



## Lilly's Jaypirca (pirtobrutinib), the first and only approved non-covalent (reversible) BTK inhibitor, significantly improved progression-free survival in patients with treatment-naïve CLL/SLL

September 8, 2025

*In the Phase 3 BRUIN CLL-313 study, treatment with pirtobrutinib demonstrated a highly statistically significant and clinically meaningful improvement in progression-free survival versus bendamustine plus rituximab, indicating one of the most compelling effect sizes ever observed for a single agent BTK inhibitor in a front-line CLL study*

*BRUIN CLL-313 is the third positive Phase 3 study from the pirtobrutinib development program in CLL*

*Results from BRUIN CLL-313 and BRUIN CLL-314 will form the basis for seeking label expansions in earlier lines of therapy, with global regulatory submissions beginning later this year*

INDIANAPOLIS, Sept. 8, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced positive topline results from the Phase 3 BRUIN CLL-313 clinical trial of Jaypirca (pirtobrutinib), a non-covalent (reversible) Bruton tyrosine kinase (BTK) inhibitor, versus chemoimmunotherapy (bendamustine plus rituximab), in treatment-naïve patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) without 17p deletions. The study met its primary endpoint, demonstrating a highly statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to chemoimmunotherapy, as assessed by an independent review committee (IRC), indicating one of the most compelling effect sizes ever observed for a single agent BTK inhibitor in a front-line CLL study.

Overall survival (OS), a key secondary endpoint, was not yet mature at this analysis, but was trending strongly in favor of pirtobrutinib and will be tested for statistical significance at the time of the primary OS analysis, which is anticipated to occur in 2026. The overall safety profile of pirtobrutinib in BRUIN CLL-313 was generally consistent with previously reported trials across treatment settings.

Detailed results will be presented at a medical congress and submitted to a peer-reviewed journal. The results from the BRUIN CLL-313 and BRUIN CLL-314 studies will form the basis for seeking label expansions in earlier lines of therapy, with global regulatory submissions beginning later this year.

"The results from BRUIN CLL-313 are striking and provocative, across both PFS and OS endpoints, further demonstrating the potential of pirtobrutinib to be a meaningful treatment option for people with untreated CLL/SLL," said Jacob Van Naarden, executive vice president and president of Lilly Oncology. "With this third positive Phase 3 study, we continue to build the clinical evidence supporting the possible role of pirtobrutinib in a variety of CLL/SLL treatment settings, including treatment-naïve, BTK inhibitor-naïve and BTK inhibitor exposed. We look forward to presenting these data, as well as data from the recently announced positive BRUIN CLL-314 study, at upcoming medical meetings and preparing global regulatory submissions, with the goal of making pirtobrutinib an option for a wider group of patients who might benefit."

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, and 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. For more information on the BRUIN Phase 3 clinical trial program, please visit [clinicaltrials.gov](https://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 chronic lymphocytic leukemia or small lymphocytic lymphoma (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 progression-free survival (PFS) as assessed by blinded independent review committee (IRC). Secondary endpoints include investigator and IRC assessed overall response rate (ORR), duration of response (DoR), and PFS, overall survival (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.<sup>1</sup> BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).<sup>2,3</sup> 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 a kinase inhibitor indicated for the treatment of

- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.
- Adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

These indications are approved under accelerated approval based on response rate. Continued approval for these indications 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. In a clinical trial, Grade  $\geq 3$  infections occurred in 24% of patients with hematologic malignancies, most commonly pneumonia (14%); fatal infections occurred (4.4%). Sepsis (6%) and febrile neutropenia (4%) occurred. In patients with CLL/SLL, Grade  $\geq 3$  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 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  $\geq 3$  bleeding or any central nervous system bleeding) occurred in 3% of patients, including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred (17%). Major hemorrhage occurred in patients taking Jaypirca with (0.7%) and without (2.3%) 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:** Jaypirca can cause cytopenias, including neutropenia, thrombocytopenia, and anemia. In a clinical trial, Grade 3 or 4 cytopenias, including decreased neutrophils (26%), decreased platelets (12%), and decreased hemoglobin (12%), developed in Jaypirca-treated patients. Grade 4 decreased neutrophils (14%) and Grade 4 decreased platelets (6%) developed. Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

**Cardiac Arrhythmias:** Cardiac arrhythmias occurred in patients who received Jaypirca. In a clinical trial of patients with hematologic malignancies, atrial fibrillation or flutter were reported in 3.2% of Jaypirca-treated patients, with Grade 3 or 4 atrial fibrillation or flutter in 1.5%. Other serious cardiac arrhythmias such as supraventricular tachycardia and cardiac arrest occurred (0.5%). 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 9% of Jaypirca-treated patients. The most frequent malignancy was non-melanoma skin cancer (4.6%). 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. Upon confirmation of DILI, discontinue Jaypirca.

**Embryo-Fetal Toxicity:** Jaypirca can cause fetal harm in pregnant women. 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 potential 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 ( $\geq 20\%$ ) ARs in the BRUIN pooled safety population of patients with hematologic malignancies (n=593) were decreased neutrophil count (46%), decreased hemoglobin (39%), fatigue (32%), decreased lymphocyte count (31%), musculoskeletal pain (30%), decreased platelet count (29%), diarrhea (24%), COVID-19 (22%), bruising (21%), cough (20%).

### Mantle Cell Lymphoma

**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 Jaypirca 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:** ARs led to dose 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 in  $>1\%$  of patients included pneumonia.

**Most common ARs ( $\geq 15\%$ ), excluding laboratory terms (all Grades %; Grade 3-4 %):** fatigue (29; 1.6), musculoskeletal pain (27; 3.9), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), pneumonia (16; 14), bruising (16; -).

**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).

### Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

**Serious ARs** occurred in 56% of patients. Serious ARs occurring in  $\geq 5\%$  of patients were pneumonia (18%), COVID-19 (9%), sepsis (7%), and febrile neutropenia (7%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 11% of patients, most commonly due to infections (10%), including sepsis (5%) and COVID-19 (2.7%).

**Dose Modifications and Discontinuations:** ARs led to dose reductions in 3.6%, treatment interruption in 42%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dose reductions in  $>1\%$  included neutropenia; treatment interruptions in  $>5\%$  of patients included

pneumonia, neutropenia, febrile neutropenia, and COVID-19; permanent discontinuation in >1% of patients included second primary malignancy, COVID-19, and sepsis.

**Most common ARs (≥20%), excluding laboratory terms (all Grades %; Grade 3-4 %):** fatigue (36; 2.7), bruising (36; -), cough (33; -), musculoskeletal pain (32; 0.9), COVID-19 (28; 7), pneumonia (27; 16), diarrhea (26; -), abdominal pain (25; 2.7), dyspnea (22; 2.7), hemorrhage (22; 2.7), edema (21; -), nausea (21; -), pyrexia (20; 2.7), headache (20; 0.9).

**Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in ≥20% of Patients:** neutrophil count decreased (63; 45), hemoglobin decreased (48; 19), calcium decreased (40; 2.8), platelet count decreased (30; 15), sodium decreased (30; -), lymphocyte count decreased (23; 8), ALT increased (23; 2.8), AST increased (23; 1.9), creatinine increased (23; -), lipase increased (21; 7), alkaline phosphatase increased (21; -). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (23).

### Drug Interactions

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

**Sensitive CYP2C8, CYP2C19, CYP3A, P-gp, or 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:** Due to 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 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, 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 increases pirtobrutinib exposure. Reduce Jaypirca dosage in patients with severe renal impairment according to approved labeling.

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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](http://Lilly.com) and [Lilly.com/news](http://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, that Jaypirca will receive additional regulatory approvals, 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.

### Endnotes and 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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The Lilly logo is rendered in a vibrant red, cursive script. The letters are thick and fluid, with a classic, elegant feel. The 'L' is particularly large and prominent, leading into the 'i', 'l', 'l', 'y' which are also written in a continuous, flowing style.

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