Lilly's Jaypirca (pirtobrutinib) significantly reduced the risk of disease progression or death by 45% when added to a venetoclax time-limited regimen in people with previously treated CLL/SLL

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BRUIN CLL-322 is the first Phase 3 study to demonstrate superiority over a venetoclax-containing control arm in CLL, and, with the majority of patients previously treated with a covalent BTK inhibitor, reflects current practice patterns

These data will be highlighted in a late-breaking oral presentation at the 2026 European Hematology Association (EHA) Annual Meeting

INDIANAPOLIS, June 14, 2026 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from the Phase 3 BRUIN CLL-322 clinical trial of Jaypirca (pirtobrutinib), a non-covalent 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). The study met its primary endpoint of independent review committee (IRC)-assessed progression-free survival (PFS), demonstrating that the addition of pirtobrutinib to a two-year venetoclax plus rituximab regimen reduced the risk of disease progression or death by 45% (HR=0.55 [95% CI, 0.40-0.75]; p=0.0001).

These data will be highlighted in a late-breaking oral presentation at the 2026 European Hematology Association (EHA) Annual Meeting taking place in Stockholm, Sweden, as well as featured in the meeting's press program.

"These results from BRUIN CLL-322 show that the addition of pirtobrutinib as part of a time-limited regimen further enhanced an already effective treatment and extended the duration of remission for patients with previously treated CLL. Importantly, the study provides the first robust evidence for such an approach in patients who received a prior BTK inhibitor," said Matthew S. Davids, M.D., M.M.Sc., Chief of the Division of Lymphoma at Dana-Farber Cancer Institute, who is the lead author on the study. "Time-limited regimens are an important option in CLL care and provide patients with meaningful treatment-free intervals. In the context of the modern CLL treatment landscape, where many patients may only receive two lines of therapy, these results speak to the potential benefits that improving second-line therapy can have. Our study has the potential to establish a new standard of care in this population."

BRUIN CLL-322 enrolled 639 relapsed or refractory patients, with 79.8% having prior covalent BTK inhibitor exposure, who were randomized 1:1 to receive pirtobrutinib plus venetoclax and rituximab (PVR, n=321) or venetoclax and rituximab alone (VR, n=318). Patients in the PVR arm received three cycles of pirtobrutinib and the first three cycles of rituximab before venetoclax was introduced. The efficacy results are based on a Feb. 2, 2026 data cutoff. At a median follow-up of 27.3 months, the primary endpoint of IRC-assessed PFS was significantly improved with the addition of pirtobrutinib to VR compared to VR alone (HR=0.55 [95% CI, 0.40-0.75]; p=0.0001). Median PFS in the PVR arm was not reached (95% CI, 43.3-NE), versus 39.7 months (95% CI, 35.9-NE) in the VR arm. The PFS results were consistent across prespecified subgroups, including patients with prior covalent BTK inhibitor exposure (PVR: not reached [95% CI, 41.5-NE] versus VR: 36.2 months [95% CI, 33.2-NE]), those who discontinued prior covalent BTK inhibitor due to progressive disease (PVR: 43.3 months [95% CI, 39.2-NE] versus VR: 33.2 months [95% CI, 28.3-37.5]), as well as those with high-risk features such as unmutated IGHV, *TP53* mutation and/or 17p deletion, and/or complex karyotype. In an exploratory analysis of second-line patients whose disease progressed after a first-line covalent BTK inhibitor, the median PFS was not reached (95% CI, 30.1-NE) in the PVR arm and was 28.3 months (95% CI, 20.5-NE) in the VR arm (HR=0.32 [95% CI, 0.14-0.73]), with 24-month PFS rates of 88% (95% CI, 75.7-94.6) and 52% (95% CI, 34.7-66.2), respectively, and consistent benefit was observed regardless of the specific prior covalent BTK inhibitor received.

Overall survival (OS), a key secondary endpoint, was not yet mature at this analysis (HR=0.89 [95% CI, 0.57-1.40]), and final testing of OS superiority is planned at a future date. An additional secondary endpoint, time to next treatment (TTNT), consistently favored the pirtobrutinib combination regimen (HR=0.50 [95% CI, 0.35-0.70]; nominal p<0.0001).

The overall safety profile of this regimen in BRUIN CLL-322 was consistent with the known safety profile of each medicine, with little additive toxicity observed with the addition of pirtobrutinib to venetoclax and rituximab. Rates of Grade ≥3 adverse events (AEs) were similar with PVR compared to VR (78.8% versus 73.0%, respectively). Low rates of any grade atrial fibrillation/flutter (3.5% versus 2.6%, respectively), hypertension (12.0% versus 7.4%, respectively), and hemorrhage (14.2% versus 10.6%, respectively) were seen with PVR versus VR. Grade ≥3 clinical AEs of interest included neutropenia (50.3% versus 43.7%, respectively) and tumor lysis syndrome (0.9% versus 3.9%, respectively) in the PVR and VR arms. Discontinuation rates due to treatment-related AEs were similar across the PVR and VR study arms (5.4% versus 5.1%, respectively). The addition of pirtobrutinib to VR also allowed for downgrading of tumor lysis risk, with 78% of high-risk patients downgraded to medium (n=20) or low risk (n=18), and 61% of medium-risk patients downgraded to low risk.

"These remarkable findings support the potential addition of two years of Jaypirca to a time-limited venetoclax-based regimen in relapsed or refractory CLL," said Jacob Van Naarden, executive vice president and president of Lilly Oncology. "BRUIN CLL-322 enrolled a mostly covalent BTK inhibitor-pretreated population, ensuring that these results have applicability to the modern CLL treatment landscape where covalent BTK inhibitor use is now common. Additionally, these data further strengthen the unique body of evidence for Jaypirca across the CLL continuum, from monotherapy to combination therapy and across multiple settings where CLL patients need effective treatment."

Lilly plans to submit results from the BRUIN CLL-322 study to global regulatory authorities with the goal of further expanding Jaypirca's label.

Lilly is studying Jaypirca in CLL/SLL in multiple Phase 3 studies. Details on the trials can be found by visiting 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, TTNT, 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 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 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 arrhythmias.

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 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

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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 (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
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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 (Media)
Michael Czapar; czapar_michael_c@lilly.com (Investors)

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