New England Journal of Medicine Publishes BRUIN Phase 1/2 Trial Data for Pirtobrutinib in BTK Inhibitor Pre-Treated Adult Patients with Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

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INDIANAPOLIS, July 6, 2023 /PRNewswire/ -- Loxo@Lilly, the oncology unit of Eli Lilly and Company (NYSE: LLY), today announced that *The New England Journal of Medicine* (NEJM) published detailed results from the BRUIN Phase 1/2 trial evaluating the efficacy and safety of an investigational use of pirtobrutinib, a non-covalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor, in adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who were previously treated with a BTK inhibitor.

The *NEJM* publication provides additional clinical details from the data set that was presented at the 2022 American Society of Hematology (ASH) Annual Meeting. The data set includes 247 BTK inhibitor pre-treated CLL/SLL patients enrolled across both the Phase 1 and Phase 2 portions of the BRUIN study.

"Patients with relapsed or refractory CLL or SLL following treatment with a covalent BTK inhibitor represent a population with limited treatment options," said the study's co-lead author Jennifer A. Woyach, M.D., professor and hematologist-oncologist at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. "These data support the potential for pirtobrutinib to extend the benefit of BTK inhibition for patients with CLL or SLL with a once-daily oral therapy."

"We are pleased to have the detailed safety and efficacy results of pirtobrutinib in adults with CLL or SLL published in *NEJM* and shared with the broader medical community," said David Hyman, M.D., chief medical officer, Loxo@Lilly. "Treating clinicians have expressed the desire to fully exhaust BTK inhibition prior to switching their patients to another therapy class. These data continue to reinforce pirtobrutinib's ability to help reestablish BTK inhibition following treatment with a covalent BTK inhibitor."

Overview of Data Published in NEJM

The efficacy cohort consisted of 247 BTK inhibitor pre-treated CLL/SLL patients enrolled across both the Phase 1 and Phase 2 portions of the BRUIN study as of July 29, 2022. The median number of prior therapies was three (range: 1-11). Most patients discontinued prior BTKi therapy due to disease progression (77%). Consistent with a very heavily pre-treated population with advanced disease, high-risk molecular features were common including the presence of a del(17p) and/or TP53 mutation (47%), complex karyotype (42%), and unmutated IGHV (85%). The primary endpoint was best overall response rate (ORR), comprising partial response (PR) or better, according to the 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) response criteria. This was assessed by an independent review committee (IRC) blinded to investigator assessments. Additional endpoints were ORR when including PR with lymphocytosis, progression-free survival (PFS), overall survival (OS), safety, and exploratory analyses of biomarkers. All efficacy data, except for OS, were assessed by both the investigator and an IRC.

Efficacy results are summarized below:

	Prior BTKi (N=247)	**Prior BTKi+BCL2i (N=100)**
Overall Response Rate, % (95% CI)	73.3 (67.3-78.7)	70.0 (60.0-78.8)
Overall Response Rate including PR-L, % (95% CI)	82.2 (76.8-86.7)	79.0 (69.7-86.5)
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	176 (71.3)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)
Progression-free Survival		
Median, months 95% CI	19.6 (16.9-22.1)	16.8 (13.2-18.7)
Censored patients, n (%)	126 (51)	44 (44)
Median follow-up, months	19.4	18.2

CI, confidence interval; CR, complete response; PR, partial response; PR-L, partial response-lymphocytosis; SD, stable disease.
Response status per iwCLL 2018 according to independent review committee assessment.

In a subgroup analysis of BCL2 inhibitor naïve patients (n=147), the ORR including PR-L was 84.4% (95% CI: 77.5-89.8) and the median PFS was 22.1 months (95% CI: 19.6-27.4).

Safety was reported in all patients with CLL/SLL who had received at least one dose of pirtobrutinib (n=317). As of the data cutoff date, 87.4% of patients had received at least one dose of pirtobrutinib at the recommended Phase 2 dose of 200 mg once daily, and the median time on treatment was 16.5 months (range: 0.2-39.9). The safety profile reported was consistent with previously reported data for pirtobrutinib. Overall, the most common treatment-emergent adverse events (TEAEs) were infections (71.0%), bleeding (42.6%), and neutropenia (32.5%). The most frequently reported TEAEs of Grade 3 or higher were infections (28.1%) and neutropenia (in 26.8%), and the most frequently reported treatment-related adverse

event (AE) of Grade 3 or higher was neutropenia (14.8%). Incidence of treatment-related Grade 3 or higher atrial fibrillation (1.3%), hemorrhage (6.9%), and hypertension (3.8%) were relatively low. In patients with CLL/SLL, treatment-related AEs leading to dose reductions occurred in 4.7% and permanent discontinuations in 2.8% of patients.

Loxo@Lilly is studying pirtobrutinib in CLL/SLL in multiple Phase 3 studies. Details on the trials can be found at lillyloxooncologypipeline.com or by visiting clinicaltrials.gov.

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 pirtobrutinib in patients previously treated for mantle cell lymphoma (MCL), CLL, SLL, or other non-Hodgkin lymphomas (NHL).

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), duration of response (DOR), PFS, OS, safety, and PK.

About Pirtobrutinib

Pirtobrutinib 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.[1] BTK plays a key role in the B-cell antigen receptor signaling pathway, which is required for the development, activation and survival of normal white blood cells, known as B-cells, and malignant B-cells. BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including CLL.[2,3] Pirtobrutinib was developed to reversibly bind BTK, deliver consistently high target coverage regardless of BTK turnover rate, and preserve activity in the presence of the C481 acquired resistance mutations.

Pirtobrutinib was approved under the FDA's Accelerated Approval pathway as Jaypirca ™ (pirtobrutinib) on January 27, 2023. Jaypirca is indicated for the treatment of adult patients with relapsed or refractory 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 Lilly's oncology portfolio and pipeline, including Jaypirca™ as a treatment for people with mantle cell lymphoma (MCL) previously treated with a BTK inhibitor and as a potential treatment for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and the timeline for future readouts, presentations, and other milestones relating to Jaypirca and their clinical trials, 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, that Jaypirca will be commercially successful, or that Lilly will execute its strategy as expected. 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. 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
2. 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
3. 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

Refer to: Kyle Owens; owens_kyle@lilly.com; 332-259-3932 – media
Joe Fletcher; jfletcher@lilly.com; 317-296-2884 – investors

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