Lilly's Jaypirca (pirtobrutinib) significantly improved progression-free survival, reducing the risk of progression or death by 80%, versus chemoimmunotherapy in patients with treatment-naïve CLL/SLL

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The risk reduction observed in BRUIN CLL-313 is among the most compelling observed for a single agent BTK inhibitor in a front-line CLL study

These data will be simultaneously published in the Journal of Clinical Oncology and highlighted in a late-breaking oral presentation at the 2025 American Society of Hematology Annual Meeting and Exposition, and were featured as part of the meeting's press program

INDIANAPOLIS, Dec. 9, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from the Phase 3 BRUIN CLL-313 clinical trial of Jaypirca (pirtobrutinib), a non-covalent Bruton tyrosine kinase (BTK) inhibitor, versus bendamustine plus rituximab (BR), in treatment-naïve patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) without 17p deletions. Pirtobrutinib met its primary endpoint demonstrating a reduction in the risk of disease progression or death by 80% (HR=0.20 [95% CI, 0.11-0.37]; p<0.0001).

These data will be highlighted in a late-breaking oral presentation at the 67th American Society of Hematology (ASH) Annual Meeting and Exposition taking place in Orlando, Florida and simultaneously published in the *Journal of Clinical Oncology*.

"The results from BRUIN CLL-313 show a significant effect size, among the most pronounced ever observed for a single agent BTK inhibitor in a front-line CLL study," said Wojciech Jurczak, MD, PhD, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland. "The magnitude of the progression-free survival benefit, early overall survival trend and safety profile observed in BRUIN CLL-313 offer highly compelling evidence for the potential role of pirtobrutinib in treatment-naïve CLL."

BRUIN CLL-313 is the first prospective, randomized Phase 3 study examining the efficacy and safety of a non-covalent BTK inhibitor, pirtobrutinib, exclusively in patients with treatment-naïve CLL/SLL. BRUIN CLL-313 enrolled 282 patients with previously untreated CLL/SLL without del(17p), who were randomized 1:1 to receive continuous pirtobrutinib monotherapy (n=141) or BR (n=141). Crossover to the pirtobrutinib arm was allowed after independent review committee (IRC)-confirmed disease progression. The efficacy results are based on a July 11, 2025, data cutoff.

At a median follow-up of 28.1 months, the primary endpoint of IRC-assessed progression-free survival (PFS) was significantly improved with pirtobrutinib compared to BR (HR=0.20 [95% CI, 0.11–0.37]; p<0.0001). PFS results favored pirtobrutinib across all pre-specified subgroups, including those with high-risk molecular features such as TP53 mutations, complex karyotype, and unmutated IGHV, and was consistently observed among investigator assessments.

Overall survival (OS), a key secondary endpoint, remains immature, but a trend favoring pirtobrutinib was observed (HR=0.257 [95% CI, 0.070–0.934]; p=0.0261) despite over half (52.9%) of patients treated with BR crossing over to receive pirtobrutinib after IRC-confirmed disease progression. Final testing of OS superiority is planned at a future date.

The overall safety profile of patients treated with pirtobrutinib in BRUIN CLL-313 was similar to previously reported trials. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 40.0% of patients who received pirtobrutinib versus 67.4% with BR. Fewer adverse event-related dose reductions (3.6% versus 31.1%) and TEAE-related discontinuations (4.3% versus 15.2%) were seen with pirtobrutinib versus BR. The incidence of all-grade and high-grade atrial fibrillation/flutter were similar between pirtobrutinib and BR, a notable finding as BR is not a regimen associated with increased risk of this side effect (1.4% versus 1.5% and 0.7% versus 0.8%, respectively).

"These findings support the potential use of pirtobrutinib in certain treatment-naïve patients and underscore its unique position as the only BTK inhibitor to show promise in treating both newly diagnosed patients with CLL or SLL and those who have progressed on a covalent BTK inhibitor," said Jacob Van Naarden, executive vice president and president, Lilly Oncology. "Alongside the recently presented BRUIN-CLL 314 results, we are excited about how collectively these data may advance the therapeutic landscape in treatment-naïve CLL and are hopeful we will receive regulatory approvals for pirtobrutinib in earlier disease settings sometime next year, further expanding treatment options for patients."

Lilly has begun submitting results from BRUIN CLL-313 and BRUIN CLL-314 studies to regulatory authorities with the goal of further expanding Jaypirca's label into earlier lines of therapy.

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-313
BRUIN CLL-313 is a Phase 3, global, randomized, open-label study of pirtobrutinib versus chemoimmunotherapy (bendamustine plus rituximab) in people with CLL/SLL without 17p deletions who have not been previously treated. The trial enrolled 282 patients who were randomized 1:1 to receive pirtobrutinib (200 mg orally, once daily) or bendamustine plus rituximab (BR) per labeled doses. BR is a chemoimmunotherapy regimen used in the treatment of CLL. The primary endpoint is PFS as assessed by blinded IRC. Secondary endpoints include investigator and IRC assessed overall response rate (ORR), duration of response (DoR), and PFS, OS, time to next treatment (TTNT), safety and tolerability and patient-reported outcomes (PRO).

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.[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.

About Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of slow-growing non-Hodgkin lymphoma that develop from white blood cells known as lymphocytes.[4] CLL is one of the most common types of leukemia in adults.[4] In the U.S., CLL accounts for about one-quarter of the new cases of leukemia and there will be approximately 23,690 new cases of CLL diagnosed this year.[4,5] SLL is identical to CLL from a pathologic and immunophenotypic standpoint, with the main difference between them being the location of the cancer cells.[4] In CLL, the cancer cells are present in the blood, and in SLL, the cancer cells are found in the lymph nodes.[4]

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

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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 adults with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have been previously treated with a covalent BTK inhibitor and as a treatment for adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor, 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

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