Lilly's Jaypirca (pirtobrutinib) met its primary endpoint in first-of-its-kind, head-to-head Phase 3 study versus Imbruvica (ibrutinib)

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In addition to meeting the primary endpoint of non-inferiority for overall response rate (ORR) in the BRUIN CLL-314 study, pirtobrutinib achieved a numerically higher ORR of 87.0% compared to 78.5% for ibrutinib in the intent-to-treat (ITT) population

Progression-free survival data were immature but trended in favor of pirtobrutinib with a 43% reduction of the risk of disease progression or death in the ITT population, and the treatment-naïve subgroup, which had the longest follow up, showed a 76% reduction

These data will be simultaneously published in the Journal of Clinical Oncology and presented at the 2025 American Society of Hematology Annual Meeting and Exposition, as well as featured as part of the meeting's press program

INDIANAPOLIS, Dec. 7, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from the Phase 3 BRUIN CLL-314 clinical trial evaluating Jaypirca (pirtobrutinib), a non-covalent (reversible) Bruton tyrosine kinase (BTK) inhibitor, versus Imbruvica (ibrutinib), a covalent BTK inhibitor, in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who were treatment-naïve or were BTK inhibitor-naïve. Pirtobrutinib met its primary endpoint of non-inferiority on overall response rate (ORR) compared to ibrutinib (87.0% [95% CI, 82.90-90.44] versus 78.5% [95% CI, 73.73-82.85]; p<0.0001) in the intent-to-treat (ITT) population. Pirtobrutinib also had numerically higher ORR rates and, while immature, progression-free survival (PFS) was also trending in favor of pirtobrutinib compared to ibrutinib across all populations, including a 76% reduction in the risk of disease progression or death (HR=0.239 [95% CI, 0.098-0.586]) in treatment-naïve patients, the subgroup with the longest follow-up.

These data will be highlighted 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*.

"These data from BRUIN CLL-314 are both novel and clinically significant, demonstrating an improved overall response rate and a favorable trend in progression-free survival outcomes with pirtobrutinib compared to ibrutinib across all populations, including treatment-naïve patients where covalent BTK inhibitors are a cornerstone of treatment," 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. "BRUIN CLL-314 is the first randomized study to compare covalent and non-covalent BTK inhibitors and to directly compare any BTK inhibitors in the treatment-naïve setting, offering findings that are important for advancing the field and patient care. These efficacy results, along with pirtobrutinib's safety profile, offer strong evidence on the role of pirtobrutinib earlier in the treatment course for patients with CLL or SLL."

The BRUIN CLL-314 study enrolled 662 patients who were randomized to receive pirtobrutinib (n=331) or ibrutinib (n=331), with the ITT population consisting of 225 treatment-naïve and 437 relapsed/refractory patients. The efficacy results utilize a June 10, 2025, data cutoff date.

The study achieved its primary endpoint demonstrating that pirtobrutinib was statistically non-inferior to ibrutinib in independent review committee (IRC)-assessed ORR for the ITT population, and results numerically favored pirtobrutinib (87.0% [95% CI, 82.90-90.44] versus 78.5% [95% CI, 73.73-82.85]; nominal p = 0.0035). Additionally, ORR consistently favored pirtobrutinib versus ibrutinib across all populations evaluated, including relapsed/refractory and treatment-naïve, as well as across pre-specified subgroups such as patients with and without 17p deletions, IGHV status and complex karyotype.

PFS, a key secondary endpoint, was not yet mature at this analysis but was trending in favor of pirtobrutinib compared to ibrutinib in the ITT (HR=0.569 [95% CI, 0.388-0.834]), relapsed/refractory (HR=0.729 [95% CI, 0.471-1.128]), and treatment-naïve (HR=0.239 [95% CI, 0.098-0.586]) populations, with a median follow-up of 22.0 months, 18.4 months, and 22.5 months, respectively. Among all subgroups, the largest PFS effect size was observed in the treatment-naïve subgroup, which had the longest follow-up at this data cut, with a 76% reduction in the risk of disease progression or death. A formal PFS analysis testing for superiority is planned at a future analysis. There was no detriment in overall survival (OS) (HR=0.961 [95% CI, 0.55-1.69]) for the ITT population.

The overall safety profile for patients treated with pirtobrutinib in BRUIN CLL-314 was similar to previously reported trials, and the most common treatment-emergent adverse events were similar between arms. Most adverse events (AE) of interest were lower with pirtobrutinib compared to ibrutinib, including atrial fibrillation/flutter (2.4% versus 13.5%) and hypertension (10.6% versus 15.1%). Fewer AE-related dose reductions (7.9% versus 18.2%) and discontinuations (9.4% versus 10.8%) were seen with pirtobrutinib versus ibrutinib.

"We are excited to share these compelling new findings for pirtobrutinib with the scientific community at ASH and in the *Journal of Clinical Oncology*," said Jacob Van Naarden, executive vice president and president, Lilly Oncology. "These data build on additional results from the BRUIN development program and the recent FDA approval for pirtobrutinib in the post-covalent BTK inhibitor setting to reinforce the medicine's potential to deliver meaningful benefit for people living with CLL or SLL across various disease settings."

As part of the Late-Breaking Abstract Session on Dec. 9, Lilly will also share results from the Phase 3 BRUIN CLL-313 study of pirtobrutinib versus chemoimmunotherapy in patients with treatment-naïve CLL/SLL without del(17p). These data were also selected to be highlighted as part of the ASH Annual Meeting press program session on Dec. 8.

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-314

BRUIN CLL-314 is a Phase 3, randomized, open-label study of Jaypirca (pirtobrutinib) versus Imbruvica (ibrutinib) in patients with CLL/SLL who were either treatment-naïve, or who were previously treated and were BTK inhibitor-naïve. The trial planned to enroll 650 patients who were randomized 1:1 to receive pirtobrutinib (200 mg orally, once daily) or ibrutinib (420 mg orally, once daily). The primary endpoint is ORR as assessed by blinded IRC. Secondary endpoints include investigator and IRC-assessed PFS, duration of response (DoR) and event-free survival (EFS), and time to next treatment (TTNT), OS, 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

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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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