



Lilly's Jaypirca (pirtobrutinib), the first-and-only approved non-covalent BTK inhibitor, receives expanded indication from U.S. FDA for certain patients with previously untreated CLL/SLL

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INDIANAPOLIS, Oct. 2, 2026 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the [U.S. Food and Drug Administration \(FDA\)](#) has approved an additional indication for Jaypirca (pirtobrutinib, 100 mg & 50 mg tablets), a non-covalent Bruton tyrosine kinase (BTK) inhibitor, for the treatment of adult patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) with no known 17p deletion. This approval allows for the use of Jaypirca as a first-line treatment for appropriate patients.

"This approval is grounded in data from BRUIN CLL-313, which showed a significant delay in disease progression for pirtobrutinib compared to chemoimmunotherapy, along with safety and tolerability consistent with its established profile," said Jennifer A. Woyach, M.D., professor, hematologist-oncologist, and Director of the Division of Hematology at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. "Doctors can now consider pirtobrutinib for appropriate patients when initial therapy is needed, not just later in a patient's treatment journey. Given the efficacy and tolerability of modern targeted therapies – coupled with factors like age or comorbidity – many people diagnosed with CLL or SLL today may only receive one or two lines of therapy, making initial treatment choices critically important."

The labeling for Jaypirca contains warnings and precautions for infections, hemorrhage, cytopenias, cardiac arrhythmias, second primary malignancies, hepatotoxicity including drug-induced liver injury and embryo-fetal toxicity. See Important Safety Information below and full [Prescribing Information](#) for additional information, including dosing modifications.

Jaypirca, the first-and-only FDA-approved non-covalent BTK inhibitor, is a highly selective kinase inhibitor that utilizes a novel non-covalent binding mechanism to target the BTK pathway in patients with CLL/SLL.^{1,2}

The FDA approval is based on results from the primary analysis of the [BRUIN CLL-313](#) clinical trial, which were presented at the American Society of Hematology Annual Meeting and Exposition in December 2025 and published in [The Journal of Clinical Oncology](#).³ BRUIN CLL-313 is the first prospective, randomized Phase 3 study to examine the efficacy and safety of a non-covalent BTK inhibitor in patients with previously untreated CLL/SLL without 17p deletion.

In BRUIN CLL-313, at a median follow-up of 28 months, the primary endpoint of Independent Review Committee (IRC)-assessed progression-free survival (PFS) was significantly improved with pirtobrutinib (n=141) compared to bendamustine plus rituximab (BR) (n=141) (HR=0.20 [95% CI, 0.11–0.37]; p<0.0001), and the median PFS was not yet reached for pirtobrutinib compared to 33.5 months for BR.⁴ IRC-assessed overall response rate (ORR) was 94% (95% CI, 89–98) in the pirtobrutinib arm (complete response [CR]=13%; partial response [PR]=81%) and 81% (95% CI, 73–87) in the BR arm (CR=21%; PR=60%). In the BRUIN CLL-313 trial, adverse reactions (ARs) led to dose reductions in 3.6% and permanent discontinuation of Jaypirca in 4.3% of patients. Serious ARs occurred in 28% of patients who received Jaypirca. Serious ARs occurring in ≥3% of patients included pneumonia (5%). The overall safety profile, including rates of atrial fibrillation or flutter, for patients treated with pirtobrutinib in the BRUIN CLL-313 trial was consistent with previously reported trials across treatment settings.

"This additional approval for Jaypirca, based on BRUIN CLL-313, marks a significant step forward, expanding its potential to reach more patients who may benefit – this time as an initial treatment for certain previously untreated patients with CLL or SLL," said Jacob Van Naarden, executive vice president and president of Lilly Oncology. "This milestone underscores Jaypirca's versatility in the CLL continuum of care, from the first-line setting for appropriate patients to its valuable role in the relapsed or refractory post-covalent BTK inhibitor setting, reinforcing Jaypirca's broad applicability as a meaningful treatment option for people with CLL or SLL."

Jaypirca is the first-and-only non-covalent BTK inhibitor recommended by the National Comprehensive Cancer Network® (NCCN®).^{1,5,6,7} Jaypirca is Category 2A recommended for treatment-naïve adult patients with CLL/SLL without del(17p), recommended for older patients with cardiac comorbidities who may only need one lifetime treatment for CLL/SLL.⁸ Jaypirca is a Category 1 preferred option for adult patients with relapsed or refractory CLL/SLL who have previously been treated with a covalent BTK inhibitor. Please see full [NCCN guidelines](#) for more information.

Lilly is studying Jaypirca in CLL/SLL in multiple Phase 3 studies. Details on the trials can be found by visiting [clinicaltrials.gov](#).

See Important Safety Information below and full [Prescribing Information](#) for additional information.

[Click here to view the CLL infographic.](#)

About the BRUIN Clinical Development Program

The BRUIN clinical development program comprises four positive Phase 3 studies evaluating pirtobrutinib across multiple lines of CLL/SLL:

- BRUIN CLL-313 is the first prospective, randomized Phase 3 study to examine the efficacy and safety of a non-covalent BTK inhibitor in patients with previously untreated CLL without 17p deletion. The BRUIN CLL-313 study is evaluating pirtobrutinib versus chemoimmunotherapy (BR) in patients with CLL/SLL without 17p deletion who have not been previously treated.
- BRUIN CLL-314 is the first head-to-head Phase 3 CLL trial to compare covalent and non-covalent BTK inhibitors in a BTKi-naïve population, which included relapsed and refractory and treatment-naïve patients. The BRUIN CLL-314 study is

evaluating pirtobrutinib versus ibrutinib in patients with CLL/SLL who were either treatment-naïve, or who were previously treated and were BTK inhibitor-naïve.

- BRUIN CLL-321 is the first randomized Phase 3 study in CLL in which all patients were previously treated with a covalent BTK inhibitor. The BRUIN CLL-321 study is evaluating pirtobrutinib versus investigator's choice of idelalisib plus rituximab (IdelaR) or BR in covalent BTK inhibitor pre-treated patients with relapsed and refractory CLL/SLL.
- BRUIN CLL-322 is the first Phase 3 readout in CLL to utilize a venetoclax-containing control arm. The BRUIN CLL-322 study is evaluating time-limited pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in previously treated CLL/SLL patients.

About BRUIN CLL-313

BRUIN CLL-313 ([NCT05023980](#)) is a Phase 3, global, randomized, open-label study of Jaypirca (pirtobrutinib) versus chemoimmunotherapy (BR) in people with CLL/SLL without 17p deletion who have not been previously treated. The trial enrolled 282 patients who were randomized 1:1 to receive pirtobrutinib (200 mg orally, once daily until disease progression or unacceptable toxicity) or 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 ORR and duration of response (DoR), investigator-assessed 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 inhibitor of the enzyme BTK, and is the first-and-only approved non-covalent BTK inhibitor binding to both wild-type and C481 mutated BTK.² BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).^{9,10} 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

CLL and SLL are forms of slow-growing non-Hodgkin lymphoma that develop from white blood cells known as lymphocytes.¹¹ CLL is one of the most common types of leukemia in adults.¹¹ In the U.S., CLL accounts for about one-quarter of the new cases of leukemia and there will be approximately 22,760 new cases of CLL diagnosed this year.^{11,12} SLL is identical to CLL from a pathologic and immunophenotypic standpoint, with the main difference between them being the location of the cancer cells.¹¹ In CLL, the cancer cells are present in the blood, and in SLL, the cancer cells are found in the lymph nodes.¹¹

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 previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) with no known 17p deletion.
- 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 all clinical trials, Grade ≥ 3 infections occurred (23%), most commonly pneumonia (13%); fatal infections (4.3%), sepsis (4.8%), and febrile neutropenia (3.3%) occurred. In patients with CLL/SLL, Grade ≥ 3 infections occurred (24%), with fatal infections occurring in 5%. 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 all clinical trials, major hemorrhage (Grade ≥ 3 bleeding or any central nervous system bleeding) occurred (3.1%), including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred (18%). Major hemorrhage occurred when taking Jaypirca with (1.3%) and without (1.8%) antithrombotic agents. Consider risks/benefits of coadministering 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 all clinical trials, Grade 3 or 4 cytopenias, including decreased neutrophils (26%), decreased platelets (9%), and decreased hemoglobin (9%), developed. Grade 4 decreased neutrophils (14%) and Grade 4 decreased platelets (4.3%) 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 all clinical trials, atrial fibrillation or flutter were reported in 3.1% 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 (0.3%). 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 all clinical trials, second primary malignancies, including non-skin carcinomas, developed in 10% of Jaypirca-

treated patients, most frequently non-melanoma skin cancer (4.9%). 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 once daily 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=1153) were decreased neutrophil count (56%) and decreased hemoglobin (38%).

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 or 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 28-56% 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 trials were pneumonia (5-21%), COVID-19 (5%), sepsis (3.4%). Across clinical trials, **fatal ARs** within 28-30 days of last Jaypirca dose occurred in 0.7-11% of patients, most commonly due to infections (7-10%), including sepsis (5%), COVID-19 (2.7-5%), pneumonia (3.4%) and septic shock (0.7%).

Dose Modifications and Discontinuations Due to ARs: Dose reductions in 3.6-10%, treatment interruption in 35-51%, and permanent discontinuation of Jaypirca in 4.3-17% 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 or 4%)—across randomized controlled trials: neutrophil count decreased (48-54; 14-26), hemoglobin decreased (24-45; 6-10), platelet count decreased (37; 17), upper respiratory tract infections (21-27; 0.9-2.1), bilirubin increased (21-30; 0.9-5), pneumonia (28; 16), ALT increased (25-27; 1.8-2.9), creatinine increased (25; -), calcium decreased (23; 0.9), sodium decreased (22; 0.9), rash (22; 0.7), COVID-19 (21; 0.7), sodium increased (20; -); **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.

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Please see [Prescribing Information](#) and [Patient Information](#) for Jaypirca.

Frequently Asked Questions

1. What is Jaypirca (pirtobrutinib)?

Jaypirca (pirtobrutinib) is a highly selective kinase inhibitor that is 300 times more selective for Bruton tyrosine kinase (BTK) versus 98% of other kinases tested in preclinical studies.² Jaypirca is the first-and-only approved non-covalent BTK inhibitor binding to both wild-type and C481 mutated BTK.² BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).^{9,10} The FDA approved Jaypirca as a monotherapy for the treatment of adult patients with previously untreated CLL or small lymphocytic lymphoma (SLL) with no known 17p deletion in October 2026.

2. What is chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)?

CLL and SLL are forms of slow-growing non-Hodgkin lymphoma that develop from white blood cells called lymphocytes.¹¹ CLL and SLL are considered different forms of the same disease and share the same pathologic and immunophenotypic characteristics.¹¹ The primary difference between CLL and SLL is where the cancer cells are located.¹¹ In CLL, the cancer cells are found primarily in the blood, while in SLL, the cancer cells are found primarily in the lymph nodes.¹¹ CLL is one of the most common forms of leukemia in adults and accounts for approximately one-quarter of new leukemia diagnoses in the United States.¹¹ An estimated 22,760 people in the U.S. will be diagnosed with CLL this year.¹²

3. What is chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) with no known 17p deletion?

For people with CLL or SLL, certain cytogenetic factors may be associated with a higher risk of disease progression.¹¹ One of these factors is a deletion in chromosome 17 [del(17p)] that is found in about 5% to 8% of patients with CLL/SLL when they are first diagnosed.^{11,13} Del(17p) typically affects the tumor protein p53 (TP53) tumor suppressor gene.¹¹

4. As the basis of this approval, what are the clinical benefits of Jaypirca (pirtobrutinib) for adults with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) with no known 17p deletion?

In the Phase 3 BRUIN CLL-313 study, pirtobrutinib significantly improved Independent Review Committee (IRC)-assessed progression-free survival (PFS) compared to bendamustine plus rituximab (BR) (HR=0.20 [95% CI, 0.11–0.37]; p<0.0001) in patients with previously untreated CLL/SLL without 17p deletion, and the median PFS was not yet reached for pirtobrutinib compared to 33.5 months for BR.⁴ IRC-assessed overall response rate (ORR) was 94% (95% CI, 89–98) in the pirtobrutinib arm (complete response [CR]=13%; partial response [PR]=81%) and 81% (95% CI, 73–87) in the BR arm (CR=21%; PR=60%).

5. What are the safety results for Jaypirca (pirtobrutinib) from the BRUIN CLL-313 trial?

The overall safety profile, including rates of atrial fibrillation or flutter, for patients treated with pirtobrutinib in the BRUIN CLL-313 trial was consistent with previously reported trials across treatment settings. In the BRUIN CLL-313 trial, in patients with previously untreated CLL/SLL without 17p deletion, a low rate of all-grades atrial fibrillation or flutter was observed, occurring in 1.4% of patients taking pirtobrutinib. Median duration of treatment with pirtobrutinib was 32 months with 92% on treatment for greater than 24 months. Clinically relevant adverse reactions in <10% of patients who received pirtobrutinib include pneumonia and headache. Patients with significant cardiovascular disease (including uncontrolled or symptomatic arrhythmias) were excluded from the CLL-313 study, and the Prescribing Information for Jaypirca includes a Cardiac Arrhythmias warning/precaution. The all-grades adverse reactions ≥20% reported for patients treated with Jaypirca were upper respiratory tract infection (27%), rash (22%), COVID-19 including COVID-19 pneumonia (21%). Select all-grades laboratory abnormalities (≥20%) that worsened from baseline were neutrophil count decreased (48%), bilirubin increased (30%), ALT increased (27%), hemoglobin decreased (24%), and sodium increased (20%).

6. How does this indication for Jaypirca (pirtobrutinib) differ from the previously approved indication for patients with CLL in the U.S.?

In December 2025, the U.S. Food and Drug Administration (FDA) [granted approval](#) to Jaypirca (pirtobrutinib) for the treatment of adults with relapsed or refractory CLL or SLL who have previously been treated with a covalent BTK inhibitor. This prior FDA action expanded the Jaypirca label to include patients earlier in their treatment course and converted the December 2023 accelerated approval for later-line CLL/SLL to a traditional approval. This new approval in the U.S. authorizes Jaypirca for adult patients with previously untreated CLL/SLL with no known 17p deletion. This expanded indication brings Jaypirca to the first-line CLL/SLL setting for certain previously untreated patients.

7. Is Jaypirca (pirtobrutinib) approved for 1L CLL treatment?

Yes, Jaypirca (pirtobrutinib) is approved for adult patients with previously untreated CLL/SLL patients with no known 17p deletion. For appropriate patients starting treatment, physicians may consider Jaypirca in 1L CLL.

8. How is Jaypirca (pirtobrutinib) different than ibrutinib, acalabrutinib and zanubrutinib?

Jaypirca (pirtobrutinib) is the first-and-only approved non-covalent BTK inhibitor, representing a newer class of BTK inhibitor compared to ibrutinib, acalabrutinib, and zanubrutinib which are all covalent BTK inhibitors. Based on preclinical studies, pirtobrutinib is different in where and how it binds to the BTK protein in the adenosine triphosphate (ATP) pocket. There are no data from trials between Jaypirca and covalent BTK inhibitors comparing the clinical significance of their different binding mechanisms.

9. Is Jaypirca (pirtobrutinib) recommended in the NCCN® Guidelines?

Jaypirca (pirtobrutinib) is the first-and-only non-covalent BTK inhibitor recommended by the National Comprehensive Cancer Network®

(NCCN®).^{1,5,6,7} Jaypirca is Category 2A recommended for treatment-naïve adult patients with CLL/SLL without del(17p), recommended for older patients with cardiac comorbidities who may only need one lifetime treatment for CLL/SLL.⁸ Jaypirca is a Category 1 preferred option for adult patients with R/R CLL/SLL who have previously been treated with a covalent BTK inhibitor. Please see full NCCN guidelines for more information.

10. In which Phase 3 clinical trials is Jaypirca (pirtobrutinib) being studied in CLL and SLL?

Jaypirca (pirtobrutinib) is currently being studied in four Phase 3 clinical trials in CLL and SLL:

- BRUIN CLL-321 ([NCT04666038](#)) is a Phase 3 open-label, randomized study of pirtobrutinib (LOXO-305) versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated CLL/SLL. More information on the [BRUIN CLL-321 study](#) can be found on [clinicaltrials.gov](#).
- BRUIN CLL-322 ([NCT04965493](#)) is a Phase 3 open-label, randomized study of fixed duration pirtobrutinib plus venetoclax and rituximab versus venetoclax and rituximab in previously treated CLL/SLL. More information on the [BRUIN CLL-322 study](#) can be found on [clinicaltrials.gov](#).
- BRUIN CLL-313 ([NCT05023980](#)) is a Phase 3 open-label, randomized study of pirtobrutinib versus bendamustine plus rituximab in untreated patients with CLL. More information on the [BRUIN CLL-313 study](#) can be found on [clinicaltrials.gov](#).
- BRUIN CLL-314 ([NCT05254743](#)) is a Phase 3 open-label, randomized study of pirtobrutinib versus ibrutinib in patients with CLL/SLL. More information on the [BRUIN CLL-314 study](#) can be found on [clinicaltrials.gov](#).

11. What makes BRUIN CLL-313 different from other CLL trials?

BRUIN CLL-313 ([NCT05023980](#)) is the first Phase 3 study to evaluate a non-covalent BTK inhibitor in patients with previously untreated CLL without 17p deletion.

12. With this approval, how many people living with CLL may now be eligible for treatment with Jaypirca (pirtobrutinib)?

There are roughly 23,000 new cases of CLL in the U.S. each year, and approximately 92% to 95% of patients diagnosed with CLL do not have a 17p deletion.^{12,13} The majority of treated patients with CLL will receive a BTK therapy at some point in their treatment, with many patients today receiving potentially only one or two lines of therapy throughout their entire treatment journey.

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 treatment for adult patients with previously untreated chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) with no known 17p deletion, adult patients with relapsed or refractory CLL/SLL who have previously been treated with a covalent Bruton tyrosine kinase (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, 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 & References

1. Jaypirca. Prescribing Information. Lilly USA, LLC.
2. 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
3. Jurczak W, Kwiatek M, Czyz J, et al. BRUIN CLL-313: Randomized Phase III Trial of Pirtobrutinib Versus Bendamustine Plus Rituximab in Untreated Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. *J Clin*

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4. Based on Kaplan-Meier estimation.
5. Lilly does not recommend use outside of its approved indications. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.⁶ To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN Defines: Category 1: Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate. Preferred intervention: interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V2.2027 ©National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed September 30, 2026. To view the most recent and complete version of the guidelines, go online to NCCN.org
7. NCCN Category recommendations for pirtobrutinib do not differ based on del(17p) and/or TP53 mutation status.
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