Lilly Highlights Verzenio® (abemaciclib) and Jaypirca™ (pirtobrutinib) Data at 2023 ASCO® Annual Meeting

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New analyses from the Phase 3 monarchE trial of two years of Verzenio treatment in node-positive, high risk early breast cancer show similar efficacy across age groups and in patients who had dose adjustments with benefit maintained at four-year follow-up; overall quality of life during the Verzenio treatment period shown to be similar to endocrine therapy alone

Updated data from the Phase 1/2 BRUIN trial of Jaypirca in patients with covalent BTK inhibitor pre-treated relapsed or refractory MCL continue to demonstrate durable efficacy and no newly identified safety signals

INDIANAPOLIS, June 2, 2023 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced Verzenio® (abemaciclib; CDK4/6 inhibitor) and Jaypirca™ (pirtobrutinib; non-covalent (reversible) BTK inhibitor) data to be presented at the 2023 ASCO® Annual Meeting in Chicago, June 2 – 6, 2023. Presentations include new analyses from the Phase 3 monarchE trial of two years of Verzenio treatment in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), node-positive, high risk early breast cancer (EBC) and updated data from the Phase 1/2 BRUIN trial for an approved use of Jaypirca in patients with covalent BTK inhibitor pre-treated relapsed or refractory mantle cell lymphoma (MCL).

"These additional data on Verzenio and Jaypirca build on the evidence supporting the role each of these medicines play in improving the treatment paradigms for patients with node-positive, high risk early breast cancer and covalent BTK inhibitor pre-treated relapsed or refractory MCL, respectively," said David Hyman, M.D., chief medical officer, Loxo@Lilly. "Mature data for Verzenio reinforce its benefit in the node-positive, high risk adjuvant setting across age groups and these data should also provide comfort that the durable efficacy observed is not compromised when dose reductions are necessary. We also continue to be encouraged by these longer-term follow up data for Jaypirca and the potential for treatment to extend the time patients with relapsed or refractory MCL may benefit from BTK inhibition therapy."

New Analyses from the Verzenio monarchE Trial
An oral presentation (Abstract #501) will highlight efficacy and safety results from age-based subgroup analyses from the Phase 3 monarchE study of Verzenio in combination with endocrine therapy (ET) in patients with HR+, HER2-, node-positive EBC at a high risk of recurrence. Previously reported four-year data from monarchE demonstrated that, with all patients off Verzenio, Verzenio with ET compared to ET alone reduced the risk of recurrence by 34% and the risk of distant relapse by 34% in this node positive, high risk EBC population, with a persistent and growing benefit demonstrated beyond the two-year treatment period with Verzenio – supporting the goal of eradicating micrometastatic disease to prevent recurrence even after patients have completed treatment.[1]

The new analyses show similar efficacy across age groups and in patients who had dose adjustments. Adjuvant Verzenio plus ET demonstrated an absolute benefit in invasive disease-free survival (IDFS) rate of 5.9% in those age 65 and older (n=850) and 6.4% in patients under 65 (n=4,787). Rates of adverse events (AEs) were also similar between age groups; 54% of patients 65 and older experienced Grade 3 and above AEs compared with 49% of patients under 65. Dose adjustments due to AEs were more common in patients age 65 and older. The impact of dose adjustments was evaluated among all patients enrolled in monarchE, regardless of age. In this analysis, patients were classified into three equal-sized subgroups according to their relative dose intensity (RDI) of Verzenio. IDFS outcomes at four years were similar across RDI subgroups (RDI from lowest dose intensity group to highest: 87.1%, 86.4%, 83.7%), showing treatment benefit is maintained despite dose modifications.

Patient-reported quality of life (QoL) data collected at baseline, 3, 6, 12, 18, and 24 months during the treatment period will also be presented, across all patients in monarchE. These results demonstrated overall QoL scores were similar for patients taking Verzenio plus ET and patients taking ET alone and were maintained in all age subgroups during the two-year Verzenio treatment period.

"The long-term efficacy and safety results from these analyses of the monarchE trial further demonstrate the benefit of adding two years of Verzenio to ET in the adjuvant setting, showing similar efficacy regardless of age, and even for those who have undergone dose modifications," said Erika P. Hamilton, M.D., medical oncologist, director of Breast Cancer Research at Sarah Cannon Research Institute and an investigator on the monarchE clinical trial. "These data, combined with new patient-reported outcomes, support the role of two years of Verzenio as the standard of care for people with HR+, HER2- early breast cancer and will be important for informing Verzenio treatment management."

These Verzenio data will be shared in an oral presentation today during the Breast Cancer—Local/Regional/Adjuvant session from 2:45 -5:45 p.m. CT.

Updated Jaypirca Data from the Phase 1/2 BRUIN Study
A poster presentation (Abstract #7514) will highlight efficacy data with a median survival follow-up time of two years for Jaypirca in relapsed or refractory MCL from the BRUIN Phase 1/2 clinical trial. The presentation uses a July 29, 2022 data cutoff date, providing an additional six months of follow-up from the data recently published in the Journal of Clinical Oncology and presented at the 2022 American Society of Hematology Annual Meeting.

The dataset includes the first 90 MCL patients enrolled who had received a prior covalent Bruton's tyrosine kinase (BTK) inhibitor. Patients had received a median of three prior lines of therapy (range 1-8). Efficacy and safety results were consistent with previously reported data. Jaypirca demonstrated an overall response rate (ORR) of 56.7% (95% CI: 45.8-67.1), a median duration of response (DOR) of 17.6 months (95% CI: 7.3-27.2), and a median progression-free survival (PFS) of 7.4 months (95% CI: 5.3-13.3). Response rates were consistent in patients with high-risk disease features, including blastoid/pleomorphic variants, elevated Ki-67 index, and TP53 mutations. In the MCL safety cohort (n=166), the most frequent

treatment-emergent adverse events (TEAEs) were fatigue (31.3%), diarrhea (22.3%), and dyspnea (16.3%).

A second poster presentation (Abstract #7513) will highlight clinical safety data in patients with relapsed or refractory B-cell malignancies, inclusive of subtypes still under investigational use, from the Phase 1/2 BRUIN trial who received long-term (≥12 months) Jaypirca treatment. These safety data, based on longer-term Jaypirca therapy, are consistent with the overall safety profile, without evidence of new or worsening toxicity signals. In this long-term safety cohort (n=326), the most common TEAEs, regardless of attribution, were fatigue (32%), diarrhea (31%), COVID-19 (29%), contusion (26%), cough (25%), and back pain (21%). With continued treatment (median of 19 months), the rates of select AEs of special interest including atrial fibrillation remained low and did not show clinically meaningful increases, particularly Grade ≥3.

Both Jaypirca data presentations will be discussed on June 5 from 1:15 – 2:45 p.m. CT during the Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia poster discussion session.

About the monarchE Study
monarchE was a global, randomized, open-label, two cohort, multicenter Phase 3 clinical trial that enrolled 5,637 adults with HR+, HER2-, node-positive EBC at high risk of recurrence. The study enrolled patients across more than 600 sites in 38 countries and is the only adjuvant study designed to investigate a CDK4/6 inhibitor in a high risk EBC population. To be enrolled in Cohort 1 (n=5,120), which is the FDA-approved population, patients had to have 4+ positive nodes or 1-3 positive nodes and at least one of the following: tumors that were ≥5 cm or Grade 3. Patients enrolled in Cohort 2 could not have met the eligibility criteria for Cohort 1. To be enrolled in Cohort 2 (n=517), patients had to have 1-3 positive nodes and Ki-67 score ≥20%. Patients in each cohort were randomized 1:1 to receive either Verzenio 150 mg twice daily plus standard-of-care adjuvant ET (Cohort 1, n=2,555; Cohort 2, n=253) or standard-of-care adjuvant ET alone (Cohort 1, n=2,565; Cohort 2, n=264) for 2 years. ET continued for at least 5 years if deemed medically appropriate. The primary endpoint was IDFS. Consistent with expert guidelines, IDFS was defined as the length of time before breast cancer comes back, any new cancer develops, or death.

About the BRUIN Phase 1/2 Trial
The BRUIN Phase 1/2 clinical trial is the ongoing first-in-human, global, multi-center evaluation of Jaypirca in patients with previously treated hematologic malignancies, including MCL.

The trial includes a Phase 1 dose-escalation phase, a Phase 1b combination arm, and a Phase 2 dose-expansion phase. The primary endpoint of the Phase 1 study is maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D). Secondary endpoints include safety, pharmacokinetics (PK), and preliminary efficacy measured by ORR for monotherapy. The primary endpoint of the Phase 1b study is safety of the drug combinations. The secondary endpoints are PK and preliminary efficacy measured by ORR for the drug combinations. The primary endpoint for the Phase 2 study is ORR as determined by an IRC. Secondary endpoints include ORR as determined by investigator, best overall response (BOR), DOR, PFS, overall survival (OS), safety, and PK.

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 and only CDK4/6 inhibitor approved to treat node-positive, high risk early breast cancer (EBC) patients.[2] 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.[3]

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, the only adjuvant study designed specifically to investigate a CDK4/6 inhibitor in a high risk population.[4] In metastatic breast cancer, Verzenio has demonstrated statistically significant OS in the Phase 3 MONARCH 2 study.[5] Verzenio has shown a consistent and generally manageable safety profile across clinical trials. In addition to breast cancer, Lilly is studying Verzenio in different forms of difficult-to-treat prostate cancer.

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.

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About Jaypirca™ (pirtobrutinib)
Jaypirca (pirtobrutinib, formerly known as LOXO-305) (pronounced jay-pihr-kaa) is a highly selective (300 times more selective for BTK versus 98% of other kinases tested in preclinical studies), non-covalent (reversible) inhibitor of the enzyme BTK.[6] BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma.[7,8] Jaypirca is a U.S. FDA-approved oral prescription medicine, 100 mg or 50 mg tablets taken as a once-daily 200 mg dose with or without food until disease progression or unacceptable toxicity.

INDICATIONS FOR JAYPIRCA
Jaypirca is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION FOR JAYPIRCA ™(pirtobrutinib)
Infections: Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients treated with Jaypirca. In the clinical trial, Grade ≥3 infections occurred in 17% of 583 patients with hematologic malignancies, most commonly pneumonia (9%); fatal infections occurred in 4.1% of patients. Sepsis (4.5%) and febrile neutropenia (2.9%) occurred. Opportunistic infections after Jaypirca treatment included, but are not limited to, *Pneumocystis jirovecii* pneumonia and fungal infection. Consider prophylaxis, including vaccinations and antimicrobial

prophylaxis, in patients at increased risk for infection, including opportunistic infections. Monitor patients for signs and symptoms, evaluate promptly, and treat appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Hemorrhage: Fatal and serious hemorrhage has occurred with Jaypirca. Major hemorrhage (Grade ≥3 bleeding or any central nervous system bleeding) occurred in 2.4% of 583 patients with hematologic malignancies treated with Jaypirca, including gastrointestinal hemorrhage; fatal hemorrhage occurred in 0.2% of patients. Bleeding of any grade, excluding bruising and petechiae, occurred in 14% of patients. Major hemorrhage occurred in patients taking Jaypirca with (0.7%) and without (1.7%) antithrombotic agents. Consider risks/benefits of co-administering antithrombotic agents with Jaypirca. Monitor patients for signs of bleeding. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca. Consider benefit/risk of withholding Jaypirca 3-7 days pre- and post-surgery depending on type of surgery and bleeding risk.

Cytopenias: Grade 3 or 4 cytopenias, including neutropenia (24%), anemia (11%), and thrombocytopenia (11%), have developed in patients with hematologic malignancies treated with Jaypirca. In a clinical trial, Grade 4 neutropenia (13%) and Grade 4 thrombocytopenia (5%) developed. Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Atrial Fibrillation and Atrial Flutter: Atrial fibrillation or flutter were reported in 2.7% of patients, with Grade 3 or 4 atrial fibrillation or flutter reported in 1% of 583 patients with hematologic malignancies treated with Jaypirca. Patients with cardiac risk factors such as hypertension or previous arrhythmias may be at increased risk. Monitor for signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea) and manage appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Second Primary Malignancies: Second primary malignancies, including non-skin carcinomas, developed in 6% of 583 patients with hematologic malignancies treated with Jaypirca monotherapy. The most frequent malignancy was non-melanoma skin cancer (3.8%). Other second primary malignancies included solid tumors (including genitourinary and breast cancers) and melanoma. Advise patients to use sun protection and monitor for development of second primary malignancies.

Embryo-Fetal Toxicity: Based on animal findings, Jaypirca can cause fetal harm in pregnant women. Administration of pirtobrutinib to pregnant rats during organogenesis caused embryo-fetal toxicity, including embryo-fetal mortality and malformations at maternal exposures (AUC) approximately 3-times the recommended 200 mg/day dose. Advise pregnant women of potential risk to a fetus and females of reproductive potential to use effective contraception during treatment and for one week after last dose.

Adverse Reactions (ARs) in Patients with Mantle Cell Lymphoma Who Received Jaypirca
Serious ARs occurred in 38% of patients. Serious ARs occurring in ≥2% of patients were pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). **Fatal ARs** within 28 days of last dose of Jaypirca occurred in 7% of patients, most commonly due to infections (4.7%), including COVID-19 (3.1%).

Dose Modifications and Discontinuations: ARs led to dosage reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dosage modification in >5% of patients included pneumonia and neutropenia. ARs resulting in permanent discontinuation of Jaypirca in >1% of patients included pneumonia.

ARs (all Grades %; Grade 3-4 %) in ≥10% of Patients: fatigue (29; 1.6), musculoskeletal pain (27; 3.9), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), pneumonia (16; 14), bruising (16; -), peripheral neuropathy (14; 0.8), cough (14; -), rash (14; -), fever (13; -), constipation (13; -), arthritis/arthralgia (12; 0.8), hemorrhage (11; 3.1), abdominal pain (11; 0.8), nausea (11; -), upper respiratory tract infections (10; 0.8), dizziness (10; -).

Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in ≥10% of Patients: hemoglobin decreased (42; 9), platelet count decreased (39; 14), neutrophil count decreased (36; 16), lymphocyte count decreased (32; 15), creatinine increased (30; 1.6), calcium decreased (19; 1.6), AST increased (17; 1.6), potassium decreased (13; 1.6), sodium decreased (13; -), lipase increased (12; 4.4), alkaline phosphatase increased (11; -), ALT increased (11; 1.6), potassium increased (11; 0.8). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (10), platelets decreased (7), lymphocytes decreased (6).

All grade ARs with higher frequencies in the total BRUIN population of patients with hematologic malignancies (n=583) were decreased neutrophil count (41%), bruising (20%), diarrhea (20%).

Drug Interactions
Strong CYP3A Inhibitors: Concomitant use with Jaypirca increased pirtobrutinib systemic exposure, which may increase risk of Jaypirca adverse reactions. Avoid use of strong CYP3A inhibitors during Jaypirca treatment. If concomitant use is unavoidable, reduce Jaypirca dosage according to the approved labeling.

Strong or Moderate CYP3A Inducers: Concomitant use with Jaypirca decreased pirtobrutinib systemic exposure, which may reduce Jaypirca efficacy. Avoid concomitant use of Jaypirca with strong or moderate CYP3A inducers. If concomitant use with moderate CYP3A inducers is unavoidable, increase the Jaypirca dosage according to the approved labeling.

Sensitive CYP2C8, CYP2C19, CYP3A, P-gP, BCRP Substrates: Concomitant use with Jaypirca increased their plasma concentrations, which may increase risk of adverse reactions related to these substrates for drugs that are sensitive to minimal concentration changes. Follow recommendations for these sensitive substrates in their approved labeling.

Use in Special Populations
Pregnancy and Lactation: Inform pregnant women of potential for Jaypirca to cause fetal harm. Verify pregnancy status in females of reproductive potential prior to starting Jaypirca and advise use of effective contraception during treatment and for one week after last dose. Presence of pirtobrutinib in human milk and effects on the breastfed child or on milk production is unknown. Advise women not to breastfeed while taking Jaypirca and for one week after last dose.

Geriatric Use: In the pooled safety population of patients with hematologic malignancies, 392 (67%) were ≥65 years of age. Patients aged ≥65 years experienced higher rates of Grade ≥3 ARs and serious ARs compared to patients <65 years of age.

Renal Impairment: Severe renal impairment (eGFR 15-29 mL/min) increases pirtobrutinib exposure. Reduce Jaypirca dosage in patients with severe renal impairment according to the approved labeling. No dosage adjustment is recommended in patients with mild or moderate renal impairment.

PT HCP ISI MCL APP

Please see Prescribing Information and Patient Information for Jaypirca.

About Lilly
Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 51 million 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/newsroom or follow us on Facebook, Instagram, Twitter and LinkedIn. P-LLY

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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 early breast cancer and Jaypirca as a treatment for people with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor, 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, or that Verzenio or Jaypirca will receive additional regulatory approvals, or that Jaypirca will be commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, 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.

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3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed May 30, 2023. 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.
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