Verzenio® Significantly Reduced the Risk of Cancer Recurrence by 25% for People with HR+, HER2- High Risk Early Breast Cancer

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Verzenio in combination with endocrine therapy is the only CDK4 & 6 inhibitor to demonstrate a statistically significant improvement in invasive disease-free survival (IDFS) in early breast cancer

The Phase 3 monarchE trial evaluating the effects of two years of Verzenio treatment added to endocrine therapy achieved the primary endpoint of IDFS, demonstrating definitive and clinically meaningful results among people whose breast cancer is at a high risk of recurrence

Data presented in the Presidential Symposium at the European Society for Medical Oncology (ESMO) 2020 Virtual Congress and simultaneously published in the Journal of Clinical Oncology (JCO)

INDIANAPOLIS, Sept. 20, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced Verzenio® (abemaciclib) in combination with standard adjuvant endocrine therapy (ET) significantly decreased the risk of breast cancer recurrence by 25 percent compared to standard adjuvant ET alone for people with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) high risk early breast cancer (HR: 0.747; 95% CI: 0.598, 0.932; p = 0.0096). This statistically significant benefit was consistent across all pre-specified subgroups and corresponds to a 3.5 percent difference between arms (92.2 percent in the Verzenio arm and 88.7 percent in the control arm) at two years. These results are from a preplanned interim analysis with 323 IDFS events observed in the intent-to-treat population across both arms, including 136 in the Verzenio arm and 187 in the control arm. The data were presented today in the Presidential Symposium at the European Society for Medical Oncology (ESMO) 2020 Virtual Congress and simultaneously published in the *Journal of Clinical Oncology*.

Safety data from monarchE were consistent with the known safety profile of Verzenio and no new safety signals were observed. At the time of analysis, approximately 70 percent of patients in each arm were still on the two-year treatment period. The median follow up was approximately 15.5 months in both arms. The median duration on Verzenio was 14 months.

"This is a major milestone for people living with high risk HR+, HER2- early breast cancer – potentially one of the most notable treatment advances in the last two decades for this population of breast cancer patients," said Stephen Johnston, M.D., Ph.D., Professor of Breast Cancer Medicine and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust (London, U.K.) and lead investigator for the monarchE trial. "Abemaciclib added to adjuvant endocrine therapy significantly improved invasive disease-free survival in women and men with HR+, HER2- early breast cancer at high risk of early recurrence, and if approved could represent a new standard of care for this population."

monarchE randomized 5,637 patients with HR+, HER2- high risk early breast cancer from more than 600 sites in 38 countries. High risk was defined by cancer that spread to the lymph nodes, a large tumor size, or high cellular proliferation (as determined by tumor grade or Ki-67 index). Patients were treated for two years (treatment period) or until meeting criteria for discontinuation. After the treatment period, all patients will continue ET for five to 10 years, as clinically indicated.

"We are excited that Verzenio has demonstrated a clinically meaningful reduction in the risk of recurrence for people with HR+, HER2- high risk early breast cancer, and Lilly would like to thank the patients and investigators around the world who made this trial possible," said Maura Dickler, M.D., vice president, late phase development, Lilly Oncology. "The results on invasive disease-free survival are significant and provide hope for people with high risk early breast cancer living with concerns of recurrence. Lilly will submit these results to regulatory bodies around the world as soon as possible and we look forward to being able to offer Verzenio as a new treatment option for these patients. We are proud of the way monarchE builds on the vast body of clinical evidence established for Verzenio."

The addition of Verzenio to endocrine therapy also resulted in an improvement in distant relapse-free survival, or the time to developing cancer that has spread to other parts of the body. The combination reduced the risk of developing metastatic disease by 28 percent (HR: 0.717; 95% CI: 0.559, 0.920), with the largest reductions occurring in rates of metastases to the liver and bone. This treatment benefit was consistent across all prespecified subgroups. Two-year distant relapse-free survival rates were 93.6 percent in the Verzenio arm and 90.3 percent in the control arm.

"The results of monarchE are welcome news for our community," said Jean Sachs, MSS, MLSP, CEO of Living Beyond Breast Cancer. "Up to 30 percent of people with hormone receptor-positive early breast cancer may have a recurrence, so this finding is an exciting development for those with high risk hormone receptor-positive, HER2- early breast cancer, especially because the trial included women of any menopausal status as well as men."

Overall survival results were immature and monarchE will continue through the completion date, estimated for June 2027. At the time of the interim analysis, the IDFS results are considered definitive. All patients on monarchE will be followed until primary analysis and beyond to assess overall survival and other endpoints. Lilly will submit the monarchE data to regulatory authorities before the end of 2020.

About the monarchE Study

monarchE is a Phase 3, multicenter, randomized, open-label trial that enrolled 5,637 patients with HR+, HER2- node-positive, high risk early breast cancer. Patients were randomized 1:1 to Verzenio (150 mg twice daily) plus standard adjuvant endocrine therapy or standard adjuvant endocrine therapy alone. Patients were treated for two years (treatment period) or until meeting criteria for discontinuation. After the treatment period, all patients will continue on endocrine therapy for five to 10 years, as clinically indicated. The primary objective is invasive disease-free survival (IDFS) defined

according to the Standard Definitions for Efficacy Endpoints (STEEP) criteria. In adjuvant breast cancer trials, this includes the length of time before any cancer comes back, a new cancer develops or death. Secondary objectives include distant relapse-free survival, overall survival, safety, pharmacokinetics and health outcomes.

High risk was specifically defined as women (any menopausal status) and men with resected HR+, HER2- invasive early breast cancer with either ≥4 pathologically positive axillary lymph nodes (ALNs) or 1 to 3 positive ALNs and at least one of the following high-risk features: primary invasive tumor size ≥5 cm, histological grade 3 tumor, or central Ki-67 index ≥20%. If applicable, patients must have also completed adjuvant chemotherapy and radiotherapy prior to enrolling and have recovered from all acute side effects.

About Early Breast Cancer

Breast cancer is the most common cancer among women worldwide.[1] An estimated 90 percent of all breast cancer is diagnosed at an early stage.[2] Approximately 70 percent of all breast cancers are HR+, HER2-, the most common subtype.[3] Even within this subtype, HR+, HER2- breast cancer is a complex disease, and many factors – such as if the cancer has spread to the lymph nodes and the biology of the tumor – can impact the risk of recurrence. Approximately 30 percent of people diagnosed with HR+ early breast cancer are at risk of their cancer returning, potentially to incurable metastatic disease.[4]

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.

INDICATION

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

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

IMPORTANT SAFETY INFORMATION FOR VERZENIO (abemaciclib)

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

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

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

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

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

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

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

fatalities reported.

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

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

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

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

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

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

Verzenio can cause **fetal harm** when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The **most common adverse reactions (all grades, ≥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.

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 health care leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. P-LLY

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

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