U.S. FDA Approves Jaypirca™ (pirtobrutinib), the First and Only Non-Covalent (Reversible) BTK Inhibitor, for Adult Patients with Relapsed or Refractory Mantle Cell Lymphoma After at Least Two Lines of Systemic Therapy, Including a BTK Inhibitor

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Jaypirca is the first BTK inhibitor of any kind specifically approved for patients with mantle cell lymphoma previously treated with a covalent BTK inhibitor

In the BRUIN Phase 1/2 trial, covalent BTK inhibitor pre-treated patients with relapsed or refractory MCL achieved an overall response rate of 50%, with 13% of patients achieving a complete response

INDIANAPOLIS, Jan. 27, 2023 /PRNewswire/ -- Loxo@Lilly, the oncology unit of Eli Lilly and Company (NYSE: LLY), today announced that the U.S. Food and Drug Administration (FDA) approved Jaypirca™ (pirtobrutinib, 100 mg & 50 mg tablets) for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor. Jaypirca was approved under the FDA's Accelerated Approval pathway based on response rate from the open-label, single-arm, international, Phase 1/2 study, called the BRUIN trial.[1] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Jaypirca, a highly selective kinase inhibitor, utilizes a novel binding mechanism and is the first and only FDA approved non-covalent (reversible) BTK inhibitor. Jaypirca can reestablish BTK inhibition in MCL patients previously treated with a covalent BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib) and extend the benefit of targeting the BTK pathway.

"The approval of Jaypirca represents an important advance for patients with relapsed or refractory MCL, who currently have limited options and historically have had a poor prognosis following discontinuation of treatment with a covalent BTK inhibitor," said Michael Wang, M.D., Puddin Clarke Endowed Professor of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center. "These data indicate that Jaypirca can provide efficacy in patients previously treated with a covalent BTK inhibitor, potentially extending the time patients may benefit from BTK inhibition therapy. Jaypirca offers a new approach to targeting the BTK pathway following treatment with a covalent BTK inhibitor and has the potential to meaningfully impact the treatment paradigm for relapsed and refractory MCL patients."

The labeling for Jaypirca contains warnings and precautions for infections, hemorrhage, cytopenias, atrial fibrillation and flutter, second primary malignancies, and embryo-fetal toxicity. See Important Safety Information below and full Prescribing Information for additional information, including dosing modifications.

"We are pleased to bring a meaningful new therapeutic option to patients with MCL that can reestablish the benefit of targeting the BTK pathway after receiving multiple prior therapies, including a covalent BTK inhibitor," said Jacob Van Naarden, chief executive officer, Loxo@Lilly. "We are grateful to the patients, investigators, and other members of the clinical care teams for their contributions. Our team has been committed to rapidly advancing the development of Jaypirca for patients with MCL, and we look forward to building on this milestone by continuing to bring forward important new treatments for people with hematologic malignancies."

The FDA approval is based on data from a subset of patients in the BRUIN Phase 1/2 trial. The assessment of efficacy was based on 120 patients with MCL treated with Jaypirca 200 mg once daily until disease progression or unacceptable toxicity. Patients with active central nervous system lymphoma or allogeneic hematopoietic stem cell transplantation or CAR T-cell therapy within 60 days were excluded. Patients had received a median of three prior lines of therapy (range: 1 to 9), with 93% having two or more prior lines; all patients received one or more prior lines of therapy containing a covalent BTK inhibitor. Eighty-three percent (83%) of patients discontinued their last BTK inhibitor due to refractory or progressive disease. Efficacy was based on overall response rate (ORR) and duration of response (DOR) as assessed by an independent review committee (IRC) using 2014 Lugano criteria. Efficacy results are summarized below:

Outcome	**Jaypirca 200 mg once daily (N=120)**
Overall Response Rate[a,b]	
ORR, n (95% CI, %)	60 (50 %) 41, 59
CR, n	15 (13 %)
PR, n	45 (38 %)
Time to Response Median (range), months	1.8 (0.8, 4.2)
Duration of Response[c]	
Number censored, n Median DOR, months (95% CI) DOR rate at 6 months, % (95% CI)	36[d] 8.3 (5.7, NE) 65.3 (49.8, 77.1)

CI, confidence interval; CR, complete response; DOR, duration of response; PR, partial response; NE, not estimable.
a. PET-CT scans were utilized in response assessments (in 41% of patients), with the remainder being assessed by CT scans only.
b. ORR using CT scan-based assessments in all patients was 48% (95% CI: 38, 57), and CR rate was 13%.

c. Based on Kaplan-Meier estimation. Estimated median follow-up was 7.3 months.
d. Thirty-six (36) of 60 responders had not progressed or died prior to data cutoff.

The pooled safety analysis of the full BRUIN study population evaluated 583 patients with hematologic malignancies administered Jaypirca 200 mg daily as a single agent. In this pooled safety population, the most common adverse reactions (ARs) to Jaypirca therapy, occurring in 20% of patients or more, were decreased neutrophil count, decreased hemoglobin, decreased platelet count, fatigue, musculoskeletal pain, decreased lymphocyte count, bruising, and diarrhea.

The safety of Jaypirca was evaluated in 128 patients with MCL, 36% of whom were exposed for six months or longer and 10% of whom were exposed for at least one year. ARs led to dosage reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. ARs that resulted in permanent discontinuation of Jaypirca in more than 1% of patients included pneumonia. Serious ARs occurred in 38% of patients who received Jaypirca. Serious ARs occurring in greater than or equal to 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%).

"Until now, people living with MCL who can no longer be treated with BTK inhibitors have had few alternatives," said Meghan Gutierrez, chief executive officer, Lymphoma Research Foundation. "The approval of Jaypirca brings a new treatment option and, along with that, new hope for people with relapsed or refractory MCL."

Jaypirca is expected to be available in the United States in the coming weeks.

The confirmatory Phase 3 trial (NCT04662255; BRUIN MCL-321) is currently enrolling patients.
See Important Safety Information below and full Prescribing Information for additional information.

Click here to view the mantle cell lymphoma infographic.

Click to view the Jaypirca product photos: 100 mg and 50 mg.

Click here to view the Jaypirca logo.

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 hematologic malignancies, including mantle cell lymphoma (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 overall response rate (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 independent review committee (IRC). Secondary endpoints include ORR as determined by investigator, best overall response (BOR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and PK.

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.[2] BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma.[3,4] 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.

About Mantle Cell Lymphoma
MCL is a rare blood cancer and a form of non-Hodgkin lymphoma (NHL). Annually, about one in 200,000 people worldwide develop MCL.[5]

MCL arises in B lymphocytes, a type of white blood cell and part of the immune system. MCL frequently begins in B cells located in the mantle zone of the outer edge of lymph nodes. As the cancer progresses, it can spread to bone marrow, the spleen, the liver, or the digestive tract.[5]

INDICATIONS FOR JAYPIRCA

Jaypirca is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory 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.

Please see Prescribing Information and Patient Information for Jaypirca.

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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 47 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

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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 Jaypirca ™ as a treatment for people with mantle cell lymphoma previously treated with a BTK inhibitor and as a potential treatment for patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or other non-Hodgkin's lymphomas (NHL) and other conditions 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 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.

1. Jaypirca. Prescribing information. Lilly USA, LLC.
2. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892-901. doi:10.1016/S0140-6736(21)00224-5
3. Hanel W, Epperla N. Emerging therapies in mantle cell lymphoma. J Hematol Oncol. 2020;13(1):79. Published 2020 Jun 17. doi:10.1186/s13045-020-00914-1
4. Gu D, Tang H, Wu J, Li J, Miao Y. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol. 2021;14(1):40. Published 2021 Mar 6. doi:10.1186/s13045-021-01049-7
5. National Organization for Rare Disorders. Mantle cell lymphoma. Accessed 26 October 2022. https://rarediseases.org/rare-diseases/mantle-cell-lymphoma/

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