Lilly's Imlunestrant, an Oral SERD, Significantly Improved Progression-Free Survival as Monotherapy and in Combination with Verzenio® (abemaciclib) in Patients with ER+, HER2- Advanced Breast Cancer

December 11, 2024

As monotherapy, imlunestrant significantly reduced the risk of progression or death by 38% compared to standard endocrine therapy (ET) in patients with ESR1 *mutations*

As combination therapy, imlunestrant plus Verzenio significantly reduced the risk of progression or death by 43%, compared to imlunestrant alone, in all patients, regardless of ESR1 *mutation status*

These data were published simultaneously in the New England Journal of Medicine and will be presented today at the 2024 San Antonio Breast Cancer Symposium

INDIANAPOLIS, Dec. 11, 2024 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from the Phase 3 EMBER-3 study of imlunestrant, an investigational, oral selective estrogen receptor degrader (SERD), in patients with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC), whose disease progressed on a prior aromatase inhibitor (AI), with or without a CDK4/6 inhibitor. Imlunestrant demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) as monotherapy in patients with an *ESR1* mutation versus standard of care endocrine therapy (SOC ET), reducing the risk of disease progression or death by 38%. Imlunestrant in combination with Verzenio (abemaciclib; CDK4/6 inhibitor) reduced the risk of progression or death by 43% versus imlunestrant alone, in all patients.

These results were published in *The New England Journal of Medicine* and will be shared in a late-breaking oral presentation at the San Antonio Breast Cancer Symposium (SABCS) today, Wednesday, December 11 at 9:15 AM CT/10:15 AM ET. These data are being submitted to regulatory health authorities globally.

"The median progression free survival observed in EMBER-3 is among the most compelling we've seen in CDK4/6 pre-treated ER+, HER2- advanced breast cancer patients and indicates a potential shift in the therapy options we provide for these patients, which are currently very limited," said Komal Jhaveri, M.D., section head, endocrine therapy research and clinical director, early drug development at Memorial Sloan Kettering Cancer Center, and one of the study's principal investigators. "The benefit and safety profile of the imlunestrant and abemaciclib combination signal a potential new all-oral option for patients."

In the EMBER-3 study, patients were randomized 1:1:1 to receive imlunestrant alone, SOC ET, or the imlunestrant-abemaciclib combination. Randomization was stratified by prior CDK4/6 inhibitor use, the presence of visceral metastases and geographic region. Patients enrolled as first line (1L) treatment for ABC (32%), following disease recurrence on or within 12 months of completing adjuvant AI, with or without CDK4/6 inhibitor for early breast cancer (EBC), or as second line (2L) treatment for ABC (64%), following progression on AI, with or without CDK4/6 inhibitor as initial therapy for ABC. Primary endpoints were investigator-assessed PFS of imlunestrant versus SOC ET therapy in patients with *ESR1* mutations, imlunestrant versus SOC ET in all patients, and imlunestrant-abemaciclib versus imlunestrant in all patients.

Imlunestrant versus standard of care endocrine therapy

Imlunestrant significantly improved PFS versus SOC ET in patients with an *ESR1* mutation. In patients with an *ESR1* mutation, median PFS was 5.5 months with imlunestrant versus 3.8 months with SOC ET [HR=0.62 (95% CI 0.46-0.82); p-value<0.001]. The overall response rate (ORR) with imlunestrant was 14% compared to 8% with SOC ET in patients with an *ESR1* mutation. In all patients, the median PFS was 5.6 months with imlunestrant versus 5.5 months with SOC ET [HR=0.87 (95% CI 0.72-1.04); p-value 0.12] and did not reach statistical significance.

Consistent with preclinical data demonstrating central nervous system (CNS) penetrance and CNS-activity of imlunestrant, CNS progression rates from a post-hoc analysis were lower with imlunestrant in all patients (HR=0.47; 95% CI, 0.16-1.38), as well as patients with an *ESR1* mutation (HR=0.18; 95% CI, 0.04-0.90), however, these analyses are limited by low event numbers and lack of mandated serial asymptomatic CNS imaging in all patients.

Imlunestrant in combination with abemaciclib versus imlunestrant alone

Imlunestrant-abemaciclib significantly improved PFS compared to imlunestrant in all patients, regardless of *ESR1* mutation status, with median PFS of 9.4 months for imlunestrant-abemaciclib versus 5.5 months for imlunestrant alone [HR=0.57 (95% CI 0.44-0.73); p-value <0.001]. The PFS benefit of the combination was consistent across subgroups, regardless of *ESR1* mutation, or PI3K pathway mutation status, and including in patients who had previously received CDK4/6 inhibitor treatment. In all patients, the ORR with imlunestrant-abemaciclib was 27% compared to 12% with imlunestrant alone.

Safety in the imlunestrant-abemaciclib arm was consistent with the known safety profile of fulvestrant in combination with abemaciclib, with mostly low-grade adverse events including diarrhea (86%), nausea (49%), neutropenia (48%) and anemia (44%), and had a low discontinuation rate (6.3%).[1,2]

Overall survival (OS) results for EMBER-3 were immature at the time of analysis. The trial will continue to assess OS as a secondary endpoint.

"EMBER-3 is the first Phase 3 trial to show benefit of combining an oral SERD with a CDK4/6 inhibitor for a patient population where an all-oral

regimen would represent a meaningful advance," said David Hyman, M.D., Chief Medical Officer, Lilly. "We're highly encouraged by these data for both imlunestrant as monotherapy and in combination with Verzenio, as well as the safety and tolerability profile, which demonstrate the potential for imlunestrant to be a meaningful new oral endocrine therapy option for patients. We look forward to sharing these results with the oncology community and completing regulatory submissions to global health authorities."

An estimated 70 to 80% of hormone receptor positive breast cancers are ER+ and after progression on initial endocrine therapy, are predominantly treated with fulvestrant, which is administered by intramuscular injection in a doctor's office.[3,4] According to patient-reported outcomes data from EMBER-3, 72% of patients receiving fulvestrant in the standard ET group reported injection site pain, swelling, or redness. Imlunestrant is an orally administered, brain penetrant, pure ER antagonist that delivers continuous ER target inhibition.

Imlunestrant is also being investigated in the adjuvant setting in people with ER+, HER2- early breast cancer (EBC) with an increased risk of recurrence. This Phase 3 trial, EMBER-4, is expected to enroll 6,000 EBC patients worldwide.

About EMBER-3
EMBER-3 is a Phase 3, randomized, open-label study of imlunestrant, investigator's choice of endocrine therapy, and imlunestrant in combination with abemaciclib in patients with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer whose disease has recurred or progressed during or following an aromatase inhibitor (AI) therapy with or without a CDK 4/6 inhibitor. The trial enrolled 874 adult patients, 32% of which enrolled from the adjuvant setting into first-line treatment of ABC and 64% as second line treatment following progression on initial therapy for ABC. Enrolled trial participants were randomized between imlunestrant, investigator's choice of fulvestrant or exemestane, or imlunestrant plus abemaciclib. More information on the EMBER-3 study can be found on clinicaltrials.gov.

About Metastatic/Advanced Breast Cancer
Metastatic/advanced breast cancer (ABC) is a cancer that has spread from the breast tissue to other parts of the body. Locally advanced breast cancer means the cancer has grown outside the organ where it started but has not yet spread to other parts of the body.[1] Of all high risk early-stage breast cancer cases diagnosed in the U.S., approximately 30% will become metastatic[5] and an estimated 6-10% of all new breast cancer cases are initially diagnosed as being metastatic.[6] Survival is lower among women with a more advanced stage of disease at diagnosis: five-year relative survival is 99% for localized disease, 86% for regional/locally advanced disease, and 30% for metastatic/advanced disease.[7] Other factors, such as tumor size, also impact five-year survival estimates.[7]

About Breast Cancer
Breast cancer is the second most commonly diagnosed cancer worldwide (following lung cancer), according to GLOBOCAN. The estimated 2.3 million new cases indicate that close to 1 in every 4 cancers diagnosed in 2022 is breast cancer. With approximately 666,000 deaths in 2022, breast cancer is the fourth-leading cause of cancer death worldwide.[8] In the U.S., it is estimated that there will be more than 310,000 new cases of breast cancer diagnosed in 2024. Breast cancer is the second leading cause of cancer death in women in the U.S.[9]

About Imlunestrant
Imlunestrant is a brain-penetrant, oral selective estrogen receptor degrader (SERD), that delivers continuous ER inhibition, including in *ESR1*-mutant cancers. The estrogen receptor (ER) is the key therapeutic target for patients with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer. Novel degraders of ER may overcome endocrine therapy resistance while providing consistent oral pharmacology and convenience of administration. Imlunestrant is currently being studied as a treatment for advanced breast cancer and as an adjuvant treatment in early breast cancer, including: NCT04975308, NCT05514054, NCT04188548, NCT05307705.

About Verzenio® (abemaciclib)
Verzenio® (abemaciclib) is approved to treat people with certain HR+, HER2- breast cancers in the adjuvant and advanced or metastatic setting. Verzenio is the first CDK4/6 inhibitor approved to treat node-positive, high risk early breast cancer (EBC) patients.[10] For HR+, HER2- breast cancer, The National Comprehensive Cancer Network® (NCCN®) recommends consideration of two years of abemaciclib (Verzenio) added to endocrine therapy as a Category 1 treatment option in the adjuvant setting.[11] NCCN® also includes Verzenio plus endocrine therapy as a preferred treatment option for HR+, HER2- metastatic breast cancer.[11]

The collective results of Lilly's clinical development program continue to differentiate Verzenio as a CDK4/6 inhibitor. In high risk EBC, Verzenio has shown a persistent and deepening benefit beyond the two-year treatment period in the monarchE trial, an adjuvant study designed specifically to investigate a CDK4/6 inhibitor in a node-positive, high risk EBC population.[12] In metastatic breast cancer, Verzenio has demonstrated statistically significant OS in the Phase 3 MONARCH 2 study.[13] Verzenio has shown a consistent and generally manageable safety profile across clinical trials.

Verzenio is an oral tablet taken twice daily and available in strengths of 50 mg, 100 mg, 150 mg, and 200 mg. Discovered and developed by Lilly researchers, Verzenio was first approved in 2017 and is currently authorized for use in more than 90 counties around the world. For full details on indicated uses of Verzenio in HR+, HER2- breast cancer, please see full Prescribing Information, available at www.Verzenio.com.

INDICATIONS FOR VERZENIO®
VERZENIO® is a kinase inhibitor indicated:

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence.
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following

endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer 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 and Patient Information for Verzenio.

AL HCP ISI 12OCT2021

About Lilly

Lilly is a medicine company turning science into healing to make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help tens of millions of people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges: redefining diabetes care; treating obesity and curtailing its most devastating long-term effects; advancing the fight against Alzheimer's disease; providing solutions to some of the most debilitating immune system disorders; and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more,

visit Lilly.com and Lilly.com/news, or follow us on Facebook, Instagram, and LinkedIn. P-LLY

MSK Disclosure: Dr. Jhaveri has financial interests related to Eli Lilly and Company.

Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Verzenio as a treatment for people with certain types of breast cancer and imlunestrant as a potential treatment for people with certain types of 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 drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, that Verzenio will receive additional regulatory approvals, or that imlunestrant will prove to be a safe and effective treatment for certain types of breast cancer or receive regulatory approval. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's 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.

References

---

[1] André F, et al. *Ann Oncol*. 2021;32(2):208-217

[2] Turner NC, et al*. N Engl J Med*. 2023;388(22):2058-2070.

[3] Hanker AB, et al. Cancer Cell. 2020;37(4):496-513.

[4] Hua H, et al. Exp Hematol Oncol. 2018;7:24.

[5] O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*. 2005;10 Suppl 3:20-9. PMID: 16368868 DOI: 10.1634/theoncologist.10-90003-20.

[6] Metastatic Breast Cancer Network. 13 Facts about Metastatic Breast Cancer. http://www.mbcn.org/13-facts-about-metastatic-breast-cancer/. Accessed July 9, 2024.

[7] American Cancer Society. Breast Cancer Facts & Figures 2022-2024. Atlanta: American Cancer Society, Inc. 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf. Accessed July 9, 2024.

[8] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.

[9] American Cancer Society. Cancer Statistics Center. http://cancerstatisticscenter.cancer.org. Accessed July 9, 2024.

[10] Verzenio. Prescribing information. Lilly USA, LLC.

[11] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed May 9, 2024. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

[12] Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomized, open-label, phase 3 trial. *Lancet Oncol*. 2023 Jan;24(1):77-90.

[13] Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2–negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial*JAMA Oncol*. 2020;6(1):116-124. doi:10.1001/jamaoncol. 2019.4782.

Refer To: Michelle Webb; (michelle.webb@lilly.com); 463-206-4463 (Media)
Michael Czapar; (czapar_michael_c@lilly.com); 317-617-0983 (Investors)

View original content to download multimedia:https://www.prnewswire.com/news-releases/lillys-imlunestrant-an-oral-serd-significantly-improved-progression-free-survival-as-monotherapy-and-in-combination-with-verzenio-abemaciclib-in-patients-with-er-her2--advanced-breast-cancer-302328271.html

SOURCE Eli Lilly and Company