Lilly Announces Updated Verzenio® (abemaciclib) Phase 3 monarchE Trial Data Presented at ESMO Virtual Plenary and Simultaneously Published in the Annals of Oncology

October 14, 2021

Adjuvant Verzenio in combination with endocrine therapy (ET) continued to demonstrate a significant improvement in reducing the risk of recurrence in patients with HR+ HER2-, node-positive, high risk early breast cancer

With additional follow up, the treatment benefit of Verzenio plus ET was maintained over time and extended beyond the two-year treatment period; mature safety analysis was also consistent with previous results

Consistent Verzenio treatment benefit in reducing risk of recurrence observed in patients regardless of Ki-67 score

INDIANAPOLIS, Oct. 14, 2021 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced updated data from the positive Phase 3 monarchE trial evaluating the investigational use of Verzenio® (abemaciclib) in combination with standard adjuvant endocrine therapy (ET) for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), node-positive, high risk early breast cancer (EBC). These data were presented at today's ESMO Virtual Plenary and simultaneously published in the *Annals of Oncology*.

As previously published in the *Journal of Clinical Oncology*,[1] monarchE met its primary endpoint of a statistically significant improvement in invasive disease-free survival (IDFS) in the intent-to-treat (ITT) population for patients treated with adjuvant Verzenio plus ET compared to those treated with ET alone. Consistent with expert guidelines, IDFS was defined as the length of time before breast cancer comes back, any new cancer develops, or death.

The trial included women and men with HR+ HER2-, node-positive EBC who had a high risk of disease recurrence based on clinical and pathological features (N=5,637). Patients were assigned to one of two cohorts. Cohort 1 enrolled patients with ≥4 positive axillary lymph nodes (ALN), or 1-3 positive ALN and either Grade 3 disease or tumor size ≥5 cm. Cohort 2 enrolled patients with 1-3 positive ALN and centrally determined Ki-67 score of ≥20% (defined in the study as "Ki-67 high"). Ki-67 is a marker of cellular proliferation. Ki-67 score was also determined centrally in Cohort 1 patients with a suitable sample, but Ki-67 determination was not required for enrollment in this cohort. The ITT population included both Cohort 1 and Cohort 2.

Data in today's presentation and publication include updated results reflecting median follow-up of 27 months. In the updated analysis, the benefit of Verzenio on IDFS and distant relapse-free survival (DRFS) was maintained (Table 1 below). At three years, the absolute improvement rates in IDFS and DRFS were 5.4% and 4.2%, respectively. Exploratory piecewise analyses of the IDFS and DRFS hazard ratio (HR) estimates within each year were also conducted, which demonstrated increasing magnitude of IDFS effect size over time: from the first year (0-1yr HR = 0.80, 95% CI: 0.59, 1.03) to the second year (1-2yr HR = 0.68, 95% CI: 0.52, 0.87), and strengthened beyond the two-year study treatment period (2+yr HR = 0.60, 95% CI: 0.40, 0.86). Similarly, the DRFS HR estimates strengthened from the first year (0-1yr HR = 0.73, 95% CI: 0.52, 0.99) to the second year (1-2yr HR = 0.68, 95% CI: 0.51, 0.88), and persisted beyond the two-year study treatment period (2+yr HR = 0.69, 95% CI: 0.45, 1.03). The impact of Ki-67 score on prognosis and likelihood of benefit from Verzenio was also analyzed. As expected, a high Ki-67 score of ≥20% was prognostic of increased recurrence risk among patients with high-risk clinical and pathological features. However, Verzenio conferred consistent benefit in reducing risk of recurrence regardless of having a low (<20%) or high (≥20%) Ki-67 score among patients with high-risk clinical and pathological features (Table 2 below). With 90 percent of patients now having completed the two-year treatment period or discontinued early, safety data are considered mature and remain consistent with the known profile of Verzenio. All patients in monarchE will continue to be followed to assess overall survival and other endpoints. Overall survival data were not yet mature.

"The results from monarchE are truly impressive and we are encouraged by the consistency of the treatment benefit and increasing magnitude of effect observed over time in reducing the risk of recurrence and development of metastatic disease," said Joyce A. O'Shaughnessy, M.D., Celebrating Women Chair in Breast Cancer Research, Baylor University Medical Center, Texas Oncology, US Oncology, Dallas Texas, monarchE investigator and presenter at today's ESMO Virtual Plenary. "These data suggest that the addition of adjuvant Verzenio to endocrine therapy in the high risk early breast cancer setting has the potential to change the way we treat these patients and may address a significant unmet need for those with clinical and pathological risk features who are in need of new treatment options."

The following table shows the evolution of IDFS and DRFS data in the ITT population.

Table 1.

	Primary Outcome[1]		**Additional Follow-Up**	
Data cut-off date	July 8, 2020		April 1, 2021	
Patients off study treatment period	41.0%		89.6%	
Efficacy Results	**Verzenio + ET**	**ET alone**	**Verzenio + ET**	**ET alone**
Median follow-up, months	19.1		27.1	
Invasive disease-free survival (IDFS)				
Events, n	163	232	232	333
IDFS rates, % (95% CI)				
2-year	92.3 (90.9, 93.5)	89.3 (87.7, 90.7)	92.7 (91.6, 93.6)	90.0 (88.8, 91.1)
3-year	Not estimable	Not estimable	88.8 (87.0, 90.3)	83.4 (81.3, 85.3)
HR (95% CI) **p-value**	0.71 (0.58, 0.87) *Nominal p-value = 0.0009		0.70 (0.59, 0.82) *Nominal p-value <0.0001	

Distant relapse-free survival (DRFS)				
Events, n	131	193	191	278
DRFS rates, % (95% CI)				
2-year	93.8 (92.6, 94.9)	90.8 (89.3, 92.1)	94.1 (93.2, 95.0)	91.6 (90.5, 92.6)
3-year	Not estimable	Not estimable	90.3 (88.6, 91.8)	86.1 (84.2, 87.9)
HR (95% CI)	0.69 (0.55, 0.86)		0.69 (0.57, 0.83)	

[1] Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE) [published online ahead of print, September 20, 2020]. *J Clin Oncol*. doi:10.1200/JCO.20.02514.

*The primary efficacy endpoint was statistically significant at interim analysis 2

The following table shows IDFS in Cohort 1 according to centrally determined Ki-67 score [low (<20%), high (≥20%)].*

Table 2.

	Verzenio + ET	ET alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year IDFS Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year IDFS Rates	91.7%	87.2%	

*Data from Additional Follow-up analysis with a data cut-off date of April 1, 2021

"We are extremely pleased with the consistency of the landmark results from monarchE and are excited to see these important data shared with the breast cancer community," said David Hyman, M.D., chief medical officer, oncology at Lilly. "Verzenio treatment benefit observed at the primary outcome analysis was maintained with 27 months of median follow-up, including beyond the Verzenio treatment period, reinforcing our confidence in the observed treatment effect."

Adverse reactions from monarchE were consistent with the known safety profile for Verzenio.[1] A higher incidence of Grade ≥3 adverse events (AEs) and serious adverse events was observed with Verzenio plus ET compared to ET alone (50% vs. 16% and 15% vs. 9%, respectively). The most frequent AEs were diarrhea, neutropenia, and fatigue in the Verzenio plus ET arm, and arthralgia, hot flush, and fatigue in the ET alone arm.

About the monarchE Study

monarchE is a global, randomized, open-label, two cohort, multicenter Phase 3 study in adult women and men with HR+ HER2-, node-positive resected EBC with clinical and pathological features consistent with a high risk of disease recurrence. A total of 5,637 patients were randomized (1:1) to receive two years of Verzenio 150 mg twice daily plus physician's choice of standard endocrine therapy, or standard endocrine therapy alone. Patients in both treatment arms were instructed to continue to receive adjuvant endocrine therapy for up to 5-10 years as recommended by their clinician. Cohort 1 enrolled patients with ≥4 positive axillary lymph nodes (ALN), or 1-3 positive ALN and either Grade 3 disease or tumor size ≥5 cm. Cohort 2 enrolled patients with 1-3 positive ALN and centrally determined Ki-67 score of ≥20%. The primary endpoint was IDFS in the ITT population (Cohorts 1 & 2). Secondary endpoints were IDFS in patients with high Ki-67 score (in the ITT population and in the Cohort 1 population), DRFS, overall survival, and safety.[1,2]

About Early Breast Cancer and Risk of Recurrence

It is estimated that 90 percent of all breast cancers are detected at an early stage. Although the prognosis for HR+ HER2- EBC is generally positive, 20 percent of patients will experience recurrence potentially to incurable metastatic disease.[3] Risk of recurrence is greatest within the initial two to three years post-diagnosis, particularly in patients with node-positive, high risk EBC.[4] Factors associated with high risk of recurrence include: positive nodal status, large tumor size (≥5 cm), high tumor grade (Grade 3), and high rate of cellular proliferation [Ki-67 score (≥20%)].[2]

Node-positive means that cancer cells from the tumor in the breast have been found in the lymph nodes in the armpit area. Although the breast cancer is removed through surgery, the presence of cancer cells in the lymph nodes signifies that there is a higher chance of the cancer returning and spreading.

About Breast Cancer

Breast cancer has now surpassed lung cancer as the most commonly diagnosed cancer worldwide, according to GLOBOCAN. The estimated 2.3 million new cases indicate that 1 in every 8 cancers diagnosed in 2020 is breast cancer. With approximately 685,000 deaths in 2020, breast cancer is the fifth-leading cause of cancer death worldwide.[5] In the U.S., it is estimated that there will be 281,550 new cases of breast cancer in 2021.[6]

Approximately 70 percent of all breast cancers are of the HR+ HER2- subtype.[6]

About Verzenio® (abemaciclib)

Verzenio® abemaciclib is a targeted treatment known as a CDK4/6 inhibitor. Verzenio is a non-chemotherapy oral tablet.

Verzenio works inside the cell to block CDK4/6 activity and help stop the growth of cancer cells, so they may eventually die (based on preclinical studies).* Cyclin-dependent kinases (CDK)4/6 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.

INDICATIONS FOR VERZENIO

Verzenio® (abemaciclib) in combination with endocrine therapy (ET) is indicated for the adjuvant treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), node-positive, early breast cancer (EBC) at high risk of recurrence and a Ki-67 score of ≥20% as determined by an FDA-approved test.

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

- in combination with an aromatase inhibitor for postmenopausal women, and men, as initial endocrine-based therapy
- in combination with fulvestrant for adult patients 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)

Severe **diarrhea** associated with dehydration and infection occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients**,** diarrhea occurred in 81 to 90% of patients who received Verzenio. Grade 3 diarrhea occurred in 8 to 20% of patients receiving Verzenio. Most patients experienced diarrhea during the first month of Verzenio treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 to 26% of patients with diarrhea required a Verzenio dose interruption and 13 to 23% required a dose reduction.

Instruct patients to start antidiarrheal therapy, such as loperamide, at the first sign of loose stools, 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, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, neutropenia occurred in 37 to 46% of patients receiving Verzenio. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19 to 32% of patients receiving Verzenio. Across trials, the median time to first episode of Grade ≥3 neutropenia ranged from 29 to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 to 16 days. Febrile neutropenia has been reported in <1% of patients exposed to Verzenio across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

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.

Severe, life-threatening, or fatal **interstitial lung disease (ILD) or pneumonitis** can occur in patients treated with Verzenio and other CDK4/6 inhibitors. In Verzenio-treated patients in EBC (monarchE), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In Verzenio-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD or 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 or pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis.

Grade ≥3 increases in alanine aminotransferase (ALT) (2 to 6%) and **aspartate aminotransferase (AST)** (2 to 3%) were reported in patients receiving Verzenio. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade ≥3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade <3 was 13 to 14 days. The median time to onset of Grade ≥3 AST increases ranged from 71 to 185 days and the median time to resolution to Grade <3 ranged from 11 to 15 days.

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 any Grade 3 or 4 hepatic transaminase elevation.

Venous thromboembolic events (VTE) were reported in 2 to 5% of patients across three clinical trials in 3559 patients treated with Verzenio (monarchE, MONARCH 2, MONARCH 3). VTE included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. In clinical trials, deaths due to VTE have been reported in patients treated with Verzenio.

Verzenio has not been studied in patients with early breast cancer who had a history of VTE. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for EBC patients with any grade VTE and for MBC patients with a Grade 3 or 4 VTE.

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 3 weeks after the last dose. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential. 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.

The **most common adverse reactions (all grades**, **≥10%)** observed in **monarchE for Verzenio plus tamoxifen or an aromatase inhibitor vs tamoxifen or an aromatase inhibitor**, **with a difference between arms of ≥2%,** were diarrhea (84% vs 9%), infections (51% vs 39%), neutropenia (46% vs 6%), fatigue (41% vs 18%), leukopenia (38% vs 7%), nausea (30% vs 9%), anemia (24% vs 4%), headache (20% vs 15%), vomiting (18% vs 4.6%), stomatitis (14% vs 5%), lymphopenia (14% vs 3%), thrombocytopenia (13% vs 2%), decreased appetite (12% vs 2.4%), ALT increased (12% vs 6%), AST increased (12% vs 5%), dizziness (11% vs 7%), rash (11% vs 4.5%), and alopecia (11% vs 2.7 %).

The **most frequently reported ≥5% Grade 3 or 4 adverse reaction** that occurred in the Verzenio arm vs the tamoxifen or an aromatase inhibitor arm of monarchE were neutropenia (19.6% vs 1%), leukopenia (11% vs <1%), diarrhea (8% vs 0.2%), and lymphopenia (5% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4) for **monarchE in ≥10% for Verzenio plus tamoxifen or an aromatase inhibitor with a difference between arms of ≥2%** were increased serum creatinine (99% vs 91%; .5% vs <.1%), decreased white blood cells (89% vs 28%; 19.1% vs 1.1%), decreased neutrophil count (84% vs 23%; 18.7% vs 1.9%), anemia (68% vs 17%; 1% vs .1%), decreased lymphocyte count (59% vs 24%; 13.2 % vs 2.5%), decreased platelet count (37% vs 10%; .9% vs .2%), increased ALT (37% vs 24%; 2.6% vs 1.2%), increased AST (31% vs 18%; 1.6% vs .9%), and hypokalemia (11% vs 3.8%; 1.3% vs 0.2%).

The **most common adverse reactions (all grades**, **≥10%)** observed in **MONARCH 3 for Verzenio plus anastrozole or letrozole vs anastrozole or letrozole, with a difference between arms of ≥2%,** were diarrhea (81% vs 30%), fatigue (40% vs 32%), neutropenia (41% vs 2%), 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 3.1%), influenza-like illness (10% vs 8%), and thrombocytopenia (10% vs 2%).

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 1%), diarrhea (9% vs 1.2%), leukopenia (7% vs <1%)), increased ALT (6% vs 2%), and anemia (6% vs 1%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 3 in ≥10% for Verzenio plus anastrozole or letrozole with a difference between arms of ≥2%** were increased serum creatinine (98% vs 84%; 2.2% vs 0%), decreased white blood cells (82% vs 27%; 13% vs 0.6%), anemia (82% vs 28%; 1.6% vs 0%), decreased neutrophil count (80% vs 21%; 21.9% vs 2.6%), decreased lymphocyte count (53% vs 26%; 7.6% vs 1.9%), decreased platelet count (36% vs 12%; 1.9% vs 0.6%), increased ALT (48% vs 25%; 6.6% vs 1.9%), and increased AST (37% vs 23%; 3.8% vs 0.6%).

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant vs fulvestrant, with a difference between arms of ≥2%,** 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 2.7%), thrombocytopenia (16% vs 3%), alopecia (16% vs 1.8%), 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 4.5%), pyrexia (11% vs 6%), and weight decreased (10% vs 2.2%).

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 (25% vs 1%), diarrhea (13% vs 0.4%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (5.7% vs 3.5%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 2 in ≥10% for Verzenio plus fulvestrant with a difference between arms of ≥2%** were increased serum creatinine (98% vs 74%; 1.2% vs 0%), decreased white blood cells (90% vs 33%; 23.7% vs .9%), decreased neutrophil count (87% vs 30%; 32.5% vs 4.2%), anemia (84% vs 34%; 2.6% vs .5%), decreased lymphocyte count (63% vs 32%; 12.2% vs 1.8%), decreased platelet count (53% vs 15%; 2.1% vs 0%), increased ALT (41% vs 32%; 4.6% vs 1.4%), and increased AST (37% vs 25%; 3.9% vs 4.2%).

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%), constipation (17%), leukopenia (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** from **MONARCH 1** with Verzenio were diarrhea (20%), neutropenia (24%), fatigue (13%), and leukopenia (5%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 1 with Verzenio were increased serum creatinine (99%; .8%), decreased white blood cells (91%; 28%), decreased neutrophil count (88%; 26.6%), anemia (69%; 0%), decreased lymphocyte count (42%; 13.8%), decreased platelet count (41%; 2.3%), increased ALT (31%; 3.1%), and increased AST (30%; 3.8%).

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 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 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.

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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 early breast cancer and reflects Lilly's current beliefs and expectations. 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.

[1] Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE) [published online ahead of print, September 20, 2020]. *J Clin Oncol*. doi:10.1200/JCO.20.02514.

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