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Lilly Reports Topline Results from Phase 3 JUNIPER Trial Evaluating Verzenio™ (abemaciclib) in KRAS-Mutated, Advanced Non-Small Cell Lung Cancer

INDIANAPOLIS, Oct. 10, 2017 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that its Phase 3 JUNIPER study evaluating Verzenio™ (abemaciclib), a cyclin-dependent kinase (CDK)4 and CDK6 inhibitor, as monotherapy in KRAS-mutated, advanced non-small lung cancer (NSCLC) did not meet its primary endpoint of overall survival (OS). However, an analysis of the secondary study endpoints of both progression-free survival (PFS) and overall response rate (ORR) showed evidence of monotherapy activity in the abemaciclib arm. In addition, the control arm showed a higher overall survival rate than expected based on historical data in this setting. Lilly will submit the data for presentation at a medical meeting in 2018.

"While the outcome is unfortunate for patients with KRAS-mutated, advanced lung cancer, we remain encouraged by the antitumor activity observed with abemaciclib in this form of lung cancer where few clinical advances have been achieved," said Levi Garraway, M.D., Ph.D., senior vice president, global development and medical affairs, Lilly Oncology.

Dr. Garraway added, "As we analyze secondary endpoints and explore specific patient subgroups in order to better evaluate the prospects for abemaciclib in NSCLC, we will continue to work with the oncology community to inform potential future treatment avenues for patients with KRAS-mutated advanced lung cancer. Moreover, we have several studies ongoing of rational combinations that include abemaciclib in non-small cell lung cancer and other malignancies. We look forward to seeing the results of these studies."

JUNIPER, a global Phase 3, interventional, open-label study was designed to evaluate the efficacy and safety of abemaciclib versus erlotinib in patients with stage IV NSCLC with a detectable KRAS mutation, who have progressed after platinum-based chemotherapy and who may have received one additional systemic therapy. A total of 453 patients were randomized to receive 200 mg of abemaciclib orally twice a day on a continuous dosing schedule, every 12 hours or 150 mg of erlotinib administered at its approved dose and schedule until disease progression, death or unacceptable toxicity. The primary endpoint of the study was OS, with key secondary endpoints of safety, ORR, and PFS. The adverse events were generally consistent with previous studies of abemaciclib, with the most common adverse events being diarrhea, fatigue, decreased appetite, and nausea.

Notes to Editor

About Verzenio™ (abemaciclib)

Verzenio (abemaciclib) is an inhibitor of CDK4 and CDK6, 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.

Verzenio disrupts the cell cycle. Preclinically, Verzenio dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size. 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). 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.[1]

INDICATION

Verzenio is indicated:

- in combination with fulvestrant for women with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy
- as monotherapy for the treatment of adult patients with HR+, HER2- advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

IMPORTANT SAFETY INFORMATION

Diarrhea occurred in 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 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.

In MONARCH 2, diarrhea incidence was greatest during the first month of Verzenio dosing. 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. Twenty-two percent of patients with diarrhea required a dose omission and 22% required a dose reduction. In the MONARCH 1 study, the time to onset and resolution for diarrhea were similar to those in MONARCH 2.

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 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 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio in MONARCH 1. In MONARCH 2 and MONARCH 1, the median time to first episode of Grade > 3 neutropenia was 29 days, and the median duration of Grade ≥3 neutropenia 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 MONARCH 2 and MONARCH 1. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

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

In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade < 3 was 14 days. For patients with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

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 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, 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 2 for Verzenio plus fulvestrant and ≥2% higher than 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 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 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than 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 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 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 other strong CYP3A inhibitors. 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 other 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 strong inhibitor. Patients should avoid grapefruit products.

Avoid concomitant use of strong CYP3A inducers and consider alternative agents. Coadministration of Verzenio with rifampin, a strong CYP3A inducer, 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).

Please see full Prescribing Information for Verzenio.

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

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and www.lilly.com/newsroom/social-channels. **(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 the potential of abemaciclib as a treatment for patients with advanced non-small cell lung cancer 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 study findings to date or that abemaciclib will be commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see the company's latest Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements.

[1] Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

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