; 4% vs  $<1\%$ ).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 2 in  $\geq 10\%$  for Verzenio plus fulvestrant and  $\geq 2\%$  higher than placebo plus fulvestrant vs placebo plus fulvestrant** were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs  $<1\%$ ), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 1 with Verzenio** were increased serum creatinine (98%;  $<1\%$ ), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 27%), anemia (68%; 0%), decreased lymphocyte count (42%; 14%), decreased platelet count (41%; 2%), increased ALT (31%; 3%), and increased AST (30%; 4%).

**Strong and moderate CYP3A inhibitors** increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

**Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.** Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

**With severe hepatic impairment** (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr  $<30$  mL/min), end stage renal disease, or in patients on dialysis **is unknown**. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr  $\geq 30$ -89 mL/min).

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

## INDICATIONS FOR CYRAMZA

### Gastric Cancer

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

### Non-Small Cell Lung Cancer

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease

progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

#### **Colorectal Cancer**

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

#### **Hepatocellular Carcinoma**

CYRAMZA, as a single agent, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have an alpha-fetoprotein (AFP) of  $\geq 400$  ng/mL and have been treated with sorafenib.

### **IMPORTANT SAFETY INFORMATION FOR CYRAMZA<sup>®</sup> (ramucirumab)**

#### **Warnings and Precautions**

##### **Hemorrhage**

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade  $\geq 3$  hemorrhagic events. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage occurred between 13-44%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in REGARD and RAINBOW; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown.
- Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from REVEL; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

##### **Gastrointestinal Perforations**

- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from  $<1$ -2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

##### **Impaired Wound Healing**

- Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. CYRAMZA, a VEGFR2 antagonist, has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 28 days following a major surgical procedure and until the wound is fully healed. Discontinue CYRAMZA in patients who develop wound healing complications that require medical intervention.

##### **Arterial Thromboembolic Events**

- Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 2-3%. Grade 3-5 ATE incidence was 1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

### **Hypertension**

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension occurred between 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

### **Infusion-Related Reactions**

- Infusion-related reactions (IRR), including severe and life threatening IRR, occurred in CYRAMZA clinical trials. The majority of IRR across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRR included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR occurred between <1-9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3-4 IRR.

### **Worsening of Pre-existing Hepatic Impairment**

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

### **Reversible Posterior Leukoencephalopathy Syndrome**

- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with CYRAMZA.
- Confirm the diagnosis of RPLS with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

### **Proteinuria Including Nephrotic Syndrome**

- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-20%. Grade  $\geq 3$  proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is 2+ or greater, perform a 24-hour urine collection for protein measurement. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

### **Thyroid Dysfunction**

- Across five clinical studies in 1916 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

### **Embryo-Fetal Toxicity**

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

### **Lactation**

- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to

breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

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

- The most commonly reported adverse reactions (all Grades; Grade 3-4) occurring in  $\geq 5\%$  of patients receiving CYRAMZA and  $\geq 2\%$  higher than placebo in REGARD were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in  $\geq 1\%$  and  $< 5\%$  of CYRAMZA-treated patients in REGARD were: neutropenia (4.7%), epistaxis (4.7%), rash (4.2%), intestinal obstruction (2.1%), and arterial thromboembolic events (1.7%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade  $\geq 3$ ) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and IRR. In REGARD, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in REGARD was 0.8% and the rate of IRR was 0.4%.

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

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

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

- The most commonly reported adverse reactions (all Grades; Grade 3-4) occurring in  $\geq 5\%$  of patients receiving CYRAMZA with docetaxel and  $\geq 2\%$  higher than placebo with docetaxel in REVEL were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%;  $< 1\%$  vs  $< 1\%$ ), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs  $< 1\%$ ), thrombocytopenia (13% vs 5%; 3% vs  $< 1\%$ ), lacrimation increased (13% vs 5%;  $< 1\%$  vs 0%), and hypertension (11% vs

5%; 6% vs 2%).

- The most common serious adverse reactions in patients who received CYRAMZA with docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA with docetaxel-treated patients versus 37% in patients who received placebo with docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA with docetaxel-treated patients (9%) than in placebo with docetaxel-treated patients (5%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were IRR (0.5%) and epistaxis (0.3%).
- For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of Grade  $\geq 3$  pulmonary hemorrhage was 1% for CYRAMZA with docetaxel compared to 6% overall incidence and 1% for Grade  $\geq 3$  pulmonary hemorrhage for placebo with docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of Grade  $\geq 3$  pulmonary hemorrhage was 2% for CYRAMZA with docetaxel compared to 12% overall incidence and 2% for Grade  $\geq 3$  pulmonary hemorrhage for placebo with docetaxel.
- Clinically relevant adverse reactions reported in  $\geq 1\%$  and  $< 5\%$  of CYRAMZA with docetaxel-treated patients in REVEL were hyponatremia (4.8%) and proteinuria (3.3%).

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

- The most commonly reported adverse reactions (all Grades; Grade  $\geq 3$ ) occurring in  $\geq 5\%$  of patients receiving CYRAMZA with FOLFIRI and  $\geq 2\%$  higher than placebo with FOLFIRI in RAISE were diarrhea (60% vs 51%; 11% vs 10%), neutropenia (59% vs 46%; 38% vs 23%), decreased appetite (37% vs 27%; 2% vs 2%), epistaxis (33% vs 15%; 0% vs 0%), stomatitis (31% vs 21%; 4% vs 2%), thrombocytopenia (28% vs 14%; 3% vs  $< 1\%$ ), hypertension (26% vs 9%; 11% vs 3%), peripheral edema (20% vs 9%;  $< 1\%$  vs 0%), proteinuria (17% vs 5%; 3% vs  $< 1\%$ ), palmar-plantar erythrodysesthesia syndrome (13% vs 5%; 1% vs  $< 1\%$ ), gastrointestinal hemorrhage events (12% vs 7%; 2% vs 1%), and hypoalbuminemia (6% vs 2%; 1% vs 0%). Twenty percent of patients treated with CYRAMZA with FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse reactions with CYRAMZA with FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA with FOLFIRI-treated patients (29%) than in placebo with FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA with FOLFIRI as compared to placebo with FOLFIRI were neutropenia (12.5% vs 5.3%) and thrombocytopenia (4.2% vs 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reaction reported in  $\geq 1\%$  and  $< 5\%$  of patients receiving CYRAMZA with FOLFIRI was gastrointestinal perforation (1.7%) including 4 fatal events.
- Thyroid-stimulating hormone (TSH) levels were evaluated in 224 patients (115 CYRAMZA with FOLFIRI-treated patients and 109 placebo with FOLFIRI-treated patients) with normal baseline TSH levels. Increased TSH levels were observed in 53 (46%) patients treated with CYRAMZA with FOLFIRI compared with 4 (4%) patients treated with placebo with FOLFIRI.

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

- The most commonly reported adverse reactions (all Grades; Grade  $\geq 3$ ) occurring in  $\geq 10\%$  of patients receiving CYRAMZA and  $\geq 2\%$  higher than placebo in REACH-2 were fatigue (36% vs 20%; 5% vs 3%), peripheral edema (25% vs 14%; 2% vs

0%), hypertension (25% vs 13%; 13% vs 5%), abdominal pain (25% vs 16%; 2% vs 2%), decreased appetite (23% vs 20%; 2% vs 1%), proteinuria (20% vs 4%; 2% vs 0%), nausea (19% vs 12%; 0% vs 0%), ascites (18% vs 7%; 4% vs 1%), headache (14% vs 5%; 0% vs 1%), epistaxis (14% vs 3%; <1% vs 0%), insomnia (11% vs 6%; 0% vs 1%), pyrexia (10% vs 3%; 0% vs 0%), vomiting (10% vs 7%; 0% vs 0%), and back pain (10% vs 7%; <1% vs 1%). The most common laboratory abnormalities (all Grades; Grade  $\geq$ 3) occurring in  $\geq$ 15% of patients receiving CYRAMZA and  $\geq$ 2% higher than placebo were thrombocytopenia (46% vs 15%; 8% vs 1%), hypoalbuminemia (33% vs 16%; <1% vs 0%), hyponatremia (32% vs 25%; 16% vs 5%), neutropenia (24% vs 12%; 8% vs 3%), and hypocalcemia (16% vs 5%; 2% vs 0%).

- The most common serious adverse reactions with CYRAMZA were ascites (3%) and pneumonia (3%).
- Treatment discontinuations due to adverse reactions occurred in 18% of CYRAMZA-treated patients, with proteinuria being the most frequent (2%).
- Clinically relevant adverse reactions reported in  $\geq$ 1% and <10% of CYRAMZA-treated patients in REACH-2 were IRR (9%), hepatic encephalopathy (5%) including 1 fatal event, and hepatorenal syndrome (2%) including 1 fatal event.

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

#### **IMPORTANT SAFETY INFORMATION FOR ALIMTA<sup>®</sup> (pemetrexed for injection)**

##### **CONTRAINDICATION**

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

##### **WARNINGS AND PRECAUTIONS**

###### **Myelosuppression and Increased Risk of Myelosuppression Without Vitamin Supplementation**

- ALIMTA can cause severe myelosuppression resulting in a requirement for transfusions and which may lead to neutropenic infection. The risk of myelosuppression is increased in patients who do not receive vitamin supplementation.
- Prior to treatment with ALIMTA, patients must be instructed to initiate supplementation with oral folic acid. Intramuscular injections of vitamin B<sub>12</sub> are also required prior to ALIMTA treatment. Folic acid and vitamin B<sub>12</sub> supplementation should be continued during treatment and for 21 days after the last dose of ALIMTA as they may reduce the severity of treatment-related hematologic and gastrointestinal toxicities. Obtain a complete blood count at the beginning of each cycle. Do not administer ALIMTA until the ANC is at least 1500 cells/mm<sup>3</sup> and platelet count is at least 100,000 cells/mm<sup>3</sup>. Permanently reduce ALIMTA in patients with an ANC of less than 500 cells/mm<sup>3</sup> or platelet count of less than 50,000 cells/mm<sup>3</sup> in previous cycles.
- In Studies JMDB and JMCH, among patients who received vitamin supplementation, incidence of Grade 3-4 neutropenia was 15% and 23%, the incidence of Grade 3-4 anemia was 6% and 4%, and incidence of Grade 3-4 thrombocytopenia was 4% and 5%, respectively. In Study JMCH, 18% of patients in the ALIMTA arm required red blood cell transfusions compared to 7% of patients in the cisplatin arm. In Studies JMEN, PARAMOUNT, and JMEI, where all patients received vitamin supplementation, incidence of Grade 3-4 neutropenia ranged from 3% to 5%, and incidence of Grade 3-4 anemia ranged from 3% to 5%.

##### **Renal Failure**

- ALIMTA can cause severe, and sometimes fatal, renal toxicity. Determine creatinine clearance before each dose and periodically monitor renal function during treatment with ALIMTA.
- The incidences of renal failure in clinical studies in which patients received ALIMTA with cisplatin were 2.1% in Study JMDB and 2.2% in Study JMCH. The incidence of renal failure in clinical studies in which patients received ALIMTA as a single agent ranged from 0.4% to 0.6% (Studies JMEN, PARAMOUNT, and JMEI).
- Withhold ALIMTA in patients with a creatinine clearance of less than 45 mL/min.

#### **Bullous and Exfoliative Skin Toxicity**

- Serious and sometimes fatal, bullous, blistering, and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson Syndrome/toxic epidermal necrolysis, can occur with ALIMTA. Permanently discontinue ALIMTA for severe and life-threatening bullous, blistering, or exfoliating skin toxicity.

#### **Interstitial Pneumonitis**

- Serious interstitial pneumonitis, including fatal cases, can occur with ALIMTA treatment. Withhold ALIMTA for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, or fever pending diagnostic evaluation. If pneumonitis is confirmed, permanently discontinue ALIMTA.

#### **Radiation Recall**

- Radiation recall can occur with ALIMTA in patients who have received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment. Permanently discontinue ALIMTA for signs of radiation recall.

#### **Increased Risk of Toxicity With Ibuprofen in Patients With Renal Impairment**

- Exposure to ALIMTA is increased in patients with mild to moderate renal impairment who take concomitant ibuprofen, increasing the risks of adverse reactions of ALIMTA. In patients with creatinine clearances between 45 mL/min and 79 mL/min, avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA. If concomitant ibuprofen use cannot be avoided, monitor patients more frequently for ALIMTA adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity.

#### **Embryo-Fetal Toxicity**

- Based on findings from animal studies and its mechanism of action, ALIMTA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intravenous administration of pemetrexed to pregnant mice during the period of organogenesis was teratogenic, resulting in developmental delays and increased malformations at doses lower than the recommended human dose of 500 mg/m<sup>2</sup>. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with ALIMTA and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALIMTA and for 3 months after the final dose.

## DRUG INTERACTIONS

- Ibuprofen increases exposure (AUC) of pemetrexed. In patients with creatinine clearance between 45 mL/min and 79 mL/min:
  - Avoid administration of ibuprofen for 2 days before, the day of, and 2 days following administration of ALIMTA.
  - Monitor patients more frequently for myelosuppression, renal, and gastrointestinal toxicity, if concomitant administration of ibuprofen cannot be avoided.

## ADVERSE REACTIONS

- Severe adverse reactions (Grade 3-4) occurring in ≥20% of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) receiving ALIMTA in combination with pembrolizumab and platinum chemotherapy (carboplatin or cisplatin) versus ALIMTA with platinum chemotherapy + placebo for initial treatment (KEYNOTE-189), respectively, were fatigue (12% vs 6%); diarrhea (5% vs 3%); dyspnea (3.7% vs 5%); vomiting (3.7% vs 3%); nausea (3.5% vs 3.5%); rash (2% vs 2.5%); decreased appetite (1.5% vs 0.5%); constipation (1% vs 0.5%); and pyrexia (0.2% vs 0%). Common adverse reactions (all grades) occurring in ≥20% of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) receiving ALIMTA in combination with pembrolizumab and platinum chemotherapy (carboplatin or cisplatin) versus ALIMTA with platinum chemotherapy + placebo for initial treatment (KEYNOTE-189), respectively, were nausea (56% vs 52%); fatigue (56% vs 58%); constipation (35% vs 32%); diarrhea (31% vs 21%); decreased appetite (28% vs 30%); rash (25% vs 17%); vomiting (24% vs 23%); cough (21% vs 28%); dyspnea (21% vs 26%); and pyrexia (20% vs 15%).

## USE IN SPECIFIC PATIENT POPULATIONS

- **Lactation:** There is no information regarding the presence of pemetrexed or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from ALIMTA, advise women not to breastfeed during treatment with ALIMTA and for one week after the last dose.
- **Males of Reproductive Potential:** ALIMTA may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible.

- **Pediatric Use:** The safety and effectiveness of ALIMTA in pediatric patients have not been established. Adverse reactions observed in pediatric patients studied were similar to those observed in adults.
- **Patients with Renal Impairment:** ALIMTA is primarily excreted by the kidneys. Decreased renal function results in reduced clearance and greater exposure (AUC) to ALIMTA compared with patients with normal renal function. No dose is recommended for patients with creatinine clearance less than 45 mL/min.
- **Geriatric:** The incidences of Grade 3-4 anemia, fatigue, thrombocytopenia, hypertension, and neutropenia were higher in patients 65 years of age and older as compared to younger patients: in at least one of five randomized clinical trials.

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**For safety and dosing guidelines for ALIMTA, see complete Warnings and Precautions, Adverse Reactions, and Dosage and Administration sections in the full [Prescribing Information](#) and [Patient Prescribing Information](#).**

#### **About Lilly Oncology**

For more than 50 years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly's commitment to people with cancer, please visit [www.LillyOncology.com](http://www.LillyOncology.com).

#### **About Eli Lilly and Company**

Lilly is a global health care 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 [lilly.com](http://lilly.com) and [lilly.com/newsroom](http://lilly.com/newsroom). P-LLY

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#### **Lilly Forward-Looking Statement**

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Lilly's oncology portfolio and pipeline, including Verzenio, seliperatinib (LOXO-292), CYRAMZA and ALIMTA, and reflects Lilly's current belief. 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 future study results will be consistent with the results to date or that Verzenio, seliperatinib (LOXO-292), CYRAMZA or ALIMTA will receive (or receive additional) regulatory approvals or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

<sup>1</sup> PINN, pending USAN approval

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