Lilly announces publication of analyses showing benefit of the addition of Verzenio® (abemaciclib) in multiple subgroups of patients with advanced breast cancer identified as having a more concerning prognosis

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- Subgroup analyses demonstrate consistent benefit in subgroups of patients with a more concerning prognosis such as those with liver metastases, PR-negative disease, high tumor grade, or shorter treatment-free interval

INDIANAPOLIS, Dec. 18, 2018 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced *npj Breast Cancer* published results from exploratory subgroup analyses of the MONARCH 2 and MONARCH 3 trials reinforcing the clinical benefit of Verzenio® (abemaciclib) plus endocrine therapy in the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer. The analyses demonstrate that while the benefit of the addition of Verzenio was seen across all patient subgroups, consistent with the individual study intent-to-treat (ITT) populations, the largest effects were observed in patients with certain disease characteristics identified as signaling a less favorable prognosis.

"Not all patients with HR+, HER2- metastatic breast cancer are the same. Each patient presents with unique patterns of clinical factors – with some patients having particularly concerning clinical characteristics that can signal a poor prognosis to oncologists. Therefore, treatment decisions must be tailored to each patient's individual presentation," said Joyce O'Shaughnessy, M.D., Celebrating Women Chair in Breast Cancer Research and chair, Breast Cancer Research Program, Baylor University Medical Center, Texas Oncology and U.S. Oncology, Dallas, TX. "Understanding the prognostic value of certain clinical factors and how patients with or without these factors may respond to the addition of Verzenio can help us as we seek to individualize treatment decisions."

These exploratory post-hoc analyses pooled data from over 1,000 patients and employed a two-step approach: first, the identification of independent prognostic variables derived from the entire population regardless of treatment assignment, and second, the description of the treatment effect of endocrine monotherapy compared to endocrine therapy plus Verzenio in each of the identified prognostic subgroups within the respective studies. Across both studies, certain prognostic factors included cancer that had spread to the liver (liver metastases), cancer that was not confined to the bone, cancer cells that were dividing more quickly (high tumor grade), and cancer cells that did not express progesterone receptors (PRs) and therefore were less likely to respond to hormonal therapy (PR-negative).

"These data further reinforce that we may be able to distinguish potential benefit of CDK4 & 6 inhibitor treatment in certain groups of patients," said Angelo Di Leo, M.D., Ph.D., medical oncologist, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy. "By pooling data across the MONARCH 2 and MONARCH 3 studies, we were able to maximize the power to detect prognostic factors, helping to lay the foundation for optimizing treatment for our patients."

The exploratory analyses concluded that while the benefit of the addition of Verzenio was seen across all patient subgroups, consistent with the individual study ITT populations, patients with poor prognostic factors received the largest benefit from the addition of Verzenio to endocrine therapy. In particular, patients with cancer that spread to the liver, PR-negative tumors, or cancer cells that divided more quickly consistently received a substantial benefit with Verzenio, with a greater than 30 percent difference in response rates. Additionally, in MONARCH 3, the exploratory Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of treatment-free interval (TFI), or how quickly the cancer returned after the completion of adjuvant endocrine therapy, showed those whose cancer returned quickly after the conclusion of adjuvant endocrine therapy derived larger benefit from the addition of Verzenio compared to endocrine therapy alone.

"The research published today illustrates our commitment to the ongoing investigation of Verzenio and our focus on understanding and meeting the needs of women with advanced breast cancer, including those with a more concerning prognosis," said Maura Dickler, M.D., vice president, late phase development, Lilly Oncology.

The subgroup analyses are hypothesis-generating and require additional evaluation in prospective clinical trials, but provide the groundwork for

considering and investigating more personalized therapy in HR+, HER2- metastatic breast cancer. Lilly is committed to continuing research aimed at helping oncologists optimize care for women with advanced disease.

About MONARCH 2
MONARCH 2 is 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 progression-free survival (PFS). Key secondary endpoints were objective response rate (ORR), overall survival (OS), and duration of response (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.

About MONARCH 3
MONARCH 3 is a Phase 3, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of Verzenio in combination with an aromatase inhibitor (anastrozole or letrozole), as initial endocrine-based therapy for postmenopausal women with HR+, HER2- advanced (locoregionally recurrent or metastatic) breast cancer who have had no prior systemic treatment for advanced disease. If neoadjuvant/adjuvant endocrine therapy was administered, a disease-free interval of more than 12 months since completion of endocrine therapy was required. A total of 493 patients were randomized 2:1 to receive 150 mg of Verzenio or placebo orally twice a day, without interruption, given in combination with either 1 mg of anastrozole or 2.5 mg of letrozole once daily until disease progression or unacceptable toxicity. The primary endpoint of the study was PFS, with key secondary endpoints of ORR, DoR, OS and safety.

About Advanced Breast Cancer
Breast cancer is the most common cancer in women worldwide, with more than 2 million new cases diagnosed in 2018.[1] An estimated 266,120 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S. in 2018.[2] Advanced breast cancer includes metastatic breast cancer, meaning 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.[3] 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.[4] 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.[5]

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
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.

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 3in ≥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 with Verzenio were increased serum creatinine (98%; <1%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 27%), anemia (68%; 0%), decreased lymphocyte count (42%; 14%), decreased platelet count (41%; 2%), increased ALT (31%; 3%), and increased AST (30%; 4%).

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

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

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis is **unknown**. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥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 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 www.lilly.com and http://newsroom.lilly.com/social-channels. **(P-LLY)**

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Fulvestrant (Faslodex®), MedImmune/AstraZeneca. MedImmune Limited/AstraZeneca provided fulvestrant for the MONARCH 2 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 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 abemaciclib 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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[1]World Cancer Research Fund International. Breast Cancer Statistics. http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics. Accessed December 5, 2018.
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