



Lilly Announces Details of Pirtobrutinib Presentations in B-Cell Malignancies at 2023 ASH Annual Meeting

November 2, 2023

INDIANAPOLIS, Nov. 2, 2023 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced that data from studies of pirtobrutinib, a non-covalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor, will be presented at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition taking place December 9-12 in San Diego.

The presentations will provide updated, longer follow-up clinical safety and efficacy data for approved and investigational uses of pirtobrutinib from the ongoing Phase 1/2 BRUIN study in multiple B-cell malignancies. In mantle cell lymphoma (MCL), an oral presentation will provide updated safety and efficacy results of pirtobrutinib in all patients, including those with biologically high-risk relapsed or refractory MCL. In chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), oral presentations include long-term follow-up data in patients with relapsed or refractory CLL/SLL in the post-cBTKi setting, including patients with or without BCL-2 inhibitor exposure, and an updated analysis of the genomic evolution of resistance mechanisms in pirtobrutinib-treated CLL patients. Additionally, poster presentations will provide data on the clinical impact of pirtobrutinib following cBTKi treatment across other B-cell malignancies.

A full list of abstract titles and viewing details are listed below:

Presentation Title: Pirtobrutinib in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) Patients with Prior cBTKi: Safety and Efficacy Including High-Risk Subgroup Analyses from the Phase 1/2 BRUIN Study

Abstract Number: 981

Oral Session: 623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological: Targeted Therapy

Presentation Date & Time: Monday, December 11, 5:00 PM PT

Location: Manchester Grand Hyatt San Diego, Grand Hall C

Presenter: Jonathon B. Cohen

Presentation Title: Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study

Abstract Number: 325

Oral Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: New Inhibitors and Cellular Therapies for Treatment of Relapsed CLL

Presentation Date & Time: Saturday, December 9, 4:00 PM PT

Location: Manchester Grand Hyatt San Diego, Grand Hall D

Presenter: Jennifer A. Woyach

Presentation Title: Genomic Evolution and Resistance during Pirtobrutinib Therapy in Covalent BTK-Inhibitor (cBTKi) Pre-Treated Chronic Lymphocytic Leukemia Patients: Updated Analysis from the BRUIN Study

Abstract Number: 326

Oral Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: New Inhibitors and Cellular Therapies for Treatment of Relapsed CLL

Presentation Date & Time: Saturday, December 9, 4:15 PM PT

Location: Manchester Grand Hyatt San Diego, Grand Hall D

Presenter: Jennifer R. Brown

Presentation Title: Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed/Refractory Follicular Lymphoma: Results from the Phase 1/2 BRUIN Study

Abstract Number: 3026

Poster Session: 623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological: Poster II

Presentation Date & Time: Sunday, December 10, 6:00 – 8:00 PM PT

Location: San Diego Convention Center, Halls G-H

Presenter: Nirav N. Shah

Presentation Title: Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed/Refractory Marginal Zone Lymphoma: Results from Phase 1/2 BRUIN Study

Abstract Number: 1660

Poster Session: 623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological: Poster I

Presentation Date & Time: Saturday, December 9, 5:30 – 7:30 PM PT

Location: San Diego Convention Center, Halls G-H

Presenter: Krish Patel

Presentation Title: Pirtobrutinib in Richter Transformation: Updated Efficacy and Safety Results with 18-Month Median Survival Follow-up from the Phase 1/2 BRUIN Study

Abstract Number: 1737

Poster Session: 626. Aggressive Lymphomas: Prospective Therapeutic Trials: Poster I

Presentation Date & Time: Saturday, December 9, 5:30 – 7:30 PM PT

Location: San Diego Convention Center, Halls G-H
Presenter: William G. Wierda

Presentation Title: Fixed-Duration Pirtobrutinib Combined with Venetoclax ± Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results, Including MRD Data, from the BRUIN Phase 1b Study

Abstract Number: 3269

Poster Session: 642. Chronic Lymphocytic Leukemia: Clinical and Epidemiological: Poster II

Presentation Date & Time: Sunday, December 10, 6:00 – 8:00 PM PT

Location: San Diego Convention Center, Halls G-H

Presenter: Lindsey E. Roeker

Presentation Title: Pirtobrutinib, a Non-Covalent (reversible) BTK Inhibitor, in Mantle Cell Lymphoma Patients Previously Treated with a Covalent BTK Inhibitor: Results from a China Phase 2 Study

Abstract Number: 3636

Poster Session: 802. Chemical Biology and Experimental Therapeutics: Poster II

Presentation Date & Time: Sunday, December 10, 6:00 – 8:00 PM PT

Location: San Diego Convention Center, Halls G-H

Presenter: Jun Zhu

Presentation Title: Real-World Use and Outcomes of Therapies, Including Venetoclax-Based Treatments, after Discontinuation of a Covalent BTK Inhibitor in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Abstract Number: 5152

Poster Session: 905. Outcomes Research—Lymphoid Malignancies: Poster III

Presentation Date & Time: Monday, December 11, 6:00 – 8:00 PM PT

Location: San Diego Convention Center, Halls G-H

Presenter: Nitin Jain

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 with previously treated hematologic malignancies, including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and 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 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 mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).^{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 $\geq 2\%$ 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 $\geq 10\%$ 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 $\geq 10\%$ 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](#) and [LinkedIn](#). P-LLY

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Lilly 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® for the potential treatment of previously treated mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), and Richter transformation (RT) 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 studies will be completed as planned, that future study results will be consistent with the results to date, that Jaypirca will prove to be a safe and effective treatment for relevant indications, or that Jaypirca will receive additional regulatory approvals or 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. 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

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