Lilly Oncology to Showcase New Data from Robust Cancer Research Pipeline at ESMO Virtual Congress 2020

September 10, 2020

Positive Phase 3 monarchE results to be presented in the Presidential Symposium highlight Verzenio® (abemaciclib) as the only CDK4 & 6 inhibitor to demonstrate a statistically significant reduction in the risk of cancer recurrence for people with high risk HR+, HER2- early breast cancer

Data from Phase 1/2 LIBRETTO-001 trial reinforce the benefits of Retevmo™ (selpercatinib) in the treatment of certain advanced RET-driven lung and thyroid cancers

Outcomes by EGFR mutation type based on data from the Phase 3 RELAY trial of CYRAMZA® (ramucirumab) in untreated EGFR-mutated metastatic NSCLC also featured

INDIANAPOLIS, Sept. 10, 2020 /PRNewswire/ -- Data from 20 studies across Eli Lilly and Company's (NYSE: LLY) oncology product portfolio will be presented at the European Society for Medical Oncology (ESMO) Virtual Congress, September 19-21, 2020. The data include positive results from the Phase 3 monarchE study of Verzenio® (abemaciclib) in combination with standard adjuvant endocrine therapy (ET) for the treatment of high risk HR+, HER2- early breast cancer. Together, the studies presented at ESMO demonstrate Lilly's commitment to researching and developing new treatments for people around the world who are living with cancer.

"We're thrilled to share the statistically significant and clinically meaningful results from monarchE, a Phase 3 study which demonstrated the impact of Verzenio, in combination with adjuvant endocrine therapy, to reduce the risk of cancer returning and potentially change the treatment landscape in high risk early breast cancer," said Maura Dickler, M.D., vice president, late phase development, Lilly Oncology. "We're eager to use this virtual time during ESMO to learn from and collaborate with doctors, researchers and advocates and to share data that can improve treatment outcomes for patients living with cancer."

Latest Results for Verzenio in Hard-to-Treat Breast Cancer

Lilly continues to investigate Verzenio across the breast cancer continuum, which has now shown positive results in people with high risk HR+, HER2- early breast cancer. At ESMO, Lilly will share detailed results from the Phase 3 monarchE study, which demonstrated Verzenio plus standard adjuvant ET significantly decreased the risk of breast cancer recurrence compared to standard adjuvant ET alone in people with high risk HR+, HER2- early breast cancer. These results make Verzenio the only CDK4 & 6 inhibitor to demonstrate statistically significant improvement in invasive disease-free survival in this setting.

Lilly also will present findings on genomic testing, biomarkers and treatment patterns in early breast cancer as well as the use of Ki-67 testing and scoring in HR+, HER2- early breast cancer – a biomarker of particular interest in the study of high risk early breast cancer. Additional Verzenio data to be presented include a final overall survival analysis of Verzenio monotherapy in patients with HR+, HER2- advanced breast cancer in the nextMONARCH trial.

Retevmo™ Data Highlights

In May 2020, Lilly's first-in-class oral precision medicine Retevmo™ (selpercatinib) received Accelerated Approval from the U.S. Food and Drug Administration (FDA) for the treatment of metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC), in adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, and in adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). The approval of Retevmo – a selective *RET* kinase inhibitor – marked the most rapid timeline in the development of an oncology medicine with multiple indications, and was based on results from the Phase 1/2 LIBRETTO-001 trial, the largest clinical trial in patients with *RET*-altered cancers. During ESMO, Lilly will present patient-reported outcomes and quality of life findings from both the *RET* fusion-positive NSCLC and *RET*-mutant MTC patient cohorts.

Lilly will also present new safety data on patients with previously treated metastatic *RET* fusion-positive NSCLC, including safety and efficacy outcomes assessed by category of last systemic therapy received prior to LIBRETTO-001 enrollment. An additional safety analysis, focusing on hypersensitivity reactions in *RET* fusion-positive NSCLC patients previously treated with immune checkpoint inhibitors, will also be presented.

Details on the study design of two confirmatory Phase 3 trials, LIBRETTO-431 and LIBRETTO-531, will additionally be shared. Both Phase 3 trials are currently enrolling patients.

CYRAMZA® Lung Cancer Data Highlights

Earlier this year, the FDA approved CYRAMZA® (ramucirumab) in combination with erlotinib for the first-line treatment of people with metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations, based on results from the Phase 3 RELAY study. With this approval, CYRAMZA has now received six FDA approvals to treat certain types of lung, liver, stomach and colorectal cancers. CYRAMZA was also approved in the European Union earlier this year based on the RELAY results.

During ESMO, Lilly will feature data from the RELAY trial looking at outcomes by EGFR mutation type in previously untreated EGFR-mutated metastatic NSCLC patients. Additionally, a systematic literature review will spotlight outcomes of treated patients with EGFR-mutated NSCLC harboring exon 19 deletions or exon 21 mutations.

A list of the data presentations along with the viewing details are highlighted below.

Verzenio:

Abstract LBA5_PR: Abemaciclib in high risk early breast cancer (Stephen R. Johnston)
Accepted for Presidential Symposium II
September 20 at 19:51-20:03 CEST

Abstract 273O: nextMONARCH: Final overall survival analysis of abemaciclib monotherapy or in combination with tamoxifen in patients with HR+, HER2- metastatic breast cancer (Erika P. Hamilton)
Accepted as Oral Presentation
September 19 at 17:28-17:40 CEST; Session: Breast Cancer, Metastatic 1

Abstract 174P: Genomic testing, biomarkers and treatment patterns in early breast cancer (Michael Method)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 181P: The use of Ki67 testing and scoring in HR+, HER2- early breast cancer (Jacqueline Brown)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 240P: A multinational real-world study on HR+, HER2- early stage breast cancer patients' disease awareness, satisfaction, and involvement in treatment decisions (Alex Rider)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 239P: Impact of clinical characteristics, patients' perception of treatment goals and endocrine therapy history on HRQOL in HR+, HER2- early stage breast cancer patients (Rhys Williams)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Retevmo:

Abstract 1291P: Hypersensitivity reactions (HR) to selpercatinib in RET fusion+ non-small cell lung cancer (NSCLC) patients (pts) following immune checkpoint inhibition (CPI) (Caroline E. McCoach)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1290P: Efficacy and safety with selpercatinib by last prior systemic therapy received in patients (Pts) with RET fusion + non-small cell lung cancer (NSCLC) (Oliver Gautschi)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1292P: Exploratory patient-reported outcomes (PROs) among patients with RET-fusion non-small cell lung cancer (NSCLC) in LIBRETTO-001: A phase I/II trial of selpercatinib (Anna R. Minchom)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1922P: Exploratory patient-reported outcomes among patients with RET-mutant medullary thyroid cancer in LIBRETTO-001: A phase I/II trial of selpercatinib (LOXO-292) (Lori J. Wirth)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1413TiP: LIBRETTO-431: Selpercatinib in treatment (Tx)-naïve patients with RET fusion-positive (RET+) non-small cell lung cancer (NSCLC) (Herbert H. Loong)
Accepted as ePoster (trial in progress; no data will be presented)
Available on-demand on September 17 at 09:00 CEST

Abstract 1927TiP: LIBRETTO-531: Selpercatinib in patients with treatment (Tx)-naïve RET-mutant medullary thyroid cancer (MTC) (Jorge Hernando)
Accepted as ePoster (trial in progress; no data will be presented)
Available on-demand on September 17 at 09:00 CEST

CYRAMZA:

Abstract 1294P: RELAY, erlotinib plus ramucirumab or placebo in untreated EGFR-mutated metastatic NSCLC: Outcomes by EGFR mutation type (Kazuhiko Nakagawa)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1357P: Outcomes of treated patients with EGFR-mutated advanced or metastatic non-small cell lung cancer harboring exon 19 deletions or L858R substitution (Exon 21) mutations: A systematic literature review (Katherine B. Winfree)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1298P: RELAY, ramucirumab plus erlotinib (RAM+ERL) versus placebo plus erlotinib (P+ERL) in untreated EGFR mutated metastatic non-small cell lung cancer (NSCLC): Exposure-response relationship (Kazuhiko Nakagawa)

Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1015TiP: Ramucirumab in patients with advanced hepatocellular carcinoma and elevated alpha fetoprotein following a non-sorafenib based systemic therapy: An expansion cohort of the phase III REACH-2 study (Richard S. Finn)
Accepted as ePoster (trial in progress; no data will be presented)
Available on-demand on September 17 at 09:00 CEST

TYVYT®:

Abstract 991P: Sintilimab plus IBI305 as first-line treatment for advanced hepatocellular carcinoma (Fan Jia)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

Abstract 1498TiP: A multi-center, randomized, open-label, phase III study of sintilimab + ramucirumab as 1st-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-106) (Ruihua Xu)
Accepted as ePoster (trial in progress; no data will be presented)
Available on-demand on September 17 at 09:00 CEST

ALIMTA®:

Abstract 1313P: Phase III LEAP-006 safety run-in (Part 1): 1L pembrolizumab (Pembro) + chemotherapy (Chemo) with lenvatinib (Len) for metastatic NSCLC (Makoto Nishio)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

ERBITUX®:

Abstract 455P: A meta-analysis of efficacy and safety of cetuximab with biweekly vs. weekly dosing (Aparna Parikh)
Accepted as ePoster
Available on-demand on September 17 at 09:00 CEST

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.

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

About Retevmo™ (selpercatinib)
Retevmo (selpercatinib, formerly known as LOXO-292) (pronounced reh-TEHV-moh) is a selective and potent RET kinase inhibitor. Retevmo may affect both tumor cells and healthy cells, which can result in side effects. Retevmo is an oral prescription medicine, taken twice daily.

Retevmo is indicated for the treatment of adult patients with metastatic rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (NSCLC), and the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, or advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). Retevmo was approved under the FDA's Accelerated Approval regulations based on the LIBRETTO-001 Phase 1/2 trial's endpoints of objective response rate (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

About CYRAMZA® (ramucirumab)
In the U.S., CYRAMZA (ramucirumab) has six 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. To date, more than 150,000 patients have been treated with CYRAMZA.

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.

U.S. 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 erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.

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 ≥400 ng/mL and have been treated with sorafenib.

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. **Limitation of Use:** ALIMTA is not indicated for the treatment of patients with squamous cell non-small cell lung cancer. For all FDA-approved indications for ALIMTA, please see full **Prescribing Information**.

Indications and Usage for ERBITUX (cetuximab) injection

Head and Neck Cancer
ERBITUX (cetuximab) is approved:

- ERBITUX, in combination with radiation therapy (RT), is indicated for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN)
- ERBITUX is indicated in combination with platinum-based therapy and fluorouracil (CT) for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN
- ERBITUX, as a single agent, is indicated for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed

Metastatic Colorectal Cancer
ERBITUX is indicated for the treatment of KRAS wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test for this use:

- In combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment
- In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
- As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan

Limitations of Use: ERBITUX is not indicated for treatment of RAS-mutant colorectal cancer or when the results of the RAS mutation tests are unknown

About TYVYT (Sintilimab Injection)
TYVYT (sintilimab injection) is an innovative drug with global quality standards jointly developed by Innovent and Lilly in China. TYVYT has been granted marketing approval by the NMPA for the treatment of relapsed or refractory classic Hodgkin's lymphoma after at least two lines of systemic chemotherapy and was included in the 2019 Guidelines of Chinese Society of Clinical Oncology for Lymphoid Malignancies.

In April 2020, the NMPA accepted the supplemental new drug application for TYVYT in combination with ALIMTA (pemetrexed for injection) and platinum as first-line therapy in advanced or recurrent non-squamous non-small cell lung cancer (NSCLC). In May 2020, TYVYT combined with gemcitabine and platinum chemotherapy met the predefined primary endpoint in the Phase 3 ORIENT-12 study as first-line therapy in patients with locally advanced or metastatic squamous NSCLC. TYVYT monotherapy met the primary endpoint in the ORIENT-2 study as second-line therapy in patients with advanced or metastatic esophageal squamous cell carcinoma as well. In August 2020, the NMPA accepted the sNDA for TYVYT in combination with gemcitabine and platinum chemotherapy as first-line therapy in patients with locally advanced or metastatic squamous NSCLC.

TYVYT is a type of immunoglobulin G4 monoclonal antibody, which binds to PD-1 molecules on the surface of T-cells, blocks the PD-1/ PD-Ligand 1 (PD-L1) pathway and reactivates T-cells to kill cancer cells. Innovent is currently conducting more than 20 clinical studies with TYVYT to evaluate its safety and efficacy in a wide variety of cancer indications, including more than 10 registrational or pivotal clinical trials.

TYVYT (sintilimab injection) is not an approved product in the United States. ALIMTA (pemetrexed for injection) is not approved for use in combination with TYVYT in the United States.

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**, **≥10%)** observed in **MONARCH 3 for Verzenio plus anastrozole or letrozole** and **≥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, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant and ≥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**, **≥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 ≥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 ≥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 ≥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 ≥10% for Verzenio plus anastrozole or letrozole and ≥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 ≥10% for Verzenio plus fulvestrant and ≥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 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 ≥30-89 mL/min).

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Please see full Prescribing Information for Verzenio.

IMPORTANT SAFETY INFORMATION FOR RETEVMO™ (selpercatinib)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with

clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure.

Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥ 3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in > 1 patient included sepsis (n = 3), cardiac arrest (n = 3) and respiratory failure (n = 3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of **acid-reducing agents** decrease selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of **strong and moderate CYP3A inhibitors** increase selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of **strong and moderate CYP3A inducers** decrease selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increase their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older.

No dosage modification is recommended for patients with **mild to moderate renal impairment** (creatinine clearance [CLcr] ≥30 mL/Min, estimated by

Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

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Please see full U.S. Prescribing Information.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)
Warnings and Precautions
Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. 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 with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving chronic therapy with NSAIDs or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major blood vessel invasion or intratumor cavitation were excluded from REVEL and RELAY; 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. In 2137 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

- CYRAMZA 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 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. 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, excluding RELAY, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. In 221 patients with NSCLC receiving CYRAMZA in combination with erlotinib in the RELAY study, the incidence of new or worsening hypertension was higher (45%), as was the incidence of Grade 3-5 hypertension (24%). Of the patients experiencing new or worsening hypertension in RELAY (N=100 CYRAMZA and erlotinib; N=27 placebo and erlotinib), 13% of those treated with CYRAMZA and erlotinib required initiation of 3 or more antihypertensive medications compared to 4% of patients treated with placebo and erlotinib.
- 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 (IRR)

- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <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%).

Posterior Reversible Encephalopathy Syndrome (PRES)

- PRES (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. 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

- In 2137 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

- CYRAMZA can cause fetal harm when administered to pregnant women. 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.

Adverse Reactions
REGARD:

- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated gastric cancer patients at a rate of ≥5% and ≥2% higher than placebo were hypertension (16% vs 8%), diarrhea (14% vs 9%), headache (9% vs 3%), and hyponatremia (6% vs 2%).
- 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 ≥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 ≥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%.

RAINBOW:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia (57% vs 44%), neutropenia (54% vs 31%), diarrhea (32% vs 23%), epistaxis (31% vs 7%), hypertension (25% vs 6%), peripheral edema (25% vs 14%), stomatitis (20% vs 7%), proteinuria (17% vs 6%), thrombocytopenia (13% vs 6%), hypoalbuminemia (11% vs 5%), and gastrointestinal hemorrhage events (10% vs 6%).
- The most common serious adverse reactions with 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 ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥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.

REVEL:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with docetaxel at a rate of ≥5% and ≥2% higher than placebo with docetaxel were neutropenia (55% vs 46%), fatigue/asthenia (55% vs 50%), stomatitis/mucosal inflammation (37% vs 19%), epistaxis (19% vs 7%), febrile neutropenia (16% vs 10%), peripheral edema (16% vs 9%), thrombocytopenia (13% vs 5%), lacrimation increased (13% vs 5%), and hypertension (11% vs 5%).
- The most common serious adverse reactions with 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 ≥3 pulmonary hemorrhage was 1% for CYRAMZA with docetaxel compared to 6% overall incidence and 1% for Grade ≥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 ≥3 pulmonary hemorrhage was 2% for CYRAMZA with docetaxel compared to 12% overall incidence and 2% for Grade ≥3 pulmonary hemorrhage for placebo with docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA with docetaxel-treated patients in REVEL were hyponatremia (4.8%) and proteinuria (3.3%).

RELAY:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with erlotinib at a rate of ≥ 5% and ≥2% higher than placebo with erlotinib were infections (81% vs 76%), diarrhea (70% vs 71%), hypertension (45% vs 12%), stomatitis (42% vs 36%), alopecia (34% vs 20%), epistaxis (34% vs 12%), proteinuria (34% vs 8%), peripheral edema (23% vs 4%), headache (15% vs 7%), gastrointestinal hemorrhage (10% vs 3%), gingival bleeding (9% vs 1%), and pulmonary hemorrhage (7% vs 2%).
- The most common serious adverse reactions with CYRAMZA with erlotinib were pneumonia (3.2%), cellulitis (1.8%), and pneumothorax (1.8%). Red blood cell transfusions were given to 3.2% of CYRAMZA-treated patients versus 0 patients who received placebo.
- Treatment discontinuation of all study drugs due to adverse reactions occurred in 13% of CYRAMZA with erlotinib-treated patients, with increased alanine aminotransferase (1.4%) and paronychia (1.4%) being the most common. The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (8.6%) and hyperbilirubinemia (6%).
- Of the 221 patients who received CYRAMZA with erlotinib, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 6%).

RAISE:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with FOLFIRI at a rate of ≥5% and ≥2% higher than placebo with FOLFIRI were diarrhea (60% vs 51%), neutropenia (59% vs 46%), decreased

appetite (37% vs 27%), epistaxis (33% vs 15%), stomatitis (31% vs 21%), thrombocytopenia (28% vs 14%), hypertension (26% vs 9%), peripheral edema (20% vs 9%), proteinuria (17% vs 5%), palmar-plantar erythrodysesthesia syndrome (13% vs 5%), gastrointestinal hemorrhage events (12% vs 7%), and hypoalbuminemia (6% vs 2%). 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 ≥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.

REACH-2:

- The most common adverse reactions (all Grades) observed in single agent CYRAMZA-treated HCC patients at a rate of ≥10% and ≥2% higher than placebo were fatigue (36% vs 20%), peripheral edema (25% vs 14%), hypertension (25% vs 13%), abdominal pain (25% vs 16%), decreased appetite (23% vs 20%), proteinuria (20% vs 4%), nausea (19% vs 12%), ascites (18% vs 7%), headache (14% vs 5%), epistaxis (14% vs 3%), insomnia (11% vs 6%), pyrexia (10% vs 3%), vomiting (10% vs 7%), and back pain (10% vs 7%).
- 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 ≥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 U.S. Prescribing Information for CYRAMZA.

IMPORTANT SAFETY INFORMATION FOR ALIMTA® (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 B12 are also required prior to ALIMTA treatment. Folic acid and vitamin B12 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/mm3 and platelet count is at least 100,000 cells/mm3. Permanently reduce ALIMTA in patients with an ANC of less than 500 cells/mm3 or platelet count of less than 50,000 cells/mm3 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/m2. 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.

IMPORTANT SAFETY INFORMATION FOR ERBITUX® (cetuximab)

WARNING: INFUSION REACTIONS AND CARDIOPULMONARY ARREST

Infusion Reactions

- **ERBITUX can cause serious and fatal infusion reactions. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients receiving ERBITUX in clinical trials.**
- **The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal).**
- **Approximately 90% of the severe infusion reactions occurred with the first infusion of ERBITUX despite premedication with antihistamines.**
  - **Serious infusion reactions, requiring immediate medical intervention, included symptoms of rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Immediately interrupt and permanently discontinue ERBITUX infusion for serious infusion reactions.**
  - **Caution must be exercised with every ERBITUX infusion as infusion reactions may occur during or several hours following completion of the infusion.**
  - **Premedicate with a histamine-1 (H1) receptor antagonist as recommended.**
  - **Monitor patients for at least 1 hour following each ERBITUX infusion in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. In patients requiring treatment for infusion reactions, monitor for more than 1 hour to confirm resolution of the reaction. Interrupt the infusion and upon recovery, resume the infusion at a slower rate or permanently discontinue ERBITUX based on severity.**

Cardiopulmonary Arrest

- **ERBITUX can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 patients with squamous cell carcinoma of the head and neck receiving radiation therapy and ERBITUX in BONNER. In 3 patients with prior history of coronary artery disease, death occurred 27, 32, and 43 days respectively after the last dose of ERBITUX. One patient with no prior history of coronary artery disease died one day after the last dose of ERBITUX. In EXTREME, fatal cardiac disorders and/or sudden death occurred in 3% of the 219 patients with squamous cell carcinoma of the head and neck treated with a cetuximab product in combination with platinum-based therapy and fluorouracil.**
  - **Carefully consider the use of ERBITUX with radiation therapy, or with platinum-based therapy with fluorouracil, in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias.**
  - **Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX therapy.**

Pulmonary Toxicity

- ERBITUX can cause interstitial lung disease (ILD). ILD, which was fatal in one case, occurred in <0.5% of 1570 patients receiving ERBITUX in clinical trials. Monitor patients for signs and symptoms of pulmonary toxicity. Interrupt or permanently discontinue ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD.

Dermatologic Toxicities

- ERBITUX can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (e.g., *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis

- Acneiform rash occurred in 82% of the 1373 patients who received ERBITUX across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first 2 weeks of therapy; the rash lasted more than 28 days after stopping ERBITUX in most patients.
- Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has been observed in patients who received ERBITUX. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis).
- Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae.
- Sun exposure may exacerbate these effects. Instruct patients to limit sun exposure during ERBITUX therapy.
- Withhold, reduce dose or permanently discontinue ERBITUX based on severity of acneiform rash or mucocutaneous disease.

Risks Associated with Use in Combination with Radiation and Cisplatin

- ERBITUX is not indicated for the treatment of SCCHN in combination with radiation and cisplatin.
- In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin, or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3 and 4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone.
- Adverse reactions with fatal outcome were reported in 4% of patients in the ERBITUX combination arm and 3% in the control arm.
- In the ERBITUX arm, 2% experienced myocardial ischemia compared to 0.9% in the control arm.
- The addition of ERBITUX to radiation and cisplatin did not improve progression-free survival (the primary endpoint).

Hypomagnesemia and Accompanying Electrolyte Abnormalities

- ERBITUX can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in study CA225-025 and two other clinical trials in patients with colorectal cancer (CRC) or head and neck cancer, including Grades 3 and 4 in 6% to 17%. In EXTREME, where a cetuximab product was administered in combination with platinum-based therapy, the addition cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No patient experienced grade 3 or 4 hypomagnesemia. The onset of hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating ERBITUX.
  - Monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of ERBITUX.
  - Replete electrolytes as necessary.

Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with *Ras*--Mutant mCRC

- ERBITUX is not indicated for the treatment of patients with CRC that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter referred to as "Ras" or when the Ras status is unknown.
- Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials, including CRYSTAL, were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. Confirm Ras mutation status in tumor specimens prior to initiating ERBITUX.

Embryo-Fetal Toxicity

- Based on animal data and its mechanism of action, ERBITUX can cause fetal harm when administered to a pregnant woman. There are no available data for ERBITUX exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryolethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ERBITUX and for 2 months after the last dose of ERBITUX. Verify pregnancy status in females of reproductive potential prior to initiating ERBITUX.

Adverse Reactions

- The most common adverse reactions in ERBITUX clinical trials (incidence ≥25%) include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.
- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with carcinomas of the head and neck

receiving ERBITUX in combination with radiation therapy (n=208) versus radiation alone (n=212) (BONNER) were acneiform rash (87% vs 10%), radiation dermatitis (86% vs 90%), weight loss (84% vs 72%), asthenia (56% vs 49%), nausea (49% vs 37%), increased alanine transaminase (43% vs 21%), increased aspartate transaminase (38% vs 24%), increased alkaline phosphatase (33% vs 24%), fever (29% vs 13%), emesis (29% vs 23%), pharyngitis (26% vs 19%) and dehydration (25% vs 19%). The most common grade 3 and 4 adverse reactions for ERBITUX in combination with radiation therapy (≥10%) versus radiation alone included: radiation dermatitis (23% vs 18%), acneiform rash (17% vs 1%), and weight loss (11% vs 7%). The overall incidence of late radiation toxicities (any grade) was higher for patients receiving ERBITUX in combination with radiation therapy, versus radiation therapy alone. The following sites were affected: salivary glands (65% vs 56%), larynx (52% vs 36%), subcutaneous tissue (49% vs 45%), mucous membrane (48% vs 39%), esophagus (44% vs 35%), skin (42% vs 33%). The incidence of Grade 3 or 4 late radiation toxicities was similar between radiation therapy alone and the ERBITUX with radiation treatment groups.

- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with carcinomas of the head and neck receiving a cetuximab product in combination with platinum-based therapy and fluorouracil (CT) (n=219) versus CT alone (n=215) (EXTREME) were acneiform rash (70% vs 2%), nausea (54% vs 47%), infection (44% vs 27%), rash (28% vs 2%), diarrhea (26% vs 16%) and anorexia (25% vs 14%). The most common grade 3 and 4 adverse reactions for a cetuximab product in combination with CT (≥10%) versus CT alone was infection (11% vs 8%). Because ERBITUX provides approximately 22% higher exposure relative to the cetuximab product used in EXTREME, the data provided above may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX.
- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with K-Ras wild-type, EGFR-expressing mCRC treated with a cetuximab product in combination with FOLFIRI (n=317) versus FOLFIRI alone (n=350) (CRYSTAL) were acne-like rash (86% vs 13%), diarrhea (66% vs 60%), neutropenia (49% vs 42%), rash (44% vs 4%), stomatitis (31% vs 19%), anorexia (30% vs 23%), dermatitis acneiform (26% vs <1%) and pyrexia (26% vs 14%). The most common grade 3 and 4 adverse reactions (≥10%) included: neutropenia (31% vs 24%), acne-like rash (18% vs <1%), and diarrhea (16% vs 10%). ERBITUX provides approximately 22% higher exposure compared to the cetuximab product used in CRYSTAL; however, the safety data from CRYSTAL is consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication.
- The most common adverse reactions (all grades; incidence ≥25%) seen in patients with K-Ras wild-type, EGFR-expressing mCRC treated with ERBITUX + best supportive care (BSC) (n=118) versus BSC alone (n=124) (CA225-025) were rash/desquamation (95% vs 21%), fatigue (91% vs 79%), nausea (64% vs 50%), pain-other (59% vs 37%), dry skin (57% vs 15%), constipation (53% vs 38%), dyspnea (49% vs 44%), pruritis (47% vs 11%), neuropathy-sensory (45% vs 38%), diarrhea (42% vs 23%), vomiting (40% vs 26%), headache (38% vs 11%), infection without neutropenia (38% vs 19%), other-dermatology (35% vs 7%), stomatitis (32% vs 10%), nail changes (31% vs 4%), cough (30% vs 19%), insomnia (27% vs 13%) and fever (25% vs 16%). The most common grade 3 and 4 adverse reactions (≥10%) included: fatigue (31% vs 29%), pain-other (18% vs 10%), rash/desquamation (16% vs 1%), dyspnea (16% vs 13%), other-gastrointestinal (12% vs 5%), and infection without neutropenia (11% vs 5%).
- The most common adverse reactions (all grades) seen in patients with EGFR-expressing recurrent mCRC (n=354) treated with ERBITUX plus irinotecan in clinical trials (CP02-9923 and BOND) were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3-4 adverse reactions included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%)

Use in Specific Populations

- **Lactation:** There is no information regarding the presence of ERBITUX in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG antibodies can be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ERBITUX, advise women not to breastfeed during treatment with ERBITUX and for at least 2 months after the last dose of ERBITUX.
- **Pediatric Use:** The safety and effectiveness of ERBITUX in pediatric patients have not been established. No new safety signals were identified in pediatric patients when ERBITUX in combination with irinotecan was administered in an open-label, single-arm dose-finding study in 27 patients with refractory solid tumors aged 1 to 12 years old and in 19 patients aged 13 to 18 years old.
- **Geriatric Use:** In mCRC clinical studies, no overall differences in safety or efficacy of ERBITUX were observed between patients >65 years of age and younger patients. In SCCHN clinical studies of ERBITUX there were insufficient number of patients >65 years of age to determine whether they respond differently from younger patients.

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Please see full Prescribing Information for ERBITUX, including Boxed Warnings regarding infusion reactions and cardiopulmonary arrest.

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TYVYT® (sintilimab injection, Innovent)

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, Retevmo, CYRAMZA, TYVYT, ALIMTA, and ERBITUX, and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date or that Verzenio, Retevmo, CYRAMZA, TYVYT, ALIMTA and ERBITUX will receive additional regulatory approvals or be (or continue to be) commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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