October 4, 2017

Lilly Receives U.S. FDA Approval of Verzenio™ (abemaciclib)

- *Verzenio provides a new treatment option for women with HR+, HER2- advanced breast cancer*
- *Verzenio is the only CDK4 & 6 inhibitor approved with a continuous dosing schedule*

INDIANAPOLIS, October 4, 2017 - Eli Lilly and Company (NYSE: LLY) announced that the U.S. Food and Drug Administration (FDA) has approved Verzenio™ (abemaciclib) in combination with fulvestrant for the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy, and 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. It is the first and only CDK4 & 6 inhibitor FDA approved in combination with fulvestrant and as monotherapy.[1] The approval of Verzenio was received on September 28, 2017.

Verzenio is a cyclin-dependent kinase (CDK)4 & 6 inhibitor that will be available as 50, 100, 150 and 200 mg tablets. The recommended dose of Verzenio, in combination with fulvestrant, is 150 mg orally twice daily. As a monotherapy, the recommended dose of Verzenio is 200 mg orally twice daily. Both doses are recommended to be continued until disease progression or unacceptable toxicity occurs.[1]

“In recent years, CDK4 & 6 inhibitors have evolved treatment expectations for those with metastatic breast cancer. Nevertheless, there is still a need for new agents to treat estrogen-receptor positive breast cancer, like Verzenio,” said George W. Sledge Jr., M.D., professor of medicine, Stanford University School of Medicine and MONARCH 2 principal investigator. “Today’s approval represents an important development for our patients, who are dealing with the uncertainty of breast cancer progression.”

The approval of Verzenio is based on the efficacy and safety demonstrated in the pivotal MONARCH 2 and MONARCH 1 clinical trials. MONARCH 2 was a Phase 3, randomized, double-blind, placebo-controlled trial evaluating Verzenio in combination with fulvestrant that enrolled 669 patients with HR+, HER2- metastatic breast cancer who progressed on endocrine therapy. MONARCH 1 was a Phase 2 single-arm trial evaluating Verzenio monotherapy that enrolled 132 patients with HR+, HER2- metastatic breast cancer who had prior endocrine therapy and chemotherapy for metastatic disease. Verzenio was given a Priority Review as part of the FDA’s Expedited Programs for Serious Conditions.

In MONARCH 2, Verzenio plus fulvestrant demonstrated a greater than 16-month median progression-free survival (PFS) in patients who progressed on endocrine therapy (16.4 months vs 9.3 months with placebo plus fulvestrant, HR: 0.553; 95% CI: 0.449-0.681, *P* <.0001). In patients with measurable disease who received Verzenio plus fulvestrant (n=318), an objective response rate (ORR; defined as complete response plus partial response [CR + PR]; PR defined as ≥30% reduction in target lesions)[2] of 48.1 percent (n=153) was achieved, with 44.7 percent (n=142) of patients having achieved a PR and 3.5 percent (n=11) having achieved a CR (95% CI: 42.6-53.6).[3] In MONARCH 1, Verzenio achieved an investigator-assessed ORR of 19.7 percent (n=26), of which all responses were partial (95% CI: 13.3-27.5) and demonstrated an 8.6-month median duration of response (DoR) (95% CI: 5.8-10.2), per investigator assessment. Assessments by independent review yielded comparable results for ORR and DoR for MONARCH 1.[4]

The labeling for Verzenio contains warnings and precautions for diarrhea, neutropenia, hepatotoxicity, venous thromboembolism, and embryofetal toxicity. Instruct patients at the first sign of loose stools to initiate antidiarrheal therapy, increase oral fluids, and notify their healthcare provider. Perform complete blood count and liver function tests prior to the start of Verzenio treatment, every two weeks for the first two months, monthly for the next two months, and as clinically indicated. Based on results, Verzenio may require dose modification. Monitor patients for signs and symptoms of thrombosis and pulmonary embolism and treat as medically appropriate. Advise patients of potential risk to a fetus and to use effective contraception. See full Prescribing Information for further management instructions.

“The FDA approval of Verzenio illustrates Lilly Oncology’s dedication to discovering, developing and delivering innovative, foundational medicines that offer a meaningful difference to patients,” said Levi Garraway, M.D., Ph.D., senior vice president, global development and medical affairs, Lilly Oncology. “Our goal at Lilly is to arm physicians with the clinical evidence and therapeutic options necessary to care for patients throughout the breast cancer care continuum. With the

approval of Verzenio, we are proud to partner with oncologists to ensure that women living with advanced breast cancer have new treatment options."

"The approval of Verzenio marks an exciting day for the metastatic breast cancer community," said Marc Hurlbert, Ph.D., chairman, Metastatic Breast Cancer Alliance. "For women living with advanced disease, every new treatment approved offers the hope of possibility – that their oncologists have more options that may help slow the spread of this deadly cancer."

Verzenio will be available in the U.S. by mid-October 2017. Lilly will work with insurers, health systems and providers to ensure patients are able to access this treatment. Patients, physicians, pharmacists or other healthcare professionals with questions about Verzenio should contact The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or visit www.lilly.com.

About MONARCH 2

MONARCH 2 was a Phase 3, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2- metastatic breast cancer who progressed on endocrine therapy. Patients were randomized 2:1 to Verzenio plus fulvestrant or placebo plus fulvestrant. Verzenio was dosed on a continuous dosing schedule until disease progression or unacceptable toxicity. The primary endpoint was PFS. Key secondary endpoints were ORR, overall survival, and DoR. Patients enrolled in the study had experienced disease progression on or within 12 months of receiving endocrine treatment in the neoadjuvant or adjuvant setting or while receiving first-line endocrine therapy for metastatic disease. Patients could not have received chemotherapy or more than one line of endocrine therapy for metastatic breast cancer.[3]

Verzenio plus fulvestrant demonstrated a greater than 16-month median PFS in patients who progressed on endocrine therapy (16.4 months vs 9.3 months with placebo plus fulvestrant, HR: 0.553; 95% CI: 0.449-0.681, P<.0001). The percentage of PFS events at the time of analysis was 49.8 percent (n=222) and 70.4 percent (n=157) in the Verzenio plus fulvestrant and placebo plus fulvestrant arms, respectively. In patients with measurable disease who received Verzenio plus fulvestrant (n=318), 48.1 percent achieved an objective response (95% CI: 42.6-53.6). Among patients with measurable disease who received placebo plus fulvestrant (n=164), 21.3 percent achieved an objective response (95% CI: 15.1-27.6).[1]DoR was not yet reached at the time of analysis with Verzenio plus fulvestrant (95% CI: 18.1-NR) and was 25.6 months with placebo plus fulvestrant (95% CI: 11.9-25.6). [3]

The most common adverse reactions (all grades, ≥20%) observed in MONARCH 2 for Verzenio 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%), and headache (20% vs 15%).

About MONARCH 1

MONARCH 1, a Phase 2, single-arm trial, enrolled 132 patients with HR+, HER2- metastatic breast cancer who were given Verzenio (200 mg) dosed orally twice daily. Patients enrolled in the study had measurable disease, progressed during or after prior endocrine therapy, and received one or two prior chemotherapy regimens in the metastatic setting. The primary endpoint was ORR and the secondary endpoint was DoR. Verzenio demonstrated single-agent efficacy in this heavily pretreated patient population. In the study, per investigator assessment, Verzenio achieved an ORR of 19.7 percent (95% CI: 13.3-27.5). Verzenio demonstrated an 8.6-month median DoR (95% CI: 5.8-10.2). Assessments by independent review yielded comparable rates and estimates.[4]

The most common adverse reactions (all grades, ≥20%) 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%), and headache (20%). Please see Important Safety Information at the end of this press release and full Prescribing Information for additional information.

About Advanced Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women worldwide with nearly 1.7 million new cases diagnosed in 2012.[5] An estimated 252,710 new cases of invasive breast cancer are expected to be diagnosed in the U.S. in women in 2017.[6] Advanced breast cancer includes metastatic breast cancer, cancer that has spread from the breast tissue to other parts of the body, and locally or regionally advanced breast cancer, meaning the cancer has grown outside the organ where it started but has not yet spread to other parts of the body.[7] Of all early stage breast cancer cases diagnosed in the U.S., approximately 30 percent will become metastatic and an estimated six to 10 percent of all new breast cancer cases are initially diagnosed as being metastatic.[8] Survival is lower among women with a more advanced stage at diagnosis: 5-year relative survival is 99 percent for localized disease, 85 percent for regional disease, and 26 percent for metastatic disease.

Other factors, such as tumor size, also impact 5-year survival estimates.[9]

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 newsroom.lilly.com/social-channels. **(P-LLY)**

Fulvestrant (Faslodex®), MedImmune/AstraZeneca. MedImmune Limited/AstraZeneca provided fulvestrant for this trial.

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 Verzenio ™ (abemaciclib) as a treatment for patients with metastatic breast 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 also be no guarantee that Verzenio will receive additional regulatory approvals or that it 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.

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