Lilly's Jaypirca (pirtobrutinib) significantly extended progression-free survival when added to a venetoclax time-limited regimen in patients with previously treated CLL/SLL

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BRUIN CLL-322 is the first Phase 3 readout in CLL to utilize and outperform a venetoclax-containing control arm

This trial predominantly enrolled a patient population previously treated with covalent BTK inhibitors, highly relevant to current practice

These results mark the fourth positive Phase 3 study of pirtobrutinib in CLL

INDIANAPOLIS, April 13, 2026 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced positive topline results from the Phase 3 BRUIN CLL-322 trial of Jaypirca (pirtobrutinib), a non-covalent (reversible) Bruton tyrosine kinase (BTK) inhibitor, plus venetoclax and rituximab versus venetoclax and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL). Treatment in both study arms was administered for up to two years, after which patients do not take any CLL therapy until their disease progresses. The study met its primary endpoint, demonstrating that the addition of pirtobrutinib to venetoclax plus rituximab led to a statistically significant and clinically meaningful improvement in progression-free survival (PFS), as assessed by an independent review committee (IRC). Results were consistent across clinically relevant subgroups and regardless of whether patients were previously treated with a covalent BTK inhibitor.

Overall survival (OS), a key secondary endpoint, was not yet mature at this analysis, but was trending in favor of the pirtobrutinib combination regimen. The overall safety profile of this regimen was consistent with the known safety profile of each medicine. Rates of adverse events were similar across the study arms, with low rates of treatment regimen discontinuations, also similar between arms.

Detailed results will be presented at a medical congress and submitted to a peer-reviewed journal. Lilly intends to submit these results to regulators later this year for a label expansion.

"BRUIN CLL-322 was an ambitious trial, building on an effective regimen, and these results outperformed our expectations," said Jacob Van Naarden, executive vice president and president of Lilly Oncology. "Modern CLL treatment regimens provide such durable disease control that the vast majority of patients see their entire disease course managed by only one or two lines of therapy. For doctors and patients who prefer a time-limited approach, these BRUIN CLL-322 data demonstrate that the addition of Jaypirca could further extend the duration of benefit in second line CLL. Together with the other Phase 3 data recently published from the BRUIN clinical program, these data reinforce the potential role that pirtobrutinib may have, whether as a time-limited combination as a second line treatment or as a continuously dosed monotherapy in either line of therapy. We look forward to sharing the detailed data later this year and pursuing regulatory approvals to enable broad access."

These data build on the previously reported positive results from the BRUIN Phase 1/2 trial, the Phase 3 BRUIN CLL-321 trial, the first randomized, controlled study ever conducted in an exclusively post-covalent BTK inhibitor population, the Phase 3 BRUIN CLL-314 trial, the first-ever head-to-head Phase 3 trial versus ibrutinib in CLL to include treatment-naïve patients, and the BRUIN CLL-313 trial, the first prospective, randomized Phase 3 study to examine the efficacy and safety of a non-covalent BTK inhibitor exclusively in patients with treatment-naïve CLL. For more information on the BRUIN Phase 3 clinical trial program, please visit clinicaltrials.gov.

About BRUIN CLL-322
BRUIN CLL-322 is a global, randomized, open-label, Phase 3 study comparing time-limited pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in previously treated CLL/SLL patients. The trial enrolled 639 patients, who were randomized 1:1 to receive pirtobrutinib (200 mg, once daily) plus venetoclax and rituximab per their labeled doses or venetoclax and rituximab alone. The primary endpoint is PFS as assessed by blinded IRC. Secondary endpoints include PFS as assessed by investigator, OS, time to next treatment, event-free survival, overall response rate, time to worsening of CLL/SLL-related symptoms, time to worsening of physical functioning, safety and tolerability.

About Jaypirca (pirtobrutinib)
Jaypirca (pirtobrutinib) (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.[1] BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).[2,3] 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 (pirtobrutinib)
Jaypirca is indicated for the treatment of

- Adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have previously been treated with a covalent BTK inhibitor.
- 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 trial benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION FOR JAYPIRCA (pirtobrutinib)

Infections: Fatal and serious infections (including bacterial, viral, fungal) and opportunistic infections occurred in Jaypirca-treated patients. Across clinical trials, Grade ≥3 infections occurred (25%), most commonly pneumonia (20%); fatal infections (5%), sepsis (6%), and febrile neutropenia (3.8%) occurred. In patients with CLL/SLL, Grade ≥3 infections occurred (32%), with fatal infections occurring in 8%. Opportunistic infections included *Pneumocystis jirovecii* pneumonia and fungal infection. Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients at increased risk for infection, including opportunistic infections. Monitor for signs and symptoms, evaluate, and treat. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Hemorrhage: Fatal and serious hemorrhage has occurred with Jaypirca. Across clinical trials, major hemorrhage (Grade ≥3 bleeding or any central nervous system bleeding) occurred (2.6%), including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred (16%). Major hemorrhage occurred when taking Jaypirca with (2.0%) and without (0.6%) antithrombotic agents. Consider risks/benefits of co-administering antithrombotic agents with Jaypirca. Monitor for signs of bleeding. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca. Consider withholding Jaypirca 3-7 days pre- and post-surgery based on surgery type and bleeding risk.

Cytopenias: Jaypirca can cause cytopenias, including neutropenia, thrombocytopenia, and anemia. Across clinical trials, Grade 3 or 4 cytopenias, including decreased neutrophils (27%), decreased platelets (13%), and decreased hemoglobin (11%), developed. Grade 4 decreased neutrophils (15%) and Grade 4 decreased platelets (6%) developed. Monitor complete blood counts regularly. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Cardiac Arrhythmias: Cardiac arrhythmias occurred in patients taking Jaypirca. Across clinical trials, atrial fibrillation or flutter were reported in 3.4% of Jaypirca treated patients, with Grade 3 or 4 atrial fibrillation or flutter in 1.6%. Other serious cardiac arrhythmias such as supraventricular tachycardia and cardiac arrest occurred (0.4%). Cardiac risk factors such as hypertension or previous arrhythmias may increase risk. Monitor and manage signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea). Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Second Primary Malignancies: Across clinical trials, second primary malignancies, including non-skin carcinomas, developed in 9% of Jaypirca-treated patients, most frequently non-melanoma skin cancer (4.4%). 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.

Hepatotoxicity, Including Drug-Induced Liver Injury (DILI): Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of DILI, has occurred in patients treated with BTK inhibitors, including Jaypirca. Evaluate bilirubin and transaminases at baseline and throughout Jaypirca treatment. For patients who develop abnormal liver tests after Jaypirca, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold Jaypirca. If DILI is confirmed, discontinue Jaypirca.

Embryo-Fetal Toxicity: Jaypirca can cause fetal harm. Administration of pirtobrutinib to pregnant rats 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 fetal risk and females of reproductive potential to use effective contraception during treatment and for one week after last dose.

Adverse Reactions (ARs) in Patients Who Received Jaypirca

The most common (≥30%) ARs in the pooled safety population of patients with hematologic malignancies (n=704) were decreased neutrophil count (54%), decreased hemoglobin (43%), decreased leukocytes (32%), fatigue (31%), decreased platelets (31%), decreased lymphocyte count (31%), calcium decreased (30%).

Mantle Cell Lymphoma

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

Dose Modifications and Discontinuations Due to ARs: Dose reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. Permanent discontinuation in >1% of patients included pneumonia.

Most common ARs (≥15%) and Select Laboratory Abnormalities (≥10%) (all Grades %; Grade 3-4 %): hemoglobin decreased (42; 9), platelet count decreased (39; 14), neutrophil count decreased (36; 16), lymphocyte count decreased (32; 15), creatinine increased (30; 1.6), fatigue (29; 1.6), musculoskeletal pain (27; 3.9), calcium decreased (19; 1.6), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), AST increased (17; 1.6), pneumonia (16; 14), bruising (16; -), potassium decreased (13; 1.6), sodium decreased (13; -), lipase increased (12; 4.4), ALT increased (11; 1.6), potassium increased (11; 0.8), alkaline phosphatase increased (11; -). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (10), platelets decreased (7), lymphocytes decreased (6).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma from Single-Arm and Randomized Controlled Clinical Trials

Serious ARs occurred in 47-56% of patients across clinical trials. Serious ARs in ≥5% of patients in the single-arm trial were pneumonia (18%), COVID-19 (9%), sepsis (7%), febrile neutropenia (7%). Serious ARs in ≥3% of patients in the randomized controlled trial were pneumonia (21%), COVID-19 (5%), sepsis (3.4%). **Fatal ARs** within 28-30 days of last Jaypirca dose occurred in 8-11% of patients, most commonly due to infections (7-10%), including sepsis (5%), COVID-19 (2.7-5%), and pneumonia (3.4%).

Dose Modifications and Discontinuations Due to ARs: Dose reductions in 3.6-10%, treatment interruption in 42-51%, and permanent discontinuation of Jaypirca in 9-17% of patients. Permanent discontinuation in >1% of patients included second primary malignancy, pneumonia, COVID-19, neutropenia, sepsis, anemia, and cardiac arrythmias.

Most common ARs and Select Laboratory Abnormalities (≥20%) (all Grades %, Grade 3-4 %)--in a randomized controlled trial: neutrophil count decreased (54; 26), hemoglobin decreased (45; 10), platelet count decreased (37; 17), pneumonia (28; 16), ALT increased (25; 1.8), creatinine increased (25; -), calcium decreased (23; 0.9), sodium decreased (22; 0.9), bilirubin increased (21; 0.9), upper respiratory tract infections (21; 0.9); **in a single-arm trial:** neutrophil count decreased (63; 45), hemoglobin decreased (48; 19), calcium decreased (40; 2.8), fatigue (36; 2.7), bruising (36; -), cough (33; -), musculoskeletal pain (32; 0.9), platelet count decreased (30; 15), sodium decreased (30; -), COVID-19 (28; 7), pneumonia (27; 16),

diarrhea (26; -), abdominal pain (25; 2.7), lymphocyte count decreased (23; 8), ALT increased (23; 2.8), AST increased (23; 1.9), creatinine increased (23; -), dyspnea (22; 2.7), hemorrhage (22; 2.7), lipase increased (21; 7), alkaline phosphatase increased (21; -), edema (21; -), nausea (21; -), pyrexia (20; 2.7), headache (20; 0.9). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (23).

Drug Interactions

Strong CYP3A Inhibitors: Concomitant use increased pirtobrutinib systemic exposure, which may increase risk of Jaypirca ARs. Avoid using strong CYP3A inhibitors with Jaypirca. If concomitant use is unavoidable, reduce Jaypirca dose according to approved labeling.

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

Sensitive CYP2C8, CYP2C19, CYP3A, P-gp, or BCRP Substrates: Use with Jaypirca increased their plasma concentrations, which may increase risk of ARs related to these substrates for drugs sensitive to minimal concentration changes. Follow recommendations for these sensitive substrates in their approved labeling.

Use in Specific Populations

Pregnancy and Lactation: Due to potential for Jaypirca to cause fetal harm, verify pregnancy status in females of reproductive potential prior to starting Jaypirca. Presence of pirtobrutinib in human milk is unknown. Advise women to use effective contraception and to not breastfeed while taking Jaypirca and for one week after last dose.

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

Renal Impairment: Because severe renal impairment increases pirtobrutinib exposure, reduce Jaypirca dose in these patients according to approved labeling.

PT HCP ISI MCL_CLL Q42025

Please see Prescribing Information and Patient Information for Jaypirca.

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

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 (pirtobrutinib), as a potential treatment for adults with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL), and the timeline for future regulatory submissions, presentations, and other milestones relating to Jaypirca and its 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, or that Jaypirca will receive additional regulatory approvals. 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.

Endnotes & References

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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